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Elfrink, A.K.E.; Kok, N.F.M.; Werf, L.R. van der; Krul, M.F.; Marra, E.; Wouters, M.W.J.M.; ... ; Dutch Hepato Biliary Audit Grp Col

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# 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. Leclercq [i], 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

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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 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.

* 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).

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*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.



## 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 trails 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 Comorbity 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).

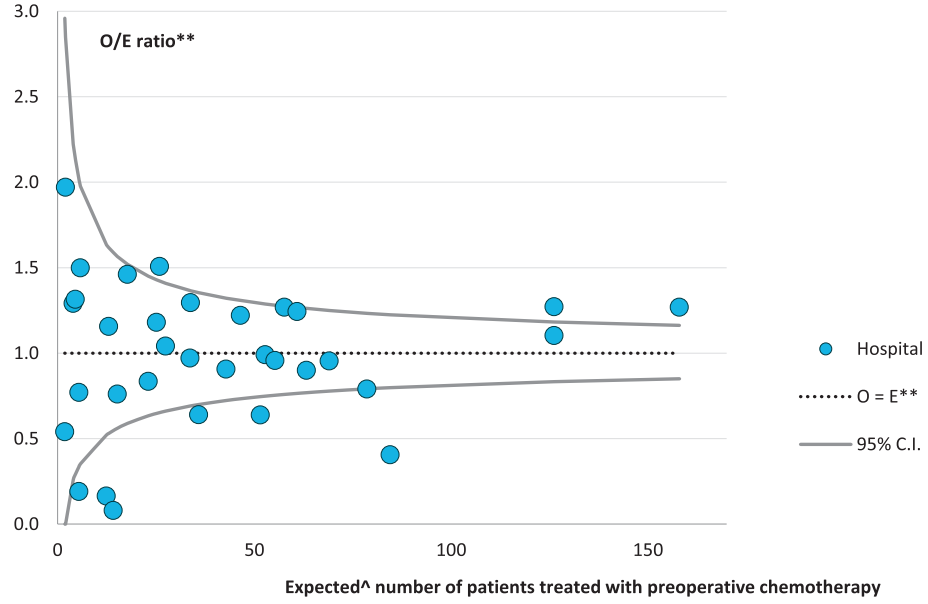


**Fig. A1.**

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).

### 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 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

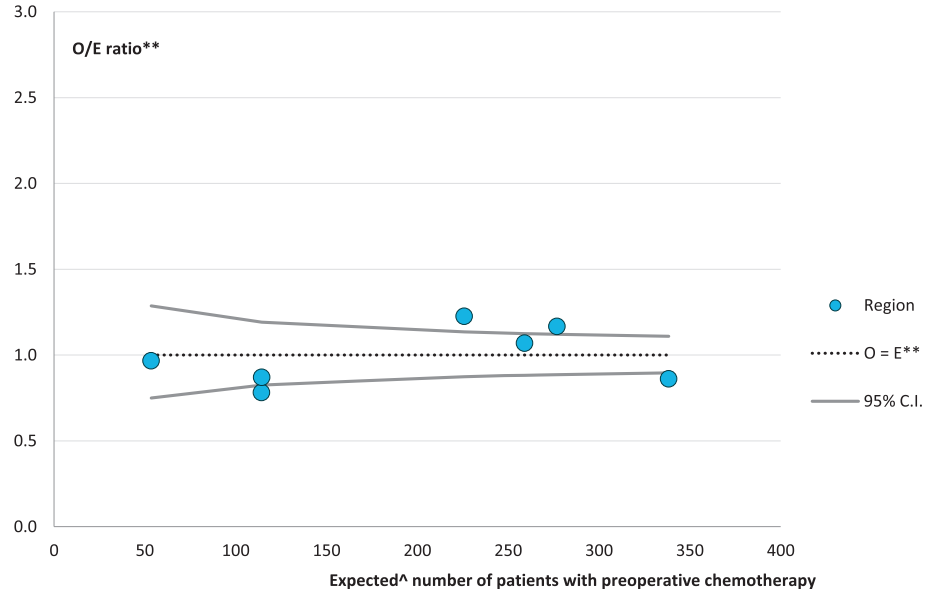


**Fig. A2.**

postoperative complicated course (OR 1.24, 0.98–1.55, p = 0.065), 30-day morbidity (OR 1.05, 0.81–1.1.39, 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.

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## 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 | Preoperative chemotherapy | P-value¶ |
|---|---|---|---|---|
| | | **N (%)** | **N (%)** | |
| **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 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 | | Univariable analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|---|
| | N | 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 primairy 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 | | Univariable analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|---|
| | N | 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 primairy 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 | | Univariable analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|---|
| | N | 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 | | Univariable analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|---|
| | N | 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 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 primairy 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 | | Univariable analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|---|
| | N | 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 | | Univariable analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|---|
| | N | 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 | | Univariable analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|---|
| | N | 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 primairy 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.

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