Hospital variation in combined liver resection and thermal ablation for colorectal liver metastases and impact on short-term postoperative outcomes: a nationwide population-based study

Elfrink, A.K.E.; Nieuwenhuizen, S.; Tol, M.P. van den; Burgmans, M.C.; Prevoo, W.; Coolsen, M.M.E.; ... ; Dutch Hepato Bili

ORIGINAL ARTICLE

Hospital variation in combined liver resection and thermal ablation for colorectal liver metastases and impact on short-term postoperative outcomes: a nationwide population-based study

Arthur K.E. Elfrink[1,2], Sanne Nieuwenhuizen[3], M. Petrousjka van den Tol[4], Mark C. Burgmans[5], Warner Prevoo[6], Marielle M.E. Coolsen[7], Peter B. van den Boezem[8], Otto M. van Delden[9], Jeroen Hagendoorn[10,18], Gijs A. Patijn[11], Wouter K.G. Leclercq[12], Mike S.L. Liem[13], Arjen M. Rijken[14], Cornelis Verhoef[15], Koert F.D. Kuhlmann[16], Simeon J.S. Ruiter[2], Dirk J. Grünhagen[15], Joost M. Klaase[2], Niels F.M. Kok[16], Martijn R. Meijerink[3], Rutger-Jan Swijnenburg[17], Dutch Hepato Biliary Audit Group[†], Collaborators

[1]Dutch Institute for Clinical Auditing, Scientific Bureau, Leiden, [2]Department of Surgery, University Medical Center Groningen, Groningen, [3]Department of Interventional Radiology, [4]Department of Surgery, Cancer Center Amsterdam, Amsterdam UMC, VU University, Amsterdam, [5]Department of Radiology, Leiden University Medical Center, Leiden, [6]Department of Interventional Radiology, OLVG, Amsterdam, [7]Department of Surgery, Maastricht University Medical Center, Maastricht, [8]Department of Surgery, Radboud Medical Center, Nijmegen, [9]Department of Radiology, Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam, [10]Department of Surgery, University Medical Center Utrecht, Utrecht, [11]Department of Surgery, Isala, Zwolle, [12]Department of Surgery, Máxima Medical Center, Veldhoven, [13]Department of Surgery, Medisch Spectrum Twente, Enschede, [14]Department of Surgery, Amphia Medical Center, Breda, [15]Department of Surgical Oncology, Erasmus MC Cancer Institute, Rotterdam, [16]Department of Surgery, Antoni van Leeuwenhoek – Dutch Cancer Institute, Amsterdam, [17]Department of Surgery, Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam, and [18]Department of Surgery, St Antonius Hospital, Nieuwegein, the Netherlands

Abstract

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

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

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

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

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Correspondence

Arthur K.E. Elfrink, Scientific Bureau, Dutch Institute of Clinical Auditing, 2333 AA Leiden, the Netherlands. E-mail: a.elfrink@dica.nl

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[†] Members of the Dutch Hepato Biliary Audit Group and all collaborators are co-authors of this study.

Introduction

Colorectal cancer (CRC) is the third most common type of cancer worldwide and colorectal liver metastases (CRLM) have been described to occur in up to 50% of patients with CRC.[1] Upfront liver resection with curative intent is thought to be possible in only 10–20% of the patients with CRLM. Induction chemotherapy and parenchymal-sparing surgery can increase surgical options.[2–4] Thermal ablation poses an alternative for resection, in particular for more centrally located, smaller metastases (<3 cm).[5,6] Resection of such lesions may imply sacrificing a significant amount of normal liver parenchyma.[7]

Combining liver resection and thermal ablation in one surgical session can extend curative options in patients with CRLM who are not eligible for conventional liver resection due to multiple CRLM, location of CRLM, bilobar disease or due to severe comorbidities.[8,9] Guidelines in the Netherlands provide insufficient guidance to support the combination of liver resection and thermal ablation in different patients and so the use of these treatment regimens may vary.[10] The present study is the first population-based nationwide study worldwide on hospital variation in the use of combined resection and ablation and on corresponding short-term postoperative outcomes.

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

Methods

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

Patient selection

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

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

Variables

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

Of all 71 hospitals in the Netherlands, only 25 performed liver surgery.[13] All regional hospitals are included in an oncological network. Seven oncological networks were classified according to treatment collaboration between hospitals or topographical location if no collaboration network was present, as described earlier.[14,15] Oncological, networks include one or two tertiary referral centers and several regional hospitals performing liver surgery. Regional centers can refer patients to tertiary referral centers if the patient or tumor requires specific tertiary care.

Outcomes

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

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

Short-term postoperative outcomes compared between groups included specific surgical complication rates and more general complication rates. Specific complications were specified as bile leakage, postoperative hemorrhage requiring reintervention, postoperative liver failure according the International Study Group of Liver Surgery, deep surgical site infection (i.e biloma or abcess), incisional surgical site infection, pneumonia, myocardial complication or a thrombo-embolic complication.[16]

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

Other major postoperative outcomes were 30-day major morbidity, defined as a complication graded Clavien-Dindo classification of grade III (CD > 3a) or higher (i.e. requiring re-intervention, medium care (MC) or intensive care (IC) management or death) within 30 days of surgery and 30-day mortality defined as death within 30 days from date of surgery or during initial hospitalization.[17]

Statistical analysis

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

Potential case-mix variables were entered in a univariable and multivariable multilevel regression model to obtain a parsimonious statistical model. Influence of case-mix factors was shown as adjusted odds ratios (aOR) with 95% Confidence Intervals (CI). In multivariable analyses two steps were undertaken. All variables were tested in a univariable model with the outcome as dependent variable. If the association was positive ($p < 0.10$) the variable was entered in the multivariable model. Multilevel analysis were performed with year, hospital and oncological network where surgery took place as a grouping covariate. Statistical significance was defined as a two-sided p-value <0.05 in the multivariable model.

Hospital and oncological network variation in the use of combined resection and ablation was corrected for case-mix variables. Case-mix correction was performed using the observed/expected ratio (O/E ratio) which is calculated by dividing the observed number of patients with type of procedure through the number of patients expected to receive a type of procedure. The expected number of patients is based on a prediction using a multivariable multilevel logistic regression model with all case-mix variables. An O/E ratio below 1 indicates that a hospital or oncological network performed less combined resection and ablation than expected and an O/E ratio above 1 indicated that a hospital or oncological network performed more combined resection and ablation than expected. This method was chosen as this constitutes the current manner of feedback for all Dutch hospitals which participate in registries from the Dutch Institute for Clinical Auditing.[18]

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

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

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

Results

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

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

Case-mix variables associated with liver resection and thermal ablation

In multivariable multilevel logistic regression analysis case-mix variables that were positively associated with combined resection and ablation included preoperative chemotherapy (aOR 1.38, CI 1.11−1.71, $p = 0.004$), higher number of CRLM (4 or more CRLM, aOR 3.56, CI 2.58−3.87, $p < 0.001$), and bilobar disease (aOR 3.16, CI 2.58−3.87, $p < 0.001$) (Table 2).

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

Factor	Resection only	Combined resection and ablation	p-value
	N (%)	*N* (%)	
Total	3697	942	
Patient characteristics			
Sex			**0.018**
Male	2300 (62)	626 (67)	
Female	1397 (38)	316 (33)	
Age in years			**0.032**
<50	252 (7)	77 (8)	
50–64	1244 (34)	349 (37)	
65–79	1919 (52)	456 (48)	
>80	277 (8)	56 (6)	
Missing	5	4	
Charlson Comorbidity Index (CCI)			**<0.001**
0/1	2676 (74)	717 (80)	
2+	934 (26)	179 (20)	
Missing	87	46	
Body Mass Index (BMI)			
Mean (sd)	26.26 (4.38)	26.32 (4.37)	0.671
American Society of Anesthesiology (ASA) classification			0.599
ASA I/II	2904 (81)	734 (81)	
ASA III+	702 (19)	168 (19)	
Missing	91	40	
History of liver resection			**<0.001**
No	2927 (81)	786 (86)	
Yes	688 (19)	127 (14)	
Missing	82	29	
History of liver disease[a]			0.135
No	3472 (99)	868 (99)	
Yes	54 (1)	7 (1)	
Missing	171	67	
History of preoperative chemotherapy			**<0.001**
No	2526 (73)	483 (55)	
Yes	925 (27)	389 (45)	
Missing	246	70	
Tumor characteristics			
Number of CRLM			**<0.001**
≤3	3007 (85)	452 (50)	
>3	540 (15)	444 (50)	
Missing	150	46	
Maximum diameter of largest CRLM (mm[b]**)**			**<0.001**
<20	954 (30)	624 (67)	
20–34	1182 (38)	326 (41)	
35–54	610 (19)	136 (17)	
>55	398 (13)	58 (7)	
Missing	553	146	
Location primary tumor			0.064
Colon	2342 (64)	624 (67)	
Rectal	1347 (37)	310 (33)	
Missing	8	8	
Type of metastases			**<0.001**
Metachronous	1981 (56)	380 (43)	
Synchronous	1550 (44)	514 (57)	
Missing	166	48	
Extrahepatic disease			0.222
No	3042 (88)	757 (86)	
Yes	623 (12)	121 (14)	
Missing	32	6	
Type of hospital[c]			**<0.001**
Regional hospital	2102 (57)	455 (48)	
Tertiary referral hospital	1595 (43)	487 (52)	
Year of procedure			0.342
2014	682 (18)	172 (18)	
2015	705 (19)	191 (20)	
2016	803 (22)	181 (19)	
2017	770 (21)	216 (23)	
2018	737 (20)	182 (19)	

Bold p-values indicate statistical significance.
[a] 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.
[b] millimeter.
[c] Type of hospital: tertiary referral centers are defined as hospitals with highest expertise on oncologic surgery.

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

Factor	*N*	Univariable analysis			Multivariable analysis		
		OR	CI (95%)	p-value	aOR	CI (95%)	p-value
Sex				0.016			**<0.001**
Male	2926	1			1		
Female	1713	0.83	0.71–0.97		0.78	0.64–0.94	
Age in years				0.030			0.989
<50	329	1			1		
50–64	1592	1.56	0.96–2.68	0.085	0.94	0.64–1.35	0.727
65–79	2375	1.76	1.11–2.99	0.025	0.95	0.66–1.36	0.767
>80	333	2.23	1.26–4.07	0.007	0.95	0.47–1.55	0.816
Missing[a]	9						
Charlson Comorbidity Index (CCI)				<0.001			0.505
0/1	3638	1			1		
2+	870	0.95	0.78–1.14		0.92	0.73–1.16	
Missing[a]	131						
Body Mass Index		1.00	0.99–1.02	0.671			
American Society of Anesthesiology (ASA) classification				0.566			
I/II	3393	1					
III+	1113	0.72	0.60–0.85				
Missing[a]	133						
History of liver disease[b]				0.104			0.734
No	4340	1			1		
Yes	61	0.52	0.21–1.07		0.86	0.33–2.17	
Missing[a]	238						
History of liver resection				0.495			
No	3713	1					
Yes	815	1.10	0.84–1.41				
Missing[a]	111						
History of preoperative chemotherapy				<0.001			**0.004**
No	3009	1			1		
Yes	1314	2.20	1.88–2.56		1.38	1.11–1.71	
Missing	316						
Number of CRLM				<0.001			**<0.001**
<3	3459	1			1		
>3	984	5.47	4.66–6.42		3.56	2.85–4.43	
Missing[a]	196						
Maximum diameter largest CRLM (mm)[a]				<0.001			**<0.001**
<20	1230	1			1		
20–34	1508	0.95	0.80–1.14	0.606	0.79	0.63–0.98	**0.035**
35–54	746	0.77	0.61–0.97	0.026	0.52	0.40–0.70	**<0.001**
>55	456	0.50	0.37–0.68	<0.001	0.28	0.19–0.40	**<0.001**
Missing[d]	699	0.91	0.73–1.14	0.428	0.75	0.54–1.05	0.092
Bilobar disease				<0.001			**<0.001**
No	2472	1			1		

(*continued on next page*)

Table 2 (*continued*)

Factor	*N*	Univariable analysis			Multivariable analysis		
		OR	CI (95%)	p-value	aOR	CI (95%)	p-value
Yes	2015	3.98	3.40–4.67		3.16	2.58–3.87	
Missing[a]	152						
Location primary tumor				0.059			**0.006**
Colon	2966	1			1		
Rectal	1657	0.86	0.74–1.00		0.76	0.63–0.93	
Missing[a]	16						
Type of metastases				<0.001			0.071
Metachronous	2361	1			1		
Synchronous	2064	1.73	1.49–2.01		1.20	0.98–1.46	
Missing[a]	214						
Extrahepatic disease				0.201			
No	3799	1					
Yes	543	1.15	0.92–1.43				
Missing[a]	297						
Type of hospital[c]				<0.001			0.418
Regional	2557	1			1		
Tertiary referral centers	2082	1.41	1.22–1.63		1.34	0.66–2.72	

Bold p-values indicate statistical significance.
Mm = millimeter.
[a] Missing not included in analyses based on relatively small group.
[b] 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.
[c] Type of hospital: tertiary referral center is defined as hospitals with highest expertise on oncologic surgery.
[d] Unclear why percentage missing is so high.

Case-mix variables negatively associated with combined resection and ablation were female sex (aOR 0.78, CI 0.64–0.94, p < 0.001), increasing diameter of the largest CRLM (>55 mm compared to <20 mm, aOR 0.28, CI 0.19–0.40, p < 0.001) and a rectal primary tumor (aOR 0.76, CI 0.63–0.93, p = 0.006) (Table 2).

Hospital variation in the use of liver resection and thermal ablation

Significant hospital variation in the use of combined resection and ablation was present in Dutch hospitals and Dutch oncological networks. The variation was observed in both uncorrected and case-mix corrected analyses.

Unadjusted percentage of patients treated per hospital using combined resection and ablation ranged between 4% and 44% (Fig. 1a). Unadjusted percentage of patients treated per oncological network using combined resection and ablation ranged between 11% and 28% (Fig. 2a).

Case-mix adjusted O/E ratios showed several outliers between hospitals in the use of combined resection and ablation (Fig. 1b). Six hospitals performed significantly more combined resection and ablation than expected on the basis of their case-mix variables. Ten hospitals performed significantly less combined resection and ablation than expected on the basis of their case-mix variables. O/E ratios ranged between 0 and 2.19 between the hospitals.

Case-mix adjusted O/E ratios showed several outliers between oncological networks in the use of combined resection and ablation (Fig. 2b). Two oncological networks performed significantly more combined resection and ablation than expected on the basis of their case-mix variables. Three oncological networks performed significantly less combined resection and ablation than expected on the basis of their case-mix variables. O/E ratios ranged between 0.49 and 1.36 between the oncological networks.

Propensity score matching: baseline- and surgical characteristics

After the matching process, 1468 patients were included in the final analyses regarding short-term postoperative outcomes, of whom 734 (50%) were included in the resection only group and of whom 734 (50%) in the combined resection and ablation group.

Standard mean differences were below 0.100 for all baseline characteristics (Table 3). The only significant difference between the groups was a higher number of patients treated in a tertiary referral hospital in the combined resection and ablation group (53% versus 43%, $p < 0.001$; smd = 0.192).

Perioperative outcomes

Minimally invasive and major resection, respectively, were performed less often in the combined resection and ablation group (6% vs. 15%, $p < 0.001$ and 15% vs. 36%, $p < 0.001$) (Table 4). Several specific complications occurred less often in the combined resection and ablation group, including bile leakage (1.6% vs. 4.3% p = 0.005) and postoperative liver failure (0.5% vs. 2.9%, p = 0.001). Hospital stay was lower in the combined resection and ablation group (median 6 days (IQR 5–9) vs. 7 days (IQR 5–10), p = 0.011). Overall morbidity and 30-day major morbidity were not different between the two groups. PCC (11% vs. 14.7%, p = 0.043) and 30-day mortality (0.7% vs. 2.3%, p = 0.018) were lower in the combined resection and ablation group.

Associated factors with postoperative complicated course and 30-day mortality

In univariable logistic regression, combined resection and ablation was associated with a reduction of PCC and 30-day

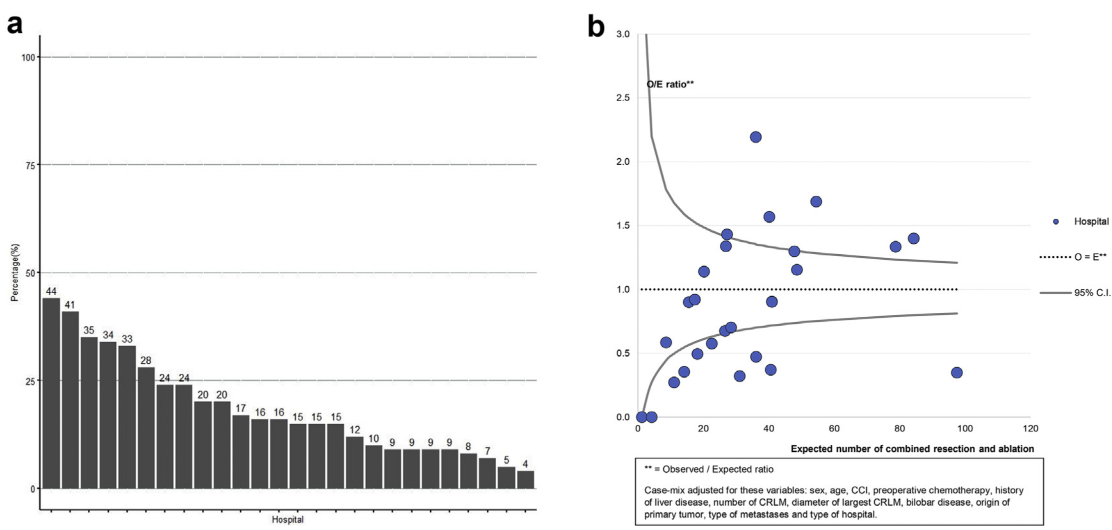

Figure 1 a. Unadjusted rates of variation in the use of combined resection and ablation between hospitals in patients with colorectal liver metastases in the Netherlands between 2014 and 2018. **b**. Case-mix adjusted funnel-plot of between-hospital variation in the use of combined resection and ablation in patients with colorectal liver metastases in the Netherlands between 2014 and 2018

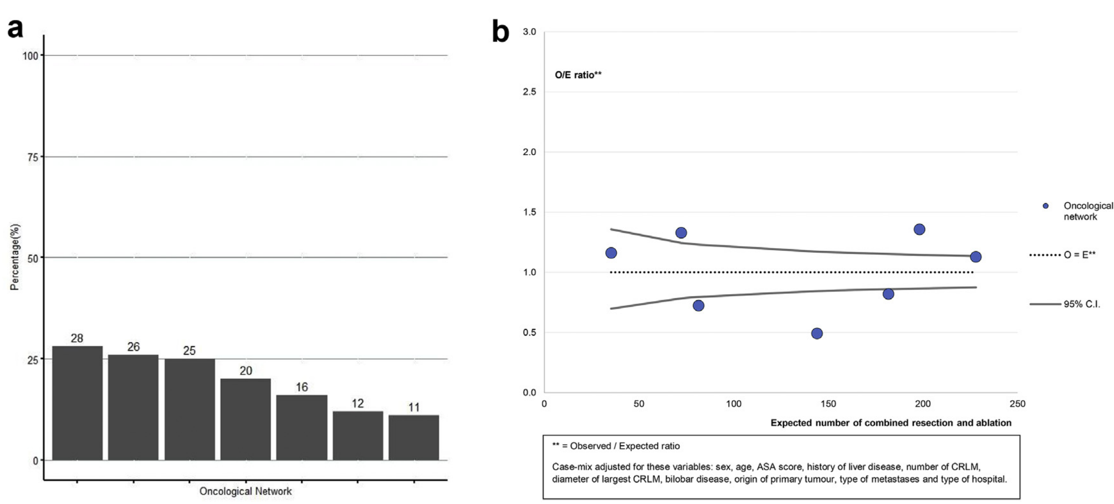

Figure 2 a. Unadjusted rates of variation in the use of combined resection and ablation between oncological networks in patients with colorectal liver metastases in the Netherlands between 2014 and 2018. **b**. Case-mix adjusted funnel-plot of between oncological network variation in the use of combined resection and ablation in patients with colorectal liver metastases in the Netherlands between 2014 and 2018

Table 3 Baseline characteristics for propensity score matched patients diagnosed with colorectal liver metastases (CRLM) between 2014 and 2018 in the Netherlands undergoing resection only or combined resection and ablation

Factor	Resection only N (%)	Combined resection and ablation N (%)	p-value	smd
Total	734	734		
Patient characteristics				
Sex			0.082	0.094
Male	453 (62)	486 (66)		
Female	281 (38)	248 (34)		
Age in years			0.367	0.093
<50	54 (7)	64 (9)		
50–64	278 (38)	295 (40)		
65–79	369 (40)	337 (46)		
>80	32 (5)	37 (5)		
Missing	1	1		
Body Mass Index (BMI)				
(mean, SD)	26 (4)	26 (4)	0.084	0.090
Charlson Comorbidity Index (CCI)			0.432	0.045
0/1	583 (81)	54 (79)		
2+	139 (19)	153 (21)		
Missing	12	7		
American Society of Anesthesiology (ASA) classification			0.747	0.020
ASA I/II	606 (83)	597 (82)		
ASA III+	127 (17)	132 (18)		
Missing	1	5		
History of liver resection			0.906	0.010
No	623 (86)	623 (86)		
Yes	105 (14)	102 (14)		
Missing	6	9		
History of liver disease[a]			0.996	0.015
No	706 (99)	709 (99)		
Yes	7 (1)	6 (1)		
Missing	21	19		
History of preoperative chemotherapy			0.970	0.005
No	372 (54)	378 (54)		
Yes	322 (46)	324 (46)		
Missing	40	24		
Tumor characteristics				
Number of lesions			0.490	0.040
≤3	355 (51)	345 (49)		
>3	347 (49)	365 (51)		
Missing	32	24		
Maximum diameter of largest CRLM (mm[b]**)**			0.968	0.028
<20	206 (32)	213 (33)		
20–34	256 (40)	257 (40)		
35–54	123 (19)	118 (18)		
>55	55 (9)	53 (8)		
Missing	94	93		
Type of metastases			0.968	0.004
Metachronous	289 (41)	288 (41)		
Synchronous	417 (59)	419 (59)		
Missing	28	27		
Type of hospital[c]			<0.001	0.192
Regional hospital	416 (57)	346 (47)		
Tertiary referral hospital	318 (43)	388 (53)		
Year of surgery			0.423	0.098
2014	123 (17)	105 (14)		
2015	169 (23)	152 (21)		
2016	140 (19)	158 (22)		
2017	159 (22)	158 (23)		
2018	143 (19)	151 (20)		

Bold p-values indicate statistical significance.
[a] 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.
[b] millimeter.
[c] Type of hospital: tertiary referral center is defined as hospitals with highest expertise on oncologic surgery.

mortality (Table 4). In multivariable logistic regression, combined resection and ablation (aOR 0.95, CI 0.65–1.38, p = 0.789) was not associated with PCC. Factors such as major liver resection (aOR 2.31, CI 1.57–3.39, p < 0.001), ASA score (aOR 1.92, CI 1.27–2.89, p = 0.001), increasing diameter of largest CRLM (<20 mm vs. >55 mm, aOR 2.18, CI 1.57–3.39, p = 0.001) and simultaneous resection of the colorectal primary tumor and CRLM (aOR 2.49, CI 1.55–3.98, p < 0.001) were associated with an increased PCC rate (Table 5).

In multivariable logistic regression, combined resection and ablation (aOR 0.54 CI 0.17–1.72, p = 0.299) was not associated

Table 4 Perioperative outcomes for patients diagnosed with colorectal liver metastases between 2014 and 2018 in the Netherlands who underwent resection only or combined resection and ablation

Factor	Resection only N (%)	Combined resection and ablation N (%)	p-value
Number of patients (total)	734	734	
Surgical approach			**<0.001**
Open	602 (82)	648 (89)	
Minimally invasive	107 (15)	47 (6)	
Conversion	20 (3)	34 (5)	
Missing	5	5	
Surgical strategy			0.431
Primary tumor first	441 (64)	453 (65)	
Liver first	172 (25)	152 (22)	
Simultaneous resection of colorectal tumor and CRLM	82 (12)	89 (13)	
Missing	39	40	
Synchronous additional resection[a]			0.171
No	379 (74)	431 (78)	
Yes	131 (26)	121 (22)	
Missing[a]	224	182	
Major liver resection			**<0.001**
No	470 (64)	627 (85)	
Yes	264 (36)	107 (15)	
Bile leakage			**0.005**
No	696 (96)	717 (99)	
Yes	31 (4)	12 (1)	
Missing[a]	7	5	
Postoperative haemorrhage			0.416
No	676 (99)	683 (99)	
Yes	9 (1)	5 (1)	
Missing[a]	49	46	
Postoperative liver failure			**0.001**
No	706 (97)	725 (99)	
Yes	21 (3)	4 (1)	
Missing[a]	7	5	
Intra-abdominal infection			0.453
No	661 (95)	660 (94)	
Yes	37 (5)	45 (6)	
Missing[a]	36	29	
Surgical site infection			0.177
No	681 (98)	677 (94)	
Yes	17 (2)	45 (6)	
Missing[a]	36	30	
Pneumonia			0.520
No	661 (94)	656 (93)	
Yes	41 (6)	48 (7)	
Missing[a]	32	30	
Cardiac complication			0.775
No	698 (96)	703 (96)	
Yes	29 (4)	26 (4)	
Missing[a]	7	5	
Thromboembolic complication			0.299
No	705 (97)	715 (98)	
Yes	21 (3)	14 (2)	
Missing[a]	8	5	
Length of stay (Median + IQR)	7 (5–10)	6 (5–9)	**0.011**
Overall 30-day morbidity			0.187
No	493 (67)	516 (71)	
Yes	240 (33)	215 (29)	
Missing[a]	1	3	
Postoperative complicated course			**0.043**
No	626 (85)	653 (89)	
Yes	240 (15)	81 (11)	
30-day major morbidity			0.712
No	672 (92)	667 (91)	
Yes	62 (8)	67 (9)	
30-day mortality			**0.018**
No	717 (98)	729 (99)	
Yes	17 (2)	5 (1)	

Bold p-values indicate statistical significance.
Synchronous additional resection was defined as any extra procedure including vascular resection or reconstruction or as additional intra-abdominal resection as a result of in-growth in other structures.
Major liver resection was defined as resection of at least 3 liver segments.
Postoperative complicated course was defined as a complication after surgery resulting in prolonged hospitalization (>14 days), or reintervention or death as a result of a complication.
Major morbidity was defined as a Clavien Dindo Grade 3 or higher complication.
[a] Missing are not included in the analysis.

Table 5 Results of stepwise multilevel logistic regression model nested for year and hospital where treatment took place with postoperative outcomes for patients with colorectal liver metastases (CRLM) who underwent liver resection in the Netherlands between 2014 and 2018

Postoperative complicated course		Multivariable analysis		
Factor	***N***	**OR**	**CI (95%)**	**p-value**
Type of procedure				0.789
Resection only	734	1		
Combined resection and ablation	734	0.95	0.65–1.38	
Major liver resection				**<0.001**
No	1097	1		
Yes	371	2.31	1.57–3.39	
American Society of Anesthesiology (ASA) classification				**0.001**
I/II	1203	1		
III+	259	1.92	1.27–2.89	
Missing[a]	6			
Maximum diameter of largest CRLM (mm)				0.057
<20	419	1		
20–34	513	1.21	0.79–1.86	0.382
35–54	241	1.56	0.95–3.96	0.081
>55	108	2.18	1.57–3.39	**0.001**
Missing[a]	187			
Surgical strategy				**<0.001**
Primary tumor first	894	1		
Liver first	324	0.89	0.58–1.41	0.687
Simultaneous resection of colorectal tumor and CRLM	171	2.49	1.55–3.98	**<0.001**
Missing[a]	79			
Type of surgery				0.265
Open	1250	1		
Minimally invasive	154	0.55	0.26–1.13	0.104
Conversion	54	1.00	0.41–2.39	0.984
Missing[a]	10			
Mortality		**Multivariable analysis**		
Factor	***N***	**OR**	**CI (95%)**	**p-value**
Type of procedure				0.299
Resection only	734	1		
Combined resection and ablation	734	0.54	0.17–1.72	
Major liver resection				0.070
No	1097	1		
Yes	371	2.49	0.93–6.65	
American Society of Anesthesiology (ASA) classification				**<0.001**
I/II	1203	1		
III+	259	5.53	2.07–14.7	
Missing[a]	6			
Maximum diameter of largest CRLM (mm)				**0.057**
<20	419	1		
20–34	513	2.22	0.45–11.1	0.231
35–54	241	6.97	1.35–34.3	**0.023**
>55	108	6.56	1.00–43.5	0.069
Missing[a]	187			

Bold p-values indicate statistical significance.
[a] Missing not included in analyses based on relatively small group.

with 30-day mortality. The odds of mortality were higher in patients with a high ASA score (aOR 5.53, CI 2.07–14.7, $p < 0.001$) increasing diameter of largest CRLM (<20 mm vs. >35–54 mm, aOR 6.97, CI 1.35–34.3, $p = 0.023$) (Table 5).

Discussion

In this nationwide population-based analysis significant variation was observed in the use of combined resection and ablation between hospitals and oncological networks in the Netherlands which persisted after case-mix correction. The propensity score-matched analysis showed lower rates of postoperative liver failure, bile leakage, shorter length of hospital stay, lower rates of PCC and 30-day mortality in the combined resection and ablation group. This effect was attributable to the extent of the liver resection performed. Oncological results of combined resection and ablation remain to be determined in order to provide a definitive advice concerning this technique in colorectal liver metastases patients.

Combining resection and ablation for CRLM in order to spare parenchyma has gained terrain over the last decade, with studies increasingly reporting postoperative- and oncological outcomes. Decreasing postoperative 30-day morbidity and 30-day mortality are first priority after surgical procedures and specifically liver surgery in order to decrease the impact of complications on quality of life, oncological outcomes and costs.[19-23] Several reports show that complications after liver surgery impact the long-term survival and should be minimized.[24,25] Using an approach that decreases complications should therefore always be considered in such patients. Promising results concerning postoperative outcomes in patients receiving the combination of resection and thermal ablation have been published.[9] Reports on short-term postoperative outcomes after combined resection and ablation are mainly small sample sized studies.[6,9,26] A large retrospective study from the United States showed that postoperative outcomes were at least similar between patients undergoing resection or combined resection and ablation.[27] When comparing two-staged procedures to combined resection and ablation several studies show that combined resection and ablation seems to provide similar postoperative- and oncological outcomes.[8,9,28] The present study shows improved short-term postoperative outcomes such as lower length of stay and lower mortality rate after combined surgery and ablative techniques compared to resection only. However, this effect was attributable to not performing major liver resection in the combined resection and ablation patients. The combination of resection and ablative techniques seems safe in patients with CRLM and should be considered in these patients either as a potentially curative option in patients who would otherwise be considered to have unresectable disease or as an alternative for more invasive surgery. In multivariable logistic regression it was shown that the positive results in our study are a result of the less invasive character of combining liver resection with thermal ablation compared to resection only. Therefore, treating physicians should try to avoid liver major liver resection, if by combining liver resection and ablation, the same result can be achieved. This can particularly be used in more frail patients. However, oncological outcomes will have to be assessed.

This population-based study reflecting daily practice in the Netherlands showed that several factors were associated with the use of combined resection and ablation. These factors include preoperative chemotherapy, >3 CRLM, and bilobar disease. Earlier reports provide information on factors that increase the use of combination of resection and ablation. These studies show that combining treatment techniques can increase resectability when CRLM are situated at a difficult location, are bilobar or when a high number of CRLM is present.[4,29] The lack of consensus in the Dutch guideline and international studies on oncological safety may be responsible for the variation in the use of combined resection and ablation between hospitals and oncological networks in the Netherlands. Another possible explanation for the variation in the use of combined resection and ablation could be the varying availability of interventional radiologists or surgeons who can perform thermal ablation across centers in the Netherlands. These specialists are more often situated in a tertiary referral center. The assessment of hospital variation in the use of combined resection and ablation provides insight in the differences in the use of combined resection and ablation between Dutch hospitals and oncological networks. Hospital variation has proven to be associated with undesired complications as well as higher costs.[30-32] We are still awaiting potentially oncological favorable outcomes of either treatment strategy. Hospital variation is a problem when one of the treatment strategies proves to be favorable and should therefore be minimized.[33]

An important limitation of this study is that long-term oncological outcomes such as overall survival and disease-free survival were not analyzed. These long-term outcomes are not part of the DHBA, and therefore no conclusions can be drawn regarding oncological outcome of combined resection and ablation. Before we can recommend resection and ablation over surgery alone as the preferred approach for this subgroup, non-inferiority with regards to overall survival should be established. Several studies show that oncological outcomes of patients who receive parenchymal sparing resection of CRLM are not significantly different from patients undergoing conventional liver resection.[4,6] Other reports concerning CRLM patients indicated that local control and oncological safety of ablative techniques were similar to liver resection.[34-37] Some reports indicate that combined resection and ablation achieves results comparable to conventional liver resection with respect to short-term postoperative outcomes and oncological outcomes.[38-42] However, oncological safety of combined resection and ablation is still under debate as multicenter randomized studies are lacking and contrasting results have been published before.[43] These are urgently needed to address the true oncological safety of the combination of combined resection and ablation. If these studies have been realized these results can pose a change in (inter)national guidelines and on the use of combined resection and ablation.[44] This study with upcoming trials could also result in health insurances reimbursing thermal ablation for CRLM. To date thermal ablation is not reimbursed by Dutch Health insurance companies for resectable CRLM.

Other limitations of this study include its retrospective design and, as a result of the audit nature of this research lacking of very detailed perioperative information. This is represented by the lack of information regarding tumor location and diameter of lesions other than the largest CRLM. When tumors are near large vessels, are very centrally located or several large lesions are in situ, combined resection and ablation might not be possible and the surgical team may have chosen a higher risk resection only strategy.

In conclusion, this population-based nationwide study reflecting daily practice in the Netherlands showed significant hospital and oncological network variation in the use of combined resection and ablation. Lower postoperative bile leakage, liver failure, length of stay, postoperative complicated course and 30-day mortality was observed in the combined resection and ablation group. Improved postoperative outcomes after combined resection and ablation are due to parenchymal sparing surgery. This implies that if technically feasible, combining resection and ablation and thereby avoiding major hepatectomy improves postoperative outcomes. Oncological results of combined resection and ablation remain to be determined in order to provide a definitive advice concerning this technique in colorectal liver metastases patients. Therefore, the implication should be that a surgeon should consider the trade-off of possible increase in local recurrence rates and the decrease in short-term postoperative risk when using ablation to avoid a major hepatectomy while treating patients with multiple liver lesions. That is particularly true for patients that are at higher risk of complications.

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Conflict of interest
None to declare.

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