

University of Groningen

Population-based study on practice variation regarding preoperative systemic chemotherapy in patients with colorectal liver metastases and impact on short-term outcomes

Dutch Hepato Biliary Audit Group; Elfrink, Arthur K E; Kok, Niels F M; van der Werf, Leonie R; Krul, Myrtle F; Marra, Elske; Wouters, Michel W J M; Verhoef, Cornelis; Kuhlmann, Koert F D; den Dulk, Marcel

Published in:

European Journal of Surgical Oncology

DOI:

[10.1016/j.ejso.2020.03.221](https://doi.org/10.1016/j.ejso.2020.03.221)

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:

2020

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

Citation for published version (APA):

Dutch Hepato Biliary Audit Group, Elfrink, A. K. E., Kok, N. F. M., van der Werf, L. R., Krul, M. F., Marra, E., Wouters, M. W. J. M., Verhoef, C., Kuhlmann, K. F. D., den Dulk, M., Swijnenburg, R-J., Te Riele, W. W., van den Boezem, P. B., Leclercq, W. K. G., Lips, D. J., Nieuwenhuijs, V. B., Gobardhan, P. D., Hartgrink, H. H., Buis, C. I., ... Klaase, J. M. (2020). 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*, 46(9), 1742-1755. <https://doi.org/10.1016/j.ejso.2020.03.221>

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.



Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Population-based study on practice variation regarding preoperative systemic chemotherapy in patients with colorectal liver metastases and impact on short-term outcomes



Arthur K.E. Elfrink^{a, b, *}, Niels F.M. Kok^c, Leonie R. van der Werf^{a, d}, Myrtle F. Krul^c, Elske Marra^a, Michel W.J.M. Wouters^a, Cornelis Verhoef^d, Koert F.D. Kuhlmann^c, Marcel den Dulk^e, Rutger-Jan Swijnenburg^f, Wouter W. te Riele^g, Peter B. van den Boezem^h, Wouter K.G. Leclercqⁱ, Daan J. Lips^j, Vincent B. Nieuwenhuijs^k, Paul D. Gobardhan^l, Henk H. Hartgrink^m, Carlijn I. Buis^b, Dirk J. Grünhagen^d, Joost M. Klaase^b, Dutch Hepato Biliary Audit Group, Collaborators

^b Department of Surgery, University Medical Centre Groningen, Groningen, the Netherlands

^e Department of Surgery, Maastricht University Medical Centre, Maastricht, the Netherlands

^f Department of Surgery, Cancer Centre Amsterdam, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands

^j Department of Surgery, Medical Spectrum Twente, Enschede, the Netherlands

^k Department of Surgery, Isala, Zwolle, the Netherlands

^a Dutch Institute for Clinical Auditing, Scientific Bureau, Leiden, the Netherlands

^c Department of Surgery, Antoni van Leeuwenhoek, Amsterdam, the Netherlands

^d Department of Surgical Oncology, Erasmus MC Cancer Institute, Erasmus University, Rotterdam, the Netherlands

^g Department of Surgery, St. Antonius Hospital, Nieuwegein, the Netherlands

^h Department of Surgery, Radboud University Medical Centre, Nijmegen, the Netherlands

ⁱ Department of Surgery, Máxima Medical Centre, Eindhoven / Veldhoven, the Netherlands

^l Department of Surgery, Amphia Hospital, Breda, the Netherlands

^m Department of Surgery, Leiden University Medical Centre, Leiden, the Netherlands

ARTICLE INFO

Article history:

Accepted 25 March 2020

Available online 5 April 2020

Keywords:

Colorectal liver metastases

Preoperative chemotherapy

Surgery

Postoperative outcomes

Hospital variation

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.

Materials and 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 multi-variable 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.

* Corresponding author. Scientific Bureau, Dutch Institute of Clinical Auditing, 2333 AA, Leiden, the Netherlands.

E-mail address: a.elfrink@dica.nl (A.K.E. Elfrink).

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.

© 2020 Elsevier Ltd, BASO ~ The Association for Cancer Surgery, and the European Society of Surgical Oncology. All rights reserved.

1. Introduction

Colorectal liver metastases (CRLM) are the main indication for liver resection in the Netherlands[1]. Five-year survival rate after liver resection for CRLM is reported to be 30–60% in Europe[2–4]. Chemotherapy is used as induction therapy to increase resectability in unresectable CRLM and as neoadjuvant chemotherapy (NAC) in resectable CRLM and to obtain longer survival[4–8]. 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 described[10–12]. 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 preference[12]. 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.

2. 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 kilometers[14]. Health care is arranged in 71 hospitals including 7 university hospitals and one comprehensive cancer centre[15]. 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 DHBA [17]. 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 2015[13].

2.1. Patient selection

All patients who underwent liver resection for CRLM between January 1, 2014 and December 31, 2018, and registered before March 22, 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 anonymized dataset and does not need ethical approval according to Dutch law.

2.3. 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.

2.4. 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 ([Supplemental figure A1](#)). 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 specialized care is needed (i.e. underlying liver disease, complexity of surgery) patients can be referred to a tertiary referral centre in the oncological network.

2.5. 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 classification [18] 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.

2.6. 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 chemotherapy [19]. 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).

3. 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.

3.1. Baseline characteristics

Patients receiving preoperative chemotherapy were significantly younger and had lower comorbidity scores ([table A1](#)). Patients with number of lesions, higher diameter of the largest tumour and synchronous metastases were significantly more likely to receive preoperative chemotherapy.

3.2. 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 B1](#)).

3.4. 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 (paragraph 1.3.2,

table B1), 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 A1).

3.5. 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 chemo-

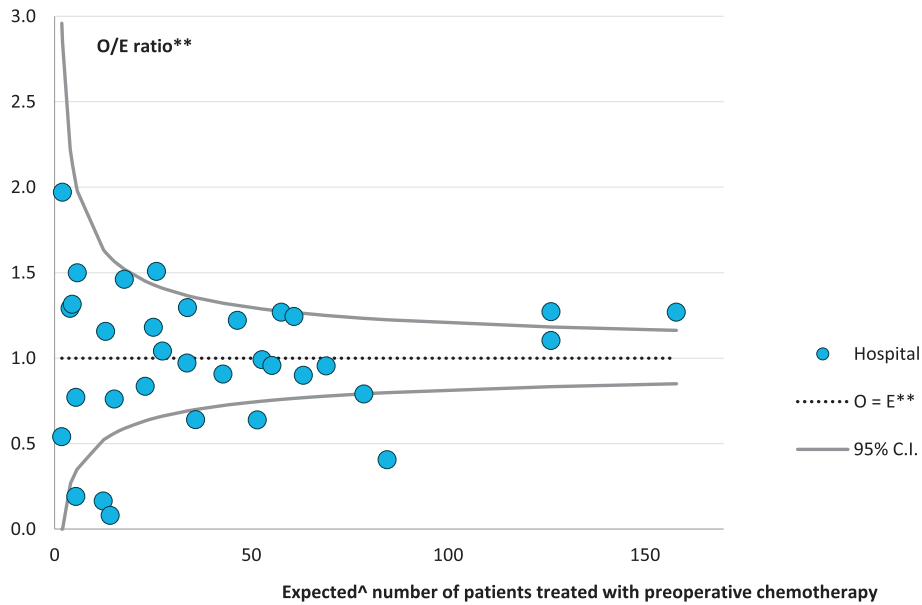


Fig. A1.

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 A2).

therapy 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

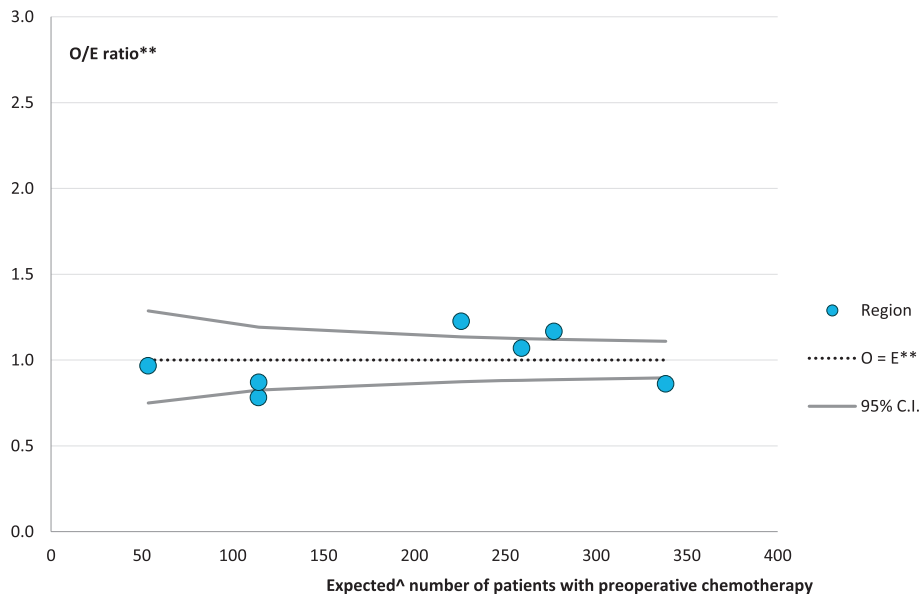


Fig. A2.

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 D1, table SA1).

In the unadjusted analysis of 3476 minor resections, no differences were observed regarding postoperative complicated course, major morbidity and mortality (table C1). In the unadjusted analysis of 993 major resections, no differences were observed regarding postoperative complicated course, major morbidity and mortality (table C1). After stratification in minor liver resection and major liver resection no association was observed between preoperative chemotherapy and postoperative complicated courses either (table D2, table D3).

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 irradical 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 elsewhere[20].

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

4. 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 chemotherapy[7]. 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 chemotherapy[23–25].

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 chemotherapy[26–28]. 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 practice[29–32].

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 CRLM[29]. 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 favorably with short-term outcome data of the EPOC-2 trial, in which patients with resectable CRLM were randomized to chemotherapy alone or chemotherapy in combination with cetuximab. Major complications occurred in 16–23% of the patients ($n = 257$) in the preoperative chemotherapy group[33]. 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 study[34]. Another study assessed 506 liver resections of whom 65% received preoperative chemotherapy for a median of 24 weeks[30]. 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 events[37].

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 lacking[13]. 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 randomized 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.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRedit authorship contribution statement

Arthur K.E. Elfrink: Conceptualization, Data curation, Writing - review & editing, Formal analysis. **Niels F.M. Kok:** Conceptualization, Data curation, Writing - review & editing, Formal analysis, Funding acquisition. **Leonie R. van der Werf:** Conceptualization, Data curation, Writing - review & editing, Formal analysis. **Myrtle F. Krul:** Conceptualization, Data curation, Writing - review & editing, Formal analysis. **Elske Marra:** Conceptualization, Data curation, Writing - review & editing, Formal analysis. **Michel W.J.M. Wouters:** Conceptualization, Data curation, Writing - review & editing, Funding acquisition. **Cornelis Verhoef:** Writing - review & editing, Funding acquisition. **Koert F.D. Kuhlmann:** Writing - review & editing, Funding acquisition. **Marcel den Dulk:** Writing - review & editing, Funding acquisition. **Rutger-Jan Swijnenburg:** Writing - review & editing, Funding acquisition. **Wouter W. te Riele:** Writing - review & editing, Funding acquisition. **Peter B. van den Boezem:** Writing - review & editing, Funding acquisition. **Wouter K.G. Leclercq:** Writing - review & editing, Funding acquisition. **Daan J. Lips:** Writing - review & editing, Funding acquisition. **Vincent B.**

Nieuwenhuijs: Writing - review & editing, Funding acquisition. **Paul D. Gobardhan:** Writing - review & editing, Funding acquisition. **Henk H. Hartgrink:** Writing - review & editing, Funding acquisition. **Carlijn I. Buis:** Writing - review & editing, Funding acquisition. **Dirk J. Grünhagen:** Conceptualization, Data curation, Writing - review & editing, Formal analysis. **Joost M. Klaase:** Conceptualization, Data curation, Writing - review & editing, Formal analysis. **Marieke T. de Boer:** Conceptualization, Data curation, Writing - review & editing. **Marc G.H. Besselink:** Conceptualization, Data curation, Writing - review & editing. **Cees H.C. Dejong:** Conceptualization, Data curation, Writing - review & editing. **Thomas H. van Gulik:** Conceptualization, Data curation, Writing - review & editing. **Jeroen Hagendoorn:** Conceptualization, Data curation, Writing - review & editing. **Frederik J.H. Hoogwater:** Conceptualization, Data curation, Writing - review & editing. **Mike S.L. Liem:** Conceptualization, Data curation, Writing - review & editing. **I. Quintus Molenaar:** Conceptualization, Data curation, Writing - review & editing. **Gijs A. Patijn:** Conceptualization, Data curation, Writing - review & editing. **Koop Bosscha:** Conceptualization, Data curation, Writing - review & editing. **Eric J.Th Belt:** Conceptualization, Data curation, Writing - review & editing. **Maarten Vermaas:** Conceptualization, Data curation, Writing - review & editing. **Michael F. Gerhards:** Conceptualization, Data curation, Writing - review & editing. **N.T. van Heek:** Conceptualization, Data curation, Writing - review & editing. **Steven J. Oosterling:** Conceptualization, Data curation, Writing - review & editing. **Hans Torrenga:** Conceptualization, Data curation, Writing - review & editing. **Hasan H. Eker:** Conceptualization, Data curation, Writing - review & editing. **Esther C.J. Consten:** Conceptualization, Data curation, Writing - review & editing. **Peter van Duijvendijk:** Conceptualization, Data curation, Writing - review & editing.

Acknowledgments

The authors would like to thank all surgeons, interventional radiologists and administrative nurses for data registration in the DHBA database, as well as the Dutch Hepato Biliary Audit Group for scientific input.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejso.2020.03.221>.

Table A1

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			0.256
Male	2001 (63)	809 (62)	
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)	

(continued on next page)

Table A1 (continued)

Factor	No preoperative chemotherapy N (%)	Preoperative chemotherapy N (%)	P-value¶
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 diseases§			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 center	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, esophageal 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.

Table B1

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 and 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, esophageal 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 C1

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 ^a
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)	

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.

^a Chi-square test was used comparing groups.

Table D1

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 and 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

(continued on next page)

Table D1 (continued)

Factor	N	Univariable analysis			Multivariable analysis		
		OR	CI (95%)	P-value	aOR	CI (95%)	P-value
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	

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

* 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.

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

Table D2

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 and 2018.

Factor	N	Univariable analysis			Multivariable analysis		
		OR	CI (95%)	P-value	aOR	CI (95%)	P-value
Sex				0.160			
Male	2187	1					
Female	1289	0.84	0.66–1.07				
Age in years				0.007			0.158
< 50	245	1			1		
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 diseases[§]				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	

Table D2 (continued)

Factor	N	Univariable analysis			Multivariable analysis		
		OR	CI (95%)	P-value	aOR	CI (95%)	P-value
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	

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

* 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.

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

Table D3

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 and 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		
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					

(continued on next page)

Table D3 (continued)

Factor	N	Univariable analysis			Multivariable analysis		
		OR	CI (95%)	P-value	aOR	CI (95%)	P-value
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	

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

* 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.

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

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):55368–76.
- [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):580–9.
- [3] 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):523–30.
- [4] Hoppener DJ, Nierop PMH, van Amerongen MJ, Olthoff PB, van Gulik TM, 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):2812–20.
- [5] Adam R, Delvart V, Pascal G, Valeanu A, Castaing D, Azoulay D, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. *Ann Surg* 2004;240(4):644–57. discussion 657–648.
- [6] 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.
- [7] Nordlinger B, Sorbye H, Glimelius B, 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):1007–16.
- [8] 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):1208–15.
- [9] Oncoline Dutch tumor guidelines. Dutch Guideline Database; 2014.
- [10] 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):1668–81.
- [11] 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):421–30.
- [12] Nasti G, Ottaiano A, Berretta M, Delrio P, Izzo F, Cassata A, et al. Pre-operative chemotherapy for colorectal cancer liver metastases: an update of recent clinical trials. *Canc Chemother Pharmacol* 2010;66(2):209–18.
- [13] 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* 2019 (Oxford).
- [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. <https://www.volksgezondheidzorg.info/onderwerp/ziekenhuiszorg/cijfers-context/aanbod#node-aantal-instellingen-voor-medisch-specialistische-zorg>; 2019.
- [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] 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): 857–64.
- [18] Clavien PA, Sanabria JR, Strasberg SM. Proposed classification of complications of surgery with examples of utility in cholecystectomy. *Surgery* 1992;111(5): 518–26.
- [19] Richardson DB, Keil AP, Cole SR, MacLehose RF. Observed and expected mortality in cohort studies. *Am J Epidemiol* 2017;185(6):479–86.
- [20] Olthof PB, Elfrink AKE, Marra E, Belt EJ, van den Boezem PB, Bosscha K, et al. Volume-outcome relationship of liver surgery: a nationwide analysis. *Br J Surg*. 2019 Epub ahead of print. 24-03-2020.
- [21] Sorbye H, Mauer M, Gruenberger T, Glimelius B, Poston G, Schlag PM, 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):534–9.
- [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):37277–87.
- [23] Adam R, Bhangui P, Poston G, Mirza D, Nuzzo G, Barroso E, et al. Is perioperative chemotherapy useful for solitary, metachronous, colorectal liver metastases? *Ann Surg* 2010;252(5):774–87.
- [24] Faron M, Chirica M, Tranchard H, Balladur P, de Gramont A, Afchain P, 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, Rothbarth J, van Meerten E, Eggermont AM, 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):859–67.
- [26] Beppu T, Miyamoto Y, Sakamoto Y, Imai K, Nitta H, Hayashi H, 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):S405–13.
- [27] Phelip JM, Mineur L, De la Fouchardiere C, Chatelut E, Quesada JL, Roblin X, 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):2161–6.
- [28] Takatsuki M, Tokunaga S, Uchida S, Sakoda M, Shirabe K, Beppu T, 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):184–9.
- [29] 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):523–32. e522.
- [30] 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.
- [31] Wolf PS, Park JO, Bao F, Allen PJ, DeMatteo RP, Fong Y, 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):41–9.
- [32] Makowiec F, Mohrle S, Neeff H, Drognitz O, Illerhaus G, Opitz OG, et al. Chemotherapy, liver injury, and postoperative complications in colorectal liver metastases. *J Gastrointest Surg*. 2011;15(1):153–64.
- [33] 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):601–11.
- [34] 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):449–55.
- [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):1073–81.
- [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):157–63.
- [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* 2016;18(6):485–93.