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ORIGINAL ARTICLE

Trends and overall survival after combined liver resection and thermal ablation of colorectal liver metastases: a nationwide population-based propensity score-matched study

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Abstract

Background: In colorectal liver metastases (CRLM) patients, combination of liver resection and ablation permit a more parenchymal-sparing approach. This study assessed trends in use of combined resection and ablation, outcomes, and overall survival (OS).

Methods: This population-based study included all CRLM patients who underwent liver resection between 2014 and 2022. To assess OS, data was linked to two databases containing date of death for patients treated between 2014 and 2018. Hospital variation in the use of combined minor liver resection and ablation versus major liver resection alone in patients with 2–3 CRLM and ≤3 cm was assessed. Propensity score matching (PSM) was applied to evaluate outcomes.

Results: This study included 3593 patients, of whom 1336 (37.2%) underwent combined resection and ablation. Combined resection increased from 31.7% in 2014 to 47.9% in 2022. Significant hospital variation (range 5.9–53.8%) was observed in the use of combined minor liver resection and ablation. PSM resulted in 1005 patients in each group. Major morbidity was not different (11.6% vs. 5%, P = 1.00). Liver failure occurred less often after combined resection and ablation (1.9% vs. 0.6%, P = 0.017). Five-year OS rates were not different (39.3% vs. 33.9%, P = 0.145).

Conclusion: Combined resection and ablation should be available and considered as an alternative to resection alone in any patient with multiple metastases.

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Introduction

Colorectal cancer (CRC) is the third leading cause of cancer worldwide. Approximately 50% of patients with CRC develops colorectal liver metastases (CRLM). To date, partial liver resection is considered the only potential curative therapy, with five-year overall survival (OS) rates of approximately 50%.[1] Only 20% of the patients with CRLM are eligible for liver resection. CRLM can be considered unresectable due to the location of CRLM, insufficient future liver remnant, or comorbidities prohibiting liver resection.

A combination of liver resection with thermal ablation can extend curative options and may permit a more parenchymal-sparing approach for patients who would otherwise require a major liver resection. Studies comparing liver resection alone with combined liver resection and ablation described improved postoperative outcomes, such as reduced morbidity and mortality. However, these effects are mostly assigned to not performing major liver resections.[2–4] Long-term oncological data are contradictory and sometimes biased. Results of randomised controlled trials comparing both treatments are still awaited.[5–7]

As a result, hospital regimens in using combined liver resection and ablation significantly differ.[4] This can be explained partly by variation in availability and expertise of thermal ablation in different centres, or by a reduced confidence by hepatobiliary surgeons in the effectiveness of thermal ablation in reaching local control.[8] To date, no clear guideline exists. Multidisciplinary teams consisting of hepatobiliary surgeons and interventional radiologists have to consider which therapy best fits each individual patient (e.g., resection, ablation or combined treatment). Before better counselling for either approach can be provided, more long-term data is needed.

The aim of this study was to compare overall survival between patients who underwent liver resection only versus a combined approach of resection and ablation using propensity score matching. Moreover, implementation, hospital variation and short-term surgical outcomes in the Netherlands were assessed.

Methods

This study was based on data from three combined registries, including the mandatory nationwide Dutch Hepatobiliary Audit (DHBA), data from a Dutch national claim database, Vektis, and the Dutch Municipal Personal Records Database (BPR). Since 2014, the DHBA records patient, tumour, and treatment characteristics and short-term outcomes of all patients who underwent liver resection and the combination of liver resection and ablation. Since 2018, the registration was extended to include (percutaneous) ablative procedures performed by an interventional radiologist or surgeon, registration of percutaneous ablative procedures was non-obligatory until 2023. In 2017, data completeness of the DHBA was 97%.[9]

The DHBA does not contain long-term follow-up data. Therefore, data were linked to the Vektis and BPR database, which contains the date of death of all Dutch inhabitants deceased with healthcare insurance (99% coverage). The linking process of the two datasets is described previously.[10,11] Between 2014 and 2018, 95.8% of both datasets could be linked. This resulted from the introduction of the General Data Protection Regulation (GDPR) law in 2018. Thereafter several centres stopped registering Citizen Service numbers.[12] For this reason, overall survival was only evaluated in patients treated between 2014 and 2018.

In the Netherlands centralisation of liver surgery is in progress. This resulted in a decreased number of hospitals that performed liver surgery: 27 in 2014 compared to 22 in 2022. National requirements to perform liver surgery include a minimum of 20 liver resections per centre per year, experienced staff and access to other local therapies, including ablation.[13] During this time, a blueprint was made for seven oncological networks.[14] An oncological network comprises at least one tertiary referral centre and several non-academic hospitals. These networks are established to optimise collaboration between hospitals and improve patient care. However, not all regional networks are optimally used.

According to Dutch law, no ethical approval or informed consent was needed since collected data was processed anonymously. The DHBA scientific committee approves the study protocol.

Patient selection

All adult patients who underwent liver resection or combined liver resection and ablation for $\geq$2 CRLM between January 1, 2014, and December 31, 2022, and registered in the DHBA were included in analyses.

Exclusion criteria were patients with a single (1) CRLM, with a history of liver resection (i.e., treatment of recurrence), who underwent thermal ablation alone, or who had missing data on date of birth, date of surgery, and tumour type. In addition, two hospitals that did not perform combined liver resection and ablation were excluded from the analysis of hospital variation.

Eligible patients were allocated between liver resection only or combined liver resection and thermal ablation.

Variables

The following patient, tumour and treatment characteristics were extracted from the DHBA included sex, age, body mass index (BMI), Charlson Comorbidity Index (CCI),[15] American Society of Anaesthesiologist (ASA) grade,[16] diameter of the largest CRLM before tumour-specific treatment, number of CRLM, bilobar disease, location of the primary tumour (colon or rectal), synchronous or metachronous metastases, extrahepatic disease, extent of surgery (major versus minor resection, major was defined as resection of $\geq$3 adjacent Couinaud segments), treatment with preoperative chemotherapy (induction and/or

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Table 1 Baseline characteristics for propensity score matched cohort of patients diagnosed with colorectal liver metastases (CRLM) and undergoing resection or combined resection and ablation between 2014 and 2022 in the Netherlands

Factor		Resection alone N (%)	Combined Resection and ablation N (%)	P value	SMD
Total		1005	1005		
Sex				0.282	0.071
	Male	627 (62.4)	644 (64.1)		
	Female	376 (37.4)	361 (35.9)		
		2 (0.2)	0 (0.0)		
Age (median, IQR)		65.00 [57, 72]	64.00 [57, 72]	0.669	0.006
BMI (mean, SD)		25.96 (4.13)	26.23 (4.30)	0.143	0.066
ASA score				0.559	0.028
	I/II	781 (77.7)	769 (76.5)		
	≥III	224 (22.3)	236 (23.5)		
CCI				0.519	0.031
	0–1	789 (78.5)	776 (77.2)		
	≥2	216 (21.5)	229 (22.8)		
Extend of liver resection				<0.001	**0.490**
	Minor	670 (66.7)	872 (86.8)		
	Major	335 (33.3)	133 (13.2)		
Preoperative chemotherapy				0.381	0.062
	No	511 (50.8)	481 (47.9)		
	Yes	442 (44.0)	465 (46.3)		
	Missing	52 (5.2)	59 (5.9)		
Origin primary tumour				0.140	0.068
	Colon	661 (65.8)	693 (69.0)		
	Rectum	344 (34.2)	312 (31.0)		
Type of metastases				1.000	0.002
	Metachronous	373 (37.1)	374 (37.2)		
	Synchronous	632 (62.9)	631 (62.8)		
	Missing	13 (1.3)	12 (1.2)		
Number of CRLM				0.622	0.059
	2	253 (25.2)	253 (25.2)		
	3	217 (21.6)	197 (19.6)		
	4	163 (16.2)	159 (15.8)		
	≥5	372 (37.0)	396 (39.4)		
Size of the largest CRLM in mm				0.920	0.031
	<20	302 (30.0)	310 (30.8)		
	20–34	396 (39.4)	401 (39.9)		
	35–49	195 (19.4)	190 (18.9)		
	≥50	112 (11.1)	104 (10.3)		
Bilobar disease				<0.001	**0.205**
	No	303 (31.3)	218 (22.3)		
	Yes	664 (68.7)	759 (77.7)		
	Missing	43 (4.1)	32 (3.1)		
Simultaneous resection	No	879 (87.5)	872 (86.8)	0.690	0.021
	Yes	126 (12.5)	133 (13.2)		

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Table 1 (*continued*)

Factor		Resection alone N (%)	Combined Resection and ablation N (%)	P value	SMD
Extrahepatic disease				0.456	0.036
	No	887 (88.3)	875 (87.1)		
	Yes	118 (11.7)	130 (12.9)		
Type of hospital				0.002	**0.138**
	Regional hospital	532 (52.9)	463 (46.1)		
	Tertiary referral centre	473 (47.1)	542 (53.9)		

Bold SMD-values indicate non-optimal balance between both treatment groups.
Abbreviations: Standardised Mean Differences (SMD), Body Mass Index (BMI), American Society of Anaesthesiology (ASA) classification, Charlson Comorbidity Index (CCI), Colorectal liver metastases (CRLM), millimetre (mm).

neoadjuvant therapy), simultaneous resection of primary colorectal tumour and CRLM, and type of hospital where treatment took place (tertiary referral centre or regional hospital). Exact location of the metastases is not the registered.

Exact type of treatment (e.g., echo or CT-guided), the reasoning for the type of treatment or the exact location of the CRLM (e.g., near large vessels or major bile ducts) and recurrence is not registered in the DHBA. Colorectal resections are registered in a separate clinical audit, the Dutch Colorectal Audit, which cannot be linked to the DHBA dataset due current GDPR. Therefore, data on specific tumour characteristics, local and distant recurrence rates and treatment of the primary tumour is unavailable.

Outcomes

The main outcome of this study was overall survival (OS) of resection and ablation. OS was calculated from the date of surgery to the date of all-cause mortality. Short-term outcomes compared between both treatment groups included overall and major morbidity (Clavien-Dindo ≥3A), and 30-day or in-hospital mortality. In addition, several specific complications, including, intra-abdominal infection, liver failure and bile leakage (defined according to the international study group of liver surgery),[17] surgical site infection, pneumonia and cardiac complications, were compared between both treatment groups.

Trends and hospital variation in the use of combined liver resection and ablation were analysed between 2014 and 2022. Hospital variation was assessed unadjusted and adjusted for case-mix factors. Case-mix variables were described before.[4]

In case of more centrally located and limited metastases (2–3 lesions) with a maximum diameter of 3 cm, an alternative treatment for a major liver resection could be a combined (minor) liver resection and ablation, considering thermal ablation is restricted by tumour size and efficacy decreases in lesions >3 cm.[18,19] To evaluate if outcomes in this specific subset of patients between both treatments were comparable, a planned subgroup analysis was performed. Patients with 2–3 lesions ≤3 cm were selected and assigned into two treatment groups (major liver resection vs. minor liver resection combined with thermal ablation). In this subgroup, OS was compared, and hospital and oncological network variation in the use of combined treatment was assessed.

Statistical analysis

Patient, tumour, and treatment characteristics were described using frequencies and proportions for both treatment groups and tested using the Chi-square or Fisher exact test.

To compare short-term outcomes and OS between both treatment groups, propensity score matching (PSM) was conducted to reduce baseline differences. For PSM, a logistic regression model was used to calculate the propensity scores of every patient using the following independent variables, age, ASA-score, CCI, diameter of the largest tumour before treatment, number of lesions, and simultaneous resection of primary tumour and CRLM. Missing values were excluded from variables used for PSM. Given the independent variables, propensity scores were defined as the probability of receiving one of the treatments compared. Patients were matched with a 1:1 ratio, using nearest neighbour method, with a calliper of 0.2 of the standard deviations of the linear-logit for the propensity scores, and exact matching on the covariate of year of surgery.[20,21] The quality of the matching process was tested using standardised mean differences (SMD). An optimal balance between confounding factors was achieved when SMD <0.10. Non-matched cases were excluded from analysis. OS was compared before and after PSM between resection and resection and ablation and was assessed using Kaplan Meier analysis with the log-rank test. Subgroup analyses were performed in the group of patients without any form of extrahepatic disease.

Hospital variation in uptake of combined resection and ablation was assessed using proportions and percentages. Variation between hospitals and oncological networks was corrected for case-mix variables. Case-mix factors are used in a multivariable regression analysis to calculate the expected use of combined liver resection and ablation. All patient's expected counts per hospital were added and divided by the actual (observed) use of combined liver resection and ablation per hospital or network. An observed/expected ratio above 1 indicated more performed combined liver resection and ablation than expected, and a ratio

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below 1 indicated less performed combined liver resection and ablation than expected.

Analyses were performed using R version 4.1.0 (R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

Results

In total 3593 patients were included, of whom 2257 (62.8%) underwent liver resection alone, and 1336 (37.2%) underwent combined liver resection and ablation (Supplementary Fig. 1). Baseline characteristics of patients before matching are described in Supplementary Table 1.

Propensity score matching: baseline and surgical characteristics

After PSM, 1005 patients remained in both groups. Matching resulted in an SMD <0.10 for all matching variables. Differences between liver resection alone and combined resection and ablation were found in the percentage of major liver resections performed (33.3% vs. 13.2% P < 0.001, SMD = 0.490), proportion of bilobar disease (68.7% vs. 77.7% P < 0.001, SMD = 0.205), and if treatment took place in tertiary referral centre (47.1% vs. 53.9%, P = 0.002, SMD = 0.138) (Table 1).

Implementation of combined liver resection and thermal ablation

In 2014, 31.7% of patients underwent combined liver resection and ablation; this increased to 47.9% in 2022. In 16 hospitals, combined liver resection and ablation performance increased between 2019 and 2022 compared to 2015 and 2018. This increase was significant in 8 (50%) hospitals (Supplementary Fig. 2).

Postoperative outcomes

After PSM, specific postoperative complications occurred less often in the combined resection and ablation group, including liver failure (1.9% vs. 0.6%, P = 0.004) and 30-day mortality (2.1% vs. 0.8% P = 0.025). Postoperative overall morbidity, major morbidity were not different between both treatment groups (Table 2).

Overall survival

1112 patients were included in OS analysis between 2014 and 2018. Median follow-up was 77.8 (IQR: 67.9–91.5) months in the liver resection alone group and 76.5 (IQR: 64.8–89.9) months in the combined liver resection and ablation group. Before PSM, OS was different, log-rank P = 0.033, with an estimated five-year OS of 38.9% (95% CI: 36.4–41.5) after liver resection and 33.6% (95% CI: 30.3–37.3) after combined liver resection and ablation (Fig. 1a). After PSM survival was not

Table 2 Postoperative outcomes for patients diagnosed with colorectal liver metastases between 2014 and 2022 in the Netherlands who underwent resection alone or combined resection and ablation

Factor	Resection alone N (%)	Combined resection and ablation N (%)	P value
Total	1005	1005	
Bile leakage			0.069
No	957 (95.8)	965 (97.4)	
Yes	42 (4.2)	26 (2.6)	
Missing[a]	19	18	
Intra-abdominal infection			0.351
No	854 (85.0)	836 (83.2)	
Yes	53 (5.3)	68 (6.8)	
Missing	98 (9.8)	101 (10.0)	
Postoperative liver failure			**0.017**
No	981 (98.1)	985 (99.4)	
Yes	19 (1.9)	6 (0.6)	
Missing[a]	5	14	
Surgical site infection			0.667
No	883 (87.9)	874 (87.0)	
Yes	22 (2.2)	28 (2.8)	
Missing	100 (10.0)	103 (10.2)	
Pneumonia			0.931
No	861 (85.7)	855 (85.1)	
Yes	46 (4.6)	48 (4.8)	
Missing	98 (9.8)	102 (10.1)	
Cardiac complications			0.295
No	967 (96.2)	956 (95.1)	
Yes	30 (3.0)	34 (3.4)	
Missing[a]	8 (0.8)	15 (1.5)	
Overall morbidity			0.659
No	681 (67.8)	693 (69.0)	
Yes	321 (31.9)	300 (29.9)	
Missing[a]	3	12	
Major morbidity[b]			1.000
No	888 (88.4)	889 (88.5)	
Yes	117 (11.6)	116 (11.5)	
30-day mortality			**0.040**
No	972 (97.7)	984 (99.2)	
Yes	21 (2.1)	8 (0.8)	
Missing[a]	10	13	

Bold P values indicate statistical significance.
[a] Missing values of less than 5% were not included in analysis.
[b] Major morbidity was defined as complications graded Clavien Dindo 3 or higher.

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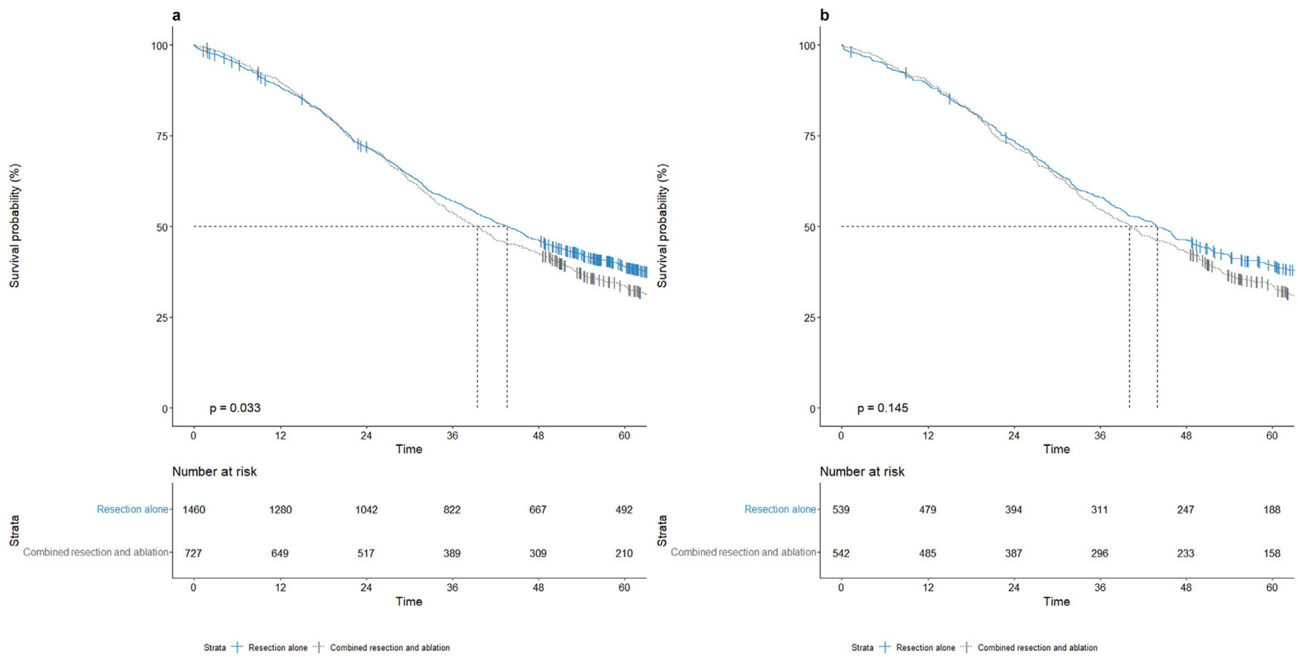

Figure 1 Kaplan Meier curves estimating overall survival of patients with colorectal liver metastases treated with liver resection or combined liver resection and ablation between 2014 and 2018 in the Netherlands. **a**: Unmatched cohort; the blue line indicates patients treated with resection alone, the grey line indicates patients treated with combined resection and ablation. **b**: Matched cohort: the blue line indicates patients treated with resection alone, the grey line indicates patients treated with combined resection and ablation. Time in months

different, log-rank P = 0.145 between both groups with an estimated five-year OS of 39.3% (95% CI: 35.3–43.7) after liver resection alone and 33.9% (95% CI: 30.1–38.2) after combined resection and ablation (Fig. 1b).

After exclusion of patients with extrahepatic disease, overall survival between both treatment groups was not different (log-rank P = 0.114) (Supplementary Fig. 3).

Patients with 2–3 metastases of ≤3 cm

In total 1114 patients had 2–3 metastases of ≤3 cm, of which 649 (58.2%) underwent minor liver resections, 322 (28.9%) combined minor liver resections and ablation and 128 (11.4%) major liver resections. In this subgroup, the use of minor combined liver resection and ablation ranged from 5.9% to 53.8% between hospitals and ranged from 17.3% to 39.4% between oncological networks. After correction for case-mix factors, two hospitals performed significantly less combined minor liver resection and ablation (and thus more major liver resections) in patients with oligometastatic CRLM ≤3 cm than expected (Fig. 2a). One oncological network performed significantly less combined minor liver resections/ablation (Fig. 2b). OS in this group of patients was not different for patients either treated with major liver resection only or combined minor liver resection and ablation, log-rank P = 0.962, with an estimated five-year OS of 47.5% (95% CI: 40.6–55.6) after major liver resection and 46.1% (95% CI: 36.8–57.8) after combined minor liver resection and ablation (Fig. 3).

Discussion

This study, using real-world data, shows no differences in morbidity, mortality and overall survival in patients treated with combined resection and ablation compared to liver resection alone. Combined liver resection and ablation was increasingly adopted from 2014 onwards. In a subgroup analysis of patients with 2–3 metastases up to 3 cm, significant hospital variation was seen in patients treated with either combined minor liver resection and ablation or major liver resection, yet OS rates were not different.

Few retrospective studies have been published on long-term outcomes of combined resection and ablation; sample sizes were small, and all studies were, by design, subjected to selection bias.[5,6,22,23] Some non-matched reports suggested unfavourable oncological outcomes in patients with CRLM treated with combined resection and ablation compared to resection alone.[3,24–26] Results of these previous studies were likely related to the heterogeneity of included patients in both treatment groups. It may well be possible that patients in the combined liver resection and ablation group were more often considered ineligible for surgery, for example, due to tumour location, insufficient liver parenchyma, or worse condition of the patient.[6] In these patients, lower OS rates could have been expected. Without propensity score matching, this could induce heterogeneity and biased results. Results of the current study were concordant with some smaller matched cohort studies.[27–32]

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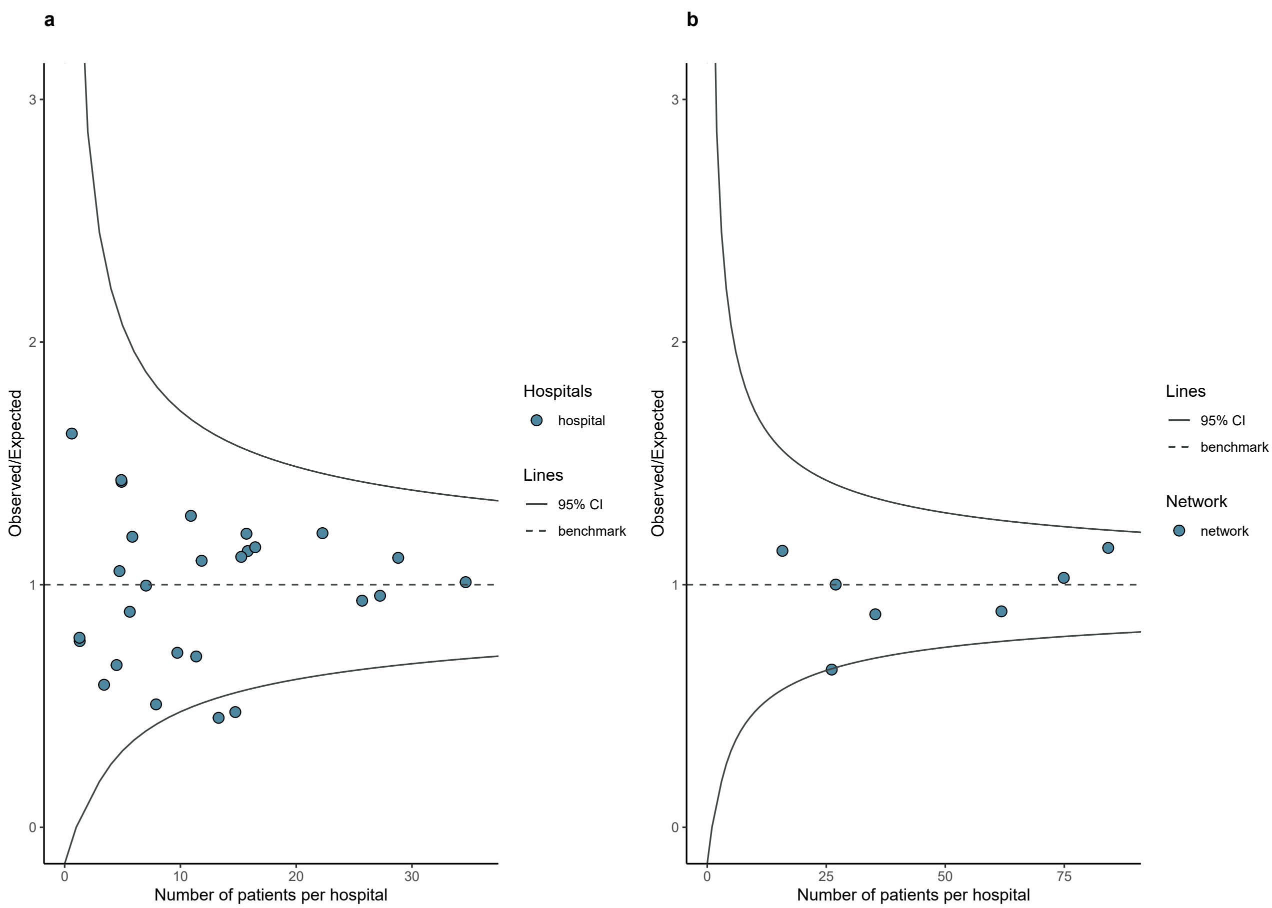

Figure 2 Case-mix adjusted funnel plot of between hospital (a) and oncological network (b) variation in the use of combined liver resection and ablation in patients with 2–3 CRLM of ≤3 cm in the Netherlands between 2014 and 2022

In the matched cohort, no significant differences in overall morbidity, major morbidity and lower 30-day mortality were observed in patients treated with liver resection compared to combined resection and ablation. Several other reports described at least similar mortality and morbidity rates after combined therapy compared to surgery alone.[2,3,28,30–32] This indicates that combined resection and ablation seems a safe treatment option.

Combined resection and ablation could permit a more parenchymal-sparing approach in patients with centrally located tumours. A recent report described improved short-term outcomes after combined liver resection and ablation, primarily due to the performance of less extensive liver resections.[4] This study showed no OS differences in patients treated with combined minor liver resection and ablation compared to major liver resection alone in case of 2–3 metastases, with a maximum of 3 cm. These data suggest that combined resection and ablation, while not superior to liver resection alone, potentially expands effective treatment options for patients who do not qualify for major liver resections.

The majority of patients with CRLM will develop recurrent disease after the first local treatment. The DHBA has no registration of (local) recurrence or disease-free survival. Previous matched studies on combined liver resection and ablation reported similar disease-free survival rates.[30–32] Contrasting results on local recurrence in the liver have been reported, with a disadvantage for patients treated with combined resection and ablation.[31,32] However, a recent retrospective study found a weak correlation between overall and recurrence-free survival and the development of recurrent CRLM after liver resection does not necessarily preclude curability.[33] When feasible, repeat local treatment of recurrent disease shows similar survival to those after first liver resection.[33,34]

Additionally, one of the theoretical advantages of parenchyma-preserving approaches like combined liver resection and ablation is that future local treatment in case of recurrence may more frequently be an option. This should be further studied.

This study, reflecting daily practice in the Netherlands, showed an ongoing implementation of combined resection and ablation in the Netherlands. Other nationwide studies in Sweden and USA also described an increasing trend in the use of ablative techniques.[27,35,36] Combined liver resection and ablation gained ground in the management of CRLM even without a clear

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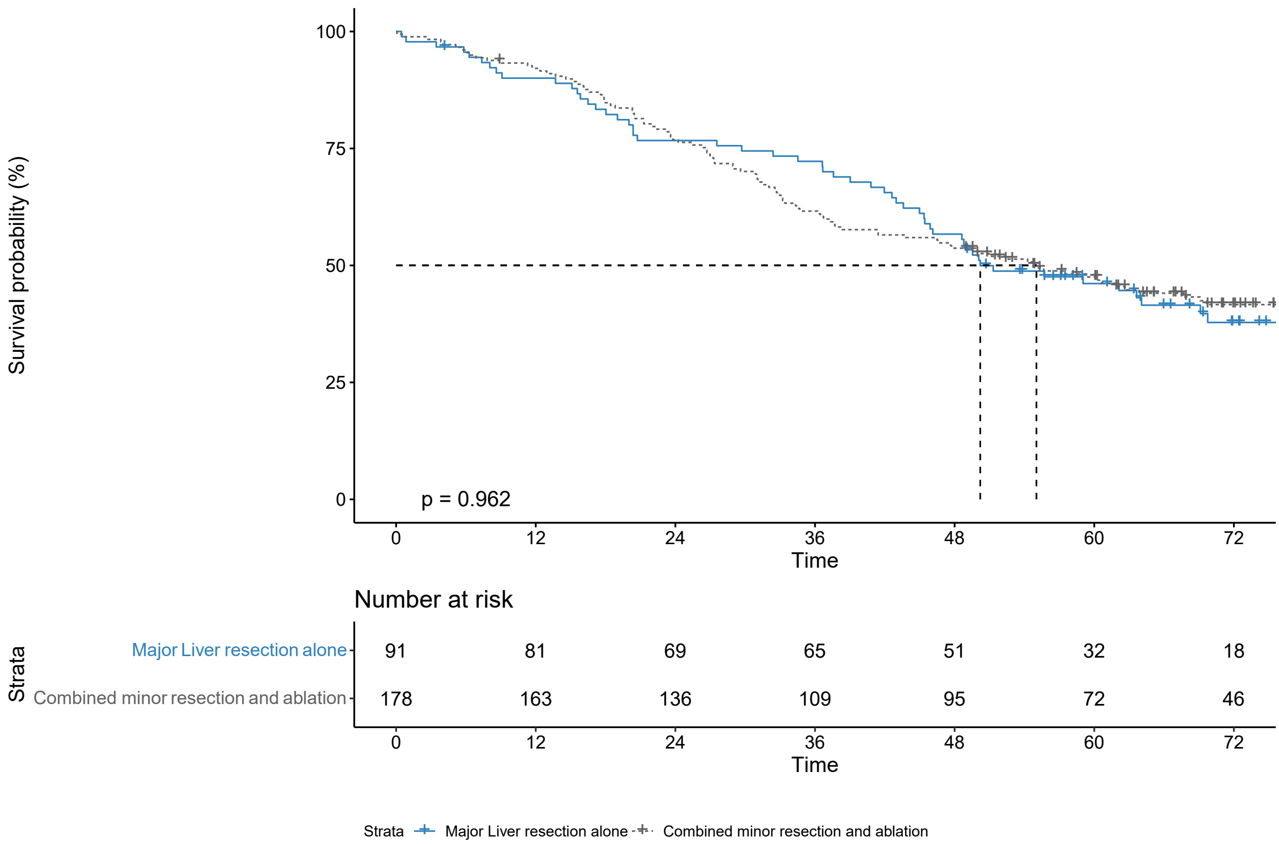

Figure 3 Kaplan Meier curves estimating overall survival of patients with 2–3 colorectal liver metastases (CRLM) ≤3 cm treated with liver resection or combined liver resection and ablation between 2014 and 2018 in the Netherlands. Time in months

international guideline on when to use combined resection and ablation. This could be explained by the increased number of patients eligible for surgery since the introduction of thermal ablation, supported by the results of two large retrospective studies which reported decreased postoperative morbidity and mortality in patients treated with combined liver resection and ablation.[2,4] As well as the ongoing COLLISION trial, which compare thermal ablation to surgical resection. Participation of Dutch centres in this trial could increase the implementation of combined treatment.[7,37] These results should be included in future versions of guidelines on treatment of CRLM.

This study showed that hospital regimes using combined liver resection and ablation significantly differed in the Netherlands. The lack of Dutch Guidelines during this study period and varying availability and experience (e.g., by participating in trials) of interventional radiologists and surgeons who could perform ablation may be responsible for demonstrated hospital variation. Another possible explanation for shown hospital variation may be caused by the adaption of percutaneous ablations and subsequent staged liver resection, as a consequence of improved results.[19,38] Since percutaneous ablations were non-obligatory registered in the DHBA up to 2023, this could not be analysed in DHBA data, but a single-centre prospective trial described an increasing trend in the use of percutaneous ablations.[19] Additionally, thermal ablation is not always feasible, especially CRLM adjacent to critical structures such as the common, left or right hepatic bile duct or peri-hepatic critical structures that cannot be distanced using surgical or interventional dissection methods. The DHBA does not contain this information about the exact location of the CRLM.

Limitations of the present study include the design and the use of clinical audit data. Details, including the decision to perform combined treatment of the multidisciplinary team (MDT), if patients were considered unresectable before treatment, and information on the diameter of the CRLM other than the largest tumour, were lacking.

In conclusion, the present study showed similar postoperative outcomes and overall survival rates in patients treated with combined liver resection/ablation to resection alone. Combined resection and ablation should be available and considered as an alternative to resection alone in any patient with multiple metastases.

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Conflict of interest

None.

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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.2023.09.012.

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