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ORIGINAL ARTICLE

Hospital variation and outcomes of simultaneous resection of primary colorectal tumour and liver metastases: a population-based study

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Abstract

Background: The optimal treatment sequence for patients with synchronous colorectal liver metastases (CRLM) remains uncertain. This study aimed to assess factors associated with the use of simultaneous resections and impact on hospital variation.

Method: This population-based study included all patients who underwent liver surgery for synchronous colorectal liver metastases between 2014 and 2019 in the Netherlands. Factors associated with simultaneous resection were identified. Short-term surgical outcomes of simultaneous resections and factors associated with 30-day major morbidity were evaluated.

Results: Of 2146 patients included, 589 (27%) underwent simultaneous resection in 28 hospitals. Simultaneous resection was associated with age, sex, BMI, number, size and bilobar distribution of CRLM, and administration of preoperative chemotherapy. More minimally invasive and minor resections were performed in the simultaneous group. Hospital variation was present (range 2.4%–83.3%) with several hospitals performing simultaneous procedures more and less frequently than expected. Simultaneous resection resulted in 13% 30-day major morbidity, and 1% mortality. ASA classification $\geq$3 was independently associated with higher 30-day major morbidity after simultaneous resection (aOR 1.97, CI 1.10–3.42, p = 0.018).

Conclusion: Distinctive patient and tumour characteristics influence the choice for simultaneous resection. Remarkable hospital variation is present in the Netherlands.

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Introduction

Patients with colorectal cancer (CRC) and synchronous colorectal liver metastases (CRLM) can be treated with curative intent if complete removal of both tumour sites is possible. The choice for a staged or simultaneous resection of primary tumour and CRLM remains under debate and depends on multiple factors including patient and tumour characteristics, surgeon's preference and hospital workflow.[1–3] Reasons in favour of a simultaneous approach include a single operation for the patient, timely management of both tumour sites and reduction of costs.[4–6] Reasons in favour of a staged approach include lower surgical morbidity rates and prevention of unnecessary surgery in case of either rapid disease progression or complete response of the primary tumour.[4] The Dutch guideline states that simultaneous resections are not standard of care but may be considered in an experienced team and after careful patient selection.[2] International consensus recommends that simultaneous resections should only be performed in patients with limited hepatic disease and easy-to-resect primary tumour.[7]

Two meta-analyses analysing the outcome of staged versus simultaneous resections show that evidence is biased and are inconclusive about the potential harm or benefit of the simultaneous approach compared to a staged approach.[8,9] The only randomised controlled trial comparing surgical outcomes of a simultaneous resection with a staged, primary-first, approach showed no difference in major complications at liver site (28% vs. 13%, $p = 0.08$) and, noteworthy, a tendency towards improved 2-year survival rates for the simultaneous group ($p = 0.05$).[10]

The aim of this study was to identify patient- and tumour characteristics discriminating for treatment approach, to assess inter-hospital variability in the use of simultaneous resections, and to identify preoperative characteristics associated with major morbidity in the simultaneous group.

Methods

This was a population-based, nationwide cohort study. Data of the Dutch Hepato Biliary Audit (DHBA) were used. Individual informed consent from patients for data collection was not required for the DHBA according to Dutch law. Data analyses were performed on an anonymized dataset and did not need ethical approval.

National database

The DHBA collects detailed information of all patients who underwent surgery for CRLM the Netherlands. Percutaneous ablations were registered in the DHBA since 2018. All hospitals have been obliged to report to the DHBA since 2014 by the Dutch inspectorate of healthcare. Since introduction of the DHBA, minimal mandatory data requirements have been updated regularly and new mandatory variables have been added. Liver surgery is not performed in each Dutch hospital, as there is a required minimum volume of 20 liver resections per centre per year. In general, inter-hospital meetings to discuss patients with a possible indication for liver surgery and subsequent referral to the appropriate hospital for treatment are available on weekly basis within an oncological network. Oncological networks are hospital collaborations with at least one tertiary referral centre and multiple regional hospitals. Regional and tertiary referral centres have been identified according to complexity of performed surgical procedures and their function in the oncological network. Tertiary referral centres perform more complex surgical procedures.

The DHBA is part of the Dutch Institute of Clinical Auditing (DICA) and the accuracy of the audit was 97% at last data verification in 2015.[11,12]

Patient selection

All patients who underwent liver surgery for liver metastases between January 1, 2014 and December 31, 2019, and registered in the DHBA before April 1, 2020 were included. Patients were excluded if the primary tumour was not of colorectal origin, liver metastases were not synchronously diagnosed (diagnosis at time of diagnosis of the primary tumour), no liver resection was performed (unresectable or ablation was the only liver directed intervention), and if data were missing regarding synchronous or metachronous diagnosis of the CRLM, type of surgery, moment of liver resection, or tumour origin.

Patients were divided in the simultaneous resection group or the staged resection group based on the registration of concomitant resection of the primary colon or rectum tumour during liver surgery.

Demographic and clinical data

Patient characteristics included sex, age, Body Mass Index (BMI), comorbidity score according to the Charlson Comorbity Index (CCI), American Society of Anesthesiologists (ASA) classification, pre-existent liver pathology (macroscopic or histopathological liver tissue abnormalities), and previous liver surgery. Tumour characteristics included location primary tumour, number of CRLM, distribution of CRLM, maximum diameter of largest CRLM before start treatment, and metachronous or synchronous metastases. Treatment characteristics included preoperative chemotherapy, staged or simultaneous resection, surgical approach (i.e. laparoscopic, open or conversion), extent of liver resection (major resection was defined as three or more adjacent Couinaud segments), type of hospital, oncological network, and year of surgery.[13,14]

Outcomes

Case-mix factors influencing use of simultaneous resection were addressed. Case-mix factors were the abovementioned patient-, tumour- and treatment characteristics that possibly influenced the association of variables on outcome and can cloud hospital comparison without proper adjustment.[15]

Table 1 Baseline characteristics stratified per treatment strategy in patients with synchronous colorectal liver metastasis (CRLM) diagnosed between 2014 and 2019 in the Netherlands

Factor	Staged resection	Simultaneous resection	*p-value*
	N (%)	*N (%)*	
Number of patients	1557 (73)	589 (27)	
Sex			**0.020**
Male	974 (63)	337 (57)	
Female	577 (37)	252 (43)	
Missing[a]	6	0	
Age (year)			**<0.001**
<50	137 (9)	44 (8)	
50 - 64	637 (41)	188 (32)	
65 - 80	708 (46)	308 (53)	
≥80	74 (5)	46 (8)	
Missing[a]	1	3	
Body Mass Index, mean (SD)	25.4 (4.1)	26.1 (4.3)	**0.001**
Charlson Comorbidity Index			0.590
0/1	1211 (78)	451 (77)	
2+	346 (22)	138 (23)	
American Society of Anesthesiology classification			0.644
I/II	1262 (83)	476 (82)	
III+	268 (18)	108 (18)	
Missing[a]	27	5	
Pre-existing liver pathology[b]			**<0.001**
No	1039 (78)	424 (87)	
Yes	296 (22)	66 (13)	
Missing[a]	222	99	
Liver resection in the past			0.619
No	1527 (99)	578 (99)	
Yes	13 (1)	3 (1)	
Missing[a]	17	8	
Location primary tumour			**<0.001**
Colon	936 (60)	463 (79)	
Rectum	615 (40)	126 (21)	
Missing[a]	6	0	
Number of CRLM			**<0.001**
1	404 (27)	269 (47)	
2	300 (20)	136 (24)	
3	228 (15)	60 (10)	
4	153 (10)	38 (7)	
≥5	412 (28)	72 (13)	
Missing[a]	60	14	
Distribution CRLM			**<0.001**
Unilobar	642 (42)	360 (62)	
Bilobar	899 (58)	223 (38)	
Missing[a]	16	6	
Maximum diameter of largest CRLM (mm)			**<0.001**
<20	384 (27)	213 (42)	
20–34	473 (34)	175 (35)	
35–54	294 (21)	64 (13)	
>55	261 (19)	50 (10)	
Missing[a]	145	87	
Preoperative chemotherapy			**<0.001**
No	718 (49)	373 (70)	
Yes	734 (51)	158 (30)	
Missing[a]	105	58	
Type of hospital[c]			0.744
Regional hospitals	853 (55)	328 (56)	
Tertiary referral centre	704 (45)	261 (44)	
Year of surgery			0.058
2014	289 (19)	84 (14)	
2015	281 (18)	97 (17)	
2016	303 (20)	126 (21)	
2017	266 (17)	127 (22)	
2018	205 (13)	77 (13)	
2019	213 (14)	78 (13)	
Surgical approach			**0.002**
Open	1186 (77)	410 (70)	
Minimally invasive	365 (23)	176 (30)	
Missing[a]	6	3	
Major liver resection[d]			**<0.001**
No	1088 (70)	527 (89)	
Yes	469 (30)	62 (11)	

CRLM = colorectal liver metastasis, SD = standard deviation.
[a] Missing not included in analyses based on relatively small group.
[b] Macroscopic or histopathological liver tissue abnormalities.
[c] Type of hospital: tertiary referral centre are defined as hospitals with highest expertise on oncologic surgery.
[d] ± Major liver resection was defined as resection of at least 3 adjacent Couinaud segments

Hospital variation in the use of simultaneous resection was compared for both individual hospitals and for oncological networks.

Surgical outcomes of simultaneous resections included treatment specific data and 30-day overall morbidity, 30-day major morbidity, 30-day mortality, length of hospital stay (LOS), and postoperative complicated course (PCC). Because no outcome parameters of the primary tumour resection for the staged

Table 2 Univariable and multivariable logistic model of patient- and tumour factors associated with simultaneous liver resection and resection of colorectal primary tumour in patients with synchronous colorectal liver metastasis (CRLM) diagnosed between 2014 and 2019 in the Netherlands

Factor	N	Univariable analysis			Multivariable analysis		
		OR	CI (95%)	*p-value*	aOR	CI (95%)	*p-value*
Sex				0.018			0.163
Male	1311	1			1		
Female	829	1.26	1.04–1.53		1.17	0.94–1.45	
Missing[a]	6						
Age (years)				<0.001			**0.040**
<50	181	1			1		
50 - 64	825	0.92	0.63–1.35	0.660	0.74	0.49–1.12	0.148
65 - 79	1016	1.35	0.95–1.97	0.103	0.97	0.65–1.46	0.876
≥80	120	1.94	1.17–3.20	0.010	1.22	0.70–2.14	0.475
Missing[a]	4						
Body Mass Index, mean (SD)		1.04	1.02–1.06	0.001	1.04	1.02–1.07	**0.001**
Charlson Comorbidity Index				0.550			
0/1	1662	1					
2+	484	1.07	0.85–1.34				
American Society of Anesthesiology classification				0.600			
I/II	1738	1					
III +	376	1.07	0.83–1.36				
Missing[a]	32						
Pre-existing liver pathology[b]				<0.001			**0.001**
No	1463	1			1		
Yes	362	0.55	0.41–0.73	<0.001	0.57	0.41–0.79	**<0.001**
Missing	321	1.09	0.84–1.42	0.508	1.09	0.81–1.47	0.567
History of liver surgery				0.441			
No	2105	1					
Yes	16	0.61	0.14–1.90				
Missing[a]	25						
Location primary tumour				<0.001			**<0.001**
Colon	1399	1			1		
Rectum	741	0.41	0.33–0.52		0.43	0.34–0.55	
Missing[a]	6						
Number of CRLM				<0.001			**<0.001**
≤3	1397	1			1		
≥4	675	0.39	0.31–0.49		0.54	0.41–0.71	
Missing[a]	74						
Distribution CRLM				<0.001			**<0.001**
Unilobar	1002	1			1		
Bilobar	1122	0.44	0.37–0.54		0.67	0.53–0.84	
Missing[a]	22						
Maximum diameter largest CRLM (mm)				<0.001			**<0.001**
<20	597	1			1		
20 - 34	648	0.67	0.52–0.85	<0.001	0.67	0.51–0.87	**0.003**
35 - 54	358	0.39	0.28–0.54	<0.001	0.40	0.28–0.56	**<0.001**

Table 2 (*continued*)

Factor	N	Univariable analysis			Multivariable analysis		
		OR	CI (95%)	*p-value*	aOR	CI (95%)	*p-value*
>55	311	0.35	0.24–0.58	<0.001	0.38	0.26–0.56	<**0.001**
Missing	232	1.08	0.79–1.48	0.624	1.16	0.81–1.67	0.409
Preoperative chemotherapy				<0.001			<**0.001**
No	1091	1			1		
Yes	892	0.41	0.33–0.51	<0.001	0.69	0.54–0.89	**0.004**
Missing	163	1.06	0.75–1.49	0.727	1.14	0.77–1.70	0.505
Type of hospital[c]				0.708			
Regional hospital	1181	1					
Tertiary referral centre	965	0.96	0.80–1.17				

CRLM = colorectal liver metastasis, OR = odds ratio, aOR = adjusted odds ratio, CI = confidence interval, SD = standard deviation.
[a] Missing not included in analyses based on relatively small group.
[b] Macroscopic or histopathological liver tissue abnormalities.
[c] Type of hospital: tertiary referral centre are defined as hospitals with highest expertise on oncologic surgery.

approach were available, no comparison in surgical outcomes between the two approaches could be performed. Practitioners register the presence of any Clavien-Dindo surgical complications grade (overall morbidity) and grade 3 or higher complications (major morbidity, CD $\geq$ 3) separately at 30-days postoperatively.[16] If any complication occurred, the registry required the type of complication(s), regardless of grade. PCC was registered when a patient was admitted longer than 14 days or if a major complication occurred. Hospital stay was calculated from the day of surgery until the day of discharge. General surgical complications registered were postoperative haemorrhage, pneumonia, surgical site infections, thromboembolic events and cardiac complications. Intra-abdominal infection, bile leakage, and liver failure (according to the International Study Group of Liver Surgery definition) are specific abdominal surgical complications of which the last two are most specific for liver surgery.[17] The complication of highest severity level was used in case of multiple complications per patient, regardless of relation to the liver resection or primary resection.

Statistical analysis

Between groups comparison of baseline characteristics was done using the $\chi 2$ test or Fisher exact test as appropriate for categorical variables. Independent student's *t*-test was used for continuous variables.

Univariable and multivariable logistic regression analyses were used to identify case-mix factors associated with performing simultaneous resection and 30-day major morbidity after simultaneous resection. Univariable and multivariable logistic regression models were performed in a two-step method. All variables with a p-value of $\leq$0.100 in univariable analysis were entered in the multivariable analysis. A two-sided p-value of <0.050 was considered statistically significant.

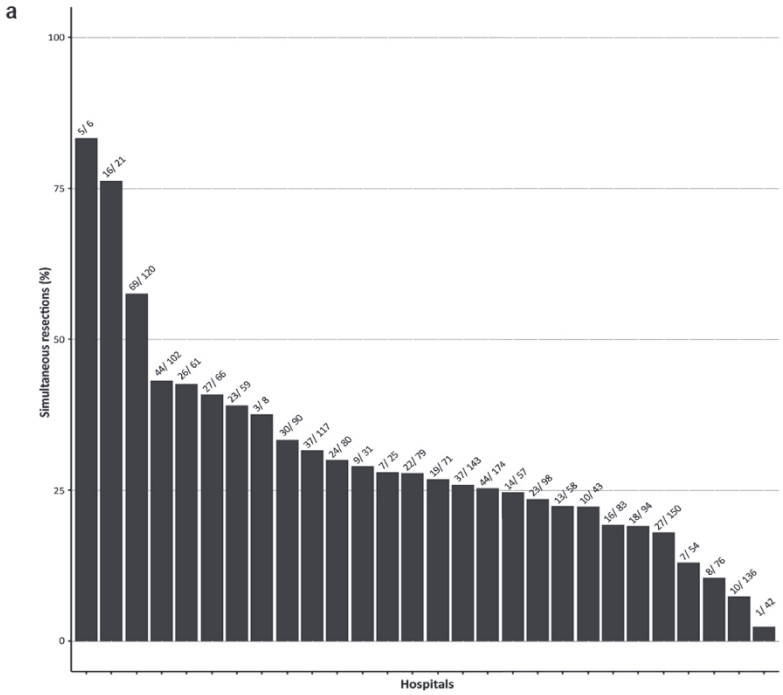
Based on patient- and tumour characteristics of all patients included expected use of simultaneous resection was calculated per patient using a multivariable logistic regression model. By grouping all patients who underwent simultaneous resection per hospital the observed use of simultaneous resection was calculated. To visualize the difference between hospitals, the observed/expected ratio (O/E ratio) was used. By dividing the observed number of simultaneous resections of every hospital by the expected simultaneous resection of that same hospital, the O/E ratio was calculated. This is the case-mix adjusted ratio indicating whether a hospital performed more or less simultaneous resections than was expected. An O/E ratio above 1 indicated that a hospital performed more simultaneous resections than expected, an O/E ratio below 1 indicated that a hospital performed less simultaneous resections than expected. The 95% confidence intervals (CI) were calculated to indicate whether the O/E ratio of a hospital was statistically different from the other hospitals.

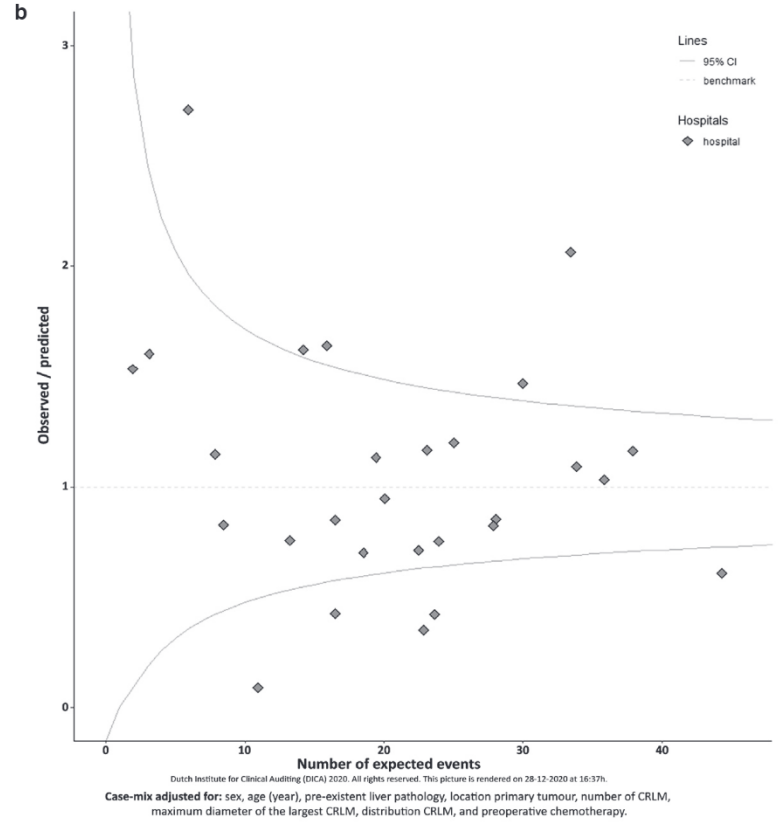
Multicollinearity was tested through the Variance Inflation Factor (VIF). A VIF of 3 or more was the cut-off value indicating multicollinearity. Patients with missing values were analysed as a separate group in multivariable logistic regression if these exceeded 5% of the total included number of patients. If the missing values in a variable were below 5%, the missing patients were excluded from the analysis.[18]

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

Results

In total, 6477 patients were identified in the DHBA of which 2482 (38.3%) had synchronous CRLM. In 258 patients no liver resection was performed, e.g. unresectable or ablation only, and in an additional 78 patients the moment of liver surgery was unknown (Supplementary Fig. 1). Included in analyses were 2146 patients of whom 589 patients (27%) underwent simultaneous resection and 1557 patients (73%) a staged liver resection for





synchronous liver metastases. In total, 28 hospitals performing liver resections within 7 oncological networks in the Netherlands reported to the DHBA between 2014 and 2019.

Baseline characteristics

Baseline characteristics of both groups are demonstrated in Table 1. Patients who underwent simultaneous resection were older ($p < 0.001$), more often female ($p = 0.020$), had a higher mean BMI ($p = 0.001$), less pre-existent liver pathology (<0.001), and less preoperative chemotherapy ($p < 0.001$). Multiple tumour characteristics of the simultaneous group differed from the staged group ($p < 0.001$). The simultaneous group had a lower median number of metastases, more frequently unilobar CRLM, smaller diameter of the largest CRLM and more often the primary tumour located in the colon. The rate of minimally invasive resection was higher ($p = 0.002$) and less major liver resections were performed ($p < 0.001$). Stratification of the simultaneous group for extent of liver resection showed multiple significant differences between the minor and major liver resection group (Supplementary Table 1). Patients in the major resection group more often received preoperative chemotherapy ($p < 0.001$), had less frequently solitary CRLM ($p < 0.001$), the maximum diameter of largest CRLM was higher ($p < 0.001$), had more often bilobar CRLM ($p = 0.046$), and were more often treated in tertiary referral centres ($p = 0.030$).

Associated factors with simultaneous resection

In multivariable analysis, seven patient- and tumour factors were associated with simultaneous resection (Table 2). BMI was associated with performing simultaneous resection (aOR 1.04, CI 1.02–1.07, $p = 0.001$). Factors associated with less frequent use of simultaneous resection were pre-existent liver pathology (aOR 0.57, CI 0.41–0.79, $p < 0.001$), preoperative chemotherapy (aOR 0.69, CI 0.54–0.89, $p = 0.004$), four or more CRLM (aOR 0.54, CI 0.41–0.71, $p < 0.001$), bilobar CRLM (aOR 0.67, 0.53–0.84, $p < 0.001$), diameter of the largest CRLM of >50 mm versus <20 mm (aOR 0.38, CI 0.26–0.56, $p < 0.001$), and a primary tumour in the rectum (aOR 0.43, CI 0.34–0.55, $p < 0.001$).

Hospital variation surgical sequence

Variation between hospitals and oncology networks was observed regarding the use of simultaneous resection. Unadjusted rates of simultaneous resections ranged between 2.4% and 83.3% between hospitals (Fig. 1a). Unadjusted rates of simultaneous resections ranged between 9.5% and 41.2% between oncological networks. All hospitals performing liver surgery have performed simultaneous resections.

Based on the case-mix factors, the expected percentage of simultaneous resection ranged between 51.4% and 17.4% for hospitals. In oncological networks analyses, the percentage of expected simultaneous resections ranged between 22.0% and 32.9%. After correction for case-mix factors, five hospitals performed simultaneous resections more often than expected and five significantly less often (Fig. 1b). One oncological network performed simultaneous resections more frequently and two networks less frequently than expected based on the case-mix factors (Supplementary Fig. 2).

Surgical outcomes

Treatment characteristics and postoperative outcomes of simultaneously resected patients are shown in Table 3. Overall 30-day morbidity was observed in 251 of 589 patients (43%) and major-morbidity in 76 of 589 patients (13%). Of all registered complications, intra-abdominal infection was the most common complication in 69 patients (13%), followed by pneumonia (7%), surgical site infections (6%), and cardiac complications (4%). Thromboembolic complications (2%), bile leakage (2%), postoperative haemorrhage (1%), and liver failure (1%) were less common. The thirty-day mortality rate was 1% (6 patients).

Table 4 shows patient-, tumour- and procedural factors association with 30-day major morbidity after simultaneous resection. ASA classification 3 or higher was independently associated with 30-day major morbidity ($p = 0.018$) in patients who underwent simultaneous resection. The absolute rate of major morbidity was 11% for patients with ASA 1 or 2 and 19% for ASA 3+ patients ($p = 0.029$). Treatment characteristics and postoperative outcomes of simultaneously resected patients stratified for ASA groups are shown in Supplementary Table 2.

Discussion

This nationwide study is one of the largest cohort studies describing simultaneous resection outcomes and reflects the current daily practice in the Netherlands. This study showed that multiple patient and tumour characteristics were discriminating for selection of a simultaneous approach, mostly reflecting limited tumour burden. Significant hospital variation in the use of simultaneous resection of the primary colorectal tumour and liver metastases was observed. Limited liver related complications were observed despite substantial overall morbidity rates of the simultaneous approach. Higher ASA

Figure 1 **a**. Unadjusted hospital variation in performing simultaneous resection of synchronous colorectal primary tumour and colorectal liver metastases (CRLM) patients diagnosed between 2014 and 2019 in the Netherlands. The bars reflect the percentage of simultaneous resections of all CRLM resections per hospital. The actual number of simultaneous/all resections are displayed above the corresponding bar. **b**. Case-mix adjusted funnel-plot of between-hospital variation in performing simultaneous resection of colorectal primary tumour and colorectal liver metastases (CRLM) synchronously diagnosed between 2014 and 2019 in the Netherlands

Table 3 Postoperative outcomes in patients with simultaneous resection of colorectal primary tumour and synchronous liver metastasis (CRLM) diagnosed between 2014 and 2019 in the Netherlands

Factor	Simultaneous resection
	N (%)
Number of patients	589
Length of stay, median (IQR)	8.0 (6.0–13.0)
Overall 30-day morbidity	
No	337 (57)
Yes	251 (43)
Missing[a]	1
30-day major morbidity[b]	
No	513 (87)
Yes	76 (13)
Postoperative complicated course[c]	
No	456 (77)
Yes	133 (23)
30-day mortality	
No	570 (99)
Yes	6 (1)
Missing[a]	13
Postoperative haemorrhage	
No	511 (99)
Yes	6 (1)
Missing[a]	72
Pneumonia	
No	515 (93)
Yes	39 (7)
Missing[a]	35
Surgical site infection	
No	518 (94)
Yes	33 (6)
Missing[a]	38
Thromboembolic complication	
No	569 (98)
Yes	12 (2)
Missing[a]	8
Cardiac complication	
No	558 (96)
Yes	24 (4)
Missing[a]	7
Intra-abdominal infection	
No	483 (87)
Yes	69 (13)
Missing[a]	37
Bile leakage	
No	570 (98)
Yes	14 (2)
Missing[a]	5
Liver failure	
No	580 (99)
Yes	3 (1)
Missing[a]	6

CRLM = colorectal liver metastasis, IQR = inter-quartile range.
[a] Missing not included in analyses based on relatively small group.
[b] Major morbidity includes all Clavien-Dindo surgical complication score grade 3 or higher (CD $\geq$ 3) complications.
[c] Postoperative complicated course is registered if hospital admittance was >14 days or if a major complication occurred.

classification was independently associated with increased 30-day major morbidity.

Several factors were associated with the chosen treatment sequence in the Netherlands. Factors including three or less CRLM, unilobar CRLM distribution, maximum CRLM diameter under 20 mm, location of the primary tumour in the colon, and no preoperative chemotherapy were associated with simultaneous resection. Intended surgery details, including possibility of laparoscopic surgery and extent of liver surgery, were also different in the between group comparison, showing selection of less invasive surgery in the simultaneous resection group. Previous studies identified similar factors, but not exclusively and consistently.[19–24] A survey polling surgeons' preference for simultaneous resection in Northern America showed that surgeons opt for simultaneous resection in case of minor liver resections and tend to prefer a staged approach in case of comorbidity and synchronous lung metastases.[25] The results of this study are in line with the general perception of eligible patients.

The current study showed that every Dutch hospital performing liver surgery selects patients for simultaneous resections. This reflects the advanced stage of centralisation in the Netherlands that allows each liver centre to select and perform simultaneous resections requiring expertise of both liver and colorectal surgery.[26] Five hospitals performed less and five hospitals performed more simultaneous procedures than expected based on case-mix factors identified in the current study. *Vallance et al.* showed wide variation in sequence applied in England and identified hospitals who did not treat any patients with simultaneous resection.[20] It is remarkable that such a variation exists in the authors' country even after centralisation with a minimum annual threshold of twenty liver resections. The national guideline only suggest that simultaneous resections may be considered in expert centres. Type of hospital, e.g. tertiary

Table 4 Univariable and multivariable logistic model of patient-, tumour- and procedural factors associated with 30-day major morbidity in patients with simultaneous resection of synchronous colorectal liver metastasis (CRLM) in the Netherlands from 2014 to 2019

Factor	N	Univariable analysis			Multivariable analysis		
		OR	CI (95%)	*p-value*	aOR	CI (95%)	*p-value*
Sex				0.383			
Male	337	1					
Female	252	0.80	0.48–1.31				
Age (years)				0.514			
<50	44	1					
50 - 64	188	1.91	0.62–8.30	0.313			
65 - 79	308	2.18	0.76–9.44	0.199			
>80	46	2.45	0.63–12.0	0.216			
Missing[a]	3						
Body Mass Index, mean (SD)		1.00	0.95–1.06	0.873			
Charlson Comorbidity Index				0.995			
0/1	451	1					
2+	138	1.02	0.56–1.76				
American Society of Anesthesiology classification				**0.021**			**0.018**
I/II	476	1			1		
III +	108	1.93	1.09–3.32		1.97	1.10–3.42	
Missing[a]	5						
Pre-existing liver pathology[b]				0.342			
No	424	1					
Yes	66	0.52	0.18–1.23	0.175			
Missing	99	0.95	0.48–1.77	0.886			
History of liver resection				NA			
No	578	NA					
Yes	3	NA	NA	NA			
Missing[a]	8	NA	NA	NA			
Location primary tumour				0.205			0.371
Colon	463	1			1		
Rectum	126	0.66	0.33–1.22		0.74	0.37–1.40	
Number of CRLM				0.759			
≤3	465	1					
≥4	110	0.90	0.46–1.67				
Missing[a]	14						
Distribution CRLM				0.285			
Unilobar	360	1					
Bilobar	223	0.81	0.51–1.10				
Missing[a]	6						
Maximum diameter largest CRLM (mm)				0.737			
<20	213	1					
20 - 34	175	1.13	0.61–2.10	0.692			
35 - 54	64	1.46	0.63–3.16	0.350			
>55	50	1.73	0.72–3.89	0.200			
Missing	87	1.14	0.51–2.39	0.736			

(*continued on next page*)

Table 4 (*continued*)

Factor	N	Univariable analysis			Multivariable analysis		
		OR	CI (95%)	*p-value*	aOR	CI (95%)	*p-value*
Preoperative chemotherapy				0.271			0.138
No	373	1			1		
Yes	158	0.62	0.33–1.11	0.121	0.58	0.30–1.07	0.090
Missing	58	0.81	0.32–1.77	0.625	0.55	0.18–1.35	0.231
Type of hospital[c]				0.936			
Regional hospital	328	1					
Tertiary referral centre	261	1.02	0.63–1.65				
Type of surgery				0.444			0.373
Open	410	1			1		
Minimally invasive	176	0.81	0.46–1.38		0.77	0.43–1.35	
Missing[a]	3						
Major liver resection				0.425			0.222
No	527	1			1		
Yes	62	1.34	0.62–2.67		1.61	0.72–3.34	

CRLM = colorectal liver metastasis, OR = odds ratio, aOR = adjusted odds ratio, CI = confidence interval, SD = standard deviation.
[a] Missing not included in analyses based on relatively small group.
[b] Macroscopic or histopathological liver tissue abnormalities.
[c] Type of hospital: tertiary referral centre are defined as hospitals with highest expertise on oncologic surgery.

referral centre or regional hospital, was not associated with the choice for simultaneous resection in the current study.

ASA classification was the only factor independently associated with major morbidity in simultaneous resections. Mortality rate after simultaneous resection was low and could be explained by adequate patient selection. Previously described characteristics including primary tumour location and extent of liver resection were not associated with major morbidity in the present study. Major liver resections were not frequently performed during simultaneous procedures and Dutch surgeons were reluctant to perform simultaneous resection in patients with rectal cancer. Long-term follow up of the present cohort is currently not available, but warranted and will be collected. In order to decrease hospital variation, clear guidelines should be conceived for patient selection based on both short-term postoperative outcomes and to be collected long term oncological outcomes.

High observed severe morbidity after simultaneous resection is concordant with the literature.[24,27] A recent meta-analysis compared both overall and major postoperative complications after simultaneous resection compared to staged resections.[8] All but one included studies had a retrospective design with a total of 44 studies included. Major morbidity was reported in 14 studies and was higher in the simultaneous group versus liver first [OR = 3.45 (95%CI: 1.01–11.78), (p = 0.05)] (I^2 = 0%, p = 0.56). There were no significant complication or major morbidity differences in simultaneous resections compared to primary first resections in pairwise and network meta-analysis. A recent study of the Dutch colorectal registry confirms this latter results when comparing laparoscopic resection of the colorectal primary tumour with simultaneous laparoscopic minor hepatic and primary tumour resections.[28] Most studies compared simultaneous resection outcomes to one of the two surgical procedures in the staged approach. The lower morbidity rates observed in the staged approach should therefore be interpreted with caution, as both surgical procedures should be included for assessment of surgical morbidity after a staged approach. Unfortunately, combining data of the resection of the primary tumour and liver metastases in a staged approach is not feasible with current national registry regulations. Thus, primary tumour surgical outcomes and completion of surgical treatment of both tumour sites could not be presented. Authors of a recently published randomized trial between staged operations (colorectal primary resection first) and simultaneous resection in France concluded that the complication rates appears not to be different between these strategies.[10] Accrual was low, over 10 years, the sample size of 85 patients does not allow for strong conclusions and colorectal first stage approach as standard sequence does not reflect the standard practice in the Netherlands/current standard practice.

Simultaneous resections can be of great value as they require only a single surgical session and provides timely treatment of both tumour sites. Future perspectives include further reduction of absolute complication rates, reducing hospital variability, and increase the number of patients who can safely undergo simultaneous resection. In order to provide evidence-based guidelines for patient selection, data of prospective studies is

required. The results of this study are being used to proceed with Codman's sessions in the Netherlands, i.e. in depth evaluations of variation between hospitals regarding the use of simultaneous resections. The aim of these sessions and future guidelines is to decrease between hospital variation and optimize (inter)national patient care.

The current study has several limitations, including the retrospective design and lack of data on primary tumour resections, preoperative treatment of the primary tumour in the staged group, and intraoperative data. The nationwide character and number of patients were strengths of the study. The DHBA was the most accurate and complete database for liver surgery in the Netherlands and included all hospitals performing oncologic liver surgery and all Dutch patients surgically treated for their CRLM. Therewith, this study accurately reflected current daily practice in the Netherlands and provided insight in patient- and tumour factors associated with choice of treatment sequence.

Conclusion

Simultaneous surgery of the primary colorectal tumour and liver metastases can be conducted safely nationally due to proper selection of patients. Selection of patients should be based on ASA score 1–2, limited liver resection, and non-rectal primary location. The observed hospital variation emphasises the current lack of (inter)national guidelines regarding simultaneous resection and can be decreased by introducing standardized international guidelines based on randomized trials assessing postoperative and oncological outcomes.

Previous communication concerning manuscript

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Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2021.06.422.