University of Groningen

Evaluating quality of care in liver surgery

Elfrink, Arthur

DOI:
[10.33612/diss.193354028](https://doi.org/10.33612/diss.193354028)

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):

Elfrink, A. (2021). *Evaluating quality of care in liver surgery: the Dutch Hepato Biliary Audit project*. [Thesis fully internal (DIV), University of Groningen]. University of Groningen.
<https://doi.org/10.33612/diss.193354028>

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.

Evaluating quality of care in liver surgery

The Dutch Hepato Biliary Audit project

Arthur Karel Ernst Elfrink

Evaluating quality of care in liver surgery
The Dutch Hepato Biliary Audit project

ISBN: 978-94-6421-430-7

Cover design: Marilou Maes | persoonlijkproefschrift.nl
Layout and design: Marilou Maes | persoonlijkproefschrift.nl
Printed by Ipskamp Printing

© Arthur Karel Ernst Elfrink
Amsterdam, 2021

The copyright of the published articles has been transferred to the respective publishers. No part of this thesis may be reproduced, stored or transmitted, in any form or by any means, without prior permission of the author.

This thesis was written at the Department of Surgery, UMCG, Groningen and the Dutch Institute for Clinical Auditing, Leiden.

The printing of this thesis was financially supported by: Dutch Institute for Clinical Auditing, SOLV, Chipsoft, UMCG, Research Institute Share and Spaarne Gasthuis.

Pap, je bent en blijft mijn baken.
Voor altijd in mijn hart.

rijksuniversiteit
 groningen

Evaluating quality of care in liver surgery

The Dutch Hepato Biliary Audit project

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 24 november 2021 om 16.15 uur

door

Arthur Karel Ernst Elfrink

geboren op 11 augustus 1992
te 's Gravenhage

Promotor

Prof. dr. J.M. Klaase

Copromotores

Dr. D.J. Grünhagen

Dr. N.F.M. Kok

Beoordelingscommissie

Prof. dr. R.J. Porte

Prof. dr. C.H.C. de Jong

Prof. dr. H.M.W. Verheul

Table of Contents

Chapter 1.	General introduction and thesis outline	10
<u>Part I.</u>	<u>Quality assessment of liver surgery</u>	
Chapter 2.	Volume-outcome relationship of liver surgery: a nationwide analysis British Journal of Surgery 2020	24
Chapter 3.	Prognostic factors associated with failure to rescue after liver resection and impact on hospital variation: a nationwide population-based study HPB 2021	48
Chapter 4.	Short-term postoperative outcomes after liver resection in the elderly patient: a nationwide population-based study HPB 2021	70
Chapter 5.	Surgical outcomes of laparoscopic and open resection of benign liver tumours in the Netherlands: a nationwide analysis HPB 2020	104
<u>Part II.</u>	<u>Impact of hospital variation on outcomes after resection of colorectal liver metastases</u>	
Chapter 6.	Preoperative imaging for colorectal liver metastases: a nationwide population-based study BJS Open 2020	132
Chapter 7.	Population-based study on practice variation regarding preoperative systemic chemotherapy in patients with colorectal liver metastases and impact on short-term outcomes European Journal of Surgical Oncology 2020	164

Chapter 8.	Case-mix adjustment to compare nationwide hospital performances after resection of colorectal liver metastases European Journal of Surgical Oncology 2020	192
Chapter 9.	Oncological networks for resection of colorectal liver metastases: differences and postoperative outcomes European Journal of Surgical Oncology 2021	222
Chapter 10.	Hospital variation in combined liver resection and thermal ablation for colorectal liver metastases and impact on short-term postoperative outcomes: a nationwide population-based study HPB 2020	250
Chapter 11.	Hospital variation and outcomes of simultaneous resection of primary colorectal tumour and liver metastases: a population-based study HPB 2021	276
Chapter 12.	Discussion and future perspectives	304
Chapter 13.	Summary	320
 <u>Appendices</u>		
	Dutch summary / Nederlandse samenvatting	330
	List of Publications	340
	PhD Portfolio	348
	Acknowledgements / Dankwoord	350
	About the author	359

CHAPTER 1

GENERAL INTRODUCTION

General introduction

Liver resection is the indicated management of primary and secondary liver tumours. In the Netherlands, approximately 1000 liver resections and 500 liver ablations are yearly performed for malignant and benign liver tumours. In 2019 most liver resections and ablations were performed for colorectal liver metastases (CRLM) (63%). Other indications for liver surgery and ablation are hepatocellular carcinoma (HCC) (16%), metastases originating from primary tumours, such as breast cancer, gynaecological cancer, urothelial cancer, sarcomas, melanomas, neuroendocrine tumours and several others (8%), biliary cancer (7%) and for benign liver tumours (6%).

Preoperative workup, treatment and both postoperative and long-term outcomes vary due to differences between these tumour types. Postoperative mortality rates range between 3-5% after resection of secondary liver tumours but increase up to 5-10% and 10-15% after liver resection for HCC or bile duct and gall bladder cancer¹⁻³. With multimodal treatment, survival rates 5 years after resection range between 30-50% for CRLM and range between 40-60% and 20-40% after liver resection for HCC or bile duct and gall bladder cancer, respectively⁴⁻⁶. Improvement of outcomes for patients with liver tumours is warranted. Therefore, treatment of liver tumours requires a multidisciplinary team with important roles for oncologists, (interventional) radiologists and radiation oncologists besides surgeons. Together, they can optimise quality of care for patients with liver tumours through improvement of the perioperative process.

Preoperative assessment of liver tumours

Before commencing treatment of liver tumours, detailed knowledge regarding anatomical location and relation to vascular structures can be obtained through preoperative imaging using various imaging modalities. Ultrasound and Computed Tomography (CT) scans are most often used as a baseline imaging for liver tumours. These imaging techniques are available in every Dutch hospital and are easily accessible. Other increasingly used imaging modalities include Magnetic Resonance Imaging (MRI) and ¹⁸Fluoro-Deoxy-Glucose Positron Emission Tomographic (¹⁸FDG-PET-CT) scans. MRI might offer a significant advantage over a conventional CT in detecting small liver tumours as well as providing detailed information on the anatomical relation of the tumour to vascular structures⁷⁻⁹. The advantage of ¹⁸FDG-PET-CT has been ascribed in detection of extrahepatic lesions¹⁰⁻¹³. However, the efficacy and added value of both MRI and ¹⁸FDG-PET-CT is under debate.

Dutch Guidelines for CRLM state that MRI has significant additional value when performed in patients undergoing local treatment¹⁴. ¹⁸FDG-PET-CT should only be used to detect extrahepatic lesions. For HCC, bile duct, and gall bladder cancer little evidence is available. The use of MRI and ¹⁸FDG-PET-CT is indicated to confirm clinical diagnosis^{15,16}. Due to inconclusive evidence regarding imaging for liver tumours it is presumed that these guidelines have not been fully incorporated in clinical practice.

Preoperative chemotherapy for liver tumours

The preoperative indication for chemotherapy for resectable colorectal liver metastases is still under debate. The role of neoadjuvant chemotherapy and induction chemotherapy for CRLM is complex and has been evolving over the years. Patients may be classified into three broad categories: patients with unequivocally unresectable disease, patients with initially unresectable but potentially resectable disease after downstaging and patients with up-front resectable disease.

The first quest is the categorisation of 'resectable disease'. Several studies have been initiated on resectability criteria to provide indications for induction chemotherapy for CRLM^{17,18}. It was shown that central decision making on resectability by a panel of hepatobiliary surgeons increases resectability rates and leads to better long-term outcomes^{19,20}. No consensus however has been reached on resectability criteria due to heterogeneity in study populations and trial designs²¹. Future outcomes of the Dutch CAIRO-5 study on the use of preoperative chemotherapy in patients with unresectable CRLM are awaited¹⁸.

Preoperative chemotherapy for up-front resectable CRLM has been studied extensively. Preoperative systemic chemotherapy has not improved overall survival benefits in these patients²²⁻²⁵. Therefore, no routine use has been incorporated in daily practice in the Netherlands. Recent advances to treat CRLM include Hepatic Artery Infusion Chemotherapy (HAIC) although level-1 evidence is still awaited²⁶. Due to rapid evolving evidence on this topic, no clear guideline for patients with up-front resectable CRLM has been implemented. Further studies are needed to assess daily practice and added value of chemotherapy in these patients. In other liver tumours such as cholangiocarcinoma, chemotherapy prior to resection is indicated in initially unresectable cholangiocarcinoma but literature on this topic is contradictory and resectability criteria are lacking^{27,28}. For HCC, literature on preoperative chemotherapy either as induction therapy or in a neoadjuvant setting is not available.

Surgical and ablative management of liver tumours

Several initiatives have been proposed to increase local treatment rates of liver tumours.

Cornerstones of technically feasible and oncological sensible liver resection include sufficient future liver remnant and clear resection margins. New options regarding liver resection include laparoscopic, robotic and parenchymal-sparing surgery which have shown to be safe. These techniques decrease postoperative morbidity and mortality by diminishing surgical trauma while not compromising long-term outcomes²⁹⁻³¹.

Thermal ablation using Radiofrequency Ablation (RFA) and Microwave Ablation (MWA) as treatment for liver tumours is rapidly gaining ground. Evidence regarding the use of ablation versus resection for liver tumours is contradictory³²⁻³⁶. Several studies, such as the COLLISION trial, have been initiated to assess long-term outcomes in order to verify the true position of ablation³⁷. The field of surgical and ablative treatment of liver tumours is changing rapidly and further advances are expected.

Organisation of liver surgery in the Netherlands

Liver surgery is accompanied by considerable morbidity and mortality as a result of invasive surgical interventions in an aging and more comorbid population^{38,39}. In order to minimise postoperative morbidity and mortality, risk assessment and preoperative staging are essential. Agreements for hospitals performing liver surgery have been implemented in the Netherlands according to the standardisation report by the Dutch Federation of Oncologic Societies (SONCOS)⁴⁰. As a result, liver surgery was centralised in 24 of 69 Dutch hospitals. Structural agreements for hospitals performing liver surgery include an annual volume requirement of 20 liver resections, 24/7 availability of an interventional radiologist, at least two hepatobiliary surgeons, and participation in the Dutch Hepato Biliary Audit to provide insight in quality of care in liver surgery.

Dutch Hepato Biliary Audit

Nationwide clinical audits are used to measure outcomes and are a tool for evaluating quality of care. The Dutch Institute for Clinical Auditing (DICA) was founded to facilitate and organise initiation of nationwide audits in a uniform format in the Netherlands⁴¹. The Dutch Hepato Biliary Audit was founded in 2013 by the Dutch Liver Surgery Group⁴². Registering all patients undergoing liver surgery is mandatory for all hospitals performing liver surgery. Since 2018, the DHBA is a multidisciplinary audit as a result of registering all thermal ablation procedures performed by interventional radiologists. Data from hospitals on liver resection and thermal ablation is collected by DICA. Benchmarked hospital data are reported to hospitals on a weekly

basis, therewith providing a platform for hospital comparison. As a result, outcomes can be evaluated which ultimately should result in improvement of quality of care.

Clinical auditing and use of quality indicators

Earnest Amory Codman was a surgeon from the Massachusetts General Hospital in Boston and was the founding father of clinical auditing⁴³. He linked information on diagnostics and treatment to outcomes of his patients in order to improve daily practice and therewith introduced clinical auditing into surgical practice. To achieve quality assessment and improvement, the clinical audit cycle uses the technique of the Plan-Do-Check-Act method which follows a systematic process of identifying an audit topic, set a standard, collect and analyse data followed by an act to improve outcomes⁴⁴.

In the DHBA, the scientific committee yearly determines audit topics and sets quality indicators. These quality indicators contain results on process of care, pathological outcomes or postoperative outcomes. Using the auditing cycle, the DHBA assesses validity of quality indicators, nationwide variation in these quality indicators and provides support to improve nationwide quality of care in liver surgery in the Netherlands.

Aims of this thesis

The aims of this thesis were to address hospital variation in selection of patients for liver surgery, preoperative workup, treatment, and outcomes of treatment. We aimed to gain insight in the quality of care in liver surgery and to provide leads to improve quality of care for patients with a liver tumour in the Netherlands.

Thesis Outline

This thesis comprises the first projects performed with population-based data from the Dutch Hepato Biliary Audit (DHBA) reflecting daily practice of treatment of liver tumours in the Netherlands. **Part I** of this thesis focuses on assessing quality of care in different liver tumours. **Part II** focuses on hospital variation in perioperative treatment of colorectal liver metastases and impact on short-term outcomes.

Part I. Quality assessment of liver surgery

In **Chapter 2**, the association of hospital volume with postoperative outcomes was reported. In **Chapter 3** the quality indicator 'Failure to Rescue' (FTR) is described. FTR is defined as complications which lead to mortality. We described hospital variation and provided leads to decrease FTR in the Netherlands. In **Chapter 4** postoperative outcomes after liver resection in elderly patients are summarised. Although postoperative outcomes in elderly patients were adequate, several complications occurred more often in these elderly patients. This emphasises the need for patient selection and risk stratification prior to liver surgery in an aging population. **Chapter 5** provides insight in postoperative outcomes and added value of laparoscopic liver resection in patients with benign liver tumours.

Part II. Impact of hospital variation on outcomes after resection of colorectal liver metastases

In **Chapter 6** trends over time regarding preoperative imaging for CRLM were evaluated. Remarkable hospital variation was observed in the preoperative workup for CRLM. **Chapter 7** provided insight in hospital variation of preoperative systemic chemotherapy and its impact on short-term outcomes. In **Chapter 8**, hospital variation in the existing quality indicators '30-day Major Morbidity', defined as a complication graded Clavien-Dindo $\geq 3a$ within 30 days of liver resection, and '30-day Mortality' for colorectal liver metastases (CRLM) are assessed. The between-hospital variation in patient demographics and disease burden and need for case-mix

adjustment was also addressed in this chapter. **Chapter 9** demonstrated oncological network formation in the Netherlands for CRLM. It described how comparison of quality indicators on an oncological network level might be more relevant as opposed to on a hospital level. Between oncological network case-mix variation was assumed similar due to composition of a tertiary referral centre together with several non-academic hospitals. In **Chapter 10** the combination of resection and thermal ablation for CRLM was described. Hospital variation was assessed and postoperative outcomes were compared between resection and resection combined with thermal ablation. In **Chapter 11** the variation between hospitals with regard to simultaneous resection versus staged resection of the colorectal primary tumour and liver metastases was evaluated. Risk factors for major morbidity were provided therewith introducing leads for patient selection and risk assessment in this group.

References

1. Gilg S, Sparrelid E, Isaksson B, Lundell L, Nowak G, Stromberg C. Mortality-related risk factors and long-term survival after 4460 liver resections in Sweden-a population-based study. *Langenbecks Arch Surg*. 2017;402(1):105-113.
2. Torzilli G, Belghiti J, Kokudo N, Takayama T, Capussotti L, Nuzzo G, et al. A snapshot of the effective indications and results of surgery for hepatocellular carcinoma in tertiary referral centers: is it adherent to the EASL/AASLD recommendations?: an observational study of the HCC East-West study group. *Ann Surg*. 2013;257(5):929-937.
3. Franken LC, Schreuder AM, Roos E, van Dieren S, Busch OR, Besselink MG, et al. Morbidity and mortality after major liver resection in patients with perihilar cholangiocarcinoma: A systematic review and meta-analysis. *Surgery*. 2019;165(5):918-928.
4. Kanas GP, Taylor A, Primrose JN, Langeberg WJ, Kelsh MA, Mowat FS, et al. Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors. *Clin Epidemiol*. 2012;4:283-301.
5. Bruix J, Gores GJ, Mazzaferro V. Hepatocellular carcinoma: clinical frontiers and perspectives. *Gut*. 2014;63(5):844-855.
6. Mazzaferro V, Gorgen A, Roayaie S, Droz Dit Busset M, Sapisochin G. Liver resection and transplantation for intrahepatic cholangiocarcinoma. *J Hepatol*. 2020;72(2):364-377.
7. Rizvi S, Gores GJ. Current diagnostic and management options in perihilar cholangiocarcinoma. *Digestion*. 2014;89(3):216-224.
8. Ayuso C, Rimola J, Vilana R, Burrel M, Darnell A, Garcia-Criado A, et al. Diagnosis and staging of hepatocellular carcinoma (HCC): current guidelines. *Eur J Radiol*. 2018;101:72-81.
9. Sivesgaard K, Larsen LP, Sorensen M, Kramer S, Schlander S, Amanavicius N, et al. Diagnostic accuracy of CE-CT, MRI and FDG PET/CT for detecting colorectal cancer liver metastases in patients considered eligible for hepatic resection and/or local ablation. *Eur Radiol*. 2018;28(11):4735-4747.
10. Lee SW, Kim HJ, Park JH, Park DI, Cho YK, Sohn CI, et al. Clinical usefulness of 18F-FDG PET-CT for patients with gallbladder cancer and cholangiocarcinoma. *J Gastroenterol*. 2010;45(5):560-566.
11. Lin CY, Chen JH, Liang JA, Lin CC, Jeng LB, Kao CH. 18F-FDG PET or PET/CT for detecting extrahepatic metastases or recurrent hepatocellular carcinoma: a systematic review and meta-analysis. *Eur J Radiol*. 2012;81(9):2417-2422.
12. Metser U, Halankar J, Langer D, Mohan R, Hussey D, Hadas M, et al. Effect of chemotherapy on the impact of FDG-PET/CT in selection of patients for surgical resection of colorectal liver metastases: single center analysis of PET-CAM randomized trial. *Ann Nucl Med*. 2017;31(2):153-162.
13. Maffione AM, Lopci E, Bluemel C, Giammarile F, Herrmann K, Rubello D. Diagnostic accuracy and impact on management of (18)F-FDG PET and PET/CT in colorectal liver metastasis: a meta-analysis and systematic review. *Eur J Nucl Med Mol Imaging*. 2015;42(1):152-163.
14. Dutch Guideline Database. Dutch Guideline - Colorectal Carcinoma https://richtlijnendatabase.nl/richtlijn/colorectaal_carcinoom_crc/startpagina_-_crhtml. 2014.
15. Dutch Guideline Database. Dutch Guideline - Hepatocellular carcinoma. https://richtlijnendatabase.nl/richtlijn/hepatocellulair_carcinoom/epidemiologie_en_etiologiehtml. 2013.
16. Dutch Guideline Database. Dutch Guideline - Bile duct and gall bladder cancer. https://richtlijnendatabase.nl/richtlijn/galweg_en_galblaascarcinoom/algemeenhtml. 2013.
17. Adam R, De Gramont A, Figueras J, Guthrie A, Kokudo N, Kunstlinger F, et al. The oncosurgery approach to managing liver metastases from colorectal cancer: a multidisciplinary international consensus. *Oncologist*. 2012;17(10):1225-1239.
18. Huiskens J, van Gulik TM, van Lienden KP, Engelbrecht MR, Meijer GA, van Grieken NC, et al. Treatment strategies in colorectal cancer patients with initially unresectable liver-only metastases, a study protocol of the randomised phase 3 CAIRO5 study of the Dutch Colorectal Cancer Group (DCCG). *BMC Cancer*. 2015;15:365.
19. Huiskens J, Bolhuis K, Engelbrecht MR, De Jong KP, Kazemier G, Liem MS, et al. Outcomes of Resectability Assessment of the Dutch Colorectal Cancer Group Liver Metastases Expert Panel. *J Am Coll Surg*. 2019;229(6):523-532 e522.

20. Isoniemi H, Uutela A, Nordin A, Lantto E, Kellokumpu I, Ovissi A, et al. Centralized repeated resectability assessment of patients with colorectal liver metastases during first-line treatment: prospective study. *Br J Surg*. 2021.
21. Bolhuis K, Kos M, van Oijen MGH, Swijnenburg RJ, Punt CJA. Conversion strategies with chemotherapy plus targeted agents for colorectal cancer liver-only metastases: A systematic review. *Eur J Cancer*. 2020;141:225-238.
22. Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *Lancet*. 2008;371(9617):1007-1016.
23. Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. *Lancet Oncol*. 2013;14(12):1208-1215.
24. Primrose J, Falk S, Finch-Jones M, Valle J, O'Reilly D, Siriwardena A, et al. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis: the New EPOC randomised controlled trial. *Lancet Oncol*. 2014;15(6):601-611.
25. Liu W, Zhou JG, Sun Y, Zhang L, Xing BC. The role of neoadjuvant chemotherapy for resectable colorectal liver metastases: a systematic review and meta-analysis. *Oncotarget*. 2016;7(24):37277-37287.
26. Datta J, Narayan RR, Kemeny NE, D'Angelica MI. Role of Hepatic Artery Infusion Chemotherapy in Treatment of Initially Unresectable Colorectal Liver Metastases: A Review. *JAMA Surg*. 2019;154(8):768-776.
27. Esnaola NF, Meyer JE, Karachristos A, Maranki JL, Camp ER, Denlinger CS. Evaluation and management of intrahepatic and extrahepatic cholangiocarcinoma. *Cancer*. 2016;122(9):1349-1369.
28. Le Roy B, Gelli M, Pittau G, Allard MA, Pereira B, Serji B, et al. Neoadjuvant chemotherapy for initially unresectable intrahepatic cholangiocarcinoma. *Br J Surg*. 2018;105(7):839-847.
29. Wakabayashi G, Cherqui D, Geller DA, Buell JF, Kaneko H, Han HS, et al. Recommendations for laparoscopic liver resection: a report from the second international consensus conference held in Morioka. *Ann Surg*. 2015;261(4):619-629.
30. Moris D, Ronnekleiv-Kelly S, Rahnama-Azar AA, Felekouras E, Dillhoff M, Schmidt C, et al. Parenchymal-Sparing Versus Anatomic Liver Resection for Colorectal Liver Metastases: a Systematic Review. *J Gastrointest Surg*. 2017;21(6):1076-1085.
31. Lim C, Salloum C, Tudisco A, Ricci C, Osseis M, Napoli N, et al. Short- and Long-term Outcomes after Robotic and Laparoscopic Liver Resection for Malignancies: A Propensity Score-Matched Study. *World J Surg*. 2019;43(6):1594-1603.
32. Berber E, Siperstein A. Local recurrence after laparoscopic radiofrequency ablation of liver tumors: an analysis of 1032 tumors. *Ann Surg Oncol*. 2008;15(10):2757-2764.
33. Chen MS, Li JQ, Zheng Y, Guo RP, Liang HH, Zhang YQ, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. *Ann Surg*. 2006;243(3):321-328.
34. Gui CH, Baey S, D'Cruz R T, Shelat VG. Trans-arterial chemoembolization + radiofrequency ablation versus surgical resection in hepatocellular carcinoma - A meta-analysis. *Eur J Surg Oncol*. 2020;46(5):763-771.
35. Liu Y, Li S, Wan X, Li Y, Li B, Zhang Y, et al. Efficacy and safety of thermal ablation in patients with liver metastases. *Eur J Gastroenterol Hepatol*. 2013;25(4):442-446.
36. van Amerongen MJ, Jenniskens SFM, van den Boezem PB, Futterer JJ, de Wilt JHW. Radiofrequency ablation compared to surgical resection for curative treatment of patients with colorectal liver metastases - a meta-analysis. *HPB (Oxford)*. 2017;19(9):749-756.
37. Puijk RS, Ruars AH, Vroomen L, van Tilborg A, Scheffer HJ, Nielsen K, et al. Colorectal liver metastases: surgery versus thermal ablation (COLLISION) - a phase III single-blind prospective randomized controlled trial. *BMC Cancer*. 2018;18(1):821.
38. Cescon M, Vetrone G, Grazi GL, Ramacciato G, Ercolani G, Ravaioli M, et al. Trends in perioperative outcome after hepatic resection: analysis of 1500 consecutive unselected cases over 20 years. *Ann Surg*. 2009;249(6):995-1002.

39. Neuwirth MG, Bierema C, Sinnamon AJ, Fraker DL, Kelz RR, Roses RE, et al. Trends in major upper abdominal surgery for cancer in octogenarians: Has there been a change in patient selection? *Cancer*. 2018;124(1):125-135.
40. SONCOS. Preserving Quality of Care in the Netherlands. 2017.
41. Beck N, van Bommel AC, Eddes EH, van Leersum NJ, Tollenaar RA, Wouters MW, et al. The Dutch Institute for Clinical Auditing: Achieving Codman's Dream on a Nationwide Basis. *Ann Surg*. 2020;271(4):627-631.
42. van der Werf LR, Kok NFM, Buis CI, Grunhagen DJ, Hoogwater FJH, Swijnenburg RJ, et al. Implementation and first results of a mandatory, nationwide audit on liver surgery. *HPB (Oxford)*. 2019;21(10):1400-1410.
43. Neuhauser D. Ernest Amory Codman MD. *Qual Saf Health Care*. 2002;11(1):104-105.
44. Limb C, Fowler A, Gundogan B, Koshy K, Agha R. How to conduct a clinical audit and quality improvement project. *Int J Surg Oncol (N Y)*. 2017;2(6):e24.

PART I

QUALITY ASSESSMENT OF LIVER SURGERY

CHAPTER 2

VOLUME-OUTCOME RELATIONSHIP OF LIVER SURGERY: A NATIONWIDE ANALYSIS

P. B. Olthof*, **A.K.E. Elfrink***, E. Marra, E.J.T. Belt, P.B. van den Boezem, K. Bosscha, E.C.J. Consten, M. den Dulk, P.D. Gobardhan, J. Hagendoorn, N.T. van Heek, J.N.M. IJzermans, J.M. Klaase, K.F.D. Kuhlmann, W.K.G. Leclercq, M.S.L. Liem, E.R. Manusama, H.A. Marsman, J.S.D. Mieog, S.J. Oosterling, G.A. Patijn, W.W te Riele, R.J. Swijnenburg, H. Torrens, P. van Duijvendijk, M. Vermaas, N.F.M. Kok, D.J. Grünhagen, [Dutch Hepato Biliary Audit Group](#)

*equal author contributions

Br J Surg. 2020 Jun;107(7):917-926.

Abstract

Introduction

Evidence for an association between hospital volume and outcomes for liver surgery is abundant. The current Dutch guideline requires a minimum volume of 20 annual procedures per centre. The aim of this study was to investigate the association between hospital volume and postoperative outcomes using data from the Dutch nationwide hepatobiliary audit.

Methods

This was a nationwide study in the Netherlands. All liver resections reported in the Dutch hepatobiliary audit between 2014 and 2017 were included. Annual centre volume was calculated and classified in categories of 20 procedures per year. Main outcomes were major morbidity (Clavien–Dindo grade IIIA or higher) and 30-day or in-hospital mortality.

Results

A total of 5590 liver resections were done across 34 centres with a median annual centre volume of 35 (i.q.r. 20–69) procedures. Overall major morbidity and mortality rates were 11.2 and 2.0 per cent respectively. The mortality rate was 1.9 per cent after resection for colorectal liver metastases (CRLMs), 1.2 per cent for non-CRLMs, 0.4 per cent for benign tumours, 4.9 per cent for hepatocellular carcinoma and 10.3 per cent for biliary tumours. Higher-volume centres performed more major liver resections, and more resections for hepatocellular carcinoma and biliary cancer. There was no association between hospital volume and either major morbidity or mortality in multivariable analysis, after adjustment for known risk factors for adverse events.

Conclusion

Hospital volume and postoperative outcomes were not associated.

Introduction

In an effort to reduce morbidity and mortality after complex surgical procedures, hospital volume has become a frequent subject of debate^{1–3}. Higher caseload leads to more experience for the entire surgical treatment team, which could benefit clinical outcomes. In upper gastrointestinal surgery, the volume– outcome relationship has been studied most extensively for esophageal and pancreatic surgery^{4–6}.

Mortality after oesophagectomy in low-volume centres is at least twice that in high-volume centres⁴. Perioperative mortality after pancreatoduodenectomy is also more than twofold lower in centres undertaking more than 40 resections compared with five procedures annually^{5,6}. In the Netherlands, these studies have led to a minimum annual case volume of at least 20 procedures per hospital for these operations. Without extensive evidence, this threshold has been extrapolated to hepatobiliary surgery, including liver resection.

Liver surgery, however, is more heterogeneous, with numerous different types of procedures and techniques for various indications, all with their distinct characteristics and risk factors for adverse outcomes. Procedures range from laparoscopic peripheral wedge resection to extended right liver resection with biliary reconstruction for perihilar cholangiocarcinoma. Currently there are no data to support the hospital volume standard of 20 resections annually in the Netherlands. Although improvements in perioperative care have reduced overall surgical morbidity, liver surgery is done in an ageing and increasingly co-morbid population, and is still associated with substantial risks^{7–15}. Adequate risk stratification across all liver surgery centres is essential to ensure optimal clinical outcomes.

This study aimed to investigate the relationship between hospital volume and postoperative outcomes after liver surgery using data from the nationwide Dutch Hepato Biliary Audit (DHBA) on all hepatobiliary resections performed in the Netherlands.

Methods

This was a retrospective nationwide study of patients who underwent liver surgery in the Netherlands. The Netherlands is a high-income country in Western Europe with over 17 million inhabitants. Healthcare is arranged in 121 hospitals, including eight university hospitals and one comprehensive cancer centre. In the Netherlands, requirements for treating several tumours have

been defined by Stichting Oncologische Samenwerking (SONCOS), which is a national establishment for multidisciplinary oncological cooperation founded by the Dutch Societies of Surgical Oncology, Radiotherapy and Medical Oncology. Liver tumours and liver surgery are included. These guidelines are also endorsed by the government and all insurance companies. They include structural requirements such as 24/7 availability of an interventional radiologist and two skilled hepatobiliary surgeons, volume requirements for resection (at least 20 resections have to be performed annually) and mandatory participation in the audit. All hepatobiliary procedures are included in the nationwide DHBA. The present study included patients who had liver surgery for any indication between 1 January 2014 and 31 December 2017. Patients who underwent exploratory laparotomy because unresectable disease was discovered during surgery, and those who underwent extrahepatic biliary resection only were excluded. Patients with essential data missing (type of tumour, type of procedure, hospital information or operation date) were also excluded.

The study protocol was approved by the scientific committee of the DHBA. All data were handled anonymously. The need for ethical approval and individual informed consent was waived by the medical ethics committee.

Dutch Hepato Biliary Audit

The DHBA is part of the Dutch Institute of Clinical Auditing and was initiated by the Dutch Liver Surgery Working Group. The DHBA started in 2013 and since 1 January 2014 it has been a mandatory audit for all Dutch centres performing liver surgery. The inclusion criteria are any resection for any type of liver tumour. In 2015 the registration was extended to include all procedures for biliary tumours, with the biliary tumour location specified. Before 2015, patients with biliary tumours were classified as unspecified, along with those who underwent liver resection for biliary tumours other than perihilar or intrahepatic cholangiocarcinoma. Besides direct feedback on potential errors in data entry using the online data form, voluntary external data verification was carried out. Based on this verification, data accuracy was considered adequate for all audited centres. Further details of the audit have been described elsewhere¹⁴.

Hospital volume

The total number of liver resections performed during the study in each centre was recorded and the median number of procedures annually was defined as the hospital volume. In centres where liver surgery was discontinued during the study interval (all owing to an annual procedural volume below 20), only the years in which liver surgery was performed were used in the volume calculation. Extrahepatic biliary resections and exploratory laparotomies without liver resection

were not included in hospital volume calculations. The annual hospital volume was classified into less than 20, 20–39, 40–59, 60–79 and 80 or more procedures. For multivariable analyses, the 20–39 category was used as reference because of the existing volume requirement of 20 resections annually.

Definitions

Major liver resection was defined as resection of at least three adjacent Couinaud segments. All complications within 30 days after surgery were scored and graded according to the Clavien–Dindo classification¹⁶. Major morbidity was defined as the presence of a grade IIIA or higher complication. A complicated postoperative course was defined by: hospital stay exceeding 14 days, major morbidity or death. Postoperative mortality was defined as death in hospital or within 30 days after surgery; 90-day mortality was not included in the audit.

Statistical analysis

Categorical variables are shown as numbers with percentages, and differences between these variables were tested using χ^2 or Fisher's exact test. Continuous variables are presented as median (i.q.r.), unless indicated otherwise, with differences tested using Mann–Whitney *U* or Kruskal–Wallis test. Univariable and multivariable logistic regression analyses were used to identify factors associated with outcomes. Variables associated with the outcome ($P < 0.100$, Wald test) in univariable analysis were included in a multivariable model. Backward selection was used in order to obtain a parsimonious model. Multivariable analyses for major morbidity and mortality were conducted on the entire cohort. The analysis for major morbidity was repeated in the subgroups of minor liver resection, major liver resection, and resection for colorectal liver metastases. Multicollinearity was assessed in all models by calculation of the variance inflation factor (VIF). A VIF of 2.5 is equivalent to an R^2 of 0.6 between two variables, and correlations with a VIF above 2.5 were considered troublesome. Sensitivity analyses were performed for every multivariable model to determine the dependency of the model outcome on specific variables. The analyses were repeated with the inclusion of additional parameters: centre volume of major liver resections (more than 10 procedures), and the year of surgery. $P < 0.050$ was considered to indicate statistical significance. All analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria).

Results

Liver surgery in the Netherlands

A total of 6094 procedures were undertaken. Seventy-four extrahepatic biliary resections and 267 procedures for unresectable tumours were excluded. A further 163 procedures were excluded owing to missing essential data. Finally, 5590 procedures were included in the analyses. These procedures were done across 34 centres with a median of 35 (i.q.r. 20–69) annually. Overall, 13.7 per cent of the patients had a complicated postoperative course. The major morbidity rate was 11.2 per cent and the postoperative mortality rate was 2.0 per cent. The postoperative course was complicated after 9.2 per cent of the 4210 minor liver resections, and major morbidity and mortality rates in these patients were 7.8 and 1.2 per cent respectively. After 1380 major liver resections, 26.0 per cent of patients had complicated a postoperative course; the major morbidity rate was 20.8 per cent and the mortality rate 5.9 per cent.

An increase in the rate of adverse events was observed in higher-volume centres in the overall cohort (*Table 1* and *Fig. 1*). Of all 1062 resections performed in centres with fewer than 40 resections per year, 816 (76.8 per cent) were minor resections for colorectal liver metastases (CRLMs) or benign lesions, and only 21 (2.0 per cent) were major resections for hepatocellular carcinoma (HCC) or biliary tumours.

Table 1. Patient and treatment characteristics and outcomes according to hospital volume in the Dutch Hepato Biliary Audit between 2014 and 2017

		Hospital volume (annual no. of liver resections)					<i>P</i> -value
		< 20	20–39	40–59	60–79	≥80	
		(<i>n</i> = 196)	(<i>n</i> = 866)	(<i>n</i> = 822)	(<i>n</i> = 1953)	(<i>n</i> = 1753)	
Baseline characteristics							
Age > 70 years		75 (38.3)	345 (39.8)	295 (35.9)	600 (30.7)	444 (25.3)	0.035
Men		117 (59.7)	503 (58.2)	462 (56.2)	1146 (58.7)	947 (54.0)	< 0.001
ASA fitness grade > III		26 (13.3)	199 (23.0)	133 (16.2)	363 (18.6)	302 (17.2)	< 0.001
BMI (kg/m ²)*		26.9 (4.4)	25.9 (4.2)	26.2 (4.6)	26.5 (4.6)	26.1 (4.5)	0.076
Charlson co-morbidity index score ≥ 2		70 (38.0)	264 (30.6)	210 (25.5)	542 (27.8)	409 (23.3)	< 0.001
Preoperative liver disease	liver	1 (0.6)	41 (4.9)	18 (2.2)	71 (3.6)	94 (5.4)	< 0.001
Previous surgery	liver	23 (12.5)	149 (17.3)	122 (14.8)	272 (13.9)	206 (11.8)	0.003

Preoperative chemotherapy		16 (8.8)	180 (22.1)	150 (18.2)	295 (15.1)	483 (27.6)	< 0.001
Preoperative portal vein embolization		0 (0.0)	10 (3.2)	10 (1.2)	34 (1.7)	61 (3.5)	<0.001
Type of tumour							<0.001
Colorectal liver metastasis		166 (84.7)	723 (83.6)	649 (79.0)	1304 (66.8)	1004 (57.3)	
Liver metastasis from other origin		11 (5.6)	34 (3.9)	61 (7.4)	146 (7.5)	150 (8.6)	
Benign liver tumour		15 (7.7)	58 (6.7)	42 (5.1)	190 (9.7)	214 (12.2)	
Hepatocellular carcinoma		4 (2.0)	36 (4.2)	55 (6.7)	201 (10.3)	254 (14.5)	
Malignant tumour of biliary tract		0	15 (1.7)	15 (1.8)	112 (5.7)	131 (7.5)	
Operative characteristics and outcomes							
Major resection	liver	29 (14.8)	130 (15.2)	240 (29.2)	432 (22.1)	549 (31.3)	< 0.001
Minimally invasive approach		17 (8.7)	259 (30.3)	140 (17.0)	488 (25.0)	198 (11.3)	< 0.001
Intraoperative ablation		7 (3.6)	109 (12.6)	161 (19.6)	292 (15.0)	289 (16.5)	< 0.001
Simultaneous colorectal resection		36 (19.3)	112 (13.1)	92 (11.2)	144 (7.4)	139 (7.9)	< 0.001
Simultaneous other resection		70 (35.7)	185 (21.4)	118 (14.4)	306 (15.7)	207 (11.8)	< 0.001
Biliary reconstruction		0 (0.0)	1 (25.0)	3 (0.4)	47 (2.4)	44 (2.5)	< 0.001
Complicated postoperative course		22 (11.2)	97 (11.2)	122 (14.8)	230 (11.8)	297 (16.9)	< 0.001
Major morbidity		16 (8.2)	73 (8.4)	90 (10.9)	197 (10.1)	249 (14.2)	< 0.001
Postoperative bile leakage	bile	5 (2.6)	28 (3.3)	27 (3.3)	67 (3.4)	111 (6.3)	< 0.001
Postoperative haemorrhage		2 (1.0)	7 (0.8)	11 (1.3)	19 (1.0)	27 (1.5)	< 0.001

Postoperative liver failure	2 (1.0)	11 (1.3)	9 (1.1)	34 (1.7)	48 (2.7)	0.016
------------------------------------	---------	----------	---------	----------	----------	-------

Death	2 (1.0)	12 (1.4)	11 (1.3)	32 (1.6)	57 (3.3)	< 0.001
--------------	---------	----------	----------	----------	----------	---------

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). † χ^2 or Fisher's exact test, except ‡Kruskal–Wallis test.

Figure 1. Major morbidity and mortality according to mean centre volume in the Dutch Hepato Billiary Audit between 2014 and 2017.

Outcomes according to disease subgroups

Table 2 shows morbidity and mortality rates according to indication for liver surgery. For minor liver resections, morbidity and mortality rates were similar across different volume centres for most diagnoses.

Morbidity and mortality for biliary tumours subdivided according to tumour location are shown in Table 2. Morbidity and mortality rates were highest for perihilar cholangiocarcinoma (47.0 and 14.0 per cent respectively).

The 550 resections for HCC over 4 years were performed across 22 centres, with 20 centres still undertaking HCC resections in 2017. The 273 resections for biliary tumours were carried out in 16 centres. Fourteen centres performed resections for perihilar and intrahepatic cholangiocarcinoma.

Table 2. Tumour-specific major morbidity and mortality rate after major and minor liver resections, and liver resection for biliary tumours according to hospital volume in the Dutch Hepato Billiary Audit between 2014 and 2017

	Hospital volume (annual no. of liver resections)					Overall
	< 20	20–39	40–59	60–79	≥ 80	
Minor liver resection						
Colorectal liver metastases						
No. of procedures	141	605	463	1057	751	3017
Morbidity (%)	7.1	7.4	7.6	6.9	9.5	9.1
Mortality (%)	0.7	0.3	0.6	0.6	1.2	1.4
Non-colorectal liver metastases						

No. of procedures	8	32	44	129	122	335
Morbidity (%)	0.0	6.2	14	8.5	4.1	7.1
Mortality (%)	0.0	0.0	0	0	0	0.3
Benign tumour						
No. of procedures	15	55	31	154	148	403
Morbidity (%)	6.7	9.1	3	7.8	6.1	6.9
Mortality (%)	0.0	0.0	0	0.6	0	0.2
Hepatocellular carcinoma						
No. of procedures	3	31	36	136	134	340
Morbidity (%)	0.0	3.2	22	7.4	11.2	10.0
Mortality (%)	0.0	0.0	6	0	3.0	2.1
Major liver resection						
Colorectal liver metastases						
Number	25	118	186	247	253	829
Morbidity	16.0	25.4	11.8	16.2	17.8	15.4
Mortality	0.0	6.8	0.5	4.0	4.7	3.7
Non-colorectal liver metastases						
No. of procedures	3	2	17	17	28	67
Morbidity (%)	0.0	50	18	24	27	24
Mortality (%)	0.0	0.0	6	6	7	5.9
Benign tumour						
No. of procedures	0	3	11	36	66	116
Morbidity (%)	0.0	0.0	36	19	23	10.2
Mortality (%)	0.0	0.0	0	3	0	0.9
Hepatocellular carcinoma						
No. of procedures	1	5	19	65	120	210
Morbidity (%)	100.0	0.0	16	20	25.0	22.4
Mortality (%)	100.0	0.0	16	8	9.2	9.5
Liver resection for biliary tumours						
Overall						
No. of procedures	0	15	15	112	131	273
Morbidity (%)	0.0	13.3	53	24.1	38.9	32.2
Mortality (%)	0.0	0.0	7	7.1	14.5	10.3
Perihilar						
No. of procedures	0	1	3	46	50	100
Morbidity (%)	0.0	0.0	100	33	58	47.0
Mortality (%)	0.0	0.0	0	11	18	14.0
Intrahepatic						
No. of procedures	0	5	4	44	44	97
Morbidity (%)	0.0	20.0	50	16	34	26
Mortality (%)	0.0	0.0	25	2	18	10
Extrahepatic / Unspecified						
No. of procedures	0	9	8	22	37	76
Morbidity (%)	0.0	11.1	38	23	19	21
Mortality (%)	0.0	0	0	9	5	5

Multivariable analyses

Although the odds ratio for major morbidity and mortality was significantly higher for centres undertaking at least 80 liver resections annually compared with those performing 20–39 procedures in univariable analyses, there was no hospital volume–outcome relationship in multivariable analyses for major morbidity and mortality in the overall cohort after correction for other confounding variables (*Table 3*; *Table S1*, supporting information). The multivariable analyses for major morbidity and mortality were repeated for minor resection only (*Table S2*,

supporting information), major resections (*Table S3*, supporting information) and resections for CRLMs (*Table S4*, supporting information). None of these analyses demonstrated a hospital volume–outcome effect. Multicollinearity was not a problem as the VIF was below 2.5 for all variables in all models. Sensitivity analyses were undertaken for all outcomes stratified by tumour type. In addition, all logistic regression analyses were performed with addition of a variable concerning annual major resection volume (more than 10) and with addition of a variable correcting for year of surgery. These variables were not significant predictors of outcomes and did not alter the results of the multivariable models.

Table 3. Univariable and multivariable logistic regression analyses for factors associated with major morbidity including hospital volume in the Dutch Hepato Biliary Audit between 2014 and 2017

	No. of patients	Univariable analysis		Multivariable analysis	
		Odds ratio	<i>P</i> -value	Odds ratio	<i>P</i> -value
Age (years)			<0.001		<0.001
≤ 70	3811	1		1	
> 70	1759	1.22 (1.03 - 1.45)		1.12 (0.93 - 1.39)	
Missing*	20				
Sex			0.026		0.221
M	3175	1		1	
F	2399	0.67 (0.57 - 0.80)		0.63 (0.53 - 0.78)	
Missing*	16				
ASA fitness grade			<0.001		<0.001
I–II	4388	1		1	
≥ III	1023	1.86 (1.53 - 2.25)		1.77 (1.39 - 2.15)	
Missing*	179				
Charlson co-morbidity index score			<0.001		0.002
0–1	3909	1		1	
≥ 2	1495	1.53 (1.28 - 1.82)		1.44 (1.14 - 1.74)	
Missing*	186				
BMI (per kg/m²)		1.00 (0.98 - 1.02)	0.963		
Liver co-morbidity			0.029		0.998
No	5043	1		1	
Yes	225	1.51 (1.03 - 2.15)		1.01 (0.63 - 1.56)	
Missing*	322				
Previous resection			0.721		
No	4620	1			
Yes	772	0.96 (0.74 - 1.21)			
Missing*	198				
Type of tumour			<0.001		<0.001
CRLM	3846	1		1	
Other liver metastasis	402	1.06 (0.74 - 1.48)	0.725	1.03 (0.69 - 1.48)	0.889
Benign	519	1.12 (0.82 - 1.50)	0.470	1.48 (1.01 - 2.09)	0.044
HCC	550	1.66 (1.28 - 2.14)	<0.001	1.20 (0.92 - 1.74)	0.147
Cholangiocarcinoma	273	4.58 (3.46 - 6.02)	<0.001	3.61 (2.60 - 3.03)	<0.001

Preoperative chemotherapy			0.367		
No	4062	1			
Yes	1124	0.91 (0.73 - 1.12)			
Missing*	404				
Procedure			0.185		
Resection	4732	1			
Resection and ablation	858	0.90 (0.76 - 1.05)			
Missing*	0				
Surgical approach			<0.001		<0.001
Open	4141	1		1	
Laparoscopic	1102	0.40 (0.30 - 0.53)	<0.001	0.57 (0.42 - 0.78)	<0.001
Conversion to open	206	0.82 (0.51 - 1.26)	0.394	0.86 (0.50 - 1.37)	0.532
Missing*	141				
Major resection			<0.001		<0.001
No	4107	1		1	
Yes	1380	3.10 (2.60 - 3.68)		2.47 (2.02 - 3.03)	
Missing*	103				
Simultaneous other resection			<0.001		<0.001
No	2713	1		1	
Yes	886	1.60 (1.28 - 2.00)	<0.001	1.57 (1.20 - 2.05)	<0.001
Missing	1991	1.23 (1.02 - 1.48)	0.031	1.14 (0.92 - 1.42)	0.238
Simultaneous colorectal resection			0.002		<0.001
No	4883	1		1	
Yes	523	1.50 (1.15 - 1.92)		2.01 (1.47 - 2.73)	
Missing*	184				
Type of hospital			<0.001		0.914
Tertiary referral centre	3057	1		1	
Other	2533	0.63 (0.53 - 0.75)		0.98 (0.71 - 1.36)	
Annual hospital volume			<0.001		0.163
20–39	866	1		1	
< 20	196	0.90 (0.51 - 1.49)	0.692	0.82 (0.45 - 1.44)	0.524
40–59	822	1.26 (0.93 - 1.71)	0.143	1.16 (0.81 - 1.67)	0.412
60–79	1953	1.11 (0.83 - 1.49)	0.485	1.05 (0.73 - 1.53)	0.783
≥ 80	1753	1.67 (1.22 - 2.02)	< 0.001	1.41 (0.91 - 2.19)	0.121

Values in parentheses are 95 per cent confidence intervals. *Not included in multivariable analysis. CRLM, colorectal liver metastasis; HCC, hepatocellular carcinoma.

Oncological margins

The association between hospital volume and oncological margin was investigated (*Table S5*, supporting information). Negative margins were achieved in 3251 patients with CRLMs (84.5 per cent), with more frequent positive resection margins in the higher-volumes centres. These results are likely to be explained by more advanced disease in these patients, as demonstrated by multivariable analyses that identified five or more metastases (odds ratio 1.57, 95 per cent c.i. 1.08 to 2.26) and major liver resection (odds ratio 1.37, 1.07 to 1.75) as predictors of positive

margins. Centre volume was not significant in multivariable analysis. Positive margins were most frequent after resection of biliary tumours, and in particular in lower-volume centres after resection of perihilar and intrahepatic cholangiocarcinoma (*Table S5*, supporting information).

Discussion

In the Dutch setting, no association between hospital volume and morbidity or mortality was observed after liver surgery. Although there is no evidence base for the current cut-off of 20 procedures, all data were gathered after the implementation of this current guideline and the data do not support the implementation of any lower, or need for a higher, procedure volume cut-off. The lack of a volume–outcome relationship is likely to be explained by the existing advanced patient selection across lower- and higher-volume centres in regional collaboration. There remains room for improvement in resections for HCC and biliary tumours. Reduction in the number of centres currently involved in treating HCC and biliary tumours to a few dedicated centres might help to improve outcomes for these high-risk patients.

Few nationwide analyses reporting on morbidity and mortality after liver resection are available, and data on hospital volume are scarce. A French nationwide study¹⁷ that included 28 708 liver resections over 4 years reported a 90-day mortality rate of 3.2 per cent. There was a median of four resections per centre and 20 per cent of patients had surgery in centres with a case volume below ten annual procedures. In multivariable analyses, a volume–mortality association was observed, with centres undertaking five or fewer procedures annually as a reference. The hazard ratios for mortality were similar for all hospital categories undertaking more than 11 procedures annually, demonstrating no further volume–outcome relationship above the cut-off of 11 resections. In a large, but not nationwide, report from the USA including 11 429 patients, the overall 90-day mortality rate was 4.9 per cent, but ranged from 7.1 per cent when the hospital volume was below ten procedures annually to 2.9 per cent when at least 50 procedures were done¹⁸. In another report¹⁹, the analyses were based on a similar data set including 2949 liver resections, with the same 4.9 per cent mortality rate. The authors concluded that only resections done in high-volume centres, by a high-volume surgeon, were associated with reduced mortality. The median hospital volume was low, with two procedures annually, and median surgeon volume was one. In a more recent nationwide analysis²⁰, including 110 332 liver resections performed across 1136 German hospitals, the overall mortality rate was 5.8 per cent. There is no centralization in Germany. For major liver resections, mortality was lower in centres undertaking at least 44 major resections annually. Although overall centre volume was not reported, the 1136

hospitals active in liver surgery suggest that median centre volume is low; of centres performing major resections, 80 per cent undertook fewer than four major hepatectomies annually. In this German report, the mortality rate was high in specific subgroups, such as 16 per cent after extended hepatectomy and 26 per cent when combined with biliary reconstruction.

Available studies that reported on the volume–outcome relationship in liver surgery and showed lower mortality rates in high-volumes centres had low median hospital volumes of two to four procedures annually. The Dutch volume requirement of 20 liver resections annually is similar to that in several other countries^{21,22}. The mortality rates reported in series that use the 20-procedure volume requirement (such as 2.0 per cent in the Netherlands and 2.1 per cent in Norway²¹) are lower than those in countries that have not implemented such a cut-off: 3.2 per cent in France¹⁷, 4.9 per cent in America^{18,19}, 5.8 per cent in Germany²⁰ and 3.1 per cent in Sweden²³. Such direct comparisons are biased by numerous factors including different inclusion criteria, definitions and cohort characteristics.

There are several possible reasons for the lack of a volume–outcome relationship in the present cohort. First, there simply might not be a volume–outcome relationship in liver surgery after setting a threshold of 20 resections annually, and above this threshold outcomes are just as favourable in the smaller-volume as in the higher-volume centres. A more likely explanation could be the higher median hospital volume of 35 procedures than in other studies, and the advanced risk stratification already performed across many Dutch regional collaborations. This is demonstrated by the predominance of minor liver resections for CRLMs in the lowest-volume centres, compared with increasing numbers of major liver resections for other indications in the higher-volume centres. The data also indicate more advanced metastatic disease in higher-volume centres, and that the majority of HCC and biliary cancers are treated in the largest centres.

Although the mortality rate of 2.0 per cent appears to be in the lower range of rates reported in literature, there are several areas for improvement. The mortality rate after major liver resection was 5.9 per cent overall and 3.7 per cent for CRLMs. These rates have led to the start of a detailed analysis into these fatalities, including failure-to-rescue parameters. This project aims to further improve stratification of patients across centres and reduce overall the mortality rate to below 1 per cent. The current Dutch guideline encourages referral of patients with HCC and biliary cancers to experienced centres; however, in 2017, 20 and 16 centres undertook surgery on HCC and biliary tumours respectively. The overall mortality rates of 4.9 per cent after HCC resection and up to 9.5 per cent after major resection are higher than rates in the largest international series

from expert centres (0.8–2.9 per cent)^{24–26}. For biliary tumours, the overall mortality rate was 10.3 per cent, with the highest rate for perihilar cholangiocarcinoma (14.0 per cent). Although this is consistent with an in-hospital mortality rate of 13 per cent in a meta-analysis²⁷ of Western series, there is significant room for improvement considering that the mortality rate after perihilar cholangiocarcinoma resections in Asian centres is usually below 4 per cent²⁷. In addition, margins were positive after biliary cancer resection in over one-third of all patients. Considering these rates, the treatment of this relatively small group across 16–20 centres is unlikely to optimise the outcomes, and further centralization of these resections to a handful of dedicated centres might help to reduce adverse outcomes.

This study had several limitations. It is possible that the lack of a volume–outcome relationship in the present analysis was the result of one or more risk-stratifying variables that were not included in the nationwide audit data set. These variables could include advanced data on (hepatic) co-morbidity, or variables in the patient evaluation such as the assessment of remnant liver volume and function. As in other national audits, there are some missing data for non-mandatory parameters^{28,29}. Furthermore, to ensure complete anonymity in the analysis from a small country such as the Netherlands, no distinction was made between hospitals' teaching status, which is a factor known to have a potential influence on outcomes³⁰. Although most perioperative deaths are likely captured by the 30-day or in-hospital mortality variable, 90-day mortality is likely more representative of true mortality, but is not included in the audit and was not therefore not available for the present study³¹. As the DHBA was designed for analysis of perioperative outcomes, no information regarding long-term outcomes is collected and therefore these could not be included in the analyses.

References

- 1 Birkmeyer JD, Siewers AE, Finlayson EVA, Stukel TA, Lucas FL, Batista I *et al.* Hospital volume and surgical mortality in the United States. *N Engl J Med* 2002; **346**: 1128–1137.
- 2 Ho V, Heslin MJ, Yun H, Howard L. Trends in hospital and surgeon volume and operative mortality for cancer surgery. *Ann Surg Oncol* 2006; **13**: 851–858.
- 3 Ho V, Aloia T. Hospital volume, surgeon volume, and patient costs for cancer surgery. *Med Care* 2008; **46**: 718–725.
- 4 van Lanschot JJ, Hulscher JB, Buskens CJ, Tilanus HW, ten Kate FJ, Obertop H. Hospital volume and hospital mortality for esophagectomy. *Cancer* 2001; **91**: 1574–1578.
- 5 Gooiker GA, van Gijn W, Wouters MWJM, Post PN, van de Velde CJH, Tollenaar RAEM *et al.*; Signalling Committee Cancer of the Dutch Cancer Society. Systematic review and meta-analysis of the volume–outcome relationship in pancreatic surgery. *Br J Surg* 2011; **98**: 485–494.
- 6 van der Geest LGM, van Rijssen LB, Molenaar IQ, de Hingh IH, Groot Koerkamp B, Busch ORC *et al.*; Dutch Pancreatic Cancer Group. Volume–outcome relationships in pancreatoduodenectomy for cancer. *HPB (Oxford)* 2016; **18**: 317–324.
- 7 Jarnagin WR, Gonen M, Fong Y, DeMatteo RP, Ben-Porat L, Little S *et al.* Improvement in perioperative outcome after hepatic resection: analysis of 1803 consecutive cases over the past decade. *Ann Surg* 2002; **236**: 397–406.
- 8 Noordzij PG, Poldermans D, Schouten O, Bax JJ, Schreiner FAG, Boersma E. Postoperative mortality in The Netherlands: a population-based analysis of surgery-specific risk in adults. *Anesthesiology* 2010; **112**: 1105–1115.
- 9 Integraal Kankercentrum Nederland (IKNL). *Cijfersoverkanke*; 2017. <https://www.iknl.nl/nkr-cijfers> [accessed 8 March 2019].
- 10 Ruzzenente A, Conci S, Ciangherotti A, Campagnaro T, Valdegamberi A, Bertuzzo F *et al.* Impact of age on short-term outcomes of liver surgery: lessons learned in 10-years' experience in a tertiary referral hepato-pancreato-biliary center. *Medicine (Baltimore)* 2017; **96**: e6955.
- 11 Makridis G, Reese T, Kantas A, Fard-Aghaie MH, Oldhafer KJ. Liver resection in octogenarians: are the outcomes worth the risk? The Hamburg Barmbek experience. *ANZ J Surg* 2019; **89**: 131–132.
- 12 Cohen ME, Liu Y, Ko CY, Hall BL. Improved surgical outcomes for ACS NSQIP hospitals over time: evaluation of hospital cohorts with up to 8 years of participation. *Ann Surg* 2016; **263**: 267–273.
- 13 Cescon M, Vetrone G, Grazi GL, Ramacciato G, Ercolani G, Ravaioli M *et al.* Trends in perioperative outcome after hepatic resection: analysis of 1500 consecutive unselected cases over 20 years. *Ann Surg* 2009; **249**: 995–1002.
- 14 van der Werf LR, Kok NFM, Buis CI, Grünhagen DJ, Hoogwater FJH, Swijnenburg RJ *et al.* Implementation and first results of a mandatory, nationwide audit on liver surgery. *HPB (Oxford)* 2019; **21**: 1400–1410.
- 15 de Ridder JAM, Lemmens VEPP, Overbeek LIH, Nagtegaal ID, de Wilt JHW; Dutch Liver Surgery Group. Liver resection for metastatic disease; a population-based analysis of trends. *Dig Surg* 2016; **33**: 104–113.
- 16 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**: 205–213.
- 17 Farges O, Goutte N, Bendersky N, Falissard B; ACHBT-French Hepatectomy Study Group. Incidence and risks of liver resection: an all-inclusive French nationwide study. *Ann Surg* 2012; **256**: 697–704.
- 18 Asiyanbola B, Chang D, Gleisner AL, Nathan H, Choti MA, Schulick RD *et al.* Operative mortality after hepatic resection: are literature-based rates broadly applicable? *J Gastrointest Surg* 2008; **12**: 842–851.
- 19 Eppsteiner RW, Csikesz NG, Simons JP, Tseng JF, Shah SA. High volume and outcome after liver resection: surgeon or center? *J Gastrointest Surg* 2008; **12**: 1709–1716.
- 20 Filmann N, Walter D, Schadde E, Bruns C, Keck T, Lang H *et al.* Mortality after liver surgery in Germany. *Br J Surg* 2019; **106**: 1523–1529.
- 21 Lassen K, Nymo LS, Olsen F, Brudvik KW, Fretland AA, Søreide K. Contemporary practice and short-term outcomes after liver resections in a complete national cohort. *Langenbecks Arch Surg* 2019; **404**: 11–19.

- 22 Torzilli G, Viganò L, Giuliente F, Pinna AD. Liver surgery in Italy. Criteria to identify the hospital units and the tertiary referral centers entitled to perform it. *Updates Surg* 2016; **68**: 135–142.
- 23 Gilg S, Sparrelid E, Isaksson B, Lundell L, Nowak G, Strömberg C. Mortality-related risk factors and long-term survival after 4460 liver resections in Sweden – a population-based study. *Langenbecks Arch Surg* 2017; **402**: 105–113.
- 24 Cucchetti A, Sposito C, Pinna AD, Citterio D, Ercolani G, Flores M *et al*. Effect of age on survival in patients undergoing resection of hepatocellular carcinoma. *Br J Surg* 2016; **103**: e93–e99.
- 25 Torzilli G, Belghiti J, Kokudo N, Takayama T, Capussotti L, Nuzzo G *et al*. A snapshot of the effective indications and results of surgery for hepatocellular carcinoma in tertiary referral centers: is it adherent to the EASL/AASLD recommendations?: an observational study of the HCC East–West study group. *Ann Surg* 2013; **257**: 929–937.
- 26 Eguchi S, Kanematsu T, Arai S, Okazaki M, Okita K, Omata M *et al*.; Liver Cancer Study Group of Japan. Comparison of the outcomes between an anatomical subsegmentectomy and a non-anatomical minor hepatectomy for single hepatocellular carcinomas based on a Japanese nationwide survey. *Surgery* 2008; **143**: 469–475.
- 27 Franken LC, Schreuder AM, Roos E, van Dieren S, Busch OR, Besselink MG *et al*. Morbidity and mortality after major liver resection in patients with perihilar cholangiocarcinoma: a systematic review and meta-analysis. *Surgery* 2019; **165**: 918–928.
- 28 Hoeijmakers F, Beck N, Wouters MWJM, Prins HA, Steup WH. National quality registries: how to improve the quality of data? *J Thorac Dis* 2018; **10**(Suppl 29): S3490–S3499.
- 29 Van Leersum NJ, Snijders HS, Henneman D, Kolfschoten NE, Gooiker GA, ten Berge MG *et al*. The Dutch surgical colorectal audit. *Eur J Surg Oncol* 2013; **39**: 1063–1070.
- 30 van Groningen JT, Eddes EH, Fabry HFJ, van Tilburg MWA, van Nieuwenhoven EJ, Snel Y *et al*.; Dutch Surgical Colorectal Cancer Audit Group and the Co-operating General Hospitals. Hospital teaching status and patients'outcomes after colon cancer surgery. *World J Surg* 2018; **42**: 3372–3380.
- 31 Mise Y, Vauthey JN, Zimmitti G, Parker NH, Conrad C, Aloia TA *et al*. Ninety-day postoperative mortality is a legitimate measure of hepatopancreatobiliary surgical quality. *Ann Surg* 2015; **262**: 1071–1078.

Supplementary material

Table S1. Univariable and multivariable logistic regression model of patient, tumour, surgical and volume factors associated with mortality.

Factor	N	Univariable			Multivariable		
		OR	CI (95%)	P-value	OR	CI (95%)	P-value
Sex				<0.01			0.36
Male	3175	1			1		
Female	2399	0.58	0.38 – 0.86		0.81	0.52 – 1.26	
Missing*	16						
Age				<0.01			<0.01
<70	3811	1			1		
>70	1759	1.88	1.29 – 2.73		1.79	1.17 – 2.74	
Missing*	20						
ASA Score				<0.01			<0.01
1 / 2	4388	1			1		
3+	1023	3.45	2.36 – 5.03		2.79	1.81 – 4.28	
Missing*	179						
Charlson comorbidity index				<0.01			0.29
1 / 2	3909	1			1		
3	1495	2.12	1.45 – 3.09		1.28	0.81 – 2.01	
Missing*	186						
Body Mass Index		1.03	0.99 – 1.07	0.20			
Comorbidity liver				<0.01			0.02
No	5043	1			1		
Yes	225	3.83	2.10 – 6.52		2.43	1.12 – 5.15	
Missing*	322						
Previous resection				0.60			
No	4620	1					
Yes	772	1.15	0.67 – 1.86				
Missing*	198						
Type of tumour				<0.01			<0.01
CRLM	3846	1			1		
Other liver metastasis	402	0.94	0.33 – 2.16	0.90	1.14	0.39 – 2.71	0.78
Benign	519	0.28	0.05 – 0.90	0.08	0.19	0.01 – 1.02	0.11
HCC	550	3.80	2.33 – 6.04	<0.01	1.45	0.77 – 2.66	0.24
Cholangiocarcinoma	273	8.17	5.01 – 13.1	<0.01	3.93	2.15 – 7.08	<0.01
Missing*							
Preoperative chemotherapy				0.40			
No	4062	1					
Yes	1124	0.82	0.49 – 1.29				
Missing*	404						
Procedure				<0.01			
Resection	4732	1					
Resection and ablation	858	0.35	0.15 – 0.71				
Major resection				<0.01			<0.01
No	4119	1			1		
Yes	1380	8.12	5.40 – 12.5		6.21	3.86 – 10.2	
Missing*	91						
Surgical approach				<0.01			0.26
Open	4141	1			1		
Laparoscopic	1102	0.25	0.10 – 0.50	<0.01	0.60	0.24 – 1.29	0.23
Conversion	206	0.19	0.01 – 0.86	<0.01	0.30	0.02 – 1.43	0.24
Missing*	141						

Simultaneous other resection				0.94			
No	2713	1					
Yes	886	0.98	0.55 – 1.66	0.94			
Missing	1991	1.09	0.73 – 1.64	0.65			
Simultaneous colorectal resection				0.35			
No	4883	1					
Yes	523	0.71	0.32 – 1.37				
Type of hospital				<0.01		0.93	
Tertiary referral centre	3057	1			1		
Other hospitals	2533	0.41	0.27 – 0.62	0.96	0.41 – 2.17		
Hospital volume per year				<0.01		0.33	
20-39	835	1			1		
<20	227	1.00	0.23 – 3.24	1.00	1.09	0.24 – 3.70	0.90
40-59	822	1.03	0.44 – 2.42	0.95	0.63	0.25 – 1.57	0.32
60-79	1953	1.34	0.69 – 2.79	0.41	0.80	0.31 – 2.03	0.63
>80	1753	2.52	1.37 – 5.09	<0.01	1.27	0.45 – 3.66	0.65

Table S2. Minor liver resections: univariable and multivariable logistic regression model of patient, tumour, surgical and volume factors associated with major morbidity (CD 3 or higher).

Surgical and volume factors associated with major morbidity (Cl 3 or higher).							
Factor	N	Univariable			Multivariable		
		OR	CI (95%)	P-value	OR	CI (95%)	P-value
Sex				<0.01			<0.01
Male	2332	1			1		
Female	1760	0.65	0.51 – 0.82		0.70	0.53 – 0.90	
Missing*	15						
Age				0.10			0.97
<70	2774	1			1		
>70	1317	1.22	0.96 – 1.55		0.96	0.76 – 1.29	
Missing*	16						
ASA Score				<0.01			<0.01
1 / 2	3191	1			1		
3+	749	2.12	1.64 – 2.73		1.94	1.46 – 2.55	
Missing*	167						
Charlson comorbidity index				<0.01			<0.01
1 / 2	2844	1			1		
3	1100	1.58	1.24 – 2.01		1.52	1.10 – 1.88	
Missing*	163						
Body Mass Index		1.00	0.97 – 1.02	0.72			
Comorbidity liver				0.53			
No	3672	1					
Yes	163	1.19	0.66 – 1.99				
Missing*	272						
Previous resection				0.90			
No	3342	1					
Yes	596	0.98	0.70 – 1.34				
Missing*	169						
Type of tumour				0.15			0.60
CRLM	3017	1			1		
Other liver metastasis	335	0.92	0.58 – 1.39	0.70	0.82	0.50 – 1.29	0.42
Benign	403	0.89	0.58 – 1.31	0.57	1.18	0.72 – 1.90	0.47
HCC	340	1.32	0.89 – 1.90	0.15	1.17	0.79 – 1.83	0.36

Cholangiocarcinoma	12	1.08	0.06 – 5.59	0.94	1.57	0.38 – 5.13	0.43
Preoperative chemotherapy				0.98			
No	3003	1					
Yes	760	1.00	0.74 – 1.33				
Missing*	344						
Procedure				0.25			
Resection	3361	1					
Resection and ablation	746	1.18	0.88 – 1.56				
Surgical approach				<0.01			0.01
Open	2865	1			1		
Laparoscopic	1021	0.58	0.42 – 0.78	<0.01	0.62	0.44 – 0.86	<0.01
Conversion	172	1.31	0.78 – 2.10	0.28	1.09	0.62 – 1.82	0.74
Missing*	49						
Simultaneous other resection				<0.01			<0.01
No	2010	1			1		
Yes	705	2.33	1.74 – 3.11	<0.01	2.05	1.46 – 2.87	<0.01
Missing	1404	1.51	1.16 – 1.97	<0.01	1.39	1.04 – 1.86	0.03
Simultaneous colorectal resection				<0.01			<0.01
No	3488	1			1		
Yes	467	2.19	1.63 – 2.91		1.70	1.20 – 2.40	
Missing*	164						
Type of hospital				0.08			0.57
Tertiary referral centre	2115	1			1		
Other hospitals	2004	0.81	0.65 – 1.02		0.89	0.60 – 1.33	
Hospital volume per year				0.34			0.32
20-39	695	1			1		
<20	197	0.80	0.40 – 1.48	0.51	0.75	0.37 – 1.42	0.40
40-59	575	1.20	0.80 – 1.80	0.37	1.31	0.86 – 2.01	0.20
60-79	1489	0.95	0.67 – 1.35	0.76	0.95	0.61 – 1.47	0.83
>80	1163	1.19	0.84 – 1.69	0.33	1.14	0.70 – 1.96	0.62

*Missing not included in the analysis.

Table S3. Major liver resections: univariable and multivariable logistic regression model of patient, tumour, surgical and volume factors associated with major morbidity (CD 3 or higher).

Factor	N	OR	Univariable		OR	Multivariable	
			CI (95%)	P-value		CI (95%)	P-value
Sex				<0.01			<0.01
Male	802	1			1		
Female	577	0.68	0.51 – 0.89		0.56	0.40 – 0.76	
Missing*	1						
Age				0.02			0.04
<70	967	1			1		
>70	409	1.39	1.05 – 1.82		1.39	1.01 – 1.91	
Missing*	4						
ASA Score				<0.01			0.06
1 / 2	1118	1			1		
3+	250	1.65	1.20 – 2.25		1.41	0.98 – 2.00	
Missing*	12						

Charlson comorbidity index				<0.01			0.14
1 / 2	997	1			1		
3	362	1.46	1.10 – 1.93		1.30	0.92 – 1.83	
Missing*	21						
Body Mass Index		1.03	1.00 – 1.06	0.07	1.03	1.00 – 1.07	0.05
Comorbidity liver				0.02			0.35
No	1276	1			1		
Yes	57	1.94	1.08 – 3.37		1.40	0.68 – 2.80	
Missing*	47						
Previous resection				0.65			
No	1181	1					
Yes	172	1.09	0.74 – 1.60				
Missing*	37						
Type of tumour				0.02			<0.01
CRLM	829	1			1		
Other liver metastasis	67	1.72	0.92 – 3.04	0.07	1.42	0.69 – 1.88	0.32
Benign	116	1.58	0.97 – 2.51	0.06	2.00	1.09 – 3.58	0.02
HCC	210	1.60	1.08 – 2.29	0.02	1.14	0.69 – 1.88	0.59
Cholangiocarcinoma	158	4.36	3.02 – 6.28	<0.01	4.00	2.50 – 6.47	<0.01
Preoperative chemotherapy				0.01			0.65
No	956	1			1		
Yes	364	0.67	0.48 – 0.91		1.10	0.73 – 1.63	
Missing*	60						
Procedure				0.05			0.28
Resection	1268	1			1		
Resection and ablation	112	0.57	0.31 – 0.96		0.72	0.37 – 1.28	
Surgical approach				0.02			0.05
Open	1260	1			1		
Laparoscopic	80	0.40	0.18 – 0.79	0.02	0.37	0.14 – 0.83	0.03
Conversion	34	0.35	0.08 – 0.98	0.08	0.42	0.10 – 1.25	0.17
Missing*	6						
Simultaneous other resection				0.57			
No	700	1					
Yes	180	1.12	0.75 – 1.65	0.57			
Missing	500	0.95	0.71 – 1.26	0.72			
Simultaneous colorectal resection				0.44			
No	1304	1					
Yes	56	1.28	0.66 – 2.31				
Missing*	20						
Type of hospital				<0.01			0.63
Tertiary referral centre	870	1			1		
Other hospitals	510	0.55	0.41 – 0.73		0.99	0.66 – 1.97	
Hospital volume per year				<0.01			0.27
20-39	129	1			1		
<20	30	1.16	0.36 – 3.21	0.79	0.96	0.25 – 3.05	0.95
40-59	240	1.02	0.57 – 1.90	0.94	0.97	0.50 – 1.94	0.92
60-79	432	1.40	0.83 – 2.46	0.23	1.17	0.58 – 2.41	0.57
>80	549	2.04	1.23 – 3.53	<0.01	1.73	0.80 – 3.86	0.17

* Missing not included in analyses based on relatively small group

Table S4. Colorectal liver resections: univariable and multivariable logistic regression model of patient, tumour, surgical and volume factors associated with major morbidity (CD 3 or higher).

Unresectable, surgical and volume factors associated with major morbidity (CR 3 or higher).								
		Univariable			Multivariable			
		N	OR	CI (95%)	P-value	OR	CI (95%)	P-value
Sex								
Male					<0.01			<0.01
Female	2393	1				1		
Missing*	1439	0.70	0.55 – 0.89			0.70	0.54 – 0.89	
Age								
	14							
<70					0.14			
>70	2467	1						
Missing*	1368	1.18	0.95 – 1.48					
ASA Score								
	11							<0.01
1 / 2					<0.01			
3+	3047	1				1		
Missing*	660	1.85	1.43 – 2.37			1.97	1.43 – 2.44	
Charlson comorbidity index								
	139							
1 / 2					0.03			0.09
3	2767	1				1		
Missing*	949	1.31	1.03 – 1.65			1.26	0.96 – 1.63	
Body Mass Index								
	130							
Comorbidity liver			1.00	0.98 – 1.03	0.83			
No					0.97			
Yes	3569	1						
Missing*	42	0.98	0.29 – 2.45					
Previous resection								
	235							
No					0.45			
Yes	3061	1						
Missing*	660	1.11	0.84 – 1.46					
Type of tumour								
	125							
CRLM					0.13			
Other liver metastasis	2439	1						
Benign	1051	1.20	0.94 – 1.52					
HCC	356							
Cholangiocarcinoma					0.88			
Preoperative chemotherapy								
	3061	1						
No	785	1.02	0.78 – 1.33					
Yes	0							
Missing*					<0.01			<0.01
Procedure								
	3017	1				1		
Resection	829	2.17	1.72 – 2.73			2.20	1.71 – 2.82	
Resection and ablation								
Surgical approach					<0.01			0.05
Open	2977	1				1		
Laparoscopic	685	0.56	0.39 – 0.77	<0.01	0.65	0.45 – 0.92	0.02	
Conversion	149	0.91	0.50 – 1.54	0.74	0.74	0.38 – 1.32	0.35	
Missing*	35							
Simultaneous other resection					<0.01			<0.01
No	1927	1				1		
Yes	638	2.10	1.59 – 2.77	<0.01	1.78	1.28 – 2.46	<0.01	
Missing	1281	1.37	1.07 – 1.76	0.01	1.28	0.97 – 1.68	0.08	
Simultaneous colorectal resection					<0.01			<0.01
No	3226	1				1		

Yes	461	2.03	1.53 – 2.66		1.96	1.40 – 2.72	
Missing*	159						
Type of hospital				0.08			0.54
Tertiary referral centre	1724	1			1		
Other hospitals	2122	0.82	0.66 – 1.02		1.00	0.59 – 1.68	
Hospital volume per year				0.12			0.41
20-39	694	1			1		
<20	195	0.86	0.46 – 1.52	0.63	0.78	0.40 – 1.42	0.43
40-59	649	1.00	0.68 – 1.46	1.00	1.00	0.68 – 1.49	0.98
60-79	1304	0.98	0.71 – 1.37	0.93	1.16	0.78 – 1.73	0.45
>80	1004	1.36	0.98 – 1.89	0.07	1.51	0.89 – 2.57	0.13

Table S5a. Negative resections margins according to tumour type and hospital volume in the Dutch Hepato Billiary Audit between 2014 and 2017

		< 20	20-39	40-59	60-79	≥ 80	All
Colorectal liver metastases	<i>Number</i>	195	694	649	1304	1004	3846
	<i>R0</i>	176	630	594	1004	847	3251
	<i>resection</i>	(90.3)	(90.8)	(91.5)	(77.0)	(84.4)	(84.5)
	<i>Missing</i>	1 (0.5)	4 (0.6)	3 (0.5)	128 (9.8)	8 (0.8)	144 (3.7)
Non colorectal liver metastases	<i>Number</i>	12	33	61	146	150	402
	<i>R0</i>	11 (91.7)	28 (84.8)	56 (91.8)	103	132	330
	<i>resection</i>	0 (-)	1 (3.0)	0 (-)	(70.5)	(88.0)	(82.1)
	<i>Missing</i>				24 (16.4)	0 (-)	25 (6.2)
HCC	<i>Number</i>	5	35	55	201	254	550
	<i>R0</i>	5 (100)	34 (97.1)	50 (90.9)	159	222	470
	<i>resection</i>	0 (-)	0 (-)	0 (-)	(79.1)	(87.4)	(85.5)
	<i>Missing</i>				21 (10.4)	7 (2.8)	28 (5.1)

Table S5b. Negative resections margins of biliary tumour resections according to hospital volume in the Dutch Hepato Billiary Audit between 2014 and 2017

		< 20	20-39	40-59	60-79	≥ 80	All
Biliary	<i>Number</i>	0	15	15	112	131	273
	<i>R0</i>	-	3 (20.0)	6 (40.0)	65 (58.0)	73 (55.7)	147 (53.8)
	<i>resection</i>	-	11 (73.3)	5 (33.3)	30 (26.8)	41 (31.3)	87 (31.7)
	<i>Missing</i>						
Perihilar	<i>Number</i>	0	1	3	46	50	100
	<i>R0</i>	-	0 (-)	1 (33.3)	31 (67.4)	35 (70.0)	67 (67.0)
	<i>resection</i>	-	1 (100)	0 (-)	4 (8.7)	1 (2.0)	6 (6.0)
	<i>Missing</i>						
Intrahepatic	<i>Number</i>	0	5	4	44	44	97
	<i>R0</i>	-	3 (60.0)	2 (50.0)	24 (54.5)	31 (70.5)	60 (61.9)
	<i>resection</i>	-	2 (40.0)	1 (25.0)	15 (34.1)	11 (25.0)	29 (29.9)
	<i>Missing</i>						
Unspecified	<i>Number</i>	0	9	8	22	37	76
	<i>R0</i>	-	0 (-)	3 (37.5)	10 (45.5)	7 (18.9)	20 (26.3)
	<i>resection</i>	-	8 (88.9)	4 (50.0)	11 (50.0)	29 (78.4)	52 (68.4)
	<i>Missing</i>

CHAPTER 3

FACTORS ASSOCIATED WITH FAILURE TO RESCUE AFTER LIVER RESECTION AND IMPACT ON HOSPITAL VARIATION: A NATIONWIDE POPULATION- BASED STUDY

A.K.E. Elfrink, P.B. Olthof, R.J. Swijnenburg, M. den Dulk, M.T. de Boer, J.S.D. Mieog, J. Hagendoorn, G. Kazemier, P.B. van den Boezem, A.M. Rijken, M.S.L. Liem, W.K.G. Leclercq, K.F.D. Kuhlmann, H.A. Marsman, J.N.M. Ijzermans, P. van Duijvendijk, J.I. Erdmann, N.F.M. Kok, D.J. Grünhagen, J.M. Klaase, [Dutch Hepato Biliary Audit Group, Collaborators](#)

HPB (Oxford). 2021 Apr 30;S1365-182X(21)00120-9

Abstract

Introduction

Failure to rescue (FTR) is defined as postoperative complications leading to mortality. This nationwide study aimed to assess factors associated with FTR and hospital variation in FTR after liver surgery.

Methods

All patients who underwent liver resection between 2014-2017 in the Netherlands were included. FTR was defined as in-hospital or 30-day mortality after complications Dindo grade $\geq 3a$. Variables associated with FTR and nationwide hospital variation were assessed using multivariable logistic regression.

Results

Of 4961 patients included, 3707 (74.4%) underwent liver resection for colorectal liver metastases, 379 (7.6%) for other metastases, 526 (10.6%) for hepatocellular carcinoma and 349 (7.0%) for biliary cancer. Thirty-day major morbidity was 11.5%. Overall mortality was 2.3%. FTR was 19.1%. Age 65-80 (aOR:2.86, CI:1.01–12.0, $p=0.049$), ASA 3+ (aOR:2.59, CI:1.66–4.02, $p<0.001$), liver cirrhosis (aOR:4.15, CI:1.81–9.22, $p<0.001$), biliary cancer (aOR:3.47, CI:1.73–6.96, $p<0.001$), and major resection (aOR:6.46, CI:3.91–10.9, $p<0.001$) were associated with FTR. Postoperative liver failure (aOR:26.9, CI:14.6–51.2, $p<0.001$), cardiac (aOR:2.62, CI:1.27–5.29, $p=0.008$) and thromboembolic complications (aOR:2.49, CI:1.16–5.22, $p=0.017$) were associated with FTR. After case-mix correction, no hospital variation in FTR was observed.

Conclusion

FTR is influenced by patient demographics, disease and procedural burden. Prevention of postoperative liver failure, cardiac and thromboembolic complications could decrease FTR.

Introduction

Major complications after liver surgery may lead to postoperative mortality and therefore adequate and early detection and management of these complications is essential^{1,2}. Mortality after experiencing a major surgical complication has been called failure to rescue (FTR)³⁻⁷. FTR is seen as a quality indicator that focusses on management of complications rather than on complications itself. For this reason, it is an important outcome to address when searching for measures to improve quality of care.

While some studies have reported on FTR after liver surgery, most studies focus on mortality, which is dependent of factors like pre-existing liver disease and extent of surgery. Postoperative mortality among patients who undergo liver resection for colorectal liver metastases (CRLM) or liver metastases from other tumour types has been described to be near 5%⁸⁻¹⁰. Mortality among patients with primary liver cancers such as hepatocellular carcinoma (HCC) and biliary cancer have been reported to be even higher, approximately 5-10% and 10-20% respectively¹¹⁻¹⁴.

Improving complication management could lead to reducing postoperative mortality. Also, hospital and oncological network or regional variation has been associated with worse outcomes and higher costs^{15,16}. Several studies on FTR have been performed but nationwide analysis of FTR rates and hospital variation in FTR after liver surgery are lacking. Also, it is unclear which patient demographics, disease burden and postoperative complications associated with occurrence of FTR. These leads can be used to improve quality of care in liver surgery.

The aim of this study was to assess patient and disease characteristics as well as complications associated with FTR and to address possible existence of nationwide hospital variation in FTR.

Methods

This was a nationwide population-based study performed in the Netherlands. Several structural requirements for performing oncological care are established by SONCOS and endorsed by the Dutch Government and insurance companies¹⁷. These structural requirements for liver surgery include 24/7 availability of an interventional radiologist, two hepatobiliary surgeons, minimal procedural hospital volume requirements for liver resection (at least 20 liver resections per

centre have to be performed annually for any indication) and participation in the Dutch Hepato Biliary Audit (DHBA). All patients should be assessed in a preoperative multidisciplinary team meeting before proceeding to surgery. Data was collected from the DHBA, the mandatory audit in which all hospitals in the Netherlands performing liver surgery register all liver resections¹⁸. Data verification was performed to provide insight in completeness and accuracy of the DHBA when compared to the Dutch Cancer Registry¹⁹. No ethical approval was needed under Dutch law as the DHBA is part of the Dutch Inspectorate of health care and the dataset is anonymised.

Patient selection

All patients who underwent liver resection for primary or secondary liver tumours between the 1st of January 2014 and the 31st of December 2017 in the Netherlands were included. Patients were excluded if no date of birth, date of surgery or type of tumour could be obtained. Patients who underwent thermal ablation only were also excluded from the study.

All hospitals performing liver resection in the Netherlands were included in the between hospital variation analysis of FTR. Oncological network variation in FTR was assessed. Oncological networks are regional collaborations between hospital performing oncological care in the Netherlands²⁰.

Outcomes

Main outcome was Failure to Rescue (FTR). Failure to rescue was defined as in-hospital or 30-day mortality after first experiencing 30-day major morbidity. The nominator was defined as all patients who died after experiencing a major complication. The denominator includes all patients who experienced major morbidity. Major morbidity was defined as a complication grade 3a or higher according the Dindo classification, within 30 days of the surgical procedure²¹. Mortality was defined as death during hospitalization or within 30 days of the surgical procedure.

Surgical complications (bile leakage, postoperative haemorrhage, liver failure defined according the International Study Group of Liver Surgery, deep and superficial surgical site infections). Thromboembolic and cardiopulmonary complications were also scored according the Dindo classification within 30 days of the surgical procedure²².

Variables

Several variables were assessed that influenced occurrence of FTR using multivariable logistic regression. These included sex, age, American Society of Anesthesiologist (ASA) classification, Body Mass Index (BMI), comorbidity scores classified according to the Charlson Comorbidity

Score (CCI), classification of liver parenchyma, earlier liver surgery and diameter of the largest tumour before the initiation of tumour-specific treatment. Treatment characteristics included use of preoperative chemotherapy, major liver resection, and hospital where treatment took place which was either a tertiary referral centre or regional hospital. Major liver resection was defined as resection of three or more Couinaud segments²³. Annual hospital volume was calculated as total number of liver resections per hospital per year and categorised <20, 20-39, 40-59, 60-79 and >80.

Statistical analysis

Distribution of data was assessed using histograms and box plots. Normally distributed continuous data were presented as mean with standard deviation. Non-normally distributed data were presented as median with interquartile ranges (IQR). Categorical data were presented as frequency accompanied by percentage. The chi-square test or fisher exact test were used to compare categorical data as appropriate.

Rates of FTR, 30-day major morbidity and 30-day mortality were assessed separately for hospital mortality quartiles. Hospitals were ranked based on mean mortality and then divided into quartiles.

Factors associated with FTR were assessed using univariable and multivariable logistic regression. All variables available were entered in the multivariable logistic regression. Backward selection was performed based on a $p < 0.100$ if necessary. Outcomes of both univariable and multivariable logistic regression were reported as adjusted odds ratios (aOR) with corresponding 95% confidence intervals (CI). Two-sided p -value < 0.05 were considered statistically significant. Patient and tumour characteristics in the multivariable model were classified as case-mix factors.

Uncorrected hospital and oncological network variation in FTR were assessed and visualised using histograms. Case-mix corrected hospital and oncological network variation in FTR were assessed using funnel plots displaying Observed / Expected (O/E) Ratios. The case-mix represents patient demographics and disease burden of the population surgically treated in a hospital⁹. For case-mix correction, the expected FTR per hospital was calculated per patient using multivariable logistic regression with all case-mix variables available. All patients in a hospital or oncological network compose the expected number of FTR. The O/E Ratio was calculated by dividing the true number of FTR through the expected number of FTR. An O/E Ratio above 1 indicates a performance worse regarding FTR than expected and an O/E ratio

below 1 indicates a better performance regarding FTR than expected. The 95% confidence intervals (CI) were calculated to indicate statistical significance in the case-mix corrected funnel plot.

Annual hospital volume was included in the analysis and was calculated as total number of liver resections for all indications in a hospital. Missing categories were included in the analyses if this exceeded 5% of the total included cohort.

Multicollinearity was assessed using the Variance Inflation Factor (VIF). A VIF of 2 or lower indicated that there was no multicollinearity. All analyses were performed in R version 3.2.2® (R Core Team (2018): A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

Results

In total 4961 patients were included of whom 3707 (74.4%) underwent liver resection for CRLM, 379 (7.6%) underwent liver resection of other metastases, 526 (10.6%) underwent liver resection for HCC and 349 (7.0%) underwent liver resection for biliary cancer (table 1). Of patients who underwent liver resection for biliary cancer, 123 (35.2%) patients underwent resection of perihilar cholangiocarcinoma, 98 (28.1%) patients underwent resection of intrahepatic cholangiocarcinoma and 109 (31.2%) patients of gallbladder carcinoma. Biliary cancer locations of 19 patients were unknown.

Table 1. Baseline characteristics for patients who underwent liver resection between 2014 and 2017 in the Netherlands.

		Overall	30-day morbidity	30-day mortality	FTR
Factor		N = 4961 (%)	N = 570 (%)	N = 113 (%)	N = 109 (%)
Sex					
	Male	2986 (60)	388 (68)	79 (70)	77 (71)
	Female	1959 (40)	182 (32)	34 (30)	32 (29)
	Missing	16 (0)	0 (0)	0 (0)	0 (0)
Age in years					
	< 50	415 (8)	32 (6)	3 (3)	3 (3)
	50 – 64	1706 (35)	181 (32)	30 (27)	30 (28)
	65 – 80	2500 (51)	314 (55)	72 (64)	70 (64)
	≥ 80	328 (7)	43 (8)	8 (7)	6 (6)
	Missing	12 (0)	0 (0)	0 (0)	0 (0)
Charlson Comorbidity Index (CCI)					
	0 / 1	3791 (76)	401 (70)	75 (66)	72 (66)
	2+	1170 (24)	159 (30)	38 (34)	37 (34)
American Society of Anesthesiology (ASA) classification					

I / II	3863 (78)	387 (68)	64 (57)	61 (56)
III+	952 (19)	167 (29)	39 (43)	48 (44)
Missing	146 (3)	16 (3)	0 (0)	0 (0)
Body Mass Index (BMI)	26.2 (4.4)	26.2 (4.3)	26.8 (4.5)	26.9 (4.5)
Mean (sd)				
Liver resection in the past				
No	4085 (82))	476 (84)	94 (83)	90 (83)
Yes	718 (15)	80 (14)	19 (17)	19 (17)
Missing	158 (3)	14 (3)	0 (0)	0 (0)
Histological diagnosis of liver parenchyma				
Normal	2983 (60)	324 (57)	55 (49)	53 (49)
Steatosis	748 (15)	102 (18)	24 (21)	24 (22)
Steato-hepatitis	111 (2)	21 (4)	5 (4)	5 (5)
Cirrhosis	163 (3)	27 (5)	13 (12)	13 (12)
Sinusoidal dilatation	49 (1)	8 (1)	2 (2)	2 (2)
Missing	907 (18)	88 (15)	14 (12)	12 (11)
Type of tumour				
CRLM	3707 (75)	359 (63)	52 (46)	49 (45)
Other liver metastases	379 (8)	38 (7)	5 (4)	4 (4)
HCC	526 (11)	81 (14)	27 (24)	27 (25)
Biliary cancer	349 (7)	92 (16)	29 (26)	29 (27)
Preoperative chemotherapy				
No	3341 (67)	395 (69)	88 (78)	85 (78)
Yes	1120 (23)	123 (22)	21 (19)	20 (18)
Missing	500 (10)	52 (9)	4 (4)	4 (4)
Maximum diameter of largest tumour (mm)				
< 20	1235 (25)	111 (20)	17 (15)	15 (14)
20 – 34	1387 (28)	126 (22)	19 (17)	17 (16)
35 – 54	780 (16)	89 (16)	18 (16)	18 (17)
> 55	632 (13)	97 (17)	22 (20)	22 (20)
Missing	927 (19)	147 (26)	37 (33)	37 (34)
Major liver resection				
No	3565 (72)	295 (52)	30 (27)	27 (25)
Yes	1235 (25)	257 (45)	80 (71)	79 (73)
Missing	161 (3)	18 (3)	3 (3)	3 (3)
Surgical approach				
Open	3747 (75)	478 (84)	102 (90)	98 (90)
Laparoscopic	1027 (21)	73 (13)	8 (7)	8 (7)
Missing	187 (4)	19 (3)	3 (3)	3 (3)
Type of hospital[∞]				
Regional hospitals	2317 (47)	211 (37)	30 (26)	27 (25)
Tertiary referral centre	2644 (53)	359 (63)	83 (74)	82 (75)
Annual hospital volume				
< 20	125 (3)	11 (2)	0 (0)	0 (0)
20 – 39	944 (19)	81 (14)	14 (12)	13 (12)
40 – 59	804 (16)	83 (15)	12 (11)	12 (11)
60 – 79	732 (15)	85 (15)	8 (7)	7 (6)
≥ 80	2356 (48)	310 (54)	79 (70)	77 (71)

[∞] Type of hospital: tertiary referral centre are defined as hospitals with highest expertise on oncologic surgery. Percentages may not add up to 100% as they are rounded to the nearest full number.

Outcomes

Of all patients, 113 (2.3%) died in-hospital or within 30 days of surgery. Thirty-day major morbidity was observed in 570 (11.5%) patients. FTR occurred in 109 (19.1%) patients who experienced 30-day major morbidity. FTR was different between CRLM, other metastases, HCC and biliary cancer ($p<0.001$) (figure 1, supplementary table 1).

Figure 1. Thirty-day major morbidity, 30-day mortality and Failure to Rescue for primary and secondary liver tumours between 2014 and 2017 in the Netherlands.

Differences in outcomes between tumour types all had p-values <0.001

Patient and tumour characteristics, and complications associated with FTR

Factors independently associated with FTR were age 65-80 (aOR 2.86, CI 1.01 – 12.0, $p=0.049$), ASA classification 3 or higher (aOR 2.59, CI 1.66 – 4.02, $p<0.001$), histopathological cirrhosis (aOR 4.15, CI 1.81 – 9.22, $p<0.001$), biliary cancer as indication for liver resection (aOR 3.47, CI 1.73 – 6.96, $p<0.001$), and major liver resection (aOR 6.46, CI 3.91 – 10.9, $p<0.001$) (table 2). No influence of annual hospital volume on FTR was observed.

Table 2. Univariable and multivariable logistic model of patient, tumour and surgical factors associated with Failure to Rescue in patients who underwent liver resection for primary and secondary liver tumours between 2014 and 2017 in the Netherlands.

Factor	Univariable analysis				Multivariable analysis		
	N	OR	CI (95%)	P-value	aOR	CI (95%)	P-value
Sex				0.028			0.235
Male	2986	1			1		
Female	1959	0.63	0.41 – 0.94		0.76	0.47 – 1.19	
Missing*	16						
Age in years				0.001			0.048
< 50	415	1			1		
50 – 64	1706	2.46	0.87 – 10.3	0.139	1.95	0.67 – 8.33	0.281
65 – 80	2500	3.96	1.47 – 16.2	0.020	2.86	1.01 – 12.0	0.049
> 80	328	2.56	0.67 – 12.2	0.186	3.03	0.74 – 15.2	0.137
Missing*	12						
Charlson Comorbidity Index (CCI)				0.011			0.243
0 / 1	3791	1			1		
2+	1170	1.69	1.12 – 2.50		1.32	0.83 – 2.06	
Body Mass Index		1.04	0.99 – 1.08	0.092	1.03	0.99 – 1.08	0.177
American Society of Anesthesiology (ASA) classification				<0.001			<0.001
I / II	3863	1		1	1		
III+	952	3.31	2.24 – 4.86		2.59	1.66 – 4.02	
Missing*	146						
History of liver resection				0.463			
No	4085	1					
Yes	718	1.21	0.71 – 1.95				
Missing*	158						
Histopathological liver disease§				<0.001			0.016
Normal	2893	1		1	1		
Steatosis	748	1.83	1.11 – 2.95	0.015	1.53	0.89 – 2.58	0.114
Steato-hepatitis	111	2.61	0.89 – 6.06	0.055	2.54	0.81 – 6.59	0.076
Cirrhosis	163	3.79	2.46 – 8.72	<0.001	4.15	1.81 – 9.22	<0.001
Sinusoidal dilatation	49	2.35	0.38 – 7.88	0.245	1.85	0.27 – 7.21	0.441
Missing	907	0.74	0.38 – 1.34	0.352	0.85	0.37 – 1.75	0.682
Type of tumour				<0.001			0.003
CRLM	3707	1		1	1		
Other LM	379	0.80	0.24 – 1.97	0.663	0.86	0.25 – 2.25	0.783
HCC	526	4.04	2.47 – 6.47	<0.001	1.25	0.63 – 2.44	0.524
Biliary cancer	349	6.77	4.17 – 10.8	<0.001	3.47	1.73 – 6.96	<0.001
Preoperative chemotherapy				0.013			0.057
No	3341	1			1		
Yes	1120	0.70	0.41 – 1.12	0.150	0.94	0.51 – 1.68	0.827
Missing	500	0.31	0.09 – 0.74	0.022	0.16	0.01 – 1.10	0.074

Maximum diameter of largest tumour (mm)				<0.001			0.818
< 20	1235	1		1			
20-34	1387	1.01	0.50 – 2.05	0.979	1.00	0.43 – 1.86	0.745
35-54	780	1.92	0.96 – 3.89	0.064	1.18	0.57 – 2.48	0.656
> 55	632	2.83	1.52 – 5.81	0.001	1.27	0.63 – 2.63	0.521
Missing	927	3.38	1.88 – 6.39	<0.001	1.27	0.64 – 2.61	0.401
Major liver resection				<0.001			<0.001
No	3565	1		1			
Yes	1235	8.95	5.83 – 14.2		6.46	3.91 – 10.9	
Missing*	161						
Surgical approach				<0.001			0.118
Open	3747	1		1			
Laparoscopic	1027	0.29	0.13 – 0.57		0.56	0.24 – 1.15	
Missing*	187						
Type of hospital[∞]				<0.001			0.929
Regional hospitals	2317	1		1			
Tertiary referral hospital	2644	2.71	1.78 – 4.28		1.04	0.49 – 2.29	
Annual hospital volume				<0.001			0.210
0 – 39	1069	1		1			
40 – 59	804	1.23	0.55 – 2.73	0.607	0.81	0.32 – 1.96	0.636
60 – 79	732	0.78	0.29 – 1.92	0.606	0.58	0.19 – 1.61	0.312
≥ 80	2356	2.74	1.57 – 5.19	<0.001	1.31	0.51 – 3.31	0.569

* Missing not included in analyses based on relatively small group

§ History of liver disease containing liver cirrhosis, oesophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis

∞ Type of hospital: tertiary referral centre are defined as hospitals with highest expertise on oncologic surgery

Postoperative liver failure (aOR 26.9, CI 14.6 – 51.2, $p < 0.001$), cardiac complications (aOR 2.62, CI 1.27 – 5.29, $p = 0.008$) and thromboembolic complications (aOR 2.49, CI 1.16 – 5.22, $p = 0.017$) were independently associated with occurrence of FTR (table 3).

Table 3. Univariable and multivariable logistic model of complications associated with Failure to Rescue in patients who underwent liver resection for primary and secondary liver tumours between 2014 and 2017 in the Netherlands.

Complication	N	Univariable analysis			Multivariable analysis		
		OR	CI (95%)	P-value	aOR	CI (95%)	P-value
Bile leakage				0.350			0.321
No	4649	1			1		
Yes	210	0.76	0.41 – 1.32		0.68	0.31 – 1.42	
Missing*	102						
Postoperative haemorrhage				<0.001			0.072
No	4793	1			1		
Yes	60	4.30	1.99 – 9.25		2.61	0.90 – 7.37	
Missing*	108						
Postoperative liver failure				<0.001			<0.001

No	4760	1		1	
Yes	101	29.1	16.6 – 52.8	26.9	14.6 – 51.2
Missing*	100				
Intra-abdominal infection				<0.001	0.002
No	4518	1		1	
Yes	339	0.37	0.23 – 0.57	0.39	0.21 – 0.71
Missing*	104				
Surgical site infection				0.005	0.047
No	4671	1		1	
Yes	186	0.29	0.11 – 0.64	0.37	0.13 – 0.92
Missing*	104				
Pneumonia				0.826	0.721
No	4572	1		1	
Yes	291	0.93	0.48 – 1.69	1.15	0.51 – 2.44
Missing*	98				
Cardiac complication				<0.001	0.008
No	4692	1		1	
Yes	166	2.64	1.50 – 4.53	2.62	1.27 – 5.29
Missing*	103				
Thromboembolic complication				<0.001	0.017
No	4741	1		1	
Yes	118	4.29	2.46 – 7.48	2.49	1.16 – 5.22
Missing*	102				

* Missing not included in analyses based on relatively small group
 Bold p-values indicate statistical significance

Hospital and oncological network variation in FTR

Uncorrected FTR ranged from 0% to 50.0% between hospitals but after case-mix correction no hospitals performed significantly better or worse than expected (figure 2a & 2b). Uncorrected FTR ranged from 4.2% to 24.2% between oncological networks but after case-mix correction no oncological networks performed significantly better or worse than expected (figure 3a & 3b).

Figure 2a. Unadjusted hospital variation in Failure to Rescue after liver surgery in the Netherlands between 2014 and 2017.

Figure 2b. Case-mix corrected hospital variation in Failure to Rescue after liver surgery in the Netherlands between 2014 and 2017.

Case-mix adjusted for: sex, age, CCI, ASA classification, BMI, history of liver disease, preoperative chemotherapy, type of tumour, diameter of largest tumour, surgical approach, major liver resection, type of hospital and hospital volume.

Figure 3a. Unadjusted oncological network variation in Failure to Rescue after liver surgery in the Netherlands between 2014 and 2017.

Figure 3b. Case-mix corrected oncological network variation in Failure to Rescue after liver surgery in the Netherlands between 2014 and 2017.

Discussion

This study found that FTR after liver resection is considerable in the Netherlands. Several patient and tumour characteristics were associated with FTR such as higher age, ASA classification 3, histopathological cirrhosis, liver resection for biliary cancer and major liver resection. Also, occurrence of postoperative liver failure, cardiac and thromboembolic complications were associated with FTR. The observed uncorrected variation in FTR between hospitals was attributable to patient demographics, disease burden and extent of resection in those hospitals and vanished after case-mix correction.

FTR rates using in hospital mortality after liver resection in the USA were described to vary between 11.8% and 16.8% in a cohort including 9874 patients from 2000 to 2010²⁴. A recent study from Italy focusing on FTR within 90 days after resection of HCC observed an overall FTR rate of 19.2% which ranged between 28.6% in low volume centres and 5.1% in high volume centres²⁵. In a German study using invoice data including 18849 patients from 2009 to 2015 the in-hospital FTR rate was 28.9%²⁶. Overall FTR rates of 19.1% in the Netherlands are therefore concordant with the literature. In these earlier studies a relationship between hospital volume and FTR was observed while no relationship between hospital volume and FTR was found in the current study. An earlier Dutch study on hospital volume and outcomes did not show any relationship. This may be explained by the fact that centralisation of liver surgery has taken place in the Netherlands⁸. This included both introduction of a required minimal annual hospital volume of 20 resections, centralisation of extended resections and resection of HCC in cirrhotic livers and biliary cancers in tertiary centres. FTR rates after HCC and biliary cancer resection in the Netherlands are high although literature is scarce regarding FTR in groups that underwent liver resection for these indications. It shows that these indications are different regarding disease and treatment characteristics than for example CRLM. However, improvement of FTR rates should be pursued as they are still considerable and during improvement focus should be on patients that undergo liver resection for HCC or biliary cancer.

In search of improvement of FTR rates, several prognostic factors were observed to be associated with FTR in the current study. Structural hospital characteristics such as hospital staffing and (surgeon) volume have been described to be associated with lower FTR^{27,28}. In this study these factors could not be assessed due to lacking of these variables in the DHBA. However, patient demographics, disease burden and complications leading to FTR were assessed in the current study. In the USA, low hospital volume, age above 70, high comorbidity scores, primary hepatic malignancy and major liver resection were independently associated with FTR²⁴. No influence of specific complications on FTR was assessed in the American study. In the Italian study on FTR after HCC resection only low centre volume was associated with FTR²⁵. The current study confirms that patient factors such as higher age, ASA classification 3, histopathological cirrhosis and disease demographics such as liver resection for biliary cancer and major liver resection are risk factors for occurrence of FTR.

It should be stressed that in the current study occurrence of postoperative liver failure, cardiac and thromboembolic complications were precursors for FTR. Infectious complications such as intra-abdominal infection and surgical site infection were observed to be associated with a

decreased FTR rate in this study. This was probably a result of selection-bias as patients without infectious complications more often had postoperative liver failure, cardiac complications and thromboembolic complications resulting in a negative association of infectious complications with FTR. Surgical teams should focus on preoperative patient selection as well as aggressive management of postoperative complications to prevent FTR and consider referral of high-risk patients to centres with the best pathways in place to treat complications adequately. This is particularly true for patients at risk for postoperative liver failure as in this study this proves to be the complication that poses greatest risk of FTR, most likely due to no effective treatment for liver failure apart from supportive measures. Risk assessment of potential liver failure should include preoperative volumetric assessment of the liver, hepatobiliary scintigraphy and liver biopsy of the future liver remnant in patients with extended resections and/or cirrhosis^{29,30}. Patients' selection using these modalities and selection for preoperative portal vein embolization may decrease postoperative liver failure^{29,31}. Also, aggressive management of complications in patients who are at risk of postoperative liver failure should be focussed on by screening for infections and subsequent aggressive management. Cardiac complications might be improved using preoperative patient optimisation through prehabilitation focusing on cardiopulmonary complications^{32,33}. Decreasing thromboembolic complications after liver surgery can be achieved by using pharmacological and non-pharmacological prophylaxis and by early mobilisation³⁴. Together, these measures can help surgical teams in decreasing complication and FTR rates.

Hospital and oncological network variation in uncorrected FTR were observed in the current study. However, this variation vanished after case-mix correction for patient demographics and disease burden⁹. This probably reflects the earlier described centralisation in the Netherlands with most patients with a high risk of complications treated in tertiary referral centres. However, further centralisation of patients who undergo extensive liver resection who are at risk of postoperative liver failure such as HCC patients with cirrhotic liver disease and perihilar cholangiocarcinoma patients could further decrease this specific complication leading to FTR. It has also been described that higher FTR rates are associated with higher costs³⁵⁻³⁷. Both reasons should encourage surgical teams to improve quality of care by decreasing FTR rates in the future. Several measures have been described in the current study to decrease FTR rates.

Limitations of this study include the use of the nationwide audit database for analysis. Most important were the lacking of 90-day morbidity and 90-day mortality in the DHBA as 90-day outcomes have been described a better proxy for true morbidity and mortality rates³⁸⁻⁴⁰. Also,

use of the audit database might influence results of the study as this means absence of specific detailed information regarding preoperative, operative and postoperative outcomes. This includes detailed surgical information during surgery regarding vascular and biliary reconstructions. Specific grading, treatment of independent complications and primary cause of death and impact on mortality could not be assessed. This was particularly true for patients who experienced liver failure as no information was available regarding preoperative and postoperative pathway leading to liver failure. The benefit of the national audit data is, that the data includes all liver resections in the Netherlands and the data is reflective of true clinical practice.

In conclusion, FTR after liver resection is different between Dutch hospitals and is explained by patient demographics, disease burden and procedural type in those hospitals. Comparing FTR between hospitals therefore warrants case-mix correction. Surgical teams should focus on decreasing mortality after liver resection by decreasing FTR. This could be achieved through better patient selection by cardiopulmonary exercise with preoperative prehabilitation, preoperative liver function tests and improving postoperative care in patients that have higher risk for FTR.

References

1. Ghaferi AA, Birkmeyer JD, Dimick JB. Variation in hospital mortality associated with inpatient surgery. *N Engl J Med*. 2009;361(14):1368-1375.
2. Ghaferi AA, Birkmeyer JD, Dimick JB. Complications, failure to rescue, and mortality with major inpatient surgery in medicare patients. *Ann Surg*. 2009;250(6):1029-1034.
3. van Rijssen LB, Zwart MJ, van Dieren S, de Rooij T, Bonsing BA, Bosscha K, et al. Variation in hospital mortality after pancreatoduodenectomy is related to failure to rescue rather than major complications: a nationwide audit. *HPB (Oxford)*. 2018;20(8):759-767.
4. Staiger RD, Gerns E, Castrejon Subira M, Domenghino A, Puhon MA, Clavien PA. Can Early Postoperative Complications Predict High Morbidity and Decrease Failure to Rescue Following Major Abdominal Surgery? *Ann Surg*. 2020;272(5):834-839.
5. Henneman D, Sniijders HS, Fiocco M, van Leersum NJ, Kolfschoten NE, Wiggers T, et al. Hospital variation in failure to rescue after colorectal cancer surgery: results of the Dutch Surgical Colorectal Audit. *Ann Surg Oncol*. 2013;20(7):2117-2123.
6. Henneman D, van Leersum NJ, Ten Berge M, Sniijders HS, Fiocco M, Wiggers T, et al. Failure-to-rescue after colorectal cancer surgery and the association with three structural hospital factors. *Ann Surg Oncol*. 2013;20(11):3370-3376.
7. Busweiler LA, Henneman D, Dikken JL, Fiocco M, van Berge Henegouwen MI, Wijnhoven BP, et al. Failure-to-rescue in patients undergoing surgery for esophageal or gastric cancer. *Eur J Surg Oncol*. 2017;43(10):1962-1969.
8. Olthof PB, Elfink AKE, Marra E, Belt EJT, van den Boezem PB, Bosscha K, et al. Volume-outcome relationship of liver surgery: a nationwide analysis. *Br J Surg*. 2020;107(7):917-926.
9. Elfink AKE, van Zwet EW, Swijnenburg RJ, den Dulk M, van den Boezem PB, Mieog JSD, et al. Case-mix adjustment to compare nationwide hospital performances after resection of colorectal liver metastases. *Eur J Surg Oncol*. 2020.
10. Filmann N, Walter D, Schadde E, Bruns C, Keck T, Lang H, et al. Mortality after liver surgery in Germany. *Br J Surg*. 2019;106(11):1523-1529.
11. Famularo S, Donadon M, Cipriani F, Ardito F, Carissimi F, Perri P, et al. Hepatocellular carcinoma surgical and oncological trends in a national multicentric population: the HERCOLES experience. *Updates Surg*. 2020;72(2):399-411.
12. Elfink AKE, al. e. Short-term postoperative outcomes after liver resection in the elderly patient: a nationwide population-based study. *Submitted*. 2021.
13. Franken LC, Schreuder AM, Roos E, van Dieren S, Busch OR, Besselink MG, et al. Morbidity and mortality after major liver resection in patients with perihilar cholangiocarcinoma: A systematic review and meta-analysis. *Surgery*. 2019;165(5):918-928.
14. Olthof PB, Miyasaka M, Koerkamp BG, Wiggers JK, Jarnagin WR, Noji T, et al. A comparison of treatment and outcomes of perihilar cholangiocarcinoma between Eastern and Western centers. *HPB (Oxford)*. 2019;21(3):345-351.
15. Birkmeyer JD, Reames BN, McCulloch P, Carr AJ, Campbell WB, Wennberg JE. Understanding of regional variation in the use of surgery. *Lancet*. 2013;382(9898):1121-1129.
16. Nelson-Williams H, Gani F, Kilic A, Spolverato G, Kim Y, Wagner D, et al. Factors Associated With Interhospital Variability in Inpatient Costs of Liver and Pancreatic Resections. *JAMA Surg*. 2016;151(2):155-163.
17. SONCOS. Preserving Quality of Care in the Netherlands. 2017.
18. van der Werf LR, Kok NFM, Buis CI, Grunhagen DJ, Hoogwater FJH, Swijnenburg RJ, et al. Implementation and first results of a mandatory, nationwide audit on liver surgery. *HPB (Oxford)*. 2019;21(10):1400-1410.
19. van der Werf LR, Voeten SC, van Loe CMM, Karthaus EG, Wouters M, Prins HA. Data verification of nationwide clinical quality registries. *BJS Open*. 2019;3(6):857-864.
20. Elfink AKE, al. e. Oncological networks for resection of colorectal liver metastases: differences and postoperative outcomes. *Submitted*. 2021.
21. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg*. 2009;250(2):187-196.

22. Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). *Surgery*. 2011;149(5):713-724.
23. Pang YY. The Brisbane 2000 terminology of liver anatomy and resections. *HPB* 2000; 2:333-39. *HPB (Oxford)*. 2002;4(2):99; author reply 99-100.
24. Spolverato G, Ejaz A, Hyder O, Kim Y, Pawlik TM. Failure to rescue as a source of variation in hospital mortality after hepatic surgery. *Br J Surg*. 2014;101(7):836-846.
25. Ardito F, Famularo S, Aldrighetti L, Grazi GL, DallaValle R, Maestri M, et al. The Impact of Hospital Volume on Failure to Rescue after Liver Resection for Hepatocellular Carcinoma: Analysis from the HE.RC.O.LE.S. Italian Registry. *Ann Surg*. 2020;272(5):840-846.
26. Baum P, Diers J, Lichthardt S, Kastner C, Schlegel N, Germer CT, et al. Mortality and Complications Following Visceral Surgery: A Nationwide Analysis Based on the Diagnostic Categories Used in German Hospital Invoicing Data. *Dtsch Arztebl Int*. 2019;116(44):739-746.
27. Buettner S, Gani F, Amini N, Spolverato G, Kim Y, Kilic A, et al. The relative effect of hospital and surgeon volume on failure to rescue among patients undergoing liver resection for cancer. *Surgery*. 2016;159(4):1004-1012.
28. Chen Q, Olsen G, Bagante F, Merath K, Idrees JJ, Akgul O, et al. Procedure-Specific Volume and Nurse-to-Patient Ratio: Implications for Failure to Rescue Patients Following Liver Surgery. *World J Surg*. 2019;43(3):910-919.
29. Cieslak KP, Bennink RJ, de Graaf W, van Lienden KP, Besselink MG, Busch OR, et al. Measurement of liver function using hepatobiliary scintigraphy improves risk assessment in patients undergoing major liver resection. *HPB (Oxford)*. 2016;18(9):773-780.
30. Dinant S, de Graaf W, Verwer BJ, Bennink RJ, van Lienden KP, Gouma DJ, et al. Risk assessment of posthepatectomy liver failure using hepatobiliary scintigraphy and CT volumetry. *J Nucl Med*. 2007;48(5):685-692.
31. Olthof PB, Aldrighetti L, Alikhanov R, Cescon M, Groot Koerkamp B, Jarnagin WR, et al. Portal Vein Embolization is Associated with Reduced Liver Failure and Mortality in High-Risk Resections for Perihilar Cholangiocarcinoma. *Ann Surg Oncol*. 2020;27(7):2311-2318.
32. Moran J, Wilson F, Guinan E, McCormick P, Hussey J, Moriarty J. Role of cardiopulmonary exercise testing as a risk-assessment method in patients undergoing intra-abdominal surgery: a systematic review. *Br J Anaesth*. 2016;116(2):177-191.
33. Berkel AEM, Bongers BC, Kotte H, Weltevreden P, de Jongh FHC, Eijsvogel MMM, et al. Effects of Community-based Exercise Prehabilitation for Patients Scheduled for Colorectal Surgery With High Risk for Postoperative Complications: Results of a Randomized Clinical Trial. *Ann Surg*. 2021.
34. Baltatzis M, Low R, Stathakis P, Sheen AJ, Siriwardena AK, Jamdar S. Efficacy and safety of pharmacological venous thromboembolism prophylaxis following liver resection: a systematic review and meta-analysis. *HPB (Oxford)*. 2017;19(4):289-296.
35. Idrees JJ, Kimbrough CW, Rosinski BF, Schmidt C, Dillhoff ME, Beal EW, et al. The Cost of Failure: Assessing the Cost-Effectiveness of Rescuing Patients from Major Complications After Liver Resection Using the National Inpatient Sample. *J Gastrointest Surg*. 2018;22(10):1688-1696.
36. Chen Q, Beal EW, Kimbrough CW, Bagante F, Merath K, Dillhoff M, et al. Perioperative complications and the cost of rescue or failure to rescue in hepato-pancreato-biliary surgery. *HPB (Oxford)*. 2018;20(9):854-864.
37. Merath K, Chen Q, Bagante F, Sun S, Akgul O, Idrees JJ, et al. Variation in the cost-of-rescue among medicare patients with complications following hepatopancreatic surgery. *HPB (Oxford)*. 2019;21(3):310-318.
38. Schiorgens TS, Dorsch M, Mittermeier L, Brand K, Kuchenhoff H, Lee SM, et al. Thirty-day mortality leads to underestimation of postoperative death after liver resection: A novel method to define the acute postoperative period. *Surgery*. 2015;158(6):1530-1537.
39. Mayo SC, Shore AD, Nathan H, Edil BH, Hirose K, Anders RA, et al. Refining the definition of perioperative mortality following hepatectomy using death within 90 days as the standard criterion. *HPB (Oxford)*. 2011;13(7):473-482.
40. Mise Y, Vauthey JN, Zimmitti G, Parker NH, Conrad C, Aloia TA, et al. Ninety-day Postoperative Mortality Is a Legitimate Measure of Hepatopancreatobiliary Surgical Quality. *Ann Surg*. 2015;262(6):1071-1078.

Supplementary material

Supplementary table 1. Thirty-day major morbidity, 30-day mortality and FTR rates for primary and secondary liver tumours between 2014 and 2017 in the Netherlands.

	N	30-day major morbidity	30-day mortality	FTR
CRLM	3707	359 (10)	52 (1)	49 (14)
Other liver metastases	379	38 (10)	3 (1)	4 (11)
HCC	526	81 (15)	27 (5)	27 (33)
Biliary cancer				
Overall	349	92 (26)	29 (8)	29 (32)
Perihilar	123	45 (37)	13 (11)	13 (29)
cholangiocarcinoma				
Intrahepatic	98	21 (21)	9 (9)	9 (43)
cholangiocarcinoma				
Gallbladder	109	25 (23)	7 (6)	7 (28)
carcinoma				
Missing*	19

CHAPTER 4

SHORT-TERM POSTOPERATIVE OUTCOMES AFTER LIVER RESECTION IN THE ELDERLY PATIENT: A NATIONWIDE POPULATION-BASED STUDY

A.K.E. Elfrink, N.F.M. Kok, M. den Dulk, C.I. Buis, G. Kazemier, J.N.M. Ijzermans, H.D. Lam, J. Hagendoorn, P.B. van den Boezem, N. Ayez, B.M. Zonderhuis, D.J. Lips, W.K.G. Leclercq, K.F.D. Kuhlmann, H.A. Marsman, C. Verhoef, G.A. Patijn, D.J. Grünhagen, J.M. Klaase, [Dutch Hepato Biliary Audit Group, Collaborators](#)

HPB (Oxford). 2021 Mar 19:S1365-182X(21)00067-8.

Abstract

Introduction

Liver resection is high-risk surgery in particular in elderly patients. The aim of this study was to explore postoperative outcomes after liver resection in elderly patients.

Methods

In this nationwide study, all patients who underwent liver resection for primary and secondary liver tumours in the Netherlands between 2014-2019 were included. Age groups were composed as younger than 70 (70-), between 70-80 (septuagenarians), and 80 years or older (octogenarians). Proportion of liver resections per age group and 30-day major morbidity and 30-day mortality were assessed.

Results

In total, 6587 patients were included of whom 4023 (58.9%) were younger than 70, 2135 (32.4%) were septuagenarians and 429 (6.5%) were octogenarians. The proportion of septuagenarians increased during the study period (aOR:1.06, CI:1.02-1.09, $p<0.001$). Thirty-day major morbidity was higher in septuagenarians (11%) and octogenarians (12%) compared to younger patients (9%, $p=0.049$). Thirty-day mortality was higher in septuagenarians (4%) and octogenarians (4%) compared to younger patients (2%, $p<0.001$). Cardiopulmonary complications occurred more frequently with higher age, liver-specific complications did not. Higher age was associated with higher 30-day morbidity and 30-day mortality in multivariable logistic regression.

Conclusion

Thirty-day major morbidity and 30-day mortality are higher after liver resection in elderly patients, attributed mainly to non-surgical cardiopulmonary complications.

Introduction

Aging of the population has been described to be accompanied by a higher incidence of malignancies¹. As liver resection has become safer over the past decades, more elderly patients undergo liver resection for varying indications such as colorectal liver metastases (CRLM), liver metastases from other origins, hepatocellular carcinoma (HCC) and biliary cancer². In the Netherlands, liver resection is most frequently performed for CRLM followed by hepatocellular carcinoma and biliary cancer³.

Postoperative morbidity and mortality after liver resection for primary and secondary liver tumours tend to increase as older patients are accompanied with more comorbidities and frailty as well as aging of the liver⁴⁻⁶. During preoperative multidisciplinary treatment meetings, preoperative optimization becomes more important to decrease the negative impact of these comorbidities of patients who face liver resection for primary and secondary liver tumours⁷. To date, age has been seen as a risk factor for complications and mortality in liver surgery but it remains unclear to what extent other patient demographics, disease burden or operative characteristics play a role.

Several international studies show contradictory results with regard to the influence of age on postoperative outcomes after liver surgery^{5,8,9}. However, these studies had small sample size or were focused on a specific liver tumour^{5,6,8}. Several initiatives have been conducted to address frailty and optimise patients before major oncological surgery, but postoperative outcomes after liver resection for primary and secondary liver tumours in the elderly are yet to be addressed in the Netherlands¹⁰⁻¹².

The aim of this study was to assess the proportion of patients who were between 70 and 80 years old (septuagenarians) and 80 years or older (octogenarians) who underwent liver resection for primary and secondary liver tumours over the years, to compare postoperative outcomes between older and younger patients and to explore risk factors for 30-day major morbidity and 30-day mortality in patients who undergo liver resection for primary and secondary liver tumours.

Methods

This nationwide population-based study was performed in the Netherlands. A volume requirement of liver resections per hospital per year is required in order to perform liver surgery in the Netherlands. Data were collected from the DHBA, a mandatory audit in which all hospitals in the Netherlands performing liver surgery register all liver resections. Data verification was performed to provide insight in completeness and accuracy of the DHBA when compared to the Dutch Cancer Registry². No ethical approval was needed under Dutch law as the DHBA is part of the Dutch Inspectorate of health care and the dataset is anonymised as described in earlier studies with data from the DHBA¹³⁻¹⁵.

Patient selection

All patients who underwent liver resection for primary and secondary liver tumours between the 1st of January 2014 and the 31st of December 2019 in the Netherlands were included if they were registered in the DHBA before the 22nd of March 2020. Patients were excluded if no date of birth, date of surgery or type of tumour could be obtained. Patients who underwent simultaneous resection of the primary tumour and liver metastases or thermal ablation only were excluded from the study.

Tumour types registered in the DHBA include: CRLM, other liver metastases (LM), HCC and biliary cancer. Bile duct cancer types registered in the DHBA are perihilar cholangiocarcinoma (pCC), intrahepatic cholangiocarcinoma (iCC) and gallbladder cancer. Registration of cholangiocarcinoma patients started in 2015 with 2016 as first full registration year. Therefore, analysis of this group were included from 2016 onwards.

Groups for analysis were based on age and were stratified as: patients of 70 years or younger, septuagenarian patients (between 70 and 80 years old) and octogenarian patients (80 years or older).

Variables

Variables used were sex, age, American Society of Anesthesiologist (ASA) classification, Body Mass Index (BMI), comorbidity scores classified according to the Charlson Comorbidity Score (CCI), histopathological classification of liver parenchyma adjacent to tumour tissue, previous liver surgery and diameter of the largest tumour before the initiation of tumour-specific treatment¹⁵. Treatment characteristics included use of preoperative chemotherapy, minor or

major liver resection, and type of hospital where treatment took place which was either a tertiary referral centre or regional hospital. Major liver resection was defined as resection of three or more Couinaud segments¹⁶. As a sensitivity analysis, hospital volume was included in multivariable models³. Annual overall volume was calculated as total number of liver resections per hospital per year and was categorised <20, 20-39, 40-59, 60-79, and >80 procedures³.

Main outcomes

The main outcomes in this study were proportion of septuagenarians and proportion of octogenarians who underwent liver resection for primary and secondary liver tumours every year during the study period and short-term postoperative outcomes in these patients.

Short-term postoperative outcomes consisted of length of stay (shown as median, with interquartile ranges (IQR)), 30-day overall morbidity, 30-day major morbidity and 30-day mortality after liver resection for primary and secondary liver tumours. Major morbidity was defined as a complication grade 3a or higher according the Clavien-Dindo classification, within 30 days of the surgical procedure¹⁷. Mortality was defined as death during hospitalization in the primary admission or within 30 days of the surgical procedure. Specific surgical complications (bile leakage, postoperative haemorrhage, liver failure defined according the International Study Group of Liver Surgery, deep and superficial surgical site infections) and cardiopulmonary complications were secondary outcomes¹⁸.

Statistical analysis

Baseline characteristics were compared between groups using the Chi-square test or Fisher exact test as appropriate for categorical variables. Continuous variables were compared using independent one-way ANOVA or Kruskal Wallis test as appropriate.

Trends in proportion of septuagenarians and octogenarians who underwent liver resection for primary and secondary liver tumours over the years was assessed using univariable logistic regression. This proportion analysis was performed from 2014 to 2019 for CRLM, other LM and HCC. The proportion analysis was performed from 2016 to 2019 for biliary cancer patients.

The association of variables with 30-day major morbidity and 30-day mortality was assessed using univariable and multivariable logistic regression. For all multivariable analyses a two-step method was undertaken. All variables were tested in a univariable models per outcome variable. If a significant association was observed ($P < 0.1$, Wald test) the variable was entered in the multivariable model. Statistical significance was defined as a two-sided p-value < 0.05 in the

multivariable model. Outcomes were adjusted odds ratios (aOR) and 95% confidence intervals (CI).

Multicollinearity was assessed using the Variance Inflation Factor (VIF). A VIF of 2 or lower indicated that there was no multicollinearity. All analyses were performed in R version 3.2.2® (R Core Team (2018): A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

Results

In total, 6587 patients were included of whom 4023 (58.9%) were 70 years or younger, 2135 (32.4%) were septuagenarians and 429 (6.5%) were octogenarians. Of the 6587 patients, 4759 (72.2%) underwent liver resection for CRLM, 479 (6.5%) for other liver metastases, 738 (11.2%) for HCC and 611 (9.3%) for biliary cancer.

Overall 30-day major morbidity was 10.0% and 30-day mortality was 2.5%. After CRLM resection, overall 30-day major morbidity was 7.8% and 30-day mortality was 1.6%. After other LM resection, overall 30-day major morbidity was 9.2% and 30-day mortality was 1.7%. After HCC resection, overall 30-day major morbidity was 14.1% and 30-day mortality was 5.1%. After bile duct and gallbladder carcinoma, overall 30-day major morbidity was 22.3% and 30-day mortality was 7.4%. Subgroup analysis for perihilar cholangiocarcinoma resection showed overall 30-day major morbidity was 32.4% and 30-day mortality was 11.1%. Subgroup analysis for intrahepatic cholangiocarcinoma resection showed overall 30-day major morbidity was 19.6% and 30-day mortality was 6.5%. Subgroup analysis for gallbladder carcinoma resection showed overall 30-day major morbidity was 16.0% and 30-day mortality was 4.7%.

Population characteristics

Septuagenarians and octogenarians were more often male, had more often CCI of 2 or higher, more often ASA classification 3 or higher and had lower BMI (table 1). Also, older patients received preoperative chemotherapy less frequently, underwent minor liver resection and laparoscopic liver resection more often and were less frequently treated in a tertiary referral centre. After subgroup analysis for CRLM, other liver metastases, HCC and bile duct and gallbladder carcinoma comparable differences between age groups were observed (supplementary table 1a,1b,1c,1d).

Table 1. Baseline characteristics stratified for age in patients who underwent liver resection for primary and secondary liver tumours between 2014 and 2019 in the Netherlands.

Factor	Age <70 N = 4023	Age 70-80 N = 2135	Age ≥80 N = 429	P-value
Sex				<0.001
Male	2319 (58)	1413 (66)	280 (65)	
Female	1696 (42)	716 (34)	146 (34)	
Missing*	8	6	3	
Charlson Comorbidity Index (CCI)				<0.001
0 / 1	3124 (78)	1338 (63)	263 (61)	
2+	899 (22)	797 (37)	166 (39)	
American Society of Anesthesiology (ASA) classification				<0.001
I / II	3229 (81)	1452 (69)	263 (63)	
III+	738 (19)	646 (31)	156 (37)	
Missing*	56	37	10	
Body Mass Index (BMI) Mean (sd)	26.3 (4.8)	26.4 (4.2)	25.5 (3.5)	0.002
Liver resection in the past				0.313
No	3267 (82)	1754 (84)	364 (86)	
Yes	691 (18)	342 (16)	58 (14)	
Missing*	65	39	7	
Histological diagnosis of liver parenchyma				0.167
Normal	2348 (71)	1260 (72)	283 (79)	
Steatosis	666 (20)	334 (19)	58 (16)	
Steato-hepatitis	89 (3)	52 (3)	6 (2)	
Cirrhosis	152 (5)	74 (4)	11 (3)	
Sinusoidal dilatation	50 (2)	24 (1)	1 (1)	
Missing*	718	391	70	
Type of tumour				<0.001
CRLM	2849 (71)	1570 (74)	340 (79)	
Other liver metastases	357 (9)	107 (5)	15 (4)	
HCC	451 (11)	242 (11)	45 (11)	
Biliary cancer	366 (9)	216 (10)	29 (7)	
Preoperative chemotherapy				<0.001
No	2557 (70)	1537 (80)	364 (90)	
Yes	1073 (30)	394 (20)	41 (10)	
Missing*	393	204	24	
Maximum diameter of largest tumour (mm)				0.027
< 20	913 (29)	502 (29)	79 (21)	
20 – 34	1108 (35)	591 (34)	141 (38)	
35 – 54	634 (20)	353 (20)	96 (26)	
> 55	539 (17)	287 (17)	58 (16)	
Missing*	829	402	55	
Major liver resection				0.001
No	2731 (71)	1480 (73)	334 (80)	
Yes	1126 (29)	560 (28)	83 (20)	
Missing*	166	95	12	
Surgical approach				0.006
Open	2911 (76)	1473 (73)	293 (70)	
Laparoscopic	940 (24)	558 (28)	124 (30)	
Missing	172	104	12	
Type of hospital[∞]				<0.001
Regional hospitals	1659 (41)	1039 (49)	262 (61)	
Tertiary referral centre	2354 (59)	1096 (51)	167 (39)	
Year of surgery				0.058
2014	651 (16)	282 (13)	64 (15)	
2015	670 (17)	320 (15)	69 (16)	

2016	714 (18)	387 (18)	69 (16)
2017	689 (17)	409 (19)	81 (19)
2018	702 (17)	387 (18)	70 (16)
2019	597 (15)	350 (16)	76 (18)

Percentages are shown in brackets and are rounded to the nearest full number. Therefore, they may not add to 100.

* Missing not included in the analysis

∞ Type of hospital: tertiary referral centre are defined as hospitals with highest expertise on oncologic surgery.

Bold p-values indicate statistical significance of $p < 0.050$.

Proportion of elderly patients over the years

Overall number of liver resections for primary and secondary liver tumours performed in the Netherlands did not change over the study period with 997 resections in 2014 and 1023 resections in 2019 (supplementary table 4). For biliary cancer, HCC, CRLM and other liver metastases, 35.4%, 32.8%, 33.0% and 22.3% of the patients respectively were septuagenarians (figure 1). These groups consisted of octogenarians for 4.7%, 6.1%, 7.1% and 3.1%, respectively.

For all tumour types combined, the proportion of patients who were younger than 70 years old decreased over time (aOR 0.95, CI: 0.92 – 0.98, $p < 0.001$). The proportion of septuagenarians for all tumour types combined increased (aOR 1.06, CI: 1.02 – 1.09, $p < 0.001$) while the proportion of octogenarians did not change (aOR 1.02, CI: 0.96 – 1.08, $p = 0.571$) (supplementary table 3, supplementary figure 1, 2 & 3).

The proportion of patients younger than 70 years old who underwent liver resection for CRLM decreased (aOR 0.96, CI: 0.93 – 1.00, $p = 0.033$). The proportion of septuagenarians who were resected for CRLM increased (aOR 1.04, CI: 1.01 – 1.08, $p = 0.025$) while the proportion of octogenarians did not change (aOR 1.00, CI: 0.94 – 1.07, $p = 0.953$).

The proportion of patients who were younger than 70 years old who underwent liver resection for HCC decreased (aOR 0.87, CI: 0.80 – 0.94, $p = 0.001$). The proportion of septuagenarians who underwent liver resection for HCC increased (aOR 1.11, CI: 1.01 – 1.21, $p = 0.024$) and the proportion of octogenarians also increased (aOR 1.18, CI: 0.01 – 1.40, $p = 0.049$). For other liver metastases and bile duct and gallbladder carcinoma, no statistically significant differences were observed regarding the proportion of patients in the different age groups

Figure 1. Percentage of patients of 70-80 years old and 80 years or older stratified for tumour type who underwent liver resection for primary and secondary liver tumours between 2014 and 2019 in the Netherlands.

Postoperative outcomes

Length of stay was longer in octogenarians (median 7.00 days, IQR 4.00 – 9.00) as compared with septuagenarians (median 6.00 days, IQR 4.00 – 8.00) and patients younger than 70 (median 6.00 days, IQR 5.00 – 10.00, $p < 0.001$) (table 2). Overall 30-day morbidity more frequently occurred in septuagenarians (36.8%) and octogenarians (37.1%) as compared with patients younger than 70 (28.1%, $p < 0.001$). Thirty-day major morbidity more frequently occurred in septuagenarians (11.0%) and octogenarians (11.7%) as compared with patients younger than 70 (9.2%). Thirty-day mortality was significantly higher in septuagenarians (3.5%) and octogenarians (4.1%) as compared to patients younger than 70 (1.9%, $p < 0.001$).

Table 2. Postoperative outcomes stratified for age in patients who underwent liver resection for primary and secondary liver tumours between 2014 and 2019 in the Netherlands.

Factor	Age <70	Age 70-79	Age ≥80	P-value
	N = 4023	N = 2135	N = 429	
Bile leakage				0.816
No	3831 (96)	2025 (95)	407 (95)	
Yes	170 (4)	95 (5)	20 (5)	
Missing*	22	15	2	
Postoperative haemorrhage				0.513
No	3630 (99)	1831 (99)	370 (99)	
Yes	31 (1)	20 (1)	5 (1)	
Missing*	362	284	54	
Postoperative liver failure				0.587
No	3906 (98)	2077 (98)	420 (98)	
Yes	95 (2)	46 (2)	7 (2)	
Missing*	22	12	2	
Intra-abdominal infection				0.110
No	3566 (93)	1809 (92)	375 (94)	
Yes	246 (7)	154 (8)	24 (6)	
Missing*	211	172	30	
Surgical site infection				0.327
No	3692 (97)	1888 (96)	384 (96)	
Yes	119 (3)	76 (4)	14 (4)	
Missing*	212	171	31	
Pneumonia				<0.001
No	3637 (95)	1813 (92)	362 (91)	
Yes	177 (5)	152 (8)	37 (9)	
Missing*	209	170	30	
Cardiac complication				<0.001
No	3914 (98)	2020 (95)	395 (92)	
Yes	85 (2)	100 (5)	33 (8)	
Missing*	24	15	1	
Thromboembolic complication				0.015
No	3913 (98)	2051 (97)	418 (98)	
Yes	85 (2)	71 (3)	10 (2)	
Missing*	24	15	1	
Length of stay (median + IQR)	6.00 (4.00 – 8.00)	6.00 (4.00 – 9.00)	7.00 (5.00 – 10.0)	<0.001
Overall 30-day morbidity				<0.001
No	2892 (82)	1349 (63)	270 (63)	
Yes	1131 (28)	786 (37)	159 (37)	
30-day major morbidity				0.049
No	3651 (91)	1901 (89)	379 (88)	
Yes	372 (9)	234 (11)	50 (12)	
30-day mortality				<0.001
No	3947 (98)	2061 (96)	414 (96)	
Yes	76 (2)	74 (4)	15 (4)	

Percentages are shown in brackets and are rounded to the nearest full number. Therefore, they may not add to 100.

*Missing are not included in the analysis.

Major liver resection was defined as resection of at least 3 liver segments.

Postoperative complicated course was defined as a complication after surgery resulting in prolonged hospitalization (>14 days), or reintervention or death as a result of a complication.

Major morbidity was defined as a Clavien-Dindo Grade 3 or higher complication.

Bold p-values indicate statistical significance of $p < 0.050$.

In minor liver resection, overall 30-day morbidity more frequently occurred in septuagenarians (29.0%) and octogenarians (32.9%) as compared with patients younger than 70 (21.1%, $p<0.001$). Thirty-day major morbidity was not different in septuagenarians (6.4%) and octogenarians (8.7%) as compared with patients younger than 70 (6.2%, $p=0.212$). Thirty-day mortality was not different in septuagenarians (1.2%) and octogenarians (1.5%) as compared to patients younger than 70 (0.6%, $p=0.065$).

In major liver resection, overall 30-day morbidity more frequently occurred in septuagenarians (57.0%) and octogenarians (48.2%) as compared with patients younger than 70 (44.8%, $p<0.001$). Thirty-day major morbidity more frequently occurred in septuagenarians (22.7%) and octogenarians (24.1%) as compared with patients younger than 70 (16.8%), $p=0.007$. Thirty-day mortality was significantly higher in septuagenarians (9.5%) and octogenarians (10.8%) as compared to patients younger than 70 (5.0%, $p=0.001$).

Rates of liver-specific complications such as bile leakage, postoperative haemorrhage and liver failure were not statistically different between age groups. Pneumonia more frequently occurred in septuagenarians (7.7%) and octogenarians (9.3%) as compared with patients younger than 70 (4.6%, $p<0.001$). Cardiac complications more often occurred in septuagenarians (4.7%) and octogenarians (7.7%) as compared with patients younger than 70 (2.1%, $p<0.001$).

In a subgroup analysis for tumour type, 30-day major morbidity ($p<0.001$) and 30-day mortality ($p=0.001$) after CRLM resection were 7.3% and 1.0% respectively in patients younger than 70, 8.3% and 2.3% in septuagenarians and 9.7% and 2.6% in octogenarians (supplementary table 2a). In patients younger than 70, the pneumonia rate was 4.3%, this was 7.0% in septuagenarians and 9.6% in octogenarians ($p<0.001$). In patients younger than 70, cardiac complications occurred in 1.6%, this was 4.1% in septuagenarians and 7.6% in octogenarians ($p<0.001$).

In a subgroup analysis for non-colorectal liver metastases, 30-day major morbidity ($p=0.200$) and 30-day mortality ($p=0.263$) were 8.4% and 1.4% respectively in patients younger than 70, 10.3% and 2.8% in septuagenarians and 20.0% and 0.0% in octogenarians (supplementary table 2b). In patients younger than 70, cardiac complications occurred in 1.4%, this was 6.5% in septuagenarians and 7.1% in octogenarians ($p=0.010$).

In a subgroup analysis for HCC, 30-day major morbidity ($p=0.348$) and 30-day mortality ($p=0.203$) were 12.6% and 4.0% respectively in patients younger than 70, 16.1% and 7.0% in septuagenarians and 17.8% and 6.7% in octogenarians (supplementary table 2c).

In a subgroup analysis for bile duct and gallbladder carcinoma, 30-day major morbidity ($p=0.484$) and 30-day mortality (0.599) were 20.8% and 6.6% respectively in patients younger than 70, 25.0% and 8.3% in septuagenarians and 20.7% and 10.3% in octogenarians (supplementary table 2d). In patients younger than 70, the pneumonia rate was 4.2%, this was 9.6% in septuagenarians and 12.5% in octogenarians ($p=0.026$).

Association of patient demographics, disease burden and operative characteristics with postoperative outcomes

Age 80 years or older (aOR 1.42, CI: 1.00 – 2.00, $p=0.045$), ASA classification 3 or higher (aOR 1.52, CI: 1.25 – 1.85, $p<0.001$) histopathological steato-hepatitis (aOR 2.16, CI: 1.33 – 3.39, $p=0.001$), resection of biliary cancer (aOR 2.98, CI: 2.21 – 4.00, $p<0.001$), and major liver resection (aOR 2.45, CI: 2.01 – 2.98, $p<0.001$) were associated with higher 30-day major morbidity (table 3). Female sex (aOR 0.66, CI: 0.55 – 0.81, $p<0.001$) and laparoscopic liver resection (aOR 0.61, CI: 0.47 – 0.78, $p<0.001$) were associated with lower 30-day major morbidity. No influence of hospital volume on 30-day major morbidity was observed (data not shown).

Age between 70 and 80 (aOR 1.78, CI: 1.25 – 2.55, $p=0.001$), age 80 years or older (aOR 2.19, CI: 1.13 – 3.00, $p=0.012$), ASA classification 3 or higher (aOR 2.39, CI: 1.69 – 3.37, $p<0.001$), histopathological steato-hepatitis (aOR 2.86, CI: 1.19 – 6.07, $p=0.011$), histopathological liver cirrhosis (aOR 2.76, CI: 1.37 – 5.34, $p=0.003$), resection of biliary cancer (aOR 3.21, CI: 1.85 – 5.55, $p<0.001$) and major liver resection (aOR 5.92, CI: 3.97 – 9.01, $p<0.001$) were associated with higher 30-day mortality (table 4). Female sex (aOR 0.65, CI: 0.44 – 0.94, $p=0.023$) was associated with lower 30-day mortality. No influence of hospital volume on 30-day mortality was observed (data not shown).

Table 3. Univariable and multivariable logistic model of patient, tumour and surgical factors associated with 30-day major morbidity in patients who underwent liver resection for primary and secondary liver tumours between 2014 and 2019 in the Netherlands.

Factor	Univariable analysis				Multivariable analysis		
	N	OR	CI (95%)	P-value	aOR	CI (95%)	P-value
Sex				<0.001			<0.001
Male	4012	1			1		
Female	2558	0.70	0.59 – 0.83		0.66	0.55 – 0.81	
Missing*	17						
Age in years				0.051			0.049
<70	4023	1			1		
70-80	2135	1.21	1.02 – 1.44	0.032	1.13	0.93 – 1.37	0.202
≥80	429	1.29	0.94 – 1.76	0.106	1.42	1.00 – 2.00	0.045
Charlson Comorbidity Index (CCI)				0.004			0.169
0 / 1	4725	1			1		
2+	1862	1.29	1.08 – 1.53		1.15	0.94 – 1.39	
Body Mass Index		1.00	0.98 – 1.02	0.933			
American Society of Anesthesiology (ASA) classification				<0.001			<0.001
I / II	4944	1			1		
III+	1540	1.66	1.39 – 1.97		1.52	1.25 – 1.85	
Missing*	103						
History of liver resection				0.711			
No	5385	1					
Yes	1091	1.04	0.84 – 1.28				
Missing*	111						
Histopathological liver disease				0.001			0.010
Normal	3891	1			1		
Steatosis	1058	1.25	1.00 – 1.55	0.050	1.26	0.99 – 1.58	0.054
Steato-hepatitis	147	2.23	1.42 – 3.39	<0.001	2.16	1.33 – 3.39	0.001
Cirrhosis	237	1.72	1.16 – 2.47	0.005	1.39	0.89 – 2.14	0.140
Sinusoidal dilatation	75	2.08	1.09 – 3.70	0.018	1.71	0.86 – 3.15	0.103
Missing	1179	1.00	0.79 – 1.24	0.938	0.95	0.71 – 1.25	0.703
Type of tumour				<0.001			<0.001
CRLM	4759	1			1		
Other LM	479	1.19	0.85 – 1.64	0.291	1.27	0.88 – 1.78	0.186
HCC	738	1.93	1.53 – 2.42	<0.001	1.22	0.92 – 1.62	0.169
Biliary cancer	611	3.38	2.71 – 4.19	<0.001	2.98	2.21 – 4.00	<0.001
Preoperative chemotherapy				0.621			
No	4458	1					
Yes	1508	0.81	0.75 – 1.11	0.377			
Missing	621	0.92	0.69 – 1.22	0.585			
Maximum diameter of largest tumour (mm)				<0.001			0.204
< 20	1494	1			1		
20-34	1840	1.08	0.81 – 1.40	0.572	0.98	0.74 – 1.29	0.871
35-54	1083	1.5	1.13 – 1.98	0.050	1.14	0.85 – 1.54	0.381
> 55	884	2.04	1.55 – 2.69	<0.001	1.20	0.88 – 1.63	0.249
Missing	1286	2.13	1.66 – 2.75	<0.001	1.32	0.99 – 1.77	0.071
Major liver resection				<0.001			<0.001
No	4545	1			1		
Yes	1769	3.42	2.89 – 4.04	<0.001	2.45	2.01 – 2.98	<0.001

Missing*	273	1.66	1.08 – 2.46	0.015	1.12	0.16 – 4.75	0.887
Surgical approach				<0.001			<0.001
Open	4677	1			1		
Laparoscopic	1622	0.44	0.36 – 0.55		0.61	0.47 – 0.78	
Missing*	288						
Type of hospital[∞]				<0.001			0.217
Regional hospitals	2960	1			1		
Tertiary referral hospital	3627	1.74	1.47 – 2.07		1.14	0.93 – 1.39	

* Missing not included in analyses based on relatively small group

(chronic) hepatitis or liver fibrosis

[∞] Type of hospital: tertiary referral centre are defined as hospitals with highest expertise on oncologic surgery

Bold p-values indicate statistical significance of p<0.050

Table 4. Univariable and multivariable logistic model of patient, tumour and surgical factors associated with 30-day mortality in patients who underwent liver resection for primary and secondary liver tumours between 2014 and 2019 in the Netherlands.

Factor	Univariable analysis				Multivariable analysis		
	N	OR	CI (95%)	P-value	aOR	CI (95%)	P-value
Sex				0.009			0.023
Male	4012	1			1		
Female	2558	0.64	0.45 – 0.89		0.65	0.44 – 0.94	
Missing*	17						
Age in years				<0.001			0.001
<70	4023	1			1		
70-80	2135	1.86	1.35 – 2.58	<0.001	1.78	1.25 – 2.55	0.001
≥80	429	1.88	1.03 – 3.21	0.028	2.19	1.13 – 4.00	0.012
Charlson Comorbidity Index (CCI)				0.349			
0 / 1	4725	1					
2+	1862	1.17	0.83 – 1.63				
Body Mass Index		1.01	0.98 – 1.05	0.404			
American Society of Anesthesiology (ASA) classification				<0.001			<0.001
I / II	4944	1			1		
III+	1540	2.90	2.12 – 3.96		2.39	1.69 – 3.37	
Missing*	103						
History of liver resection				0.500			
No	5385	1					
Yes	1091	1.15	0.76 – 1.68				
Missing*	111						
Histopathological liver disease				<0.001			0.015
Normal	3891	1			1		
Steatosis	1058	1.43	0.92 – 2.16	0.103	1.45	0.91 – 2.26	0.103
Steato-hepatitis	147	2.81	1.23 – 5.60	0.007	2.86	1.19 – 6.07	0.011
Cirrhosis	237	3.54	1.97 – 6.00	<0.001	2.76	1.37 – 5.34	0.003
Sinusoidal dilatation	75	3.49	1.20 – 8.09	<0.001	2.39	0.75 – 6.01	0.096
Missing	1179	1.19	0.76 – 1.82	0.440	1.23	0.71 – 2.04	0.433
Type of tumour				<0.001			<0.001
CRLM	4759	1			1		
Other LM	479	1.07	0.47 – 2.11	0.847	1.33	0.57 – 2.75	0.465
HCC	738	3.44	2.28 – 5.09	<0.001	1.51	0.87 – 2.49	0.145
Biliary cancer	611	5.04	3.42 – 7.33	<0.001	3.21	1.85 – 5.55	<0.001
Preoperative chemotherapy				0.029			0.003
No	4458	1			1		
Yes	1508	0.75	0.50 – 1.10	0.154	1.06	0.66 – 1.67	0.817

Missing	621	0.45	0.20 – 0.87	0.031	0.10	0.02 – 0.55	0.023
Maximum diameter of largest tumour (mm)				<0.001			0.121
< 20	1494	1			1		
20-34	1840	1.31	0.73 – 2.42	0.367	1.24	0.67 – 2.40	0.352
35-54	1083	2.18	1.21 – 4.02	0.011	1.53	0.81 – 2.97	0.124
> 55	884	3.18	1.80 – 5.80	<0.001	1.46	0.77 – 2.85	0.110
Missing	1286	3.80	2.27 – 6.68	<0.001	2.12	1.17 – 4.02	<0.001
Major liver resection				<0.001			<0.001
No	4545	1			1		
Yes	1769	8.05	5.65 – 11.7	<0.001	5.92	3.97 – 9.01	<0.001
Missing*	273	1.12	0.76 – 1.45	0.567	1.03	0.82 – 1.35	0.631
Surgical approach				<0.001			0.159
Open	4677	1			1		
Laparoscopic	1622	0.39	0.23 – 0.61		0.69	0.40 – 1.15	
Missing*	288						
Type of hospital[∞]				<0.001			0.847
Regional hospitals	2960	1			1		
Tertiary referral hospital	3627	2.08	1.39 – 2.96		1.02	0.63 – 1.36	

* Missing not included in analyses based on relatively small group

[∞] Type of hospital: tertiary referral centre are defined as hospitals with highest expertise on oncologic surgery

Bold p-values indicate statistical significance of $p < 0.050$.

Discussion

In this nationwide population-based study postoperative outcomes, including 30-day overall morbidity, 30-day major morbidity, 30-day mortality and length of stay, were all worse in septuagenarians and octogenarians compared to patients who were younger than 70 years old. Not liver-specific complications, but cardiopulmonary complications were mainly responsible. This association remained significant after correction for patient demographics, disease burden and operative characteristics.

Overall number of liver resections for primary and secondary liver tumours did not increase during the study period in the Netherlands and an increase in the proportion of older patients resected 2014 to 2019 was attributed to a decrease in patients who were younger than 70 years. Aging of the Dutch population has been described since 2000 and could induce an increase of primary and secondary liver tumours at older age which has been observed in this study¹⁹. This is comparable to earlier studies which stated that an increase in patients undergoing liver resection would be observed over time in CRLM, HCC and cholangiocarcinoma patients^{9,20-22}. Recent studies showed a significant increase of several types of primary and secondary liver tumours^{23,24}. Stabilization of the number of liver resections could have several reasons such as other treatment options for primary and secondary liver tumours such as definitive chemotherapy, thermal ablation, stereotactic radiotherapy or liver transplantation

which are not included in the DHBA might be increasingly used. Another explanation might be that colorectal cancer is treated at an earlier stage in our country due to the nationwide screening for colorectal cancer²⁵. This could have decreased the incidence of CRLM in the Netherlands and could have attributed to the stabilization of liver resection. Future studies will have to show whether there is a shift from surgery to other definitive treatments in the Netherlands for primary and secondary liver tumours and what this means for postoperative and oncological outcomes.

The more complicated course in elderly patients is concordant with two studies from the UK which addressed postoperative outcomes after CRLM resection in elderly patients, and found comparable overall morbidity of 49% and mortality of 3% in the elderly patient^{6,7}. A large cohort from the UK confirmed that age is associated with worse postoperative outcomes²⁶. In Australia, a report showed that octogenarians had postoperative major morbidity of 27%⁵. It was described that elderly patients may benefit more from laparoscopic resection of CRLM with better postoperative outcomes^{27,28}. In the present study the same beneficial effect of minimally invasive surgery was observed in elderly patients. As expected, cardiopulmonary complications have occurred more often in patients who underwent liver resection in the current study, while no differences were observed regarding liver-specific complications. This implies that patients may benefit from additional perioperative physiotherapy focusing on specifically breathing exercises to decrease cardiopulmonary complications²⁹. The UK studies showed that no differences in survival was seen between younger and older patients²⁶. However, the current study did not assess oncological outcomes. With respect to short-term postoperative outcomes, resection of primary and secondary liver tumours can be performed in elderly patients and is safe as demonstrated in the current study. Laparoscopic liver resection could improve postoperative outcomes as well as preoperative and postoperative optimization of frail patients. Several options such as comprehensive cardiopulmonary screening and possibilities regarding prehabilitation could be explored to achieve better postoperative outcomes in elderly patients³⁰.

In accordance with literature, postoperative outcomes observed after liver resection for HCC and biliary cancer are significantly worse in elderly patients^{8,31-38}. Long-term survival after resection of HCC or biliary cancer was not different in elderly patients^{36,38-40}. The nationwide data from this study and previous reports show that liver resection of primary and secondary liver tumours in elderly patients can be performed with relatively low mortality. Preoperative patient selection is key, in particular in HCC and biliary cancer patients.

Several characteristics such as preoperative higher age, ASA classification, histopathological liver diseases, biliary cancer and major liver resection were independently associated with 30-day major morbidity and 30-day mortality. These risk factors for major morbidity and mortality can be used by surgeons treating patients with primary and secondary liver tumours. This study may help to counsel and select patients before resection and to discuss aforementioned strategies to reduce complication rates in elderly patients.

This study from a national surgical database has several limitations including the retrospective design which inherently induces selection and indication bias that could have influenced the results. In this kind of auditing data, several important operative and postoperative data such as exact tumour location, intraoperative complications and detailed operative characteristics are lacking. Ninety-day postoperative outcomes and oncological outcomes are lacking and could influence the results and conclusions drawn from the present study.

In conclusion, this study shows higher 30-day major morbidity and 30-day mortality in elderly patients mainly due to non-surgical cardiopulmonary complications. Therefore, perioperative patient optimization should be stressed to improve postoperative outcomes in the elderly patient.

References

1. Pericleous M, Khan SA. Epidemiology of HPB malignancy in the elderly. *Eur J Surg Oncol*. 2021;47(3 Pt A):503-513.
2. van der Werf LR, Kok NFM, Buis CI, Grunhagen DJ, Hoogwater FJH, Swijnenburg RJ, et al. Implementation and first results of a mandatory, nationwide audit on liver surgery. *HPB (Oxford)*. 2019;21(10):1400-1410.
3. Olthof PB, Elfrink AKE, Marra E, Belt EJT, van den Boezem PB, Bosscha K, et al. Volume-outcome relationship of liver surgery: a nationwide analysis. *Br J Surg*. 2020;107(7):917-926.
4. Neuwirth MG, Bierema C, Sinnamon AJ, Fraker DL, Kelz RR, Roses RE, et al. Trends in major upper abdominal surgery for cancer in octogenarians: Has there been a change in patient selection? *Cancer*. 2018;124(1):125-135.
5. Riffat F, Chu F, Morris DL. Liver resection in octogenarians. *HPB (Oxford)*. 2006;8(3):206-210.
6. Tufo A, Dunne DFJ, Manu N, Joshi H, Lacasia C, Jones L, et al. Hepatectomy for octogenarians with colorectal liver metastasis in the era of enhanced recovery. *Eur J Surg Oncol*. 2018;44(7):1040-1047.
7. Tufo A, Dunne DF, Manu N, Lacasia C, Jones L, de Liguori Carino N, et al. Changing outlook for colorectal liver metastasis resection in the elderly. *Eur J Surg Oncol*. 2019;45(4):635-643.
8. Sanyal S, Kron P, Wylie N, Hildalgo E, Toogood GJ, Lodge P. Outcomes of liver resection for hepatocellular carcinoma in octogenarians. *HPB (Oxford)*. 2020;22(9):1324-1329.
9. Zhou Y, Zhang X, Zhang Z, Liu X, Wu L, Li Y, et al. Hepatectomy in elderly patients: does age matter? *World J Surg*. 2013;37(12):2899-2910.
10. van Rooijen S, Carli F, Dalton S, Thomas G, Bojesen R, Le Guen M, et al. Multimodal prehabilitation in colorectal cancer patients to improve functional capacity and reduce postoperative complications: the first international randomized controlled trial for multimodal prehabilitation. *BMC Cancer*. 2019;19(1):98.
11. van Rooijen SJ, Molenaar CJL, Schep G, van Lieshout R, Beijer S, Dubbers R, et al. Making Patients Fit for Surgery: Introducing a Four Pillar Multimodal Prehabilitation Program in Colorectal Cancer. *Am J Phys Med Rehabil*. 2019;98(10):888-896.
12. Berkel AEM, Bongers BC, van Kamp MS, Kotte H, Weltevreden P, de Jongh FHC, et al. The effects of prehabilitation versus usual care to reduce postoperative complications in high-risk patients with colorectal cancer or dysplasia scheduled for elective colorectal resection: study protocol of a randomized controlled trial. *BMC Gastroenterol*. 2018;18(1):29.
13. Elfrink AKE, Kok NFM, van der Werf LR, Krul MF, Marra E, Wouters M, et al. Population-based study on practice variation regarding preoperative systemic chemotherapy in patients with colorectal liver metastases and impact on short-term outcomes. *Eur J Surg Oncol*. 2020;46(9):1742-1755.
14. Elfrink AKE, Pool M, van der Werf LR, Marra E, Burgmans MC, Meijerink MR, et al. Preoperative imaging for colorectal liver metastases: a nationwide population-based study. *BJS Open*. 2020;4(4):605-621.
15. Elfrink AKE, van Zwet EW, Swijnenburg RJ, den Dulk M, van den Boezem PB, Mieog JSD, et al. Case-mix adjustment to compare nationwide hospital performances after resection of colorectal liver metastases. *Eur J Surg Oncol*. 2021;47(3 Pt B):649-659.
16. Pang YY. The Brisbane 2000 terminology of liver anatomy and resections. *HPB 2000*; 2:333-39. *HPB (Oxford)*. 2002;4(2):99; author reply 99-100.
17. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg*. 2009;250(2):187-196.
18. Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). *Surgery*. 2011;149(5):713-724.
19. CBS. Geographical and population overview of the Netherlands. 2019.
20. Gonzalez HD, Figueras J. Practical questions in liver metastases of colorectal cancer: general principles of treatment. *HPB (Oxford)*. 2007;9(4):251-258.
21. Papis D, Vagliasindi A, Maida P. Hepatobiliary and pancreatic surgery in the elderly: Current status. *Ann Hepatobiliary Pancreat Surg*. 2020;24(1):1-5.

22. Akashi K, Ebata T, Mizuno T, Yokoyama Y, Igami T, Yamaguchi J, et al. Surgery for perihilar cholangiocarcinoma from a viewpoint of age: Is it beneficial to octogenarians in an aging society? *Surgery*. 2018;164(5):1023-1029.
23. van der Geest LG, Lam-Boer J, Koopman M, Verhoef C, Elferink MA, de Wilt JH. Nationwide trends in incidence, treatment and survival of colorectal cancer patients with synchronous metastases. *Clin Exp Metastasis*. 2015;32(5):457-465.
24. Reinders MTM, van Meer S, Burgmans MC, de Jong KP, Klumpen HJ, de Man RA, et al. Trends in incidence, diagnosis, treatment and survival of hepatocellular carcinoma in a low-incidence country: Data from the Netherlands in the period 2009-2016. *Eur J Cancer*. 2020;137:214-223.
25. Toes-Zoutendijk E, Kooyker AI, Elferink MA, Spaander MCW, Dekker E, Koning HJ, et al. Stage distribution of screen-detected colorectal cancers in the Netherlands. *Gut*. 2018;67(9):1745-1746.
26. Vallance AE, Young AL, Kuryba A, Braun M, Hill J, Jayne DG, et al. The impact of advancing age on incidence of hepatectomy and post-operative outcomes in patients with colorectal cancer liver metastases: a population-based cohort study. *HPB (Oxford)*. 2019;21(2):167-174.
27. Zarzavadjian Le Bian A, Tabchouri N, Bennamoun M, Louvet C, Tubbax C, Sarran A, et al. After laparoscopic liver resection for colorectal liver metastases, age does not influence morbidity. *Surg Endosc*. 2019;33(11):3704-3710.
28. Wabitsch S, Haber PK, Ekwelle N, Kastner A, Krenzien F, Benzing C, et al. Minimally Invasive Liver Surgery in Elderly Patients-A Single-Center Experience. *J Surg Res*. 2019;239:92-97.
29. Wang B, Shelat VG, Chow JLL, Huey TCW, Low JK, Woon WWL, et al. Prehabilitation Program Improves Outcomes of Patients Undergoing Elective Liver Resection. *J Surg Res*. 2020;251:119-125.
30. Snowden CP, Prentis J, Jacques B, Anderson H, Manas D, Jones D, et al. Cardiorespiratory fitness predicts mortality and hospital length of stay after major elective surgery in older people. *Ann Surg*. 2013;257(6):999-1004.
31. Franken LC, Schreuder AM, Roos E, van Dieren S, Busch OR, Besselink MG, et al. Morbidity and mortality after major liver resection in patients with perihilar cholangiocarcinoma: A systematic review and meta-analysis. *Surgery*. 2019;165(5):918-928.
32. Hoffmann K, Hinz U, Stravodimos C, Knoblich T, Schon MR, Buchler MW, et al. Risk assessment for liver resection. *Surgery*. 2018;164(5):998-1005.
33. Famularo S, Donadon M, Cipriani F, Ardito F, Carissimi F, Perri P, et al. Hepatocellular carcinoma surgical and oncological trends in a national multicentric population: the HERCOLES experience. *Updates Surg*. 2020;72(2):399-411.
34. Wu H, Xing H, Liang L, Huang B, Li C, Lau WY, et al. Real-world role of performance status in surgical resection for hepatocellular carcinoma: A multicenter study. *Eur J Surg Oncol*. 2019;45(12):2360-2368.
35. Olthof PB, Miyasaka M, Koerkamp BG, Wiggers JK, Jarnagin WR, Noji T, et al. A comparison of treatment and outcomes of perihilar cholangiocarcinoma between Eastern and Western centers. *HPB (Oxford)*. 2019;21(3):345-351.
36. Bartsch F, Baumgart J, Tripke V, Hoppe-Lotichius M, Heinrich S, Lang H. Resection of intrahepatic cholangiocarcinoma in elderly patients - is it reasonable? *BMC Surg*. 2019;19(1):157.
37. Serenari M, Zanello M, Schadde E, Toschi E, Ratti F, Gringeri E, et al. Importance of primary indication and liver function between stages: results of a multicenter Italian audit of ALPPS 2012-2014. *HPB (Oxford)*. 2016;18(5):419-427.
38. Vitale A, Spolverato G, Bagante F, Gani F, Popescu I, Marques HP, et al. A multi-institutional analysis of elderly patients undergoing a liver resection for intrahepatic cholangiocarcinoma. *J Surg Oncol*. 2016;113(4):420-426.
39. Cucchetti A, Sposito C, Pinna AD, Citterio D, Ercolani G, Flores M, et al. Effect of age on survival in patients undergoing resection of hepatocellular carcinoma. *Br J Surg*. 2016;103(2):e93-99.
40. Gomez-Gavara C, Doussot A, Lim C, Salloum C, Lahat E, Fuks D, et al. Impact of intraoperative blood transfusion on short and long term outcomes after curative hepatectomy for intrahepatic cholangiocarcinoma: a propensity score matching analysis by the AFC-IHCC study group. *HPB (Oxford)*. 2017;19(5):411-420.

Supplementary material

Supplementary figure 1. Trends in percentage of patients who were below 70 years old stratified for tumour type who underwent liver resection for primary and secondary liver tumours between 2014 and 2019 in the Netherlands.

Supplementary figure 2. Trends in percentage of patients who were 70-80 years old stratified for tumour type who underwent liver resection between for primary and secondary liver tumours between 2014 and 2019 in the Netherlands.

Supplementary figure 3. Trends in percentage of patients of 80 years or older stratified for tumour type who underwent liver resection between for primary and secondary liver tumours between 2014 and 2019 in the Netherlands.

Supplementary table 1a. Baseline characteristics stratified for age in patients who underwent liver resection for colorectal liver metastases between 2014 and 2019 in the Netherlands.

Factor		Age <70	Age 70-80	Age ≥80	P-value
		N = 2849	N = 1570	N = 340	
Sex					<0.001
	Male	1754 (62)	1067 (68)	223 (66)	
	Female	1089 (38)	497 (32)	114 (34)	
	Missing*	6	6	3	
Charlson Comorbidity Index (CCI)					<0.001
	0 / 1	2282 (80)	1035 (66)	209 (62)	
	2+	567 (20)	535 (34)	131 (39)	
American Society of Anesthesiology (ASA) classification					<0.001
	I / II	2347 (84)	1113 (72)	209 (63)	
	III+	450 (16)	424 (28)	123 (37)	
	Missing*	52	33	8	
Body Mass Index (BMI)	Mean (sd)	26.3 (4.7)	26.3 (4.2)	25.6 (3.5)	0.008
Liver resection in the past					0.057
	No	2203 (78)	1231 (80)	279 (84)	
	Yes	609 (22)	307 (20)	55 (16)	
	Missing*	37	32	6	
Histological diagnosis of liver parenchyma					0.218
	Normal	1796 (75)	1003 (76)	234 (82)	
	Steatosis	485 (20)	265 (20)	45 (16)	
	Steato-hepatitis	56 (2)	24 (2)	3 (1)	
	Cirrhosis	20 (1)	16 (1)	2 (1)	
	Sinusoidal dilatation	35 (2)	18 (1)	1 (0)	
	Missing*	457	244	55	
Preoperative chemotherapy					<0.001
	No	1699 (63)	1105 (74)	291 (88)	
	Yes	980 (37)	380 (26)	39 (12)	
	Missing*	170	85	10	
Maximum diameter of largest tumour (mm)					0.007
	< 20	740 (30)	422 (31)	71 (23)	
	20 – 34	924 (38)	503 (37)	121 (39)	
	35 – 54	475 (19)	269 (20)	86 (28)	
	> 55	306 (13)	163 (12)	30 (10)	
	Missing*	404	213	32	
Major liver resection					0.006
	No	2148 (75)	1218 (78)	281 (83)	
	Yes	701 (25)	352 (22)	59 (17)	
Surgical approach					0.011
	Open	2131 (75)	1125 (72)	234 (69)	
	Laparoscopic	708 (25)	439 (28)	105 (31)	
	Missing*	10	6	1	
Type of hospital[∞]					<0.001
	Regional hospitals	1458 (51)	919 (59)	235 (69)	
	Tertiary referral centre	1391 (49)	651 (42)	105 (31)	
Year of surgery					0.163
	2014	471 (17)	217 (14)	53 (16)	
	2015	488 (17)	248 (16)	57 (17)	
	2016	504 (18)	295 (19)	57 (17)	

2017	480 (17)	298 (19)	70 (21)
2018	503 (18)	271 (17)	49 (14)
2019	403 (14)	241 (16)	54 (16)

Percentages are shown in brackets and are rounded to the nearest full number. Therefore, they may not add to 100.

* Missing not included in the analysis

§ History of liver disease containing liver cirrhosis, oesophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis

∞ Type of hospital: tertiary referral centre are defined as hospitals with highest expertise on oncologic surgery.

Supplementary table 1b. Baseline characteristics stratified for age in patients who underwent liver resection for liver metastases which were not of colorectal origin between 2014 and 2019 in the Netherlands.

Factor		Age <70	Age 70-80	Age ≥80	P-value
		N = 357	N = 107	N = 15	
Sex					0.015
	Male	142 (40)	56 (52)	10 (67)	
	Female	213 (60)	51 (48)	5 (33)	
	Missing*	2	0	0	
Charlson Comorbidity Index (CCI)					0.001
	0 / 1	244 (68)	52 (49)	8 (53)	
	2+	113 (32)	55 (51)	7 (47)	
American Society of Anesthesiology (ASA) classification					<0.001
	I / II	293 (83)	67 (63)	9 (69)	
	III+	61 (17)	40 (37)	4 (31)	
	Missing*	3	0	2	
Body Mass Index (BMI)					0.064
	Mean (sd)	26.1 (4.5)	26.4 (4.3)	23.3 (2.6)	
Liver resection in the past					0.265
	No	319 (91)	95 (89)	12 (86)	
	Yes	30 (9)	12 (11)	2 (14)	
	Missing*	8	0	1	
Histological diagnosis of liver parenchyma					0.339
	Normal	247 (79)	82 (86)	13 (100)	
	Steatosis	52 (17)	9 (10)	0 (0)	
	Steato-hepatitis	5 (2)	3 (3)	0 (0)	
	Cirrhosis	6 (2)	0 (0)	0 (0)	
	Sinusoidal dilatation	4 (1)	1 (1)	0 (0)	
	Missing*	43	12	2	
Preoperative chemotherapy					0.009
	No	249 (75)	89 (88)	12 (92)	
	Yes	83 (25)	12 (12)	1 (8)	
	Missing*	25	6	2	
Maximum diameter of largest tumour (mm)					0.413
	< 20	87 (32)	15 (18)	4 (33)	
	20 – 34	64 (24)	22 (26)	3 (25)	
	35 – 54	58 (21)	22 (26)	2 (17)	
	> 55	61 (23)	26 (31)	3 (25)	
	Missing*	86	22	3	
Major liver resection					0.262
	No	280 (78)	91 (85)	13 (87)	
	Yes	77 (22)	16 (15)	2 (13)	
	Missing*	0	0	0	
Surgical approach					0.472
	Open	253 (72)	67 (63)	12 (80)	

	Laparoscopic	101 (29)	39 (37)	3 (20)	
	Missing*	3	1	0	
Type of hospital[∞]					0.004
	Regional hospitals	102 (29)	48 (45)	7 (47)	
	Tertiary referral centre	255 (71)	59 (55)	8 (53)	
Year of surgery					0.648
	2014	64 (18)	13 (12)	4 (27)	
	2015	53 (15)	15 (14)	3 (20)	
	2016	63 (18)	19 (18)	3 (20)	
	2017	61 (17)	16 (15)	0 (0)	
	2018	56 (16)	23 (22)	3 (20)	
	2019	60 (17)	21 (20)	2 (13)	

Percentages are shown in brackets and are rounded to the nearest full number. Therefore, they may not add to 100.

* Missing not included in the analysis

§ History of liver disease containing liver cirrhosis, oesophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis

[∞] Type of hospital: tertiary referral centre are defined as hospitals with highest expertise on oncologic surgery.

Supplementary table 1c. Baseline characteristics stratified for age in patients who underwent liver resection for hepatocellular carcinoma between 2014 and 2019 in the Netherlands.

Factor		Age <70	Age 70- 80	Age ≥80	P- value
		N = 451	N = 242	N = 45	
Sex					<0.001
	Male	261 (58)	181 (75)	29 (64)	
	Female	190 (42)	61 (25)	16 (36)	
	Missing*	0	0	0	
Charlson Comorbidity Index (CCI)					<0.001
	0 / 1	324 (72)	121 (50)	26 (58)	
	2+	127 (28)	121 (50)	19 (42)	
American Society of Anesthesiology (ASA) classification					0.001
	I / II	299 (66)	124 (52)	24 (53)	
	III+	151 (34)	114 (48)	21 (47)	
	Missing*	1	4	0	
Body Mass Index (BMI)	Mean (sd)	26.6 (5.1)	26.9 (4.2)	26.7 (3.2)	0.759
Liver resection in the past					0.377
	No	401 (92)	218 (92)	44 (98)	
	Yes	34 (8)	19 (8)	1 (2)	
	Missing*	16	5	0	
Histological diagnosis of liver parenchyma					0.235
	Normal	173 (41)	99 (43)	23 (51)	
	Steatosis	100 (24)	53 (23)	10 (22)	
	Steato- hepatitis	21 (5)	22 (10)	3 (7)	
	Cirrhosis	120 (28)	53 (23)	9 (20)	
	Sinusoidal dilatation	9 (2)	2 (1)	0 (0)	
	Missing*	28	13	0	
Preoperative chemotherapy					0.683
	No	433 (99)	238 (99)	43 (98)	
	Yes	6 (1)	2 (1)	1 (2)	
	Missing*	12	2	1	
Maximum diameter of largest tumour (mm)					0.252
	< 20	51 (15)	31 (16)	3 (8)	

	20 – 34	75 (22)	37 (20)	9 (23)
	35 – 54	69 (20)	48 (25)	5 (13)
	> 55	144 (43)	74 (39)	23 (58)
	Missing*	112	52	5
Major liver resection				0.154
	No	264 (59)	146 (60)	33 (73)
	Yes	187 (42)	96 (40)	12 (27)
Surgical approach				0.800
	Open	327 (73)	168 (70)	32 (71)
	Laparoscopic	123 (27)	71 (30)	13 (29)
	Missing*	1	3	0
Type of hospital[∞]				<0.001
	Regional hospitals	56 (12)	45 (19)	15 (33)
	Tertiary referral centre	395 (88)	197 (81)	30 (67)
Year of surgery				0.340
	2014	116 (26)	51 (21)	7 (16)
	2015	87 (19)	43 (18)	8 (18)
	2016	60 (13)	26 (11)	3 (7)
	2017	65 (14)	37 (15)	7 (16)
	2018	61 (13)	40 (17)	10 (22)
	2019	62 (14)	45 (17)	10 (22)

Percentages are shown in brackets and are rounded to the nearest full number. Therefore, they may not add to 100.

* Missing not included in the analysis

§ History of liver disease containing liver cirrhosis, oesophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis

∞ Type of hospital: tertiary referral centre are defined as hospitals with highest expertise on oncologic surgery.

Supplementary table 1d. Baseline characteristics stratified for age in patients who underwent liver resection for intrahepatic, perihilar cholangiocarcinoma or gallbladder carcinoma between 2014 and 2019 in the Netherlands.

Factor		Age <70	Age 70-80	Age ≥80	P-value
		N = 366	N = 216	N = 29	
Sex					0.093
	Male	162 (44)	109 (51)	18 (62)	
	Female	204 (56)	107 (49)	11 (38)	
Charlson Comorbidity Index (CCI)					0.001
	0 / 1	274 (75)	130 (60)	20 (69)	
	2+	92 (25)	86 (40)	9 (31)	
American Society of Anesthesiology (ASA) classification					0.015
	I / II	290 (79)	148 (69)	21 (72)	
	III+	76 (21)	58 (27)	8 (28)	
Body Mass Index (BMI) Mean (sd)		25.9 (5.9)	26.4 (4.5)	24.5 (4.5)	0.186
Liver resection in the past					0.089
	No	344 (95)	210 (98)	29 (100)	
	Yes	18 (5)	4 (2)	0 (0)	
	Missing*	4	2	0	
Histological diagnosis of liver parenchyma					0.433
	Normal	132 (75)	76 (81)	13 (81)	
	Steatosis	29 (17)	7 (7)	3 (19)	
	Steato-hepatitis	7 (4)	3 (3)	0 (0)	
	Cirrhosis	6 (3)	5 (5)	0 (0)	

Sinusoidal dilatation	2 (1)	3 (3)	0 (0)	
Missing*	190	122	13	
Indication for resection				0.668
Perihilar cholangiocarcinoma	122 (35)	77 (39)	8 (29)	
Intrahepatic cholangiocarcinoma	92 (27)	54 (27)	7 (25)	
Gallbladder carcinoma / unspecified location	133 (38)	67 (34)	13 (46)	
Missing*	19	18	1	
Preoperative chemotherapy				0.250
No	176 (98)	105 (100)	18 (100)	
Yes	4 (2)	0 (0)	0 (0)	
Missing*	186	111	11	
Maximum diameter of largest tumour (mm)				0.118
< 20	35 (25)	34 (34)	1 (7)	
20 – 34	44 (32)	29 (29)	8 (57)	
35 – 54	32 (23)	14 (14)	3 (21)	
> 55	28 (20)	24 (24)	2 (14)	
Missing*	227	115	15	
Major liver resection				0.108
No	39 (20)	25 (21)	7 (41)	
Yes	161 (80)	96 (79)	10 (59)	
Surgical approach				0.051
Open	200 (96)	113 (93)	15 (83)	
Laparoscopic	8 (4)	9 (7)	3 (17)	
Missing*	158	94	11	
Type of hospital[∞]				0.681
Regional hospitals	43 (12)	27 (13)	5 (17)	
Tertiary referral centre	323 (88)	189 (88)	24 (83)	
Year of surgery				0.248
2014	0 (0)	1 (0)	0 (0)	
2015	42 (12)	14 (7)	1 (3)	
2016	87 (24)	47 (22)	6 (21)	
2017	93 (23)	58 (27)	4 (14)	
2018	82 (22)	53 (25)	8 (28)	
2019	72 (20)	53 (25)	10 (35)	

Percentages are shown in brackets and are rounded to the nearest full number. Therefore, they may not add to 100.

* Missing not included in the analysis

§ History of liver disease containing liver cirrhosis, oesophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis

[∞] Type of hospital: tertiary referral centre are defined as hospitals with highest expertise on oncologic surgery.

Supplementary table 2a. Postoperative outcomes stratified for age in patients who underwent liver resection for colorectal liver metastases between 2014 and 2019 in the Netherlands.

Factor	Age <70	Age 70-79	Age ≥80	P-value
	N = 2849	N = 1570	N = 340	
Bile leakage				0.465
No	2762 (97)	1510 (96)	327 (96)	
Yes	71 (3)	45 (4)	12 (4)	
Missing*	16	15	1	
Postoperative haemorrhage				0.193
No	2621 (99)	1380 (99)	300 (99)	
Yes	14 (1)	12 (1)	4 (1)	
Missing*	214	178	36	
Postoperative liver failure				0.758
No	2787 (98)	1531 (98)	335 (99)	
Yes	45 (2)	27 (2)	4 (1)	
Missing*	17	12	1	

Intra-abdominal infection					0.125
	No	2581 (95)	1368 (93)	302 (95)	
	Yes	139 (5)	97 (7)	17 (5)	
	Missing*	129	105	21	
Surgical site infection					0.255
	No	2659 (98)	1422 (97)	311 (97)	
	Yes	59 (2)	44 (3)	8 (3)	
	Missing*	131	104	21	
Pneumonia					<0.001
	No	2605 (96)	1364 (93)	290 (90)	
	Yes	116 (4)	103 (7)	30 (10)	
	Missing*	128	103	20	
Cardiac complication					<0.001
	No	2787	1492	314	
	Yes	44 (2)	63 (4)	26 (8)	
	Missing*	18	15	0	
Thromboembolic complication					0.032
	No	2786 (98)	1515 (97)	334 (98)	
	Yes	45 (2)	42 (3)	5 (2)	
	Missing*	18	13	1	
Length of stay (median + IQR)		6.00 (4.00 – 8.00)	6.00 (4.00 – 9.00)	7.00 (5.00 – 10.0)	<0.001
Overall 30-day morbidity					<0.001
	No	2180 (77)	1058 (67)	222 (65)	
	Yes	667 (23)	512 (33)	118 (35)	
30-day major morbidity					0.216
	No	2640 (93)	1440 (92)	307 (90)	
	Yes	209 (7)	130 (8)	33 (10)	
30-day mortality					0.001
	No	2820 (99)	1534 (98)	331 (97)	
	Yes	29 (1)	36 (2)	9 (3)	

Percentages are shown in brackets and are rounded to the nearest full number. Therefore, they may not add to 100.

*Missing are not included in the analysis.

Synchronous additional resection was defined as any extra procedure including vascular resection or reconstruction or as additional intra-abdominal resection as a result of in-growth in other structures.

Major liver resection was defined as resection of at least 3 liver segments.

Postoperative complicated course was defined as a complication after surgery resulting in prolonged hospitalization (>14 days), or reintervention or death as a result of a complication.

Major morbidity was defined as a Clavien-Dindo Grade 3 or higher complication.

Supplementary table 2b. Postoperative outcomes stratified for age in patients underwent liver resection for liver metastases which were not of colorectal origin between 2014 and 2019 in the Netherlands.

Factor		Age <70	Age 70-79	Age ≥80	P-value
		N = 357	N = 107	N = 15	
Bile leakage					0.690
	No	340 (96)	104 (96)	13 (93)	
	Yes	14 (4)	3 (3)	1 (7)	
	Missing*	3	0	1	
Postoperative haemorrhage					0.288
	No	317 (98)	93 (99)	12 (92)	
	Yes	7 (2)	1 (1)	1 (8)	
	Missing*	33	13	2	
Postoperative liver failure					0.762
	No	348 (98)	106 (99)	14 (100)	
	Yes	6 (2)	1 (1)	0 (0)	

	Missing*	3	0	1	
Intra-abdominal infection					0.128
	No	323 (96)	95 (92)	13 (86)	
	Yes	15 (4)	8 (8)	2 (14)	
	Missing*	19	9	0	
Surgical site infection					0.813
	No	330 (97)	95 (97)	13 (100)	
	Yes	9 (3)	3 (3)	0 (0)	
	Missing*	18	9	2	
Pneumonia					0.332
	No	325 (96)	91 (93)	13 (100)	
	Yes	14 (4)	7 (7)	0 (0)	
	Missing*	18	9	2	
Cardiac complication					0.010
	No	349 (9)	100 (93)	13 (97)	
	Yes	5 (1)	7 (7)	1 (7)	
	Missing*	3	0	1	
Thromboembolic complication					0.454
	No	346 (98)	103 (96)	14 (93)	
	Yes	8 (2)	4 (4)	1 (7)	
	Missing*	3	0	0	
Length of stay (median + IQR)		6.00 (4.00 – 8.00)	6.00 (4.00 – 10.0)	6.00 (5.00 – 11.0)	0.850
Overall 30-day morbidity					0.157
	No	264 (74)	74 (69)	8 (53)	
	Yes	93 (26)	33 (31)	7 (47)	
30-day major morbidity					0.284
	No	327 (92)	96 (90)	12 (80)	
	Yes	30 (8)	11 (10)	3 (20)	
30-day mortality					0.535
	No	352 (99)	104 (97)	15 (100)	
	Yes	5 (1)	3 (3)	0 (0)	

Percentages are shown in brackets and are rounded to the nearest full number. Therefore, they may not add to 100.

*Missing are not included in the analysis.

Synchronous additional resection was defined as any extra procedure including vascular resection or reconstruction or as additional intra-abdominal resection as a result of in-growth in other structures.

Major liver resection was defined as resection of at least 3 liver segments.

Postoperative complicated course was defined as a complication after surgery resulting in prolonged hospitalization (>14 days), or reintervention or death as a result of a complication.

Major morbidity was defined as a Clavien-Dindo Grade 3 or higher complication.

Supplementary table 2c. Postoperative outcomes stratified for age in patients underwent liver resection for hepatocellular carcinoma between 2014 and 2019 in the Netherlands.

Factor	Age <70	Age 70-79	Age ≥80	P-value
	N = 451	N = 242	N = 45	
Bile leakage				0.237
	No	415 (93)	230 (95)	44 (98)
	Yes	33 (7)	12 (5)	1 (2)
	Missing*	3	0	0
Postoperative haemorrhage				0.572
	No	405 (99)	201 (98)	39 (100)
	Yes	5 (1)	4 (2)	0 (0)
	Missing*	41	37	6
Postoperative liver failure				0.501
	No	434 (97)	234 (97)	42 (93)
	Yes	15 (3)	8 (3)	3 (7)
	Missing*	2	0	0

Intra-abdominal infection					0.174
	No	390 (92)	203 (95)	41 (98)	
	Yes	33 (8)	10 (5)	1 (2)	
	Missing*	28	20	3	
Surgical site infection					0.930
	No	402 (95)	201 (94)	40 (95)	
	Yes	21 (5)	12 (6)	2 (5)	
	Missing*	28	29	3	
Pneumonia					0.351
	No	390 (92)	189 (89)	39 (90)	
	Yes	33 (8)	24 (11)	4 (10)	
	Missing*	28	29	3	
Cardiac complication					0.085
	No	435 (97)	227 (94)	42 (93)	
	Yes	13 (3)	15 (6)	3 (7)	
	Missing*	3	0	0	
Thromboembolic complication					0.075
	No	436 (97)	227 (94)	43 (96)	
	Yes	12 (3)	15 (6)	2 (4)	
	Missing*	3	0	0	
Length of stay (median + IQR)		7.00 (5.00 – 11.00)	7.00 (5.00 – 10.75)	7.00 (5.00 – 10.00)	0.881
Overall 30-day morbidity					0.171
	No	272 (60)	130 (54)	29 (64)	
	Yes	179 (40)	112 (46)	16 (36)	
30-day major morbidity					0.348
	No	394 (87)	203 (84)	37 (82)	
	Yes	57 (13)	39 (16)	8 (18)	
30-day mortality					0.203
	No	433 (96)	225 (93)	42 (93)	
	Yes	18 (4)	17 (7)	3 (7)	

Percentages are shown in brackets and are rounded to the nearest full number. Therefore, they may not add to 100.

*Missing are not included in the analysis.

Synchronous additional resection was defined as any extra procedure including vascular resection or reconstruction or as additional intra-abdominal resection as a result of in-growth in other structures.

Major liver resection was defined as resection of at least 3 liver segments.

Postoperative complicated course was defined as a complication after surgery resulting in prolonged hospitalization (>14 days), or reintervention or death as a result of a complication.

Major morbidity was defined as a Clavien-Dindo Grade 3 or higher complication.

Supplementary table 2d. Postoperative outcomes stratified for age in patients underwent liver resection for bile duct and gallbladder carcinoma between 2014 and 2019 in the Netherlands.

Factor	Age <70	Age 70-79	Age ≥80	P-value
	N = 366	N = 216	N = 29	
Bile leakage				0.570
	No	314 (86)	181 (84)	23 (79)
	Yes	52 (14)	35 (16)	6 (21)
	Missing*	0	0	0
Postoperative haemorrhage				0.836
	No	287 (98)	157 (98)	19 (100)
	Yes	5 (2)	3 (2)	0 (0)
	Missing*	74	56	10
Postoperative liver failure				0.103
	No	337 (92)	206 (95)	29 (100)
	Yes	29 (8)	10 (5)	0 (0)
	Missing*	0	0	0
Intra-abdominal infection				0.672

	No	272 (82)	148 (79)	20 (83)	
	Yes	59 (18)	39 (21)	4 (17)	
	Missing*	35	29	5	
Surgical site infection					0.460
	No	301 (91)	170 (91)	20 (83)	
	Yes	30 (9)	17 (9)	4 (17)	
	Missing*	35	29	5	
Pneumonia					0.026
	No	317 (96)	169 (90)	21 (90)	
	Yes	14 (4)	18 (10)	3 (13)	
	Missing*	35	29	5	
Cardiac complication					0.692
	No	343 (94)	201 (93)	26 (90)	
	Yes	23 (6)	15 (7)	3 (10)	
	Missing*	0	0	0	
Thromboembolic complication					0.834
	No	345 (94)	206 (95)	27 (93)	
	Yes	20 (6)	10 (5)	2 (7)	
	Missing*	1	0	0	
Length of stay (median + IQR)		7.50 (5.00 – 15.00)	9.00 (6.00 – 19.00)	8.00 (6.00 – 14.25)	0.126
Overall 30-day morbidity					0.179
	No	174 (47)	87 (40)	11 (38)	
	Yes	192 (53)	129 (60)	18 (62)	
30-day major morbidity					0.484
	No	290 (79)	162 (75)	23 (79)	
	Yes	76 (21)	54 (25)	6 (21)	
30-day mortality					0.599
	No	342 (93)	198 (92)	26 (90)	
	Yes	24 (7)	18 (8)	3 (10)	

Percentages are shown in brackets and are rounded to the nearest full number. Therefore, they may not add to 100.

*Missing are not included in the analysis.

Synchronous additional resection was defined as any extra procedure including vascular resection or reconstruction or as additional intra-abdominal resection as a result of in-growth in other structures.

Major liver resection was defined as resection of at least 3 liver segments.

Postoperative complicated course was defined as a complication after surgery resulting in prolonged hospitalization (>14 days), or reintervention or death as a result of a complication.

Major morbidity was defined as a Clavien-Dindo Grade 3 or higher complication.

Supplemental table 3. Trend analysis between 2014 and 2019 using univariable logistic regression for elderly patients who underwent liver resection for primary and secondary liver tumours.

Factor	Age <70 years			Age 70-80 years			Age >80 years		
	OR	CI (95%)	P-value	aOR	CI (95%)	P-value	aOR	CI (95%)	P-value
Trend in proportion of patients per year									
Overall	0.95	0.92 – 0.98	<0.001	1.06	1.02 – 1.09	<0.001	1.02	0.96 – 1.08	0.571
Colorectal liver metastases	0.96	0.93 – 1.00	0.033	1.04	1.01 – 1.08	0.025	1.00	0.94 – 1.07	0.953
Other liver metastases	0.93	0.82 – 1.05	0.233	1.11	0.98 – 1.26	0.109	0.85	0.62 – 1.14	0.285
Hepatocellular carcinoma	0.87	0.80 – 0.94	0.001	1.11	1.01 – 1.21	0.024	1.18	1.01 – 1.40	0.051
Bile duct and gallbladder carcinoma*	0.96	0.82 – 1.12	0.682	1.02	0.87 – 1.20	0.770	1.34	0.94 – 1.93	0.108

*trend analysis performed between 2016 and 2019

Supplemental table 4. Number of liver resections for primary and secondary liver tumours between 2014 and 2019 stratified for indication.

	Overall	Colorectal liver metastases	Other liver metastases	Hepatocellular carcinoma	Bile duct and gallbladder carcinoma
2014	996	741	81	174	1
2015	1002	793	71	138	57
2016	1170	856	85	89	140
2017	1179	845	77	109	145
2018	1159	823	82	111	143
2019	1023	698	83	117	125

CHAPTER 5

SURGICAL OUTCOMES OF LAPAROSCOPIC AND OPEN RESECTION OF BENIGN LIVER TUMOURS IN THE NETHERLANDS: A NATIONWIDE ANALYSIS

A.K.E. Elfrink, M.P.D. Haring, V.E. de Meijer, J.N.M. Ijzermans, R.J. Swijnenburg, A.E. Braat, J.I. Erdmann, T. Terkivatan, W.W. te Riele, P.B. van den Boezem, M.M.E. Coolen, W.K.G. Leclercq, D.J. Lips, R.F. de Wilde, N.F.M. Kok, D.J. Grünhagen, J.M. Klaase, [Dutch Hepato Biliary Audit Group Collaborators](#)

HPB (Oxford). 2020 Nov 17:S1365-182X(20)31189-8.

Abstract

Introduction

Data on surgical outcomes of laparoscopic liver resection (LLR) versus open liver resection (OLR) of benign liver tumour (BLT) are scarce. This study aimed to provide a nationwide overview of postoperative outcomes after LLR and OLR of BLT.

Methods

This was a nationwide retrospective study including all patients who underwent liver resection for hepatocellular adenoma, haemangioma and focal nodular hyperplasia in the Netherlands from 2014 to 2019. Propensity score matching (PSM) was applied to compare 30-day overall and major morbidity and 30-day mortality after OLR and LLR.

Results

In total, 415 patients underwent BLT resection of whom 230 (55.4%) underwent LLR. PSM for OLR and LLR resulted in 250 matched patients. Median (IQR) length of stay was shorter after LLR than OLR (4 versus 6 days, 5.0–8.0, $p<0.001$). Postoperative 30-day overall morbidity was lower after LLR than OLR (12.0% vs. 22.4%, $p=0.043$). LLR was associated with reduced 30-day overall morbidity in multivariable analysis (aOR:0.46, CI:0.22–0.95, $p=0.043$). Both 30-day major morbidity and 30-day mortality were not different.

Conclusion

LLR for BLT is associated with shorter hospital stay and reduced overall morbidity and is preferred if technically feasible.

Introduction

The role of liver resection in the treatment of benign liver tumours (BLT) remains challenging^{1,2}. Indications for resection differ per tumour type as clinical implications across BLT (sub)types vary significantly². The majority of BLT are comprised of hepatocellular adenoma (HCA), haemangioma, and focal nodular hyperplasia (FNH)³. The majority of these tumours occur mainly in middle-aged women and are most accurately radiologically characterised through hepatobiliary contrast enhanced magnetic resonance imaging (CE-MRI)⁴.

HCAs are associated with long term oral contraceptive pill use and obesity^{5,6}. Tumours of >50mm diameter are associated with haemorrhage (15-20%) and malignant transformation to hepatocellular carcinoma has been described^{7,8}. Conservative treatment, by oestrogen lowering life style advices including oral contraceptive pill cessation and weight loss, can lead to HCA regression^{9,10}. Current European guidelines recommend a wait-and-see period of six months after commencing life style advices. Current guidelines advocate surgery if tumour size remains >50mm². This period, though, may be too short for large HCAs to regress to sub-50mm size¹¹.

Indications for resection in FNH or haemangioma are less distinct, as risk of haemorrhage in haemangiomas and FNHs is very rare in the former, and non-existent in the latter^{12,13}. However, both haemangioma and FNHs are known to cause abdominal complaints such as pain, nausea or bloatedness by compression¹⁴. A rare complication associated with large haemangiomas (>50mm) is Kasabach-Merritt syndrome - a consumptive coagulopathy¹⁵. These consequences could warrant surgical intervention in selected patients as the FNH or haemangioma burden could outweigh the risk of adverse events associated with liver resection².

As indications for BLT surgery are ambiguous, therapeutic strategies are often drafted through shared decision making by patient and clinician. This process necessitates availability of accurate and elaborate information with regards to surgical outcomes as surgical burden should outweigh risks of postoperative morbidity. Up to now limited series on outcomes after surgery for benign liver tumours have been performed and evidence is scarce. Additionally, potential strategies to decrease adverse events remain controversial¹⁶⁻¹⁹. As for malignant tumours, laparoscopic liver resection (LLR) may have potential benefits over open liver resection (OLR) by decreasing blood loss, length of hospital stay (LOS), and postoperative morbidity^{16,20,21}. However, the role of laparoscopy in BLT surgery has been scientifically underexposed too.

The current study aimed to provide an evaluation of postoperative surgical outcomes after liver resection for BLT, to assess laparoscopy influence on postoperative outcomes, and to identify predisposing factors for post-operative complications using a multivariable analysis in a nationwide, population-based design.

Methods

A nationwide population-based study was performed in the Netherlands. Data were retrieved from the Dutch Hepato Biliary Audit (DHBA), a nationwide registry in which all Dutch hospitals eligible for liver surgery are obliged to record all liver resections performed. Data verification was performed by a trusted third-party to provide insight into DHBA data completeness and quality²². No ethical approval to perform this study was needed under Dutch law as the DHBA is part of the Dutch inspectorate of health care and research is carried out with an anonymised dataset.

Patient selection

Included were patients who underwent liver resection for HCA, haemangioma or FNH in the Netherlands between the 1st of January 2014 and December 31st 2019 and were registered in the DHBA before the 1st of April 2020. Patients were excluded if information regarding date of birth, date of surgery, or type of intervention was missing. Patients who underwent liver resection for unspecified type of BLT were excluded.

Definitions and outcomes

Major liver resection was defined as resection of three or more adjacent segments as per Couinaud classification²³. Outcomes were stratified for type of BLT and for surgical approach. Surgical approach was categorised for OLR and LLR, converted procedures were included as LLR in the intention to treat analysis.

Postoperative outcomes included 30-day overall morbidity (i.e. any complication within 30-days of surgery), and LOS calculated as time between date of surgery and the date of discharge. Furthermore, 30-day major morbidity, defined as a Clavien-Dindo grade IIIa or higher complication (i.e. requiring re-intervention, medium care or intensive care management or death) within 30 days of surgery, and 30-day mortality defined as death within 30 days of surgery or during initial hospitalization were assessed²⁴.

Other postoperative outcomes included specific complication rates such as bile leakage, postoperative haemorrhage requiring reintervention, postoperative liver failure according the

International Study Group of Liver Surgery, deep surgical site infection (i.e biloma or abscess), incisional surgical site infection, pneumonia, myocardial complication or a thrombo-embolic complication²⁵.

Variables

Patient characteristics included age, sex, American Society of Anesthesiologists (ASA) classification, comorbidity score according the Charlson Comorbidity Index (CCI), history of liver disease and a history of liver resection. Tumour characteristics included type of BLT, number of BLT and diameter of largest BLT prior to treatment. Treatment characteristics included surgical approach, extensiveness of liver resection (major or minor), and type of hospital (i.e. tertiary referral hospital or regional hospital) where treatment took place.

Statistical analysis

Baseline characteristics and postoperative outcomes were compared between groups using the Chi-square test or Fisher exact test as appropriate for categorical variables. The independent two-sample t-test was used for continuous outcomes which were presented as medians with interquartile ranges (IQR).

Funnel plots were plotted for evaluation of hospitals performance relative to mean outcome rates in the Netherlands to address hospital variation concerning 30-day overall and major morbidity after resection.

Univariable and multivariable logistic regression was performed to assess risk factors for adverse events in the complete population. The association of risk factors with adverse events were reported as adjusted odds ratio (aOR) with 95% confidence interval (CI). Variables were entered into multivariable analysis after univariable testing with the outcome as dependent variable. Variables were included in multivariable analysis if $p < 0.20$ after univariable analysis. Statistical significance was defined as a two-sided $p < 0.05$ in the multivariable model. To assess the influence of annual overall and BLT resection volume on postoperative outcomes in the complete BLT population, both variables were included in these logistic regression models. Annual overall volume and BLT resection volume were calculated as total number of liver resections and BLT indicated liver resections performed per hospital per year, respectively. Overall volume was categorised for <20 , 20-39, 40-59, 60-79, and >80 procedures, with the first two categories merged for analysis due two low inclusions. Annual hospital volume for BLT resection was categorised <5 , 5-15, and >15 procedures. Multicollinearity was assessed in all

logistic regression models, and indicated if the calculated variance inflation factor was higher than 2.5.

Differences in postoperative outcomes between OLR and LLR were assessed after propensity score matching (PSM). As a first step in PSM, a multivariable logistic regression was used to estimate propensity scores per patient. Hereafter, PSM was performed with a 1:1 ratio using the nearest neighbor method with a caliper of 0.01. Covariates for PSM were, ASA score, type of BLT, history of liver resection, number of BLT, diameter of largest BLT, bilobar disease, and major liver resection. In order to assess the quality of the matching process standardised mean differences (smd) were used. Standard mean differences below 0.1 for baseline characteristics between the two groups indicate negligible differences between the OLR and LLR groups after PSM. Differences in tumour and operative techniques needed to be negligible in order to decrease possible selection bias. After PSM, baseline characteristics and outcomes were compared between the groups using the Chi-square test or Fisher exact test for categorical variables. Continuous outcomes were presented as medians with interquartile ranges (IQR). A multivariable logistic regression model was performed using backward selection to identify which variables were associated with 30-day overall morbidity and 30-day major morbidity corrected for possible confounders in the PSM population.

All analyses were performed in R version 3.2.2® (R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 415 patients were included of whom 246 (59.0%) underwent resection for HCA, 87 (20.7%) for haemangioma, and 85 (20.3%) for FNH. Laparoscopic resection was performed in 230 (55.4%) patients (table 1).

Patients who underwent resection because of HCA or FNH were more often female, were younger, had lower CCI, and had lower ASA scores versus patients who underwent resection because of haemangioma (supplementary table 1). Resection of HCA was more frequently performed for a higher number of tumours, and for a larger tumour diameter compared to haemangioma or FNH, resulting in more frequent major liver resections. Likewise, resection of HCA was performed more often in tertiary referral centres.

The total number of BLT resection did not increase during the study period. Laparoscopic liver resection was performed more frequently over the years as 16 LLR were performed in 2014, 56 in 2018 and 29 in 2019 ($p < 0.001$). Laparoscopic resection was less often applied in case of bilobar disease or when a major liver resection was performed (table 1).

Table 1. Baseline characteristics for patients diagnosed with a benign liver tumour (BLT) between 2014 and 2019 in the Netherlands who underwent liver resection stratified for surgical approach.

Factor		Open Liver Resection	Laparoscopic Liver Resection	P-value
		N (%)	N (%)	
Total		185	220	
Patient characteristics				
Sex				0.371
	Male	18 (10)	30 (13)	
	Female	167 (90)	200 (87)	
Age in years				0.101
	< 50	118 (64)	160 (70)	
	50 - 64	51 (28)	42 (18)	
	65 - 79	16 (9)	27 (12)	
	≥ 80	0 (0)	1 (0)	
Charlson Comorbidity Index (CCI)				0.543
	0 / 1	156 (84)	200 (87)	
	2 +	29 (16)	30 (13)	
Body Mass Index (BMI)				0.723
	Mean (sd)	27.5 (5.7)	27.3 (6.0)	0.097
American Society of Anesthesiology (ASA) classification				
	ASA I / II	168 (92)	198 (86)	
	ASA III+	15 (8)	32 (14)	
	Missing	2	0	
History of liver resection				0.017
	No	172 (97)	228 (100)	
	Yes	6 (3)	0 (0)	
	Missing	7	2	
History of liver disease§				0.728
	No	177 (97)	220 (98)	
	Yes	6 (3)	5 (2)	
	Missing	2	5	
Histopathological liver disease				
	Normal liver	121 (70)	140 (68)	0.362
	Steatosis	36 (21)	55 (27)	
	Steato-hepatitis	7 (4)	7 (3)	
	Cirrhosis	3 (2)	3 (1)	
	Sinusoidal dilatation	6 (3)	2 (1)	
	Missing	12	23	
Tumour- and operative characteristics				
Number of BLT				0.835
	1	119 (73)	161 (75)	
	2	17 (10)	17 (8)	
	3	9 (6)	14 (7)	

	≥4	18 (11)	23 (10)	
	Missing	22	15	
Maximum diameter of largest BLT (mm*)				0.770
	< 50	40 (27)	56 (29)	
	≥ 50	109 (73)	138 (71)	
	Missing	36	36	
Bilobar disease				0.011
	No	107 (58)	161 (71)	
	Yes	77 (42)	67 (29)	
	Missing	1	2	
Major liver resection				<0.001
	No	117 (63)	208 (90)	
	Yes	68 (37)	22 (10)	
Type of BLT				0.513
	Hepatocellular adenoma	114 (62)	131 (57)	
	Haemangioma	38 (21)	48 (21)	
	Focal nodular hyperplasia	33 (18)	51 (22)	
Type of hospital[∞]				0.223
	Regional hospital	50 (27)	76 (33)	
	Tertiary referral hospital	135 (73)	154 (67)	

Bold p-values indicate statistical significance of $p < 0.05$

§ History of liver disease containing liver cirrhosis, oesophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis

*millimetre

[∞] Type of hospital: tertiary referral centre are defined as hospitals with highest expertise on oncologic surgery

Postoperative outcomes and hospital variation

After BLT resection, 30-day overall morbidity after BLT resection occurred in 73 patients (17.5%), and 30-day major morbidity occurred in 24 patients (5.7%). Thirty-day mortality did not occur (0%). Overall 30-day morbidity rates ranged from 8.3% to 50% between hospitals. None of the hospitals performing liver surgery for BLT had a significantly higher 30-day overall morbidity rate compared to the mean 30-day overall morbidity (supplementary Figure 1a). Six hospitals had a significantly lower 30-day overall morbidity compared to the mean 30-day overall morbidity. Major morbidity rates between hospitals ranged from 3.5% to 19.4%. None of the hospitals performing liver surgery for BLT had a significantly higher 30-day major morbidity rate compared to the mean 30-day major morbidity rate (supplementary Figure 1b). Five hospitals had a significantly lower 30-day major morbidity compared to the mean 30-day major morbidity.

Risk factors for adverse events and influence of hospital volume

In univariable logistic regression and multivariable logistic regression, several risk factors for adverse events were observed. Age above 65 (aOR 2.65, CI 1.17 – 5.80, $p=0.016$), history of liver disease (aOR 4.20, CI 1.01 – 16.0, $p=0.037$) and major liver resection (aOR 1.94, CI 1.04 – 3.61, $p=0.037$) were independently associated with higher 30-day overall morbidity (table 2a). Laparoscopic liver resection (aOR 0.55, CI 0.41 – 0.98, $p=0.044$) was associated with lower 30-day overall morbidity. No influence of type of BLT or hospital volume was observed for 30-day overall morbidity.

Also, CCI higher than 2 (aOR 3.20, CI 1.06 – 8.81, $p=0.029$) and major liver resection (aOR 3.48, CI 1.32 – 9.14, $p=0.011$) were associated with higher 30-day major morbidity (table 2b). No influence of surgical approach, type of BLT or hospital volume was observed for 30-day major morbidity.

Table 2a. Univariable and multivariable logistic regression model to assess the association of patient-, tumour- and surgical characteristics with 30-day overall morbidity after benign liver tumour (BLT) resection in the Netherlands between 2014-2019.

Factor	N	Univariable analysis			Multivariable analysis		
		OR	CI (95%)	P-value	aOR	CI (95%)	P-value
Sex				0.556			
Male	48	1					
Female	367	1.29	0.59 – 3.25				
Age (years)				0.080			0.016
≤ 65	371	1			1		
> 65	44	1.90	0.90 – 3.81		2.65	1.17 – 5.80	
Missing*							
Charlson Comorbidity Index (CCI)				0.340			
0 / 1	356	1					
2+	59	1.39	0.68 – 2.67				
Body Mass Index		0.99	0.94 – 1.03	0.569			
American Society of Anesthesiology (ASA) classification				0.742			
I / II	366	1					
III +	47	1.14	0.50 – 2.38				
Missing*	2						
History of liver disease§				0.020			0.037
No	397	1			1		
Yes	11	4.26	1.20 – 14.5		4.20	1.01 – 16.0	
Missing*	7						
Histopathological liver disease¶				0.344			
No	261	1					
Yes	119	1.18	0.66 – 2.07	0.563			
Missing	35	1.88	0.78 – 4.19	0.137			
Number of BLT				0.808			
1	280	1					
2	34	0.83	0.27 – 2.09	0.720			

3	23	0.73	0.17 – 2.22	0.615			
≥4	41	1.36	0.58 – 2.93	0.453			
Missing	37	1.38	0.56 – 3.09	0.454			
Maximum diameter largest BLT (mm)*				0.287			
< 50	96	1					
≥ 50	247	0.74	0.40 – 1.40	0.342			
Missing	72	1.58	0.76 – 3.32	0.220			
Bilobar disease				0.195			0.160
No	268	1			1		
Yes	144	1.41	0.83 – 2.36		1.48	0.85 – 2.57	
Missing*	3						
Type of benign liver tumour				0.841			0.951
Hepatocellular adenoma	245	1			1		
Haemangioma	86	1.18	0.62 – 2.19	0.595	1.04	0.51 – 2.06	0.905
Focal nodular hyperplasia	84	0.96	0.48 – 1.83	0.909	1.12	0.53 – 2.25	0.753
Major liver resection				0.005			0.037
No	325	1			1		
Yes	90	2.21	1.26 – 3.83		1.94	1.04 – 3.61	
Surgical approach				0.003			0.044
OLR	185	1			1		
LLR	230	0.46	0.27 – 0.77		0.55	0.41 – 0.98	
Type of hospital[∞]				0.535			
Regional hospital	126	1					
Tertiary referral hospital	289	1.20	0.69 – 2.14				
Annual hospital volume of BLT resection				0.457			
<5	150	1					
5-15	163	1.14	0.62 – 2.09	0.678			
>15	102	1.51	0.79 – 2.89	0.215			
Overall annual hospital volume				0.827			
0-39	58	1					
40-59	31	0.57	0.15 – 1.82	0.366			
60-79	55	0.85	0.33 – 2.17	0.737			
>80	271	0.81	0.41 – 1.70	0.555			

Bold p-values indicate statistical significance of $p < 0.05$

* Missing not included in analyses based on relatively small group

§ History of liver disease containing liver cirrhosis, oesophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis

Mm = millimetre

OLR: Open liver resection; LLR: Laparoscopic liver resection

[∞] Type of hospital: tertiary referral centres are defined as hospitals with highest expertise on oncologic surgery

¥ All patients with a nonnormal histological diagnosis of liver tissue are placed under 'Yes'.

Table 2b. Univariable and multivariable logistic regression model to assess the association of patient and tumour characteristics with 30-day major morbidity after benign liver tumour (BLT) resection in the Netherlands between 2014-2019.

Factor	N	Univariable analysis			Multivariable analysis		
		OR	CI (95%)	P-value	aOR	CI (95%)	P-value
Sex				0.612			
Male	48	1					
Female	367	1.47	0.41 – 9.35				
Age (years)				0.756			
≤ 65	371	1					
> 65	44	1.22	0.28- 3.74				

Charlson Comorbidity Index (CCI)					0.127			0.029
0 / 1	356	1				1		
2+	59	2.21	0.74 – 5.33	0.315	3.20	1.06 – 8.81		
Body Mass Index		0.96	0.89 – 1.03					
American Society of Anesthesiology (ASA) classification				0.859				
I / II	366	1						
III +	47	1.12	0.26 – 3.42					
Missing*	2							
History of liver disease§				0.619				
No	397	1						
Yes	11	1.70	0.09 – 9.52					
Missing*	7							
Histopathological liver disease¥				0.327				
No	261	1						
Yes	119	0.72	0.23 – 1.91	0.533				
Missing*	35	2.12	0.58 – 6.27	0.207				
Number of BLT				0.314				
1	280	1						
2	34	0.13	0.01 – 36.8	0.989				
3	23	0.61	0.04 – 3.45	0.694				
≥4	41	0.75	0.12 – 2.72	0.702				
Missing	37	1.28	0.29 – 4.05	0.700				
Maximum diameter largest BLT (mm)*				0.526				
< 50	96	1						
≥ 50	247	1.38	0.48 – 4.97	0.577				
Missing	72	2.09	0.57 – 8.45	0.268				
Bilobar disease				0.864				
No	268	1						
Yes	144	0.92	0.37 – 2.16					
Missing*	3							
Type of benign liver tumour				0.236				0.099
Hepatocellular adenoma	245	1			1			
Haemangioma	86	0.71	0.15 – 2.06	0.502	0.61	0.13 – 2.01	0.457	
Focal nodular hyperplasia	84	1.06	0.72 – 4.63	0.178	2.41	0.90 – 6.22	0.071	
Major liver resection				0.018				0.011
No	325	1			1			
Yes	90	2.78	1.16 – 6.44		3.48	1.32 – 9.14		
Surgical approach				0.333				0.934
OLR	185	1						
LLR	230	0.66	0.29 – 1.52		0.96	0.39 – 2.41		
Type of hospital[∞]				0.896				
Regional hospital	126	1						
Tertiary referral hospital	289	1.06	0.45 – 2.81					
Annual hospital volume of BLT resection				0.983				
<5	150	1						
5-15	163	0.92	0.35 – 2.41	0.856				
>15	102	0.98	0.32 – 2.80	0.969				
Overall annual hospital volume				0.269				
0-39	58	1						
40-59	31	1.57	0.36 – 6.41	0.526				

60-79	55	0.61	0.12 – 2.62	0.515
>80	271	0.50	0.17 – 1.60	0.199

Bold p-values indicate statistical significance of $p < 0.05$

* Missing not included in analyses based on relatively small group

§ History of liver disease containing liver cirrhosis, esophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis

OLR: Open liver resection; LLR: Laparoscopic liver resection

∞ Type of hospital: tertiary referral centers are defined as hospitals with highest expertise on oncologic surgery

¥ All patients with a nonnormal histological diagnosis of liver tissue are placed under 'Yes'.

Propensity Score Matching: baseline- and surgical characteristics

PSM was performed to minimise baseline differences in the OLR and LLR groups (table 3).

Matching resulted in balanced covariates as the standard mean difference was 0.100 or lower for all variables except for histological diagnosis as more patients with parenchymal liver disease were included in the LLR group. This minor imbalance proved insignificant as no significant differences in baseline characteristics were observed between both resection groups. For analysis of postoperative outcomes, 125 patients (50%) who underwent OLR and 125 patients (50%) who underwent LLR were included.

Table 3. Baseline characteristics after propensity score matching for patients diagnosed with a benign liver tumour (BLT) between 2014 and 2019 in the Netherlands who underwent liver resection stratified for surgical approach.

Factor		Open Liver Resection	Laparoscopic Liver Resection	P-value	smd
		N (%)	N (%)		
Total		125	125		
Patient characteristics					
Sex				0.570	0.096
	Male	14 (11)	18 (14)		
	Female	111 (89)	107 (86)		
Age in years				0.684	0.077
	< 65	113 (90)	110 (88)		
	≥ 65	12 (10)	15 (12)		
Charlson Comorbidity Index (CCI)				0.487	0.098
	0 / 1	102 (82)	109 (87)		
	2 +	23 (18)	16 (13)		
Body Mass Index (BMI)				0.652	0.081
American Society of Anesthesiology (ASA) classification				0.342	0.100
	ASA I / II	115 (92)	109 (87)		
	ASA III+	10 (8)	16 (13)		
History of liver resection				1.000	<0.001
	No	124 (99)	124 (99)		
	Yes	1 (1)	1 (1)		
	Missing*	1	1		
History of liver disease§				1.000	0.045
	No	121 (97)	119 (98)		
	Yes	4 (3)	3 (99)		
	Missing*	0	3		
Histopathological liver disease				0.342	0.104

	Normal liver	83 (80)	73 (72)		
	Abnormal liver parenchyma [^]	21 (20)	29 (28)		
	Missing*	21	23		
Tumour- and operative characteristics					
Number of BLT				1.000	<0.001
	≤3	102 (82)	102 (82)		
	≥4	13 (18)	13 (18)		
	Missing*	10	10		
Maximum diameter of largest BLT (mm*)				0.911	0.035
	< 50	35 (32)	32 (30)		
	≥ 50	75 (68)	74 (70)		
	Missing*	15	19		
Bilobar disease				1.000	<0.001
	No	81 (65)	81 (65)		
	Yes	43 (34)	43 (34)		
	Missing*	1	1		
Major liver resection				1.000	<0.001
	No	105 (84)	105 (84)		
	Yes	20 (16)	20 (16)		
Type of BLT				0.951	0.040
	Hepatocellular adenoma	70 (56)	72 (58)		
	Haemangioma	26 (21)	26 (21)		
	Focal nodular hyperplasia	29 (23)	27 (22)		
Type of hospital[∞]				0.893	0.034
	Regional hospital	42 (34)	40 (32)		
	Tertiary referral hospital	84 (66)	85 (68)		

Bold p-values indicate statistical significance of $p < 0.05$

Smd = standard mean difference

§ History of liver disease containing liver cirrhosis, oesophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis

[^] Abnormal liver parenchyma includes steatosis, sinusoidal dilatation, cirrhosis and steatohepatitis

*millimetre

[∞] Type of hospital: tertiary referral centre are defined as hospitals with highest expertise on oncologic surgery

Postoperative outcomes

Median LOS was shorter after LLR compared to OLR (4 days (3 – 6) vs. 6 days (5 – 8), $p < 0.001$). Thirty-day overall morbidity occurred in 15 patients after LLR 12.0% which was lower compared to the 28 patients (22.4%, $p = 0.043$) in which a complication occurred after OLR (figure 1a). The 30-day major morbidity rate was not different between LLR and OLR. Six patients (4.8%) and 8 patients (6.4%) experienced 30-day major morbidity after LLR and OLR respectively ($p = 0.783$).

Postoperative outcomes stratified for LLR and OLR did not show differences in specific liver-related complication rates (figure 1b). Similarly, no differences were observed in other complication rates (i.e. pneumonia, cardiac, thrombo-embolic, or infectious) between LLR and OLR (data not shown).

Figure 1a and 1b. Overview of percentage of patients included after propensity score matching with main outcomes and liver-specific outcomes after benign liver tumour resection in the Netherlands stratified for open liver resection (OLR) and laparoscopic liver resection (LLR).

P-values are the result of the chi-squared test or fisher exact test as appropriate per outcome stratified for OLR versus LLR. Patients who had missing values for the outcome were excluded from the analysis.

Associated factors with 30-day overall morbidity and 30-day major morbidity after PSM

Multivariable logistic regression in the PSM population showed that bilobar disease (aOR 2.11, CI 1.04 – 4.28, $p=0.037$) was associated with higher 30-day overall morbidity (table 4).

Performing LLR was independently associated with lower 30-day overall morbidity (aOR 0.46, CI 0.22 – 0.95, $p=0.043$). No variables were independently associated with 30-day major morbidity.

Table 4. Results of stepwise multivariable logistic regression model after propensity score matching for patients diagnosed with a benign liver tumour (BLT) between 2014 and 2019 in the Netherlands who underwent liver resection

Multivariable analysis				
30-day overall morbidity				
Factor	N	OR	CI (95%)	P-value
Charlson Comorbidity Index (CCI)				0.786
0 / 1	211	1		
2 +	39	1.14	0.43 – 2.78	
American Society of Anesthesiology (ASA) classification				0.820
I / II	224	1		
III+	26	1.15	0.33 – 3.47	
Histopathological liver disease				0.911
Normal liver	156	1		
Abnormal liver parenchyma	50	1.19	0.51 – 2.74	0.684
Missing	44	1.16	0.29 – 3.74	0.817
Maximum diameter of largest BLT (mm)				0.240
< 50	67	1		
≥ 50	149	0.58	0.25 – 1.35	0.197
Missing	34	1.23	0.42 – 3.44	0.691
Bilobar disease				0.037
No	162	1		
Yes	86	2.11	1.04 – 4.28	
Missing*	2			
Type of BLT				0.805
Hepatocellular adenoma	142	1		
Haemangioma	52	1.21	0.47 – 3.04	0.685
Focal nodular hyperplasia	56	0.85	0.32 – 2.11	0.727
Major liver resection				0.171
No	210	1		
Yes	40	1.85	0.74 – 4.38	
Surgical approach				0.038
OLR	125	1		
LLR	125	0.46	0.22 – 0.95	
Multivariable analysis				
Factor	N	OR	CI (95%)	P-value
Charlson Comorbidity Index (CCI)				0.253
0 / 1	211	1		
2 +	39	3.44	0.85 – 12.1	
American Society of Anesthesiology (ASA) classification				0.072
I / II	224	1		
III+	26	2.48	0.45 – 10.6	
Histopathological liver disease				0.889
Normal liver	156	1		
Abnormal liver parenchyma	50	0.97	0.22 – 3.78	0.966
Missing	44	1.34	0.20 – 7.58	0.632
Type of BLT				0.275
Hepatocellular adenoma	142	1		
Haemangioma	52	0.53	0.07 – 2.73	0.488

	Focal nodular hyperplasia	56	2.10	0.55 – 7.70	0.259
Major liver resection					0.145
	No	210	1		
	Yes	40	2.72	0.68 – 9.37	
Surgical approach					0.600
	OLR	125	1		
	LLR	125	0.73	0.21 – 2.40	

* Bold p-values indicate statistical significance of $p < 0.05$

Missing not included in analyses based on relatively small group

Discussion

This population-based, propensity score matched, study comprises a nationwide study on surgical outcomes for BLT and encompasses one of the largest series up to date. Overall 30-day morbidity was 17.5%, and 30-day major morbidity was 5.7% without mortality. Minimal hospital variation for postoperative outcomes was present. Several hospitals demonstrated better than average performance. Risk factors for 30-day overall morbidity included age above 65, history of liver disease and major liver resection, while risk factors for 30-day major morbidity were CCI above 2 and major liver resection. No influence of hospital volume or type of BLT was observed. PSM was performed and resulted in 250 matched patients who underwent OLR and LLR. LLR proved beneficial with regards to postoperative outcomes such as LOS and 30-day overall morbidity. A more favourable outcome regarding 30-day overall morbidity was also observed for LLR after adjusting for confounding factors, as LLR was associated with lower 30-day overall morbidity. This could indicate that use of LLR may assist in postoperative morbidity reduction when performing BLT indicated liver resection.

Historically, limited series on surgical outcomes of BLT have been reported. Previous studies show overall morbidity rates of 10-20% and major morbidity rates around 10% after resection of BLT^{13,20,21,26,27,28}. Previously reported surgical outcomes after BLT resection range 10-35% and 5-15% for overall and major morbidity, respectively. Hence, the current observations are concordant and indicate resection of haemangioma and FNH in the Netherlands to be comparable to earlier studies²⁹⁻³¹.

Several risk factors were observed in all resected BLT patients for adverse events. Higher age, higher comorbidity scores and factors associated with the extent of the liver resection were associated with 30-day overall morbidity and 30-day major morbidity. These risk factors are comparable with earlier described risk factors in liver resection for malignant indications^{32,33}. Hospital variation concerning postoperative outcomes of BLT resection is present in the Netherlands without any hospitals performing significantly worse than the nationwide average.

Most BLT resections were performed in higher volume centres. Some high-volume centres performed better than average (no statistical significance). Overall annual hospital volume for all liver resections and annual hospital of BLT resection, though, were not correlated with postoperative outcomes, similar to prior observations³⁴. This observation, alongside the aforementioned results equal to malignant liver resection indicates safety of BLT resection in all hospital qualifying for malignant liver resection by sufficient case load.

LLR was associated with reduced postoperative morbidity compared to OLR and similar to outcomes of LLR for liver malignancies in general³⁵⁻³⁷. The current results are similar to previous reports on minimally invasive liver surgery. A nationwide study from the Netherlands showed similar results as the current study (30% vs. 42% of complications after LLR and OLR respectively, $p=0.040$)³⁸. Previous results with regard to laparoscopic BLT resection showed postoperative morbidity incidence of 13.9%; similar to 13% overall 30-day morbidity³⁹. This study confirms that if technically feasible, LLR is preferred over OLR concerning resection of BLT.

Potential limitations of this study are registry data associated problems regarding accuracy and coverage. Although third-party data verification deemed 97% of the data accurate, not all specific information concerning operative outcomes could be obtained²². Another potential limitation is the lack of information regarding preoperative decision-making process, specific tumour location and preoperative indication for surgery. These were not registered in the DHBA. This could have influenced the decision to perform resection of BLT and could be a possible explanation for the surgical intervention in the haemangioma and FNH patients as the European Guideline advocates a wait-and-see policy². Lack of information regarding the preoperative specific tumour location and indication for surgery could thereby lead to confounding by indication despite correction for patient and tumour characteristics. Also, specific tumour location could have been a reason to perform LLR or OLR and this may reflect in the differences in postoperative outcomes. However, this information is not registered in the DHBA and could not be obtained. Another limitation is the lacking of perioperative details such as perioperative outcomes which can be attributed to the audit nature of this cohort.

Future studies will have to be conducted on improving outcomes after BLT resection. Resection of BLT is often performed in young and healthy patients and therefore major complications of any sort should be avoided. BLT resection should be used only in a highly selected group of patients after a weighted shared-decision making process by patient and surgeon. Outcomes

such as morbidity and mortality are very important in this process. However, possible influence of BLT resection on quality of life should be part of the evaluation of these patients to further assess which patients benefit from BLT resection^{16,40}. The role of a composite outcome measure such as Textbook Outcome, which has been described in other fields, is therefore even more relevant for BLT patients⁴¹. The authors propose surgeons and treating physicians to aspire results comparable to i.e. donors participating in living liver transplantation⁴². The authors will therefore initiate drafting of an international Textbook Outcome in BLT patients.

In conclusion, 30-day postoperative outcomes after resection of BLT in this nationwide population-based study are good. BLT resection is safe and can be performed when indicated. LLR is preferred over OLR in appropriately selected patients because of short-term benefits. Although the current study encompasses observations in the Netherlands, the nationwide design and inclusion size provides insights for shared decision making as well as an international benchmark for quality evaluation.

References

1. Margonis GA, Ejaz A, Spolverato G, Rastegar N, Anders R, Kamel IR, et al. Benign solid tumors of the liver: management in the modern era. *J Gastrointest Surg*. 2015;19(6):1157-1168.
2. European Association for the Study of the L. EASL Clinical Practice Guidelines on the management of benign liver tumours. *J Hepatol*. 2016;65(2):386-398.
3. Kaltenbach TE, Engler P, Kratzer W, Oeztuerk S, Seufferlein T, Haenle MM, et al. Prevalence of benign focal liver lesions: ultrasound investigation of 45,319 hospital patients. *Abdom Radiol (NY)*. 2016;41(1):25-32.
4. Colli A, Fraquelli M, Massironi S, Colucci A, Paggi S, Conte D. Elective surgery for benign liver tumours. *Cochrane Database Syst Rev*. 2007(Issue 1). Article number: CD005164.
5. Edmondson HA, Henderson B, Benton B. Liver-cell adenomas associated with use of oral contraceptives. *N Engl J Med*. 1976;294(9):470-472.
6. Stoot JH, Coelen RJ, De Jong MC, Dejong CH. Malignant transformation of hepatocellular adenomas into hepatocellular carcinomas: a systematic review including more than 1600 adenoma cases. *HPB (Oxford)*. 2010;12(8):509-522.
7. van Aalten SM, de Man RA, JN IJ, Terkivatan T. Systematic review of haemorrhage and rupture of hepatocellular adenomas. *Br J Surg*. 2012;99(7):911-916.
8. Farges O, Ferreira N, Dokmak S, Belghiti J, Bedossa P, Paradis V. Changing trends in malignant transformation of hepatocellular adenoma. *Gut*. 2011;60(1):85-89.
9. Dokmak S, Belghiti J. Will weight loss become a future treatment of hepatocellular adenoma in obese patients? *Liver Int*. 2015;35(10):2228-2232.
10. Haring MPD, Gouw ASH, de Haas RJ, Cuperus FJC, de Jong KP, de Meijer VE. The effect of oral contraceptive pill cessation on hepatocellular adenoma diameter: A retrospective cohort study. *Liver Int*. 2019;39(5):905-913.
11. Klompenhouwer AJ, Broker MEE, Thomeer MGJ, Gaspersz MP, de Man RA, JNM IJ. Retrospective study on timing of resection of hepatocellular adenoma. *Br J Surg*. 2017;104(12):1695-1703.
12. Giuliani F, Ardito F, Vellone M, Giordano M, Ranucci G, Piccoli M, et al. Reappraisal of surgical indications and approach for liver hemangioma: single-center experience on 74 patients. *Am J Surg*. 2011;201(6):741-748.
13. Charny CK, Jarnagin WR, Schwartz LH, Frommeyer HS, DeMatteo RP, Fong Y, et al. Management of 155 patients with benign liver tumours. *Br J Surg*. 2001;88(6):808-813.
14. Belghiti J, Cauchy F, Paradis V, Vilgrain V. Diagnosis and management of solid benign liver lesions. *Nat Rev Gastroenterol Hepatol*. 2014;11(12):737-749.
15. Hoekstra LT, Bieze M, Erdogan D, Roelofs JJ, Beuers UH, van Gulik TM. Management of giant liver hemangiomas: an update. *Expert Rev Gastroenterol Hepatol*. 2013;7(3):263-268.
16. van Rosmalen BV, de Graeff JJ, van der Poel MJ, de Man IE, Besselink M, Abu Hilal M, et al. Impact of open and minimally invasive resection of symptomatic solid benign liver tumours on symptoms and quality of life: a systematic review. *HPB (Oxford)*. 2019;21(9):1119-1130.
17. Hoffmann K, Unsinn M, Hinz U, Weiss KH, Waldburger N, Longerich T, et al. Outcome after a liver resection of benign lesions. *HPB (Oxford)*. 2015;17(11):994-1000.
18. Bieze M, Busch OR, Tanis PJ, Verheij J, Phoa SS, Gouma DJ, et al. Outcomes of liver resection in hepatocellular adenoma and focal nodular hyperplasia. *HPB (Oxford)*. 2014;16(2):140-149.
19. Kneuert PJ, Marsh JW, de Jong MC, Covert K, Hyder O, Hirose K, et al. Improvements in quality of life after surgery for benign hepatic tumors: Results from a dual center analysis. *Surgery*. 2012;152(2):193-201.
20. Herman P, Coelho FF, Perini MV, Lupinacci RM, D'Albuquerque LA, Cecconello I. Hepatocellular adenoma: an excellent indication for laparoscopic liver resection. *HPB (Oxford)*. 2012;14(6):390-395.
21. Landi F, De' Angelis N, Scatton O, Vidal X, Ayav A, Muscari F, et al. Short-term outcomes of laparoscopic vs. open liver resection for hepatocellular adenoma: a multicenter propensity score adjustment analysis by the AFC-HCA-2013 study group. *Surg Endosc*. 2017;31(10):4136-4144.
22. van der Werf LR, Kok NFM, Buis CI, Grunhagen DJ, Hoogwater FJH, Swijnenburg RJ, et al. Implementation and first results of a mandatory, nationwide audit on liver surgery. *HPB (Oxford)*. 2019;21(10):1400-1410.

23. Couinaud C. [The anatomy of the liver]. *Ann Ital Chir.* 1992;63(6):693-697.
24. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg.* 2009;250(2):187-196.
25. Rahbari NN, Garden OJ, Padbury R, Maddern G, Koch M, Hugh TJ, et al. Post-hepatectomy haemorrhage: a definition and grading by the International Study Group of Liver Surgery (ISGLS). *HPB (Oxford).* 2011;13(8):528-535.
26. Hughes MJ, Chong J, Harrison E, Wigmore S. Short-term outcomes after liver resection for malignant and benign disease in the age of ERAS. *HPB (Oxford).* 2016;18(2):177-182.
27. Wabitsch S, Kastner A, Haber PK, Benzing C, Krenzien F, Andreou A, et al. Laparoscopic Versus Open Liver Resection for Benign Tumors and Lesions: A Case Matched Study with Propensity Score Matching. *J Laparoendosc Adv Surg Tech A.* 2019;29(12):1518-1525.
28. Kim Y, Amini N, He J, Margonis GA, Weiss M, Wolfgang CL, et al. National trends in the use of surgery for benign hepatic tumors in the United States. *Surgery.* 2015;157(6):1055-1064.
29. Abdel Wahab M, El Nakeeb A, Ali MA, Mahdy Y, Shehta A, Abdulrazek M, et al. Surgical Management of Giant Hepatic Hemangioma: Single Center's Experience with 144 Patients. *J Gastrointest Surg.* 2018;22(5):849-858.
30. Erdogan D, Busch OR, Gouma DJ, van Gulik TM. Morbidity and mortality after liver resection for benign and malignant hepatobiliary lesions. *Liver Int.* 2009;29(2):175-180.
31. Kamphues C, Engel S, Denecke T, Bova R, Hippler-Benscheidt M, Puhl G, et al. Safety of liver resection and effect on quality of life in patients with benign hepatic disease: single center experience. *BMC Surg.* 2011;11:16.
32. Dokmak S, Fteriche FS, Borscheid R, Cauchy F, Farges O, Belghiti J. 2012 Liver resections in the 21st century: we are far from zero mortality. *HPB (Oxford).* 2013;15(11):908-915.
33. Tohme S, Varley PR, Landsittel DP, Chidi AP, Tsung A. Preoperative anemia and postoperative outcomes after hepatectomy. *HPB (Oxford).* 2016;18(3):255-261.
34. Olthof PB, Elfrink AKE, Marra E, Belt EJT, van den Boezem PB, Bosscha K, et al. Volume-outcome relationship of liver surgery: a nationwide analysis. *Br J Surg.* 2020;107(7):917-926.
35. Cipriani F, Rawashdeh M, Stanton L, Armstrong T, Takhar A, Pearce NW, et al. Propensity score-based analysis of outcomes of laparoscopic versus open liver resection for colorectal metastases. *Br J Surg.* 2016;103(11):1504-1512.
36. Ciria R, Cherqui D, Geller DA, Briceno J, Wakabayashi G. Comparative Short-term Benefits of Laparoscopic Liver Resection: 9000 Cases and Climbing. *Ann Surg.* 2016;263(4):761-777.
37. Schiffman SC, Kim KH, Tsung A, Marsh JW, Geller DA. Laparoscopic versus open liver resection for metastatic colorectal cancer: a metaanalysis of 610 patients. *Surgery.* 2015;157(2):211-222.
38. van der Poel MJ, Fichtinger RS, Bemelmans M, Bosscha K, Braat AE, de Boer MT, et al. Implementation and outcome of minor and major minimally invasive liver surgery in the Netherlands. *HPB (Oxford).* 2019;21(12):1734-1743.
39. Ardito F, Aldrighetti L, Guglielmi A, Jovine E, Cillo U, Ferrero A, et al. Surgical Management of Hepatic Benign Disease: Have the Number of Liver Resections Increased in the Era of Minimally Invasive Approach? Analysis from the I Go MILS (Italian Group of Minimally Invasive Liver Surgery) Registry. *J Gastrointest Surg.* 2020;24(10):2233-2243.
40. van Rosmalen BV, Bieze M, Besselink MG, Tanis P, Verheij J, Phoa SS, et al. Long-term outcomes of resection in patients with symptomatic benign liver tumours. *HPB (Oxford).* 2016;18(11):908-914.
41. van Roessel S, Mackay TM, van Dieren S, van der Schelling GP, Nieuwenhuijs VB, Bosscha K, et al. Textbook Outcome: Nationwide Analysis of a Novel Quality Measure in Pancreatic Surgery. *Ann Surg.* 2020;271(1):155-162.
42. Soubrane O, Eguchi S, Uemoto S, Kwon CHD, Wakabayashi G, Han HS, et al. Minimally Invasive Donor Hepatectomy for Adult Living Donor Liver Transplantation: An International, Multi-Institutional Evaluation of Safety, Efficacy and Early Outcomes. *Ann Surg.* 2020. Epub ahead of print.

Supplementary material

Table S1. Baseline characteristics for patients diagnosed with a benign liver tumour (BLT) between 2014 and 2019 in the Netherlands who underwent liver resection stratified per type of BLT.

Factor	Hepatocellular adenoma	Haemangioma	Focal nodular hyperplasia	p-value
	N (%)	N (%)	N (%)	
Total	245	86	84	
Patient characteristics				
Sex				<0.001
Male	16 (7)	23 (27)	9 (11)	
Female	229 (93)	63 (73)	75 (89)	
Missing				
Age in years				<0.001
< 50	193 (79)	22 (26)	63 (75)	
50 - 64	38 (16)	30 (47)	15 (18)	
65 - 79	13 (5)	24 (27)	6 (7)	
> 80	1 (0)	0 (0)	0 (0)	
Charlson Comorbidity Index (CCI)				
0 / 1	214 (87)	65 (76)	77 (92)	0.006
2 +	31 (13)	21 (24)	7 (8)	
Body Mass Index (BMI)	Mean (sd)	28.2 (5.8)	26.2 (5.1)	26.0 (6.4)
American Society of Anesthesiology (ASA) classification				0.002
ASA I / II	218 (89)	71 (84)	77 (92)	0.214
ASA III+	26 (11)	14 (16)	7 (8)	
Missing	1	1	0	
History of liver resection				0.386
No	235 (98)	81 (99)	84 (100)	
Yes	5 (2)	1 (1)	0 (0)	
Missing	5	4	0	
History of liver diseases				0.947
No	233 (97)	83 (98)	81 (98)	
Yes	7 (3)	2 (2)	2 (2)	
Missing	5	1	1	
Histopathological liver disease				<0.001
Normal liver	129 (56)	65 (88)	67 (87)	
Steatosis	79 (36)	5 (8)	7 (10)	
Steato-hepatitis	12 (5)	1 (1)	1 (1)	
Cirrhosis	3 (1)	2 (2)	1 (1)	
Sinusoidal dilatation	6 (2)	1 (1)	1 (1)	
Missing	16	12	7	
Tumour- and operative characteristics				
Number of BLT				0.020
1	149 (69)	64 (77)	68 (84)	
2	21 (10)	10 (12)	3 (4)	
3	12 (6)	5 (6)	6 (7)	
≥4	33 (15)	4 (5)	4 (5)	
Missing	30	4	3	
Maximum diameter of largest BLT (mm*)				0.030
< 50	47 (23)	27 (40)	22 (30)	
≥ 50	155 (77)	41 (60)	51 (70)	
Missing	43	18	11	

Bilobar disease				0.268
	No	151 (62)	60 (70)	57 (70)
	Yes	93 (38)	26 (30)	25 (30)
	Missing	1	0	2
Major liver resection				0.051
	No	182 (74)	71 (83)	72 (86)
	Yes	63 (26)	15 (17)	12 (14)
Type of liver resection				0.036
	Right hemihepatectomy	39 (15)	10 (12)	9 (11)
	Left hemihepatectomy	12 (5)	2 (2)	1 (1)
	Extended right hemihepatectomy	1 (0)	3 (4)	0 (0)
	Extended left hemihepatectomy	1 (0)	0 (0)	0 (0)
	Segment resection	143 (59)	43 (51)	57 (69)
	Wedge resection	45 (19)	26 (31)	16 (19)
	Missing	4	2	1
Surgical approach				0.820
	OLR	114 (47)	38 (44)	33 (39)
	LLR	131 (53)	48 (56)	51 (61)
Type of hospital[∞]				0.003
	Regional hospital	64 (26)	39 (45)	23 (27)
	Tertiary referral hospital	181 (74)	47 (55)	61 (73)
Year of procedure				0.852
	2014	36 (15)	14 (16)	13 (16)
	2015	37 (15)	19 (32)	14 (16)
	2016	52 (21)	13 (15)	14 (16)
	2017	51 (21)	20 (23)	19 (23)
	2018	40 (16)	12 (14)	15 (18)
	2019	29 (12)	8 (9)	9 (11)

§ History of liver disease containing liver cirrhosis, oesophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis

OLR: Open liver resection; LLR: Laparoscopic liver resection

*millimetre

[∞] Type of hospital: tertiary referral centre are defined as hospitals with highest expertise on oncologic surgery

Figure S1a. Funnel-plot of between-hospital variation in 30-day overall morbidity after liver resection for benign liver tumours in the Netherlands between 2014 - 2019.

Figure S1b. Funnel-plot of between-hospital variation in 30-day major morbidity after liver resection for benign liver tumours in the Netherlands between 2014 - 2019.

PART II

**IMPACT OF HOSPITAL VARIATION ON
OUTCOMES AFTER RESECTION OF
COLORECTAL LIVER METASTASES**

CHAPTER 6

PREOPERATIVE IMAGING FOR COLORECTAL LIVER METASTASES: A NATIONWIDE POPULATION-BASED STUDY

A.K.E. Elfrink, M. Pool, L.R. van der Werf, E. Marra, M.C. Burgmans, M.R. Meijerink, M. den Dulk, P.B. van den Boezem, W.W. te Riele, G.A. Patijn, M.W.J.M. Wouters, W.K.G. Leclercq, M.S.L. Liem, P.D. Gobardhan, C.I. Buis, K.F.D. Kuhlmann, C. Verhoef, M.G. Besselink, D.J. Grünhagen, J.M. Klaase, N.F.M. Kok, [Dutch Hepato Biliary Audit Group, Collaborators](#)

BJS Open. 2020 Aug;4(4):605-621

Abstract

Introduction

In patients with colorectal liver metastases (CRLM) preoperative may include contrast-enhanced(ce)MRI and ^{18}F -FDG-PET-CT. This study assessed trends and variation between hospitals and oncological networks in the use of preoperative imaging in the Netherlands.

Methods

All patients who underwent liver resection for CRLM in the Netherlands between 2014 and 2018 were retrieved from a nationwide auditing database. Multivariable logistic regression analysis was used to assess use of ceMRI, ^{18}F -FDG-PET-CT and combined ceMRI and ^{18}F -FDG-PET-CT and trends in preoperative imaging and hospital and oncological network variation.

Results

In total 4510 patients were included of whom 1562 underwent ceMRI, 872 underwent ^{18}F -FDG-PET-CT and 1293 underwent combined ceMRI and ^{18}F -FDG-PET-CT. Use of ceMRI increased over time from 9.6% to 26.2% ($p < 0.001$), use of ^{18}F -FDG-PET-CT decreased (25.0% to 6.0%, $p < 0.001$) and use of ceMRI and ^{18}F -FDG-PET-CT (16.9%) remained stable. Unadjusted variation in use of ceMRI, ^{18}F -FDG-PET-CT and combined ceMRI and ^{18}F -FDG-PET-CT ranged from 6.0% to 100% between hospitals. After case-mix correction, hospital and oncological network variation was present regarding all imaging.

Conclusion

Significant variation exists concerning use of preoperative imaging for CRLM between hospitals and oncological networks in the Netherlands. The use of MRI is increasing whereas use of ^{18}F -FDG-PET-CT is decreasing.

Introduction

Colorectal liver metastases (CRLM) are the leading indication for liver surgery in the Netherlands accounting for approximately 1000 liver resections each year¹.

Current multidisciplinary management of CRLM by surgeons, interventional radiologists, radiation therapist and oncologists demands detailed preoperative knowledge consisting of anatomical location in relation to vascular structures, number and size of CRLM and individual patients risks and preferences^{2,3}.

Increasingly used options include Contrast Enhanced Magnetic Resonance Imaging (ceMRI) and ¹⁸Fluoro-Deoxy-Glucose Positron Emission Tomography (¹⁸F-FDG-PET-CT) scan⁴⁻⁶. CeMRI has been suggested to have a significant advantage over CT in detecting additional (small) liver metastases, in particular of subcapsular or peribiliary origin^{4,7-11}. The oncological advantage of a preoperative ¹⁸F-FDG-PET-CT to assess CRLM is doubtful¹². ¹⁸F-FDG-PET-CT, however seems to have an advantage to identify extrahepatic metastases of colorectal cancer¹³. Some authors propose to use ¹⁸F-FDG-PET-CT during follow up to assess intrahepatic and extrahepatic metastases^{14,15}. Several European countries have preoperative imaging guidelines which contain advice regarding the use of both ceMRI and ¹⁸F-FDG-PET-CT¹⁶.

Guidelines in the United Kingdom, Japan, as well as the ESMO Consensus Guideline on Metastatic Colorectal Cancer point out that ceMRI and ¹⁸F-FDG-PET-CT can be performed in the preoperative workup¹⁷⁻²⁰. However, these guidelines indicate that more research is needed to address the added value of preoperative imaging in CRLM patients.

The Dutch guidelines indicate that at baseline either a CT should be performed to assess the presence of CRLM^{21,22}. If treatment is considered, ceMRI is can be performed to detect lesions smaller than 10 millimetre (mm). The guideline further states that ¹⁸F-FDG-PET-CT should not be performed as part of preoperative work-up. ¹⁸F-FDG-PET-CT should only be used on indication, if extrahepatic metastases are suspected.

The aims of this study were to give a population-based overview of factors associated with the use of different types of preoperative imaging modalities, to report on trends over the years and to assess variation between hospitals and oncological networks in the Netherlands.

Methods

This was a population-based nationwide cohort study performed in the Netherlands with data from the Dutch Hepato Biliary Audit (DHBA)²³. The Netherlands is a Western-Europe country with approximately 17 million inhabitants living on 33.883 square kilometers²⁴. Health care has been arranged in 71 hospitals including 7 university hospitals and one comprehensive cancer centre^{23,25}. Twenty-five hospitals perform liver surgery. A national minimum annual centre volume of 20 liver resections and infrastructural (i.e. 24/7 availability of an interventional radiologist) requirements have led to concentration of liver surgery²⁶. Hospitals performing liver surgery in the Netherlands have been obliged to register liver resections in the DHBA since 2013. Detailed information on patient- and disease characteristics as well as diagnostic- and treatment information was collected from 2013 onwards. Earlier, information regarding the formation and content of the DHBA has been described²³. Data verification provided insight in completeness and accuracy of the DHBA²⁷. During this process, data in the DHBA was compared to the Dutch Cancer Registry. The completeness of data retrieved from 2015 was 97%²³.

Patient selection

All consecutive patients who underwent liver resection for CRLM between 1 January 2014 and 31 December 2018, and were registered in the DHBA before 22 March 2019 were included in this study. Patients who underwent ablation alone for CRLM were not included in this study as registration in the DHBA commenced on 1 January 2018 onwards. Patients were considered not eligible for analysis when missing data included date of birth, preoperative imaging modalities used, date of surgery, type of procedure or type of origin of the tumour for which resection was performed. No ethical approval was needed as the DHBA is an obligatory audit from the Dutch inspectorate of healthcare and all analyses were performed on an anonymised dataset.

Patient groups

In all patients a CT scan of the abdomen and chest was performed as baseline imaging. Patients were divided in four groups for analysis: 1) no additional imaging of the liver, 2) preoperative imaging consisting of CT and ceMRI of the liver, 3) preoperative imaging consisting of CT and ¹⁸F-FDG-PET-CT, and 4) preoperative imaging consisting of CT, ceMRI and ¹⁸F-FDG-PET-CT.

Variables

Studied variables included patient characteristics (age, sex, American Society of Anesthesiologists (ASA) classification, comorbidity score according the Charlson Comorbidity Index (CCI), liver disease prior to surgery, previous liver surgery for CRLM and year of surgery), tumour characteristics (number of CRLM, diameter of largest CRLM prior to treatment on preoperative CT-scan and synchronous or metachronous metastases, presence of extrahepatic metastases and if metastases were bilobar) and type of and oncological network where treatment took place. Factors contributing to the use of ceMRI, ^{18}F -FDG-PET-CT and combined use of ceMRI and ^{18}F -FDG-PET-CT were primary variables for case-mix correction. Other studied variables and parameters were the use of the different preoperative imaging modalities over the years and the between-hospital and between oncological network variation in the use of preoperative imaging modalities. Both were corrected for case-mix variables.

All variables concerning tumour characteristics were based on normal preoperative workup before surgery and therefore assessed using preoperative CT-scan before additional imaging was performed. However, as a result of the retrospective nature of this study these variables might resemble characteristics of the CRLM after ceMRI or ^{18}F -FDG-PET-CT. Sensitivity analyses were performed in all statistical models which consisted of dropping tumour characteristics.

As described previously, oncological networks were classified according to treatment collaboration between hospitals or topographical location if no collaboration network was present (supplementary figure 1)²⁸. An oncological network consists of one or more tertiary referral centres, including one of the seven university hospitals in the Netherlands. All regional hospitals are included in an oncological network of which a few perform liver surgery. Regional hospitals not performing liver surgery refer patients to either a regional hospital performing liver surgery or tertiary referral centre for the treatment of CRLM based on agreements in the oncology network. All hospitals in an oncological network have multidisciplinary meetings using video conference to discuss patients with CRLM in order to obtain a patient-centered treatment plan. If necessary, patients can be referred to tertiary referral centres in case of patients with high surgical risk as a result of comorbidities or more complex surgical procedures²⁸.

Statistical analysis

Baseline characteristics were compared between all groups using the Chi-square test or Fisher exact test as appropriate for categorical variables. Continuous variables were compared using independent two-sample t-test.

Identification of case-mix factors, defined as factors which are non-modifiable patient- and tumour-characteristics influencing the use of the different preoperative imaging modalities, was performed. Potential case-mix factors were entered in univariable and multivariable multilevel logistic regression models, one model for each preoperative imaging modality. A multilevel analysis was used to take into account the changes in hospital policy as well as unmeasured similarities of patients within the year of surgery. Separate analysis for trends in preoperative imaging over the years was performed using univariable and multivariable logistic regression for each treatment modality. These models were performed using case-mix variables to correct for confounding factors associated with the use of the specific preoperative treatment modality.

Case-mix correction was performed using the observed / expected ratio (O / E ratio). This ratio is calculated by dividing the observed number of patients with a preoperative imaging modality by the number of patients expected to receive a preoperative imaging modality. The expected number of patients was based on a multivariable multilevel logistic regression model including case-mix variables, resulting in case-mix corrected variability in the use of preoperative imaging modalities between hospitals and oncological networks. An O / E ratio of 1 is considered to implicate that a hospital or oncological network performed exactly the expected of preoperative imaging. If the O / E ratio is below 1 a hospital or oncological network performed less preoperative imaging than expected. If the O / E ratio is higher than 1 a hospital or oncological network performed more preoperative imaging than expected. On the basis of the model and O / E ratios of all hospitals or oncological networks 95% Confidence Intervals (CI) are calculated indicating statistically significant outliers.

For all multivariable analyses a two-step method was undertaken. All variables were tested in a univariable models per outcome variable. If a significant association was found ($P < 0.1$, Wald test) the variable was entered in the multivariable model. Statistical significance was defined as a two-sided p-value < 0.05 in the multivariable model. Outcomes were adjusted odds ratios (aOR) and 95% confidence intervals (CI). Multicollinearity was assessed in all multivariable models. This was done by calculation of the variance inflation factor (VIF). A VIF higher than 2.5 was considered to be an indication for multicollinearity.

All analyses were performed in R version 3.2.2® (R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

Results

During the inclusion period 4846 patients underwent surgical liver resection for CRLM. Of these 336 patients were excluded because of missing information regarding baseline characteristics, preoperative imaging techniques, postoperative outcomes and postoperative oncologic classification. A total of 4510 patients were analysed of whom 1562 (35%) patients underwent ceMRI and of whom 872 (19%) patients underwent a ¹⁸F-FDG-PET-CT. Some 1293 (29%) patients underwent both a ceMRI and a ¹⁸F-FDG-PET-C. The remaining 783 (17%) patients did not receive any additional imaging apart from CT-scan.

Regarding baseline characteristics, in patients with a history of liver disease, preoperative chemotherapy, synchronous metastases and rectal primary tumour a ceMRI or combined ceMRI and ¹⁸F-FDG-PET-CT was used more often. In case of a larger maximum diameter of largest CRLM a ceMRI was used less often. If more CRLM were present ceMRI or combined ceMRI and ¹⁸F-FDG-PET-CT was used more often. In patients with extrahepatic metastases ¹⁸F-FDG-PET-CT was used more often (table 1).

Table 1. Baseline characteristics regarding preoperative imaging in patients diagnosed with colorectal liver metastases between 2014 and 2018 in the Netherlands.

Factor		No additional imaging	MRI-scan	PET-CT scan	Both MRI and PET-CT scan	P-value
		N (%)	N (%)	N (%)	N (%)	
Total		783	1562	872	1293	
Sex						0.078
	Male	468 (60)	1012 (65)	555 (64)	796 (62)	
	Female	315 (40)	550 (35)	317 (36)	497 (38)	
Age in years						0.038
	≤70	496 (63)	1001 (64)	520 (60)	867 (67)	
	>70	285 (37)	559 (36)	351 (40)	424 (33)	
	Missing	2	2	1	2	
Charlson Comorbidity Index (CCI)						<0.001
	0 / 1	593 (77)	1186 (73)	598 (69)	955 (75)	
	2 +	180 (23)	352 (23)	269 (31)	324 (25)	
	Missing	10	24	5	14	
Body Mass Index (BMI)						0.124
	Mean (sd)	26.1 (4.4)	26.3 (4.3)	26.1 (4.4)	26.5 (4.4)	
American Society of Anesthesiology (ASA) classification						0.032
	ASA I / II	606 (78)	1271 (82)	654 (79)	1058 (83)	

	ASA III+	172 (22)	286 (18)	171 (21)	223 (17)	
	Missing	5	5	47	12	
Liver resection in the past						0.002
	No	615 (80)	1303 (85)	681 (79)	1063 (83)	
	Yes	156 (20)	238 (15)	181 (21)	222 (17)	
	Missing	12	21	10	8	
History of liver disease§						0.145
	No	758 (99)	1499 (98)	839 (98)	1225 (99)	
	Yes	9 (1)	29 (2)	13 (2)	11 (1)	
	Missing	16	34	20	57	
History of preoperative chemotherapy						<0.001
	No	457 (65)	1004 (70)	581 (75)	800 (69)	
	Yes	252 (35)	429 (30)	194 (25)	367 (31)	
	Missing	74	129	97	126	
Number of lesions						<0.001
	1	353 (47)	617 (41)	440 (52)	515 (41)	
	2	153 (21)	339 (22)	199 (24)	260 (20)	
	3	91 (12)	160 (11)	95 (11)	157 (12)	
	4	52 (7)	112 (7)	41 (5)	110 (9)	
	5	28 (4)	81 (5)	24 (3)	57 (5)	
	>5	66 (9)	214 (14)	45 (5)	162 (13)	
	Missing	40	39	28	32	
Maximum diameter of largest CRLM* (mm)						<0.001
	< 20	169 (26)	514 (36)	180 (25)	369 (31)	
	20-34	232 (36)	544 (38)	297 (41)	437 (37)	
	35-54	137 (21)	239 (17)	157 (21)	231 (20)	
	> 55	106 (17)	137 (9)	94 (13)	141 (12)	
	Missing	139	128	144	115	
Location primary tumour						<0.001
	Colon	527 (67)	974 (63)	614 (70)	793 (61)	
	Rectal	254 (23)	584 (37)	258 (30)	500 (29)	
	Missing	2	4	0	0	
Nodal stage primary tumour						0.109
	pN0	194 (36)	405 (37)	281 (41)	366 (37)	
	pN1	206 (36)	406 (37)	233 (34)	349 (36)	
	pN2	145 (27)	284 (26)	165 (25)	267 (27)	
	Unknown	238	467	193	311	
Type of metastasis						<0.001
	Metachronous	390 (50)	723 (47)	552 (64)	697 (55)	
	Synchronous	384 (50)	827 (53)	312 (36)	580 (45)	
	Missing	9	12	8	16	
Extrahepatic disease						<0.001
	No	628 (91)	1383 (94)	702 (89)	1110 (91)	
	Yes	61 (9)	92 (6)	91 (11)	109 (9)	
	Missing	94	87	79	74	
Type of hospital						<0.001
	Regional hospitals	350 (45)	928 (59)	499 (57)	713 (55)	
	Tertiary referral centres	433 (55)	634 (41)	373 (43)	580 (56)	
Year of surgery						<0.001
	2014	178 (23)	150 (10)	249 (28)	194 (15)	
	2015	142 (18)	250 (16)	219 (25)	273 (21)	
	2016	155 (19)	340 (22)	224 (26)	289 (22)	
	2017	150 (20)	413 (26)	128 (15)	318 (25)	
	2018	158 (20)	409 (26)	52 (6)	219 (17)	

§ History of liver disease containing liver cirrhosis, oesophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis

Factors associated with the use of different preoperative imaging modalities

In multivariable multilevel logistic regression analysis factors positively associated with preoperative use of ceMRI included having an increasing number of CRLM (five or tumours versus 1 tumour, aOR 2.45, CI 1.89 – 3.17, $p < 0.001$), a rectal primary tumour (aOR 1.44, CI 1.26 – 1.67, $p < 0.001$) and synchronous metastases (aOR 1.22, 1.05 – 1.41, $p = 0.012$) (table 2a). Factors negatively associated with preoperative use of ceMRI included high ASA score (aOR 0.74, CI 0.62 – 0.88, $p = 0.001$), history of liver resection (aOR 0.79, CI 0.66 – 0.94, $p = 0.006$), larger maximum diameter of the largest CRLM (<20 mm vs. >55mm aOR 0.32, CI 0.25 – 0.40, $p < 0.001$), extrahepatic metastases (aOR 0.74, CI 0.60 – 0.90, $p = 0.003$) and treatment in a tertiary referral centre (aOR 0.79, CI 0.66 – 0.89, $p < 0.001$) (table 2a).

Table 2a. Association model of patient and tumour factors with the utilization of preoperative ceMRI in patients with colorectal liver metastases in the Netherlands between 2014-2018.#

Factor	N	Univariable logistic regression			Multivariable logistic regression		
		OR	CI (95%)	P-value	aOR	CI (95%)	P-value
Sex				0.310			
Male	2831	1					
Female	1679	0.94	0.83 – 1.06				
Age in years				0.015			0.632
< 50	315	1			1		
50 - 64	1543	0.93	0.72 – 1.21	0.603	0.96	0.50 – 1.96	0.762
65 - 79	2331	0.81	0.63 – 1.04	0.097	0.88	0.71 – 1.28	0.383
> 80	314	0.67	0.48 – 0.93	0.016	0.86	0.66 – 1.17	0.418
Missing*	7						
Charlson Comorbidity Index (CCI)				0.012			0.753
0 / 1	3332	1			1		
2+	1125	0.84	0.73 – 0.96		0.98	0.83 – 1.14	
Missing*	53						
Body Mass Index		1.02	1.00 – 1.04	0.023	1.02	1.01 – 1.04	0.014
American Society of Anesthesiology (ASA) classification				0.005			0.001
I / II	3589	1			1		
III +	852	0.80	0.69 – 0.94		0.74	0.62 – 0.88	
Missing*	69						
History of liver disease§				0.811			
No	4321	1					
Yes	62	1.07	0.64 – 1.83				
Missing*	127						
History of liver resection				<0.001			0.006
No	3662	1			1		
Yes	797	0.75	0.64 – 0.87		0.79	0.66 – 0.94	
Missing*	51						
History of preoperative chemotherapy				0.708			

No	2842	1					
Yes	1242	1.03	0.89 – 1.18				
Missing*	426						
Number of CRLM				<0.001			<0.001
1	1925	1			1		
2	951	1.19	1.02 – 1.40	0.031	1.19	1.00 – 1.42	0.051
3	503	1.19	0.98 – 1.46	0.086	1.28	1.02 – 1.60	0.047
4	315	1.67	1.30 – 2.17	<0.001	1.71	1.29 – 2.27	0.001
5	190	1.86	1.34 – 2.61	<0.001	1.86	1.29 – 2.69	0.002
>5	487	2.37	1.89 – 3.00	<0.001	2.45	1.89 – 3.17	<0.001
Missing*	139						
Maximum diameter of largest CRLM (mm)				<0.001			<0.001
< 20	1232	1			1		
20 - 34	1510	0.73	0.62 – 0.86	<0.001	0.72	0.61 – 0.87	<0.001
35 - 54	764	0.63	0.52 – 0.77	<0.001	0.66	0.53 – 0.81	<0.001
> 55	478	0.55	0.44 – 0.69	<0.001	0.56	0.44 – 0.72	<0.001
Missing	526	0.34	0.27 – 0.42	<0.001	0.32	0.25 – 0.40	<0.001
Bilobar disease				0.716			
No	2423	1					
Yes	2043	1.02	0.91 – 1.16				
Missing*	44						
Location primary tumour				<0.001			<0.001
Colon	2908	1			1		
Rectal	1596	1.37	1.20 – 1.56		1.44	1.25 – 1.67	
Missing*	6						
Nodal stage primary tumour				0.607			
pN0	1246	1					
pN1	1194	1.06	0.90 – 1.25	0.489			
pN2	861	1.10	0.91 – 1.31	0.323			
Missing	1209	1.11	0.94 – 1.31	0.204			
Type of metastases				<0.001			0.012
Metachronous	2362	1			1		
Synchronous	2103	1.34	1.19 – 1.52		1.22	1.05 – 1.41	
Missing*	45						
Extrahepatic metastases				<0.001			0.003
No	3823	1			1		
Yes	566	0.66	0.56 – 0.80		0.74	0.60 – 0.90	
Missing	121						
Type of hospital[∞]				<0.001			<0.001
Regional hospitals	2490	1			1		
Tertiary referral centres	2020	0.78	0.69 – 0.88		0.79	0.66 – 0.89	

Univariable and multivariable multilevel logistic regression model with individuals nested for year of surgery

(a)OR (Adjusted) odds ratio

CI Confidence interval

* Missing not included in analyses based on relatively small group

§ History of liver disease containing liver cirrhosis, oesophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis

∞ Type of hospital: tertiary referral centre are defined as hospitals with highest expertise on oncologic surgery

In multivariable multilevel logistic regression analysis, factors positively associated with preoperative use of ¹⁸F-FDG-PET-CT included higher CCI (aOR 1.22, CI 1.05 – 1.40, p=0.003), larger maximum diameter of the largest CRLM (<20 mm vs. >55mm aOR 1.29, CI 1.03 – 1.62, p=0.027) and extrahepatic metastases (aOR 1.45, CI 1.20 – 1.75, p<0.001) (table 2b). Factors

negatively associated with preoperative use of ^{18}F -FDG-PET-CT included only synchronous metastases (aOR 0.66, CI 0.58 – 0.76, $p < 0.001$) (table 2b).

Table 2b. Association model of patient and tumour factors with the utilization of preoperative ^{18}F -FDG-PET-CT in patients with colorectal liver metastases in the Netherlands between 2014-2018.#

Factor	N	Univariable multivariable regression			Multivariable logistic regression		
		OR	CI (95%)	P-value	aOR	CI (95%)	P-value
Sex				0.622			
Male	2831	1					
Female	1679	1.03	0.91 – 1.16				
Age in years				0.314			
< 50	315	1					
50 - 64	1543	1.13	0.88 – 1.44	0.333			
65 - 79	2331	1.22	0.97 – 1.55	0.096			
> 80	314	1.17	0.86 – 1.61	0.319			
Missing*	7						
Charlson Comorbidity Index (CCI)				<0.001			0.003
0 / 1	3332	1			1		
2+	1125	1.28	1.12 – 1.46		1.22	1.05 – 1.40	
Missing*	53						
Body Mass Index		1.00	0.99 – 1.02	0.815			
American Society of Anesthesiology (ASA) classification				0.444			
I / II	3589	1					
III +	852	0.94	0.81 – 1.10				
Missing*	69						
History of liver diseases§				0.156			
No	4321	1					
Yes	62	0.69	0.41 – 1.15				
Missing*	127						
History of liver resection				0.132			
No	3662	1					
Yes	797	1.12	0.97 – 1.31				
Missing*	51						
History of preoperative chemotherapy				0.044			0.164
No	2842	1			1		
Yes	1242	0.87	0.77 – 1.00		0.97	0.94 – 1.32	
Missing*	426						
Number of CRLM				0.056			0.235
1	1925	1			1		
2	951	0.95	0.81 – 1.11	0.498	0.89	0.75 – 1.06	0.170
3	503	1.02	0.84 – 1.24	0.845	1.04	0.85 – 1.34	0.786
4	315	0.94	0.74 – 1.19	0.582	0.96	0.73 – 1.26	0.561
5	190	0.75	0.56 – 1.02	0.067	0.80	0.57 – 1.12	0.206
>5	487	0.75	0.61 – 0.92	0.005	0.81	0.64 – 1.04	0.091
Missing*	139						
Maximum diameter of largest CRLM (mm)				0.060			0.018
< 20	1232	1			1		
20 - 34	1510	1.17	1.02 – 1.37	0.035	1.18	1.01 – 1.39	0.034
35 - 54	764	1.28	1.07 – 1.54	0.007	1.30	1.08 – 1.62	0.002

> 55	478	1.20	0.97 – 1.49	0.087	1.29	1.03 – 1.62	0.027
Missing	526	1.21	0.98 – 1.48	0.072	1.34	1.06 – 1.68	0.009
Bilobar disease				0.041			0.096
No	2423	1			1		
Yes	2043	1.13	1.01 – 1.27		1.15	0.97 – 1.36	
Missing*	44						
Location primary tumour				0.567			
Colon	2908	1					
Rectal	1596	0.96	0.85 – 1.09				
Missing*	6						
Nodal stage primary tumour				<0.001			0.104
pN0	1246	1			1		
pN1	1194	0.88	0.75 – 1.03	0.117	0.89	0.75 – 1.05	0.184
pN2	861	0.93	0.78 – 1.11	0.429	0.96	0.80 – 0.96	0.591
Missing	1209	0.66	0.56 – 0.78	<0.001	0.80	0.67 – 0.96	0.024
Type of metastases				<0.001			<0.001
Metachronous	2362	1			1		
Synchronous	2103	0.66	0.58 – 0.74		0.66	0.58 – 0.76	
Missing*	45						
Extrahepatic metastases				<0.001			<0.001
No	3823	1			1		
Yes	566	1.44	1.21 – 1.73		1.45	1.20 – 1.75	
Missing	121						
Type of hospital[∞]				0.317			
Regional hospitals	2490	1					
Tertiary referral centres	2020	0.94	0.84 – 1.06				

Univariable and multivariable multilevel logistic regression model with individuals nested for year of surgery

(a)OR (Adjusted) odds ratio

CI Confidence interval

* Missing not included in analyses based on relatively small group

§ History of liver disease containing liver cirrhosis, oesophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis

[∞] Type of hospital: tertiary referral centre is defined as hospitals with highest expertise on oncologic surgery

In multivariable multilevel logistic regression analysis, factors associated positively with preoperative use of a combination of ceMRI and ¹⁸F-FDG-PET-CT included rectal primary tumours only (aOR 1.23, CI 1.06 – 1.42, p=0.005) (table 2c). There were no factors associated negatively with the combined use of ceMRI and ¹⁸F-FDG-PET-CT.

Table 2c. Association model of patient and tumour factors with the utilization of preoperative ceMRI and ¹⁸F-FDG-PET-CT in patients with colorectal liver metastases in the Netherlands between 2014-2018.#

Factor	Univariable logistic regression				Multivariable logistic regression		
	N	OR	CI (95%)	P-value	aOR	CI (95%)	P-value
Sex				0.287			
Male	2831	1					
Female	1679	1.07	0.94 – 1.23				
Age in years				0.289			
< 50	315	1					
50 - 64	1543	1.04	0.80 – 1.36	0.802			
65 - 79	2331	0.96	0.74 – 1.24	0.730			
> 80	314	0.80	0.56 – 1.14	0.218			

Missing*	7							
Charlson Comorbidity Index (CCI)				0.929				
0 / 1	3332	1						
2+	1125	1.01	0.87 – 1.17					
Missing*	53							
Body Mass Index		1.01	1.00 – 1.03	0.091	1.01	0.99 – 1.04	0.204	
American Society of Anesthesiology (ASA) classification				0.056			0.126	
I / II	3589	1			1			
III +	852	0.85	0.72 – 1.00		0.87	0.73 – 1.04		
Missing*	69							
History of liver disease§				0.057			0.057	
No	4321	1			1			
Yes	62	0.54	0.27 – 1.01		0.51	0.26 – 1.02		
Missing*	127							
History of liver resection				0.010			0.760	
No	3662	1			1			
Yes	797	0.75	0.64 – 0.87		0.97	0.81 – 1.17		
Missing*	51							
History of preoperative chemotherapy				0.324				
No	2842	1						
Yes	1242	1.07	0.93 – 1.24					
Missing	426							
Number of CRLM				0.005			0.126	
1	1925	1			1			
2	951	1.03	0.86 – 1.23	0.738	0.93	0.76 – 1.13	0.467	
3	503	1.24	1.00 – 1.54	0.051	1.21	0.95 – 1.55	0.129	
4	315	1.47	1.14 – 1.89	0.002	1.28	0.95 – 1.71	0.099	
5	190	1.17	0.84 – 1.62	0.341	1.06	0.74 – 1.53	0.752	
>5	487	1.37	1.10 – 1.69	0.004	1.22	0.94 – 1.58	0.140	
Missing*	139							
Maximum diameter of largest CRLM (mm)				0.005			0.024	
< 20	1232	1			1			
20 - 34	1510	0.95	0.81 – 1.12	0.563	0.95	0.80 – 1.14	0.615	
35 - 54	764	1.01	0.83 – 1.23	0.892	1.04	0.85 – 1.28	0.691	
> 55	478	0.98	0.78 – 1.23	0.854	0.98	0.77 – 1.26	0.897	
Missing	526	0.65	0.51 – 0.83	<0.001	0.65	0.50 – 0.86	<0.001	
Bilobar disease				0.007			0.107	
No	2423	1			1			
Yes	2043	1.19	1.05 – 1.36		1.16	0.97 – 1.39		
Missing*	44							
Location primary tumour				0.004			0.005	
Colon	2908	1			1			
Rectal	1596	1.22	1.06 – 1.39		1.23	1.06 – 1.42		
Missing*	6							
Nodal stage primary tumour				0.047			0.016	
pN0	1246	1			1			
pN1	1194	0.99	0.83 – 1.18	0.837	0.93	0.77 – 1.12	0.430	
pN2	861	1.08	0.89 – 1.31	0.421	1.04	0.86 – 1.27	0.675	
Missing	1209	0.83	0.70 – 0.99	0.043	0.76	0.63 – 0.93	0.006	
Type of metastases				0.155				
Metachronous	2362	1						
Synchronous	2103	0.91	0.80 – 1.04					

Missing*	45			
Extrahepatic metastases				0.687
No	3823	1		
Yes	566	1.04	0.86 – 1.26	
Missing	121			
Type of hospital[∞]				0.954
Regional hospitals	2490	1		
Tertiary referral centres	2020	1.00	0.88 – 1.14	

Univariable and multivariable multilevel logistic regression model with individuals nested for year of surgery

(a)OR (Adjusted) odds ratio

CI Confidence interval

* Missing not included in analyses based on relatively small group

§ History of liver disease containing liver cirrhosis, oesophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis

[∞] Type of hospital: tertiary referral centre is defined as hospitals with highest expertise on oncologic surgery

Trends in use of different imaging modalities over the years

In the Netherlands, an increase in the use of ceMRI from 9.6% in 2014 to 26.2% in 2018 was observed. Univariable and multivariable logistic regression for trend over the years showed that this increase in use of preoperative ceMRI from 2014 to 2018 in the Netherlands was statistically significant (aOR 4.72, CI 3.69 – 6.05, $p < 0.001$) (figure 1, supplementary table 2a).

Figure 1. Case-mix corrected trend analysis using multivariable logistic regression for the use of pretreatment modalities for CRLM in the Netherlands between 2014 and 2018.

Displayed are adjusted Odds Ratios and 95% confidence intervals.

The use of preoperative ^{18}F -FDG-PET-CT between 2014 to 2016 was stable around 25%, although the use decreased in 2017 (14.7%) and 2018 (6.0%). Univariable and multivariable logistic regression for trend over the years showed that the decreasing trend was statistically significant (aOR 0.42, CI 0.29 – 0.54, $p < 0.001$) (figure 1, supplementary table 2b).

The use of combined preoperative ceMRI and ^{18}F -FDG-PET-CT was 15.0% in 2014. During 2015 to 2017 this increased to 24.6%. In 2018 in only 16.9% of the patients combined ceMRI and ^{18}F -FDG-PET-CT was used. Univariable and multivariable logistic regression for trend over the years showed concordant results regarding in the use of combined preoperative ceMRI and ^{18}F -FDG-PET-CT (figure 1, supplementary table 2c).

Variation in the use of different imaging modalities

Variation between hospitals and oncological networks was present in all forms of preoperative imaging modalities. After case-mix correction, significant hospital and oncological network variation was still present concerning all different types of preoperative imaging.

Unadjusted rates of percentage of patients with CRLM receiving ceMRI in Dutch hospitals ranged between 15.4% and 96.2% (figure 2a). After case-mix correction, widespread variation in the use of ceMRI in the Netherlands was observed. Seven hospitals performed more and eight hospitals performed less preoperative ceMRI than expected based on their case-mix (figure 2b). O / E ratios concerning the use of ceMRI between hospitals ranged between 0.21 – 1.51. Also, two oncological networks performed more preoperative ceMRI while two other oncological networks performed less preoperative ceMRI than expected with O/E ratios ranging between 0.75 – 1.23 (figure 2c).

Figure 2a. Unadjusted rates of between-hospital variation in the use of preoperative imaging with ceMRI in patients with colorectal liver metastases in the Netherlands between 2014 - 2018.

Figure 2b. Case-mix corrected funnel-plot of between-hospital variation in the use of preoperative imaging with ceMRI in patients with colorectal liver metastases in the Netherlands between 2014 - 2018.

Figure 2c. Case-mix corrected funnel-plot of oncological network variation in the use of preoperative imaging with an ceMRI in patients with colorectal liver metastases in the Netherlands between 2014 - 2018.

Unadjusted rates of percentage of patients with CRLM receiving ^{18}F -FDG-PET-CT in Dutch hospitals ranged between 10.0% and 100% (figure 3a). After case-mix correction, a widespread variation in the use of ^{18}F -FDG-PET-CT in the Netherlands was observed. Nine hospitals performed more preoperative ^{18}F -FDG-PET-CT and ten hospitals performed less preoperative ^{18}F -FDG-PET-CT than expected based on their case-mix (figure 3b). O/E ratios concerning the use of ^{18}F -FDG-PET-CT between hospitals ranged between 0.24 – 2.20. Also, three oncological networks performed preoperative ^{18}F -FDG-PET-CT more often while three other oncological networks performed preoperative ^{18}F -FDG-PET-CT than expected less often with O/E ratios ranging between 0.50 - 1.67 (figure 3c).

Figure 3a. Unadjusted rates of between-hospital variation in the use of preoperative imaging with ^{18}F -FDG-PET-CT in patients with colorectal liver metastases in the Netherlands between 2014 - 2018.

Figure 3b. Case-mix corrected funnel-plot of between-hospital variation in the use of preoperative imaging with a ¹⁸F-FDG-PET-CT scan in patients with colorectal liver metastases in the Netherlands between 2014 - 2018.

Figure 3c. Case-mix corrected funnel-plot of oncological network variation in the use of preoperative imaging with ^{18}F -FDG-PET-CT in patients with colorectal liver metastases in the Netherlands between 2014 - 2018.

Case-mix corrected for: CCI, preoperative chemotherapy, number of CRLM, maximum diameter of largest CRLM, bilobar disease, location primary tumour, nodal stage primary tumour, extrahepatic metastases and type of hospital.

Unadjusted rates of percentage of patients with CRLM receiving ceMRI and ^{18}F -FDG-PET-CT in Dutch hospitals ranged between 5.6% and 94.9% (figure 4a). After case-mix correction, widespread variation in the use of both ceMRI and ^{18}F -FDG-PET-CT was present in the Netherlands. Eight hospitals performed preoperative ceMRI and ^{18}F -FDG-PET-CT more often and eleven hospitals performed preoperative ceMRI and ^{18}F -FDG-PET-CT less often than expected based on their case-mix (figure 4b). O/E ratios concerning the use of ceMRI and ^{18}F -FDG-PET-CT between hospitals ranged between 0.19 – 3.25. Also, two oncological networks performed preoperative ceMRI and ^{18}F -FDG-PET-CT more often while three other oncological networks performed preoperative ceMRI and ^{18}F -FDG-PET-CT less often than expected with O/E ratios ranging between 0.29 – 2.12 (figure 4c). Multicollinearity was not observed in any of the reported models in this study as the VIF was always below 2.0. Sensitivity analyses in which tumour characteristics were dropped from the analyses did not present differences in any of the outcomes.

Figure 4a. Unadjusted rates of between-hospital variation in the use of preoperative imaging with ceMRI and ^{18}F -FDG-PET-CT in patients with colorectal liver metastases in the Netherlands between 2014 - 2018.

Figure 4b. Case-mix corrected funnel-plot of between-hospital variation in the use of preoperative imaging with a ceMRI and ¹⁸F-FDG-PET-CT scan in patients with colorectal liver metastases in the Netherlands between 2014 – 2018.

Figure 4c. Case-mix corrected funnel-plot of between oncological network variation in the use of preoperative imaging with ceMRI and ^{18}F -FDG-PET-CT in patients with colorectal liver metastases in the Netherlands between 2014 - 2018.

Discussion

In this nationwide population-based analysis, ceMRI as preoperative imaging for CRLM was increasingly used in the Netherlands over time, whereas the use ^{18}F -FDG-PET-CT as preoperative imaging decreased. The use of combined ceMRI and ^{18}F -FDG-PET-CT remained stable over the years. The use of MRI was associated with smaller diameter of CRLM or more CRLM. The use of ^{18}F -FDG-PET-CT was associated with extrahepatic metastases and larger diameters of CRLM. Remarkable variation was present regarding the use of preoperative ceMRI, ^{18}F -FDG-PET-CT and combined ceMRI and ^{18}F -FDG-PET-CT between hospitals and oncological networks in the Netherlands.

Very low number of studies on trends and variation in the use of preoperative imaging have been published in the past. One French study showed that the use of preoperative liver ceMRI increased from 53% to 80% from 2009 to 2013. Seventy-two per cent of patients with resectable CRLM received a preoperative ceMRI²⁹. In a Swedish population-based study only 2% of all colorectal cancer patients received a preoperative ceMRI of the liver³⁰. Unfortunately, this study did not report on trends or report a subanalysis concerning CRLM patients.

The available evidence is not conclusive regarding the use of additional preoperative imaging modalities which causes variability in the use of ceMRI and ¹⁸F-FDG-PET-CT. Over the last few years several studies reported superior per lesion detection with MRI compared to conventional CT-scan in CRLM patients^{8,10,11}. An earlier report by Rojas Llimpe et al. provided insight in the additional value of ceMRI in patients treated with preoperative chemotherapy³¹. Mostly retrospective studies have been performed in order to assess the differences between different types of MRI such as ceMRI, diffusion weighted MRI or gadoxetic acid-enhanced liver MRI. New insights in the added value of different types of MRI in a prospective setting are needed. For this reason, the CAMINO trial has started in the Netherlands (clinicaltrials.gov number: NCT01015833). This is a Dutch multicentre trial which starts in 2019 and aims to provide information concerning clinical additional value of ceMRI in CRLM patients.

¹⁸F-FDG-PET-CT is thought to have lower sensitivity compared to ceMRI and is not favoured in detection of CRLM^{4,32}. Detection rates are lower in patients who received preoperative chemotherapy³². One randomised controlled trial investigated the additional value of ¹⁸F-FDG-PET-CT in CRLM and concluded that ¹⁸F-FDG-PET-CT did not influence survival, whereas several non-randomised studies indicate that in case of extrahepatic metastases there could be added value of ¹⁸F-FDG-PET-CT^{12,15,33,34}.

Large randomized trials or prospective multicentre studies concerning the use of ceMRI or ¹⁸F-FDG-PET-CT in patients with CRLM have not been conducted and therefore existing guidelines such as the Dutch do not provide a recommendation on what is needed. The Dutch guidelines does not favour either ceMRI or CT in the work-up prior to liver resection. It advises using ¹⁸F-FDG-PET-CT only in case of extrahepatic metastases²². In this study, an increase in the use of ceMRI in the Netherlands was observed while the use of ¹⁸F-FDG-PET-CT decreased. These trends are probably the results of the appearance of international publications reporting the additional value of these imaging modalities^{4,7,8,10,12,13,15,31,34}.

Interestingly, ceMRI is thought to provide better insight in tumour burden in patients with a medical history of liver disease and literature provides insight that in case of preoperative chemotherapy or previous liver resection ceMRI could be useful as preoperative imaging^{10,32}. ¹⁸F-FDG-PET-CT might have added value in higher nodal stage of the colorectal primary tumour and could possibly be an option in these patients. This was however not the case in the present study as these factors were not associated with the use of either of the imaging modalities in this population-based cohort. Also, ceMRI was used less often in tertiary referral centres, while no difference was observed in the use of ¹⁸F-FDG-PET-CT in the different types of hospital.

Variation in the use of imaging in the Netherlands could be explained by the fact that the Dutch guideline allowed for different approaches³⁵. Remarkable variation in imaging both on a hospital level and oncological network level reflects lack of consensus on both levels. This is probably because of several problems: first the insufficient evidence and guidelines concerning the use of preoperative imaging in patients with CRLM. Second, health economic discussions could influence the use of these imaging modalities as both ceMRI and ¹⁸F-FDG-PET-CT as both are more expensive than baseline ultrasound and CT³⁶. As there are quite some differences in the costs of all imaging modalities it is important to further acknowledge differences and to assess cost-effectiveness of imaging modalities for CRLM in the future.

Hospital variation is undesired from a national health care perspective and not the best manner to provide health care. Either unnecessary imaging was performed or different approaches to imaging led to different patient selection for treatment. It is interesting to explore whether or not these differences in preoperative imaging lead to differences in treatment selection and disease-free and overall survival. A next step in the audit is to incorporate long-term follow-up to further investigate these associations, this ensures that conclusions can be drawn concerning survival data. The authors advocate clear and evidence-based guidelines regarding preoperative imaging for CRLM. This study and the upcoming CAMINO trial can be used to revise the Dutch, and maybe international guidelines.

The current study has several limitations. First, the disadvantage of the audit data may be accuracy, design and selection of patients. Details including information on the moment of registration of tumour characteristics, multidisciplinary meetings and outcomes of these meetings are missing and could not be retrieved in this retrospective study. The denominator (i.e. the sum of patients surgically treated and treated otherwise) is unclear. Second, open-close

procedures are not mandatory to register in the DHBA. This makes it hard to evaluate the impact of the use of preoperative imaging on perioperative outcomes.

The strength of the study is the nationwide collection of data through mandatory participation of all Dutch hospitals performing liver surgery. Through the nationwide coverage the results are reflecting daily clinical practice. It is possible to reflect on how Dutch clinicians use preoperative imaging and to evaluate hospital and oncological network variation.

In conclusion, trends over the years show increasingly applied ceMRI and decreasing use of ^{18}F -FDG-PET-CT for CRLM in the Netherlands. Lacking guidelines concerning preoperative imaging encourage hospital and oncological network variation in application of ceMRI, ^{18}F -FDG-PET-CT and combined ceMRI and ^{18}F -FDG-PET-CT. Convincing evidence concerning effective preoperative imaging modalities for CRLM is needed in order to decrease nationwide variation.

References

1. IKNL. Dutch Cancer Registry - Comprehensive Cancer Organisation. 2018.
2. Takahashi H, Kahramangil B, Kose E, Berber E. A comparison of microwave thermosphere versus radiofrequency thermal ablation in the treatment of colorectal liver metastases. *HPB (Oxford)*. 2018;20(12):1157-1162.
3. Mitchell D, Puckett Y, Nguyen QN. Literature Review of Current Management of Colorectal Liver Metastasis. *Cureus*. 2019;11(1):e3940.
4. Maffione AM, Lopci E, Bluemel C, Giammarile F, Herrmann K, Rubello D. Diagnostic accuracy and impact on management of (18)F-FDG PET and PET/CT in colorectal liver metastasis: a meta-analysis and systematic review. *Eur J Nucl Med Mol Imaging*. 2015;42(1):152-163.
5. Parikh U, Marcus C, Sarangi R, Taghipour M, Subramaniam RM. FDG PET/CT in Pancreatic and Hepatobiliary Carcinomas: Value to Patient Management and Patient Outcomes. *PET Clin*. 2015;10(3):327-343.
6. Choi SH, Kim SY, Park SH, et al. Diagnostic performance of CT, gadoxetate disodium-enhanced MRI, and PET/CT for the diagnosis of colorectal liver metastasis: Systematic review and meta-analysis. *J Magn Reson Imaging*. 2018;47(5):1237-1250.
7. Schulz A, Viktil E, Godt JC, et al. Diagnostic performance of CT, MRI and PET/CT in patients with suspected colorectal liver metastases: the superiority of MRI. *Acta Radiol*. 2016;57(9):1040-1048.
8. Sivesgaard K, Larsen LP, Sorensen M, et al. Diagnostic accuracy of CE-CT, MRI and FDG PET/CT for detecting colorectal cancer liver metastases in patients considered eligible for hepatic resection and/or local ablation. *Eur Radiol*. 2018;28(11):4735-4747.
9. Niekel MC, Bipat S, Stoker J. Diagnostic imaging of colorectal liver metastases with CT, MR imaging, FDG PET, and/or FDG PET/CT: a meta-analysis of prospective studies including patients who have not previously undergone treatment. *Radiology*. 2010;257(3):674-684.
10. Granata V, Fusco R, de Lutio di Castelguidone E, et al. Diagnostic performance of gadoxetic acid-enhanced liver MRI versus multidetector CT in the assessment of colorectal liver metastases compared to hepatic resection. *BMC Gastroenterol*. 2019;19(1):129.
11. Sibinga Mulder BG, Visser K, Feshtali S, et al. Gadoxetic acid-enhanced magnetic resonance imaging significantly influences the clinical course in patients with colorectal liver metastases. *BMC Med Imaging*. 2018;18(1):44.
12. Moulton CA, Gu CS, Law CH, et al. Effect of PET before liver resection on surgical management for colorectal adenocarcinoma metastases: a randomized clinical trial. *JAMA*. 2014;311(18):1863-1869.
13. Metser U, Halankar J, Langer D, et al. Effect of chemotherapy on the impact of FDG-PET/CT in selection of patients for surgical resection of colorectal liver metastases: single center analysis of PET-CAM randomized trial. *Ann Nucl Med*. 2017;31(2):153-162.
14. Nielsen K, Scheffer HJ, Pieters IC, et al. The use of PET-MRI in the follow-up after radiofrequency- and microwave ablation of colorectal liver metastases. *BMC Med Imaging*. 2014;14:27.
15. Lake ES, Wadhwani S, Subar D, et al. The influence of FDG PET-CT on the detection of extrahepatic disease in patients being considered for resection of colorectal liver metastasis. *Ann R Coll Surg Engl*. 2014;96(3):211-215.
16. Tamandl D, Ba-Ssalamah A, Bohm G, et al. Austrian consensus guidelines on imaging requirements prior to hepatic surgery and during follow-up in patients with malignant hepatic lesions. *Wien Klin Wochenschr*. 2018;130(21-22):665-672.
17. Garden OJ, Rees M, Poston GJ, et al. Guidelines for resection of colorectal cancer liver metastases. *Gut*. 2006;55 Suppl 3:iii1-8.
18. GDG. UK Guideline Colorectal Cancer. 2011.
19. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol*. 2016;27(8):1386-1422.
20. Hashiguchi Y, Muro K, Saito Y, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. *Int J Clin Oncol*. 2019.
21. Bipat S, van Leeuwen MS, Ijzermans JN, et al. Evidence-base guideline on management of colorectal liver metastases in the Netherlands. *Neth J Med*. 2007;65(1):5-14.
22. Oncoline Dutch Tumour Database. Dutch Guideline - Colorectal Carcinoma <https://www.oncoline.nl/colorectaalcarcinoom>. 2014.

23. van der Werf LR, Kok NFM, Buis CI, et al. Implementation and first results of a mandatory, nationwide audit on liver surgery. *HPB (Oxford)*. 2019.
24. CBS. Geographical and population overview of the Netherlands. 2019. <https://www.cbs.nl/nl-nl/maatschappij/bevolking>
21. RIVM. Regional and academic hospital distribution in the Netherlands. *RIVM*. 2018. <https://www.volksgezondheidenzorg.info/onderwerp/ziekenhuiszorg/regionaal-internationaal/locaties>.
22. SONCOS. Requirements in oncological care in the Netherlands. 2017. <https://www.soncos.org/wp-content/uploads/2017/10/43SONCOS-normeringsrapport-versie-5.pdf>
27. Werf LRvd, Voeten SC, Loe CMMv, Karthaus EG, Wouters MWJM, Prins HA. Data verification of nationwide clinical quality registries. *BJS Open*. 2019.
28. Elfrink AKE KN, et al. Population-based study on practice variation regarding preoperative systemic chemotherapy in patients with colorectal liver metastases and impact on short-term outcomes. *Submitted*. 2019.
29. Pech L, Cercueil JP, Jooste V, Krause D, Facy O, Bouvier AM. Current use of MRI in patients with liver metastatic colorectal cancer: a population-based study. *Eur J Gastroenterol Hepatol*. 2017;29(10):1126-1130.
30. Sjovall A, Blomqvist L, Martling A. Pretreatment staging of colon cancer in the Swedish population. *Colorectal Dis*. 2013;15(11):1361-1366.
31. Rojas Llimpe FL, Di Fabio F, Ercolani G, et al. Imaging in resectable colorectal liver metastasis patients with or without preoperative chemotherapy: results of the PROMETEO-01 study. *Br J Cancer*. 2014;111(4):667-673.
32. van Kessel CS, Buckens CF, van den Bosch MA, van Leeuwen MS, van Hillegersberg R, Verkooijen HM. Preoperative imaging of colorectal liver metastases after neoadjuvant chemotherapy: a meta-analysis. *Ann Surg Oncol*. 2012;19(9):2805-2813.
33. Patel S, McCall M, Ohinmaa A, Bigam D, Dryden DM. Positron emission tomography/computed tomographic scans compared to computed tomographic scans for detecting colorectal liver metastases: a systematic review. *Ann Surg*. 2011;253(4):666-671.
34. Lopez-Lopez V, Robles R, Brusadin R, et al. Role of (18)F-FDG PET/CT vs CT-scan in patients with pulmonary metastases previously operated on for colorectal liver metastases. *Br J Radiol*. 2018;91(1081):20170216.
35. Bipat S, van Leeuwen MS, Ijzermans JN, Bossuyt PM, Greve JW, Stoker J. Imaging and treatment of patients with colorectal liver metastases in the Netherlands: a survey. *Neth J Med*. 2006;64(5):147-151.
36. Sistrom CL, McKay NL. Costs, charges, and revenues for hospital diagnostic imaging procedures: differences by modality and hospital characteristics. *J Am Coll Radiol*. 2005;2(6):511-519.

Supplementary material

Supplementary table 1a. Trend analysis using multivariable logistic regression for the utilization of ceMRI in patients with colorectal liver metastases (CRLM) in the Netherlands over during 2014 – 2018.

Factor	Univariable logistic regression				Multivariable logistic regression		
	N	OR	CI (95%)	P-value	aOR	CI (95%)	P-value
Year of surgery				<0.001			<0.001
2014	771	1			1		
2015	884	1.80	1.48 – 2.19	<0.001	1.74	1.39 – 2.16	<0.001
2016	1008	2.06	1.70 – 2.49	<0.001	1.95	1.57 – 2.41	<0.001
2017	1009	3.26	1.68 – 3.98	<0.001	3.37	2.68 – 4.21	<0.001
2018	838	3.71	3.00 – 4.59	<0.001	4.72	3.69 – 6.05	<0.001

Multivariable model corrected for: Age in years, CCI, BMI, ASA score, history of liver resection, number of CRLM, maximum diameter of largest CRLM, location primary tumour, type of metastases, extrahepatic metastases and type of hospital.

Supplementary table 1b. Trend analysis using multivariable logistic regression for the utilization of ¹⁸F-FDG-PET-CT in patients with colorectal liver metastases in the Netherlands over during 2014 – 2018.

Factor	Univariable logistic regression				Multivariable logistic regression		
	N	OR	CI (95%)	P-value	aOR	CI (95%)	P-value
Year of surgery				<0.001			<0.001
2014	771	1			1		
2015	884	0.93	0.76 – 1.13	0.461	0.99	0.80 – 1.20	0.841
2016	1008	0.77	0.64 – 0.93	0.005	0.89	0.70 – 1.10	0.116
2017	1009	0.59	0.49 – 0.71	<0.001	0.69	0.50 – 0.86	<0.001
2018	838	0.35	0.29 – 0.43	<0.001	0.42	0.29 – 0.54	<0.001

Multivariable model corrected for: CCI, preoperative chemotherapy, number of CRLM, maximum diameter of largest CRLM, bilobar disease, location primary tumour, nodal stage primary tumour, extrahepatic metastases and type of hospital.

Supplementary table 1c. Trend analysis using multivariable logistic regression for the utilization of ceMRI and ¹⁸F-FDG-PET-CT in patients with colorectal liver metastases in the Netherlands over during 2014 – 2018.

Factor	Univariable logistic regression				Multivariable logistic regression		
	N	OR	CI (95%)	P-value	aOR	CI (95%)	P-value
Year of surgery				0.009			0.008
2014	771	1			1		
2015	884	1.33	1.07 – 1.65	0.010	1.36	1.07 – 1.73	0.012
2016	1008	1.20	0.97 – 1.48	0.099	1.27	1.01 – 1.62	0.045
2017	1009	1.37	1.11 – 1.69	0.003	1.51	1.19 – 1.92	<0.001
2018	838	1.05	0.84 – 1.32	0.655	1.16	0.91 – 1.51	0.221

Multivariable model corrected for: ASA score, BMI, history of liver disease, history of liver resection, number of CRLM, maximum diameter of largest CRLM, bilobar disease, location primary tumour and nodal stage primary tumour.

Supplementary figure 1. Overview of the layout of Dutch Oncological Networks.

CHAPTER 7

POPULATION-BASED STUDY ON PRACTICE VARIATION REGARDING PREOPERATIVE SYSTEMIC CHEMOTHERAPY IN PATIENTS WITH COLORECTAL LIVER METASTASES AND IMPACT ON SHORT-TERM OUTCOMES

A.K.E. Elfrink, N.F.M. Kok, L.R. van der Werf, M.F. Krul, E. Marra, M.W.J.M. Wouters, C. Verhoef, K.F.D. Kuhlmann, M. den Dulk, R.J. Swijnenburg, W.W. te Riele, P.B. van den Boezem, W.K.G. Leclercq, D.J. Lips, V.B. Nieuwenhuijs, P.D. Gobardhan, H.H. Hartgrink, C.I. Buis, D.J. Grünhagen, J.M. Klaase, [Dutch Hepato Biliary Audit Group, Collaborators](#)

Eur J Surg Oncol. 2020 Sep;46(9):1742-1755.

Abstract

Introduction

Definitions regarding resectability and hence indications for preoperative chemotherapy vary. Use of preoperative chemotherapy may influence postoperative outcomes. This study aimed to assess the variation in use of preoperative chemotherapy for CRLM and related postoperative outcomes in the Netherlands.

Methods

All patients who underwent liver resection for CRLM in the Netherlands between 2014 and 2018 were included from a national database. Case-mix factors contributing to the use of preoperative chemotherapy, hospital variation and postoperative outcomes were assessed using multivariable logistic regression. Postoperative outcomes were postoperative complicated course (PCC), 30-day morbidity and 30-day mortality.

Results

In total, 4469 patients were included of whom 1314 patients received preoperative chemotherapy and 3155 patients did not. Patients receiving chemotherapy were significantly younger (mean age (+SD) 66.3 (10.4) versus 63.2 (10.2) $p < 0.001$) and had less comorbidity (Charlson scores 2+ (24% versus 29%, $p = 0.010$). Unadjusted hospital variation concerning administration of preoperative chemotherapy ranged between 2% and 55%. After adjusting for case-mix factors, three hospitals administered significantly more preoperative chemotherapy than expected and six administered significantly less preoperative chemotherapy than expected. PCC was 12.1%, 30-day morbidity was 8.8% and 30-day mortality was 1.5%. No association between preoperative chemotherapy and PCC (OR 1.24, 0.98 – 1.55, $p = 0.065$), 30-day morbidity (OR 1.05, 0.81 – 1.39, $p = 0.703$) or with 30-day mortality (OR 1.22, 0.75 – 2.09, $p = 0.467$) was found.

Conclusion

Significant hospital variation in the use of preoperative chemotherapy for CRLM was present in the Netherlands. No association between postoperative outcomes and use of preoperative chemotherapy was found.

Introduction

Colorectal liver metastases (CRLM) are the main indication for liver resection In the Netherlands¹. Five-year survival rate after liver resection for CRLM is reported to be 30-60% in Europe²⁻⁴. Chemotherapy is used as induction therapy to increase resectability in unresectable CRLM and as neoadjuvant chemotherapy (NAC) in resectable CRLM and to obtain longer survival⁴⁻⁸. Although results concerning NAC were inconclusive, several countries worldwide interpreted these studies in favor of giving NAC.

Standard of care in the Netherlands is to administer preoperative chemotherapy only when CRLM are not resectable (i.e. induction chemotherapy or conversion chemotherapy)⁹. The Dutch guideline also indicates that large trials indicating a benefit of adjuvant chemotherapy in CRLM patients are lacking and for this reason, there is no place for adjuvant chemotherapy in current daily practice in the Netherlands. In case of resectable lesions, upfront resection is advocated as preoperative chemotherapy is known to induce higher morbidity as a result of damaged liver tissue through sinusoidal dilatation or steatohepatitis and no clear improvement of survival has been described¹⁰⁻¹². As a result of lacking evidence regarding administration of preoperative chemotherapy for CRLM, the use of preoperative chemotherapy appears to vary in Dutch clinical practice.

In general practice, the probability of administering preoperative chemotherapy is influenced by both patient- and tumour characteristics, including age, comorbidities, clinical and pathological tumour stages, synchronous metastases or because of treating physicians preference¹². However, the relative contribution of these patient- and tumour characteristics and variability between hospitals and oncological networks for liver surgery is unclear.

The first aim of this study was to identify patient- and tumour characteristics that were associated with administering preoperative chemotherapy for CRLM in the Netherlands. Additionally, the variability in the use of preoperative chemotherapy between hospitals and oncological networks in the Netherlands was evaluated. The second aim was to evaluate the association of preoperative chemotherapy with postoperative outcomes.

Methods

This was a national cohort study with data derived from the Dutch Hepato Biliary Audit (DHBA)¹³. The Netherlands is a high-income country in Western Europe with 17 million inhabitants living on 33.883 square kilometers¹⁴. Health care is arranged in 71 hospitals including 7 university hospitals and one comprehensive cancer centre¹⁵. Not all hospitals perform liver surgery as a result of national agreements on minimal structural requirements (i.e. 24/7 availability of an interventional radiologist) and volume (at least 20 resections annually)¹⁶. Hospitals performing liver surgery in the Netherlands have been obliged to register liver resections in the DHBA since 2013. Since 2018 all procedures for CRLM performed by interventional radiologists, such as thermal ablation, have also been registered in the DHBA. Long-term follow up will be registered from 2018 onwards.

Detailed information on patient- and disease specific characteristics as well as diagnostic- and treatment information was collected. Recently, data verification of the audit was performed and provided insight in completeness and accuracy of the DHBA¹⁷. During data verification data in the DHBA was compared to the Dutch Cancer Registry. The completeness of data in the DHBA proved to be 97% in 2015¹³.

Patient selection

All patients who underwent liver resection for CRLM between 1 January 2014 and 31 December 2018, and registered before 22 March 2019 in the DHBA were included in this analysis. Patients were considered not eligible for analysis when missing information included date of birth, the use of preoperative chemotherapy received before the operation, date of surgery, type of procedure or type of tumour. Patients were also excluded if they proved to have irresectable metastases and if thermal ablation was the only procedure performed. The DHBA comprises an obligatory audit from the inspectorate of healthcare, which required no informed consent from patients for data collection. Data analyses were performed on an anonymised dataset and does not need ethical approval according to Dutch law.

Treatment groups

Baseline characteristics concerning patients surgically treated in the Netherlands for CRLM were analysed according preoperative chemotherapy regime. For analysis of outcomes, patients were divided between two treatment categories including patients receiving or not receiving preoperative chemotherapy. Preoperative chemotherapy was defined as any

chemotherapy before surgery, aimed at the CRLM and excluding adjuvant chemotherapy for the primary tumour. No preoperative chemotherapy were all patients who did not receive any preoperative chemotherapy aimed at the CRLM or who only received adjuvant chemotherapy. Detailed information regarding the chemotherapy, such as the number of chemotherapy cycles or type of chemotherapy was not available in the audit data.

Variables

Studied variables included patient characteristics (age, sex, American Society of Anesthesiologists (ASA) classification, comorbidity score according to the Charlson Comorbidity Index (CCI), history of liver disease, previous liver surgery and year of surgery), tumour characteristics (number of CRLM lesions, largest lesion before initiation of treatment, metachronous or synchronous metastases) and treatment characteristics (preoperative chemotherapy, primary tumour or liver first or simultaneous resection, type of surgery (i.e. laparoscopic, open or conversion) and extent of surgery (i.e. major or minor liver resection). Major liver resection was defined as resection of 3 or more adjacent Couinaud segments.

Distinction was made between regional hospitals performing liver surgery and tertiary referral centres. Tertiary referral centres are hospitals in which more complex tumours and surgery are treated based on referral patterns in the oncological networks. Oncological networks were classified according the treatment collaboration between hospitals. If no collaboration network was present this was based on topographical location (supplementary figure 1). An oncological network is formed by one or two tertiary referral centres and several regional hospitals. Only a few hospitals per oncological network perform liver surgery. Regional hospitals not performing liver surgery refer patients to either a regional hospital performing liver surgery or tertiary referral centre according to the agreements in the oncological network. All hospitals in an oncological network have preoperative multidisciplinary meetings through video conference to discuss patients with CRLM. The personalised treatment plan is based on these meetings. When more specialised care is needed (i.e underlying liver disease, complexity of surgery) patients can be referred to a tertiary referral centre in the oncological network.

Outcomes

Hospital stay was calculated as time between date of surgery and the date of discharge. A postoperative complicated course (PCC) was defined as a complication leading to a prolonged hospitalization (>14 days), any surgical, endoscopic or radiological re-intervention or death. Major morbidity was defined as a complication graded Clavien-Dindo classification¹⁸ of grade III

(CD >3a) or higher (i.e. requiring re-intervention, medium care (MC) or intensive care (IC) management or death) within 30 days of surgery. Postoperative mortality was defined as death within 30 days from date of surgery or during initial hospitalization. Outcomes were analysed for the whole cohort as well as separate analyses for major and minor liver resection.

Statistical analysis

Baseline characteristics were compared between all strategies using the Chi-square test or Fisher exact tests for categorical variables as appropriate and the independent two-sample t-test for continuous variables.

Identification of case-mix factors, which were the non-modifiable patient and tumour characteristics possibly influencing the use of preoperative chemotherapy, was carried out. These case-mix factors entered in a univariable and multivariable logistic regression model with outcome of preoperative chemotherapy included sex, age, ASA classification, CCI, liver disease, CEA, nodal stage primary tumour, metachronous or synchronous metastases, previous liver surgery, year of surgery, size of the largest lesion and number of CRLM lesions.

Variation in the use of preoperative chemotherapy between hospitals and oncology networks was corrected for the case-mix factors. Case-mix correction was performed using the observed / expected ratio which is calculated by dividing the observed number of patients receiving preoperative chemotherapy through the number of patients expected to receive preoperative chemotherapy¹⁹. The expected number of patients is based on a multivariable logistic regression model for case-mix variables.

The association of all variables in univariable and multivariable logistic regression model were used to quantify the association of patient-, tumour-factors and treatment characteristics with the primary outcomes (PCC, 30-day morbidity (CD >3a) and 30-day mortality).

For all multivariable analyses a two-step method was undertaken. All variables were tested in a univariable models per outcome variable. If a significant association was found ($P < 0.1$, Wald test) the variable was entered in the multivariable model. Statistical significance was defined as a two-sided p-value < 0.05 in the multivariable model. Multicollinearity was assessed in all multivariable models. This was done by calculation of the variance inflation factor (VIF). A VIF higher than 2.5 was considered to be an indication for multicollinearity.

Several sensitivity analyses were performed. All multivariable models were performed including year of surgery in order to assess a change in use of preoperative chemotherapy over the

years. Second, the cohort was split in the first two and last three years in order to perform all models again to assess outcomes as a result of change in daily practice over the years. Third, the model with respect to the variables associated with the use of preoperative chemotherapy was performed with and without height of the carcinoembryonic antigen (CEA). This variable was missing in a lot of cases, but might influence the use of preoperative chemotherapy and was therefore assessed. Also, the influence of preoperative chemotherapy on irradical (R1) resection was assessed. Finally, the association of annual hospital volume (<20, 20-39, 40-59, 60-79 and >80) was assessed.

All analyses were performed in R version 3.2.2® (R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

Results

Overall, 4776 patients who underwent surgical liver resection for CRLM were included during the study period. Four hundred and fifty-three patients were excluded because of missing data. Of the remaining 4469 patients, 3009 (67.3%) did not receive chemotherapy and 1165 (26.1%) patients received only preoperative chemotherapy. One hundred and forty-nine (3.3%) patients received both preoperative and adjuvant chemotherapy and were analysed as patients receiving preoperative chemotherapy. Another 146 (3.3%) patients (received only adjuvant chemotherapy and were therefore included in the no preoperative chemotherapy group. Overall, 3155 patients (70.5%) were included in the preoperative chemotherapy group and 1314 (29.5%) in the no preoperative chemotherapy group.

Baseline characteristics

Patients receiving preoperative chemotherapy were significantly younger and had lower comorbidity scores (table 1). Patients with number of lesions, higher diameter of the largest tumour and synchronous metastases were significantly more likely to receive preoperative chemotherapy.

Table 1. Baseline characteristics concerning preoperative systemic chemotherapy in patients diagnosed with colorectal liver metastases between 2014 and 2018 in the Netherlands.

Factor		No preoperative chemotherapy	Preoperative chemotherapy	P-value¶
		N (%)	N (%)	
Total		3155	1314	
Sex	Male	2001 (63)	809 (62)	0.256
	Female	1154 (37)	505 (38)	
Age in years				<0.001

	< 50	187 (6)	134 (10)	
	50 - 64	994 (32)	539 (41)	
	65 - 80	1683 (53)	602 (46)	
	> 80	288 (9)	35 (3)	
	Missing	3 (0)	4 (0)	
Charlson Comorbidity Index (CCI)				<0.001
	0 / 1	2261 (72)	1047 (80)	
	2+	848 (27)	242 (18)	
	Missing	48 (1)	25 (1)	
Body Mass Index (BMI)	Mean (sd)	26.5 (4.47)	25.7 (4.14)	<0.001
American Society of Anesthesiology (ASA) classification				0.023
	I / II	2474 (78)	1075 (82)	
	III+	627 (20)	225 (17)	
	Missing	54 (2)	14 (1)	
Liver resection in the past				0.646
	No	2547 (81)	1075 (82)	
	Yes	565 (18)	224 (17)	
	Missing	43 (1)	15 (1)	
Carcinoembryonic antigen (CEA)				<0.001
	<5	1015 (32)	333 (25)	
	5-10	565 (18)	242 (18)	
	>10	827 (26)	421 (32)	
	Missing	748 (24)	318 (24)	
History of liver disease§				0.148
	No	3006 (95)	1251 (95)	
	Yes	48 (2)	12 (1)	
	Missing	101 (3)	51 (4)	
Number of lesions				<0.001
	1	1681 (53)	254 (19)	
	2	72 (23)	221 (17)	
	3	327 (10)	176 (13)	
	4	155 (5)	148 (11)	
	5	80 (3)	104 (8)	
	>5	136 (4)	331 (25)	
	Missing	55 (2)	80 (6)	
Maximum diameter of largest CRLM* (mm)				<0.001
	< 20	913 (29)	288 (22)	
	20 - 34	1114 (35)	353 (27)	
	35 - 54	494 (16)	242 (19)	
	> 55	227 (7)	215 (16)	
	Missing	407 (13)	216 (16)	
Location primary tumour				0.001
	Colon	2074 (66)	788 (60)	
	Rectum	1077 (34)	522 (40)	
	Missing	4 (0)	4 (0)	
Nodal stage primary tumour				<0.001
	pN0	1002 (32)	265 (20)	
	pN1	884 (28)	304 (23)	
	pN2	619 (19)	237 (18)	
	Unknown	650 (21)	508 (39)	
Type of metastases				<0.001
	Metachronous	1911 (61)	394 (30)	
	Synchronous	1136 (36)	870 (66)	
	Missing	108 (3)	50 (4)	
Type of hospital[∞]				<0.001

	Regional hospitals	1915 (61)	577 (44)	
	Tertiary referral centre	1240 (39)	737 (56)	
Year of surgery				0.480
	2014	549 (17)	214 (16)	
	2015	617 (20)	240 (18)	
	2016	666 (21)	305 (23)	
	2017	685 (22)	283 (22)	
	2018	638 (20)	272 (21)	

¶ Chi-square test was used comparing groups.

§ History of liver disease containing liver cirrhosis, oesophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis

*Colorectal liver metastases

∞ Type of hospital: tertiary referral centre are defined as hospitals with highest expertise on oncologic surgery.

Factors associated with the use of preoperative chemotherapy

In multivariable analysis, factors associated positively with the administration of preoperative chemotherapy included more lesions, maximum diameter of largest lesion, synchronous metastases and a primary tumour located in the rectum. Factors negatively associated with the use of preoperative chemotherapy included higher age, high Charlson comorbidity scores and not being treated in a tertiary referral centre (table 2).

Hospital and oncological network variation in the use of preoperative chemotherapy

Unadjusted hospital variance in the administration of preoperative chemotherapy ranged between 2% and 55%. Unadjusted oncological network variance ranged between 20% and 44%.

After correction for case-mix factors contributing to the administration of preoperative chemotherapy (table 2), still several hospitals fell out of the 95% confidence interval of variance for preoperative chemotherapy. Three hospitals administered preoperative chemotherapy significantly more often compared to what would be expected based on case-mix factors in that hospital. Six hospitals administered preoperative chemotherapy significantly less often compared to what would be expected based on case-mix factors in that hospital (figure 1a).

Oncological network variation, after case-mix correction, in the use of preoperative chemotherapy was observed with two oncological networks administering preoperative chemotherapy significantly less often and with two oncological networks administering preoperative chemotherapy significantly more compared to what would be expected based on case-mix factors (figure 1b).

Table 2. Univariable and multivariable logistic regression model of patient and tumour factors associated with treatment with preoperative chemotherapy in patients diagnosed with colorectal liver metastases (CRLM) in the Netherlands between 2014-2018.

Factor	N	Univariable analysis			Multivariable analysis		
		OR	CI (95%)	P-value	aOR	CI (95%)	P-value
Sex				0.242			
Male	2810	1					
Female	1659	1.08	0.95 – 1.24				
Age in years				<0.001			<0.001
< 50	321	1			1		
50 - 64	1533	0.76	0.59 – 0.97	0.026	0.98	0.70 – 1.32	0.791
65 - 79	2285	0.50	0.39 – 0.64	<0.001	0.87	0.64 – 1.20	0.410
> 80	323	0.17	0.11 – 0.25	<0.001	0.35	0.20 – 0.57	<0.001
Missing*							
Charlson Comorbidity Index (CCI)				<0.001			0.025
0 / 1	3308	1			1		
2+	1088	0.62	0.53 – 0.72		0.89	0.65 – 0.97	
Missing*	73						
Body Mass Index		0.95	0.94 – 0.97	<0.001	0.97	0.95 – 0.99	<0.001
American Society of Anesthesiology (ASA) classification				0.026			0.994
I / II	3549	1			1		
III +	852	0.93	0.70 – 0.98		0.99	0.80 – 1.24	
Missing*	68						
History of liver disease§				0.116			0.808
No	3622	1			1		
Yes	789	0.60	0.31 – 1.10		0.91	0.42 – 1.86	
Missing*	58			<0.001			
Number of lesions							<0.001
1	1935	1			1		
2	942	2.03	1.66 - 2.48	<0.001	1.93	1.54 – 2.40	<0.001
3	503	3.56	2.84 – 4.46	<0.001	2.90	2.25 – 3.73	<0.001
4	303	6.32	4.87 – 8.21	<0.001	4.97	3.71 – 6.66	<0.001
5	184	8.60	6.16 – 11.9	<0.001	6.70	4.69 – 9.61	<0.001
>5	467	16.1	12.7 – 20.5	<0.001	12.6	9.60 – 16.5	<0.001
Missing*	135						
Maximum diameter of largest lesion (mm)				<0.001			<0.001
< 20	1201	1			1		
20 - 34	1467	1.00	0.84 – 1.20	0.960	1.01	0.80 – 1.22	0.884
35 - 54	736	1.55	1.27 – 1.90	<0.001	1.54	1.21 – 1.97	<0.001
> 55	442	3.00	2.39 – 3.78	<0.001	3.02	2.28 – 3.99	<0.001
Missing	623	1.64	1.36 – 2.09	<0.001	1.46	1.09 – 1.95	0.011
Location primary tumour				<0.001			0.016
Colon	2862	1			1		
Rectum	1599	1.28	1.12 – 1.46		1.24	1.04 – 1.46	
Missing*	8						
Nodal stage primary tumour				<0.001			0.004
pN0	1267	1			1		
pN1	1188	1.30	1.08 – 1.60	0.006	1.16	0.92 – 1.46	0.211
pN2	856	1.45	1.18 – 1.77	<0.001	1.16	0.90 – 1.49	0.248

Missing	1158	2.96	2.47 – 3.54	<0.001	1.52	1.21 – 1.93	0.001
Type of metastases				<0.001			<0.001
Metachronous	2305	1			1		
Synchronous	2006	3.71	3.23 – 4.28		2.22	1.87 – 2.65	
Missing*	158						
Type of hospital[∞]				<0.001			<0.001
Regional hospitals	2492	1			1		
Tertiary referral centre	1977	1.97	1.73 – 2.25		1.62	1.38 – 1.91	
Year of surgery				0.482			
2014	763	1					
2015	857	1.00	0.80 – 1.24	0.985			
2016	971	1.18	0.95 – 1.45	0.129			
2017	968	1.06	0.86 – 1.31	0.587			
2018	910	1.09	0.88 – 1.35	0.408			

* Missing not included in analyses based on relatively small group

§ History of liver disease containing liver cirrhosis, oesophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis

[∞] Type of hospital: tertiary referral centre are defined as hospitals with highest expertise on oncologic surgery

aOR (Adjusted) odds ratio; CI Confidence interval; mm millimetre

Figure 1a. Case-mix adjusted funnel plot of between-hospital variation in treatment with preoperative chemotherapy for colorectal liver metastases in the Netherlands between 2014 - 2018.

Case-mix corrected for: age in years, Charlson Comorbidity Index, ASA score, history of liver disease, number of lesions, maximum diameter of the largest lesion, location primary tumour, nodal stage primary tumour, type of metastasis and type of hospital

Figure 1b. Case-mix adjusted funnel plot of between oncological network variation in treatment with preoperative chemotherapy for colorectal liver metastases in the Netherlands between 2014 - 2018.

Case-mix corrected for: age in years, Charlson Comorbidity Index, ASA score, history of liver disease, number of lesions, maximum diameter of the largest lesion, location primary tumour, nodal stage primary tumour, type of metastasis and type of hospital

Association of preoperative chemotherapy and postoperative outcomes

An overall postoperative complicated course occurred in 12.1% of patients, major morbidity was 8.8% and mortality was 1.5%. In the unadjusted analysis of the overall cohort a postoperative complicated course occurred in 345 (10.9%) patients in the no chemotherapy group and in the preoperative chemotherapy group in 196 patients (14.9%, $p < 0.001$). Major morbidity occurred in 263 (8.3%) patients in the no chemotherapy group and in 129 (9.8%, $p = 0.124$) patients in the preoperative chemotherapy group. Forty (1.3%) versus 25 (1.9%, $p = 0.139$) patients died postoperatively in the no chemotherapy group and in the preoperative chemotherapy group, respectively. After correction for case-mix factors in the overall cohort preoperative chemotherapy was not associated with a postoperative complicated course (OR 1.24, 0.98 – 1.55, $p = 0.065$), 30-day morbidity (OR 1.05, 0.81 – 1.139, $p = 0.703$) or with 30-day mortality (OR 1.22, 0.75 – 2.09, $p = 0.467$) (table 3a, 3b, 3c, supplementary table 1).

Table 3a. Univariable and multivariable logistic regression model of patient, tumour and surgical factors associated with postoperative complicated course for liver resections in patients with colorectal liver metastases in the Netherlands between 2014-2018.

Factor	N	Univariable analysis			Multivariable analysis		
		OR	CI (95%)	P-value	aOR	CI (95%)	P-value
Sex				0.002			0.003
Male	2810	1			1		
Female	1659	0.74	0.61 – 0.89		0.74	0.59 – 0.90	
Age in years				0.009			0.070
< 50	321	1			1		
50 - 64	1533	1.15	0.77 – 1.76	0.514	1.16	0.76 – 1.81	0.525
65 - 79	2285	1.45	0.99 – 2.19	0.066	1.38	0.91 – 2.14	0.146
> 80	323	1.82	1.13 – 2.97	0.015	1.84	1.06 – 3.09	0.030
Missing*	7						
Charlson Comorbidity Index (CCI)				0.014			0.095
0 / 1	3308	1			1		
2+	1088	1.29	1.05 – 1.57		1.21	0.97 – 1.51	
Missing*	73						
Body Mass Index		1.00	0.98 – 1.02	0.738			
American Society of Anesthesiology (ASA) classification				<0.001			<0.001
I / II	3549	1			1		
III+	852	1.85	1.50 – 2.26		1.78	1.40 – 2.21	
Missing*	68						
History of liver disease§				0.522			
No	4257	1					
Yes	60	1.26	0.58 – 2.45				
Missing*	152						
History of liver resection				0.838			
No	3622	1					
Yes	789	0.98	0.77 – 1.21				
Missing*	58						
Number of lesions				0.124			
1	1935	1					
2	942	1.11	0.87 – 1.41	0.407			
3	503	1.21	0.89 – 1.62	0.211			
4	303	1.23	0.84 – 1.75	0.274			
5	184	1.69	1.10 – 2.51	0.013			
>5	467	1.34	1.00 – 1.80	0.053			
Missing*	135						
Maximum diameter of largest lesion (mm)				<0.001			0.040
< 20	1201	1			1		
20-34	1467	1.19	0.93 – 1.53	0.178	1.17	0.89 – 1.52	0.262
35-54	736	1.30	0.97 – 1.74	0.080	1.13	0.82 – 1.53	0.482
> 55	442	2.48	1.84 – 3.35	<0.001	1.74	1.22 – 2.38	0.002
Missing	623	1.41	1.04 – 1.91	0.026	1.16	0.81 – 1.63	0.416
Location primary tumour				<0.001			0.065
Colon	2862	1			1		
Rectum	1599	0.70	0.57 – 0.85		0.82	0.65 – 1.01	
Missing*	8						

Nodal stage primary tumour				0.161			
pN0	1267	1					
pN1	1188	1.10	0.86 – 1.40	0.435			
pN2	856	0.85	0.64 – 1.12	0.251			
Missing	1158	1.14	0.90 – 1.45	0.280			
Type of metastases				<0.001		0.169	
Metachronous	2305	1			1		
Synchronous	2006	1.60	1.31 – 1.89		1.22	0.92 – 1.60	
Missing*	158						
Preoperative chemotherapy				<0.001		0.065	
No	3155	1			1		
Yes	1314	1.43	1.18 – 1.72		1.24	0.98 – 1.55	
Major liver resection				<0.001		<0.001	
No	3476	1			1		
Yes	993	2.55	2.11 – 3.08		2.33	1.87 – 2.91	
Synchronous additional resection				<0.001		<0.001	
No	2372	1			1		
Yes	821	2.40	1.93 – 2.99	<0.001	1.77	1.36 – 2.29	<0.001
Missing	1276	1.39	1.12 – 1.73	0.003	1.30	1.02 – 1.65	0.034
Surgical strategy				<0.001		<0.001	
Primary tumour first	3044	1			1		
Liver first	690	1.07	0.82 – 1.39	0.590	0.89	0.63 – 1.26	0.514
Combined resection	515	2.47	1.95 – 2.12	<0.001	2.17	1.55 – 3.05	<0.001
Missing*	220						
Type of surgery				<0.001		<0.001	
Open	3348	1			1		
Laparoscopic	920	0.44	0.33 – 0.56	<0.001	0.58	0.42 – 0.78	<0.001
Conversion	187	1.28	0.85 – 1.88	0.224	1.30	0.82 – 2.00	0.243
Missing*	14						
Type of hospital[∞]				0.037		0.141	
Regional hospitals	2492	1			1		
Tertiary referral hospital	1977	1.21	1.01 – 1.45		1.17	0.95 – 1.43	

* Missing not included in analyses based on relatively small group

§ History of liver disease containing liver cirrhosis, oesophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis

[∞] Type of hospital: tertiary referral centre are defined as hospitals with highest expertise on oncologic surgery

aOR (Adjusted) odds ratio; CI Confidence interval; mm millimetre

Table 3b. Univariable and multivariable logistic regression model of patient, tumour and surgical factors associated with postoperative complicated course for minor liver resections in patients with colorectal liver metastases in the Netherlands between 2014-2018.

Factor	Univariable analysis				Multivariable analysis		
	N	OR	CI (95%)	P-value	aOR	CI (95%)	P-value
Sex							
Male	2187	1		0.160			
Female	1289	0.84	0.66 – 1.07				
Age in years							
< 50	245	1		0.007	1		0.158
50 - 64	1161	1.26	0.75 – 2.26	0.408	1.27	0.74 – 2.32	0.409
65 - 79	1791	1.62	0.98 – 2.85	0.075	1.40	0.83 – 2.52	0.233
> 80	272	2.32	1.28 – 4.40	0.007	2.00	1.05 – 3.95	0.040
Missing*	7						

Charlson Comorbidity Index (CCI)				0.052			0.247
0 / 1	2567	1			1		
2+	849	1.28	0.99 – 1.65		1.18	0.89 – 1.55	
Missing*	60						
Body Mass Index		1.00	0.97 – 1.02	0.834			
American Society of Anesthesiology (ASA) classification				<0.001			<0.001
I / II	2751	1			1		
III+	667	2.04	1.58 – 2.61		1.98	0.50 – 2.60	
Missing*	58						
History of liver disease§				0.919			
No	3308	1					
Yes	42	0.99	0.29 – 2.47				
Missing*	126						
History of liver resection				0.543			
No	2829	1					
Yes	599	0.90	0.66 – 1.23				
Missing*	48						
Number of lesions				0.736			
1	1653	1					
2	757	0.88	0.65 – 1.19	0.429			
3	372	1.08	0.73 – 1.55	0.707			
4	209	1.15	0.70 – 1.80	0.573			
5	121	1.38	0.75 – 2.35	0.267			
>5	295	0.94	0.60 – 1.43	0.784			
Missing*	69						
Maximum diameter of largest lesion (mm)				0.019			0.042
<20	1055	1			1		
20-34	1210	1.09	0.81 – 1.46	0.574	1.14	0.84 – 1.56	0.396
35-54	518	1.23	0.85 – 1.75	0.267	1.23	0.84 – 1.81	0.285
> 55	216	2.12	1.38 – 3.22	<0.001	2.12	1.33 – 3.33	0.001
Missing	477	1.20	0.82 – 1.73	0.334	1.08	0.70 – 1.65	0.708
Location primary tumour				<0.001			0.019
Colon	2204	1			1		
Rectum	1266	0.64	0.50 – 0.83		0.72	0.54 – 0.95	
Missing*	6						
Nodal stage primary tumour				0.033			0.113
pN0	1014	1			1		
pN1	950	1.06	0.79 – 1.43	0.691	1.03	0.74 – 1.41	0.813
pN2	658	0.70	0.48 – 1.01	0.060	0.66	0.44 – 0.98	0.040
Missing	854	1.20	0.89 – 1.62	0.240	0.98	0.68 – 1.41	0.918
Type of metastases				<0.001			0.004
Metachronous	1873	1			1		
Synchronous	1472	1.69	1.34 – 2.13		1.32	1.12 – 1.94	
Missing*	131						
Preoperative chemotherapy				0.082			0.181
No	2605	1			1		
Yes	871	1.25	0.97 – 1.60		1.22	0.91 – 1.64	
Synchronous additional resection				<0.001			<0.001
No	1843	1			1		
Yes	657	3.13	2.38 – 4.12	<0.001	1.97	1.41 – 2.73	<0.001
Missing	976	1.67	1.26 – 2.20	<0.001	1.43	1.05 – 1.95	<0.001
Surgical strategy				<0.001			<0.001
Primary tumour first	2384	1			1		

Liver first	459	0.96	0.65 – 1.36	0.849	1.05	0.66 – 1.66	0.822
Combined resection	453	3.27	2.49 – 4.26	<0.001	2.65	1.90 – 3.68	<0.001
Missing*	180						
Type of surgery				<0.001			0.001
Open	2466	1			1		
Laparoscopic	843	0.50	0.36 – 0.68	<0.001	0.57	0.40 – 0.80	<0.001
Conversion	159	1.51	0.94 – 2.33	0.075	1.30	0.76 – 2.12	0.315
Missing*	8						
Type of hospital[∞]				0.051			0.056
Regional hospitals	1961	1			1		
Tertiary referral centre	1515	1.25	0.99 – 1.57		1.28	0.99 – 1.66	

* Missing not included in analyses based on relatively small group

§ History of liver disease containing liver cirrhosis, oesophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis

∞ Type of hospital: tertiary referral centre are defined as hospitals with highest expertise on oncologic surgery

aOR (Adjusted) odds ratio; CI Confidence interval; mm millimetre

Table 3c. Univariable and multivariable logistic regression model of patient, tumour and surgical factors associated with postoperative complicated course for major liver resections in patients with colorectal liver metastases in the Netherlands between 2014-2018.

Factor	N	Univariable analysis			Multivariable analysis		
		OR	CI (95%)	P-value	aOR	CI (95%)	P-value
Sex				<0.001			0.001
Male	623	1		1	1		
Female	370	0.56	0.40 – 0.78		0.56	0.39 – 0.80	
Age in years				0.249			0.462
< 50	76	1			1		
50 - 64	372	0.99	0.54 – 1.94	0.977	0.93	0.48 – 1.89	0.826
65 - 79	494	1.34	0.75 – 2.58	0.349	1.22	0.64 – 2.48	0.554
> 80	51	1.52	0.64 – 3.58	0.342	1.35	0.52 – 3.46	0.533
Missing*	0						
Charlson Comorbidity Index (CCI)				0.102			0.241
0 / 1	741	1			1		
2+	239	1.33	0.94 – 1.87		1.25	0.86 – 1.82	
Missing*	13						
Body Mass Index		1.01	0.98 – 1.05	0.495			
American Society of Anesthesiology (ASA) classification				0.009			0.085
I / II	798	1			1		
III +	185	1.62	1.11 – 2.33		1.44	0.95 – 2.15	
Missing*	10						
History of liver disease§				0.516			
No	949	1					
Yes	18	1.41	0.45 – 3.80				
Missing*	26						
History of liver resection				0.905			
No	793	1					
Yes	190	1.02	0.69 – 1.49				
Missing*	10						
Number of lesions				0.490			
1	282	1					
2	185	1.48	0.95 – 2.30	0.083			

3	131	1.10	0.65 – 1.82	0.728			
4	94	0.93	0.50 – 1.68	0.819			
5	63	1.44	0.74 – 2.68	0.267			
>5	172	1.24	0.78 – 1.97	0.367			
Missing*	66						
Maximum diameter of largest lesion (mm)				0.232			
< 20	146	1					
20-34	257	1.20	0.72 – 2.03	0.486			
35-54	218	0.90	0.52 – 1.57	0.709			
> 55	226	1.49	0.90 – 2.52	0.131			
Missing	146	1.34	0.76 – 2.37	0.314			
Location primary tumour				0.302			
Colon	658	1					
Rectum	333	0.84	0.60 – 1.17				
Missing*	2						
Nodal stage primary tumour				0.595			
pN0	253	1					
pN1	238	1.19	0.78 – 1.82	0.426			
pN2	198	1.02	0.64 – 1.60	0.946			
Missing	304	0.89	0.59 – 1.35	0.582			
Type of metastases				0.490			
Metachronous	432	1					
Synchronous	534	1.12	0.82 – 1.53				
Missing*	27						
Preoperative chemotherapy				0.324			0.072
No	550	1			1		
Yes	443	1.17	0.86 – 1.58		1.40	0.97 – 1.96	
Missing*							
Synchronous additional resection				0.049			0.207
No	529	1			1		
Yes	164	1.66	1.11 – 2.47	0.013	1.50	0.96 – 2.34	0.073
Missing	300	1.03	0.72 – 1.47	0.854	1.08	0.81 – 1.59	0.716
Order of resection				0.158			0.143
Primary tumour first	660	1			1		
Liver first	231	0.88	0.60 – 1.28	0.515	0.86	0.57 – 1.28	0.461
Combined resection	62	1.66	0.92 – 2.89	0.084	1.75	0.91 – 3.26	0.083
Missing*	40						
Type of surgery				0.287			
Open	882	1					
Laparoscopic	77	0.67	0.34 – 1.23	0.222			
Conversion	28	1.21	0.47 – 2.77	0.662			
Missing*	6						
Type of hospital[∞]				0.608			0.747
Regional hospitals	531	1			1		
Tertiary referral hospital	462	1.08	0.80 – 1.47		1.06	0.75 – 1.49	

* Missing not included in analyses based on relatively small group

§ History of liver disease containing liver cirrhosis, oesophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis

[∞] Type of hospital: tertiary referral centre are defined as hospitals with highest expertise on oncologic surgery

aOR (Adjusted) odds ratio; CI Confidence interval; mm millimetre

In the unadjusted analysis of 3476 minor resections, no differences were observed regarding postoperative complicated course, major morbidity and mortality (table 4). In the unadjusted analysis of 993 major resections, no differences were observed regarding postoperative complicated course, major morbidity and mortality (table 4). After stratification in minor liver resection and major liver resection no association was observed between preoperative chemotherapy and postoperative complicated courses either.

Table 4. Postoperative outcomes for patients diagnosed with colorectal liver metastases between 2014 and 2018 in the Netherlands receiving preoperative chemotherapy compared to patients receiving no preoperative chemotherapy.

Factor		No preoperative chemotherapy	Preoperative chemotherapy	P-value¶
Minor liver resection		N (%)	N (%)	
Number of patients (total)		2605	871	
Surgical strategy				<0.001
	Primary tumour first	1945 (78)	439 (54)	
	Liver first	200 (8)	256 (32)	
	Combined resection	338 (14)	115 (14)	
	Missing	122	58	
Procedure				<0.001
	Resection	2151 (83)	551 (63)	
	Resection and Ablation	454 (17)	320 (37)	
Synchronous additional resection*				0.870
	No	1392 (74)	451 (74)	
	Yes	499 (26)	158 (26)	
	Missing	714	262	
Surgical approach				<0.001
	Open	1732 (67)	734 (85)	
	Laparoscopic	728 (28)	115 (13)	
	Conversion	138 (5)	21 (2)	
	Missing	7	1	
30-day morbidity				0.583
	No	2424 (93)	805 (92)	
	Yes	181 (7)	66 (8)	
30-day mortality				0.913
	No	2587 (99)	864 (99)	
	Yes	18 (1)	7 (1)	
Postoperative complicated course				0.094
	No	2370 (91)	775 (89)	
	Yes	235 (9)	69 (11)	
Major liver resection		N (%)	N (%)	
Number of patients (total)		550	443	
Surgical strategy				<0.001
	Primary tumour first	421 (80)	239 (56)	
	Liver first	77 (15)	154 (36)	
	Combined resection	29 (5)	33 (8)	
	Missing	23	17	
Procedure				0.014

	Resection	494 (90)	374 (84)	
	Resection and Ablation	56 (10)	69 (16)	
Synchronous additional resection*				0.242
	No	280 (75)	249 (79)	
	Yes	96 (25)	58 (21)	
	Missing	174	126	
Surgical approach				0.044
	Open	478 (87)	404 (92)	
	Laparoscopic	50 (9)	27 (16)	
	Conversion	20 (4)	8 (2)	
	Missing	2	4	
30-day morbidity				0.830
	No	468 (85)	380 (86)	
	Yes	82 (15)	63 (14)	
30-day mortality				1.000
	No	528 (96)	425 (96)	
	Yes	22 (4)	18 (4)	
Postoperative complicated course				0.363
	No	440 (80)	343 (77)	
	Yes	11 (20)	100 (23)	

¶ Chi-square test was used comparing groups.

Synchronous additional resection was defined as any extra procedure including vascular resection or reconstruction or as additional intra-abdominal resection as a result of in-growth in other structures.

Several sensitivity analyses were performed, first the addition of a variable concerning the height of CEA on use of preoperative chemotherapy and outcomes was assessed, although approximately 1000 patients were excluded because of missing data in this variable. No influence of CEA was found. Inclusion of a variable concerning the year of surgery did not reveal differences in outcome, nor did a separate analysis for the 2014 and 2015 versus 2016 until 2018. No influence was found regarding the association preoperative chemotherapy and unradical resection. Also, there was no association between hospital volume variable and outcomes and there was collinearity with the variable concerning type of hospital and therefore this variable was not reported in this study. The effect of hospital volume on postoperative outcomes of this cohort was described elsewhere²⁰.

Multicollinearity was not observed in any of the models since all VIF were below 2.5.

Discussion

This nationwide analysis found that, significant variation in the use of preoperative chemotherapy for colorectal liver metastases is present in the Netherlands, even after correction for case-mix variables. Preoperative chemotherapy is not associated with a postoperative complicated course, major morbidity or mortality in the first 30 days after liver surgery. Worldwide, opinions are contradictory concerning the value of preoperative chemotherapy in patients with resectable CRLM. No clear guidelines concerning the application of preoperative

chemotherapy exist with respect to overall survival. Nordlinger et al. reported results in 2008 suggesting improved disease-free survival after preoperative chemotherapy⁷. Also, a meta-analysis from Asia suggested improved disease-free survival and overall survival after peri-operative chemotherapy^{21,22}. Several other reports showed no difference in overall survival for patients receiving preoperative chemotherapy versus no preoperative chemotherapy²³⁻²⁵.

The use of preoperative chemotherapy for resectable CRLM is not evidence based but a large part is explained by other factors. In the current population-based study, these factors include patient- and tumour characteristics as well as treating physician's preference. In the Netherlands, factors such as lower age, lower comorbidity scores, higher number of tumours, and larger diameter of the lesion were independently associated with the administration of preoperative chemotherapy. In irresectable CRLM, upfront surgery is obviously not possible and therefore induction (i.e. aiming for conversion to surgery) chemotherapy can increase resectability and improve survival. Several studies have shown improved resection rates after induction chemotherapy²⁶⁻²⁸. However, interpretation of these results is hampered by the variation concerning the definition for irresectable, potentially resectable and irresectable CRLM are used in these studies and in daily practice²⁹⁻³².

The hospital and oncological network variation in the Netherlands reflect the absence of unambiguous trials which provide Dutch practice with adequate reasons for administering preoperative chemotherapy for resectable CRLM as well as clear definitions concerning resectability of CRLM which encourages hospital variation.

Therefore, studies initiated to assess the oncologic advantage of preoperative chemotherapy for resectable CRLM are still needed to inform clinicians about possible advantages. Reports that assess criteria for patient- and tumour-factors that lead to clear definition of resectable, potentially resectable and irresectable are needed in order to provide worldwide definitions and guidelines concerning preoperative chemotherapy for CRLM. The CAIRO5 study group aims to investigate the optimal induction therapy for upfront irresectable CLRM and will report on outcomes and information regarding induction therapy and the definition of irresectable and potentially resectable CRLM²⁹. In the CAIRO5 protocol unresectability at baseline is defined as the follows: "The expected failure of achieving a complete resection of all lesions in one single surgical procedure by surgical resection only, leaving a minimum remnant liver volume of 25-30% in normal liver or 35-40% in compromised livers."

The second aim of the present study was to assess 30-day morbidity, 30-day mortality and postoperative complicated course after preoperative chemotherapy in our population-based

cohort. Thirty-day morbidity in the preoperative chemotherapy group was 9.8%, mortality was 1.9%, postoperative complicated course was 14.9% and no relationship between preoperative chemotherapy and postoperative outcomes was found. These results compared favourably with short-term outcome data of the EPOC-2 trial, in which patients with resectable CRLM were randomised to chemotherapy alone or chemotherapy in combination with cetuximab. Major complications occurred in 16-23% of the patients (n = 257) in the preoperative chemotherapy group³³. In the present study, treatment by indication bias could be a possible explanation, as the fitter and younger patients received preoperative chemotherapy more often in the Netherlands. A priori, these patients had lower chances of developing a complicated course postoperatively, therefore masking the effect of preoperative chemotherapy. On the contrary, our cohort was a mixture of upfront resectable and unresectable patients which could oppose this explanation of selection bias. The limited adverse effect of preoperative chemotherapy on postoperative outcomes has been supported by other studies. Liver regeneration was not affected by preoperative chemotherapy as shown by a Canadian study³⁴. Another study assessed 506 liver resections of whom 65% received preoperative chemotherapy for a median of 24 weeks³⁰. Major morbidity was 12% with 90-day mortality of 0.8%. Here, no relationship between preoperative chemotherapy and postoperative outcomes was observed. Other reports confirmed these outcomes with similar rates concerning major morbidity after preoperative chemotherapy^{31,35,36}. These results were supported by the data from other trials in which no association was found between preoperative chemotherapy and higher adverse events³⁷.

This study has several limitations. First, the disadvantage of these audit data might be the accuracy and coverage. Although the coverage of 97% of the DHBA of all liver resections is good, some details including the number of chemotherapy cycles, type of chemotherapy and complications of chemotherapy are lacking¹³. Second, the short-term quality of care assessment and therefore long-term follow-up information concerning oncological outcome is lacking in this study. However, the main purpose of auditing is to improve health care with respect to short-term outcomes. Therefore, long-term oncological outcome is not part of the DHBA and of this study. Third, data is missing on patients who were not eligible for resection as patients were either not being treated or receiving palliative therapy only are not included in the surgical database. Fourth, differences in patient- and tumour-characteristics explain selection for preoperative chemotherapy, these same differences bias outcome and therefore, limiting the conclusions to be drawn in this observational cohort.

The strength of the study is the nationwide collection of data of all patients who underwent liver surgery through mandatory participation of all Dutch hospitals performing liver surgery.

Therefore, it is a reflection of daily practice and representative of the Dutch population. This is an advantage as randomised controlled trials are often conducted within strict controlled situations with explicit inclusion and exclusion criteria.

In conclusion, in this population-based cohort study reflecting daily practice in the Netherlands, no association between 30-day postoperative complicated course, 30-day major morbidity and 30-day mortality and the use of preoperative chemotherapy was found. Significant outliers regarding hospital and oncological network variation in the use of preoperative chemotherapy for CRLM were present in the Netherlands, probably as a result of varying definitions concerning resectable, potentially resectable and irresectable disease. There is need for uniform definitions and evidence regarding the added value of preoperative chemotherapy for CRLM.

References

1. de Ridder J, de Wilt JH, Simmer F, Overbeek L, Lemmens V, Nagtegaal I. Incidence and origin of histologically confirmed liver metastases: an explorative case-study of 23,154 patients. *Oncotarget*. 2016;7(34):55368-55376.
2. Angelsen JH, Horn A, Sorbye H, Eide GE, Loes IM, Viste A. Population-based study on resection rates and survival in patients with colorectal liver metastasis in Norway. *Br J Surg*. 2017;104(5):580-589.
3. van Amerongen MJ, van der Stok EP, Futterer JJ, et al. Short term and long term results of patients with colorectal liver metastases undergoing surgery with or without radiofrequency ablation. *Eur J Surg Oncol*. 2016;42(4):523-530.
4. Hoppener DJ, Nierop PMH, van Amerongen MJ, et al. The Disease-Free Interval Between Resection of Primary Colorectal Malignancy and the Detection of Hepatic Metastases Predicts Disease Recurrence But Not Overall Survival. *Ann Surg Oncol*. 2019;26(9):2812-2820.
5. Adam R, Delvart V, Pascal G, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. *Ann Surg*. 2004;240(4):644-657; discussion 657-648.
6. Kanas GP, Taylor A, Primrose JN, et al. Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors. *Clin Epidemiol*. 2012;4:283-301.
7. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *Lancet*. 2008;371(9617):1007-1016.
8. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. *Lancet Oncol*. 2013;14(12):1208-1215.
9. Oncoline Dutch Tumor guidelines. *Dutch Guideline Database*. 2014.
10. Duwe G, Knitter S, Pesthy S, et al. Hepatotoxicity following systemic therapy for colorectal liver metastases and the impact of chemotherapy-associated liver injury on outcomes after curative liver resection. *Eur J Surg Oncol*. 2017;43(9):1668-1681.
11. Tamandl D, Klinger M, Eipeldauer S, et al. Sinusoidal obstruction syndrome impairs long-term outcome of colorectal liver metastases treated with resection after neoadjuvant chemotherapy. *Ann Surg Oncol*. 2011;18(2):421-430.
12. Nasti G, Ottaiano A, Berretta M, et al. Pre-operative chemotherapy for colorectal cancer liver metastases: an update of recent clinical trials. *Cancer Chemother Pharmacol*. 2010;66(2):209-218.
13. van der Werf LR, Kok NFM, Buis CI, et al. Implementation and first results of a mandatory, nationwide audit on liver surgery. *HPB (Oxford)*. 2019.
14. CBS. Geographical and population overview of the Netherlands. 2019. <https://opendata.cbs.nl/statline/#/CBS/nl/dataset/37296ned/table?ts=1573034522039>
15. RIVM. Regional and academic hospital distribution in the Netherlands. 2019. <https://www.volksgezondheidenzorg.info/onderwerp/ziekenhuiszorg/cijfers-context/aanbod#node-aantal-instellingen-voor-medisch-specialistische-zorg>
16. SONCOS. Preserving Quality of Care in the Netherlands. 2017. https://www.soncos.org/wp-content/uploads/2018/08/Soncos_norm-rapp2016_vdef.pdf17.
17. Werf LRvd, Voeten SC, Loe CMMv, Karthaus EG, Wouters MWJM, Prins HA. Data verification of nationwide clinical quality registries. *BJS Open*. 2019.
18. Clavien PA, Sanabria JR, Strasberg SM. Proposed classification of complications of surgery with examples of utility in cholecystectomy. *Surgery*. 1992;111(5):518-526.
19. Richardson DB, Keil AP, Cole SR, MacLehose RF. Observed and Expected Mortality in Cohort Studies. *Am J Epidemiol*. 2017;185(6):479-486.
20. Olthof PB, Elfrink AKE, al e. Volume-outcome relationship of liver surgery in a nationwide analysis. *Submitted*. 2019.
21. Sorbye H, Mauer M, Gruenberger T, et al. Predictive factors for the benefit of perioperative FOLFOX for resectable liver metastasis in colorectal cancer patients (EORTC Intergroup Trial 40983). *Ann Surg*. 2012;255(3):534-539.

22. Liu W, Zhou JG, Sun Y, Zhang L, Xing BC. The role of neoadjuvant chemotherapy for resectable colorectal liver metastases: a systematic review and meta-analysis. *Oncotarget*. 2016;7(24):37277-37287.
23. Adam R, Bhangu P, Poston G, et al. Is perioperative chemotherapy useful for solitary, metachronous, colorectal liver metastases? *Ann Surg*. 2010;252(5):774-787.
24. Faron M, Chirica M, Tranchard H, et al. Impact of preoperative and postoperative FOLFOX chemotherapies in patients with resectable colorectal liver metastasis. *J Gastrointest Cancer*. 2014;45(3):298-306.
25. Ayez N, van der Stok EP, Grunhagen DJ, et al. The use of neo-adjuvant chemotherapy in patients with resectable colorectal liver metastases: Clinical risk score as possible discriminator. *Eur J Surg Oncol*. 2015;41(7):859-867.
26. Beppu T, Miyamoto Y, Sakamoto Y, et al. Chemotherapy and targeted therapy for patients with initially unresectable colorectal liver metastases, focusing on conversion hepatectomy and long-term survival. *Ann Surg Oncol*. 2014;21 Suppl 3:S405-413.
27. Phelip JM, Mineur L, De la Fouchardiere C, et al. High Resectability Rate of Initially Unresectable Colorectal Liver Metastases After UGT1A1-Adapted High-Dose Irinotecan Combined with LV5FU2 and Cetuximab: A Multicenter Phase II Study (ERBIFORT). *Ann Surg Oncol*. 2016;23(7):2161-2166.
28. Takatsuki M, Tokunaga S, Uchida S, et al. Evaluation of resectability after neoadjuvant chemotherapy for primary non-resectable colorectal liver metastases: A multicenter study. *Eur J Surg Oncol*. 2016;42(2):184-189.
29. Huiskens J, van Gulik TM, van Lienden KP, et al. Treatment strategies in colorectal cancer patients with initially unresectable liver-only metastases, a study protocol of the randomised phase 3 CAIRO5 study of the Dutch Colorectal Cancer Group (DCCG). *BMC Cancer*. 2015;15:365.
30. Wolf PS, Park JO, Bao F, et al. Preoperative chemotherapy and the risk of hepatotoxicity and morbidity after liver resection for metastatic colorectal cancer: a single institution experience. *J Am Coll Surg*. 2013;216(1):41-49.
31. Makowiec F, Mohrle S, Neeff H, et al. Chemotherapy, liver injury, and postoperative complications in colorectal liver metastases. *J Gastrointest Surg*. 2011;15(1):153-164.
32. Huiskens J, Bolhuis K, Engelbrecht MR, et al. Outcomes of Resectability Assessment of the Dutch Colorectal Cancer Group Liver Metastases Expert Panel. *J Am Coll Surg*. 2019.
33. Primrose J, Falk S, Finch-Jones M, et al. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis: the New EPOC randomised controlled trial. *Lancet Oncol*. 2014;15(6):601-611.
34. Simoneau E, Alanazi R, Alshenaifi J, et al. Neoadjuvant chemotherapy does not impair liver regeneration following hepatectomy or portal vein embolization for colorectal cancer liver metastases. *J Surg Oncol*. 2016;113(4):449-455.
35. Fukuoka K, Nara S, Honma Y, Kishi Y, Esaki M, Shimada K. Hepatectomy for Colorectal Cancer Liver Metastases in the Era of Modern Preoperative Chemotherapy: Evaluation of Postoperative Complications. *World J Surg*. 2017;41(4):1073-1081.
36. Spelt L, Hermansson L, Tingstedt B, Andersson R. Influence of preoperative chemotherapy on the intraoperative and postoperative course of liver resection for colorectal cancer metastases. *World J Surg*. 2012;36(1):157-163.
37. Khoo E, O'Neill S, Brown E, Wigmore SJ, Harrison EM. Systematic review of systemic adjuvant, neoadjuvant and perioperative chemotherapy for resectable colorectal-liver metastases. *HPB (Oxford)*. 2016;18(6):485-493.

Supplementary material

Supplementary table 1. Univariable and multivariable logistic regression model of patient, tumour and surgical factors associated with postoperative mortality for liver resections in patients with colorectal liver metastases in the Netherlands between 2014-2018.

Factor	N	Univariable analysis			Multivariable analysis		
		OR	CI (95%)	P-value	aOR	CI (95%)	P-value
Sex				0.02			0.06
Male	2715	1			1		
Female	1608	0.50	0.27 – 0.87		0.56	0.30 – 0.96	
Age in years				0.06			0.09
< 50	308	1			1		
50 - 64	1471	3.59	0.73 – 65.1	0.22	3.90	0.77 – 71.2	0.19
65 - 79	2219	5.78	1.25 – 103	0.08	5.96	1.23 – 107	0.08
> 80	318	5.90	1.00 - 112	0.10	6.55	1.03 – 128	0.09
Missing*							
Charlson Comorbidity Index (CCI)				0.16			0.75
0 / 1	3196	1			1		
2+	1056	1.45	0.84 – 2.42		1.01	0.51 – 1.59	
Missing*	71						
Body Mass Index		1.00	0.98 – 1.02	0.81			
American Society of Anesthesiology (ASA) classification				<0.01			<0.01
I / II	3439	1			1		
III +	937	4.65	2.84 – 7.65		4.36	2.58 – 7.41	
Missing*	47						
History of liver disease§				0.92			
No	4118	1					
Yes	60	1.11	0.06 – 5.16				
Missing*	145						
History of liver resection				<0.01			<0.01
No	3497	1			1		
Yes	770	2.05	1.18 – 3.43		2.15	1.20 – 3.74	
Missing*	56						
Number of lesions				0.16			
1	1881	1					
2	908	1.35	0.65 – 2.70	0.40			
3	478	2.20	1.01 – 4.53	0.04			
4	291	0.97	0.23 – 2.85	0.96			
5	177	2.15	0.62 – 5.76	0.17			
>5	460	2.28	1.05 – 4.71	0.03			
Missing*	128						
Maximum diameter of largest lesion (mm)				0.10			0.88
< 20	1155	1			1		
20-34	1414	1.56	0.74 – 3.50	0.26	1.33	0.62 – 3.05	0.47
35-54	7171	2.28	1.01 – 5.32	0.05	1.57	0.68 – 3.78	0.30
> 55	434	2.98	1.26 – 7.20	0.01	1.40	0.55 – 3.57	0.47
Missing	603	2.13	0.89 – 5.13	0.09	1.22	0.48 – 3.11	0.67
Location primary tumour				0.14			
Colon	2745	1					
Rectum	1571	0.67	0.38 – 1.13				
Missing*	7						

Nodal stage primary tumour				0.25			
pN0	1234	1					
pN1	1153	1.58	0.82 – 3.12	0.18			
pN2	810	0.81	0.32 – 1.88	0.63			
Missing	1126	1.47	0.75 – 2.93	0.26			
Type of metastases				1.00			
Metachronous	2252	1					
Synchronous	1914	1.00	0.60 – 1.66				
Missing*	157						
Preoperative chemotherapy				0.16			0.55
No	3009	1			1		
Yes	1314	1.44	0.86 – 2.37		1.18	0.68 – 2.01	
Major liver resection				<0.01			<0.01
No	3359	1			1		
Yes	964	5.78	3.51 – 9.68		5.68	3.32 – 9.89	
Synchronous additional resection				0.19			0.06
No	2325	1			1		
Yes	782	1.71	0.90 – 3.15	0.09	1.99	1.02 – 3.78	0.04
Missing	1216	1.44	0.81 – 2.54	0.21	1.78	0.96 – 3.29	0.06
Order of resection				0.62			
Primary tumour first	2944	1					
Liver first	679	1.38	0.71 – 2.52	0.31			
Combined resection	483	1.04	0.43 – 2.19	0.92			
Missing*	217						
Type of surgery				0.20			
Open	3221	1					
Laparoscopic	905	0.66	0.31 – 1.24	0.22			
Conversion	184	0.32	0.02 – 1.47	0.26			
Missing*	13						
Type of hospital[∞]				0.07			0.13
Regional hospitals	2405	1			1		
Tertiary referral centre	1918	1.57	0.96 – 2.58		1.51	0.89 – 2.59	

* Missing not included in analyses based on relatively small group

§ History of liver disease containing liver cirrhosis, oesophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis

[∞] Type of hospital: tertiary referral centre are defined as hospitals with highest expertise on oncologic surgery

Supplementary figure 1. Overview of the layout of Dutch Oncological Networks.

CHAPTER 8

CASE-MIX ADJUSTMENT TO COMPARE NATIONWIDE HOSPITAL PERFORMANCES AFTER RESECTION OF COLORECTAL LIVER METASTASES

A.K.E. Elfrink, E.W. van Zwet, R.J. Swijnenburg, M. den Dulk, P.B. van den Boezem, J.S.D. Mieog, W.W. te Riele, G.A. Patijn, W.K.G. Leclercq, D.J. Lips, A.M. Rijken, C. Verhoef, K.F.D. Kuhlmann, C.I. Buis, K. Bosscha, E.J.T. Belt, M. Vermaas, N.T. van Heek, S.J. Oosterling, H. Torrena, H.H. Eker, E.C.J. Consten, H.A. Marsman, M.W.J.M. Wouter, N.F.M. Kok, D.J. Grünhagen, J.M. Klaase, [Dutch Hepato Biliary Audit Group](#)

Eur J Surg Oncol. 2021 Mar;47(3 Pt B):649-659.

Abstract

Introduction

Differences in patient demographics and disease burden can influence comparison of hospital performances. This study aimed to provide a case-mix model to compare short-term postoperative outcomes for patients undergoing liver resection for colorectal liver metastases (CRLM).

Methods

This retrospective, population-based study included all patients who underwent liver resection for CRLM between 2014 and 2018 in the Netherlands. Variation in case-mix variables between hospitals and influence on postoperative outcomes was assessed using multivariable logistic regression. Primary outcomes were 30-day major morbidity and 30-day mortality. Validation of results was performed on the data from 2019.

Results

In total, 4639 patients were included in 28 hospitals. Major morbidity was 6.2% and mortality was 1.4%. Uncorrected major morbidity ranged from 3.3% to 13.7% and mortality ranged from 0.0% to 5.0% between hospitals. Significant differences between hospitals were observed for age higher than 80 (0.0% to 17.1%, $p < 0.001$), ASA 3 or higher (3.3% to 36.3%, $p < 0.001$), histopathological parenchymal liver disease (0.0% to 47.1%, $p < 0.001$), history of liver resection (8.1% to 36.3%, $p < 0.001$), major liver resection (6.7% to 38.0%, $p < 0.001$) and synchronous metastases (35.5% to 62.1%, $p < 0.001$). Expected 30-day major morbidity between hospitals ranged from 6.4% to 11.9% and expected 30-day mortality ranged from 0.6% to 2.9%. After case-mix correction no significant outliers concerning major morbidity and mortality remained. Validation on patients who underwent liver resection for CRLM in 2019 affirmed these outcomes.

Conclusion

Case-mix adjustment is a prerequisite to allow for institutional comparison of short-term postoperative outcomes after liver resection for CRLM.

Introduction

Colorectal liver metastases occur in 25-50% of patients with colorectal cancer^{1,2}. Resection is still the cornerstone of curative treatment of CRLM but is accompanied by considerable morbidity and mortality³⁻⁶. Strategies to further improve postoperative outcomes after liver resection are therefore still needed.

Clinical auditing of surgical procedures has been described as a powerful tool to assess and improve quality of care⁷. In clinical auditing, the first step is to determine endpoints such as postoperative outcomes. After data collection on the endpoints one is able to reflect on these in order to improve them afterwards⁸⁻¹⁰. The Dutch HepatoBiliary Audit (DHBA) was founded by the board of the Dutch Liver Study Group, representing more than 75% of all Dutch liver surgeons in 2013. From 2013 a minimal required annual volume of 20 liver resections per hospital was mandatory in order to pursue liver surgery, which resulted from new insights during centralization of liver surgery in the Netherlands between 2005 and 2013¹¹. From 2014 onwards, registration of all liver resections in the DHBA was mandatory for all hospitals performing liver surgery. The DHBA was explicitly designed to monitor and compare quality of care between hospitals performing liver surgery in the Netherlands¹².

Quality of care in the DHBA is monitored and compared using several quality indicators¹³, which can cover structure of care, process of care or (short-term) postoperative outcomes. Patient- and tumour characteristics that may influence outcomes are often referred to as case-mix factors. Together they show the population treated in a hospital. The case-mix of a hospital can positively or negatively impact the comparison of outcomes as observed in other fields of surgery¹⁴⁻¹⁶. Case-mix adjustment therefore seems obligatory to produce a reliable and valid comparison of outcomes between hospitals. Contrasting other oncological surgical procedures which are straight forward, for CRLM numerous types of liver resection can be performed¹⁷. All these anatomical variations of liver resection have their own technical difficulty and associated postoperative outcomes^{18,19}. This makes that case-mix adjustment for liver resection is heterogeneous and has not been described earlier.

The aim of this study was to address variation in patient demographics and disease burden between hospitals and to develop and validate a case-mix adjustment model to compare the differences in 30-day major morbidity and 30-day mortality after liver resection for CRLM between hospitals in the Netherlands.

Methods

This was a population-based study performed in the Netherlands. Data were retrieved from the DHBA, a mandatory nationwide audit in which all Dutch hospitals performing liver surgery register all liver resections. The DHBA is an opt-out registry. Data verification was performed to provide insight in completeness and accuracy of the DHBA when compared to the Dutch Cancer Registry^{12,20}. No ethical approval was needed under Dutch law as the DHBA is part of the Dutch Inspectorate of health care and research is carried out with an anonymised dataset.

Patient selection

All patients who underwent liver resection for CRLM between the 1st of January 2014 and 31st of December 2018 in the Netherlands and who were registered in the DHBA before 22nd of March 2019 were included in this study. Patients were excluded if date of birth, date of surgery type of tumour, type of surgical intervention, and occurrence of major morbidity or mortality was missing. All patients who only underwent thermal ablation without resection for CRLM were excluded.

As a sensitivity analysis, the variation in case-mix factors and final case-mix correction model in the 2014 to 2018 study period was validated on the complete 2019 cohort of the DHBA. Inclusion of patients and analysis were the same for the core set of 2014 to 2018 and for the validation on the 2019 cohort.

Main outcomes

Main outcomes were major morbidity and mortality after liver resection. Both are existing quality indicators in the DHBA calculated per hospital for the last two consecutive years of full registration in the DHBA. Major morbidity was defined as a complication grade 3a or higher according to Clavien-Dindo classification, within 30 days of the liver resection²¹. Mortality was defined as death during hospitalization or within 30 days of the liver resection. Both quality indicators are public for all hospitals registering in the DHBA both for all resections and stratified for minor and major liver resection. Case-mix corrected funnel plots are calculated for both quality indicators over two consecutive years in the DHBA its daily practice and were calculated over 2018 and 2019 for the validation.

Case-mix factors

Several categories of variables were assessed to represent the case-mix in the DHBA. Variables were selected on the basis of expert opinion. The DHBA scientific committee, consisting of 23 liver surgeons and interventional radiologists from the Netherlands, acted as experts. Patient characteristics included sex, age, American Society of Anesthesiologist (ASA) classification, Body Mass Index (BMI), comorbidity scores according the Charlson Comorbidity Score (CCI), histopathological classification of liver parenchyma adjacent to tumour tissue and previous liver surgery. Tumour characteristics included number of CRLM, diameter of the largest CRLM before the initiation of tumour-specific treatment such as preoperative chemotherapy and synchronous (within 6 months of detection of the primary tumour) or metachronous diagnosis of the CRLM. Treatment characteristics included use of preoperative chemotherapy, use of thermal ablation in combination with resection, minor or major liver resection, and type of hospital where resection was performed. Latter was either a regional hospital or a tertiary referral centre. Major liver resection was defined as resection of three or more adjacent Couinaud segments.

Statistical analysis

The mean percentage accompanied by the minimum and maximum percentage for every variable in every hospital was calculated to assess between hospital variation regarding possible case-mix factors. These percentages and ranges were displayed in a violin graph. Using univariable logistic regression models with case-mix factors as dependent variable and hospitals as independent variable the significance of this variation between hospitals was calculated.

The association of case-mix factors with major morbidity and mortality was investigated using two separate multivariable logistic regression models. For this multivariable model, all possible case-mix factors were selected. Case-mix factors were included through univariable logistic regression ($p < 0.10$) after checking for multicollinearity when a restriction of the multivariable logistic regression model was needed due to the number of degrees of freedom. For major morbidity, all possible case-mix factors were included as no restriction was needed because of high number of events. For mortality restriction of case-mix factors was performed, due to low number of events.

Based on the case-mix of all patients, the expected morbidity and mortality was calculated per patient using a multivariable logistic regression model. As a result of all patients operated on in

a hospital, the expected morbidity and mortality per hospital was calculated. To visualise the difference in quality indicators between hospitals, the observed / expected ratio (O/E ratio) was used. By dividing the observed morbidity of every hospital by the expected morbidity of that same hospital, the O/E ratio was calculated. This is the case-mix adjusted ratio indicating the performance of a hospital. An O/E ratio above 1 indicated that a hospital performed worse than expected, an O/E ratio below 1 indicated that a hospital performed better than expected. The 95% confidence intervals (CI) were calculated to indicate whether the O/E ratio of a hospital was statistically different from the other hospitals.

Multicollinearity was tested through the Variance Inflation Factor (VIF). A VIF of 3 or more was the cut-off value indicating multicollinearity. Patients with missing values were analysed as a separate group in multivariable logistic regression if these exceeded 5% of the total included number of patients. If the missing values in a variable was below 5%, the missing patients were excluded from the analysis.

As a sensitivity analysis, the association of annual hospital volume (<20, 20-39, 40-59, 60-79, and >80) with postoperative major morbidity and mortality was assessed. This variable was added in both multivariable logistic regression models (not shown).

All analyses were performed in R version 3.2.2® (R Core Team (2018): A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

Results

Population characteristics

In total 4776 patients who underwent liver resection for CRLM were included during the study period (table 1). One hundred and thirty-seven patients were excluded because of missing information regarding critical variables. In the remaining 4639 patients, 30-day major morbidity was 6.2% and 30-day mortality was 1.4%.

Table 1. Baseline characteristics of patients diagnosed with colorectal liver metastases (CRLM) between 2014 and 2018 in the Netherlands.

Factor	N (%)
Total	4639
Patient characteristics	
Sex	
Male	2926 (63)
Female	1713 (37)
Age (years)	
< 50	329 (7)
50 - 64	1593 (34)

	65 - 79	2375 (51)
	≥ 80	333 (7)
	Missing	9 (0)
Charlson Comorbidity Index (CCI)		
	0 / 1	3393 (73)
	≥2	1113 (24)
	Missing	133 (3)
Body Mass Index (BMI)		
	Mean (sd)	26.3 (4.4)
American Society of Anesthesiology (ASA) classification		
	ASA I / II	3638 (78)
	ASA III+	870 (19)
	Missing	131 (3)
History of liver resection		
	No	3713 (80)
	Yes	815 (18)
	Missing	111 (2)
Histopathology liver parenchyma§		
	Normal liver	2907 (63)
	Steatosis	720 (16)
	Steato-hepatitis	76 (2)
	Cirrhosis	35 (1)
	Sinusoidal dilatation	51 (1)
	Missing	850 (18)
Preoperative chemotherapy		
	No	3009 (70)
	Yes	1314 (30)
Tumour characteristics		
Number of lesions		
	1	1978 (43)
	2	969 (21)
	3	512 (11)
	4	316 (6)
	≥5	668 (15)
	Missing	196 (4)
Maximum diameter of largest CRLM (mm*)		
	< 20	1230 (27)
	20-34	1508 (33)
	35-54	746 (16)
	≥ 55	456 (9)
	Missing	699 (15)
Location primary tumour		
	Colon	2966 (64)
	Rectal	1657 (46)
	Missing	16 (0)
Major liver resection		
	No	3620 (78)
	Yes	1019 (22)
Bilobar disease		
	No	2472 (53)
	Yes	2015 (44)
	Missing	152 (3)
Timing of metastases		
	Metachronous	2361 (51)
	Synchronous	2064 (45)
	Missing	214 (4)

Extra-hepatic disease		
	No	3799 (82)
	Yes	543 (12)
	Missing	297 (6)
Type of hospital[∞]		
	Regional hospitals	2557 (55)
	Tertiary referral centres	2082 (45)
Year of surgery		
	2014	854 (19)
	2015	896 (19)
	2016	984 (21)
	2017	986 (21)
	2018	919 (20)

§ Histopathology of the liver on the basis of pathological examination.

*millimetre

[∞] Type of hospital: tertiary referral centre is defined as hospitals with highest expertise on oncologic surgery

Between-hospital variation in case-mix factors

Considerable differences in the case-mix variables between hospitals were observed (figure 1, supplementary table 1). Differences between hospitals in the range of mean percentages were observed in age higher than 80 (0.0% to 17.1%, $p<0.001$), ASA 3 or higher (3.3% to 36.3%, $p<0.001$), a CCI of 2 or higher (19.7% to 63.3%, $p<0.001$), histopathological parenchymal liver disease (0.0% to 47.1%, $p<0.001$), history of liver resection (8.1% to 36.3%, $p<0.001$), preoperative chemotherapy (1.5% to 55.1%, $p<0.001$), resection of more than 3 CRLM in one surgical session (7.0% to 36.9%, $p<0.001$), resection of largest CRLM with a diameter of 55mm or larger (0.0% to 26.4%, $p<0.001$), major liver resection (6.7% to 38.0%, $p<0.001$), bilobar disease (5.0% to 60.6%, $p<0.001$), synchronous metastases (35.5% to 62.1%, $p<0.001$) and rectal primary tumour (20.4% to 46.6%, $p<0.001$) and extra-hepatic disease (3.9% to 38.5%, $p<0.001$). The proportion of female patients did not differ between hospitals (25.0% to 47.0%, $p=0.232$).

Figure 1a. Violin graph showing the distribution of mean percentages (range) of case-mix variables per hospital in the Netherlands in patients who underwent liver resection for colorectal liver metastases between 2014 and 2018.

Case-mix factors for 30-day major morbidity and 30-day mortality

Several case-mix factors were associated with the occurrence of 30-day major morbidity. The factors male sex, age above 65, ASA classification 3 or higher, histopathological steato-hepatitis or sinusoidal dilatation, major liver resection, synchronous diagnosis of metastases, extra-hepatic disease and treatment in a tertiary referral centre were all statistically significant case-mix factors for 30-day major morbidity (table 2a). Rectal primary tumour was associated with lower 30-day major morbidity. Based on table 2a we observe that age, ASA classification and major liver resection were most important to correct for concerning 30-day morbidity.

Charlson Comorbidity index, Body Mass Index, histopathological steatosis or cirrhosis, history of liver resection, history of preoperative chemotherapy, number of CRLM, diameter of largest CRLM and bilobar disease were also included in the 30-day morbidity case-mix model but were not significant case-mix factors. No restriction in the case-mix model was needed due to the high number of events (n = 286).

Table 2a. Univariable and multivariable logistic regression model to assess the association of patient and tumour characteristics with 30-day morbidity in patients with colorectal liver metastasis (CRLM) in the Netherlands between 2014-2018.

Factor	Univariable analysis				Multivariable analysis		
	N	OR	CI (95%)	P-value	aOR	CI (95%)	P-value
Sex				0.001			<0.001
Male	2926	1			1		
Female	1713	0.69	0.55 – 0.86		0.63	0.49 – 0.81	
Age (years)				0.030			0.049
< 50	329	1			1		
50 - 64	1593	1.56	0.96 – 2.68	0.085	1.68	0.91 – 3.25	0.083
65 - 79	2375	1.76	1.11 – 2.99	0.025	1.73	1.02 – 3.37	0.048
≥ 80	333	2.23	1.26 – 4.07	0.007	2.27	1.21 – 4.97	0.015
Missing*	9						
Charlson Comorbidity Index (CCI)				0.015			0.315
0 / 1	3393	1			1		
≥2	1113	1.32	1.05 – 1.65		1.15	0.88 – 1.48	
Missing*	133						
Body Mass Index		1.01	0.98 – 1.03	0.545	1.00	0.97 – 1.03	0.813
American Society of Anesthesiology (ASA) classification				<0.001			<0.001
I / II	3638	1			1		
III +	870	1.80	1.42 – 2.26		1.76	1.36 – 2.31	
Missing*	131						
Histopathology liver parenchyma§				<0.001			0.134
Normal liver	2907	1			1		
Steatosis	720	1.35	1.02 – 1.75	0.028	1.19	0.88 – 1.62	0.300
Steato-hepatitis	76	1.80	0.89 – 3.31	0.078	2.02	1.02 – 3.94	0.042
Cirrhosis	35	1.00	0.24 – 2.80	1.000	0.51	0.03 – 2.37	0.479
Sinusoidal dilatation	51	2.59	1.21 – 5.03	0.008	2.35	1.00 – 4.67	0.050
Missing	850	0.71	0.52 – 0.95	0.027	0.91	0.60 – 1.30	0.581
History of liver resection				0.495			0.804
No	3713	1			1		
Yes	815	1.10	0.84 – 1.41		1.03	0.75 – 1.52	
Missing*	111						
Preoperative chemotherapy				0.124			0.672
No	3009	1			1		
Yes	1315	1.19	0.95 – 1.49		1.03	0.71 – 1.25	
Missing*	316						
Number of lesions				0.312			0.702
1	1978	1			1		
2	969	0.97	0.73 – 1.29	0.857	0.92	0.62 – 1.23	0.458
3	512	1.30	0.93 – 1.80	0.112	1.28	0.80 – 1.76	0.385
4	316	1.23	0.81 – 1.81	0.320	1.31	0.63 – 1.66	0.872
≥5	668	1.24	0.91 – 1.66	0.165	1.09	0.65 – 1.50	0.965
Missing*	196						
Maximum diameter largest CRLM (mm)*				<0.001			0.233
< 20	1230	1			1		
20 - 34	1508	1.13	0.85 – 1.50	0.420	1.05	0.67 – 1.25	0.566
35 - 54	746	1.47	1.06 – 2.03	0.020	1.09	0.78 – 1.58	0.564
≥ 55	465	2.26	1.61 – 3.17	<0.001	1.41	0.93 – 2.06	0.105

Missing	699	1.23	0.87 – 1.73	0.230	1.22	0.80 – 1.87	0.343
Major liver resection				<0.001			<0.001
No	3620	1			1		
Yes	1019	2.20	1.77 – 2.72		2.04	1.54 – 2.60	
Bilobar disease				0.344			0.942
No	2472	1			1		
Yes	2015	1.10	0.90 – 1.36		1.11	0.75 – 1.31	
Missing*	152						
Location primary tumour				<0.001			<0.001
Colon	2966	1			1		
Rectal	1657	0.63	0.50 – 0.77		0.64	0.50 – 0.83	
Missing*	16						
Timing of metastasis				0.001			0.002
Metachronous	2361	1			1		
Synchronous	2064	1.41	1.15 – 1.73		1.50	1.16 – 1.94	
Missing*	214						
Extra-hepatic disease				0.083			0.023
No	3799	1			1		
Yes	543	1.29	0.96 – 1.72		1.46	1.05 – 2.00	
Missing	297						
Type of hospital[∞]				0.030			0.041
Regional centres	2557	1			1		
Tertiary referral centres	2082	1.25	1.02 – 1.54		1.29	1.02 – 1.64	

* Missing not included in analyses based on relatively small group

§ History of liver disease containing liver cirrhosis, oesophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis

Mm = millimetre

[∞] Type of hospital: tertiary referral centre is defined as hospitals with highest expertise on oncologic surgery

\$ Unclear why percentage missing is so high.

Several case-mix factors were significantly associated with 30-day mortality. These case-mix factors included age above 80, ASA classification 3 or higher, histopathological steato-hepatitis or sinusoidal dilatation, history of liver resection, and major liver resection (table 2b). Based on table 2b we observe that age above 80, ASA classification 3 or higher, history of liver resection and major liver resection were most important to correct for concerning 30-day mortality. Sex, BMI, preoperative chemotherapy, number of CRLM and type of hospital were all non-significant case-mix factors for 30-day mortality. Due to the low number of events (n = 66), Body Mass Index, Charlson comorbidity index, maximum diameter of largest CRLM, bilobar disease, location of primary tumour, synchronous or metachronous diagnosis of the metastases and extra-hepatic disease were not included in the case-mix model for 30-day mortality.

Table 2b. Univariable and multivariable logistic regression model to assess the association of patient and tumour characteristics with 30-day mortality in patients with colorectal liver metastasis (CRLM) in the Netherlands between 2014-2018.

Factor	Univariable analysis				Multivariable analysis		
	N	OR	CI (95%)	P-value	aOR	CI (95%)	P-value
Sex				0.034			0.200
Male	2926	1			1		
Female	1713	0.54	0.30 – 0.93		0.68	0.37 – 1.20	
Age (years)				0.044			0.122
< 50	329	1			1		
50 - 64	1593	3.54	0.72 – 63.9	0.220	3.11	0.62 – 57.4	0.280
65 - 79	2375	5.90	1.28 – 105	0.080	4.81	0.97 – 87.8	0.131
≥ 80	333	6.02	1.02 – 114	0.010	6.73	1.03 – 133	0.049
Missing*	9						
Charlson Comorbidity Index (CCI)				0.179			
0 / 1	3393	1					
≥2	1113	1.43	0.83 – 2.38				
Missing*	133						
Body Mass Index		1.05	1.00 – 1.10	0.046	1.03	0.97 – 1.09	0.264
American Society of Anesthesiology (ASA) classification				<0.001			<0.001
I / II	3638	1			1		
III +	870	4.58	2.81 – 7.50		4.30	2.51 – 7.40	
Missing*	131						
Histopathology liver parenchyma§				0.011			0.078
Normal liver	2907	1			1		
Steatosis	720	1.73	0.89 – 3.18	0.089	1.62	0.84 – 3.10	0.161
Steato-hepatitis	76	4.84	1.42 – 12.6	0.004	4.93	1.46 – 14.1	0.007
Cirrhosis	35	5.28	0.83 – 18.4	0.026	2.77	0.14 – 16.8	0.361
Sinusoidal dilatation	51	5.44	1.28 – 15.9	0.006	4.29	1.13 – 14.2	0.041
Missing	850	1.04	0.48 – 2.04	0.921	1.39	0.63 – 2.82	0.382
History of liver resection				0.004			0.022
No	3713	1			1		
Yes	815	2.16	1.25 – 3.59		1.96	1.18 – 3.72	
Missing*	111						
History of preoperative chemotherapy				0.156			0.873
No	3009	1			1		
Yes	1315	1.44	0.86 – 2.37		1.05	0.57 – 1.91	
Missing*	316						
Number of CRLM				0.072			0.231
1	1978	1			1		
2	969	1.33	0.64 – 2.66	0.425	1.29	0.61 – 2.65	0.487
3	512	2.35	1.11 – 4.77	0.021	2.26	1.03 – 4.77	0.071
4	316	0.94	0.22 – 2.76	0.919	0.74	0.18 – 2.26	0.639
≥5	668	2.26	1.13 – 4.40	0.019	1.54	0.73 – 3.16	0.245
Missing*	196						
Maximum diameter largest CRLM (mm)*				0.103			
< 20	1230	1					
20 - 34	1508	1.64	0.78 – 3.67	0.204			
35 - 54	746	2.33	1.04 – 5.44	0.042			

≥ 55	465	3.02	1.26 – 7.29	0.012		
Missing	699	1.95	0.82 – 4.70	0.129		
Major liver resection				<0.001		<0.001
No	3620	1			1	
Yes	1019	6.03	3.67 – 10.1		6.08	3.56 – 10.6
Bilobar disease				0.115		
No	2472	1				
Yes	2015	1.49	0.91 – 2.46			
Missing*	152					
Location primary tumour				0.146		
Colon	2966	1				
Rectal	1657	0.67	0.38 – 1.13			
Missing*	16					
Timing of metastasis				0.814		
Metachronous	2361	1				
Synchronous	2064	0.94	0.57 – 1.56			
Missing*	214					
Extra-hepatic disease				0.593		
No	3799	1				
Yes	543	1.21	0.56 – 2.36			
Missing	297					
Type of hospital[∞]				0.068		0.219
Regional	2557	1			1	
Tertiary referral centres	2082	1.58	0.97 – 2.59		1.39	0.82 – 2.37

* Missing not included in analyses based on relatively small group

§ History of liver disease containing liver cirrhosis, oesophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis

Mm = millimetre

[∞] Type of hospital: tertiary referral centre is defined as hospitals with highest expertise on oncologic surgery

\$ Unclear why percentage missing is so high.

The sensitivity analysis concerning inclusion of annual hospital volume (<20, 20-39, 40-59, 60-79, >80) did not reveal significant differences concerning 30-day major morbidity and 30-day mortality and was therefore not reported here.

Also, multicollinearity was assessed in all models and was ruled out as the VIF was below 2.0 in all models for all variables.

Hospital comparison of 30-day major morbidity and 30-day mortality

Uncorrected 30-day major morbidity between hospitals ranged from 3.3% to 13.7% (supplementary figure 1a). Uncorrected 30-day mortality between hospitals ranged from 0.0% to 5.0% (supplementary figure 1b). Expected 30-day major morbidity between hospitals ranged from 6.4% to 11.9% (figure 2a). Expected 30-day mortality between hospitals ranged from 0.6% to 2.9% (figure 2b).

After adjustment for case-mix factors, O/E ratios for 30-day morbidity ranged from 0.41 to 1.42 (table 2a). None of the hospitals performing liver surgery had a significantly higher 30-day major

morbidity rate than expected (figure 3a). Two hospitals had significantly lower 30-day major morbidity rates than expected.

After correction for case-mix factors, O/E ratios for 30-day mortality ranged from 0.0 to 5.18 (table 2b). None of the hospitals performing liver surgery had a significantly higher 30-day mortality rate than expected (figure 3b). In four hospitals a significantly lower 30-day mortality rate than expected was observed.

Figure 2a. Expected percentage of 30-day major morbidity in hospitals in performing liver resection for colorectal liver metastases in the Netherlands between 2014 - 2018.

Figure 2b. Expected percentage of 30-day mortality in hospitals in performing liver resection for colorectal liver metastases in the Netherlands between 2014 - 2018.

Figure 3a. Case-mix adjusted funnel-plot of between-hospital variation in 30-day major morbidity in patients with colorectal liver metastases in the Netherlands between 2014 - 2018.

Case-mix adjusted for: sex, age in years, ASA III / IV, Charlson Comorbidity Index, histopathology of liver parenchyma, history of liver resection, preoperative chemotherapy, number of CRLM, maximum diameter of the largest CRLM prior to treatment, major liver resection, location of the primary tumour, bilobar disease, synchronous metastases, extra-hepatic disease and type of hospital.

Figure 3b. Case-mix adjusted funnel-plot of between-hospital variation in 30-day mortality in patients with colorectal liver metastases in the Netherlands between 2014 - 2018.

Case-mix adjusted for: sex, age in years, ASA III / IV, histopathology of liver parenchyma, preoperative chemotherapy, history of liver resection, number of CRLM, major liver resection and type of hospital.

Validation on patients who underwent liver resection for CRLM in 2019 in the Netherlands

778 patients who underwent liver resection for CRLM in the Netherlands in 2019 were included from all 23 hospitals still performing liver surgery (supplementary table 2). Significant differences between hospitals in the range of mean percentages were observed in ASA 3 or higher (11.9% to 86.1%, $p < 0.001$), a CCI of 2 or higher (6.7% to 100%, $p < 0.001$), histopathological parenchymal liver disease (0.0% to 100%, $p < 0.001$), preoperative chemotherapy (0.0% to 72.2%, $p < 0.001$), resection of more than 3 CRLM in one surgical session (0.0% to 57.1%, $p < 0.001$), major liver resection (0.0% to 40.3%, $p < 0.001$), bilobar disease (6.7% to 65.0%, $p < 0.001$), synchronous metastases (20.4% to 80.0%, $p < 0.001$) and rectal primary tumour (12.5% to 58.2%, $p < 0.001$). No differences in sex, age higher than 80, history of liver resection, resection of largest diameter CRLM with a diameter of 55mm and extra-hepatic disease were observed in this validation cohort. Uncorrected 30-day morbidity ranged from 0.0% and 28.6%

uncorrected 30-day mortality ranged from 0.0% to 8.6% in 2019. Expected 30-day morbidity ranged from 2.9% to 13.3% between hospitals. Expected 30-day mortality ranged from 0.1% to 2.6% between hospitals.

Case-mix corrected funnel plots based on data from 2018 and 2019 combined showed that one hospital performed significantly worse than expected and one hospital performed significantly better than expected concerning 30-day major morbidity (supplementary figure 2a). No significant outliers were observed regarding 30-day mortality in after case-mix correction (supplementary figure 2b). However, validation of the case-mix corrected funnel plot concerning 30-day mortality was performed on a underpowered cohort with only 29 events.

Discussion

This study confirms that adjustment for several patient demographics and disease burden in hospitals (i.e. case-mix factors) is required when comparing postoperative outcomes between hospitals after liver resection for CRLM. Significant differences observed in the distribution of mean percentages of case-mix factors between hospitals in the Netherlands result in expected 30-day major morbidity which ranged between hospitals 6.4% to 11.9% and expected 30-day mortality which ranged from 0.6% to 2.9% respectively. After adjustment for case-mix factors, no significant outliers were observed. Moreover, uncorrected 30-day mortality ranged between hospitals from 0% to 5% and no significant outliers were observed after case-mix correction. Validation on the 2019 cohort in the Netherlands confirmed significant variation in case-mix, variation in expected outcomes and need for case-mix correction to compare postoperative outcomes between hospitals. Age above 80, high ASA classification, presence of steatohepatitis or sinusoidal dilatation, previous history of liver resection and major liver resection were the most important case-mix factors for 30-day major morbidity and for 30-day mortality.

Oncological liver resection is heterogeneous compared to other oncological resections. This is due the large variety in localization of tumours within the liver and different surgical approaches that exist each having their own technical difficulty. As a result, daily practice of case-mix correction for liver surgery has not been described to date. However, risk factors for adverse postoperative outcomes have been described earlier. One study on major liver surgery in the USA that focused on case-mix correction for major morbidity and mortality showed that cardiac and renal comorbidities negatively impacted postoperative outcomes, which is concordant with results in this study²². Several studies observed comparable case-mix factors such as higher

number of CRLM, synchronous detection of CRLM, and major resection being risk factors for major morbidity and mortality^{23,24}. Recently, an Italian study showed that complexity of the resection, earlier liver resection and concomitant liver disease influenced postoperative outcomes in benchmarking laparoscopic liver resections²⁵. The current study shows that variation in major morbidity from 3.3% to 13.7% and variation in mortality from 0% to 5% between hospitals in the Netherlands was deemed non-significant after case-mix correction. This underlines the importance of case-mix adjustment when comparing outcomes after resection of CRLM.

The observed variation in distribution of percentages of patient demographics and disease burden between hospitals found in this study is not unexpected given the referral patterns in oncological networks that have been established in the Netherlands over the last years. There are seven oncological networks. Each consists of one or two tertiary referral centres which perform liver surgery and several regional hospitals of which a few perform liver surgery²⁶. This structure of oncological care can be a reason for the variation in case-mix between hospitals and this variation in case-mix is in concordance with earlier studies on colorectal cancer and thoracic surgery in the Netherlands^{15,27}.

The primary objective of this study was to create a case-mix model to perform a valid comparison of hospital performances regarding major morbidity and mortality after CRLM resection. A case-mix model should include only not patient- and tumour characteristics that are not in the preoperative decisional pathway and that cannot be influenced. Including decisions from the treating team that are in the preoperative decisional pathway would distort or nullify the measurement of quality of surgical care in a hospital as one would correct for decisions made by the treating physician or its team²⁸.

In this study we included tertiary referral centre as a case-mix factor because patient characteristics and disease burden in these centres can be different from regional hospitals due to specific tertiary care. These differences between tertiary and regional hospitals include more patients with abnormalities regarding anatomy or histological liver parenchyma such as liver cirrhosis, centrally located, CRLM located diffuse in the liver and the more frequent use of two-stage procedures which have been proven a risk for worse postoperative outcomes as these procedures are technically more demanding and cannot be easily captured in the existing case-mix variables available in the DHBA^{29,30}. In the Netherlands patients are also referred to tertiary centres if a treating physician in a regional hospital is unsure about the capability to perform a

certain surgical procedure. However, this type of detailed information is lacking in the DHBA which is the reason for instead including tertiary centre as factor in the case-mix.

Also included in the case-mix model was synchronous diagnosis of the primary colorectal tumour and CRLM. This variable was associated with higher major morbidity but not with mortality. This association was not found in earlier studies^{31,32}. The negative effect from synchronous diagnosis of primary colorectal tumour and CRLM is possibly a result of patients in this group who underwent simultaneous resection of both the colorectal primary tumour and CRLM in one surgical session. Earlier studies have shown a negative effect on postoperative outcomes of this treatment regime^{33,34}.

Not included in the case-mix model was a minimally invasive approach. Several studies showed less postoperative morbidity after minimally invasive liver resection compared to open liver resection and it is increasingly used^{9,35,36}. However, whether a liver resection is performed minimally invasive and is successful depends mainly on patient selection by the surgical team and their technical capability. For this reason, minimally invasive approach finds itself in the decisional pathway and was not included in the case-mix model.

Comparing postoperative outcomes is the main purpose of the DHBA and several other clinical audits affiliated to the Dutch Institute of Clinical Auditing. The authors think that it is important to also provide unadjusted outcomes to caregivers as every opportunity should be given to reflect and improve on adverse events. This is important to address possible outliers that have been positively or negatively been affected by case-mix correction independent from patient characteristics and disease burden. Some hospitals 'choose' to operate only patient with certain characteristics. This can reflect on outcomes before and after case-mix correction and is the main reason for showing both uncorrected and corrected outcomes to caregivers. After adjusting for case-mix factors, several hospitals showed to perform better (figure 3a&3b) than expected on the basis of their case-mix. It is reassuring that none of the centres had higher morbidity and mortality than expected in the overall cohort. It is intriguing that some had significantly lower rates, and other centres should try to learn from their decisional process in order to improve their own process and outcomes.

Limitations of the study include the lack of 90-day morbidity and mortality data as these could be a better estimate of postoperative outcomes as well as the possible heterogeneity in the reporting of complications between hospitals³⁷⁻³⁹. Also, as this study was performed from an auditing database several possible case-mix factors that might influence postoperative

outcomes such as technical difficulty of the procedure and patients' muscle mass index could not be included in the case-mix model. It should be noted that the case-mix corrected funnel plots are underpowered mainly for the 30-day mortality, which could cloud the absence of significance of hospitals who suffered higher or lower mortality than expected. Future studies should also evaluate oncological long-term outcomes which are not present in our audit. Finally, external validation of the presented case-mix model is lacking. Internal validation proved that this case-mix model based on CRLM patients who underwent surgery between 2014 and 2018 in the Netherlands was valid, but external validation should be performed in another country to establish the model and prove its use in practice.

In conclusion, the large between-hospital variation in population demographics and disease burden of patients who underwent liver resection for CRLM results in a wide range of expected 30-day major morbidity and expected 30-day mortality. This emphasises the use of a case-mix adjustment model in order to properly compare postoperative outcomes between Dutch hospitals in a national audit.

References

1. Hackl C, Neumann P, Gerken M, Loss M, Klinkhammer-Schalke M, Schlitt HJ. Treatment of colorectal liver metastases in Germany: a ten-year population-based analysis of 5772 cases of primary colorectal adenocarcinoma. *BMC Cancer*. 2014;14:810.
2. Manfredi S, Lepage C, Hatem C, Coatmeur O, Faivre J, Bouvier AM. Epidemiology and management of liver metastases from colorectal cancer. *Ann Surg*. 2006;244(2):254-259.
3. Angelsen JH, Horn A, Sorbye H, Eide GE, Loes IM, Viste A. Population-based study on resection rates and survival in patients with colorectal liver metastasis in Norway. *Br J Surg*. 2017;104(5):580-589.
4. Olthof P.B. E, A.K.E., J.M. Klaase, E.M. Marra, N.F.M. Kok, D. Grunhagen. Volume outcome association for liver surgery: a nationwide analysis. *British Journal of Surgery*. 2020.
5. Farges O, Goutte N, Bendersky N, Falissard B, Group AC-FHS. Incidence and risks of liver resection: an all-inclusive French nationwide study. *Ann Surg*. 2012;256(5):697-704; discussion 704-695.
6. Filmann N, Walter D, Schadde E, et al. Mortality after liver surgery in Germany. *Br J Surg*. 2019;106(11):1523-1529.
7. Dreyer NA, Garner S. Registries for robust evidence. *JAMA*. 2009;302(7):790-791.
8. Van Leersum NJ, Snijders HS, Henneman D, et al. The Dutch surgical colorectal audit. *Eur J Surg Oncol*. 2013;39(10):1063-1070.
9. Pahlman L, Bohe M, Cedermark B, et al. The Swedish rectal cancer registry. *Br J Surg*. 2007;94(10):1285-1292.
10. Wouters MW, Jansen-Landheer ML, van de Velde CJ. The Quality of Cancer Care initiative in the Netherlands. *Eur J Surg Oncol*. 2010;36 Suppl 1:S3-S13.
11. SONCOS. Requirements for oncological liver surgery in the Netherlands. 2017.
12. van der Werf LR, Kok NFM, Buis CI, et al. Implementation and first results of a mandatory, nationwide audit on liver surgery. *HPB (Oxford)*. 2019;21(10):1400-1410.
13. Mainz J, Hansen AM, Palshof T, Bartels PD. National quality measurement using clinical indicators: the Danish National Indicator Project. *J Surg Oncol*. 2009;99(8):500-504.
14. Lijftogt N, Vahl AC, Wilschut ED, et al. Adjusted Hospital Outcomes of Abdominal Aortic Aneurysm Surgery Reported in the Dutch Surgical Aneurysm Audit. *Eur J Vasc Endovasc Surg*. 2017;53(4):520-532.
15. Beck N, Hoeijmakers F, van der Willik EM, et al. National Comparison of Hospital Performances in Lung Cancer Surgery: The Role of Case Mix Adjustment. *Ann Thorac Surg*. 2018;106(2):412-420.
16. Fischer C, Lingsma HF, van Leersum N, Tollenaar RA, Wouters MW, Steyerberg EW. Comparing colon cancer outcomes: The impact of low hospital case volume and case-mix adjustment. *Eur J Surg Oncol*. 2015;41(8):1045-1053.
17. DeMatteo RP, Palese C, Jarnagin WR, Sun RL, Blumgart LH, Fong Y. Anatomic segmental hepatic resection is superior to wedge resection as an oncologic operation for colorectal liver metastases. *J Gastrointest Surg*. 2000;4(2):178-184.
18. Lee MKt, Gao F, Strasberg SM. Perceived complexity of various liver resections: results of a survey of experts with development of a complexity score and classification. *J Am Coll Surg*. 2015;220(1):64-69.
19. Lee MKt, Gao F, Strasberg SM. Completion of a Liver Surgery Complexity Score and Classification Based on an International Survey of Experts. *J Am Coll Surg*. 2016;223(2):332-342.
20. van der Werf LR, Voeten SC, van Loe CMM, Karthaus EG, Wouters M, Prins HA. Data verification of nationwide clinical quality registries. *BJS Open*. 2019;3(6):857-864.
21. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg*. 2009;250(2):187-196.
22. Dimick JB, Pronovost PJ, Cowan JA, Jr., Lipsett PA. Postoperative complication rates after hepatic resection in Maryland hospitals. *Arch Surg*. 2003;138(1):41-46.
23. Vigano L, Ferrero A, Lo Tesoriere R, Capussotti L. Liver surgery for colorectal metastases: results after 10 years of follow-up. Long-term survivors, late recurrences, and prognostic role of morbidity. *Ann Surg Oncol*. 2008;15(9):2458-2464.

24. Gilg S, Sparrelid E, Isaksson B, Lundell L, Nowak G, Stromberg C. Mortality-related risk factors and long-term survival after 4460 liver resections in Sweden-a population-based study. *Langenbecks Arch Surg*. 2017;402(1):105-113.
25. Russolillo N, Aldrighetti L, Cillo U, et al. Risk-adjusted benchmarks in laparoscopic liver surgery in a national cohort. *Br J Surg*. 2020.
26. Elfrink AKE, Kok NFM, van der Werf LR, et al. Population-based study on practice variation regarding preoperative systemic chemotherapy in patients with colorectal liver metastases and impact on short-term outcomes. *Eur J Surg Oncol*. 2020;46(9):1742-1755.
27. Kolfsooten NE, Marang van de Mheen PJ, Gooiker GA, et al. Variation in case-mix between hospitals treating colorectal cancer patients in the Netherlands. *Eur J Surg Oncol*. 2011;37(11):956-963.
28. Fischer C, Lingsma H, Hardwick R, Cromwell DA, Steyerberg E, Groene O. Risk adjustment models for short-term outcomes after surgical resection for oesophagogastric cancer. *Br J Surg*. 2016;103(1):105-116.
29. Linecker M, Bjornsson B, Stavrou GA, et al. Risk Adjustment in ALPPS Is Associated With a Dramatic Decrease in Early Mortality and Morbidity. *Ann Surg*. 2017;266(5):779-786.
30. Moris D, Ronnekleiv-Kelly S, Kostakis ID, et al. Operative Results and Oncologic Outcomes of Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) Versus Two-Stage Hepatectomy (TSH) in Patients with Unresectable Colorectal Liver Metastases: A Systematic Review and Meta-Analysis. *World J Surg*. 2018;42(3):806-815.
31. Kelly ME, Spolverato G, Le GN, et al. Synchronous colorectal liver metastasis: a network meta-analysis review comparing classical, combined, and liver-first surgical strategies. *J Surg Oncol*. 2015;111(3):341-351.
32. Wang K, Liu W, Yan XL, Xing BC. Role of a liver-first approach for synchronous colorectal liver metastases. *World J Gastroenterol*. 2016;22(6):2126-2132.
33. Jones TJ, Murphy AE, Tameron A, et al. Trends and Outcomes of Synchronous Resection of Colorectal Metastasis in the Modern Era-Analysis of Targeted Hepatic NSQIP Database. *J Surg Res*. 2019;238:35-40.
34. Snyder RA, Hao S, Irish W, Zervos EE, Tuttle-Newhall JE, Parikh AA. Thirty-Day Morbidity after Simultaneous Resection of Colorectal Cancer and Colorectal Liver Metastasis: American College of Surgeons NSQIP Analysis. *J Am Coll Surg*. 2020.
35. Fretland AA, Dagenborg VJ, Bjornelv GMW, et al. Laparoscopic Versus Open Resection for Colorectal Liver Metastases: The OSLO-COMET Randomized Controlled Trial. *Ann Surg*. 2018;267(2):199-207.
36. Abu Hilal M, Aldrighetti L, Dagher I, et al. The Southampton Consensus Guidelines for Laparoscopic Liver Surgery: From Indication to Implementation. *Ann Surg*. 2018;268(1):11-18.
37. Mayo SC, Shore AD, Nathan H, et al. Refining the definition of perioperative mortality following hepatectomy using death within 90 days as the standard criterion. *HPB (Oxford)*. 2011;13(7):473-482.
38. Mise Y, Vauthey JN, Zimmitti G, et al. Ninety-day Postoperative Mortality Is a Legitimate Measure of Hepatopancreatobiliary Surgical Quality. *Ann Surg*. 2015;262(6):1071-1078.
39. Schiorgens TS, Dorsch M, Mittermeier L, et al. Thirty-day mortality leads to underestimation of postoperative death after liver resection: A novel method to define the acute postoperative period. *Surgery*. 2015;158(6):1530-1537.

Supplementary material

Supplementary table 1. Mean percentages (range) of case-mix variables per hospital in the Netherlands in patients with colorectal liver metastases (CRLM) who underwent liver resection between 2014 and 2018.

N Hospitals = 28		N patients = 4639	
Case-mix variables	Mean %	Min – Max %	p-value
Patient characteristics			
Female sex	36.9	25.0 – 47.0	0.232
Age ≥ 80	7.8	0.0 – 17.1	<0.001
Charlson Comorbidity Index (CCI) ≥ 2	27.2	10.7 – 63.3	<0.001
American Society of Anesthesiology (ASA) classification ≥ 3	19.5	3.3 – 36.3	<0.001
History of liver resection	18.5	8.1 – 30.3	<0.001
Liver disease§	20.4	0.0 – 47.1	<0.001
History of preoperative chemotherapy	26.2	1.5 – 55.1	<0.001
Tumour characteristics			
>3 CRLM	20.0	7.0 – 36.9	<0.001
Maximum diameter of largest CRLM (mm*) ≥ 55mm	15.4	0.0 – 26.4	<0.001
Major liver resection	20.9	6.7 – 38.0	<0.001
Rectal primary tumour	35.1	20.4 – 46.6	<0.001
Bilobar disease	43.5	5.0 – 60.6	<0.001
Synchronous metastases	46.2	35.5 – 62.1	<0.001
Extra-hepatic disease	12.3	3.9 – 38.5	<0.001

§ Based on histopathology of the liver on the basis of pathological examination. This includes steatosis, steato-hepatitis, cirrhosis and sinusoidal dilatation.

*millimetre

∞ Type of hospital: tertiary referral centre are defined as hospitals with highest expertise on oncologic surgery

P values were calculated using univariable logistic regression with case-mix factor as dependent variable and hospitals as independent variable.

Supplementary table 2. Baseline characteristics of patients diagnosed with colorectal liver metastases (CRLM) in 2019 in the Netherlands.

Factor	N (%)
Total	778
Patient characteristics	
Sex	
Male	510 (66)
Female	268 (34)
Age (years)	
< 50	57 (7)
50 - 64	287 (37)
65 - 79	372 (48)
≥ 80	62 (8)
Charlson Comorbidity Index (CCI)	
0 / 1	439 (57)
≥ 2	339 (44)
Missing	
Body Mass Index (BMI)	
Mean (sd)	26.4 (4.5)
American Society of Anesthesiology (ASA) classification	
ASA I / II	537 (69)
ASA III+	240 (31)

	Missing	1
History of liver resection		
	No	613 (79)
	Yes	165 (21)
	Missing	
Histopathology liver parenchyma§		
	Normal liver	575 (74)
	Steatosis	143 (18)
	Steato-hepatitis	9 (1)
	Cirrhosis	6 (1)
	Sinusoidal dilatation	6 (1)
	Missing	39 (5)
Preoperative chemotherapy		
	No	487 (65)
	Yes	260 (35)
	Missing	
Tumour characteristics		
Number of lesions		
	1	334 (43)
	2	145 (19)
	3	81 (10)
	4	57 (7)
	≥5	136 (18)
	Missing	25 (3)
Maximum diameter of largest CRLM (mm*)		
	< 20	223 (29)
	20-34	231 (30)
	35-54	155 (20)
	≥ 55	95 (12)
	Missing	74 (10)
Location primary tumour		
	Colon	527 (68)
	Rectal	251 (32)
	Missing	
Major liver resection		
	No	611 (78)
	Yes	168 (22)
Bilobar disease		
	No	506 (66)
	Yes	163 (34)
	Missing	9
Timing of metastases		
	Metachronous	391 (56)
	Synchronous	309 (44)
	Missing	78
Extrahepatic disease		
	No	649 (85)
	Yes	119 (15)
	Missing	10
Type of hospital[∞]		
	Regional hospitals	418 (55)
	Tertiary referral centres	360 (45)

Supplementary figure 1a. Unadjusted between-hospital variation in 30-day major morbidity in patients undergoing liver resection for colorectal liver metastases in the Netherlands between 2014 - 2018.

Supplementary figure 1b. Unadjusted between-hospital variation in 30-day mortality in patients undergoing liver resection for colorectal liver metastases in the Netherlands between 2014 - 2018.

Supplementary figure 2a. Case-mix adjusted funnel-plot of between-hospital variation in 30-day major morbidity in patients with colorectal liver metastases in the Netherlands in 2018 – 2019.

Case-mix adjusted for: sex, age in years, ASA III / IV, Charlson Comorbidity Index, histopathology of liver parenchyma, history of liver resection, preoperative chemotherapy, number of CRLM, maximum diameter of the largest CRLM prior to treatment, major liver resection, location of the primary tumour, bilobar disease, synchronous metastases, extra-hepatic disease and type of hospital.

Supplementary figure 2b. Case-mix adjusted funnel-plot of between-hospital variation in 30-day mortality in patients with colorectal liver metastases in the Netherlands in 2018 – 2019.

Case-mix adjusted for: sex, age in years, ASA III / IV, histopathology of liver parenchyma, preoperative chemotherapy, history of liver resection, number of CRLM, major liver resection and type of hospital.

CHAPTER 9

ONCOLOGICAL NETWORKS FOR RESECTION OF COLORECTAL LIVER METASTASES: DIFFERENCES AND POSTOPERATIVE OUTCOMES

A.K.E. Elfrink, N.F.M. Kok, R.J. Swijnenburg, M. den Dulk, P.B. van den Boezem, H.H. Hartgrink, W.W. te Riele, G.A. Patijn, W.K.G. Leclercq, D.J. Lips, N. Ayez, C. Verhoef, K.F.D. Kuhlmann, C.I. Buis, K. Bosscha, E.J.T. Belt, M. Vermaas, N.T. van Heek, S.J. Oosterling, H. Torrens, H.H. Eker, E.C.J. Consten, H.A. Marsman, G. Kazemier, M.W.J.M. Wouters, D.J. Grünhagen[∞], J.M. Klaase[∞], [Dutch Hepato Biliary Audit Group](#)

[∞] Shared senior author contributions

In press European Journal of Surgical Oncology

Abstract

Introduction

Widespread differences in patient demographics and disease burden between hospitals for resection of colorectal liver metastases (CRLM) have been described. In the Netherlands, networks consisting of at least one tertiary referral centre and several regional hospitals have been established to optimise treatment and outcomes. The aim of this study was to assess variation in case-mix, and outcomes between these networks.

Methods

This was a population-based study including all patients who underwent CRLM resection in the Netherlands between 2014 and 2019. Variation in case-mix and outcomes between seven networks covering the whole country was evaluated. Differences in case-mix, expected 30-day major morbidity (Clavien-Dindo $\geq 3a$) and 30-day mortality between networks were assessed.

Results

In total 5383 patients were included. Thirty-day major morbidity was 5.7% and 30-day mortality was 1.5%. Significant differences between networks were observed for Charlson Comorbidity Index, ASA 3+, previous liver resection, liver disease, preoperative MRI, preoperative chemotherapy, ≥ 3 CRLM, diameter of largest CRLM ≥ 55 mm, major resection, combined resection and ablation, rectal primary tumour, bilobar and extrahepatic disease. Uncorrected 30-day major morbidity ranged between 3.3% and 13.1% for hospitals, 30-day mortality ranged between 0.0% and 4.5%. Uncorrected 30-day major morbidity ranged between 4.4% and 6.0% for networks, 30-day mortality ranged between 0.0% and 2.5%. No negative outliers were observed after case-mix correction.

Conclusion

Variation in case-mix and outcomes are considerably smaller on a network level as compared to a hospital level. Therefore, auditing is more meaningful at a network level and collaboration of hospitals within networks should be pursued.

Introduction

Resection of colorectal liver metastases (CRLM) is performed in 20-50% of all patients with CRLM and is the cornerstone of curative treatment^{1,2}. Postoperative morbidity and mortality rates are still considerable in the Netherlands³.

In the Netherlands, centralization of surgery was nationwide initiated and led by tumour specific committees on the basis of the standardisation report of the Dutch Federation of Oncologic Societies (SONCOS)⁵. During this process, liver surgery was centralised in 28 of 69 Dutch hospitals and seven oncological networks were formed for all oncological conditions^{4,5}. The intention of these oncological networks was to optimise referral patterns between hospitals and to decrease hospital variation in preoperative and operative care⁶. As a result, quality of care for patients should be comparable in each oncological network.

Oncological networks for liver surgery consist of at least one tertiary referral centre performing liver surgery, several regional hospitals performing liver surgery and several regional hospitals not performing liver surgery⁷. Within oncological networks, tumour-specific multidisciplinary (MDT) meetings are attended by hepatobiliary physicians and surgeons according to the Dutch Guideline and the standardisation report of SONCOS with balanced patient-centered treatment plans developed by these teams^{5,8}. Several oncological networks have specific agreements on preoperative workup, multidisciplinary team meetings, and criteria for referral of patients to more specialised care centres within the network. These oncological networks have synchronised guidelines and protocols between all hospitals in the oncological network. Other oncological networks have agreements on which hospitals perform which type of (tertiary) liver surgery, while preoperative workup and treatment can be hospital-specific^{6,9}.

The main objective of these oncological networks is to decrease variation in preoperative workup and treatment for CRLM which has been described in the Netherlands on a hospital level^{7,10,11}. This variation is attributed to differences in patient demographics and disease burden (i.e. case-mix) of a hospital and translates to variation in treatment patterns and postoperative outcomes¹². Due to oncological network formation, variation in case-mix on a hospital level has increased. Assessing quality of care on a hospital level could therefore pose problems. However, variation in case-mix might be comparable among oncological networks as each network serves the population of a region and has at least one tertiary care centre in the network to which complex cases are referred. Comparable workup and treatment in every oncological network might positively affect outcomes as patients receive standardised best-

practice treatment independent of oncological network where treatment takes place. For these reasons, assessing quality of care on an oncological network level as well as auditing could be preferred.

The aim of this study was to assess variation in patient demographics and disease burden between oncological networks performing liver surgery and to compare differences in 30-day major morbidity and 30-day mortality between oncological networks.

Methods

This was a nationwide, population-based retrospective study performed in the Netherlands. The Netherlands is a country with approximately 17 million inhabitants. Health care is arranged in 69 hospitals including 8 university hospitals and 1 comprehensive cancer centre. Structural requirements for performing oncological care are established by SONCOS, endorsed by the Dutch Government and insurance companies⁵. These structural requirements for liver surgery include 24/7 availability of a skilled interventional radiologist, at least two skilled hepatobiliary surgeons, minimal procedural hospital volume requirements for liver resection (at least 20 liver resections per centre have to be performed annually for any indication) and participation in the Dutch Hepato Biliary Audit (DHBA); the mandatory audit in which all hospitals in the Netherlands performing liver surgery register all liver resections¹³.

The 7 oncological networks in the Netherlands are based on topographical location and on agreements between hospitals (figure 1). All Dutch hospitals are included in an oncological network. Within oncological networks, agreements exist regarding hospitals with a tertiary referral status and the type of care that is delivered in the other hospitals. Variation exists between oncological networks regarding collaboration agreements. In several oncological networks, agreements concerning guidelines and referral criteria between hospitals have been established while in others every hospital performs care for hepatobiliary patients according to their own protocols. These collaboration agreements regarding preoperative workup and treatment of CRLM between oncological networks were assessed using a questionnaire. Data for this study were collected from the DHBA. Data verification of the audit provided insight in completeness of 97% and accuracy of 96% in the DHBA when compared to the Dutch Cancer Registry¹⁴. No ethical approval was needed under Dutch law for this study.

Figure 1. Overview of the layout of Dutch Oncological Networks.

Only hospitals performing liver surgery are shown.
Hospitals not performing liver surgery refer patients to regional hospitals.
Tertiary referral centres perform more specialised and difficult types of care and often treat patients referred from regional hospitals.

Patient selection

All patients who underwent liver resection for CRLM between the 1st of January 2014 and 31st of December 2019 in the Netherlands and who were registered in the DHBA before 22nd of March 2020 were included in the study. Patients were excluded if information on date of surgery, type of tumour, or data regarding 30-day morbidity or 30-day mortality was missing. All patients who underwent thermal ablation without resection for CRLM were excluded.

Main outcomes

Main outcomes were variation in patient demographics, disease burden, 30-day major morbidity and 30-day mortality after liver resection. Major morbidity was defined as a complication Grade 3a or higher according to Clavien-Dindo classification, within 30 days after liver resection¹⁵. Mortality was defined as death during hospitalization or within 30 days after liver resection.

Variables

The case-mix of an oncological network can be explained by several factors: patient demographics, disease burden and treatment characteristics. Patient demographics included sex, age, American Society of Anesthesiologist (ASA) classification, Body Mass Index (BMI), comorbidity scores classified in the Charlson Comorbidity Index (CCI), histopathological classification of liver parenchyma adjacent to tumour tissue and previous liver surgery. Disease burden included number of CRLM, diameter of the largest CRLM before the initiation of tumour-specific treatment and synchronous (within 6 months of detection of the primary tumour) or metachronous diagnosis of the CRLM. Differences in treatment characteristics were assessed. These variables included use of preoperative MRI, use of preoperative chemotherapy, minor or major liver resection, combined liver resection and thermal ablation, type of hospital where treatment took place which was either a tertiary referral centre (i.e. academic centre or comprehensive cancer centre) or regional hospital and annual oncological network volume. Major liver resection was defined as resection of three or more adjacent Couinaud segments¹⁶.

Statistical analysis

Mean percentage and upper and lower limits of separate factors in all oncological networks was calculated to assess variation between oncological networks. The significance of these differences in factors between oncological networks was assessed using univariable logistic regression models. Differences between oncological networks were assessed also grouped by oncological network size as differences might be attributable to the size of oncological networks. Oncological networks were categorised in low procedural volume (<500 resections), middle procedural volume (500 – 1000 resections) and high procedural volume (>1000 resections).

Association of case-mix factors with outcomes was assessed using multivariable logistic regression. Case-mix factors were included in multivariable analysis based on the p-value observed in univariable logistic regression ($p < 0.10$). Restriction of the multivariable logistic regression model was needed due to the number of degrees of freedom in the model for mortality due to low number of events.

To visualise differences in 30-day major morbidity and 30-day mortality, uncorrected funnel plots were created. These funnel plots show the number of patients treated in an oncological network compared to the mean number of events in the same oncological network. This is plotted and compared to the mean number of events of all included patients. If an oncological network is above the mean outcome of all included patients, the oncological network performs worse compared to other oncological networks. If an oncological network is under the mean outcome, it performs better than average. Also, 95% confidence intervals are created on the basis of the mean outcomes and total included patients indicating statistical significance of outliers.

In case-mix corrected funnel plots, the observed / expected ratio (O/E ratio) was used to assess differences between oncological networks. Using multivariable logistic regression, expected 30-day morbidity and 30-day mortality was calculated per patient. All patients in an oncological network together compose the expected morbidity and mortality per oncological network. By dividing the observed morbidity of every oncological network by the expected morbidity of that oncological network, the O/E ratio was calculated. An O/E ratio above 1 indicated that an oncological network performed worse than expected, an O/E ratio below 1 indicated that an oncological network performed better than expected. The 95% confidence intervals (CI) were calculated to indicate whether the O/E ratio of an oncological network was statistically different compared to the average O/E ratio of all oncological networks together. All plots were compared between on a hospital level and an oncological network level.

Multicollinearity in multivariable models was tested using the Variance Inflation Factor (VIF). A VIF of 3 was the cut-off value indicating multicollinearity and if so, one variable was excluded of the analysis. Patients with missing values were analysed as a separate group in multivariable logistic regression if these exceeded 5% of the total included number of patients. If the missing values in a variable was below 5%, the missing patients were excluded from the analysis. All analyses were performed in R version 3.2.2[®] (R Core Team (2018): A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

Results

In total 5383 patients who underwent liver resection for CRLM in the Netherlands were included from 28 hospitals together assembling 7 oncological networks. Oncological networks were different in size with the largest oncological network treating 1189 patients and the smallest treating 226 patients during the study period (table 1). Overall 30-day major morbidity was 5.7% and 30-day mortality was 1.5%. Different collaboration agreements regarding preoperative workup and treatment of CRLM were observed between oncological networks (supplementary table 1).

Table 1. Baseline characteristics of patients diagnosed with colorectal liver metastases (CRLM) between 2014 and 2019 in the Netherlands stratified for oncological network.

Factor	Network A	Network B	Network C	Network D	Network E	Network F	Network G	P-value
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	
Total	1098	1189	1135	732	585	226	418	
Patient characteristics								
Sex								0.390
Male	710 (65)	738 (62)	727 (65)	477 (65)	354 (61)	144 (64)	255 (61)	
Female	387 (35)	449 (38)	401 (35)	252 (35)	231 (39)	82 (36)	161 (39)	
Missing*	1	2	7	3	0	0	2	
Age in years								0.050
< 50	63 (6)	99 (8)	89 (8)	53 (7)	41 (7)	11 (5)	30 (7)	
50 – 64	374 (34)	426 (36)	380 (33)	261 (36)	192 (33)	79 (35)	159 (38)	
65 – 79	592 (54)	567 (48)	573 (51)	365 (50)	306 (52)	128 (57)	191 (46)	
≥ 80	66 (6)	95 (8)	92 (8)	53 (7)	45 (8)	8 (4)	36 (9)	
Missing*	3	2	1	0	1	0	2	
Charlson Comorbidity Index (CCI)								<0.001
0 / 1	836 (76)	926 (78)	871 (77)	546 (75)	428 (73)	170 (75)	239 (57)	
≥2	262 (24)	263 (22)	264 (23)	186 (25)	157 (27)	56 (25)	179 (43)	
Body Mass Index (BMI)								<0.001
Mean (sd)	26.7 (4.5)	25.9 (4.4)	26.3 (4.5)	26.3 (4.5)	26.1 (4.2)	26.4 (4.4)	26.4 (4.1)	
American Society of Anesthesiology (ASA) classification								<0.001
ASA I / II	882 (80)	924 (81)	790 (74)	565 (77)	459 (78)	186 (86)	346 (84)	
ASA III+	216 (20)	216 (19)	284 (26)	167 (23)	126 (22)	30 (14)	68 (16)	
Missing*	0	49	61	0	0	10	4	
History of liver resection								<0.001
No	873 (80)	956 (84)	913 (82)	544 (75)	467 (81)	192 (87)	354 (86)	
Yes	213 (20)	182 (16)	205 (18)	180 (25)	108 (19)	30 (14)	57 (14)	
Missing*	12	51	17	8	10	4	7	
Histopathology liver parenchyma§								<0.001
Normal liver	727 (66)	872 (73)	747 (66)	329 (45)	354 (61)	120 (53)	318 (76)	
Steatosis	170 (16)	162 (14)	189 (17)	160 (22)	69 (12)	38 (17)	68 (16)	
Steato-hepatitis	20 (2)	19 (2)	4 (0)	28 (4)	6 (1)	7 (3)	2 (1)	
Cirrhosis	5 (1)	10 (1)	5 (0)	6 (1)	2 (1)	2 (1)	10 (2)	

Sinusoidal dilatation	8 (1)	30 (3)	7 (1)	8 (1)	4 (1)	0 (0)	0 (0)
Missing*	168	96	183	201	149	59	20
Preoperative MRI							<0.001
No	324 (30)	343 (31)	498 (44)	155 (26)	211 (37)	41 (20)	198 (49)
Yes	759 (70)	757 (69)	623 (56)	437 (74)	361 (63)	168 (80)	208 (51)
Missing*	15	89	14	140	13	17	12
Preoperative chemotherapy							<0.001
No	740 (71)	765 (71)	712 (66)	388 (57)	423 (77)	154 (77)	298 (75)
Yes	308 (29)	316 (29)	373 (34)	290 (43)	124 (23)	124 (23)	101 (25)
Tumour characteristics							
Number of lesions							<0.001
1	496 (46)	462 (41)	471 (42)	285 (42)	305 (53)	115 (53)	168 (44)
2	242 (22)	266 (24)	238 (22)	126 (19)	126 (19)	47 (22)	87 (23)
3	107 (10)	123 (11)	137 (12)	73 (11)	73 (11)	24 (11)	50 (13)
4	70 (7)	90 (8)	72 (7)	62 (9)	62 (9)	12 (6)	21 (6)
≥5	167 (15)	179 (16)	189 (17)	135 (20)	135 (20)	19 (9)	54 (14)
Missing*	16	69	28	51	7	9	38
Maximum diameter of largest CRLM (mm*)							0.050
< 20	339 (33)	313 (30)	310 (31)	138 (26)	172 (36)	74 (36)	99 (30)
20-34	408 (39)	372 (36)	357 (36)	209 (39)	175 (36)	71 (35)	135 (40)
35-54	191 (18)	215 (21)	199 (20)	118 (22)	83 (17)	36 (18)	57 (17)
≥ 55	100 (10)	131 (13)	123 (12)	75 (14)	52 (11)	24 (12)	44 (13)
Missing*	60	158	146	192	103	21	83
Combined resection and ablation							<0.001
No	909 (83)	887 (75)	811 (72)	647 (88)	516 (88)	185 (82)	318 (76)
Yes	189 (17)	302 (25)	324 (29)	85 (12)	69 (12)	41 (18)	100 (24)
Major liver resection							<0.001
No	831 (76)	951 (80)	926 (82)	593 (81)	418 (72)	191 (85)	294 (70)
Yes	267 (24)	238 (20)	209 (18)	139 (19)	157 (29)	35 (15)	124 (30)
Location primary tumour							<0.001
Colon	700 (64)	779 (66)	724 (64)	434 (59)	415 (71)	145 (66)	273 (65)
Rectal	397 (36)	308 (34)	407 (36)	298 (41)	169 (29)	74 (34)	145 (35)
Missing*	1	2	4	0	1	7	0
Bilobar disease							<0.001
No	651 (59)	610 (51)	636 (57)	315 (52)	358 (62)	143 (64)	250 (60)
Yes	447 (41)	578 (49)	473 (43)	295 (48)	219 (38)	81 (36)	166 (40)
Missing*	0	1	26	122	8	2	2
Timing of metastases							0.090
Metachronous	423 (47)	466 (49)	491 (52)	240 (50)	237 (49)	111 (59)	177 (39)
Synchronous	480 (53)	487 (51)	461 (48)	244 (50)	244 (51)	78 (41)	188 (52)
Missing*	195	236	183	248	104	37	53
Extrahepatic disease							<0.001
No	964 (89)	951 (84)	996 (89)	530 (87)	440 (83)	197 (92)	345 (87)
Yes	115 (11)	177 (16)	122 (11)	82 (13)	92 (17)	18 (18)	52 (13)
Missing*	19	61	17	120	53	11	21
Surgical approach							<0.001
Open	830 (76)	917 (78)	765 (68)	542 (75)	384 (66)	179 (80)	309 (75)
Laparoscopy	268 (24)	263 (22)	365 (32)	183 (25)	201 (34)	45 (20)	106 (25)
Missing*	0	9	5	7	0	2	3
Type of hospital[∞]							<0.001
Regional hospitals	836 (76)	353 (30)	759 (67)	313 (43)	449 (77)	58 (26)	184 (44)
Tertiary referral centres	262 (24)	836 (70)	376 (33)	419 (57)	136 (23)	168 (74)	234 (56)

Year of surgery	<0.001						
2014	147 (13)	188 (16)	218 (19)	120 (16)	78 (13)	29 (13)	79 (19)
2015	216 (20)	201 (17)	130 (12)	115 (16)	100 (17)	46 (20)	86 (21)
2016	213 (19)	244 (21)	194 (17)	159 (22)	100 (17)	43 (19)	23 (6)
2017	172 (16)	207 (17)	218 (19)	114 (16)	108 (19)	56 (25)	103 (25)
2018	176 (16)	206 (17)	187 (17)	127 (17)	100 (17)	33 (15)	72 (17)
2019	174 (16)	143 (12)	188 (17)	97 (13)	99 (17)	19 (8)	55 (13)

Bold font represents significant p-value

* Missing not included in analyses based on relatively small group

§ History of liver disease containing liver cirrhosis, oesophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis

∞ Type of hospital: tertiary referral centre are defined as hospitals with highest expertise on oncologic surgery

\$ Unclear why percentage missing is so high. Mm = millimetre

Between-hospital and oncological network variation

Differences in patient characteristics between hospitals were observed for age (80 years or older, 0.0% - 18.2%, $p<0.001$), CCI (2 or higher, 5.0% - 63.3%, $p<0.001$), ASA classification (3 or higher, 3.3% - 37.4%, $p<0.001$), history of liver resection (8.1% - 30.3%, $p<0.001$), liver disease (0.0% - 45.6%, $p<0.001$), use of preoperative MRI (14.3% - 96.0%, $p<0.001$) and use of preoperative chemotherapy (1.5% - 52.6%, $p<0.001$). Variation in tumour characteristics between hospitals included: number of metastases (3 or more CRLM, 7.0 - 37.0, $p<0.001$), maximum diameter of largest CRLM prior to treatment of 55 mm (0.0 - 30.8, $p<0.001$), use of combined resection and ablation (0.0% - 42.7%, $p<0.001$), major liver resection performed (7.0% - 37.0%, $p<0.001$), rectal primary tumour (19.1% - 46.6%, $p<0.001$), bilobar disease (5.0% - 60.6%, $p<0.001$), and extrahepatic disease (4.4% - 26.9%, $p<0.001$) (figure 2a & supplementary table 2a).

Differences in patient and tumour characteristics between oncological networks were smaller as compared to hospital variation in case-mix factors. Differences regarding patient characteristics were observed with regard to CCI (2 or higher, 22.1% - 42.3%, $p<0.001$), ASA classification (3 or higher, 13.9% - 26.4%, $p<0.001$), history of liver resection (13.5% - 24.9%, $p<0.001$), liver disease (18.8% - 38.0%, $p<0.001$), use of preoperative MRI (51.2% - 80.4%, $p<0.001$) and use of preoperative chemotherapy (22.7% - 42.8%, $p<0.001$). Variation in tumour characteristics observed between oncological networks included: number of metastases (3 or more CRLM, 14.3% - 28.9%, $p<0.001$), maximum diameter of largest CRLM prior to treatment of 55 mm (12.4% - 20.6%, $p<0.001$), use of combined resection and ablation (11.8% - 28.5%, $p<0.001$), major liver resection performed (15.5% - 29.7%, $p<0.001$), rectal primary tumour (28.9% - 40.7%, $p=0.002$), bilobar disease (36.2% - 48.7%, $p<0.001$), and extrahepatic disease (8.4% - 17.3%, $p<0.001$) (figure 2b, supplementary table 2b). Other case-mix factors were not different between oncological networks.

Figure 2a&b. Violin graph showing the distribution of mean percentages (range) of case-mix variables per hospital and per oncological network in the Netherlands in patients who underwent liver resection for colorectal liver metastases between 2014 and 2019.

Factors associated with 30-day major morbidity and 30-day mortality

Factors associated with 30-day major morbidity included sex (female, aOR 0.64, CI 0.48 – 0.86, $p=0.003$), age (80 or higher aOR 2.31, CI 1.12 – 5.07, $p=0.028$), ASA classification (3 or higher aOR 1.44, CI 1.07 – 1.91, $p=0.015$), major liver resection (aOR 1.98, CI 1.49 – 2.62, $p<0.001$), rectal primary tumour (aOR 0.73, CI 0.55 – 0.96, $p=0.024$), and synchronous metastases (aOR 1.84, CI 1.38 – 2.47, $p<0.001$) (table 2a).

Table 2a. Univariable and multivariable logistic regression model to assess the association of patient and tumour characteristics with 30-day major morbidity in patients with colorectal liver metastasis (CRLM) in the Netherlands between 2014-2019.

Factor	Univariable analysis				Multivariable analysis		
	N	OR	CI (95%)	P-value	aOR	CI (95%)	P-value
Sex				<0.001			0.003
Male	3405	1			1		
Female	1963	0.64	0.49 – 0.82		0.64	0.48 – 0.86	
Missing*	15						
Age in years				0.012			0.039
< 50	386	1			1		
50 - 64	1871	1.88	1.05 – 3.76	0.050	1.60	0.88 – 3.22	0.154

65 - 79	2722	2.26	1.27 – 4.45	0.010	1.79	0.99 – 3.59	0.072
≥ 80	395	2.70	1.37 – 5.72	0.006	2.31	1.12 – 5.07	0.028
Missing*	9						
Charlson Comorbidity Index (CCI)				0.079			0.519
0 / 1	4016	1			1		
≥2	1367	1.25	0.97 – 1.61		1.09	0.82 – 1.45	
Body Mass Index		1.00	0.97 – 1.02	0.715	1.01	0.98 – 1.01	0.623
American Society of Anesthesiology (ASA) classification				<0.001			0.015
I / II	4152	1			1		
III +	1107	1.57	1.20 – 2.03		1.44	1.07 – 1.91	
Missing*	124						
Histopathology liver parenchyma§				0.116			0.368
Normal liver	3467	1			1		
Steatosis	856	1.36	1.01 – 1.82	0.042	1.33	0.96 – 1.91	0.081
Steato-hepatitis	86	1.55	0.64 – 3.17	0.278	1.70	0.70 – 3.56	0.196
Cirrhosis	41	1.38	0.33 – 3.85	0.597	0.50	0.03 – 2.39	0.499
Sinusoidal dilatation	57	2.05	0.78 – 4.48	0.101	1.49	0.50 – 3.60	0.416
Missing	876	0.86	0.60 – 1.20	0.380	0.98	0.65 – 3.56	0.924
History of liver resection				0.469			0.422
No	4299	1			1		
Yes	975	1.11	0.83 – 1.48		1.36	0.63 – 2.78	
Missing*	109						
History of preoperative chemotherapy				0.855			0.763
No	3480	1			1		
Yes	1563	1.04	0.80 – 1.34	0.756	1.01	0.82 – 1.41	0.652
Missing	340	1.11	0.68 – 1.72	0.663	1.03	0.71 – 1.74	0.813
Number of lesions				0.697			0.368
1	2302	1			1		
2	1113	0.89	0.64 – 1.21	0.458	1.09	0.78 – 1.53	0.625
3	580	1.17	0.80 – 1.69	0.406	1.16	0.78 – 1.71	0.456
4	372	0.85	0.50 – 1.37	0.527	1.35	0.87 – 2.06	0.172
≥5	798	1.05	0.73 – 1.46	0.799	1.31	0.82 – 2.03	0.243
Missing*	218						
Maximum diameter largest CRLM (mm)*				0.007			0.638
< 20	1445	1			1		
20 - 34	1727	1.12	0.81 – 1.56	0.491	0.77	0.54 – 1.11	0.166
35 - 54	899	1.41	0.98 – 2.04	0.062	1.12	0.70 – 1.51	0.713
≥ 55	549	2.00	1.36 – 2.94	<0.001	1.54	0.84 – 1.97	0.099
Missing	763	1.40	0.95 – 2.05	0.083	0.75	0.48 – 1.15	0.190
Major liver resection				<0.001			<0.001
No	4204	1			1		
Yes	1179	2.06	1.61 – 2.62		1.98	1.49 – 2.62	
Bilobar disease				0.982			0.802
No	2963	1			1		
Yes	2259	1.00	0.79 – 1.26		1.04	0.77 – 1.41	
Missing*	161						
Location primary tumour				0.005			0.024
Colon	3470	1			1		
Rectal	1898	0.70	0.54 – 0.90		0.73	0.55 – 0.96	
Missing*	15						

Type of metastasis				0.010			
Metachronous	2145	1					
Synchronous	2182	1.48	1.15 – 1.93	0.003			
Missing	1056	1.15	0.82 – 1.61	0.398			
Extrahepatic disease				0.122			0.267
No	4423	1			1		
Yes	658	1.22	0.87 – 1.68	0.235	1.34	0.93 – 1.88	0.102
Missing	302	0.63	0.32 – 1.11	0.139	0.91	0.34 – 2.00	0.836
Type of hospital[∞]				0.145			0.263
Regional	2952	1			1		
Tertiary referral centres	2431	1.19	0.94 – 1.49		1.15	0.90 – 1.50	

Bold font represents significant p-value

* Missing not included in analyses based on relatively small group

§ History of liver disease containing liver cirrhosis, oesophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis

Mm = millimetre

[∞] Type of hospital: tertiary referral centre are defined as hospitals with highest expertise on oncologic surgery

\$ Unclear why percentage missing is so high.

Factors associated with 30-day mortality included age of 80 or higher (aOR 9.32, CI 1.66 – 1.75, p=0.037), ASA classification of 3 or higher (aOR 3.61, CI 2.27 – 5.75, p>0.001), histological steatohepatitis (aOR 4.66, CI 1.32 – 12.7, p=0.006), histological sinusoidal dilatation (aOR 4.08, CI 1.08 – 12.1, p=0.020), history of liver resection (aOR 2.00, CI 1.19 – 3.26, p=0.007), and major liver resection (aOR 5.80, CI 3.58 – 9.52, p<0.001) (table 2b).

Multicollinearity was assessed in all models and synchronous metastases was excluded from the statistical model for 30-day major morbidity due to multicollinearity with previous liver surgery.

Table 2b. Univariable and multivariable logistic regression model to assess the association of patient and tumour characteristics with 30-day mortality in patients with colorectal liver metastasis (CRLM) in the Netherlands between 2014-2019.

Factor	N	Univariable analysis		P-value	Multivariable analysis		
		OR	CI (95%)		aOR	CI (95%)	P-value
Sex				0.047			0.120
Male	3405	1			1		
Female	1963	0.60	0.36 – 0.98		0.66	0.39 – 1.10	
Missing*	15						
Age in years				0.006			0.014
< 50	386	1			1		
50 - 64	1871	4.16	0.86 – 74.8	0.165	4.14	0.84 – 74.8	0.169
65 - 79	2722	7.35	1.61 – 130	0.049	6.97	1.48 – 125	0.057
≥ 80	395	8.98	1.68 – 165	0.038	9.32	1.66 – 175	0.037
Missing*	9						
Charlson Comorbidity Index (CCI)				0.713			
0 / 1	4016	1					
≥2	1367	1.10	0.66 – 1.77				
Body Mass Index		1.03	0.99 – 1.08	0.144			
American Society of Anesthesiology (ASA) classification				<0.001			<0.001

I / II	4152	1			1		
III +	1107	4.16	2.67 – 6.48		3.61	2.27 – 5.75	
Missing*	1234						
Histopathology liver parenchyma§				0.013			0.043
Normal liver	3467	1			1		
Steatosis	856	1.52	0.83 – 2.65	0.158	1.41	0.75 – 2.52	0.259
Steato-hepatitis	86	3.88	1.15 – 9.88	0.011	4.66	1.32 – 12.7	0.006
Cirrhosis	41	4.08	0.65 – 13.9	0.058	3.79	0.55 – 15.1	0.099
Sinusoidal dilatation	57	6.01	1.76 – 15.5	<0.001	4.08	1.08 – 12.1	0.020
Missing	876	1.11	0.56 – 2.04	0.759	1.16	0.56 – 2.21	0.676
History of liver resection				0.002			0.007
No	4299	1			1		
Yes	975	2.11	1.30 – 3.35		2.00	1.19 – 3.26	
Missing*	109						
History of preoperative chemotherapy				0.024			0.292
No	3480	1			1		
Yes	1563	1.42	0.89 – 2.22	0.132	1.10	0.67 – 1.80	0.697
Missing	340	0.21	0.01 – 0.95	0.049	0.30	0.02 – 1.40	0.235
Number of CRLM				0.107			
1	2302	1					
2	1113	1.20	0.62 – 2.24	0.584			
3	580	2.01	1.00 – 3.85	0.042			
4	372	0.71	0.17 – 2.03	0.579			
≥5	798	2.02	1.08 – 3.68	0.023			
Missing*	218						
Maximum diameter largest CRLM (mm)*				0.009			0.222
< 20	1445	1			1		
20 - 34	1727	2.02	0.99 – 4.44	0.062	1.76	0.85 – 3.93	0.145
35 - 54	899	2.93	1.37 – 6.63	0.007	2.05	0.93 – 4.75	0.078
≥ 55	549	3.48	1.52 – 8.20	0.003	1.69	0.70 – 4.19	0.243
Missing	763	3.07	1.41 – 7.05	0.006	2.56	1.12 – 6.06	0.027
Major liver resection				<0.001			<0.001
No	4204	1			1		
Yes	1179	5.96	3.81 – 9.47		5.80	3.58 – 9.52	
Bilobar disease				0.184			
No	2963	1					
Yes	2259	1.35	0.87 – 2.11				
Missing*	161						
Location primary tumour				0.395			
Colon	3470	1					
Rectal	1898	0.81	0.50 – 1.30				
Missing*	15						
Type of metastasis				0.379			
Metachronous	2145	1					
Synchronous	2182	0.98	0.59 – 1.64	0.947			
Missing	1056	1.43	0.80 – 2.50	0.212			
Extrahepatic disease				0.752			
No	4423	1					
Yes	658	1.27	0.65 – 2.27	0.459			
Missing	302	1.15	0.40 – 2.60	0.770			
Type of hospital[∞]				0.321			
Regional	2952	1					
Tertiary referral centres	2431	1.25	0.80 – 1.94				

Bold font represents significant p-value

* Missing not included in analyses based on relatively small group

§ History of liver disease containing liver cirrhosis, oesophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis

Mm = millimetre

∞ Type of hospital: tertiary referral centre are defined as hospitals with highest expertise on oncologic surgery

\$ Unclear why percentage missing is so high.

Comparison of 30-day major morbidity and 30-day mortality on hospital and oncological network level

Uncorrected 30-day major morbidity ranged between 3.3% and 13.1% for hospitals (figure 3a).

Uncorrected 30-day mortality ranged between 0.0% and 4.5% for hospitals (figure 4a).

Expected 30-day morbidity between hospitals ranged between 4.8% and 6.9%. Expected 30-day mortality between hospitals ranged between 0.9% and 3.1%. After case-mix correction, variation between hospitals in both outcomes was observed with a few positive outliers (figure 5a & figure 6a).

Uncorrected 30-day major morbidity ranged between 4.4% and 6.0% for oncological networks (figure 3b). Uncorrected 30-day mortality ranged between 0.0% and 2.5% (figure 4b). Expected 30-day major morbidity ranged between 5.5% and 6.0% between oncological networks and expected 30-day mortality ranged between 1.0% and 2.2%. After case-mix correction, variation between oncological networks in both outcomes was observed but this variation was smaller as compared to comparison on a hospital level (figure 5b & figure 6b).

Figure 3a&b. Uncorrected funnel plot of between-hospital and between oncological-network variation in 30-day major morbidity in patients with colorectal liver metastases in the Netherlands between 2014 - 2019.

Figure 4a&b. Uncorrected funnel plot of between-hospital and between oncological-network variation in 30-day mortality in patients with colorectal liver metastases in the Netherlands between 2014 - 2019.

Figure 5a&b. Case-mix corrected funnel plot of between-hospital and between oncological-network variation in 30-day major morbidity in patients with colorectal liver metastases in the Netherlands between 2014 - 2019.

Figure 6a&b. Case-mix corrected funnel plot of between-hospital and between oncological-network variation in 30-day mortality in patients with colorectal liver metastases in the Netherlands between 2014 - 2019.

Variation case-mix and outcomes in high procedural oncological networks

In the three largest oncological networks differences in case-mix variables observed included ASA classification (3 or higher 19.0% - 26.4%, $p < 0.001$), use of preoperative MRI (55.6% - 70.1%, $p < 0.001$), use of preoperative chemotherapy (29.2% - 34.4%, $p = 0.014$), size of largest CRLM (maximum diameter prior to treatment of 55 mm 12.4% - 20.3%, $p < 0.001$), bilobar disease (40.7% - 48.9%, $p < 0.001$), extrahepatic disease (10.7% - 15.7%, $p < 0.001$), combined resection and ablation (17.2% - 28.5%, $p < 0.001$) and major liver resection performed (18.4% - 24.3%, $p = 0.002$).

Uncorrected 30-day morbidity ranged between 7.0% and 9.2% between these large oncological networks and uncorrected 30-day mortality ranged between 1.2% and 1.8%. Expected 30-day morbidity ranged between 5.5% and 5.8% between these large oncological networks and expected 30-day mortality ranged between 1.4% and 1.7%.

Discussion

This study is the first to describe nationwide oncological network formation, and to assess differences in patient demographics, disease burden and postoperative outcomes between oncological networks for CRLM surgery. Collaboration of hospitals within oncological networks has been initiated in the Netherlands to decrease variation in clinical practice and to improve outcomes. Differences in patient demographics, disease burden and treatment characteristics were observed between oncological networks and reflects current variation in workup and treatment between Dutch oncological networks. However, variability between oncological networks regarding case-mix and outcomes was considerably smaller as compared to between-hospital variation. This results from procedural volumes of oncological networks, topographical orientation of oncological networks and inclusion of at least one tertiary referral centre and several regional hospitals in every oncological network. Therefore, comparing outcomes and auditing on an oncological network level should be pursued instead of on a hospital level.

Oncological networks were formed during centralization of surgery in the Netherlands to create referral patterns within oncological networks resulting in decreased variation in preoperative assessment, operative treatment and outcomes^{12,17,18}. Due to centralization of liver surgery, differences between hospitals have increased as more complex cases are referred to tertiary centres while regional hospitals perform less complex resections. For this reason, it is harder to compare quality of care on a hospital level as variation in treatment plans is present between hepatobiliary specialists and probability of resection depends on outcomes of MDT meetings^{9,19-27}. In this study, variation in case-mix and outcomes existed on an oncological network level but was much smaller as compared to on a hospital level. This might be a result of inconsistencies that exist between oncological networks regarding criteria of resectability and differences in therapeutic strategies regarding CRLM^{19,21}. However, formation of oncological networks has improved collaboration of hospitals in oncological networks and decreases variability in case-mix and outcomes between oncological networks. For this reason, comparing quality of care should be pursued on an oncological network level as differences between oncological networks are smaller due to inclusion of at least one tertiary referral centre and several regional hospitals.

Although differences in case-mix exist between oncological networks, influence of several case-mix factors on 30-day major morbidity and 30-day mortality were comparable to an earlier study regarding use of case-mix correction to compare hospital performances using data from the DHBA¹². However, differences in case-mix factors and expected outcomes between oncological

networks as observed in the current study are smaller compared to differences between hospitals¹². Differences in uncorrected and expected outcomes are the main reason for case-mix correction as the difference between observed and expected outcomes is a result of factors that cannot be influenced by the surgical team^{12,17,18}. The authors hypothesise that due to the procedural volume in oncological networks as well as inclusion of both tertiary referral centres and regional hospitals from a specific topographical region differences in case-mix play a minor role in comparing outcomes between oncological networks. Centralization and formation of oncological networks has decreased variation in practice and outcomes on an oncological network level compared to on a hospital level. However, variation is still present. Therefore, collaboration of hospitals within oncological networks and between oncological networks should be intensified to further equalise quality of care between oncological networks.

The authors' perspective for the future of these oncological networks includes a more intensive collaboration of hospitals within oncological networks using best practice guidelines for preoperative screening and interventions to optimise modifiable risk factors. Current variation regarding collaboration agreements within Dutch oncological networks is present and has been described by differences in case-mix and treatment strategies in the Dutch oncological networks. Intensifying collaboration of hospitals within oncological networks based on strict best practice nationwide guidelines will address and decrease practice variation in treatment strategies between oncological networks. As a result, all oncological networks will provide care for CRLM patients according nationwide guidelines on preoperative workup and treatment thus providing equal quality of care in every oncological network independent of the oncological network where treatment takes place. Important reasons to decrease the observed practice variation are the associated better outcomes for patients and lower costs^{4,28,29}. From an auditing perspective, comparing outcomes between oncological networks instead of between hospitals can be more valuable as the influence of confounding factors is smaller as compared to comparing quality of care on a hospital level. This is particularly true for high procedural oncological networks. In the authors opinion, striving for comparable oncological networks regarding procedural volume will make comparison of outcomes more valid as influence of case-mix is decreasing as procedural volume increase. As a result, patients will receive comparable quality of care and possibilities regarding outcomes will be equal and will not depend on the oncological network where the patient is treated. This study can be used for formation and comparison of oncological networks in several oncological surgical fields as this is the first to referral patterns of specialised oncological care on a nationwide basis.

Limitations of this study include lacking of 90-day postoperative outcomes which have shown to be a better estimate of postoperative outcomes compared to 30-day postoperative outcomes³⁰. Technical complexity of the procedure and several other factors that might be thought of as case-mix factors were not retrievable as this study was performed from an auditing database. Type of hospital was included in the case-mix model as this reflects complexity of procedures of which data was not available in the DHBA¹². Future studies on oncological networks should also include variation in oncological outcomes of CRLM patients to assess which case-mix factors influence disease-free survival, overall survival and compare oncological networks on these outcomes. To date, no long-term oncological outcomes are available in the DHBA.

In conclusion, this study shows that patient demographics, disease burden, therapeutic strategies and surgical outcomes are different between oncological networks consisting of tertiary care centres and regional hospitals from a topographical region in the Netherlands. This reflects that differences in workup and treatment of CRLM is still present between oncological networks the Netherlands. However, the observed variation is much smaller as compared to between-hospital variation. This underlines that auditing and measuring quality of care should be pursued on an oncological network level rather than on a hospital level. To further decrease variation between oncological network, nationwide agreements regarding preoperative and operative treatment of CRLM should be focused on as well as intensifying collaboration of hospitals within oncological networks. Ultimately, the objective is that treatment of patients will be independent of the oncological network where they receive treatment.

References

1. Manfredi S, Lepage C, Hatem C, Coatmeur O, Faivre J, Bouvier AM. Epidemiology and management of liver metastases from colorectal cancer. *Ann Surg.* 2006;244(2):254-259.
2. Hackl C, Neumann P, Gerken M, Loss M, Klinkhammer-Schalke M, Schlitt HJ. Treatment of colorectal liver metastases in Germany: a ten-year population-based analysis of 5772 cases of primary colorectal adenocarcinoma. *BMC Cancer.* 2014;14:810.
3. Olthof PB, Elfrink AKE, Marra E, Belt EJT, van den Boezem PB, Bosscha K, et al. Volume-outcome relationship of liver surgery: a nationwide analysis. *Br J Surg.* 2020;107(7):917-926.
4. Birkmeyer JD, Reames BN, McCulloch P, Carr AJ, Campbell WB, Wennberg JE. Understanding of regional variation in the use of surgery. *Lancet.* 2013;382(9898):1121-1129.
5. SONCOS. Preserving Quality of Care in the Netherlands. 2017. <https://www.soncos.org/kwaliteit/>
6. t Lam-Boer J, van der Stok EP, Huiskens J, Verhoeven RH, Punt CJ, Elfrink MA, et al. Regional and inter-hospital differences in the utilisation of liver surgery for patients with synchronous colorectal liver metastases in the Netherlands. *Eur J Cancer.* 2017;71:109-116.
7. Elfrink AKE, Kok NFM, van der Werf LR, Krul MF, Marra E, Wouters M, et al. Population-based study on practice variation regarding preoperative systemic chemotherapy in patients with colorectal liver metastases and impact on short-term outcomes. *Eur J Surg Oncol.* 2020;46(9):1742-1755.
8. Dutch Guideline - Colorectal Carcinoma <https://www.oncoline.nl/colorectaalcarcinoom>. 2014.
9. t Lam-Boer J, Al Ali C, Verhoeven RH, Roumen RM, Lemmens VE, Rijken AM, et al. Large variation in the utilization of liver resections in stage IV colorectal cancer patients with metastases confined to the liver. *Eur J Surg Oncol.* 2015;41(9):1217-1225.
10. Elfrink AKE, Pool M, van der Werf LR, Marra E, Burgmans MC, Meijerink MR, et al. Preoperative imaging for colorectal liver metastases: a nationwide population-based study. *BJS Open.* 2020.
11. Elfrink AKE, S. N, van den Tol MP, Kok NFM, Grunhagen DJ, Klaase JM, et al. Hospital variation in combined liver resection and thermal ablation for colorectal liver metastases and impact on short-term postoperative outcomes: a nationwide population-based study *HPB (Oxford)*. 2020;Accepted for publication.
12. Elfrink AKE, Kok NFM, Grunhagen DJ, Klaase JM, Group DHBA. Case-mix adjustment to compare hospital performances after resection of colorectal liver metastases. *Eur J Surg Oncol.* 2020;Accepted for publication.
13. Beck N, van Bommel AC, Eddes EH, van Leersum NJ, Tollenaar RA, Wouters MW, et al. The Dutch Institute for Clinical Auditing: Achieving Codman's Dream on a Nationwide Basis. *Ann Surg.* 2020;271(4):627-631.
14. van der Werf LR, Kok NFM, Buis CI, Grunhagen DJ, Hoogwater FJH, Swijnenburg RJ, et al. Implementation and first results of a mandatory, nationwide audit on liver surgery. *HPB (Oxford)*. 2019;21(10):1400-1410.
15. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg.* 2009;250(2):187-196.
16. Pang YY. The Brisbane 2000 terminology of liver anatomy and resections. *HPB 2000*; 2:333-39. *HPB (Oxford)*. 2002;4(2):99; author reply 99-100.
17. Beck N, Hoeijmakers F, van der Willik EM, Heineman DJ, Braun J, Tollenaar R, et al. National Comparison of Hospital Performances in Lung Cancer Surgery: The Role of Case Mix Adjustment. *Ann Thorac Surg.* 2018;106(2):412-420.
18. Kolfsoorten NE, Marang van de Mheen PJ, Gooiker GA, Eddes EH, Kievit J, Tollenaar RA, et al. Variation in case-mix between hospitals treating colorectal cancer patients in the Netherlands. *Eur J Surg Oncol.* 2011;37(11):956-963.
19. Ignatavicius P, Oberkofler CE, Chapman WC, DeMatteo RP, Clary BM, D'Angelica MI, et al. Choices of Therapeutic Strategies for Colorectal Liver Metastases Among Expert Liver Surgeons: A Throw of the Dice? *Ann Surg.* 2020;272(5):715-722.
20. Krell RW, Reames BN, Hendren S, Frankel TL, Pawlik TM, Chung M, et al. Surgical Referral for Colorectal Liver Metastases: A Population-Based Survey. *Ann Surg Oncol.* 2015;22(7):2179-2194.

21. Huiskens J, Bolhuis K, Engelbrecht MR, De Jong KP, Kazemier G, Liem MS, et al. Outcomes of Resectability Assessment of the Dutch Colorectal Cancer Group Liver Metastases Expert Panel. *J Am Coll Surg*. 2019;229(6):523-532 e522.
22. Fenton HM, Taylor JC, Lodge JPA, Toogood GJ, Finan PJ, Young AL, et al. Variation in the Use of Resection for Colorectal Cancer Liver Metastases. *Ann Surg*. 2019;270(5):892-898.
23. Hellingman T, de Swart ME, Joosten JJA, Meijerink MR, de Vries JJJ, de Waard JWD, et al. The value of a dedicated multidisciplinary expert panel to assess treatment strategy in patients suffering from colorectal cancer liver metastases. *Surg Oncol*. 2020;35:412-417.
24. Engstrand J, Kartalis N, Stromberg C, Broberg M, Stillstrom A, Lekberg T, et al. The Impact of a Hepatobiliary Multidisciplinary Team Assessment in Patients with Colorectal Cancer Liver Metastases: A Population-Based Study. *Oncologist*. 2017;22(9):1067-1074.
25. Lordan JT, Karanjia ND, Quiney N, Fawcett WJ, Worthington TR. A 10-year study of outcome following hepatic resection for colorectal liver metastases - The effect of evaluation in a multidisciplinary team setting. *Eur J Surg Oncol*. 2009;35(3):302-306.
26. Vallance AE, vanderMeulen J, Kuryba A, Botterill ID, Hill J, Jayne DG, et al. Impact of hepatobiliary service centralization on treatment and outcomes in patients with colorectal cancer and liver metastases. *Br J Surg*. 2017;104(7):918-925.
27. Basso M, Corallo S, Calegari MA, Zurlo IV, Ardito F, Vellone M, et al. The impact of multidisciplinary team management on outcome of hepatic resection in liver-limited colorectal metastases. *Sci Rep*. 2020;10(1):10871.
28. Nelson-Williams H, Gani F, Kilic A, Spolverato G, Kim Y, Wagner D, et al. Factors Associated With Interhospital Variability in Inpatient Costs of Liver and Pancreatic Resections. *JAMA Surg*. 2016;151(2):155-163.
29. Idrees JJ, Johnston FM, Canner JK, Dillhoff M, Schmidt C, Haut ER, et al. Cost of Major Complications After Liver Resection in the United States: Are High-volume Centers Cost-effective? *Ann Surg*. 2019;269(3):503-510.
30. Schiergens TS, Dorsch M, Mittermeier L, Brand K, Kuchenhoff H, Lee SM, et al. Thirty-day mortality leads to underestimation of postoperative death after liver resection: A novel method to define the acute postoperative period. *Surgery*. 2015;158(6):1530-1537.

Supplementary material

Supplementary table 1a. Collaboration agreements within the several oncological networks in 2019 in the Netherlands.

	Network A	Network B	Network C	Network D
Oncological network supported by the Dutch Comprehensive Cancer Organisation	Yes	No	No	Yes
Oncological network with formal board and protocol	Yes	No	Yes	Yes
Preoperative workup aligned within oncological network	Yes	No	No	No
Central liver specific MDT for all hospitals in the oncological network	Yes	No	Yes	Yes
Clear referral patterns within the oncological network based on formal agreements	Yes	No	Yes	Yes

	Network E	Network F	Network G
Oncological network supported by the Dutch Comprehensive Cancer Organisation	No	No	No
Oncological network with formal board and protocol	Yes	Yes	No
Preoperative workup within oncological network	Yes	Yes	No
Central liver specific MDT for all hospitals in the oncological network	Yes	Yes	No
Clear referral patterns within the oncological network based on formal agreements	Yes	Yes	No

Preoperative workup indicates that clear agreements in the oncological network have been made on type of preoperative imaging, preoperative laboratory tests and preoperative physiological assessment of patients who undergo resection of CRLM.

Central MDT indicates that all patients who are eligible for resection of CRLM are discussed at a central MDT in which all hospitals in the oncological network participate.

Clear referral patterns indicates that agreements within the oncological network are in place regarding which type of patients or resection are treated in which hospital (for example: older patients with several hilar lesions in tertiary referral centre more superficial lesions in need of a more simple wedge resection in regional hospital).

Supplementary table 2a. Mean percentages (range) of case-mix variables per hospital in the Netherlands in patients with colorectal liver metastases (CRLM) who underwent liver resection between 2014 and 2019.

Number of hospitals = 28		N patients = 5383	
Case-mix variables			
	Mean %	Min – Max %	p-value
Patient characteristics			
Female sex	36.8	25.0 – 47.0	0.370
Age ≥ 80	7.0	0.0 – 18.2	<0.001
Charlson Comorbidity Index (CCI) ≥2	27.0	5.0 – 63.3	<0.001
American Society of Anesthesiology (ASA) classification ≥3	20.0	3.3 – 37.4	<0.001
History of liver resection	17.9	8.1 – 30.3	<0.001
Liver disease§	24.1	0.0 – 45.6	<0.001
Preoperative MRI	63.5	14.3 – 96.0	<0.001
History of preoperative chemotherapy	29.8	1.5 – 52.6	<0.001
Tumor characteristics			
>3 CRLM	21.4	7.0 – 37.0	<0.001
Maximum diameter of largest CRLM (mm*) ≥55mm	17.5	0.0 – 30.8	<0.001
Combined resection and ablation	17.5	0.0 – 42.7	<0.001
Major liver resection	22.2	7.0 – 37.0	<0.001
Rectal primary tumor	35.0	19.1 – 46.6	<0.001
Bilobair disease	42.1	5.0 – 60.6	<0.001
Synchronous metastases	49.5	38.2 – 69.8	<0.001
Extrahepatic disease	12.8	4.4 – 26.9	<0.001

§ Based on histopathology of the liver on the basis of pathological examination. This includes steatosis, steato-hepatitis, cirrhosis and sinusoidal dilatation.

*millimeter

∞ Type of hospital: tertiary referral center are defined as hospitals with highest expertise on oncologic surgery

P values were calculated using univariable logistic regression

Supplemental table 2b. Mean percentages (range) of case-mix variables per oncological network in the Netherlands in patients with colorectal liver metastases (CRLM) who underwent liver resection between 2014 and 2019.

N Oncological networks = 7		N patients = 5383	
Case-mix variables			
	Mean %	Min – Max %	p-value
Patient characteristics			
Female sex	36.8	34.6 – 39.5	0.389
Age ≥ 80	7.0	3.5 – 8.7	0.071
Charlson Comorbidity Index (CCI) ≥2	27.0	22.1 – 42.3	<0.001
American Society of Anesthesiology (ASA) classification ≥3	20.0	13.9 – 26.4	<0.001
History of liver resection	17.9	13.5 – 24.9	<0.001
Liver disease§	24.1	18.8 – 38.0	<0.001
Preoperative MRI	63.5	51.2 – 80.4	<0.001
History of preoperative chemotherapy	29.8	22.7 – 42.8	<0.001
Tumor characteristics			
>3 CRLM	21.4	14.3 – 28.9	<0.001
Maximum diameter of largest CRLM (mm*) ≥55mm	17.5	12.4 – 20.6	<0.001
Combined resection and ablation	17.5	11.6 – 28.6	<0.001
Major liver resection	22.2	15.5 – 29.7	<0.001
Rectal primary tumor	35.0	28.9 – 40.7	0.002
Bilobair disease	42.1	36.2 – 48.7	<0.001
Synchronous metastases	49.5	41.3 – 53.2	0.090
Extrahepatic disease	12.8	8.4 – 17.3	<0.001

§ Based on histopathology of the liver on the basis of pathological examination. This includes steatosis, steato-hepatitis, cirrhosis and sinusoidal dilatation.

*millimeter

∞ Type of hospital: tertiary referral center are defined as hospitals with highest expertise on oncologic surgery

P values were calculated using univariable logistic regression with case-mix factor as dependent variable and hospitals as independent variable.

CHAPTER 10

HOSPITAL VARIATION IN COMBINED LIVER
RESECTION AND THERMAL ABLATION FOR
COLORECTAL LIVER METASTASES AND IMPACT ON
SHORT-TERM POSTOPERATIVE OUTCOMES:
A NATIONWIDE POPULATION-BASED STUDY

A.K.E. Elfrink, S. Nieuwenhuizen, M.P. van den Tol, M.C. Burgmans, W. Prevoo, M.M.E. Coolsen, P.B. van den Boezem, O.M. van Delden, J. Hagendoorn, G.A. Patijn, W.K.G. Leclercq, M.S.L. Liem, A.M. Rijken, C. Verhoef, K.F.D. Kuhlmann, S.J.S. Ruiter, D.J. Grünhagen, J.M. Klaase, N.F.M. Kok, M.R. Meijerink, R.J. Swijnenburg, [Dutch Hepato Biliary Audit Group](#)

HPB (Oxford). 2020 Nov 17:S1365-182X(20)31189-8.

Abstract

Introduction

Combining resection and thermal ablation can improve short-term postoperative outcomes in patients with colorectal liver metastases (CRLM). This study assessed nationwide hospital variation and short-term postoperative outcomes after combined resection and ablation.

Methods

In this population-based study, all CRLM patients who underwent resection in the Netherlands between 2014-2018 were included. After propensity score matching for age, ASA-score, Charlson-score, diameter of largest CRLM, number of CRLM and earlier resection, postoperative outcomes were compared. Postoperative complicated course (PCC) was defined as discharge after 14 days or a major complication or death within 30 days of surgery.

Results

Of 4639 included patients, 3697 (80%) underwent resection and 942 (20%) resection and ablation. Unadjusted percentage of patients who underwent resection and ablation per hospital ranged between 4-44%. Hospital variation persisted after case-mix correction. After matching, 734 patients remained in each group. Hospital stay (median 6vs.7 days, $p=0.011$), PCC (11%vs.14.7%, $p=0.043$) and 30-day mortality (0.7%vs.2.3%, $p=0.018$) were lower in the resection and ablation group. Differences faded in multivariable logistic regression due to inclusion of major hepatectomy.

Conclusion

Significant hospital variation was observed in the Netherlands. Short-term postoperative outcomes were better after combined resection and ablation, attributed to avoiding complications associated with major hepatectomy.

Introduction

Colorectal cancer (CRC) is the third most common type of cancer worldwide and colorectal liver metastases (CRLM) have been described to occur in up to 50% of patients with CRC¹. Upfront liver resection with curative intent is thought to be possible in only 10-20% of the patients with CRLM. Induction chemotherapy and parenchymal-sparing surgery can increase surgical options²⁻⁴. Thermal ablation poses an alternative for resection, in particular for more centrally located, smaller metastases (<3 cm)^{5,6}. Resection of such lesions may imply sacrificing a significant amount of normal liver parenchyma⁷.

Combining liver resection and thermal ablation in one surgical session can extend curative options in patients with CRLM who are not eligible for conventional liver resection due to multiple CRLM, location of CRLM, bilobar disease or due to severe comorbidities^{8,9}. Guidelines in the Netherlands provide insufficient guidance to support the combination of liver resection and thermal ablation in different patients and so the use of these treatment regimens may vary¹⁰. The present study is the first population-based nationwide study worldwide on hospital variation in the use of combined resection and ablation and on corresponding short-term postoperative outcomes.

The aims of this nationwide population-based cohort study were to assess hospital variation in the combined use of liver resection and thermal ablation in the Netherlands and to compare short-term postoperative outcomes between patients who underwent resection only and patients who underwent combined resection and ablation.

Methods

This nationwide cohort study was carried out with data from the Dutch HepatoBiliary Audit (DHBA), a nationwide obligatory audit in which all hospitals in the Netherlands performing liver surgery register all liver resections. Information about the formation and content of the DHBA has been described previously¹¹. Data verification was performed to provide insight in the completeness and accuracy of the DHBA^{11,12}. Ethical approval was considered unnecessary under Dutch law as the audit is part of the Dutch Inspectorate of Health Care and provides an anonymised dataset.

Patient selection

All patients who underwent liver resection or liver resection combined with ablation within one surgical session for CRLM between 1st of January 2014 and 31st of December 2018 and were registered in the DHBA before 22nd March of 2019 were included in the analyses. Patients were excluded if information was missing regarding date of birth, date of surgery or type of tumour for which treatment took place. All patients who only underwent ablation without liver resection for CRLM were also excluded. Patients were divided between two treatment groups for analysis depending on the type of treatment of CRLM. These groups were resection only or combined resection and ablation.

For assessment of patient- and tumour-characteristics that could possibly influence the use of combined resection and ablation and hospital variation in the use of combined resection and ablation, all eligible patients were included. For the comparison of short-term postoperative outcomes between resection and combined resection and ablation using propensity score matching, only patients with two or more CRLM could be included in the matching process.

Variables

Studied variables included patient characteristics (age in years, sex, American Society of Anesthesiologists (ASA) classification, comorbidity score according the Charlson Comorbidity Index (CCI), history of liver disease and a history of liver resection), tumour characteristics (number of CRLM, diameter of largest CRLM prior to treatment and time of diagnosis of metastases) and treatment characteristics (preoperative chemotherapy, resection only or combined resection and ablation, minimally invasive or open approach of the procedure, major or minor liver resection, simultaneous resection of colorectal primary tumour and CRLM, type of hospital where treatment took place and oncological network where treatment took place). Major liver resection was defined as resection of 3 or more adjacent Couinaud segments.

Of all 71 hospitals in the Netherlands, only 25 performed liver surgery¹³. All regional hospitals are included in an oncological network. Seven oncological networks were classified according to treatment collaboration between hospitals or topographical location if no collaboration network was present, as described earlier^{14,15}. Oncological networks include one or two tertiary referral centres and several regional hospitals performing liver surgery. Regional centres can refer patients to tertiary referral centres if the patient or tumour requires specific tertiary care.

Outcomes

Case-mix variables, defined as factors which are non-modifiable patient- and tumour- characteristics influencing the use of the type of procedure and possible hospital variation in the use of combined resection and ablation were assessed.

Perioperative outcomes comparing resection and combined resection and ablation were open or minimally invasive approach of the procedure, additional resection (i.e. bile duct resection, portal vein resection and arterial reconstruction), and extent of liver resection (i.e. major liver resection).

Short-term postoperative outcomes compared between groups included specific surgical complication rates and more general complication rates. Specific complications were specified as bile leakage, postoperative haemorrhage requiring reintervention, postoperative liver failure according the International Study Group of Liver Surgery, deep surgical site infection (i.e. biloma or abscess), incisional surgical site infection, pneumonia, myocardial complication or a thrombo-embolic complication¹⁶.

Other postoperative outcomes included length of hospital stay (LOS), calculated as time between date of surgery and the date of discharge and postoperative complicated course (PCC), defined as a complication leading to a hospitalization longer than 14 days, any surgical, endoscopic or radiological re-intervention or death. This composite outcome measure takes into account having several low-graded complications resulting in longer hospitalization.

Other major postoperative outcomes were 30-day major morbidity, defined as a complication graded Clavien-Dindo classification of grade III (CD >3a) or higher (i.e. requiring re-intervention, medium care (MC) or intensive care (IC) management or death) within 30 days of surgery and 30-day mortality defined as death within 30 days from date of surgery or during initial hospitalization¹⁷.

Statistical analysis

Baseline characteristics were compared between groups using the Chi-square test or Fisher exact test as appropriate for categorical variables. The independent two-sample t-test was used for continuous variables.

Potential case-mix variables were entered in a univariable and multivariable multilevel regression model to obtain a parsimonious statistical model. Influence of case-mix factors was shown as adjusted odds ratios (aOR) with 95% Confidence Intervals (CI). In multivariable

analyses two steps were undertaken. All variables were tested in a univariable model with the outcome as dependent variable. If the association was positive ($p < 0.10$) the variable was entered in the multivariable model. Multilevel analysis were performed with year, hospital and oncological network where surgery took place as a grouping covariate. Statistical significance was defined as a two-sided p -value < 0.05 in the multivariable model.

Hospital and oncological network variation in the use of combined resection and ablation was corrected for case-mix variables. Case-mix correction was performed using the observed / expected ratio (O / E ratio) which is calculated by dividing the observed number of patients with type of procedure through the number of patients expected to receive a type of procedure. The expected number of patients is based on a prediction using a multivariable multilevel logistic regression model with all case-mix variables. An O / E ratio below 1 indicates that a hospital or oncological network performed less combined resection and ablation than expected and an O / E ratio above 1 indicated that a hospital or oncological network performed more combined resection and ablation than expected. This method was chosen as this constitutes the current manner of feedback for all Dutch hospitals which participate in registries from the Dutch Institute for Clinical Auditing¹⁸.

To evaluate differences in postoperative outcomes between resection and combined resection and ablation propensity score matching (PSM) was performed. As a first step, a multivariable logistic regression model was used to estimate propensity scores. Afterwards, PSM was performed with a 1:1 ratio using the nearest neighbor method with a caliper of 0.015. As covariates used for PSM were age, ASA score, Charlson Comorbidity Index, diameter of the largest CRLM prior to treatment, number of CRLM, and history of liver resection. Major liver resection was not used as covariate in the analyses as this represents the difference between resection and combined resection and ablation in the authors opinion. To assess the quality of the matching process standardised mean differences (smd) were used. Standard mean differences below 0.1 for baseline characteristics between the two groups indicate negligible differences between both groups after PSM. After PSM, baseline characteristics and outcomes were compared between the groups using the Chi-square test or Fisher exact test for categorical variables. Continuous outcomes were presented as medians with interquartile ranges (IQR). A multivariable logistic regression model was performed using backward selection for all postoperative outcomes which differed significantly after PSM to identify variables associated with these outcomes.

Multicollinearity was assessed in all logistic regression models. This was carried out by calculation of the Variance Inflation Factor (VIF). A VIF higher than 2.5 was considered to indicate multicollinearity.

All analyses were performed in R version 3.2.2® (R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

Results

In total, 4776 patients underwent resection only or resection combined with ablation for CRLM. Of these patients, 137 were excluded because of missing information concerning type of tumour, and date of surgery. A total of 4639 patients were analysed of whom 3697 (80%) underwent resection only and 942 (20%) underwent combined resection and ablation.

Patients who underwent combined resection and ablation were younger, had lower CCI, had a history of liver resection less often, and received preoperative chemotherapy less often compared to patients who underwent resection only (table 1). Patients who underwent combined resection and ablation also had higher total number of CRLM, smaller diameter of the largest CRLM, synchronous metastases more often and were treated in a tertiary referral centre more often compared to patients who underwent resection only.

Table 1. Baseline characteristics for patients diagnosed with colorectal liver metastases (CRLM) between 2014 and 2018 in the Netherlands undergoing resection only or combined resection and ablation.

Factor		Resection only	Combined resection and ablation	P-value
		N (%)	N (%)	
Total		3697	942	
Patient characteristics				
Sex				0.018
	Male	2300 (62)	626 (67)	
	Female	1397 (38)	316 (33)	
Age in years				0.032
	< 50	252 (7)	77 (8)	
	50 - 64	1244 (34)	349 (37)	
	65 - 79	1919 (52)	456 (48)	
	> 80	277 (8)	56 (6)	
	Missing	5	4	
Charlson Comorbidity Index (CCI)				<0.001
	0 / 1	2676 (74)	717 (80)	
	2 +	934 (26)	179 (20)	
	Missing	87	46	
Body Mass Index (BMI)				
	Mean (sd)	26.26 (4.38)	26.32 (4.37)	0.671

American Society of Anesthesiology (ASA) classification			0.599
	ASA I / II	2904 (81)	734 (81)
	ASA III+	702 (19)	168 (19)
	Missing	91	40
History of liver resection			<0.001
	No	2927 (81)	786 (86)
	Yes	688 (19)	127 (14)
	Missing	82	29
History of liver disease§			0.135
	No	3472 (99)	868 (99)
	Yes	54 (1)	7 (1)
	Missing	171	67
History of preoperative chemotherapy			<0.001
	No	2526 (73)	483 (55)
	Yes	925 (27)	389 (45)
	Missing	246	70
Tumor characteristics			
Number of CRLM			<0.001
	≤3	3007 (85)	452 (50)
	>3	540 (15)	444 (50)
	Missing	150	46
Maximum diameter of largest CRLM (mm*)			<0.001
	< 20	954 (30)	624 (67)
	20-34	1182 (38)	326 (41)
	35-54	610 (19)	136 (17)
	> 55	398 (13)	58 (7)
	Missing	553	146
Location primary tumour			0.064
	Colon	2342 (64)	624 (67)
	Rectal	1347 (37)	310 (33)
	Missing	8	8
Type of metastases			<0.001
	Metachronous	1981 (56)	380 (43)
	Synchronous	1550 (44)	514 (57)
	Missing	166	48
Extrahepatic disease			0.222
	No	3042 (88)	757 (86)
	Yes	623 (12)	121 (14)
	Missing	32	6
Type of hospital[∞]			<0.001
	Regional hospital	2102 (57)	455 (48)
	Tertiary referral hospital	1595 (43)	487 (52)
Year of procedure			0.342
	2014	682 (18)	172 (18)
	2015	705 (19)	191 (20)
	2016	803 (22)	181 (19)
	2017	770 (21)	216 (23)
	2018	737 (20)	182 (19)

Bold p-values indicate statistical significance.

§ History of liver disease containing liver cirrhosis, oesophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis

*millimetre

[∞] Type of hospital: tertiary referral centres are defined as hospitals with highest expertise on oncologic surgery

Case-mix variables associated with liver resection and thermal ablation

In multivariable multilevel logistic regression analysis case-mix variables that were positively associated with combined resection and ablation included preoperative chemotherapy (aOR 1.38, CI 1.11 – 1.71, $p=0.004$), higher number of CRLM (4 or more CRLM, aOR 3.56, CI 2.58 – 3.87, $p<0.001$), and bilobar disease (aOR 3.16, CI 2.58– 3.87, $p<0.001$) (table 2). Case-mix variables negatively associated with combined resection and ablation were female sex (aOR 0.78, CI 0.64 - 0.94, $p<0.001$), increasing diameter of the largest CRLM (>55mm compared to <20mm, aOR 0.28, CI 0.19 – 0.40, $p<0.001$) and a rectal primary tumour (aOR 0.76, CI 0.63 – 0.93, $p=0.006$) (table 2).

Table 2. Univariable and multivariable logistic regression model nested for year of surgery and hospital where treatment took place to assess the association of patient and tumour characteristics with combined resection and ablation in patients with colorectal liver metastases (CRLM) in the Netherlands between 2014 and 2018.

Factor	N	Univariable analysis			Multivariable analysis		
		OR	CI (95%)	P-value	aOR	CI (95%)	P-value
Sex				0.016			<0.001
Male	2926	1			1		
Female	1713	0.83	0.71 – 0.97		0.78	0.64 – 0.94	
Age in years				0.030			0.989
< 50	329	1			1		
50 - 64	1592	1.56	0.96 – 2.68	0.085	0.94	0.64 - 1.35	0.727
65 - 79	2375	1.76	1.11 – 2.99	0.025	0.95	0.66 – 1.36	0.767
> 80	333	2.23	1.26 – 4.07	0.007	0.95	0.47 – 1.55	0.816
Missing*	9						
Charlson Comorbidity Index (CCI)				<0.001			0.505
0 / 1	3638	1			1		
2+	870	0.95	0.78 – 1.14		0.92	0.73 – 1.16	
Missing*	131						
Body Mass Index		1.00	0.99 – 1.02	0.671			
American Society of Anesthesiology (ASA) classification				0.566			
I / II	3393	1					
III +	1113	0.72	0.60 – 0.85				
Missing*	133						
History of liver disease§				0.104			0.734
No	4340	1			1		
Yes	61	0.52	0.21 – 1.07		0.86	0.33 – 2.17	
Missing*	238						
History of liver resection				0.495			
No	3713	1					
Yes	815	1.10	0.84 – 1.41				
Missing*	111						
History of preoperative chemotherapy				<0.001			0.004
No	3009	1			1		
Yes	1314	2.20	1.88 – 2.56		1.38	1.11 – 1.71	

Missing	316						
Number of CRLM				<0.001			<0.001
≤3	3459	1			1		
>3	984	5.47	4.66 – 6.42		3.56	2.85 – 4.43	
Missing*	196						
Maximum diameter largest CRLM (mm)*				<0.001			<0.001
< 20	1230	1			1		
20 - 34	1508	0.95	0.80 – 1.14	0.606	0.79	0.63 – 0.98	0.035
35 - 54	746	0.77	0.61 – 0.97	0.026	0.52	0.40 – 0.70	<0.001
> 55	456	0.50	0.37 – 0.68	<0.001	0.28	0.19 – 0.40	<0.001
Missing [§]	699	0.91	0.73 – 1.14	0.428	0.75	0.54 – 1.05	0.092
Bilobar disease				<0.001			<0.001
No	2472	1			1		
Yes	2015	3.98	3.40 – 4.67		3.16	2.58 – 3.87	
Missing*	152						
Location primary tumour				0.059			0.006
Colon	2966	1			1		
Rectal	1657	0.86	0.74 – 1.00		0.76	0.63 – 0.93	
Missing*	16						
Type of metastases				<0.001			0.071
Metachronous	2361	1			1		
Synchronous	2064	1.73	1.49 – 2.01		1.20	0.98 – 1.46	
Missing*	214						
Extrahepatic disease				0.201			
No	3799	1					
Yes	543	1.15	0.92 – 1.43				
Missing	297						
Type of hospital[∞]				<0.001			0.418
Regional	2557	1			1		
Tertiary referral centres	2082	1.41	1.22 – 1.63		1.34	0.66 – 2.72	

Bold p-values indicate statistical significance.

* Missing not included in analyses based on relatively small group

§ History of liver disease containing liver cirrhosis, oesophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis

Mm = millimetre

∞ Type of hospital: tertiary referral centre is defined as hospitals with highest expertise on oncologic surgery

\$ Unclear why percentage missing is so high.

Hospital variation in the use of liver resection and thermal ablation

Significant hospital variation in the use of combined resection and ablation was present in Dutch hospitals and Dutch oncological networks. The variation was observed in both uncorrected and case-mix corrected analyses.

Unadjusted percentage of patients treated per hospital using combined resection and ablation ranged between 4% and 44% (figure 1a). Unadjusted percentage of patients treated per oncological network using combined resection and ablation ranged between 11% and 28% (figure 2a).

Figure 1a. Unadjusted rates of variation in the use of combined resection and ablation between hospitals in patients with colorectal liver metastases in the Netherlands between 2014 – 2018.

Figure 1b. Case-mix adjusted funnel-plot of between-hospital variation in the use of combined resection and ablation in patients with colorectal liver metastases in the Netherlands between 2014 - 2018.

Case-mix adjusted O / E ratios showed several outliers between hospitals in the use of combined resection and ablation (figure 1b). Six hospitals performed significantly more combined resection and ablation than expected on the basis of their case-mix variables. Ten hospitals performed significantly less frequently combined resection and ablation than expected on the basis of their case-mix variables. O / E ratios ranged between 0 – 2.19 between the hospitals.

Case-mix adjusted O / E ratios showed several outliers between oncological networks in the use of combined resection and ablation (figure 2b). Two oncological networks performed significantly more combined resection and ablation than expected on the basis of their case-mix variables. Three oncological networks performed significantly less combined resection and ablation than expected on the basis of their case-mix variables. O / E ratios ranged between 0.49 – 1.36 between the oncological networks

Figure 2a. Unadjusted rates of variation in the use of combined resection and ablation between oncological networks in patients with colorectal liver metastases in the Netherlands between 2014 – 2018.

Figure 2b. Case-mix adjusted funnel-plot of between oncological network variation in the use of combined resection and ablation in patients with colorectal liver metastases in the Netherlands between 2014 - 2018.

Propensity Score Matching: baseline- and surgical characteristics

After the matching process, 1468 patients were included in the final analyses regarding short-term postoperative outcomes, of whom 734 (50%) were included in the resection only group and of whom 734 (50%) in the combined resection and ablation group.

Standard mean differences were below 0.100 for all baseline characteristics (table 3). The only significant difference between the groups was a higher number of patients treated in a tertiary referral hospital in the combined resection and ablation group (53% versus 43%, $p < 0.001$; $smd = 0.192$).

Table 3. Baseline characteristics for propensity score matched patients diagnosed with colorectal liver metastases (CRLM) between 2014 and 2018 in the Netherlands undergoing resection only or combined resection and ablation.

Factor		Resection only	Combined resection and ablation	P-value	smd
		N (%)	N (%)		
Total		734	734		
Patient characteristics					
Sex				0.082	0.094
	Male	453 (62)	486 (66)		
	Female	281 (38)	248 (34)		
Age in years				0.367	0.093
	< 50	54 (7)	64 (9)		
	50 - 64	278 (38)	295 (40)		
	65 - 79	369 (40)	337 (46)		
	> 80	32 (5)	37 (5)		
	Missing	1	1		
Body Mass Index (BMI)				0.084	0.090
Charlson Comorbidity Index (CCI)				0.432	0.045
	(mean, SD)	26 (4)	26 (4)		
	0 / 1	583 (81)	54 (79)		
	2 +	139 (19)	153 (21)		
	Missing	12	7		
American Society of Anesthesiology (ASA) classification				0.747	0.020
	ASA I / II	606 (83)	597 (82)		
	ASA III+	127 (17)	132 (18)		
	Missing	1	5		
History of liver resection				0.906	0.010
	No	623 (86)	623 (86)		
	Yes	105 (14)	102 (14)		
	Missing	6	9		
History of liver disease§				0.996	0.015
	No	706 (99)	709 (99)		
	Yes	7 (1)	6 (1)		
	Missing	21	19		
History of preoperative chemotherapy				0.970	0.005
	No	372 (54)	378 (54)		
	Yes	322 (46)	324 (46)		
	Missing	40	24		
Tumor characteristics					
Number of lesions				0.490	0.040
	≤3	355 (51)	345 (49)		
	>3	347 (49)	365 (51)		
	Missing	32	24		
Maximum diameter of largest CRLM (mm*)				0.968	0.028
	< 20	206 (32)	213 (33)		
	20-34	256 (40)	257 (40)		
	35-54	123 (19)	118 (18)		
	> 55	55 (9)	53 (8)		
	Missing	94	93		
Type of metastases				0.968	0.004
	Metachronous	289 (41)	288 (41)		
	Synchronous	417 (59)	419 (59)		

	Missing	28	27		
Type of hospital[∞]				<0.001	0.192
	Regional hospital	416 (57)	346 (47)		
	Tertiary referral hospital	318 (43)	388 (53)		
Year of surgery				0.423	0.098
	2014	123 (17)	105 (14)		
	2015	169 (23)	152 (21)		
	2016	140 (19)	158 (22)		
	2017	159 (22)	158 (23)		
	2018	143 (19)	151 (20)		

Bold p-values indicate statistical significance.

§ History of liver disease containing liver cirrhosis, oesophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis

*millimetre

[∞] Type of hospital: tertiary referral centre is defined as hospitals with highest expertise on oncologic surgery

Perioperative outcomes

Minimally invasive and major resection, respectively, were performed less often in the combined resection and ablation group (6% vs 15%, $p<0.001$ and 15% vs 36%, $p<0.001$) (table 4).

Several specific complications occurred less often in the combined resection and ablation group, including bile leakage (1.6% vs 4.3% $p=0.005$) and postoperative liver failure (0.5% vs 2.9%, $p=0.001$). Hospital stay was lower in the combined resection and ablation group (median 6 days (IQR 5-9) vs 7 days (IQR 5-10), $p=0.011$). Overall morbidity and 30-day major morbidity were not different between the two groups. PCC (11% vs. 14.7%, $p=0.043$) and 30-day mortality (0.7% vs 2.3%, $p=0.018$) were lower in the combined resection and ablation group.

Table 4. Perioperative outcomes for patients diagnosed with colorectal liver metastases between 2014 and 2018 in the Netherlands who underwent resection only or combined resection and ablation.

Factor		Resection only	Combined resection and ablation	p-value
		N (%)	N (%)	
Number of patients (total)		734	734	
Surgical approach				<0.001
	Open	602 (82)	648 (89)	
	Minimally invasive	107 (15)	47 (6)	
	Conversion	20 (3)	34 (5)	
	Missing	5	5	
Surgical strategy				0.431
	Primary tumour first	441 (64)	453 (65)	
	Liver first	172 (25)	152 (22)	
	Simultaneous resection of colorectal tumour and CRLM	82 (12)	89 (13)	
	Missing	39	40	

Synchronous additional resection*				0.171
	No	379 (74)	431 (78)	
	Yes	131 (26)	121 (22)	
	Missing*	224	182	
Major liver resection				<0.001
	No	470 (64)	627 (85)	
	Yes	264 (36)	107 (15)	
Bile leakage				0.005
	No	696 (96)	717 (99)	
	Yes	31 (4)	12 (1)	
	Missing*	7	5	
Postoperative haemorrhage				0.416
	No	676 (99)	683 (99)	
	Yes	9 (1)	5 (1)	
	Missing*	49	46	
Postoperative liver failure				0.001
	No	706 (97)	725 (99)	
	Yes	21 (3)	4 (1)	
	Missing*	7	5	
Intra-abdominal infection				0.453
	No	661 (95)	660 (94)	
	Yes	37 (5)	45 (6)	
	Missing*	36	29	
Surgical site infection				0.177
	No	681 (98)	677 (94)	
	Yes	17 (2)	45 (6)	
	Missing*	36	30	
Pneumonia				0.520
	No	661 (94)	656 (93)	
	Yes	41 (6)	48 (7)	
	Missing*	32	30	
Cardiac complication				0.775
	No	698 (96)	703 (96)	
	Yes	29 (4)	26 (4)	
	Missing*	7	5	
Thromboembolic complication				0.299
	No	705 (97)	715 (98)	
	Yes	21 (3)	14 (2)	
	Missing*	8	5	
Length of stay (Median + IQR)		7 (5-10)	6 (5-9)	0.011
Overall 30-day morbidity				0.187
	No	493 (67)	516 (71)	
	Yes	240 (33)	215 (29)	
	Missing*	1	3	
Postoperative complicated course				0.043
	No	626 (85)	653 (89)	
	Yes	240 (15)	81 (11)	
30-day major morbidity				0.712
	No	672 (92)	667 (91)	

	Yes	62 (8)	67 (9)	
30-day mortality	No	717 (98)	729 (99)	0.018
	Yes	17 (2)	5 (1)	

Bold p-values indicate statistical significance.

*Missing are not included in the analysis.

Synchronous additional resection was defined as any extra procedure including vascular resection or reconstruction or as additional intra-abdominal resection as a result of in-growth in other structures.

Major liver resection was defined as resection of at least 3 liver segments.

Postoperative complicated course was defined as a complication after surgery resulting in prolonged hospitalization (>14 days), or reintervention or death as a result of a complication.

Major morbidity was defined as a Clavien Dindo Grade 3 or higher complication.

Associated factors with postoperative complicated course and 30-day mortality

In univariable logistic regression, combined resection and ablation was associated with a reduction of PCC and 30-day mortality (table 4). In multivariable logistic regression, combined resection and ablation (aOR 0.95, CI 0.65 – 1.38, p=0.789) was not associated with PCC.

Factors such as major liver resection (aOR 2.31, CI 1.57 – 3.39, p<0.001), ASA score (aOR 1.92, CI 1.27 – 2.89, p=0.001), increasing diameter of largest CRLM (<20mm vs. >55mm, aOR 2.18, CI 1.57 – 3.39, p=0.001) and simultaneous resection of the colorectal primary tumour and CRLM (aOR 2.49, CI 1.55 – 3.98, p<0.001) were associated with an increased PCC rate (table 5).

In multivariable logistic regression, combined resection and ablation (aOR 0.54 CI 0.17 – 1.72, p=0.299) was not associated with 30-day mortality. The odds of mortality were higher in patients with a high ASA score (aOR 5.53, CI 2.07– 14.7, p<0.001), increasing diameter of largest CRLM (<20mm vs. >35-54mm, aOR 6.97, CI 1.35 – 34.3, p=0.023) (table 5).

Table 5. Results of stepwise multilevel logistic regression model nested for year and hospital where treatment took place with postoperative outcomes for patients with colorectal liver metastases (CRLM) who underwent liver resection in the Netherlands between 2014 and 2018.

Postoperative complicated course		Multivariable analysis			
Factor		N	OR	CI (95%)	P-value
Type of procedure					0.789
	Resection only	734	1		
	Combined resection and ablation	734	0.95	0.65 – 1.38	
Major liver resection					<0.001
	No	1097	1		
	Yes	371	2.31	1.57 – 3.39	
American Society of Anesthesiology (ASA) classification					0.001
	I / II	1203	1		
	III+	259	1.92	1.27 – 2.89	
	Missing*	6			

Maximum diameter of largest CRLM (mm)					0.057
	< 20	419	1		
	20-34	513	1.21	0.79 – 1.86	0.382
	35-54	241	1.56	0.95 – 3.96	0.081
	> 55	108	2.18	1.57 – 3.39	0.001
	Missing*	187			
Surgical strategy					<0.001
	Primary tumour first	894	1		
	Liver first	324	0.89	0.58 – 1.41	0.687
	Simultaneous resection of colorectal tumour and CRLM	171	2.49	1.55 – 3.98	<0.001
	Missing*	79			
Type of surgery					0.265
	Open	1250	1		
	Minimally invasive	154	0.55	0.26 – 1.13	0.104
	Conversion	54	1.00	0.41 – 2.39	0.984
	Missing*	10			
Mortality		Multivariable analysis			
Factor		N	OR	CI (95%)	P-value
Type of procedure					0.299
	Resection only	734	1		
	Combined resection and ablation	734	0.54	0.17 – 1.72	
Major liver resection					0.070
	No	1097	1		
	Yes	371	2.49	0.93 – 6.65	
American Society of Anesthesiology (ASA) classification					<0.001
	I / II	1203	1		
	III+	259	5.53	2.07 – 14.7	
	Missing*	6			
Maximum diameter of largest CRLM (mm)					0.057
	< 20	419	1		
	20-34	513	2.22	0.45 – 11.1	0.231
	35-54	241	6.97	1.35 – 34.3	0.023
	> 55	108	6.56	1.00 – 43.5	0.069
	Missing*	187			

Bold p-values indicate statistical significance.

* Missing not included in analyses based on relatively small group

Discussion

In this nationwide population-based analysis significant variation was observed in the use of combined resection and ablation between hospitals and oncological networks in the Netherlands which persisted after case-mix correction. The propensity score-matched analysis showed lower rates of postoperative liver failure, bile leakage, shorter length of hospital stay, lower rates of PCC and 30-day mortality in the combined resection and ablation group. This effect was attributable to the extent of the liver resection performed. Oncological results of combined resection and ablation remain to be determined in order to provide a definitive advice concerning this technique in colorectal liver metastases patients.

Combining resection and ablation for CRLM in order to spare parenchyma has gained terrain over the last decade, with studies increasingly reporting postoperative- and oncological outcomes. Decreasing postoperative 30-day morbidity and 30-day mortality are first priority after surgical procedures and specifically liver surgery in order to decrease the impact of complications on quality of life, oncological outcomes and costs¹⁹⁻²³. Several reports show that complications after liver surgery impact the long-term survival and should be minimised^{24,25}. Using an approach that decreases complications should therefore always be considered in such patients. Promising results concerning postoperative outcomes in patients receiving the combination of resection and thermal ablation have been published⁹. Reports on short-term postoperative outcomes after combined resection and ablation are mainly small sample sized studies^{6,9,26}. A large retrospective study from the United States showed that postoperative outcomes were at least similar between patients undergoing resection or combined resection and ablation²⁷. When comparing two-staged procedures to combined resection and ablation several studies show that combined resection and ablation seems to provide similar postoperative- and oncological outcomes^{8,9,28}. The present study shows improved short-term postoperative outcomes such as lower length of stay and lower mortality rate after combined surgery and ablative techniques compared to resection only. However, this effect was attributable to not performing major liver resection in the combined resection and ablation patients. The combination of resection and ablative techniques seems safe in patients with CRLM and should be considered in these patients either as a potentially curative option in patients who would otherwise be considered to have unresectable disease or as an alternative for more invasive surgery. In multivariable logistic regression it was shown that the positive results in our study are a result of the less invasive character of combining liver resection with thermal ablation compared to resection only. Therefore, treating physicians should try to avoid

liver major liver resection, if by combining liver resection and ablation, the same result can be achieved. This can particularly be used in more frail patients. However, oncological outcomes will have to be assessed.

This population-based study reflecting daily practice in the Netherlands showed that several factors were associated with the use of combined resection and ablation. These factors include preoperative chemotherapy, >3 CRLM, and bilobar disease. Earlier reports provide information on factors that increase the use of combination of resection and ablation. These studies show that combining treatment techniques can increase resectability when CRLM are situated at a difficult location, are bilobar or when a high number of CRLM is present^{4,29}. The lack of consensus in the Dutch guideline and international studies on oncological safety may be responsible for the variation in the use of combined resection and ablation between hospitals and oncological networks in the Netherlands. Another possible explanation for the variation in the use of combined resection and ablation could be the varying availability of interventional radiologists or surgeons who can perform thermal ablation across centres in the Netherlands. These specialists are more often situated in a tertiary referral centre. The assessment of hospital variation in the use of combined resection and ablation provides insight in the differences in the use of combined resection and ablation between Dutch hospitals and oncological networks. Hospital variation has proven to be associated with undesired complications as well as higher costs³⁰⁻³². We are still awaiting potentially oncological favourable outcomes of either treatment strategy. Hospital variation is a problem when one of the treatment strategies proves to be favourable and should therefore be minimised³³.

An important limitation of this study is that long-term oncological outcomes such as overall survival and disease-free survival were not analysed. These long-term outcomes are not part of the DHBA, and therefore no conclusions can be drawn regarding oncological outcome of combined resection and ablation. Before we can recommend resection and ablation over surgery alone as the preferred approach for this subgroup, non-inferiority with regards to overall survival should be established. Several studies show that oncological outcomes of patients who receive parenchymal sparing resection of CRLM are not significantly different from patients undergoing conventional liver resection^{4,6}. Other reports concerning CRLM patients indicated that local control and oncological safety of ablative techniques were similar to liver resection³⁴⁻³⁷. Some reports indicate that combined resection and ablation achieves results comparable to conventional liver resection with respect to short-term postoperative outcomes and oncological outcomes³⁸⁻⁴². However, oncological safety of combined resection and ablation is still under

debate as multicentre randomised studies are lacking and contrasting results have been published before⁴³. These are urgently needed to address the true oncological safety of the combination of combined resection and ablation. If these studies have been realised these results can pose a change in (inter)national guidelines and on the use of combined resection and ablation⁴⁴. This study with upcoming trials could also result in health insurances reimbursing thermal ablation for CRLM. To date thermal ablation is not reimbursed by Dutch Health insurance companies for resectable CRLM.

Other limitations of this study include its retrospective design and, as a result of the audit nature of this research lacking of very detailed perioperative information. This is represented by the lack of information regarding tumour location and diameter of lesions other than the largest CRLM. When tumours are near large vessels, are very centrally located or several large lesions are in situ, combined resection and ablation might not be possible and the surgical team may have chosen a higher risk resection only strategy.

In conclusion, this population-based nationwide study reflecting daily practice in the Netherlands showed significant hospital and oncological network variation in the use of combined resection and ablation. Lower postoperative bile leakage, liver failure, length of stay, postoperative complicated course and 30-day mortality was observed in the combined resection and ablation group. Improved postoperative outcomes after combined resection and ablation are due to parenchymal sparing surgery. This implies that if technically feasible, combining resection and ablation and thereby avoiding major hepatectomy improves postoperative outcomes.

Oncological results of combined resection and ablation remain to be determined in order to provide a definitive advice concerning this technique in colorectal liver metastases patients. Therefore, the implication should be that a surgeon should consider the trade-off of possible increase in local recurrence rates and the decrease in short-term postoperative risk when using ablation to avoid a major hepatectomy while treating patients with multiple liver lesions. That is particularly true for patients that are at higher risk of complications.

References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*. 2010;127(12):2893-2917.
2. Adam R, De Gramont A, Figueras J, Guthrie A, Kokudo N, Kunstlinger F, et al. The oncosurgery approach to managing liver metastases from colorectal cancer: a multidisciplinary international consensus. *Oncologist*. 2012;17(10):1225-1239.
3. Alvarez FA, Sanchez Claria R, Oggero S, de Santibanes E. Parenchymal-sparing liver surgery in patients with colorectal carcinoma liver metastases. *World J Gastrointest Surg*. 2016;8(6):407-423.
4. Moris D, Ronnekleiv-Kelly S, Rahnama-Azar AA, Felekouras E, Dillhoff M, Schmidt C, et al. Parenchymal-Sparing Versus Anatomic Liver Resection for Colorectal Liver Metastases: a Systematic Review. *J Gastrointest Surg*. 2017;21(6):1076-1085.
5. Wang LJ, Zhang ZY, Yan XL, Yang W, Yan K, Xing BC. Radiofrequency ablation versus resection for technically resectable colorectal liver metastasis: a propensity score analysis. *World J Surg Oncol*. 2018;16(1):207.
6. Barabino M, Gatti A, Santambrogio R, Polizzi M, Luigiano C, Opocher E. Intraoperative Local Ablative Therapies Combined with Surgery for the Treatment of Bilobar Colorectal Liver Metastases. *Anticancer Res*. 2017;37(5):2743-2750.
7. Evrard S, Torzilli G, Caballero C, Bonhomme B. Parenchymal sparing surgery brings treatment of colorectal liver metastases into the precision medicine era. *Eur J Cancer*. 2018;104:195-200.
8. Philips P, Groeschl RT, Hanna EM, Swan RZ, Turaga KK, Martinie JB, et al. Single-stage resection and microwave ablation for bilobar colorectal liver metastases. *Br J Surg*. 2016;103(8):1048-1054.
9. van Amerongen MJ, van der Stok EP, Futterer JJ, Jenniskens SF, Moelker A, Grunhagen DJ, et al. Short term and long term results of patients with colorectal liver metastases undergoing surgery with or without radiofrequency ablation. *Eur J Surg Oncol*. 2016;42(4):523-530.
10. (iKNL) CCOtN. National evidence-based guideline: Colorectaalcarcinoom. 2014.
11. van der Werf LR, Kok NFM, Buis CI, Grunhagen DJ, Hoogwater FJH, Swijnenburg RJ, et al. Implementation and first results of a mandatory, nationwide audit on liver surgery. *HPB (Oxford)*. 2019;21(10):1400-1410.
12. van der Werf LR, Voeten SC, van Loe CMM, Karthaus EG, Wouters M, Prins HA. Data verification of nationwide clinical quality registries. *BJS Open*. 2019;3(6):857-864.
13. RIVM. Regional and academic hospital distribution in the Netherlands. 2019.
14. Elfink AKE, Kok NFM, van der Werf LR, Krul MF, Marra E, Wouters M, et al. Population-based study on practice variation regarding preoperative systemic chemotherapy in patients with colorectal liver metastases and impact on short-term outcomes. *Eur J Surg Oncol*. 2020;46(9):1742-1755.
15. Elfink AKE, Pool M, van der Werf LR, Marra E, Burgmans MC, Meijerink MR, et al. Preoperative imaging for colorectal liver metastases: a nationwide population-based study. *BJS Open*. 2020.
16. Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). *Surgery*. 2011;149(5):713-724.
17. Clavien PA, Sanabria JR, Strasberg SM. Proposed classification of complications of surgery with examples of utility in cholecystectomy. *Surgery*. 1992;111(5):518-526.
18. Beck N, van Bommel AC, Eddes EH, van Leersum NJ, Tollenaar RA, Wouters MW, et al. The Dutch Institute for Clinical Auditing: Achieving Codman's Dream on a Nationwide Basis. *Ann Surg*. 2020;271(4):627-631.
19. Kauppila JH, Johar A, Lagergren P. Medical and Surgical Complications and Health-related Quality of Life After Esophageal Cancer Surgery. *Ann Surg*. 2020;271(3):502-508.
20. Archer S, Pinto A, Vuik S, Bicknell C, Faiz O, Byrne B, et al. Surgery, Complications, and Quality of Life: A Longitudinal Cohort Study Exploring the Role of Psychosocial Factors. *Ann Surg*. 2019;270(1):95-101.
21. Pandanaboyana S, Bell R, White A, Pathak S, Hidalgo E, Lodge P, et al. Impact of parenchymal preserving surgery on survival and recurrence after liver resection for colorectal liver metastasis. *ANZ J Surg*. 2018;88(1-2):66-70.

22. Memeo R, de Blasi V, Adam R, Goere D, Laurent A, de'Angelis N, et al. Postoperative Infectious Complications Impact Long-Term Survival in Patients Who Underwent Hepatectomies for Colorectal Liver Metastases: a Propensity Score Matching Analysis. *J Gastrointest Surg*. 2018;22(12):2045-2054.
23. Chen Q, Beal EW, Kimbrough CW, Bagante F, Merath K, Dillhoff M, et al. Perioperative complications and the cost of rescue or failure to rescue in hepato-pancreato-biliary surgery. *HPB (Oxford)*. 2018;20(9):854-864.
24. Matsuda A, Matsumoto S, Seya T, Matsutani T, Kishi T, Yokoi K, et al. Does postoperative complication have a negative impact on long-term outcomes following hepatic resection for colorectal liver metastasis?: a meta-analysis. *Ann Surg Oncol*. 2013;20(8):2485-2492.
25. Tzeng CW, Vauthey JN. Postoperative complications and oncologic outcomes after resection of colorectal liver metastases: the importance of staying on track. *Ann Surg Oncol*. 2013;20(8):2457-2459.
26. Philips P, Scoggins CR, Rostas JK, McMasters KM, Martin RC. Safety and advantages of combined resection and microwave ablation in patients with bilobar hepatic malignancies. *Int J Hyperthermia*. 2017;33(1):43-50.
27. Xourafas D, Pawlik TM, Ejaz A, Dillhoff M, Abdel-Misih S, Tsung A, et al. Impact of concomitant ablation on the perioperative outcomes of patients with colorectal liver metastases undergoing hepatectomy: a propensity score matched nationwide analysis. *HPB (Oxford)*. 2019;21(8):1079-1086.
28. Faitot F, Faron M, Adam R, Elias D, Cimino M, Cherqui D, et al. Two-stage hepatectomy versus 1-stage resection combined with radiofrequency for bilobar colorectal metastases: a case-matched analysis of surgical and oncological outcomes. *Ann Surg*. 2014;260(5):822-827; discussion 827-828.
29. Desjardin M, Desolneux G, Brouste V, Degrandi O, Bonhomme B, Fonck M, et al. Parenchymal sparing surgery for colorectal liver metastases: The need for a common definition. *Eur J Surg Oncol*. 2017;43(12):2285-2291.
30. Idrees JJ, Johnston FM, Canner JK, Dillhoff M, Schmidt C, Haut ER, et al. Cost of Major Complications After Liver Resection in the United States: Are High-volume Centers Cost-effective? *Ann Surg*. 2019;269(3):503-510.
31. Birkmeyer JD, Reames BN, McCulloch P, Carr AJ, Campbell WB, Wennberg JE. Understanding of regional variation in the use of surgery. *Lancet*. 2013;382(9898):1121-1129.
32. Nelson-Williams H, Gani F, Kilic A, Spolverato G, Kim Y, Wagner D, et al. Factors Associated With Interhospital Variability in Inpatient Costs of Liver and Pancreatic Resections. *JAMA Surg*. 2016;151(2):155-163.
33. McCulloch P, Nagendran M, Campbell WB, Price A, Jani A, Birkmeyer JD, et al. Strategies to reduce variation in the use of surgery. *Lancet*. 2013;382(9898):1130-1139.
34. Elias D, Baton O, Sideris L, Matsuhisa T, Pocard M, Lasser P. Local recurrences after intraoperative radiofrequency ablation of liver metastases: a comparative study with anatomic and wedge resections. *Ann Surg Oncol*. 2004;11(5):500-505.
35. Tanaka K, Shimada H, Nagano Y, Endo I, Sekido H, Togo S. Outcome after hepatic resection versus combined resection and microwave ablation for multiple bilobar colorectal metastases to the liver. *Surgery*. 2006;139(2):263-273.
36. Desolneux G, Vara J, Razafindratsira T, Isambert M, Brouste V, McKelvie-Sebileau P, et al. Patterns of complications following intraoperative radiofrequency ablation for liver metastases. *HPB (Oxford)*. 2014;16(11):1002-1008.
37. Razafindratsira T, Isambert M, Evrard S. Complications of intraoperative radiofrequency ablation of liver metastases. *HPB (Oxford)*. 2011;13(1):15-23.
38. Meijerink MR, Puijk RS, van Tilborg A, Henningsen KH, Fernandez LG, Neyt M, et al. Radiofrequency and Microwave Ablation Compared to Systemic Chemotherapy and to Partial Hepatectomy in the Treatment of Colorectal Liver Metastases: A Systematic Review and Meta-Analysis. *Cardiovasc Intervent Radiol*. 2018;41(8):1189-1204.
39. Sasaki K, Margonis GA, Andreatos N, Kim Y, Wilson A, Gani F, et al. Combined resection and RFA in colorectal liver metastases: stratification of long-term outcomes. *J Surg Res*. 2016;206(1):182-189.
40. Imai K, Allard MA, Castro Benitez C, Vibert E, Sa Cunha A, Cherqui D, et al. Long-term outcomes of radiofrequency ablation combined with hepatectomy compared with hepatectomy alone for colorectal liver metastases. *Br J Surg*. 2017;104(5):570-579.

41. Tinguely P, Dal G, Bottai M, Nilsson H, Freedman J, Engstrand J. Microwave ablation versus resection for colorectal cancer liver metastases - A propensity score analysis from a population-based nationwide registry. *Eur J Surg Oncol.* 2020;46(3):476-485.
42. Scherman P, Syk I, Holmberg E, Naredi P, Rizell M. Impact of patient, primary tumor and metastatic pattern including tumor location on survival in patients undergoing ablation or resection for colorectal liver metastases: A population-based national cohort study. *Eur J Surg Oncol.* 2020 Aug 6;S0748-7984(20)30657.
43. Weng M, Zhang Y, Zhou D, Yang Y, Tang Z, Zhao M, et al. Radiofrequency ablation versus resection for colorectal cancer liver metastases: a meta-analysis. *PLoS One.* 2012;7(9):e45493.
44. Puijk RS, Ruars AH, Vroomen L, van Tilborg A, Scheffer HJ, Nielsen K, et al. Colorectal liver metastases: surgery versus thermal ablation (COLLISION) - a phase III single-blind prospective randomized controlled trial. *BMC Cancer.* 2018;18(1):821.

CHAPTER 11

HOSPITAL VARIATION AND OUTCOMES OF SIMULTANEOUS RESECTION OF PRIMARY COLORECTAL TUMOUR AND LIVER METASTASES: A POPULATION-BASED STUDY

M.F. Krul*, **A.K.E. Elfrink***, C.I. Buis, R.J. Swijnenburg, W.W. te Riele, C. Verhoef, P.D. Gobardhan, M. den Dulk, M.S.L. Liem, P.J. Tanis, J.S.D. Mieog, P.B. van den Boezem, W.K.G. Leclercq, V.B. Nieuwenhuijs, M.F. Gerhards, J.M. Klaase, D.J. Grünhagen, N.F.M. Kok**, K.F.D. Kuhlmann**, [Dutch Hepato Biliary Audit Group, Collaborators](#)

* equal author contribution (first)

** equal author contribution (senior)

HPB (Oxford). 2021 Jul 10;S1365-182X(21)00604-3.

Abstract

Introduction

The optimal treatment sequence for patients with synchronous colorectal liver metastases (CRLM) remains uncertain. This study aimed to assess factors associated with the use of simultaneous resections and impact on hospital variation.

Methods

This population-based study included all patients who underwent liver surgery for synchronous colorectal liver metastases between 2014 and 2019 in the Netherlands. Factors associated with simultaneous resection were identified. Short-term surgical outcomes of simultaneous resections and factors associated with 30-day major morbidity were evaluated, .

Results

Of 2 146 patients included, 589 (27%) underwent simultaneous resection in 28 hospitals. Simultaneous resection was associated with age, sex, BMI, number, size and bilobar distribution of CRLM, and administration of preoperative chemotherapy. More minimally invasive and minor resections were performed in the simultaneous group. Hospital variation was present (range 2.4% to 83.3%) with several hospitals performing simultaneous procedures more and less frequently than expected. Simultaneous resection resulted in 13% 30-day major morbidity, and 1% mortality. ASA classification ≥ 3 was independently associated with higher 30-day major morbidity after simultaneous resection (aOR 1.97, CI 1.10 – 3.42, $p=0.018$).

Conclusion

Distinctive patient and tumour characteristics influence the choice for simultaneous resection. Remarkable hospital variation is present in the Netherlands.

Introduction

Patients with colorectal cancer (CRC) and synchronous colorectal liver metastases (CRLM) can be treated with curative intent if complete removal of both tumour sites is possible. The choice for a staged or simultaneous resection of primary tumour and CRLM remains under debate and depends on multiple factors including patient and tumour characteristics, surgeon's preference and hospital workflow¹⁻³. Reasons in favour of a simultaneous approach include a single operation for the patient, timely management of both tumour sites and reduction of costs⁴⁻⁶. Reasons in favour of a staged approach include lower surgical morbidity rates and prevention of unnecessary surgery in case of either rapid disease progression or complete response of the primary tumour⁴.

The Dutch guideline states that simultaneous resections are not standard of care but may be considered in an experienced team and after careful patient selection². International consensus recommends that simultaneous resections should only be performed in patients with limited hepatic disease and easy-to-resect primary tumour⁷.

Two meta-analyses analysing the outcome of staged versus simultaneous resections show that evidence is biased and are inconclusive about the potential harm or benefit of the simultaneous approach compared to a staged approach^{8,9}. The only randomised controlled trial comparing surgical outcomes of a simultaneous resection with a staged, primary-first, approach showed no difference in major complications at liver site (28% vs. 13%, $p=0.08$) and, noteworthy, a tendency towards improved 2-year survival rates for the simultaneous group ($p=0.05$)¹⁰.

The aim of this study was to identify patient- and tumour characteristics discriminating for treatment approach, to assess inter-hospital variability in the use of simultaneous resections, and to identify preoperative characteristics associated with major morbidity in the simultaneous group.

Methods

This was a population-based, nationwide cohort study. Data of the Dutch Hepato Biliary Audit (DHBA) were used. Individual informed consent from patients for data collection was not required for the DHBA according to Dutch law. Data analyses were performed on an anonymised dataset and did not need ethical approval.

National database

The DHBA collects detailed information of all patients who underwent surgery for CRLM the Netherlands. Percutaneous ablations were registered in the DHBA since 2018. All hospitals have been obliged to report to the DHBA since 2014 by the Dutch inspectorate of healthcare. Since introduction of the DHBA, minimal mandatory data requirements have been updated regularly and new mandatory variables have been added. Liver surgery is not performed in each Dutch hospital, as there is a required minimum volume of 20 liver resections per centre per year. In general, inter-hospital meetings to discuss patients with a possible indication for liver surgery and subsequent referral to the appropriate hospital for treatment is available on weekly basis within an oncological network. Oncological networks are hospital collaborations with at least one tertiary referral centre and multiple regional hospitals. Regional and tertiary referral centres have been identified according to complexity of performed surgical procedures and their function in the oncological network. Tertiary referral centres perform more complex surgical procedures. The DHBA is part of the Dutch Institute of Clinical Auditing (DICA) and the accuracy of the audit was 97% at last data verification in 2015^{11,12}.

Patient selection

All patients who underwent liver surgery for liver metastases between January 1, 2014 and December 31, 2019, and registered in the DHBA before April 1, 2020 were included. Patients were excluded if the primary tumour was not of colorectal origin, liver metastases were not synchronously diagnosed (diagnosis at time of diagnosis of the primary tumour), no liver resection was performed (unresectable or ablation was the only liver directed intervention), and if data were missing regarding synchronous or metachronous diagnosis of the CRLM, type of surgery, moment of liver resection, or tumour origin.

Patients were divided in the simultaneous resection group or the staged resection group based on the registration of concomitant resection of the primary colon or rectum tumour during liver surgery.

Demographic and clinical data

Patient characteristics included sex, age, Body Mass Index (BMI), comorbidity score according to the Charlson Comorbidity Index (CCI), American Society of Anesthesiologists (ASA) classification, pre-existent liver pathology (macroscopic or histopathological liver tissue abnormalities), and previous liver surgery. Tumour characteristics included location primary tumour, number of CRLM, distribution of CRLM, maximum diameter of largest CRLM before start treatment, and metachronous or synchronous metastases. Treatment characteristics

included preoperative chemotherapy, staged or simultaneous resection, surgical approach (i.e. laparoscopic, open or conversion), extent of liver resection (major resection was defined as three or more adjacent Couinaud segments), type of hospital, oncological network, and year of surgery^{13,14}.

Outcomes

Case-mix factors influencing use of simultaneous resection were addressed. Case-mix factors were the abovementioned patient-, tumour- and treatment characteristics that possibly influenced the association of variables on outcome and can cloud hospital comparison without proper adjustment¹⁵. Hospital variation in the use of simultaneous resection was compared for both individual hospitals and for oncological networks.

Surgical outcomes of simultaneous resections included treatment specific data and overall 30-day morbidity, 30-day major morbidity, 30-day mortality, length of hospital stay (LOS), and postoperative complicated course (PCC). Because no outcome parameters of the primary tumour resection for the staged approach was available, no comparison in surgical outcomes between the two approaches could be performed. Major morbidity included all Clavien-Dindo surgical complications grade 3 or higher (CD ≥ 3)¹⁶. PCC was registered when a patient was admitted longer than 14 days or if a major complication occurred. Hospital stay was calculated from the day of surgery until the day of discharge. General surgical complications registered were postoperative haemorrhage, pneumonia, surgical site infections, thromboembolic events and cardiac complications. Intra-abdominal infection, bile leakage, and liver failure (according to the International Study Group of Liver Surgery definition) are specific abdominal surgical complications of which the last two are most specific for liver surgery¹⁷. The complication of highest severity level was used in case of multiple complications per patient, regardless of relation to the liver resection or primary resection.

Statistical analysis

Between groups comparison of baseline characteristics was done using the χ^2 test or Fisher exact test as appropriate for categorical variables. Independent student's *t*-test was used for continuous variables.

Univariable and multivariable logistic regression analyses were used to identify case-mix factors associated with performing simultaneous resection and 30-day major morbidity after simultaneous resection. Univariable and multivariable logistic regression models were

performed in a two-step method. All variables with a p-value of ≤ 0.100 in univariable analysis were entered in the multivariable analysis. A two-sided p-value of < 0.050 was considered statistically significant.

Based on patient- and tumour characteristics of all patients included expected use of simultaneous resection was calculated per patient using a multivariable logistic regression model. By grouping all patients who underwent simultaneous resection per hospital the observed use of simultaneous resection was calculated. To visualise the difference between hospitals, the observed / expected ratio (O/E ratio) was used. By dividing the observed number of simultaneous resections of every hospital by the expected simultaneous resection of that same hospital, the O/E ratio was calculated. This is the case-mix adjusted ratio indicating whether a hospital performed more or less simultaneous resections than was expected. An O/E ratio above 1 indicated that a hospital performed more simultaneous resections than expected, an O/E ratio below 1 indicated that a hospital performed less simultaneous resections than expected. The 95% confidence intervals (CI) were calculated to indicate whether the O/E ratio of a hospital was statistically different from the other hospitals.

Multicollinearity was tested through the Variance Inflation Factor (VIF). A VIF of 3 or more was the cut-off value indicating multicollinearity. Patients with missing values were analysed as a separate group in multivariable logistic regression if these exceeded 5% of the total included number of patients. If the missing values in a variable was below 5%, the missing patients were excluded from the analysis¹⁸.

All analyses were performed in R version 3.2.2® (R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

Results

In total, 6477 patients were identified in the DHBA of which 2482 (38.3%) had synchronous CRLM. In 258 patients no liver resection was performed, e.g. unresectable or ablation only, and in an additional 78 patients the moment of liver surgery was unknown (supplementary figure 1). Included in analyses were 2146 patients of whom 589 patients (27%) underwent simultaneous resection and 1557 patients (73%) a staged liver resection for synchronous liver metastases. In total, 28 hospitals performing liver resections within 7 oncological networks in the Netherlands reported to the DHBA between 2014 and 2019.

Baseline characteristics

Baseline characteristics of both groups are demonstrated in table 1. Patients who underwent simultaneous resection were older ($p<0.001$), more often female ($p=0.020$), had a higher mean BMI ($p=0.001$), less pre-existent liver pathology (<0.001), and less preoperative chemotherapy ($p<0.001$). Multiple tumour characteristics of the simultaneous group differed from the staged group ($p<0.001$). The simultaneous group had a lower median number of metastases, more frequently unilobar CRLM, smaller diameter of the largest CRLM and more often the primary tumour located in the colon. The rate of minimally invasive resection was higher ($p=0.002$) and less major liver resections were performed ($p<0.001$). Stratification of the simultaneous group for extent of liver resection showed multiple significant differences between the minor and major liver resection group (supplementary table 1). Patients in the major resection group more often received preoperative chemotherapy ($p<0.001$), had less frequently solitary CRLM ($p<0.001$), the maximum diameter of largest CRLM was higher ($p<0.001$), had more often bilobar CRLM ($p=0.046$), and were more often treated in tertiary referral centres ($p=0.030$).

Table 1. Baseline characteristics stratified per treatment strategy in patients with synchronous colorectal liver metastasis (CRLM) diagnosed between 2014 and 2019 in the Netherlands.

Factor		Staged resection	Simultaneous resection	P-value
		N (%)	N (%)	
Number of patients		1 557 (73)	589 (27)	
Sex				0.020
	Male	974 (63)	337 (57)	
	Female	577 (37)	252 (43)	
	Missing*	6	0	
Age (year)				<0.001
	< 50	137 (9)	44 (8)	
	50 - 64	637 (41)	188 (32)	
	65 - 80	708 (46)	308 (53)	
	≥ 80	74 (5)	46 (8)	
	Missing*	1	3	
Body Mass Index, mean (SD)		25.4 (4.1)	26.1 (4.3)	0.001
Charlson Comorbidity Index				0.590
	0 / 1	1211 (78)	451 (77)	
	2+	346 (22)	138 (23)	
American Society of Anesthesiology classification				0.644
	I / II	1 262 (83)	476 (82)	
	III+	268 (18)	108 (18)	
	Missing*	27	5	
Pre-existing liver pathology §				<0.001
	No	1039 (78)	424 (87)	
	Yes	296 (22)	66 (13)	
	Missing*	222	99	
Liver resection in the past				0.619
	No	1527 (99)	578 (99)	
	Yes	13 (1)	3 (1)	
	Missing*	17	8	

Location primary tumour			<0.001
	Colon	936 (60)	463 (79)
	Rectum	615 (40)	126 (21)
	Missing*	6	0
Number of CRLM			<0.001
	1	404 (27)	269 (47)
	2	300 (20)	136 (24)
	3	228 (15)	60 (10)
	4	153 (10)	38 (7)
	≥5	412 (28)	72 (13)
	Missing*	60	14
Distribution CRLM			<0.001
	Unilobar	642 (42)	360 (62)
	Bilobar	899 (58)	223 (38)
	Missing*	16	6
Maximum diameter of largest CRLM (mm)			<0.001
	< 20	384 (27)	213 (42)
	20 – 34	473 (34)	175 (35)
	35 – 54	294 (21)	64 (13)
	> 55	261 (19)	50 (10)
	Missing*	145	87
Preoperative chemotherapy			<0.001
	No	718 (49)	373 (70)
	Yes	734 (51)	158 (30)
	Missing*	105	58
Type of hospital[∞]			0.744
	Regional hospitals	853 (55)	328 (56)
	Tertiary referral centre	704 (45)	261 (44)
Year of surgery			0.058
	2014	289 (19)	84 (14)
	2015	281 (18)	97 (17)
	2016	303 (20)	126 (21)
	2017	266 (17)	127 (22)
	2018	205 (13)	77 (13)
	2019	213 (14)	78 (13)
Surgical approach			0.002
	Open	1 186 (77)	410 (70)
	Minimally invasive	365 (23)	176 (30)
	Missing*	6	3
Major liver resection[§]			<0.001
	No	1 088 (70)	527 (89)
	Yes	469 (30)	62 (11)

CRLM = colorectal liver metastasis, SD = Standard Deviation

* Missing not included in analyses based on relatively small group.

§ Macroscopic or histopathological liver tissue abnormalities.

∞ Type of hospital: tertiary referral centre are defined as hospitals with highest expertise on oncologic surgery.

± Major liver resection was defined as resection of at least 3 adjacent Couinaud segments.

Associated factors with simultaneous resection

In multivariable analysis, seven patient- and tumour factors were associated with simultaneous resection (table 2). BMI was associated with performing simultaneous resection (aOR 1.04, CI 1.02 – 1.07, $p=0.001$). Factors associated with less frequent use of simultaneous resection were pre-existent liver pathology (aOR 0.57, CI 0.41 – 0.79, $p<0.001$), preoperative chemotherapy

(aOR 0.69, CI 0.54 – 0.89, p=0.004), four or more CRLM (aOR 0.54, CI 0.41 – 0.71, p<0.001), bilobar CRLM (aOR 0.67, 0.53 – 0.84, p<0.001), diameter of the largest CRLM of >50 mm versus <20mm (aOR 0.38, CI 0.26 – 0.56, p<0.001), and a primary tumour in the rectum (aOR 0.43, CI 0.34 – 0.55, p<0.001).

Table 2. Univariable and multivariable logistic model of patient- and tumour factors associated with simultaneous liver resection and resection of colorectal primary tumour in patients with synchronous colorectal liver metastasis (CRLM) diagnosed between 2014 and 2019 in the Netherlands.

Factor	Univariable analysis				Multivariable analysis		
	N	OR	CI (95%)	P-value	aOR	CI (95%)	P-value
Sex				0.018			0.163
Male	1311	1			1		
Female	829	1.26	1.04 – 1.53		1.17	0.94 – 1.45	
Missing*	6						
Age (years)				<0.001			0.040
< 50	181	1			1		
50 - 64	825	0.92	0.63 – 1.35	0.660	0.74	0.49 – 1.12	0.148
65 - 79	1016	1.35	0.95 – 1.97	0.103	0.97	0.65 – 1.46	0.876
≥ 80	120	1.94	1.17 – 3.20	0.010	1.22	0.70 – 2.14	0.475
Missing*	4						
Body Mass Index mean (SD)		1.04	1.02 – 1.06	0.001	1.04	1.02 – 1.07	0.001
Charlson Comorbidity Index				0.550			
0 / 1	662	1					
2+	484	1.07	0.85 – 1.34				
American Society of Anesthesiology classification				0.600			
I / II	1738	1					
III +	376	1.07	0.83 – 1.36				
Missing*	32						
Pre-existing liver pathology§				<0.001			0.001
No	1463	1			1		
Yes	362	0.55	0.41 – 0.73	<0.001	0.57	0.41 – 0.79	<0.001
Missing	321	1.09	0.84 – 1.42	0.508	1.09	0.81 – 1.47	0.567
History of liver surgery				0.441			
No	2105	1					
Yes	16	0.61	0.14 – 1.90				
Missing*	25						
Location primary tumour				<0.001			<0.001
Colon	1399	1			1		
Rectum	741	0.41	0.33 – 0.52		0.43	0.34 – 0.55	
Missing*	6						
Number of CRLM				<0.001			<0.001
≤3	1	1			1		
397							
≥4	675	0.39	0.31 – 0.49		0.54	0.41 – 0.71	
Missing*	74						

Distribution CRLM				<0.001			<0.001
Unilobar	1002	1			1		
Bilobar	1122	0.44	0.37 – 0.54		0.67	0.53 – 0.84	
Missing*	22						
Maximum diameter largest CRLM (mm)				<0.001			<0.001
< 20	597	1			1		
20 - 34	648	0.67	0.52 – 0.85	<0.001	0.67	0.51 – 0.87	0.003
35 - 54	358	0.39	0.28 – 0.54	<0.001	0.40	0.28 – 0.56	<0.001
> 55	311	0.35	0.24 – 0.58	<0.001	0.38	0.26 – 0.56	<0.001
Missing	232	1.08	0.79 – 1.48	0.624	1.16	0.81 – 1.67	0.409
Preoperative chemotherapy				<0.001			<0.001
No	1091	1			1		
Yes	892	0.41	0.33 – 0.51	<0.001	0.69	0.54 – 0.89	0.004
Missing	163	1.06	0.75 – 1.49	0.727	1.14	0.77 – 1.70	0.505
Type of hospital[∞]				0.708			
Regional hospital	1181	1					
Tertiary referral centre	965	0.96	0.80 – 1.17				

CRLM = colorectal liver metastasis, SD = Standard Deviation

* Missing not included in analyses based on relatively small group.

§ Macroscopic or histopathological liver tissue abnormalities.

∞ Type of hospital: tertiary referral centre are defined as hospitals with highest expertise on oncologic surgery.

± Major liver resection was defined as resection of at least 3 adjacent Couinaud segments.

Hospital variation surgical sequence

Variation between hospitals and oncology networks was observed regarding the use of simultaneous resection. Unadjusted rates of simultaneous resections ranged between 2.4% and 83.3% between hospitals (figure 1a). Unadjusted rates of simultaneous resections ranged between 9.5% and 41.2% between oncological networks. All hospitals performing liver surgery have performed simultaneous resections

Figure 1a. Unadjusted hospital variation in performing simultaneous resection of synchronous colorectal primary tumour and colorectal liver metastases (CRLM) patients diagnosed between 2014 and 2019 in the Netherlands.

Based on the case-mix factors, the expected percentage of simultaneous resection ranged between 51.4% and 17.4% for hospitals. In oncological networks analyses, the percentage of expected simultaneous resections ranged between 22.0% and 32.9%. After correction for case-mix factors, five hospitals performed simultaneous resections more often than expected and five significantly less often (figure 1b). One oncological network performed simultaneous resections more frequently and two networks less frequently than expected based on the case-mix factors (supplementary figure 2).

Figure 1b. Case-mix adjusted funnel-plot of between-hospital variation in performing simultaneous resection of colorectal primary tumour and colorectal liver metastases (CRLM) synchronously diagnosed between 2014 and 2019 in the Netherlands.

Surgical outcomes

Treatment characteristics and postoperative outcomes of simultaneously resected patients are shown in table 3. Overall 30-day morbidity was observed in 251 of 589 patients (43%) and major-morbidity in 76 of 589 patients (13%). Of all registered complications, intra-abdominal infection was the most common complication in 69 patients (13%), followed by pneumonia (7%), surgical site infections (6%), and cardiac complications (4%). Thromboembolic complications (2%), bile leakage (2%), postoperative haemorrhage (1%), and liver failure (1%) were less common. The thirty-day mortality rate was 1% (6 patients).

Table 3. Postoperative outcomes in patients with simultaneous resection of colorectal primary tumour and synchronous liver metastasis (CRLM) diagnosed between 2014 and 2019 in the Netherlands.

Factor		Simultaneous resection
		N (%)
Number of patients		589
Length of stay, median (IQR)		8.0 (6.0 – 13.0)
Overall 30-day morbidity		
	No	337 (57)
	Yes	251 (43)
	Missing*	1
30-day major morbidity ‡		
	No	513 (87)
	Yes	76 (13)
Postoperative complicated course[§]		
	No	456 (77)
	Yes	133 (23)
30-day mortality		
	No	570 (99)
	Yes	6 (1)
	Missing*	13
Postoperative haemorrhage		
	No	511 (99)
	Yes	6 (1)
	Missing*	72
Pneumonia		
	No	515 (93)
	Yes	39 (7)
	Missing*	35
Surgical site infection		
	No	518 (94)
	Yes	33 (6)
	Missing*	38
Thromboembolic complication		
	No	569 (98)
	Yes	12 (2)
	Missing*	8
Cardiac complication		
	No	558 (96)
	Yes	24 (4)
	Missing*	7
Intra-abdominal infection		
	No	483 (87)
	Yes	69 (13)
	Missing*	37
Bile leakage		
	No	570 (98)
	Yes	14 (2)
	Missing*	5
Liver failure		
	No	580 (99)
	Yes	3 (1)
	Missing*	6

CRLM = colorectal liver metastasis, SD = Standard Deviation

* Missing not included in analyses based on relatively small group.

§ Macroscopic or histopathological liver tissue abnormalities.

∞ Type of hospital: tertiary referral centre are defined as hospitals with highest expertise on oncologic surgery.

± Major liver resection was defined as resection of at least 3 adjacent Couinaud segments.

Table 4 shows patient-, tumour- and procedural factors association with 30-day major morbidity after simultaneous resection. ASA classification 3 or higher was independently associated with 30-day major morbidity ($p=0.018$) in patients who underwent simultaneous resection. The absolute rate of major morbidity was 11% for patients with ASA 1 or 2 and 19% for ASA 3+ patients ($p=0.029$). Treatment characteristics and postoperative outcomes of simultaneously resected patients stratified for ASA groups are shown in supplementary table 2.

Table 4. Univariable and multivariable logistic model of patient-, tumour- and procedural factors associated with 30-day major morbidity in patients with simultaneous resection of synchronous colorectal liver metastasis (CRLM) in the Netherlands from 2014-2019.

Factor		Univariable analysis				Multivariable analysis		
		N	OR	CI (95%)	P-value	aOR	CI (95%)	P-value
Sex					0.383			
	Male	337	1					
	Female	252	0.80	0.48 – 1.31				
	Missing*							
Age (years)					0.514			
	<50	44	1					
	50 - 64	188	1.91	0.62 – 8.30	0.313			
	65 - 79	308	2.18	0.76 – 9.44	0.199			
	>80	46	2.45	0.63 – 12.0	0.216			
	Missing*	3						
Body Mass Index, mean (SD)			1.00	0.95 – 1.06	0.873			
Charlson Comorbidity Index					0.995			
	0 / 1	451	1					
	2+	138	1.02	0.56 – 1.76				
American Society of Anesthesiology classification					0.021			0.018
	I / II	476	1			1		
	III +	108	1.93	1.09 – 3.32		1.97	1.10– 3.42	
	Missing*	5						
Pre-existing liver pathology§					0.342			
	No	424	1					
	Yes	66	0.52	0.18 – 1.23	0.175			
	Missing	99	0.95	0.48 – 1.77	0.886			
History of liver resection					NA			
	No	578	NA					
	Yes	3	NA	NA	NA			
	Missing*	8	NA	NA	NA			
Location primary tumour					0.205			0.371
	Colon	463	1			1		
	Rectum	126	0.66	0.33 – 1.22		0.74	0.37 – 1.40	
	Missing*	0						
Number of CRLM					0.759			
	≤3	465	1					
	≥4	110	0.90	0.46 – 1.67				
	Missing*	14						
Distribution CRLM					0.285			
	Unilobar	360	1					

	Bilobar	223	0.81	0.51 – 1.10				
	Missing*	6						
Maximum diameter largest CRLM (mm)					0.737			
	< 20	213	1					
	20 - 34	175	1.13	0.61 – 2.10	0.692			
	35 - 54	64	1.46	0.63 – 3.16	0.350			
	> 55	50	1.73	0.72 – 3.89	0.200			
	Missing	87	1.14	0.51 – 2.39	0.736			
Preoperative chemotherapy					0.271			0.138
	No	373	1			1		
	Yes	158	0.62	0.33 – 1.11	0.121	0.58	0.30 – 1.07	0.090
	Missing	58	0.81	0.32 – 1.77	0.625	0.55	0.18 – 1.35	0.231
Type of hospital[∞]					0.936			
	Regional hospital	328	1					
	Tertiary referral centre	261	1.02	0.63 – 1.65				
Type of surgery					0.444			0.373
	Open	410	1			1		
	Minimally invasive	176	0.81	0.46 – 1.38		0.77	0.43 – 1.35	
	Missing*	3						
Major liver resection					0.425			0.222
	No	527	1			1		
	Yes	62	1.34	0.62 – 2.67		1.61	0.72 – 3.34	

* CRLM = colorectal liver metastasis, SD = Standard Deviation

§ Missing not included in analyses based on relatively small group.

∞ Macroscopic or histopathological liver tissue abnormalities.

∞ Type of hospital: tertiary referral centre are defined as hospitals with highest expertise on oncologic surgery.

± Major liver resection was defined as resection of at least 3 adjacent Couinaud segments.

Discussion

This nationwide study is one of the largest cohort studies describing simultaneous resection outcomes and reflects the current daily practice in the Netherlands. This study showed that multiple patient and tumour characteristics were discriminating for selection of a simultaneous approach, mostly reflecting limited tumour burden. Significant hospital variation in the use of simultaneous resection of the primary colorectal tumour and liver metastases was observed. Limited liver related complications were observed despite substantial overall morbidity rates of the simultaneous approach. Higher ASA classification was independently associated with increased 30-day major morbidity.

Several factors were associated with the chosen treatment sequence in the Netherlands. Factors including three or less CRLM, unilobar CRLM distribution, maximum CRLM diameter under 20 mm, location of the primary tumour in the colon, and no preoperative chemotherapy were associated with simultaneous resection. Intended surgery details, including possibility of

laparoscopic surgery and extent of liver surgery, were also different in the between group comparison, showing selection of less invasive surgery in the simultaneous resection group. Previous studies identified similar factors, but not exclusively and consistently¹⁹⁻²⁴. A survey polling surgeons' preference for simultaneous resection in Northern America showed that surgeons opt for simultaneous resection in case of minor liver resections and tend to prefer a staged approach in case of comorbidity and synchronous lung metastases²⁵. The results of this study are in line with the general perception of eligible patients.

The current study showed that every Dutch hospital performing liver surgery selects patients for simultaneous resections. This reflects the advanced stage of centralisation in the Netherlands that allows each liver centre to select and perform simultaneous resections requiring expertise of both liver and colorectal surgery²⁶. Five hospitals performed less and five hospitals performed more simultaneous procedures than expected based on case-mix factors identified in the current study. *Vallance et al.* showed wide variation in sequence applied in England and identified hospitals who did not treat any patients with simultaneous resection²⁰. It is remarkable that such a variation exists in the authors' country even after centralisation with a minimum annual threshold of twenty liver resections. The national guideline only suggest that simultaneous resections may be considered in expert centres. Type of hospital, e.g. tertiary referral centre or regional hospital, was not associated with the choice for simultaneous resection in the current study.

ASA classification was the only factor independently associated with major morbidity in simultaneous resections. Mortality rate after simultaneous resection was low and could be explained by adequate patient selection. Previously described characteristics including primary tumour location and extent of liver resection were not associated with major morbidity in the present study. Major liver resections were not frequently performed during simultaneous procedures and Dutch surgeons were reluctant to perform simultaneous resection in patients with rectal cancer. Long-term follow up of the present cohort is currently not available, but warranted and will be collected. In order to decrease hospital variation, clear guidelines should be conceived for patient selection based on both short-term postoperative outcomes and to be collected long term oncological outcomes.

High observed severe morbidity after simultaneous resection is concordant with the literature^{24,27}. A recent meta-analysis compared both overall and major postoperative complications after simultaneous resection compared to staged resections⁸. All but one included

studies had a retrospective design with a total of 44 studies included. Major morbidity was reported in 14 studies and was higher in the simultaneous group versus liver first [OR= 3.45 (95%CI: 1.01-11.78), (p= 0.05)] (I^2 = 0%, p=0.56). There were no significant complication or major morbidity differences in simultaneous resections compared to primary first resections in pairwise and network meta-analysis. A recent study of the Dutch colorectal registry confirms this latter results when comparing laparoscopic resection of the colorectal primary tumour with simultaneous laparoscopic minor hepatic and primary tumour resections²⁸. Most studies compared simultaneous resection outcomes to one of the two surgical procedures in the staged approach. The lower morbidity rates observed in the staged approach should therefore be interpreted with caution, as both surgical procedures should be included for assessment of surgical morbidity after a staged approach. Unfortunately, combining data of the resection of the primary tumour and liver metastases in a staged approach is not feasible with current national registry regulations. Thus, primary tumour surgical outcomes and completion of surgical treatment of both tumour sites could not be presented.

Authors of a recently published randomised trial between staged operations (colorectal primary resection first) and simultaneous resection in France concluded that the complication rates appears not to be different between these strategies¹⁰. Accrual was low, over 10 years, the sample size of 85 patients does not allow for strong conclusions and colorectal first stage approach as standard sequence does not reflect the standard practice in the Netherlands / current standard practice.

Simultaneous resections can be of great value as they require only a single surgical session and provides timely treatment of both tumour sites. Future perspectives include further reduction of absolute complication rates, reducing hospital variability, and increase the number of patients who can safely undergo simultaneous resection. In order to provide evidence-based guidelines for patient selection, data of prospective studies is required. The results of this study are being used to proceed with Codman's sessions in the Netherlands, i.e. in debt evaluations of variation between hospitals regarding the use of simultaneous resections. The aim of these sessions and future guidelines is to decrease between hospital variation and optimise (inter)national patient care.

The current study has several limitations, including the retrospective design and lack of data on primary tumour resections, preoperative treatment of the primary tumour in the staged group, and intraoperative data. The nationwide character and number of patients were strengths of the study. The DHBA was the most accurate and complete database for liver surgery in the

Netherlands and included all hospitals performing oncologic liver surgery and all Dutch patients surgically treated for their CRLM. Therewith, this study accurately reflected current daily practice in the Netherlands and provided insight in patient- and tumour factors associated with choice of treatment sequence.

Simultaneous surgery of the primary colorectal tumour and liver metastases can be conducted safely nationally due to proper selection of patients. Selection of patients should be based on ASA score 1-2, limited liver resection, and non-rectal primary location. The observed hospital variation emphasises the current lack of (inter)national guidelines regarding simultaneous resection and can be decreased by introducing standardised international guidelines based on randomised trials assessing postoperative and oncological outcomes.

References

1. National Institute for Health and Care Excellence. Colorectal Cancer (Update): Evidence Review D2a. Treatment for Metastatic Colorectal Cancer in the Liver Amenable to Treatment with Curative Intent. 2020 [accessed 16 April 2021] [Available from: <https://www.nice.org.uk/guidance/ng151/evidence/d2a-treatment-for-metastatic-colorectal-cancer-in-the-liver-amenable-to-treatment-with-curative-intent-pdf-253058083672>]
2. Nederlandse Vereniging voor Heelkunde. Landelijke richtlijn colorectaal carcinoom. 2019 [accessed 16 April 2021] [Available from: https://richtlijnendatabase.nl/richtlijn/colorectaal_carcinoom_crc/startpagina_-_crc.html]
3. Y. Hashiguchi, K. Muro, Y. Saito, Y. Ito, Y. Ajioka, T. Hamaguchi, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. *International journal of clinical oncology*. 2020;25(1):1-42.10.1007/s10147-019-01485-z
4. R. W. Krell and M. I. D'Angelica. Treatment sequencing for simultaneous colorectal liver metastases. *Journal of surgical oncology*. 2019;119(5):583-93.10.1002/jso.25424
5. L. J. Wang, H. W. Wang, K. M. Jin, J. Li and B. C. Xing. Comparison of sequential, delayed and simultaneous resection strategies for synchronous colorectal liver metastases. *BMC surgery*. 2020;20(1):16.10.1186/s12893-020-0681-7
6. J. J. Idrees, F. Bagante, F. Gani, B. F. Rosinski, Q. Chen, K. Merath, et al. Population level outcomes and costs of single stage colon and liver resection versus conventional two-stage approach for the resection of metastatic colorectal cancer. *HPB : the official journal of the International Hepato Pancreato Biliary Association*. 2019;21(4):456-64.10.1016/j.hpb.2018.08.007
7. R. Adam, A. de Gramont, J. Figueras, N. Kokudo, F. Kunstlinger, E. Loyer, et al. Managing synchronous liver metastases from colorectal cancer: a multidisciplinary international consensus. *Cancer treatment reviews*. 2015;41(9):729-41.10.1016/j.ctrv.2015.06.006
8. M. Ghiasloo, D. Pavlenko, M. Verhaeghe, Z. Van Langenhove, O. Uyttebroek, G. Berardi, et al. Surgical treatment of stage IV colorectal cancer with synchronous liver metastases: A systematic review and network meta-analysis. *European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology*. 2020;46(7):1203-13.10.1016/j.ejso.2020.02.040
9. S. Hajibandeh, S. Hajibandeh, A. Sultana, G. Ferris, J. Mwendwa, A. Y. Y. Mohamedahmed, et al. Simultaneous versus staged colorectal and hepatic resections for colorectal cancer with synchronous hepatic metastases: a meta-analysis of outcomes and clinical characteristics. *International journal of colorectal disease*. 2020;35(9):1629-50.10.1007/s00384-020-03694-9
10. K. Boudjema, C. Locher, C. Sabbagh, P. Ortega-Deballon, B. Heyd, P. Bachellier, et al. Simultaneous Versus Delayed Resection for Initially Resectable Synchronous Colorectal Cancer Liver Metastases: A Prospective, Open-label, Randomized, Controlled Trial. *Annals of surgery*. 2020.10.1097/sla.0000000000003848
11. L. R. van der Werf, S. C. Voeten, C. M. M. van Loe, E. G. Karthaus, M. Wouters and H. A. Prins. Data verification of nationwide clinical quality registries. *BJS open*. 2019;3(6):857-64.10.1002/bjs5.50209
12. L. R. van der Werf, N. F. M. Kok, C. I. Buis, D. J. Grünhagen, F. J. H. Hoogwater, R. J. Swijnenburg, et al. Implementation and first results of a mandatory, nationwide audit on liver surgery. *HPB : the official journal of the International Hepato Pancreato Biliary Association*. 2019;21(10):1400-10.10.1016/j.hpb.2019.02.021
13. M. E. Charlson, P. Pompei, K. L. Ales and C. R. MacKenzie. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of chronic diseases*. 1987;40(5):373-83.10.1016/0021-9681(87)90171-8
14. The American Society of Anesthesiologists: ASA physical status classification system. 2014 [Available from: <https://www.asahq.org/standards-and-guidelines/asa-physical-status-classification-system>].
15. A. K. E. Elfink, E. W. van Zwet, R. J. Swijnenburg, M. den Dulk, P. B. van den Boezem, J. S. D. Mieog, et al. Case-mix adjustment to compare nationwide hospital performances after resection of colorectal liver metastases. *European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology*. 2020.10.1016/j.ejso.2020.10.016

16. D. Dindo, N. Demartines and P. A. Clavien. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Annals of surgery*. 2004;240(2):205-13.10.1097/01.sla.0000133083.54934.ae
17. N. N. Rahbari, O. J. Garden, R. Padbury, G. Maddern, M. Koch, T. J. Hugh, et al. Post-hepatectomy haemorrhage: a definition and grading by the International Study Group of Liver Surgery (ISGLS). *HPB : the official journal of the International Hepato Pancreato Biliary Association*. 2011;13(8):528-35.10.1111/j.1477-2574.2011.00319.x
18. G. Stewart. Collinearity and Least Squares Regression. *Statistical Science*. Statistical Science1987.doi:10.1214/ss/1177013439
19. J. Bogach, J. Wang, C. Griffiths, S. Parpia, R. Saskin, J. Hallet, et al. Simultaneous versus staged resection for synchronous colorectal liver metastases: A population-based cohort study. *International journal of surgery (London, England)*. 2020;74:68-75.10.1016/j.ijsu.2019.12.009
20. A. E. Vallance, J. van der Meulen, A. Kuryba, S. C. Charman, I. D. Botterill, K. R. Prasad, et al. The timing of liver resection in patients with colorectal cancer and synchronous liver metastases: a population-based study of current practice and survival. *Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland*. 2018;20(6):486-95.10.1111/codi.14019
21. B. H. Kye, S. H. Lee, W. K. Jeong, C. S. Yu, I. J. Park, H. R. Kim, et al. Which strategy is better for resectable synchronous liver metastasis from colorectal cancer, simultaneous surgery, or staged surgery? Multicenter retrospective analysis. *Annals of surgical treatment and research*. 2019;97(4):184-93.10.4174/astr.2019.97.4.184
22. R. Martin, P. Paty, Y. Fong, A. Grace, A. Cohen, R. DeMatteo, et al. Simultaneous liver and colorectal resections are safe for synchronous colorectal liver metastasis. *Journal of the American College of Surgeons*. 2003;197(2):233-41; discussion 41-2.10.1016/s1072-7515(03)00390-9
23. R. C. Martin, 2nd, V. Augenstein, N. P. Reuter, C. R. Scoggins and K. M. McMasters. Simultaneous versus staged resection for synchronous colorectal cancer liver metastases. *Journal of the American College of Surgeons*. 2009;208(5):842-50; discussion 50-2.10.1016/j.jamcollsurg.2009.01.031
24. T. J. Jones, A. E. Murphy, A. Tameron, L. R. Hussain, K. Grannan, H. Guend, et al. Trends and Outcomes of Synchronous Resection of Colorectal Metastasis in the Modern Era-Analysis of Targeted Hepatic NSQIP Database. *The Journal of surgical research*. 2019;238:35-40.10.1016/j.jss.2019.01.021
25. C. Griffiths, J. Bogach, M. Simunovic, S. Parpia, L. Ruo, J. Hallet, et al. Simultaneous resection of colorectal cancer with synchronous liver metastases; a practice survey. *HPB : the official journal of the International Hepato Pancreato Biliary Association*. 2020;22(5):728-34.10.1016/j.hpb.2019.09.012
26. P. B. Olthof, A. K. E. Elfrink, E. Marra, E. J. T. Belt, P. B. van den Boezem, K. Bosscha, et al. Volume-outcome relationship of liver surgery: a nationwide analysis. *The British journal of surgery*. 2020;107(7):917-26.10.1002/bjs.11586
27. R. A. Snyder, S. Hao, W. Irish, E. E. Zervos, J. E. Tuttle-Newhall and A. A. Parikh. Thirty-Day Morbidity After Simultaneous Resection of Colorectal Cancer and Colorectal Liver Metastasis: American College of Surgeons NSQIP Analysis. *Journal of the American College of Surgeons*. 2020.10.1016/j.jamcollsurg.2019.12.018
28. M. J. van der Poel, P. J. Tanis, H. A. Marsman, A. M. Rijken, E. C. Gertsen, S. Ovaere, et al. Laparoscopic combined resection of liver metastases and colorectal cancer: a multicenter, case-matched study using propensity scores. *Surgical endoscopy*. 2019;33(4):1124-30.10.1007/s00464-018-6371-1

Supplementary material

Supplementary table 1. Baseline characteristics stratified for extent of liver resection in patients with simultaneous resection of colorectal primary tumour and liver metastasis (CRLM) diagnosed between 2014 and 2019 in the Netherlands.

Factor	Minor liver resection N (%)	Major liver resection ± N (%)	P-value
Number of patients	527	62	
Sex			0.058
Male	309 (59)	28 (45)	
Female	218 (41)	34 (55)	
Age (year)			0.215
< 50	40 (8)	4 (7)	
50 - 64	161 (31)	27 (44)	
65 - 80	280 (53)	28 (45)	
> 80	43 (8)	3 (5)	
Missing*	3	0	
Body Mass Index, mean (SD)	26.1 (4.29)	25.5 (3.95)	0.282
Charlson Comorbidity Index			0.202
0 / 1	399 (76)	52 (84)	
2+	128(24)	10 (16)	
American Society of Anesthesiology classification			0.096
I / II	421 (81)	55 (90)	
III+	102 (19)	6 (10)	
Missing*	4	1	
Pre-existing liver pathology §			0.100
No	280 (88)	44 (79)	
Yes	54 (13)	12 (21)	
Missing*	93	6	
Liver resection in the past			0.736
No	517 (99)	61 (98)	
Yes	2 (1)	1 (2)	
Missing*	8	0	
Location primary tumour			0.803
Colon	412 (78)	50 (81)	
Rectum	114 (22)	12 (19)	
Number of CRLM			<0.001
1	257 (50)	12 (20)	
2	120 (23)	16 (27)	
3	51 (10)	9 (15)	
4	28 (5)	10 (17)	
≥5	59 (12)	13 (22)	
Missing*	12	2	
Distribution CRLM			0.046
Unilobar	330 (63)	30 (49)	
Bilobar	192 (37)	31 (51)	
Missing*	5	1	
Maximum diameter of largest CRLM (mm)			<0.001
< 20	201 (45)	12 (21)	
20 - 34	159 (36)	16 (28)	
35 - 54	53(12)	11 (19)	
> 55	32 (7)	18 (32)	
Missing*	82	5	
Preoperative chemotherapy			<0.001
No	347 (73)	26 (47)	

Yes	129 (27)	29 (53)	
Missing*	51	7	
Type of hospital[∞]			0.030
Regional hospitals	302 (57)	26 (42)	
Tertiary referral centre	225 (43)	36 (58)	
Year of surgery			0.621
2014	76 (14)	8 (13)	
2015	89 (17)	8 (13)	
2016	115 (22)	11 (18)	
2017	114 (22)	13 (21)	
2018	57 (13)	10 (16)	
2019	66 (13)	12 (19)	
Surgical approach			<0.001
Open	351 (67)	59 (79)	
Laparoscopic	174 (33)	2 (3)	
Missing*	2	1	

CRLM = colorectal liver metastasis, SD = Standard Deviation

* Missing not included in analyses based on relatively small group.

§ Macroscopic or histopathological liver tissue abnormalities.

[∞] Type of hospital: tertiary referral centre are defined as hospitals with highest expertise on oncologic surgery.

± Major liver resection was defined as resection of at least 3 adjacent Couinaud segments.

Supplementary table 2. Postoperative outcomes stratified for ASA groups in patients with simultaneous resection of colorectal primary tumour and synchronous liver metastasis (CRLM) diagnosed between 2014 and 2019 in the Netherlands.

Factor	ASA 1 / 2	ASA 3+	P-value
	N (%)	N (%)	
Number of patients^o	476	108	
Length of stay, median (IQR)	8.00 (6.00 – 12.75)	9.00 (6.00 - 16.25)	0.188
Overall 30-day morbidity			0.195
No	280 (59)	55 (51)	
Yes	196 (41)	52 (49)	
Missing*	0	1	
30-day major morbidity ±			0.029
No	423 (89)	88 (81)	
Yes	53 (11)	21 (19)	
Postoperative complicated course[∞]			0.035
No	376 (79)	75 (69)	
Yes	98 (21)	33 (31)	
30-day mortality			0.134
No	465 (99)	101 (97)	
Yes	3 (1)	3 (3)	
Missing*	0	0	
Postoperative haemorrhage			0.629
No	419 (99)	88 (98)	
Yes	4 (1)	2 (2)	
Missing*	53	18	
Pneumonia			0.050
No	423 (94)	89 (88)	
Yes	26 (6)	12 (12)	
Missing*	27	7	
Surgical site infection			0.118
No	417 (93)	97 (98)	
Yes	30 (7)	2 (2)	
Missing*	29	9	

Thromboembolic complication			0.811
No	463 (98)	102 (97)	
Yes	9 (2)	3 (3)	
Missing*	4	3	
Cardiac complication			0.071
No	457 (97)	98 (92)	
Yes	15 (3)	8 (8)	
Missing*	4	2	
Intra-abdominal infection			0.304
No	395 (88)	84 (84)	
Yes	52 (12)	16 (16)	
Missing*	29	8	
Bile leakage			0.967
No	462 (97)	104 (98)	
Yes	12 (3)	2 (2)	
Missing*	2	2	
Liver failure			1.000
No	471 (99)	105 (99)	
Yes	2 (1)	1 (1)	
Missing*	3	2	

CRLM = colorectal liver metastasis, SD = Standard Deviation

* Missing not included in analyses based on relatively small group.

§ Macroscopic or histopathological liver tissue abnormalities.

∞ Type of hospital: tertiary referral centre are defined as hospitals with highest expertise on oncologic surgery.

± Major liver resection was defined as resection of at least 3 adjacent Couinaud segments.

Supplementary figure 1. Flowchart patient selection of all patients with colorectal cancer liver metastases (CRLM) surgery diagnosed between 2014 and 2019 in the Netherlands.

Supplementary figure 2a. Unadjusted between-oncological network variation in performing simultaneous resection of synchronous colorectal primary tumour and colorectal liver metastases (CRLM) patients diagnosed between 2014 and 2019 in the Netherlands.

Supplementary figure 2b. Case-mix adjusted funnel-plot of between-oncological network variation in performing simultaneous resection of colorectal primary tumour and colorectal liver metastases (CRLM) synchronously diagnosed between 2014 and 2019 in the Netherlands.

CHAPTER 12

DISCUSSION AND
FUTURE PERSPECTIVES

Discussion and future perspectives

Clinical auditing has been a strong tool to improve outcomes and quality of care by continuously evaluating the current daily practice. Measurement of preset perioperative outcomes is the cornerstone of clinical auditing. These outcomes can be referred to as quality indicators. Quality indicators can focus on process of care and outcomes. Several examples include preoperative imaging, perioperative treatment strategies and postoperative outcomes. Research based on clinical auditing registries compares perioperative treatment strategies and outcomes among hospitals thereby evaluating standards set by clinicians. It can reveal undesired hospital variation in perioperative quality indicators. This may be a result of absent guidelines. An association with higher costs and worse outcomes has been described^{1,2}. In 2013, the Dutch Hepato Biliary Audit (DHBA) was initiated to evaluate daily practice and outcomes ultimately leading to improvement initiatives to further enhance care for patients with liver tumours. In this thesis, perioperative treatment strategies and outcomes according preset standards were assessed to evaluate current quality of care for patients with liver tumours in the Netherlands.

Quality assessment of liver surgery

Current standards regarding liver surgery indicate a volume requirement of 20 liver resections per hospital in order to pursue liver resection in the Netherlands. Outcomes after liver surgery are demonstrated in the DHBA for secondary, primary and benign liver tumours. Liver resection includes a spectrum of operations varying from a wedge resection to extended hepatectomies with vascular and biliary reconstructions. It is important to assess the usefulness of current guidelines, validity of quality indicators used in the DHBA, and to address variation in clinical practice.

In pancreatic surgery and oesophageal surgery, a significant relationship between higher hospital volume and better outcomes was observed^{3,4}. In **Chapter 2**, the annual volume requirement of 20 liver resections per hospital was not associated with postoperative outcomes such as complications graded Clavien-Dindo $\geq 3a$ or mortality⁵. The median annual hospital volume between 2014 and 2017 was 35 procedures in the Netherlands. More complex procedures such as two-stage procedures, major liver resection or resection of biliary cancer were mainly performed in high volume hospitals as a result of centralisation of liver surgery. Earlier studies demonstrated an effect of hospital volume on outcomes. These studies had low median hospital volumes which probably had major effect on the relationship between hospital

volume and outcomes⁶⁻⁸. The threshold to perform liver surgery and the established referral patterns in oncological networks during centralisation of surgery attribute to the conclusion that there is no relationship between hospital volume and postoperative outcomes in the Netherlands.

Although no volume-outcome relationship was observed in the Netherlands, complications and mortality after liver surgery should be assessed to improve quality of care. Complications occur often after liver surgery due to its complex nature and sometimes lead to postoperative mortality. Additionally, differences in outcomes after liver resection might exist between age categories. This is important to address due to aging of the population which is also accompanied by more comorbidity. In **Chapter 3**, the phenomenon of Failure to Rescue (FTR) is described which is defined as major complications leading to mortality. The overall FTR rate in the Netherlands was 19.1% of all patients with a major complication. Significant variation was present in Dutch hospitals performing liver surgery but this hospital variation was attributable to patient demographics and disease burden. Although a 19.1% rate of FTR is comparable to other countries, improvement is warranted⁹⁻¹¹. FTR occurs mainly in older and more comorbid patients, in those who undergo major liver resection or resection for biliary cancer and is most often a result of postoperative liver failure or cardiac and thromboembolic complications. In **Chapter 4**, postoperative outcomes in elderly patients were evaluated. It was demonstrated that postoperative morbidity and mortality were worse in septuagenarians and octogenarians compared to patients who were younger than 70 years. These outcomes were mainly influenced by cardiopulmonary complications, and not by liver-specific surgical complications.

Prevention and management of postoperative liver failure, cardiac complications, and thromboembolic complications could lead to a decrease of FTR and improvement of postoperative outcomes in the elderly. Several initiatives have to be explored to address preoperative and postoperative optimisation of patients who undergo liver resection. Treatment of postoperative liver failure is difficult once a patient suffers this complication. Preoperative volumetric assessment of the liver, hepatobiliary scintigraphy and portal vein embolization to increase the future liver remnant, may decrease occurrence of postoperative liver failure^{12,13}. Postoperative options are limited and include aggressive screening for infections and immediate management of these infections. Cardiopulmonary complications can be decreased using prehabilitation to optimise frail or elderly patients before major surgery by preoperative exercise training¹⁴. Prehabilitation is gathering momentum and proved to have a positive influence on quality of life and fitness after liver surgery¹⁵. However, in colorectal surgery patients a benefit

was observed from preoperative exercise training combined with a diet to optimise aerobic fitness which leads to a decrease in postoperative complications¹⁶. Also, decreasing thromboembolic complications could be achieved using pharmacological and non-pharmacological prophylaxis perioperatively¹⁷.

Liver resection is mainly performed for malignant tumours, in 90% of patients in the Netherlands. Little is known about the quality of liver surgery for benign tumours. It is essential to minimise risks of surgical morbidity and mortality after liver resection for a benign indication. Several initiatives such as introduction of minimally invasive liver resection have been implemented over the years to improve postoperative outcomes. **In Chapter 5**, the added value of laparoscopy for resection of benign liver tumours was described. Resection of benign liver tumours was deemed safe in the Netherlands as overall morbidity was 17.5% and no mortality occurred in the total population. These overall morbidity rates were lower in the laparoscopic group after propensity score matching. These results indicate that, if technically feasible, laparoscopic resection of benign liver tumours should be considered. Future work should include development of a composite outcome for benign liver surgery assessing several components of quality of care such as patient reported outcomes on quality of life to enhance shared-decision making.

In **Part I**, assessment of quality of liver surgery over the last 5 years in primary and secondary liver tumours in the Netherlands provided insight in current outcomes and provided leads for improvement. Between 2014 and 2017 the median number of resections per hospital was 35 which increased in 2019 to a median number of 57 resections per hospital. This is higher as compared to the annual volume requirement of 20 resections per year per hospital. Exploration of the current volume requirement for liver surgery in the Netherlands should include studies on the optimal hospital volume for liver resections. These studies should include analyses on the optimal volume stratified by indication for primary and secondary liver tumours. Further centralization of patients with complex liver resections, or HCC and biliary cancer is necessary and these resections should be performed solely in high-volume centres. Also, the effect of initiating new perioperative treatment strategies to decrease FTR rates, improve outcomes in the elderly and in those who undergo liver resection for benign liver tumours should be monitored through DHBA data.

Impact of hospital variation on outcomes after resection of colorectal liver metastases

In **Part II**, secondary liver tumours such as colorectal liver metastases (CRLM) account for 60-70% of all liver resections in the Netherlands. Current guidelines on treatment of CRLM are under debate and new insights regarding imaging, chemotherapy and surgical techniques have been established over the last years. Clinical auditing can evaluate guideline adherence and can provide recommendations on guideline revisions if combined with high-level evidence on a certain topic. In the second part of this thesis, current practice variation on perioperative treatment of CRLM was evaluated and outcomes were assessed using existing quality indicators such as 30-day major morbidity and 30-day mortality.

Preoperative imaging to identify CRLM has been evolving over the years. In **chapter 6**, the use of Magnetic Resonance Imaging (MRI) and ¹⁸Fluoro-Deoxy-Glucose Positron Emission Computed Tomography (¹⁸FDG-PET-CT) was evaluated. It was shown that the use of MRI increased over the years while the use of ¹⁸FDG-PET-CT decreased in the Netherlands. This is probably due to several international studies that showed superior per lesion detection of MRI and because MRI provides detailed information on the location of CRLM and relation to vascular structures¹⁸. The observed decrease in the use of ¹⁸FDG-PET-CT is most likely a result of studies which showed that its main use is limited to detection of extrahepatic metastases without increasing survival¹⁸. ¹⁸FDG-PET-CT has been observed to increase false-positive results^{19,20}. However, widespread variation between Dutch hospitals regarding both imaging modalities was observed which reflect the debate on preoperative workup before resection of CRLM. This variation in clinical practice also provides leads for improvement regarding guidelines on preoperative imaging in these patients. To date, evidence regarding this workup is lacking. The CAMINO trial aims to provide information concerning additional value of MRI in CRLM patients (clinicaltrials.gov number: NCT01015833). Results of this trial are awaited but a strict implementation of a new guideline on preoperative workup should be strived for. This should decrease undesired practice variation in preoperative workup for CRLM patients. Guideline implementation and adherence should be monitored using the DHBA.

Other aspects of perioperative care for patients with CRLM include preoperative administration of chemotherapy. In **Chapter 7**, administration of preoperative chemotherapy in the Netherlands was demonstrated. Significant hospital variation was observed reflecting contradictory evidence and lacking of resectability criteria. The current understanding is to use chemotherapy in upfront unresectable metastases to make resection possible in the Netherlands²¹. This was concluded

from randomised trials which could not demonstrate improved survival after preoperative chemotherapy in patients with resectable metastases^{22,23}. It is important to limit the discussion to administer preoperative chemotherapy or not to patients who were eligible in these trials as patients up to 4 CRLM were included in the EPOC-1 trial by Nordlinger et al^{22,23}. There is a knowledge gap in patients with resectable but rather extensive CRLM. The CHARISMA trial tried to focus on these patients but failed due to lack on accrual²⁴. Another reason to refrain from preoperative chemotherapy is its association with hepatotoxicity which may reflect on postoperative outcomes²⁵⁻²⁷. However, in the study described in this chapter postoperative outcomes were comparable between patients who did and did not receive preoperative chemotherapy. This was concordant to other studies which did not reveal higher adverse event rates in patients who were administered preoperative chemotherapy^{28,29}.

Decreasing hospital variation regarding the use of preoperative chemotherapy for CRLM patients should be pursued based on international guidelines. These guidelines should address resectability criteria based on randomised trials which also assess the added value of preoperative chemotherapy for CRLM. The CAIRO-5 study aims to reach consensus regarding criteria for resectability which is defined in the study as complete resection in one surgical session without ablation leaving the future liver remnant with less than 25-30% in normal livers or 45-50 in compromised livers³⁰. This trial will also evaluate long-term outcomes regarding preoperative chemotherapy in initially unresectable CRLM³¹. Monitoring adherence to the afterwards internationally drafted guideline may be evaluated using data from the DHBA. An option is to propose a quality indicator which focusses on the administration of preoperative chemotherapy in upfront unresectable and resectable CRLM.

In **Chapter 8**, the use of the quality indicators 30-day major morbidity and 30-day mortality were evaluated. Hospitals performed liver surgery in patients with differences in patient demographics and disease burden. This is called the case-mix of a hospital. Earlier studies provided insight in risk factors for adverse events such as comorbidities, higher number of CRLM and major liver resection³²⁻³⁵. In the current study, case-mix varied significantly between hospitals demonstrating the need for case-mix correction when comparing postoperative outcomes between Dutch hospitals. Case-mix adjustment in clinical practice for quality indicators on 30-day major morbidity and 30-day mortality was described. Therewith, a more valid comparison of outcomes on a hospital level can be performed. In **Chapter 9**, the formation of oncological networks in the Netherlands for treatment of CRLM and comparing outcomes on an oncological network level was described. These oncological networks are based on a topographical area

and include at least one tertiary referral centre and several regional hospitals performing liver surgery. Main purpose of these oncological networks is to decrease treatment variation and improve outcomes within oncological networks. It was demonstrated that when comparing oncological networks, differences in case-mix and postoperative outcomes were smaller as compared to on a hospital level.

Differences in case-mix and therewith in outcomes between hospitals are expected due to referral patterns in the Netherlands. More complex high-risk surgical procedures are referred to more specialised centres while smaller centres perform lower-risk surgical procedures. This is a result of centralisation of liver surgery based on the tumor-specific committees and the standardisation report of the Dutch Federation of Oncologic Societies in which liver surgery was centralised in 24 Dutch hospitals³⁶. It is intriguing that differences in case-mix are smaller but exist on an oncological network level as compared to on a hospital level. This might be the result of the differences between oncological networks regarding collaboration agreements. These agreements include aligned preoperative workup and referral patterns in an oncological network as well as liver-specific multidisciplinary team meetings attended by all hospitals in the oncological network. Several oncological networks in the Netherlands do not have these type of collaboration agreements resulting in differences between oncological networks. Another explanation might be the lacking of clear guidelines on perioperative workup as evaluated in this thesis. Collaboration of hospitals in oncological networks should be pursued and evaluated to align and improve quality of care throughout the Netherlands. Eventually, every single patient with a liver tumour should receive comparable quality of care irrespective of hospital or region of diagnosis.

Treatment of liver metastases has expanded from solely staged surgical resection to thermal ablation and simultaneous resection of the colorectal tumour and liver metastases. In **Chapter 10**, the combination of liver resection and thermal ablation for CRLM was evaluated between Dutch hospitals and associated postoperative outcomes. Significant hospital variation in the use of this combined strategy was observed. Due to less invasive treatment of the combination, postoperative outcomes were better in this group. Earlier studies mainly had small sample size but showed concordant results confirming safety of the combination of liver resection and thermal ablation³⁷⁻³⁹. However, long-term oncological outcomes will have to be assessed before a definite conclusion can be drawn. The observed variation between hospitals is probably a result of 'believers' and 'non-believers' in the combined resection and ablation approach but may also reflect varying availability of skilled interventional radiologists and surgeons with

experience in thermal ablation. Stricter guidelines on parenchymal sparing options such as the combination of liver resection and thermal ablation based on randomised trials comparing postoperative and oncological outcomes are necessary in order to create a 'standard of care'.

The nationwide daily practice regarding simultaneous resection of the colorectal tumour and synchronous liver metastases was evaluated in **Chapter 11**. Overall, it was observed that the simultaneous approach was more often preferred in patients with limited liver metastases and an easy-to-resect primary tumour which is according to the Dutch guideline. However, significant hospital variation was found between Dutch hospitals and adverse events often occurred in the simultaneous group. This can be explained by inconclusive evidence which to date has not led to a treatment strategy which can be referred to as standard of care. Several studies showed higher adverse events in the simultaneous group while in one large randomised trial no differences in outcomes were observed between the groups⁴⁰⁻⁴³. This chapter also revealed that patients with higher ASA classification are at risk for postoperative major morbidity. Therefore, surgeons should be cautious to treat the primary tumour and metastases simultaneously. To decrease current practice variation, oncological outcomes will have to be awaited.

Future perspectives

Feedback information and quality improvement

This thesis included assessment and clinical use of the first quality indicators for liver surgery from the DHBA. Interestingly, it was shown that significant hospital variation existed in the Netherlands regarding perioperative treatment strategies in liver surgery and outcomes. As described in the Plan-Do-Act-Check cycle, liver surgeons in the Netherlands should now get together to initiate improvement measures. Further assessment of aforementioned quality indicators for trends on a national and hospital level should be pursued to monitor improvement. After implementation of changes, the ultimate goal is to deliver comparable quality of care to all patients in the Netherlands independent of hospital of diagnosis.

Providing feedback information for registry users has been recognised by the Dutch Institute for Clinical Auditing (DICA) as one of the key points of the institute and its registries. For the past years, all information was available on an online portal in which all data and quality indicators were displayed. However, usage of feedback information has been a problem for the past years for DICA due to low user friendliness. The Codman Dashboard is a new feature from DICA in

which the DHBA users have daily updated information available on their hospital performance⁴⁴. Another upgrade in the Codman Dashboard is that the DHBA user can filter for specific patient groups, indication for liver surgery, and even filter on surgical procedures. This tailored information can support users in assessing their own trends in quality indicators and in other areas of interest. This dashboard will be the basis of initiating and measuring improvement for the upcoming years.

As described, the Codman Dashboard is a tool for quality improvement. However, just providing feedback information is not enough to improve quality of care in liver surgery. To truly assess hospital performances and start improvement initiatives, so-called 'Codman Sessions' should be organised. In 'Codman Sessions', performances of hospitals on single or multiple quality indicators are discussed by the participating clinicians in order to learn from each other and initiate improvement measures wherever necessary with help of each other. For the DHBA, these sessions have not started yet but will be organised in the near future and will be held annually.

Comparing outcomes in the Netherlands

This thesis described several quality indicators on a hospital and oncological network level. Centralisation of liver surgery has led to a decrease of hospitals performing liver surgery and collaboration agreements between these hospitals. There is still room for improvement. Extensive surgery including two-stage procedures, surgery for recurrent metastases, hepatocellular carcinoma (HCC), and biliary cancer require specific tertiary care. Resection of HCC and biliary cancer should be performed in hospitals that perform high volumes of these resections to improve quality of care. Further centralisation of patients with these tumours to only a few hospitals in the Netherlands should be strived for. Collaboration within and between oncological networks can also be improved as differences exist between the oncological networks as demonstrated in this thesis. Aligning protocols between oncological networks according to evidence-based guidelines and intensifying collaborations of hospitals within a certain oncological network can decrease unwanted treatment variation and improve outcomes.

Maturation of the Dutch Hepato Biliary Audit

At the start of an audit, it focuses mainly on data acquisition and process indicators while a next step is the evaluation of quality of care as a whole using both process and outcome indicators. In the past few years, the DHBA has matured enormously as all liver resections performed in the Netherlands were included in the DHBA from 2016 onwards after adding resection of biliary

cancer to the inclusion criteria. Since then, surgeons in the DHBA evaluated the current volume requirement and displayed their first outcome indicators and implemented case-mix correction for Failure to Rescue, 30-day major morbidity, and 30-day mortality⁴⁵⁻⁴⁸. The different projects to assess current daily practice regarding perioperative treatment of CRLM were very successful by revealing hospital variation and therefore initiating improvement measures on a national level⁴⁹⁻⁵². This might also initiate guideline recommendations. Adherence to altered guidelines can be monitored using DHBA data. One of the largest achievements was the cooperation between surgeons and interventional radiologists in 2018. From this year onwards, the DHBA became a multidisciplinary registry as ablations for liver tumours were registered. Several initiatives on process and outcome quality indicators for ablation of liver tumours have been started and will be used and published in the upcoming years.

Several limitations exist in the current form of the DHBA. For example, at this moment only patients who undergo treatment of liver tumours such as ablation or resection are registered. No information is available therefore on other treatment modalities such as radiotherapy or definitive chemotherapy. Therefore, no comparison of resection rates can be performed between hospitals or oncological networks. Furthermore, data is provided by surgeons themselves which might pose problems regarding validity of data. The data verification in 2018 provided insight in completeness and accuracy of data in the DHBA. Completeness was 97% in 2015 and accuracy of outcomes was 96%⁵³. Data verification should therefore be performed more often to check whether data validity is still adequate. DICA has initiated a program starting in 2021 in which data verification can be performed every 1-2 years for each registry.

What holds the future of the audit?

Adding value to the DHBA on both a national and international level can be achieved in the near future. After joining of interventional radiologists, both oncologists and radiation oncologists should consider to join the DHBA. This would be a huge step resulting in all treatment strategies for liver tumours to be included in the DHBA. Decreasing the high burden of registration in the DHBA should be a priority during expansion of the registry. The DHBA has started several audit-specific projects such as the initiation of standardised reports by radiologists and surgeons including a lot of DHBA items, the usage of standardised comorbidity (Charlson Comorbidity Index) and complications scores (Clavien-Dindo)⁵. The Scientific Committee of the DHBA is initiating a merge with the Dutch ColoRectal Audit (DCRA) to further decrease registration burden. This is due to the fact that 63% of patients in the DHBA are also registered in the DCRA. Also, DICA has initiated several larger projects such as a link between hospital files and

the DHBA using SNOMED CT coding and a link between the Dutch Pathology Database (PALGA) which will definitely decrease registration burden if this succeeds. However, merging hospital files and PALGA is challenging due to current Dutch and European law on privacy.

Other future aspects include the draft of new outcome quality indicators for both the surgical and interventional radiology section and to assess differences in outcomes on an international level. Several initiatives are worth mentioning here such as the start to draft of the composite quality indicator 'Textbook Outcome'. This quality indicator measures several aspects of care and therewith the ideal outcome. Textbook Outcome will be assessed for both surgery and ablation in the DHBA. Analyses regarding this composite outcome measure have started and will be presented shortly. Textbook Outcome however only reflects short-term quality of care. As the DHBA comprises of 90% of malignant liver tumours, the assessment of oncological outcomes is warranted. Since 2018, long-term parameters on disease-free and overall survival can be registered in the DHBA but registration is time-consuming. Moreover, after local treatment patients often return to the referring centre. Currently, several options are investigated by the DHBA Scientific Committee to overcome the registration burden that is associated with long-term oncological outcomes. Merging of the Dutch Government data on mortality to the DHBA has been realised in 2020. This marks a first step in decreasing registration burden for long-term outcomes and assessing overall survival of patients in the DHBA will therefore become possible. However, more promising is a merge between the Dutch Cancer Registry and the DHBA. This would mean that all oncological outcomes of patients in the DHBA will become available. However, this is a difficult merge between two highly appreciated associations in the Netherlands, but should be strived for.

As mentioned, assessing postoperative outcomes using DHBA data may improve outcomes on a national level. Comparing postoperative outcomes from the Netherlands to other countries to learn from each other can increase international value of the DHBA. Several countries such as the United States of America, Norway, Sweden and Denmark have national databases regarding outcomes after liver surgery. Options are explored to match the DHBA to these national databases on liver surgery and will be interesting to follow.

Conclusion

The DHBA is now a multidisciplinary audit containing data on perioperative treatment strategies for patients with liver tumours and associated outcomes. Clinical auditing and evaluation of current daily practice in liver surgery provides important information to improve quality of care. This thesis demonstrated that quality of care in Dutch hospitals is adequate on average. Significant variation between hospitals and oncological networks was observed. Recognising differences in perioperative treatment strategies and outcomes is the first step to improve quality of care. These insights should be discussed at a national level to initiate structural improvement measures. The effect of improvement measures can be monitored through the DHBA. In the near future, quality improvement can be initiated by drafting new quality indicators and continuous monitoring of existing quality indicators. To further improve care, collaboration of hospitals and oncological networks including centralisation of patients with highest risk of morbidity and mortality should be insisted on. In the future, the DHBA could better serve participating hospitals by providing tailored feedback, decreasing registration burden and initiation of sessions to address differences between hospitals and oncological networks on quality indicators in so-called 'Codman Sessions'.

References

1. Birkmeyer JD, Reames BN, McCulloch P, Carr AJ, Campbell WB, Wennberg JE. Understanding of regional variation in the use of surgery. *Lancet*. 2013;382(9898):1121-1129.
2. Nelson-Williams H, Gani F, Kilic A, Spolverato G, Kim Y, Wagner D, et al. Factors Associated With Interhospital Variability in Inpatient Costs of Liver and Pancreatic Resections. *JAMA Surg*. 2016;151(2):155-163.
3. Markar SR, Karthikesalingam A, Thrumurthy S, Low DE. Volume-outcome relationship in surgery for esophageal malignancy: systematic review and meta-analysis 2000-2011. *J Gastrointest Surg*. 2012;16(5):1055-1063.
4. van Heek NT, Kuhlmann KF, Scholten RJ, de Castro SM, Busch OR, van Gulik TM, et al. Hospital volume and mortality after pancreatic resection: a systematic review and an evaluation of intervention in the Netherlands. *Ann Surg*. 2005;242(6):781-788, discussion 788-790.
5. 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.
6. Asiyanbola B, Chang D, Gleisner AL, Nathan H, Choti MA, Schulick RD, et al. Operative mortality after hepatic resection: are literature-based rates broadly applicable? *J Gastrointest Surg*. 2008;12(5):842-851.
7. Eppsteiner RW, Csikesz NG, Simons JP, Tseng JF, Shah SA. High volume and outcome after liver resection: surgeon or center? *J Gastrointest Surg*. 2008;12(10):1709-1716; discussion 1716.
8. Filmann N, Walter D, Schadde E, Bruns C, Keck T, Lang H, et al. Mortality after liver surgery in Germany. *Br J Surg*. 2019;106(11):1523-1529.
9. Spolverato G, Ejaz A, Hyder O, Kim Y, Pawlik TM. Failure to rescue as a source of variation in hospital mortality after hepatic surgery. *Br J Surg*. 2014;101(7):836-846.
10. Baum P, Diers J, Lichthardt S, Kastner C, Schlegel N, Germer CT, et al. Mortality and Complications Following Visceral Surgery: A Nationwide Analysis Based on the Diagnostic Categories Used in German Hospital Invoicing Data. *Dtsch Arztebl Int*. 2019;116(44):739-746.
11. Ardito F, Famularo S, Aldrighetti L, Grazi GL, DallaValle R, Maestri M, et al. The Impact of Hospital Volume on Failure to Rescue after Liver Resection for Hepatocellular Carcinoma: Analysis from the HE.RC.O.LE.S. Italian Registry. *Ann Surg*. 2020;272(5):840-846.
12. Cieslak KP, Bennink RJ, de Graaf W, van Lienden KP, Besselink MG, Busch OR, et al. Measurement of liver function using hepatobiliary scintigraphy improves risk assessment in patients undergoing major liver resection. *HPB (Oxford)*. 2016;18(9):773-780.
13. Olthof PB, Aldrighetti L, Alikhanov R, Cescon M, Groot Koerkamp B, Jarnagin WR, et al. Portal Vein Embolization is Associated with Reduced Liver Failure and Mortality in High-Risk Resections for Perihilar Cholangiocarcinoma. *Ann Surg Oncol*. 2020;27(7):2311-2318.
14. Thomas G, Tahir MR, Bongers BC, Kallen VL, Slooter GD, van Meeteren NL. Prehabilitation before major intra-abdominal cancer surgery: A systematic review of randomised controlled trials. *Eur J Anaesthesiol*. 2019;36(12):933-945.
15. Dunne DF, Jack S, Jones RP, Jones L, Lythgoe DT, Malik HZ, et al. Randomized clinical trial of prehabilitation before planned liver resection. *Br J Surg*. 2016;103(5):504-512.
16. Berkel AEM, Bongers BC, Kotte H, Weltevreden P, de Jongh FHC, Eijsvogel MMM, et al. Effects of Community-based Exercise Prehabilitation for Patients Scheduled for Colorectal Surgery With High Risk for Postoperative Complications: Results of a Randomized Clinical Trial. *Ann Surg*. 2021.
17. Baltatzis M, Low R, Stathakis P, Sheen AJ, Siriwardena AK, Jamdar S. Efficacy and safety of pharmacological venous thromboembolism prophylaxis following liver resection: a systematic review and meta-analysis. *HPB (Oxford)*. 2017;19(4):289-296.
18. Sivesgaard K, Larsen LP, Sorensen M, Kramer S, Schlender S, Amanavicius N, et al. Diagnostic accuracy of CE-CT, MRI and FDG PET/CT for detecting colorectal cancer liver metastases in patients considered eligible for hepatic resection and/or local ablation. *Eur Radiol*. 2018;28(11):4735-4747.
19. Metser U, Halankar J, Langer D, Mohan R, Hussey D, Hadas M, et al. Effect of chemotherapy on the impact of FDG-PET/CT in selection of patients for surgical resection of colorectal liver metastases: single center analysis of PET-CAM randomized trial. *Ann Nucl Med*. 2017;31(2):153-162.

20. Patel S, McCall M, Ohinmaa A, Bigam D, Dryden DM. Positron emission tomography/computed tomographic scans compared to computed tomographic scans for detecting colorectal liver metastases: a systematic review. *Ann Surg*. 2011;253(4):666-671.
21. Lam VW, Spiro C, Laurence JM, Johnston E, Hollands MJ, Pleass HC, et al. A systematic review of clinical response and survival outcomes of downsizing systemic chemotherapy and rescue liver surgery in patients with initially unresectable colorectal liver metastases. *Ann Surg Oncol*. 2012;19(4):1292-1301.
22. Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *Lancet*. 2008;371(9617):1007-1016.
23. Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. *Lancet Oncol*. 2013;14(12):1208-1215.
24. Ayez N, van der Stok EP, de Wilt H, Radema SA, van Hillegersberg R, Roumen RM, et al. Neo-adjuvant chemotherapy followed by surgery versus surgery alone in high-risk patients with resectable colorectal liver metastases: the CHARISMA randomized multicenter clinical trial. *BMC Cancer*. 2015;15:180.
25. Duwe G, Knitter S, Pesthy S, Beierle AS, Bahra M, Schmelzle M, et al. Hepatotoxicity following systemic therapy for colorectal liver metastases and the impact of chemotherapy-associated liver injury on outcomes after curative liver resection. *Eur J Surg Oncol*. 2017;43(9):1668-1681.
26. Tamandl D, Klinger M, Eipeldauer S, Herberger B, Kaczirek K, Gruenberger B, et al. Sinusoidal obstruction syndrome impairs long-term outcome of colorectal liver metastases treated with resection after neoadjuvant chemotherapy. *Ann Surg Oncol*. 2011;18(2):421-430.
27. Kishi Y, Zorzi D, Contreras CM, Maru DM, Kopetz S, Ribero D, et al. Extended preoperative chemotherapy does not improve pathologic response and increases postoperative liver insufficiency after hepatic resection for colorectal liver metastases. *Ann Surg Oncol*. 2010;17(11):2870-2876.
28. Fukuoka K, Nara S, Honma Y, Kishi Y, Esaki M, Shimada K. Hepatectomy for Colorectal Cancer Liver Metastases in the Era of Modern Preoperative Chemotherapy: Evaluation of Postoperative Complications. *World J Surg*. 2017;41(4):1073-1081.
29. Simoneau E, Alanazi R, Alshenaifi J, Molla N, Aljiffry M, Medkhali A, et al. Neoadjuvant chemotherapy does not impair liver regeneration following hepatectomy or portal vein embolization for colorectal cancer liver metastases. *J Surg Oncol*. 2016;113(4):449-455.
30. Huiskens J, Bolhuis K, Engelbrecht MR, De Jong KP, Kazemier G, Liem MS, et al. Outcomes of Resectability Assessment of the Dutch Colorectal Cancer Group Liver Metastases Expert Panel. *J Am Coll Surg*. 2019;229(6):523-532 e522.
31. Huiskens J, van Gulik TM, van Lienden KP, Engelbrecht MR, Meijer GA, van Grieken NC, et al. Treatment strategies in colorectal cancer patients with initially unresectable liver-only metastases, a study protocol of the randomised phase 3 CAIRO5 study of the Dutch Colorectal Cancer Group (DCCG). *BMC Cancer*. 2015;15:365.
32. Dimick JB, Pronovost PJ, Cowan JA, Jr., Lipsett PA. Postoperative complication rates after hepatic resection in Maryland hospitals. *Arch Surg*. 2003;138(1):41-46.
33. Gilg S, Sparrelid E, Isaksson B, Lundell L, Nowak G, Stromberg C. Mortality-related risk factors and long-term survival after 4460 liver resections in Sweden-a population-based study. *Langenbecks Arch Surg*. 2017;402(1):105-113.
34. Vigano L, Ferrero A, Lo Tesoriere R, Capussotti L. Liver surgery for colorectal metastases: results after 10 years of follow-up. Long-term survivors, late recurrences, and prognostic role of morbidity. *Ann Surg Oncol*. 2008;15(9):2458-2464.
35. Russolillo N, Aldrighetti L, Cillo U, Guglielmi A, Ettorre GM, Giuliante F, et al. Risk-adjusted benchmarks in laparoscopic liver surgery in a national cohort. *Br J Surg*. 2020;107(7):845-853.
36. SONCOS. Preserving Quality of Care in the Netherlands. 2017.
37. van Amerongen MJ, van der Stok EP, Futterer JJ, Jenniskens SF, Moelker A, Grunhagen DJ, et al. Short term and long term results of patients with colorectal liver metastases undergoing surgery with or without radiofrequency ablation. *Eur J Surg Oncol*. 2016;42(4):523-530.

38. Philips P, Scoggins CR, Rostas JK, McMasters KM, Martin RC. Safety and advantages of combined resection and microwave ablation in patients with bilobar hepatic malignancies. *Int J Hyperthermia*. 2017;33(1):43-50.
39. Xourafas D, Pawlik TM, Ejaz A, Dillhoff M, Abdel-Misih S, Tsung A, et al. Impact of concomitant ablation on the perioperative outcomes of patients with colorectal liver metastases undergoing hepatectomy: a propensity score matched nationwide analysis. *HPB (Oxford)*. 2019;21(8):1079-1086.
40. Boudjema K, Locher C, Sabbagh C, Ortega-Deballon P, Heyd B, Bachellier P, et al. Simultaneous Versus Delayed Resection for Initially Resectable Synchronous Colorectal Cancer Liver Metastases: A Prospective, Open-label, Randomized, Controlled Trial. *Ann Surg*. 2021;273(1):49-56.
41. Jones TJ, Murphy AE, Tameron A, Hussain LR, Grannan K, Guend H, et al. Trends and Outcomes of Synchronous Resection of Colorectal Metastasis in the Modern Era-Analysis of Targeted Hepatic NSQIP Database. *J Surg Res*. 2019;238:35-40.
42. Snyder RA, Hao S, Irish W, Zervos EE, Tuttle-Newhall JE, Parikh AA. Thirty-Day Morbidity after Simultaneous Resection of Colorectal Cancer and Colorectal Liver Metastasis: American College of Surgeons NSQIP Analysis. *J Am Coll Surg*. 2020;230(4):617-627 e619.
43. Ghiasloo M, Pavlenko D, Verhaeghe M, Van Langenhove Z, Uyttebroek O, Berardi G, et al. Surgical treatment of stage IV colorectal cancer with synchronous liver metastases: A systematic review and network meta-analysis. *Eur J Surg Oncol*. 2020;46(7):1203-1213.
44. Beck N, van Bommel AC, Eddes EH, van Leersum NJ, Tollenaar RA, Wouters MW, et al. The Dutch Institute for Clinical Auditing: Achieving Codman's Dream on a Nationwide Basis. *Ann Surg*. 2020;271(4):627-631.
45. Elfrink A.K.E. KNFM, Grunhagen D.J., Klaase J.M. Factors associated with Failure to Rescue and impact on hospital variation: a nationwide cohort study. *Submitted*. 2021.
46. Elfrink AKE, van Zwet EW, Swijnenburg RJ, den Dulk M, van den Boezem PB, Mieog JSD, et al. Case-mix adjustment to compare nationwide hospital performances after resection of colorectal liver metastases. *Eur J Surg Oncol*. 2021;47(3 Pt B):649-659.
47. Olthof PB, Elfrink AKE, Marra E, Belt EJT, van den Boezem PB, Bosscha K, et al. Volume-outcome relationship of liver surgery: a nationwide analysis. *Br J Surg*. 2020;107(7):917-926.
48. Elfrink A.K.E. KNFM, Grunhagen D.J., Klaase J.M. Oncological networks for resection of colorectal liver metastases: differences and postoperative outcomes. *Submitted*. 2021.
49. Elfrink AKE, Kok NFM, van der Werf LR, Krul MF, Marra E, Wouters M, et al. Population-based study on practice variation regarding preoperative systemic chemotherapy in patients with colorectal liver metastases and impact on short-term outcomes. *Eur J Surg Oncol*. 2020;46(9):1742-1755.
50. Elfrink AKE, Nieuwenhuizen S, van den Tol MP, Burgmans MC, Prevoo W, Coolen MME, et al. Hospital variation in combined liver resection and thermal ablation for colorectal liver metastases and impact on short-term postoperative outcomes: a nationwide population-based study. *HPB (Oxford)*. 2020.
51. Elfrink AKE, Pool M, van der Werf LR, Marra E, Burgmans MC, Meijerink MR, et al. Preoperative imaging for colorectal liver metastases: a nationwide population-based study. *BJS Open*. 2020;4(4):605-621.
52. Krul MF, Elfrink A.K.E. KNFM, Grunhagen D.J., Klaase J.M. Simultaneous resection of primary colorectal tumour and synchronous liver metastases: a population-based study. *Submitted*. 2021.
53. van der Werf LR, Kok NFM, Buis CI, Grunhagen DJ, Hoogwater FJH, Swijnenburg RJ, et al. Implementation and first results of a mandatory, nationwide audit on liver surgery. *HPB (Oxford)*. 2019;21(10):1400-1410.

CHAPTER 13

SUMMARY

Summary

Optimising treatment and outcomes for patients with liver tumours includes quality assessment on a national and hospital level. Clinical auditing is considered to provide insight in daily practice and outcomes using benchmarked feedback information and is a tool to measure, evaluate, and improve quality of care. This thesis demonstrates current daily practice regarding the treatment of liver tumours in the Netherlands. Therewith, leads are provided to evaluate and improve quality of care for liver tumours. Population-based data from the nationwide Dutch Hepato Biliary Audit (DHBA) was used.

Part I. Quality assessment of liver surgery

In **Part I**, the current standards and outcomes after liver surgery for different indications is evaluated and provides insights in options to improve outcomes.

Chapter 2. Relationship between hospital volume and postoperative outcomes

The current annual volume requirement to perform liver surgery in the Netherlands is 20 resections per hospital. In this chapter, the association of annual number of performed liver resections and postoperative morbidity and mortality was evaluated. Overall major morbidity was 11.2% and mortality was 2.0%. Higher volume centres performed more major liver resections and more liver resections for hepatocellular carcinoma and biliary cancer. However, no association between hospital volume, and postoperative outcomes was observed after correction for patient demographics, disease burden, and treatment characteristics. This absent volume outcome relationship is likely due to the already advanced patient selection across lower and higher volume centres in regional collaborations.

Chapter 3. Failure to rescue after liver surgery

Failure to Rescue is a quality indicator defined as postoperative complications leading to mortality. It focuses on the management of complications rather than on complications themselves. Several risk factors for Failure to Rescue were defined such as higher age, American Society of Anesthesiologists score of 3 or higher, liver cirrhosis, resection of biliary cancer, and major liver resection. Overall Failure to Rescue was 19.1% in the Netherlands and uncorrected Failure to Rescue ranging between 0.0% and 50.0% between hospitals. After correction for patient demographics and disease burden, no significant hospital variation was observed. Postoperative liver failure, cardiac complications, and thromboembolic complications were most often the reason for Failure to Rescue. Conclusions drawn from this chapter are that

Failure to Rescue is influenced by patient demographics and disease burden. Prevention of postoperative liver failure, cardiac complications, and thromboembolic complications could lead to improvement of Failure to Rescue rates.

Chapter 4. Postoperative outcomes after liver surgery in the elderly

Due to the aging and more comorbid population in the Netherlands that undergo liver resection, insight in outcomes in older patients is needed ultimately leading to better preoperative selection and workup. This chapter assessed differences in outcomes between patients younger than 70 years, septuagenarians (between 70 and 80 years old) and octogenarians (80 years or older). Postoperative major morbidity and mortality were worse in septuagenarians and octogenarians as compared to younger patients. Interestingly, not liver-specific complications but cardiopulmonary complications were mainly responsible. Therefore, this chapter provides leads regarding perioperative patient optimisation to improve postoperative outcomes in the elderly patient.

Chapter 5. Comparison of laparoscopic and open resection of benign liver tumours

The role of liver resection of benign liver tumours is debated as risks for postoperative morbidity and mortality has to be weighed up against potential benefits. Resection occurs mainly for specific indications such as hepatocellular adenoma, haemangioma, and focal nodular hyperplasia. Laparoscopic liver resection has been described to decrease postoperative morbidity and mortality. In this chapter, risk factors for morbidity were assessed and a propensity score matched analysis was performed to evaluate the added value of laparoscopy for resection of benign liver tumours. Patients who were 65 years or older, had a history of liver disease or in whom major liver resection for benign liver tumours was performed were at risk for morbidity. Less overall morbidity occurred in the laparoscopic liver resection group, but other outcomes were not different between laparoscopic and open liver resection. These insights could aid patients and surgeons in shared-decision-making regarding resection of benign liver tumours. If technically feasible, the use of laparoscopy could help decrease overall morbidity.

Part II. Impact of hospital variation on outcomes after resection of colorectal liver metastases

In **Part II**, hospital variation regarding perioperative treatment of colorectal liver metastases (CRLM) and its impact on postoperative outcomes is demonstrated.

Chapter 6. Trends over time and between hospitals in the use of preoperative imaging

Current Dutch guidelines on the use of preoperative imaging for CRLM advice to perform a ceMRI before initiation of treatment. A PET-CT should only be performed to assess possible extrahepatic metastases. However, randomised controlled trials on these subjects are lacking and therefore the use of both modalities is under debate. In this chapter, the current daily practice regarding ceMRI and PET-CT in patients with CRLM in the Netherlands was assessed. A significant increase in the use of ceMRI between 2014 and 2018 was observed while the use of PET-CT decreased. Significant hospital variation was observed in the use of both imaging modalities. Therefore, there is need for randomised controlled trials in order to end the debate on which imaging modality should be used additionally to conventional CT. Also, current guidelines should incorporate a stepwise approach for CRLM based on these trials to decrease hospital variation resulting in comparable preoperative quality of care for CRLM patients.

Chapter 7. The use of preoperative chemotherapy and impact on outcomes

According to Dutch guidelines preoperative chemotherapy is only indicated in unresectable metastases. Also, chemotherapy is believed to result in higher morbidity as a result of damaged liver tissue. It was demonstrated that preoperative chemotherapy is used mainly in patients with more and larger CRLM, synchronous metastases, rectal cancer as primary tumour, and higher nodal stage of the primary tumour. Patients who were older or had more comorbidity were less likely to receive preoperative chemotherapy. Both unadjusted hospital variation and case-mix corrected hospital variation in the use of preoperative chemotherapy was observed in the Netherlands. Interestingly, no effect of preoperative chemotherapy on postoperative outcomes were found. Therefore, this chapter unveils the need for strict resectability criteria and guidelines for the use of preoperative chemotherapy in patients with CRLM to decrease hospital variation and further studies are needed to assess the influence on outcomes.

Chapter 8. Comparing hospital performances using case-mix correction

Quality indicators such as 30-day major morbidity and 30-day mortality are currently used in the DHBA to assess postoperative outcomes after resection of CRLM. In this chapter, it was demonstrated that differences in hospital performance can be a result of the case-mix which relies on patient demographics and disease burden in a certain hospital. These differences in case-mix proved to be significantly different between Dutch hospitals performing liver surgery. Based on the case-mix model provided in this chapter for both outcomes, expected outcomes were also significantly different between hospitals. Expected 30-day major morbidity ranged between 6.4% and 11.9% and expected 30-day mortality ranged between 0.6% and 2.9%.

However, it was shown that after correction for case-mix no outliers regarding hospital performance were observed. This emphasises that case-mix adjustment is a prerequisite in order to properly compare postoperative outcomes between hospitals.

Chapter 9. Oncological networks

As observed in Chapter 8, differences in case-mix were significant between Dutch hospitals. During centralisation of liver surgery, oncological networks consisting of at least one tertiary referral centre and several regional hospitals were established to optimise treatment and outcomes of CRLM resection. Differences between the seven oncological networks in the Netherlands regarding patient demographics, disease burden and outcomes were assessed in this study compared to on a hospital level. These differences were demonstrated to be smaller on an oncological network level as compared to on a hospital level. This resulted from procedural volumes, topographical orientation and inclusion of both tertiary referral centres and several regional hospitals in the different oncological networks. Therefore, auditing on an oncological network level instead of on a hospital level should be pursued. There are still significant differences in case-mix and treatment between oncological networks. Nationwide agreements on these topics between oncological networks are needed to further decrease treatment variation and outcomes.

Chapter 10. Combining liver resection with thermal ablation

Parenchymal-sparing liver surgery is believed to increase resectability of CRLM due to larger future liver remnant. Several methods of parenchymal-sparing surgery have been established such as combining liver resection with thermal ablation. However, current guidelines do not provide sufficient guidance to support this combination and evidence regarding outcomes are scarce. In this chapter, the unadjusted and case-mix corrected use of combined liver resection and thermal ablation between Dutch hospitals was evaluated. Significant hospital variation was observed which is a result of lacking guidelines and evidence. It was also demonstrated that the combination of liver resection and thermal ablation is more often used in patients with bilobar CRLM and more than 4 CRLM. The propensity-score-matched analysis showed better postoperative outcomes in the combined resection and ablation group due to avoidance of major liver resection. Therefore, this combination seems safe with regards to postoperative outcomes. Randomised trials are needed to assess long-term outcomes eventually resulting in strict best-practice guidelines on the use of liver resection combined with thermal ablation.

Chapter 11. Simultaneous resection of primary colorectal tumour and liver metastases

Resection of the primary colorectal tumour and synchronous liver metastases in one surgical session is increasingly performed as this results in timely management of both tumour sites and might decrease costs. However, these types of simultaneous resections should only be performed in easy-to-resect primary tumour and limited liver metastases according to international guidelines. This chapter described patient demographics and disease burden in which Dutch surgeons perform these simultaneous resections, hospital variation regarding this treatment strategy, and postoperative outcomes. It was demonstrated that simultaneous resection was omitted in patients with pre-existing liver pathology, rectal primary tumours, more than 4 or larger CRLM or who received preoperative chemotherapy. Both unadjusted and case-mix corrected rates of simultaneous resection of the colorectal tumour and liver metastases were significantly different between Dutch hospitals as a result of lacking guidelines. Postoperative outcomes were similar in the Netherlands compared to earlier studies. Future studies should provide a fair comparison of both postoperative and oncological outcomes in order to pursue evidence-based use of simultaneous resection of the colorectal tumour and synchronous liver metastases.

APPENDICES

DUTCH SUMMARY / NEDERLANDSE SAMENVATTING

LIST OF PUBLICATIONS

PHD PORTFOLIO

ACKNOWLEDGEMENTS / DANKWOORD

ABOUT THE AUTHOR

DUTCH SUMMARY /
NEDERLANDSE SAMENVATTING

Dutch summary / Nederlandse samenvatting

Primaire en secundaire levertumoren komen vaak voor in Nederland. In 2019 zijn er ongeveer 1000 leverresecties en 500 thermale ablaties voor levertumoren uitgevoerd. Dit gebeurt in ongeveer 63% van de gevallen in verband met colorectale levermetastasen (CRLM). Andere levertumoren die worden behandeld in Nederland zijn hepatocellulaire carcinomen (16%), metastasen van een andere origine (8%) en galwegtumoren (7%).

In het gehele perioperatieve traject van de behandeling bestaan er keuzes voor zowel de patiënt als de behandelaar als het gaat om het uitvoeren van beeldvorming of het kiezen van een behandelstrategie. Het evalueren van de behandeling en uitkomsten van patiënten met levertumoren geeft inzicht in de kwaliteit van zorg op nationaal- en ziekenhuisniveau. Dit proces wordt 'Clinical Auditing' genoemd en zorgt voor inzichten in behandelstrategieën en uitkomsten uit de dagelijkse praktijk door gebruik te maken van geijkte feedback informatie. Het meten van uitkomsten en evalueren van behandelingen zorgt voor aanknopingspunten om de kwaliteit van zorg verbeteren.

De 'Dutch Hepato Biliary Audit' (DHBA) is in 2013 opgericht om de kwaliteit van chirurgische resectie van levertumoren te monitoren. Sinds 2018 wordt daarnaast ook de kwaliteit van thermale ablaties in kaart gebracht middels de DHBA. Het monitoren van de kwaliteit van zorg gebeurt met kwaliteitsindicatoren, welke vooraf worden vastgesteld. Uitkomsten van deze kwaliteitsindicatoren worden teruggekoppeld aan de ziekenhuizen, en eenmaal per jaar openbaar gemaakt.

In dit proefschrift wordt de dagelijkse praktijk van de behandeling van levertumoren in Nederland geëvalueerd en worden manieren aangedragen om de kwaliteit van zorg verder te verbeteren. Daarnaast worden er aanknopingspunten gegeven om de uitkomsten van de behandeling van levertumoren te verbeteren.

Deel I. Beoordeling van de kwaliteit van leverchirurgie

In Deel I van dit proefschrift worden de huidige standaarden en daaraan gelieerde uitkomsten na leverchirurgie voor verschillende levertumoren geëvalueerd. Daarnaast worden in dit deel van het proefschrift verschillende inzichten aangedragen om de uitkomsten te verbeteren.

Hoofdstuk 2. De relatie tussen ziekenhuisvolume en postoperatieve uitkomsten

De huidige volumenorm voor leverchirurgie ligt in Nederland op 20 leverresecties per ziekenhuis per jaar. In dit hoofdstuk wordt de relatie tussen ziekenhuisvolume en postoperatieve uitkomsten zoals ernstige complicaties (Clavien-Dindo $\geq 3a$) en mortaliteit geëvalueerd. In Nederland kwamen ernstige complicaties na 11.2% van alle leverresecties voor en was de mortaliteit 2%. In hoog-volume ziekenhuizen bleken majeure leverresecties en leverresecties vanwege hepatocellulaire carcinomen of galwegcarcinoom vaker te worden uitgevoerd. Er was echter geen relatie tussen ziekenhuisvolume en postoperatieve uitkomsten na correctie voor patiënt-, tumor- en behandelkenmerken. De afwezige relatie tussen ziekenhuisvolume en postoperatieve uitkomsten kan te verklaren te zijn door de goede patiëntselectie in hoog- en laagvolume centra en de verwijspatronen die er op regionaal niveau zijn in Nederland.

Hoofdstuk 3. 'Failure to Rescue' na leverchirurgie

Failure to Rescue is een kwaliteitsindicator die gedefinieerd is als een zware postoperatieve complicatie (Clavien-Dindo $\geq 3a$) die leidt tot overlijden. Deze kwaliteitsindicator evalueert met name de behandeling van complicaties. Verschillende risicofactoren voor Failure to Rescue werden gevonden zoals hoge leeftijd, ASA score van 3 of hoger, levercirrose, resectie in verband met galwegcarcinoom en majeure leverresectie. Gemiddeld was het Failure to Rescue percentage in Nederland 19% met een spreiding van 0% tot 50% tussen ziekenhuizen. Na correctie voor patiënt- en tumorkenmerken bleek er geen significante ziekenhuisvariatie wat betreft Failure to Rescue. Postoperatief leverfalen, cardiale complicaties en trombo-embolische complicaties waren geassocieerd met het optreden van Failure to Rescue. Concluderend is het optreden van Failure to Rescue geassocieerd met patiënt- en tumorkenmerken en kan het tegengaan en tijdig herkennen van leverfalen, cardiale complicaties en trombo-embolische complicaties vermoedelijk leiden tot het verlagen van Failure to Rescue.

Hoofdstuk 4. Postoperatieve uitkomsten na leverchirurgie bij oudere patiënten

Patiënten die een leverresectie ondergaan in Nederland worden steeds ouder en hebben meer comorbiditeit. Daarom is het belangrijk om postoperatieve uitkomsten inzichtelijk te maken in oudere patiënten wat kan leiden tot een betere preoperatieve patiëntselectie en optimalisatie voor een leverresectie. In dit hoofdstuk worden de postoperatieve uitkomsten beschreven van patiënten die jonger dan 70 jaar oud waren, patiënten die tussen de 70 en 80 jaar oud waren en patiënten die 80 jaar of ouder waren. Postoperatieve ernstige complicaties en sterfte komen meer voor onder zeventig- en tachtigjarigen dan onder patiënten die jonger waren dan 70. Dit wordt met name door cardiopulmonale complicaties veroorzaakt. Verbeteracties gericht op het

verminderen van cardiopulmonale complicaties door een betere patiëntselectie en preoperatieve optimalisatie kunnen bijdragen aan het verminderen van complicaties en mortaliteit in oudere patiënten.

Hoofdstuk 5. Laparoscopische en open resectie van benigne levertumoren

Bij de afweging om benigne levertumoren te verwijderen gaat het om de balans tussen chirurgische complicaties en mortaliteit enerzijds en voordelen van het verwijderen van de benigne levertumor anderzijds. Resectie wordt vaak uitgevoerd in verband met een hepatocellulair adenoom, hemangioom of focale nodulaire hyperplasie. Het uitvoeren van een laparoscopische leverresectie gaat gepaard met minder postoperatieve complicaties en mortaliteit. In dit hoofdstuk worden de risicofactoren voor postoperatieve complicaties beschreven en de toegevoegde waarde van laparoscopische leverresectie bij benigne levertumoren onderzocht. Patiënten die 65 jaar of ouder waren, leverziekte(n) in de voorgeschiedenis hadden of een majeure leverresectie ondergingen bleken grotere kans op postoperatieve complicaties te hebben. Er bleken minder complicaties op te treden bij laparoscopisch geopereerde patiënten. Deze inzichten kunnen patiënten en chirurgen helpen in het nemen van een beslissing aangaande resectie van een benigne levertumor.

Deel II. Invloed van ziekenhuisvariatie op uitkomsten na resectie van colorectale levermetastasen

In Deel II van het proefschrift wordt de ziekenhuisvariatie aangaande perioperatieve behandeling van colorectale levermetastasen (CRLM) uiteengezet en de invloed daarvan op postoperatieve uitkomsten.

Hoofdstuk 6. Variatie in het gebruik van preoperatieve beeldvorming over de tijd en tussen ziekenhuizen

De huidige Nederlandse richtlijn omtrent preoperatieve beeldvorming voor colorectale levermetastasen (CRLM) adviseert om een Magnetic Resonance Imaging (MRI)-scan uit te voeren alvorens te starten met de behandeling. Een Positron Emissie Tomografie Computed Tomographie (PET-CT) scan dient alleen uitgevoerd te worden voor het in kaart brengen van eventuele extrahepatische metastasering. Resultaten van randomised controlled trials zijn echter tegenstrijdig. Derhalve is er geen consensus betreffende het gebruik van preoperatieve beeldvorming. In dit hoofdstuk wordt de dagelijkse praktijk aangaande het gebruik van MRI en PET-CT bij patiënten met CRLM in Nederland geëvalueerd. Tussen 2014 en 2018 werd steeds vaker een MRI gemaakt maar het gebruik van de PET-CT nam af. Tussen de ziekenhuizen was

er aanzienlijke variatie in het gebruik van beide typen beeldvorming. Het is gewenst om in de toekomst op basis van studies met een betere kwaliteit een uitspraak te kunnen doen welke beeldvorming er naast een conventionele CT gebruikt dient te worden bij patiënten met CRLM. Consensus zal de aangetoonde ziekenhuisvariatie verminderen. Uiteindelijk zal dit leiden tot vergelijkbare preoperatieve beeldvorming voor patiënten met CRLM in Nederland, onafhankelijk van het ziekenhuis waar de patiënt behandeld wordt.

Hoofdstuk 7. Het gebruik van preoperatieve chemotherapie en invloed op uitkomsten

Preoperatieve chemotherapie bij patiënten met colorectale levermetastasen (CRLM) wordt in Nederland alleen geadviseerd bij patiënten waarbij leverresectie niet mogelijk is door uitgebreide metastasering. Een reden om af te zien van preoperatieve chemotherapie is dat dit invloed heeft op het leverparenchym, met slechtere postoperatieve uitkomsten tot gevolg. In dit hoofdstuk wordt beschreven dat preoperatieve chemotherapie met name gebruikt wordt in Nederland bij patiënten met meerdere of grotere metastasen, synchrone metastasering, een primaire rectale tumor en hoger klierstadium van de primaire tumor. Er wordt minder vaak gekozen voor preoperatieve chemotherapie bij oudere patiënten of patiënten met veel comorbiditeit. Daarnaast is er ongecorrigeerde en gecorrigeerde ziekenhuisvariatie in het gebruik van preoperatieve chemotherapie in Nederland. In tegenstelling tot eerdere studies is er echter geen invloed van preoperatieve chemotherapie op postoperatieve uitkomsten. Dit hoofdstuk laat zien dat er duidelijke criteria omtrent resectabiliteit opgesteld dienen te worden. Een duidelijke richtlijn omtrent het gebruik van preoperatieve chemotherapie bij patiënten met CRLM is noodzakelijk. Dit zal leiden tot een afname van de huidige ziekenhuisvariatie. Grotere studies zijn noodzakelijk om de invloed van preoperatieve chemotherapie op (postoperatieve) uitkomsten te onderzoeken.

Hoofdstuk 8. Vergelijken van ziekenhuisprestaties middels case-mix correctie

Kwaliteitsindicatoren zoals 30-dagen ernstige complicaties en 30-dagen mortaliteit worden op dit moment gebruikt in de DHBA om postoperatieve uitkomsten na resectie van colorectale levermetastasen (CRLM) te vergelijken op landelijk niveau. In dit hoofdstuk is aangetoond dat ziekenhuisvariatie in deze kwaliteitsindicatoren een gevolg kan zijn van de 'case-mix' van een ziekenhuis. De case-mix is gebaseerd op de populatie van een ziekenhuis en de bijhorende patiënt- en tumorkenmerken. De verschillen in case-mix tussen Nederlandse ziekenhuizen bleek significant verschillend. Gebaseerd op het case-mix model dat in dit hoofdstuk wordt gepresenteerd bleken daarnaast de verwachte uitkomsten significant te verschillen tussen ziekenhuizen. De verwachte 30-dagen ernstige complicaties varieerde van 6.4% tot 11.9% en

de verwachte 30-dagen mortaliteit varieerde van 0.6% tot 2.9%. Na case-mix correctie bleken er echter geen positieve en negatieve uitschieters als het gaat om prestaties van de verschillende ziekenhuizen. Dit benadrukt dat corrigeren voor case-mix noodzakelijk is bij het vergelijken van ziekenhuisprestaties aangaande resectie van CRLM.

Hoofdstuk 9. Oncologische netwerken

Verschillen in case-mix tussen ziekenhuizen zoals beschreven in hoofdstuk 8 zijn het gevolg van de centralisatie van leverchirurgie in Nederland. Tijdens deze centralisatie zijn er zeven oncologische netwerken vastgesteld welke opgebouwd zijn uit ten minste één tertiair verwijscentrum en verschillende regionale ziekenhuizen. Het doel van deze oncologische netwerken is het optimaliseren van de behandeling en uitkomsten na leverresectie voor colorectale levermetastasen (CRLM). In dit hoofdstuk worden de verschillen in case-mix tussen de zeven oncologische netwerken onderzocht en vergeleken met verschillen in case-mix op ziekenhuisniveau. Op oncologisch netwerkniveau waren de verschillen in case-mix en uitkomsten aanzienlijk kleiner. Dit is waarschijnlijk het gevolg van de grote procedurele volumes, de topografische oriëntatie en de inclusie van zowel tertiaire en regionale centra in oncologische netwerken. Het lijkt beter om te auditen op netwerkniveau in plaats van op ziekenhuisniveau. Om de variatie in case-mix, behandeling en uitkomsten tussen netwerken verder te verkleinen zijn er afspraken nodig binnen en tussen de oncologische netwerken.

Hoofdstuk 10. Combineren van leverresectie met thermale ablatie

Parenchym sparende behandeling van levertumoren vergroot de kansen op een succesvolle resectie als gevolg van de grotere hoeveelheid leverparenchym die overblijft na de operatie. Verschillende methoden van parenchym sparende leverresectie zijn geïntroduceerd zoals het combineren van leverresectie met thermale ablatie. In de huidige richtlijn voor colorectale levermetastasen (CRLM) is echter geen advies over parenchym sparende leverresectie opgenomen. Verschillende studies hebben namelijk geen eenduidig beeld kunnen schetsen als het gaat om postoperatieve en oncologische uitkomsten van de combinatie van leverresectie met thermale ablatie. In dit hoofdstuk wordt de variatie in het gebruik van de combinatie van leverresectie met thermale ablatie in ziekenhuizen in Nederland beschreven alsmede ook de postoperatieve uitkomsten van deze techniek. Er bleek aanzienlijke variatie op ziekenhuisniveau vanwege de op dit moment afwezige adviezen ten aanzien van het gebruik van leverresectie en thermale ablatie in de richtlijn. Het bleek dat de combinatie van leverresectie met thermale ablatie in Nederland met name gebruikt wordt bij patiënten met bilobaire ziekte of patiënten met meer dan 4 metastasen. Postoperatieve uitkomsten waren

beter na het uitvoeren van gecombineerde leverresectie met thermale ablatie door het minder vaak verrichten van een majeure leverresectie. Verder gerandomiseerd onderzoek is noodzakelijk om een uitspraak te kunnen doen over oncologische uitkomsten. Hierna zal een duidelijk standpunt omtrent het gebruik van gecombineerde leverresectie en thermale ablatie kunnen worden geformuleerd en kan dit worden opgenomen in de Nederlandse richtlijn.

Hoofdstuk 11. Simultane resectie van de primaire colorectale tumor en levermetastasen

Het reseceren van de primaire colorectale tumor en synchrone levermetastasen in één operatiesessie wordt steeds frequenter uitgevoerd om zo tot tijdige behandeling van alle tumoren te komen. Daarnaast zou het uitvoeren van een gelijktijdige resectie de impact op de patiënt verminderen en zou het de kosten van de behandeling omlaag kunnen brengen. Op dit moment wordt in internationale richtlijnen een gelijktijdige resectie van de colorectale tumor en synchrone levermetastasen alleen geadviseerd bij een gemakkelijk te reseceren primaire colorectale tumor en een beperkt aantal levermetastasen. In dit hoofdstuk worden patiënt- en tumorfactoren beschreven die in Nederland bijdragen aan de keuze om een gelijktijdige resectie uit te voeren, de ziekenhuisvariatie in de gelijktijdige resecties en postoperatieve uitkomsten. Het bleek dat Nederlandse chirurgen ervoor kiezen om minder frequent een gelijktijdige resectie uit te voeren bij patiënten met leverziekten in de voorgeschiedenis, een primaire rectale tumor, bij meer dan 4 levermetastasen en bij patiënten die preoperatieve chemotherapie hebben ondergaan. Daarnaast bleek er significante ziekenhuisvariatie in het uitvoeren van de gelijktijdige resecties. Dit kan deels verklaard worden door afwezigheid van een eenduidig advies omtrent het uitvoeren van gelijktijdige resecties. De postoperatieve uitkomsten in Nederland waren vergelijkbaar met de resultaten van eerdere studies. In de toekomst is het nodig om tot een eenduidig advies over de simultane resectie van primaire colorectale tumor en levermetastasen te komen.

Conclusie

De DHBA is een multidisciplinaire audit die informatie bevat over perioperatieve behandelstrategieën van patiënten met levertumoren in Nederland en de daaraan gelieerde uitkomsten. Clinical auditing en het evalueren van de dagelijkse praktijk geeft belangrijke informatie om de kwaliteit van zorg voor deze patiënten te verbeteren.

In dit proefschrift wordt beschreven dat de kwaliteit van zorg in Nederlandse ziekenhuizen voor patiënten met levertumoren goed is. Er is echter wel significante variatie op ziekenhuis- en op oncologisch netwerkniveau als het gaat om perioperatieve behandeling van levertumoren en uitkomsten. Het inzichtelijk maken van deze verschillen in behandeling en uitkomsten is de eerste stap in het verbeteren van de kwaliteit van zorg voor patiënten met levertumoren. De resultaten beschreven in dit proefschrift zullen op nationaal niveau besproken worden. Dat zou moeten leiden tot verbetertrajecten. De DHBA kan gebruikt worden om de uitkomsten van de verbetertrajecten te evalueren en monitoren middels bestaande kwaliteitsindicatoren.

Verder zal de kwaliteit van zorg verbeteren als gevolg van een nauwere samenwerking tussen ziekenhuizen binnen oncologische netwerken door zogenaamde hoog-risico patiënten en behandelingen verder te centraliseren in gespecialiseerde centra. Daarnaast zullen de laag-risico patiënten minder vaak in de hoog gespecialiseerde centra behandeld moeten worden. De DHBA kan zich verder ontwikkelen door participerende ziekenhuizen beter inzicht te geven in hun uitkomsten, het verlagen van de registratielast en door het aansturen op zogenaamde 'Codman Sessions'. In deze sessies zullen chirurgen en interventieradiologen hun uitkomsten bespreken en de discussie met elkaar aangaan om zo de kwaliteit van zorg voor patiënten met levertumoren te verbeteren.

LIST OF PUBLICATIONS

List of publications

Case-mix adjustment to compare hospital performances after hip fracture surgery

Würdemann FS, [Elfrink AKE](#), Wildschut JA, van den Brand CL, Schipper IB, Hegeman JH; the Dutch Hip Fracture Audit Group. Submitted.

The impact of performing gastric cancer surgery during holiday periods. A population-based study using Dutch Upper Gastrointestinal Cancer Audit (DUCA) data.

Voeten DM, [Elfrink AKE](#), Gisbertz SS, Ruurda JP, van Hillegersberg R, van Berge Henegouwen MI; Dutch Upper GI Cancer (DUCA) Audit Group. Submitted.

Oncological networks for resection of colorectal liver metastases: differences and postoperative outcomes

[Elfrink AKE](#), Kok NFM, Swijnenburg RJ, den Dulk M, van den Boezem PB, Hartgrink HH, te Riele WW, Leclercq WKG, Lips DJ, Ayez N, Verhoef C, Kuhlmann KFD, Buis CI, Bosscha K, Belt EJT, Vermaas M, Oosterling SJ, Eker HH, Marsman HA, Kazemier G, Wouters MWJM, Grünhagen DJ, Klaase JM; Dutch Hepato Biliary Audit Group. In press European Journal of Surgical Oncology.

Case-mix adjustment to compare colonoscopy performance between endoscopy services: a nationwide cohort study

Nass KJ, van der Vlugt M, [Elfrink AKE](#), van den Brand CL, Ledeboer M, van der Schaar PJ, van Esch AAJ, van der Beek A, Hummel T, Lacle M, van Leerdam ME, Ouwendijk RJT, Spaander VMCW, Verhagen MAMT, Wildschut JA, Fockens P, Dekker E, Wouters MWJM. In press Endoscopy.

Hospital variation and outcomes of simultaneous resection of primary colorectal tumour and liver metastases: a population-based study.

Krul MF, [Elfrink AKE](#), Buis CI, Swijnenburg RJ, Te Riele WW, Verhoef C, Gobardhan PD, Dulk MD, Liem MSL, Tanis PJ, Mieog JSD, van den Boezem PB, Leclercq WKG, Nieuwenhuijs VB, Gerhards MF, Klaase JM, Grünhagen DJ, Kok NFM, Kuhlmann KFD; Collaborators; Dutch Hepato Biliary Audit Group. HPB (Oxford). 2021 Jul 10:S1365-182X(21)00604

Impact of weekday of surgery on short-term outcomes after minimally invasive oncologic upper-gastrointestinal surgery: a nationwide cohort study

Voeten DM, Elfrink AKE, Gisbertz SS, Ruurda JP, van Hillegersberg R, van Berge Henegouwen MI; Dutch Upper GI Cancer (DUCA) Audit Group. World J Surg. 2021 May 25. doi: 10.1007/s00268-021-06160-x.

Prognostic factors for failure to rescue after liver resection and impact on hospital variation: a nationwide population-based study

Elfrink AKE, Olthof PB, Swijnenburg RJ, den Dulk M, de Boer MT, Mieog JSD, Hagendoorn J, Kazemier G, van den Boezem PB, Rijken AM, Liem MSL, Leclercq WKG, Kuhlmann KFD, Marsman HA, Ijzermans JNM, van Duijvendijk P, Erdmann JI, Kok NFM, Grünhagen DJ, Klaase JM; Dutch Hepato Biliary Audit Group; Collaborators. HPB (Oxford). 2021 Apr 30:S1365-182X(21)00120-9.

Short-term postoperative outcomes after liver resection in the elderly patient: a nationwide population-based study

Elfrink AKE, Kok NFM, den Dulk M, Buis CI, Kazemier G, Ijzermans JNM, Lam HD, Hagendoorn J, van den Boezem PB, Ayez N, Zonderhuis BM, Lips DJ, Leclercq WKG, Kuhlmann KFD, Marsman HA, Verhoef C, Patijn GA, Grünhagen DJ, Klaase JM; Dutch Hepato Biliary Audit Group. HPB (Oxford). 2021 Mar 19:S1365-182X(21)00067-8.

Surgical Outcomes of Laparoscopic and Open Resection of Benign Liver Tumours in the Netherlands: a Nationwide Analysis

Elfrink AKE, Haring MPD, de Meijer VE, Ijzermans JNM, Swijnenburg RJ, Braat AE, Erdmann JI, Terkivatan T, te Riele WW, van den Boezem PB, Coolen MME, Leclercq WKG, Lips DJ, de Wilde RF, Kok NFM, Grünhagen DJ, Klaase JM; Dutch Hepato Biliary Audit Group. HPB (Oxford). 2020 Dec 29:S1365-182X(20)32399-6.

Hospital variation in combined liver resection and thermal ablation for colorectal liver metastases and impact on short-term postoperative outcomes: a nationwide population-based study

Elfrink AKE, Nieuwenhuizen S, van den Tol MP, Burgmans MC, Prevoo W, Coolsen MME, van den Boezem PB, van Delden OM, Hagendoorn J, Patijn GA, Leclercq WKG, Liem MSL, Rijken AM, Verhoef C, Kuhlmann KFD, Ruiter SJS, Grünhagen DJ, Klaase JM, Kok NFM, Meijerink MR, Swijnenburg RJ; Dutch Hepato Biliary Audit Group. HPB (Oxford). 2020 Nov 17:S1365-182X(20)31189-8.

Case-mix adjustment to compare nationwide hospital performances after resection of colorectal liver metastases.

Elfrink AKE, van Zwet EW, Swijnenburg RJ, den Dulk M, van den Boezem PB, Mieog JSD, Te Riele WW, Patijn GA, Leclercq WKG, Lips DJ, Rijken AM, Verhoef C, Kuhlmann KFD, Buis CI, Bosscha K, Belt EJT, Vermaas M, van Heek NT, Oosterling SJ, Torrens H, Eker HH, Consten ECJ, Marsman HA, Wouters MWJM, Kok NFM, Grünhagen DJ, Klaase JM; Dutch Hepato Biliary Audit Group. Eur J Surg Oncol. 2021 Mar;47(3 Pt B):649-659.

Population-based study on practice variation regarding preoperative systemic chemotherapy in patients with colorectal liver metastases and impact on short-term outcomes.

Elfrink AKE, Kok NFM, van der Werf LR, Krul MF, Marra E, Wouters MWJM, Verhoef C, Kuhlmann KFD, den Dulk M, Swijnenburg RJ, Te Riele WW, van den Boezem PB, Leclercq WKG, Lips DJ, Nieuwenhuijs VB, Gobardhan PD, Hartgrink HH, Buis CI, Grünhagen DJ, Klaase JM; Dutch Hepato Biliary Audit Group; Collaborators. Eur J Surg Oncol. 2020 Sep;46(9):1742-1755.

Volume-outcome relationship of liver surgery: a nationwide analysis.

Olthof PB*, Elfrink AKE*, Marra E, Belt EJT, van den Boezem PB, Bosscha K, Consten ECJ, den Dulk M, Gobardhan PD, Hagendoorn J, van Heek TNT, IJzermans JNM, Klaase JM, Kuhlmann KFD, Leclercq WKG, Liem MSL, Manusama ER, Marsman HA, Mieog JSD, Oosterling SJ, Patijn GA, Te Riele W, Swijnenburg RJ, Torrens H, van Duijvendijk P, Vermaas M, Kok NFM, Grünhagen DJ; Dutch Hepato Biliary Audit Group. *Shared author contributions. Br J Surg. 2020 Jun;107(7):917-926.

Preoperative imaging for colorectal liver metastases: a nationwide population-based study.

Elfrink AKE, Pool M, van der Werf LR, Marra E, Burgmans MC, Meijerink MR, den Dulk M, van den Boezem PB, Te Riele WW, Patijn GA, Wouters MWJM, Leclercq WKG, Liem MSL, Gobardhan PD, Buis CI, Kuhlmann KFD, Verhoef C, Besselink MG, Grünhagen DJ, Klaase JM, Kok NFM; the Dutch Hepato-Biliary Audit Group. BJS Open. 2020 Aug;4(4):605-621.

Transanal total mesorectal excision (TaTME) for rectal cancer: effects on patient-reported quality of life and functional outcome.

Koedam TW, van Ramshorst GH, Deijen CL, Elfrink AKE, Meijerink WJ, Bonjer HJ, Sietses C, Tuynman JB. Tech Coloproctol. 2017 Jan;21(1):25-33.

Intracorporeal versus extracorporeal anastomosis in right hemicolectomy: a systematic review and meta-analysis.

van Oostendorp S, Elfrink AKE, Borstlap W, Schoonmade L, Sietses C, Meijerink J, Tuynman J. Surg Endosc. 2017 Jan;31(1):64-77.

Results of long-term retrograde rectal cleansing in patients with constipation or fecal incontinence.

Vollebregt PF, Elfrink AKE, Meijerink WJ, Felt-Bersma RJ. Tech Coloproctol. 2016 Sep;20(9):633-9.

Previous thesis from the UMCG Research Institute SHARE

Bosáková L

Breaking the cycle of poverty; routes to counteract intergenerational transmission of socioeconomic health differences
(*prof SA Reijneveld, prof A Madarasová-Gecková*)

Vendeloo SN van

Optimizing learning environments and resident well-being in postgraduate medical education
(*prof PLP Brand, prof SK Bulstra, dr CCPM Verheyen*)

Sampurna MTA

Improving the management of hyperbilirubinemia in a limited-resource area
(*prof AF Bos, dr CV Hulzebos, dr PH Dijk, dr R Etika*)

Siswanto JE

Retinopathy of prematurity; how to prevent retinopathy of prematurity in preterm infants in Indonesia?
(*prof AF Bos, prof A Adisasmita, dr PH Dijk*)

Kaper MS

Improving communication in healthcare for patients with low health literacy; building competencies of health professionals and shifting towards health literacy friendly organizations
(*prof SA Reijneveld, prof AF de Winter*)

Schuurmans J

Population-based expanded carrier screening reporting couple results only: a mixed methods approach
(*prof IM van Langen, prof AM Lucassen, prof AV Ranchor, dr M Plantinga*)

Vrijsen J

Towards dementia risk reduction among individuals with a parental family history of dementia
(*dr N Smidt, prof SEJA de Rooij*)

Dams AC

Achilles tendon rupture; current clinical practice, imaging and outcome
(*prof RL Diercks, prof J Zwerver, dr I van den Akker-Scheek, dr I Reininga*)

Buitenhuis AH

It takes two: the role of a non-smoking partner in a quit attempt; a look at dyadic planning and daily interactions
(*prof M Hagedoorn, dr MA Tuinman*)

Minh A

Mental health, education and work in Canada, the Netherlands, and the United States; a comparative, life course investigation
(*prof U Bültmann, dr CB McLeod, prof SA Reijneveld, dr M Guhn*)

Marcus-Varwijk AE

Perspectives on health and health promotion in community-dwelling older people; a mixed-methods study
(*prof JPJ Slaets, prof AV Ranchor, dr CHM Smits, dr TLS Visscher*)

Bochane MI

Uniform screening for atypical language development in Dutch child health care
(*prof CP van der Schans, prof SA Reijneveld, dr MR Luinge*)

Stegmann ME

Communication in oncology; positioning the general practitioner in shared decision making for patients with cancer
(*prof MY Berger, dr AJ Berendsen*)

Zhang Y

Toxic effects of heavy metals on the immune system; evidence from population and in vitro studies
(*dr MM Faas, dr X Xu, dr X Hou, dr P de Vos*)

Rienstra W

Beyond the joint; measurement and treatment of sensitisation in patients undergoing total knee or hip arthroplasty
(*prof SK Bulstra, dr I van den Akker-Scheek, dr M Stevens*)

Kuilman L

Antecedents of Ethical Decision Making by physician assistants and nurse practitioners: validation of instruments and their application
(*prof P Roodbol, dr GJ Jansen, dr LB Mulder*)

Waanders JB

Functional relevance of eccentric strength maintenance with age during walking
(*prof T Hortobagyi, dr A Murgia, dr JR Franz*)

Kok D

Memory metal in lumbar spinal fusion; biological, mechanical, clinical and radiological studies
(*prof SK Bulstra, dr M Stevens, dr FH Wapstra*)

Kristoffersen MB

Serious gaming for learning the intuitive, non-natural control of prosthetic hands
(*prof CK van der Sluis, dr RM Bongers, dr A Murgia*)

Noh JW

Key factors to improve maternal and child health in Sindh province, Pakistan
(*prof J Stekelenburg, dr YM Kim, dr YD Kwon*)

PHD PORTFOLIO

PhD Portfolio

Name PhD student: Arthur Karel Ernst Elfrink

UMCG Department: Surgery

PhD Period: December 2018 – June 2021

Item	Year	ECTS
Courses / lectures / organisation		
R Basic Course	2018	1,25
R Advanced Course	2019	1
Biomedical Statistics E-course	2019	2
Scientific Integrity Course	2019	2,5
Research Data Management Course	2019	
Scientific Writing in English	2019	3
Supervising Thesis Students	2020	1.5
Research meetings at Dutch Institute of Clinical Auditing (weekly)	2018 - 2021	5
Educational lectures at Dutch Institute of Clinical Auditing (weekly)	2018 - 2021	5
Coordination DICA Verbeter Project	2021	-
Presentations		
<u>Chirurgendagen Veldhoven</u> Oral pitch: "Volume outcomes in liver surgery"	2019	0.5
<u>E-AHPBA Amsterdam</u> Oral presentation: "Implementation of the Dutch Hepato Biliary Audit:	2019	0.5
<u>E-AHPBA Amsterdam</u> Oral presentation: "Volume outcomes in liver surgery"	2019	0.5
<u>39th Congress of European Society of Surgical Oncology Rotterdam</u> Poster presentation: "Postoperative outcomes after preoperative chemotherapy for CRLM"	2019	0.5
<u>Digestive Disease Days Veldhoven</u> Oral presentation: "Population-based study on practice variation regarding preoperative systemic chemotherapy in patients with colorectal liver metastases and impact on short-term outcomes"	2019	0.5
<u>I-AHPBA Virtual</u> Oral presentation: "Population-based study on practice variation regarding preoperative systemic chemotherapy in patients with colorectal liver metastases and impact on short-term outcomes"	2020	0.5

<u>I-AHPBA Virtual</u> Poster presentation: 'Hospital variation in preoperative imaging of colorectal liver metastases'	2020	0.5
<u>I-AHPBA Virtual</u> Poster presentation: "Liver resection and concomitant ablation: hospital variation and outcomes"	2020	0.5
<u>E-AHPBA Virtual</u> Oral presentation: "Nationwide oncological networks for resection of colorectal liver metastases in the Netherlands: differences and postoperative outcomes"	2021	0.5
<u>E-AHPBA Virtual</u> Talking poster: "Short-term postoperative outcomes after liver resection in the elderly patient: a nationwide population-based study"	2021	0.5
<u>E-AHPBA Virtual</u> Talking poster: "Factors associated with Failure to Rescue after liver resection and impact on hospital variation: a nationwide population-based study"	2021	0.5
Students supervision		
Bachelor student		2.0
Master student		2.0

ACKNOWLEDGEMENTS / DANKWOORD

Acknowledgements / Dankwoord

De afgelopen jaren zijn voorbij gevlogen en het eindresultaat van een bijzonder mooie tijd is daar: mijn proefschrift is af. Ik wil dan ook **iedereen** bedanken die op zijn of haar manier hier aan heeft bijgedragen. Er zijn echter een aantal mensen die ik in het bijzonder wil bedanken.

Prof. dr. J.M. Klaase, beste Joost, jij was als oud-voorzitter van de DHBA de aangewezen persoon om de eerste promovendus op de DHBA te begeleiden. Onze eerste kennismaking bestond behalve uit het traditionele handen schudden (dat mocht toen nog) ook over het bespreken van onze carrière tot dan toe, over familie en vrienden, en we aanschouwden samen de traumahelikopter die net de landing had ingezet vanuit jouw kamer in het UMCG. Het was het begin van een bijzondere reis die we denk ik op een mooie manier met dit proefschrift afronden. Jouw passie om de patiëntenzorg te verbeteren door middel van onderzoek heeft mij altijd enorm geïnspireerd. Daarnaast ben ik onder de indruk van jouw menselijke kant: je staat altijd klaar voor de mensen om je heen en bent altijd bereid om mee te denken op professioneel en persoonlijk gebied. Ik ben trots dat jij mijn promotor bent. Heel veel dank voor alles!

Dr. N.F.M. Kok, beste Niels, vanaf het begin was het duidelijk: ik zou mijn onderzoeksdagen niet in Leiden maar in Amsterdam doorbrengen in het Antoni van Leeuwenhoek. Wat een goede keuze is dat geweest. Elke nieuwe onderzoeksvraag, elke tabel en ieder manuscript hebben wij op jouw kamer de revue laten passeren. Wat waren dat mooie en inspirerende momenten, altijd de intentie om het stuk nog beter te maken. Naast jouw vertrouwen op professioneel gebied ben ik je enorm dankbaar voor de steun en lieve woorden in de moeilijke tijd die ik heb doorgemaakt. Ik kan je daarvoor niet vaak genoeg bedanken wat mij betreft. Motivatie was er dankzij jou altijd genoeg om door te zetten en om mijn doelen te bereiken. Het proefschrift is af en jouw vertrouwen in mij om een opleidingsplek te bemachtigen heeft zich ook uitbetaald. Ik ben heel blij dat jij mijn co-promotor was en ben je dankbaar voor alles de afgelopen jaren!

Dr. D.J. Grünhagen, beste Dirk, naast mijn co-promotor was jij ook de voorzitter van de DHBA. Dit resulteerde in wekelijkse mails en belletjes over onderzoek en over het reilen en zeilen van de DHBA. Auditing is leuk om te doen en kan heel nuttig zijn, sommige randzaken zijn dat wat minder. Daar waren wij het vaak over eens. Naast de professionele kijk op het onderzoek dat we hebben verricht, heb jij je altijd hard gemaakt om de DHBA verder te helpen en uit te bouwen. Voor enkele zaken hebben wij de afgelopen een mooie voorzet gedaan zoals het auditen op netwerkniveau, het organiseren van een verdiepingsavond en het verder uitbouwen

van de DHBA met nieuwe beroepsgroepen. We zijn er nog niet, maar we zijn wel op de juiste weg denk ik. Ik ben blij dat jij de rol van inspirerende en soms kritische co-promotor kon combineren met het voorzitterschap van de DHBA. Daarnaast kon ik altijd op je rekenen op professioneel maar ook zeker op persoonlijk vlak. Dank voor alles tijdens mijn onderzoeksperiode!

Prof. dr. C.H.C. Dejong, prof. dr. R.J. Porte, prof. dr. H. Verheul, dank voor het zitting nemen in mijn leescommissie. Daarnaast wil ik de overige leden van mijn promotiecommissie hartelijk bedanken: prof. dr. C. Verhoef, prof. dr. M.R. Meijerink, prof. dr. E.C.J. Consten en prof. dr. B.L. van Leeuwen.

Carlijn Buis, de levertransplantatie in het UMCG was waanzinnig om mee te maken en staat in mijn geheugen gegrift: wat een mooie en motiverende dag was dat. Je was daarnaast nauw betrokken bij vele projecten van de DHBA en als kers op de taart mocht ik komen presenteren voor de hele chirurgische vakgroep van het UMCG. Dank voor je vertrouwen in mij maar vooral ook voor de gezelligheid de afgelopen jaren.

Mark Burgmans, Martijn Meijerink en Chris van der Leij, na het toetreden van de interventieradiologen tot de DHBA stonden we voor de opgave om deze sectie uit te bouwen middels het uitbreiden van de Survey en het opbouwen van indicatoren. Dit was zonder jullie niet zo goed gelukt waarvoor veel dank.

Alle andere DHBA Wetenschappelijke Commissieleden en co-auteurs, altijd was er de drive om de zorg voor patiënten met levertumoren in Nederland inzichtelijk te maken en te verbeteren. Daarnaast veel dank voor jullie altijd goede en soms kritische bijdragen aan mijn onderzoek. Het was een eer maar bovenal heel erg leuk om de eerste promovendus op de DHBA te mogen zijn, mede dankzij jullie!

Michel Wouters, jouw visie op kwaliteitsregistraties en het onderzoek wat we daarmee verrichten is denk ik waardevol voor iedere DICA-onderzoeker en is dat zeker ook voor mij geweest. Veel dank voor de vele brainstorm sessies en input tijdens AO-halfuurtjes.

Crispijn van den Brand, wij hebben veel samengewerkt in mijn tijd als clusterhoofd en coördinator van DICA Verbeterd. Daarnaast heb je me veel rust gebracht in een moeilijke periode waarvoor ik je heel dankbaar ben. Het ga je goed in het Erasmus MC.

Pim Olthof, toen ik net startte als onderzoeker op de DHBA durfde jij het aan om ons eerste onderzoek samen uit te voeren. Jouw rust, vertrouwen en kritische blik hebben mij gemotiveerd de afgelopen jaren.

Elske Marra, jij was gedurende mijn eerste periode als onderzoeker mijn rots in de branding op statistisch gebied. Je had de rust om met mij alle R-scripts en analyses door te spreken, zelfs toen je DICA had verlaten. De avonden R en statistiek aan jouw keukentafel waren de basis van dit proefschrift. Waanzinnig bedankt dat je daarvoor naast je nieuwe werk nog tijd wilde maken!

Karlijn, Anna, Babette, Juliet, waar moet ik beginnen? Woensdag en donderdag waren door jullie een hoogtepunt in de week. Naast oneindig veel vervelende filmpjes en muziekjes die in onze kamer werden afgespeeld konden we ook altijd met elkaar sparren, lachen, klagen en huilen. Het waren 3 goede jaren, dat is niet in de laatste plaats jullie verdienste. Ik heb genoten!

Daan, het kostte mij wat moeite maar uiteindelijk ben je me toch vanuit het Spaarne Gasthuis achterna gekomen naar DICA. Wat hebben wij veel overleg gehad over onderzoek, over hardlopen, wielrennen, voetbal en over andere belangrijke onderdelen van het leven. Hopelijk mogen we in de toekomst weer samenwerken!

Michelle, jij hebt als nieuwe arts-onderzoeker op de DHBA het stokje van mij overgenomen. Je komt op een prachtige plek terecht met veel gemotiveerde mensen. Ik heb al gemerkt dat het met jou helemaal goed gaat komen bij de DHBA en met je proefschrift, zet hem op!

Alle andere arts-onderzoekers van DICA, wat hebben we legendarische AO-weekenden, (kerst)borrels en congressen meegemaakt. Alle momenten naast het werk waren wat mij betreft sowieso fantastisch en altijd chaotisch, maar ik wil jullie ook bedanken voor alle momenten waarop we konden sparren over onderzoek en DICA-werk.

Alle andere DICA-collega's, in Leiden op het DICA kantoor weten we de sfeer er altijd goed in te houden. Zonder jullie was deze tijd niet hetzelfde geweest. Het secretariaat met Q, Els en later Ingeborg en Elly: altijd fijn om even het reilen en zeilen van de gemiddelde DICA-dag met jullie te delen. Daarnaast kan ik het natuurlijk enorm waarderen dat er altijd aan me gedacht werd door een extra zakje Engelse Drop in te slaan. Zonder jullie is DICA niet hetzelfde!

Alle onderzoekers in het O-gebouw van het Antoni van Leeuwenhoek, dank voor de gastvrijheid. Het skiën met de HOD en vrijdagmiddagborrels waren hoogtepunten van mijn tijd bij jullie. Myrtle, bedankt voor de leuke en fijne samenwerking op de verschillende leveronderzoeken: met jouw proefschrift komt het helemaal goed, succes met de laatste loodjes! Willem en Mathilde, we hebben dat O-gebouw vaak op zijn kop gezet en wat kon ik genieten van jullie. De gemiddelde 'werk'-dag was daardoor altijd briljant.

Alle oud & huidige collega's van de chirurgie in het Spaarne Gasthuis, bedankt voor een leerzame ANIOS periode bij jullie en ik vind het een eer dat ik bij jullie aan mijn carrière als AIOS mag beginnen.

Steven Oosterling, waar ik eerst nog dacht er zonder onderzoek te komen heb jij mij toch op andere gedachten weten te brengen. Ik denk dat dit een enorm schot in de roos is geweest. Jouw mensenkennis en motivatie om jonge dokters te begeleiden is inspirerend en ik weet daar persoonlijk alles van. Bedankt voor het vertrouwen dat je in mij hebt en de steun die ik van jou heb gevoeld en nog steeds voel als opleider Heelkunde in het Spaarne Gasthuis.

Al mijn vrienden van de Basic Suturing Course, naast dat ik trots ben op de cursus die wij hebben neergezet ben ik ook trots op de ambitie die wij zijn allen hebben laten zien de afgelopen jaren. De een na de ander begint aan zijn vervolgopleiding of rondt zijn/haar proefschrift af. Dank voor jullie interesse en steun de afgelopen jaren. Jorn en Thomas, jullie wil ik speciaal bedanken voor de alles wat we naast de BSC hebben meegemaakt: de borrels, de etentjes en middagen Ajax kijken. Natuurlijk wil ik jullie ook enorm bedanken voor de steun richting mijn sollicitaties voor de opleiding Heelkunde. Jullie zijn goud!

E.N.E.R.G.I.A.'en, en dan met name het jaar '10 en '11. Jullie zijn een fantastische uitlaatklep om even niet aan werk te denken: van vrijdagavonden in de Pijp tot een huwelijk in Mexico: het was altijd feest. Dat mijn proefschrift af is komt zeker ook door jullie. Laten we erop drinken!

Ewoud en Justus, zo'n kleine 18 jaar beleven we avonturen samen van stapavonden tot samen de Marathon van Valencia. Onze bijzondere vriendschap is me veel waard en die zal ik altijd koesteren! Op naar nieuwe doelen en uitdagingen.

Er zijn nog zoveel andere vrienden die hier niet genoemd zijn maar die wel continu betrokken zijn geweest bij wat ik aan het doen was en waar ik op moeilijke momenten op terug kon vallen, mijn hart kon luchten of gewoon het leven kon vieren: wat is het fijn dat mijn proefschrift af is, laten we het vieren!

Hans, wat fijn dat jij mij bijstaat als paranimf tijdens de verdediging van mijn proefschrift. Het begin van onze vriendschap kan je stroef noemen maar heeft ons wel gevormd. Ons compleet tegenovergestelde karakter complementeert elkaar en dit zorgt er denk ik voor dat we het beste in elkaar naar boven halen. Tiet, als jaargenoten wisten we elkaar altijd te vinden in goede en slechte tijden, als huisgenoten en als fietsmaten: geen berg was ons te hoog. Naast al het plezier vormen we ook een perfect duo als het gaat om serieuze aangelegenheden en daarom ben ik erg blij dat je naast me staat tijdens mijn promotie.

Vrienden van de Curaçaostraat, dank dat jullie mij bij willen staan op deze bijzondere dag!

Lieve Oma, wat is het leuk om te zien hoe trots jij bent op je kleinzoon met wie je vroeger heel Nederland doorkruiste met een railrunner in de hand. Kleine jochies worden groot en wat vind ik het fijn dat je zo geniet van dit alles! Opa Soest, Opa Elfrink en Oma Elfrink kijken mee, dat weet ik zeker.

Lieve Mama, ik ben zo trots op hoe jij je staande hebt gehouden de afgelopen jaren. We zijn eigenlijk alleen maar sterker geworden samen en dat koester ik als nooit tevoren. Het leven is niet altijd makkelijk en dat was zeker de afgelopen jaren niet zo. Ik had hier echter zonder jou en zonder papa nooit gestaan. Bedankt voor het overbrengen van alle liefde, levenslessen en energie die jij in je hebt, ik hou van jou. Wat is het jammer dat Papa dit niet mee kan maken. Ik weet zeker dat hij waanzinnig trots is op mij, maar dat hij net zo trots is op jou.

Lieve Pap, ik mis je elke dag. Ik kan mij geen betere vader wensen en zal voor altijd van jou houden! Je bent en blijft mijn baken. Voor altijd in mijn hart.

Allerliefste Simone, ik ben je dankbaar voor de rust die jij mij biedt als het even tegenzit of als het even niet loopt. We hebben het goed samen en ik ben trots op hoe jij in het leven staat, daar kan ik soms nog veel van leren. Je staat altijd voor me klaar en samen kunnen wij de grootste problemen aan. Op naar vele avonturen samen en laten we samen genieten van al het moois dat het leven ons te bieden heeft. Love you!

ABOUT THE AUTHOR

About the author

Arthur Karel Ernst Elfrink was born on the 11th of August 1992 in the Hague. He graduated in 2010 from the Rijnlands Lyceum Wassenaar. Afterwards he moved to Amsterdam to study Medicine at the VUmc School of Medical Sciences for which he was selected through the decentral selection procedure.

During the first year of his study, his enthusiasm for anatomy was sparked and he became a teacher in the VU Student Anatomy Project after which he became a student teacher for the Anatomy Department of the University. His first steps in clinical research at the Department of Surgery at the VU Medical Centre were a result from his early interest in Surgery and resulted in several publications. During clinical rotations, the ambition to become a surgeon was further strengthened. From 2014 onwards, he was a teacher and board member for the Basic Suturing Course which is a student to student extracurricular course founded at the VU in 2013 to teach students basic suturing skills.

After graduating Medical School in 2017, he started working in the Department of Surgery at the Spaarne Gasthuis as a resident not in training under supervision of dr. H. Rijna.

In 2018, he started a PhD Program at the UMCG, Groningen and Dutch Institute for Clinical Auditing (DICA), Leiden under supervision of his promotor prof.dr. J.M. Klaase, and his copromotores dr. N.F.M. Kok and dr. D.J. Grünhagen. His research focused on the variation in perioperative treatment and outcomes of patients with liver tumours using data from the Dutch Hepato Biliary Audit (DHBA).

At DICA, he was responsible for coordination of the DHBA registry and for 2 years he represented his fellow PhD colleagues in weekly management team meetings. In the last year of his work at DICA he coordinated 'DICA Verbeterd', a project to provide insight in the added value of all 23 quality registries at DICA.

In July 2021, he started his residency in General Surgery in the region of the VU medical center at the Spaarne Gasthuis under supervision of dr. S.J. Oosterling.