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Joost Huiskens, MD, Karen Bolhuis, MD, Marc RW Engelbrecht, MD, PhD, Koert P De Jong, MD, PhD, Geert Kazemier, MD, PhD, Mike SL Liem, MD, PhD, Cornelis Verhoef, MD, PhD, Johannes HW de Wilt, MD, PhD, Cornelis JA Punt, MD, PhD, Thomas M van Gulik, MD, PhD, for the Dutch Colorectal Cancer Group

BACKGROUND: Decision making on optimal treatment strategy in patients with initially unresectable colorectal cancer liver metastases (CRLM) remains complex because uniform criteria for (un) resectability are lacking. This study reports on the feasibility and short-term outcomes of The Dutch Colorectal Cancer Group Liver Expert Panel.

STUDY DESIGN: The Expert Panel consists of 13 hepatobiliary surgeons and 4 radiologists. Resectability assessment is performed independently by 3 randomly assigned surgeons, and CRLM are scored as resectable, potentially resectable, or permanently unresectable. In absence of consensus, 2 additional surgeons are invited for a majority consensus. Patients with potentially resectable or unresectable CRLM at baseline are evaluated every 2 months of systemic therapy. Once CRLM are considered resectable, a treatment strategy is proposed.

RESULTS: Overall, 398 panel evaluations in 183 patients were analyzed. The median time to panel conclusion was 7 days (interquartile range [IQR] 5−11 days). Intersurgeon disagreement was observed in 205 (52%) evaluations, with major disagreement (resectable vs permanently unresectable) in 42 (11%) evaluations. After systemic treatment, 106 patients were considered to have resectable CRLM, 84 of whom (79%) underwent a curative procedure. R0 resection (n = 41), R0 resection in combination with ablative treatment (n = 26), or ablative treatment only (n = 4) was achieved in 67 of 84 (80%) patients.

CONCLUSIONS: This study analyzed prospective resectability evaluation of patients with CRLM by a panel of radiologists and liver surgeons. The high rate of disagreement among experienced liver surgeons reflects the complexity in defining treatment strategies for CRLM and supports the use of a panel rather than a single-surgeon decision. (J Am Coll Surg 2019;229:523−532. © 2019 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

Survival rates in patients with metastatic colorectal carcinoma (CRC) have increased over the past decades, owing to the increased resection rate of metastases and the development of effective systemic drugs. In 30% to 40% of patients, CRC metastases are limited to the liver.[1,2] Resection of colorectal liver metastases (CRLM) offers the chance of long-term disease-free survival or cure, with 5-year survival rates ranging between 25% and 58%.[3-5]

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Drs Huiskens and Bolhuis contributed equally to this study.

Members of the Dutch Colorectal Cancer Group who co-authored this article are listed in the Appendix.

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From the Departments of Surgery (Huiskens, van Gulik), Medical Oncology (Huiskens, Bolhuis, Punt), and Radiology (Engelbrecht), Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands; and the Departments of Surgery, University Medical Center Groningen, University of Groningen, Groningen (De Jong), Amsterdam UMC, VU University, Cancer Center Amsterdam, Amsterdam (Kazemier), Medical Spectrum Twente, Enschede (Liem), Erasmus Medical Center, Rotterdam (Verhoef), and Radboud UMC, Nijmegen (de Wilt), The Netherlands.

Correspondence address: Karen Bolhuis, MD, Amsterdam UMC, University of Amsterdam, Department of Medical Oncology, Meibergdreef 9 1105 AZ, Amsterdam, The Netherlands. email: k.bolhuis@amsterdamumc.nl

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Abbreviations and Acronyms

ALPPS = associating liver partition and portal vein ligation for staged hepatectomy
CRC = colorectal carcinoma
CRLM = colorectal cancer liver metastases
DCCG = Dutch Colorectal Cancer Group
FU = follow-up
IQR = interquartile range
MDT = multidisciplinary team

In addition to standard 1-stage resections, several other options are currently available to achieve clearance of all tumors from the liver. The combination of resection with local ablative techniques enables sparing of parenchyma, and preoperative portal vein embolization can be used to induce hypertrophy of the future liver remnant, rendering patients with an upfront too small liver remnant amenable to resection.[6] Two-stage hepatectomy and associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) are strategies to allow extensive resections in patients with bilobar metastases. Despite these novel techniques, only a minority of patients with CRLM (20%) present with metastases that are considered upfront resectable.[7,8] In patients with upfront unresectable CRLM, a number of studies have shown that downsizing of CRLM by induction of systemic treatment may allow secondary resections with survival rates comparable to those with primary resections.[9-11]

The lack of criteria for (un)resectability in most studies induces selection bias and thereby complicates interpretation of patient outcomes. Historically, the number and size of CRLM and 1-cm resection margins were the dominant criteria that were used to define (un)resectability. These criteria have gradually been abandoned because multiple studies have shown significant survival benefits of liver resection, even in patients with very advanced CRLM.[12,13] Currently, the main issue is whether a complete resection with tumor-free margins is feasible while preserving at least 20% to 30% of total liver volume, with adequate vascular in- and outflow and biliary drainage.[14] To enable adequate assessment of resectability, the presence of at least 1 experienced liver surgeon in a dedicated multidisciplinary team conference is considered mandatory.[15,16] However, the criteria for resectability are subject to individual interpretation.[17,18] Although there may be consensus on the extremes of upfront resectable vs permanently unresectable CRLM, large interobserver variability concerning resectability has been observed, even among experienced liver surgeons.[19-22]

The ongoing CAIRO5, multicenter, randomized, phase 3 trial of the Dutch Colorectal Cancer Group (DCCG) investigates the optimal systemic induction regimen in patients with initially unresectable, colorectal liver-only metastases.[23] An innovative aspect of the study design is that all patients are prospectively evaluated for resectability by an expert panel consisting of experienced hepatobiliary surgeons and radiologists according to predefined criteria. We hypothesized that the use of such a panel may decrease individual subjectivity in defining (un)resectability, and subsequently may improve consensus on criteria for resection of CRLM.

This study analyzes the feasibility and outcomes of the CAIRO5 national DCCG Liver Expert Panel in resectability assessment for patients with CRLM at baseline and during induction systemic treatment.

METHODS

Patients

All patients registered between November 2014 and August 2017 in the ongoing CAIRO5 study; a multicenter, randomized, phase 3 trial of the DCCG (EudraCT 2013-005435-24, ClinicalTrials.gov: NCT02162563) were selected for this analysis.[23] The CAIRO5 study randomizes patients with unresectable or potentially resectable CRLM and no extrahepatic metastases in doublet chemotherapy plus either bevacizumab or panitumumab for left-sided primary, *RAS* and *BRAF* wild-type tumors, or doublet or triplet chemotherapy, both with bevacizumab for *RAS* or *BRAF* mutated tumors or right-sided primary tumors. Patients were evaluated for resectability by the panel at baseline and during systemic treatment. The following outcomes parameters were recorded: time required by the expert panel to reach a panel conclusion, intersurgeon variation on resectability assessment, and adherence to the panel recommendation for local treatment by the collaborating center.

Patient imaging

Tumor staging and response analysis were assessed using contrast-enhanced, abdomen-pelvic CT scan and thoracic helical CT scan or a conventional thoracic radiograph at baseline and every 8 to 9 weeks after baseline imaging. Use of MRI of the liver or PET scan was left to the discretion of the local treatment team because these imaging modalities were not mandated by the Dutch colorectal cancer guideline. If results of these studies were available and showed additional information concerning the metastases, these scans were reviewed by the expert panel as well.

Predefined resectability criteria

For the purpose of transparency and homogeneity of the trial population and to reduce selection bias, consensus among liver surgeons was achieved on criteria for initial (un)resectability during a meeting of the Dutch Liver Surgery working group.[24] Resectability at baseline was defined as the ability to obtain a complete (R0) resection of all lesions in 1 single surgical procedure (ie, excluding 2-stage resections and/or use of portal vein embolization) by resection only (ie, excluding the use of additional ablative treatments or other local methods), leaving an estimated minimum remnant liver volume of 25% to 30% in uncompromised livers, or 35% to 40% in compromised livers before treatment (fibrosis, cirrhosis, or steatosis). Options for local treatment during induction systemic therapy included 2-stage resections, use of preoperative portal vein embolization, ALPPS, and combinations with local ablative treatments.

Design of the Dutch Colorectal Cancer Group Liver Metastases Expert Panel

The DCCG Liver Expert Panel consists of 13 liver surgeons and 4 radiologists from 12 hospitals. The liver surgeons are all members of the Dutch Study Group for Liver Surgery and have extensive experience in treating patients with CRLM. All liver surgeons are part of a local surgical team that performs more than 20 liver resections per year.[25] A digital online platform was designed that allowed uploading of the images by the local hospital and the independent assessment of resectability by each panel member (ALEA, FormsVision).

CT scans were digitally anonymized and reviewed by a panel radiologist. The radiologist evaluated metastases according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria 1.1. When the panel radiologist confirmed that no extrahepatic metastases were present, 3 liver surgeons were randomly selected. Based on the available imaging studies and the accompanying radiology report, all 3 panel surgeons individually voted on resectability by choosing 1 of the following 3 categories: resectable, potentially resectable, or permanently unresectable. In case CRLM were considered to be potentially resectable, the panel surgeons were requested to differentiate between technically unresectable, but potentially resectable after (further) downsizing, and technically resectable, but start/continuation of systemic treatment is preferred. If no consensus was reached among the 3 panel surgeons, 2 additional panel surgeons were randomly selected to evaluate resectability. Minor disagreement was defined as: a panel evaluation in which 1 of the panel surgeons assessed the CRLM as potentially resectable and 1 other surgeon in the same panel assessed the CRLM as resectable or permanently unresectable. Major disagreement was defined as: a panel evaluation in which at least 1 of the panel surgeons assessed the CRLM as resectable and another surgeon in the same panel voted for permanently unresectable CRLM. The final decision on resectability was made according to the majority of votes among the selected panel members. The chairman of the panel, who is not one of the voting members, coordinated the voting process, confirmed the final decision of the panel, and strived for a panel conclusion within 14 days. One central study coordinator (JH, KB) monitored the progress of the evaluation and solved problems such as questions from the participating hospitals or technical problems experienced by the panel members. The logistics of the panel are schematically represented in Figure 1.

To confirm unresectability of CRLM, panel evaluation was performed at baseline before randomization and after every 8 weeks, equal to 4 treatment cycles. At baseline, patients with CRLM assessed as resectable, did not qualify for inclusion in the CAIRO5 study. At follow-up evaluations, further resectability assessments were discontinued when CRLM were assessed as permanently unresectable or resectable. In case CRLM were considered resectable, the local treatment team was notified and a surgical plan was proposed. All patients assessed as having potentially resectable CRLM at first follow-up evaluation, corresponding to 4 treatment cycles, are re-evaluated after 8 treatment cycles at 16 weeks and, if still considered potentially resectable, for a final assessment after 12 treatment cycles at 24 weeks.

To evaluate the feasibility and predictive accuracy of the panel conclusions, clinical outcomes in terms of resection rate, type of resection with adjunctive use of local additional modalities (ablative treatments, portal vein embolization, 2-stage resection, ALPPS), and R0 resection rate were analyzed. Reasons for deviation from panel conclusions were documented.

Outcomes of resections were evaluated by type of resection as well as the R0 resection rate. R0 resection was defined as microscopically margin-negative resection, in which no microscopic tumor cells have remained in the resection margins of surgically removed metastases. R1 resection indicates the removal of all macroscopic disease, but microscopic margins are positive for tumor cells. In case only local ablative treatment was performed, no R status could be defined. The local physician judged the local ablative procedure to be complete or incomplete. Discrepancies between the local treatment plan proposed by the DCCG Liver Expert Panel and the actual treatment procedures were also documented. The design of

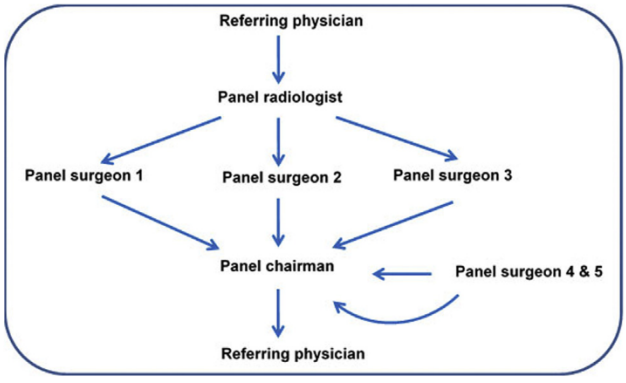

Figure 1. Logistics of resectability assessment by the Dutch Colorectal Cancer Group Liver Expert Panel.

the DCCG Liver Expert Panel, including the procedure of assessment, was part of the study protocol and approved by the Institutional Review Board of the Amsterdam UMC.

The proposed surgical plan for patients with CRLM assessed as resectable at follow-up, should attempt to include all lesions as demonstrated at baseline imaging. However, pretreatment lesions in complete radiologic remission and not detectable during surgery were left in situ. The decision to perform resection by laparoscopic or by open procedure was left to the discretion of the operating surgeon.[26]

Patients with synchronous metastatic disease were eligible for study participation, provided that the primary tumor was deemed resectable by the local multidisciplinary team (MDT) in case of few or absent symptoms of this primary tumor or in case patient had recovered from immediate surgery necessitated by symptoms of primary tumor. Patients with a primary tumor in situ, whose liver metastases became resectable upon induction of systemic treatment were to undergo subsequent surgical treatment for the primary tumor, usually at the end of protocol treatment.

Statistical analysis

Continuous variables were displayed as median with interquartile range (IQR) and categorical variables by number with percentages. Categorical variables were analyzed using chi-square test. Statistical analyses were performed using SPSS 25.0 (IBM). Chi-square tests were 2-tailed, and $p < 0.05$ was considered significant.

RESULTS

Between June 2014 and August 2017, 200 patients with CRLM, from 41 Dutch hospitals, were registered and screened for eligibility for the CAIRO5 trial (Fig. 2). Of these patients, 17 were found to be ineligible for study participation at registration before panel evaluation: 13 patients did not meet the inclusion criteria, 7 of whom had extrahepatic metastases, and 4 patients withdrew from participation before panel conclusion at baseline was reached.

Evaluation of resectability

Overall, 398 panel evaluations in 183 patients were analyzed (183 baseline, 215 follow-up evaluations). At baseline, 10 patients were assessed to have initially resectable CRLM. These patients were considered ineligible for participation in the CAIRO5 study. The panel conclusion, along with the proposed surgical plan, was forwarded to the referring treatment team. The remaining 173 patients were assessed as having initially unresectable CRLM; 127 of these were potentially resectable and 46 were permanently unresectable CRLM. Of the 173 patients with initially unresectable CRLM, 6 patients were not re-evaluated at first follow-up. Reasons why patients were not re-evaluated are presented in Figure 2.

At first follow-up evaluation (FU1), 73 of 167 (45%) patients were considered to have resectable CRLM: 48 (29%) had permanently unresectable CRLM, and 46 (28%) had potentially resectable CRLM. In patients with potentially resectable CRLM, systemic treatment was continued with a panel evaluation after 4 more cycles of systemic therapy. Five of 46 (11%) patients with CRLM considered as potentially resectable at FU1 were not re-evaluated by the panel at second follow-up evaluation (FU2), leaving 41 patients for second follow-up evaluation (FU2).

At FU2, 27 of 41 (66%) patients were considered to have resectable CRLM, 6 (15%) had permanently unresectable CRLM, and 8 (20%) potentially resectable CRLM. At FU3, 5 of 6 patients (83%) were considered to have resectable CRLM, while in 1 patient, the scan showed ongoing response with still extensive CRLM. In this case, the panel preferred to continue systemic treatment for another 4 cycles, ie for a total of 8 months. At the fourth follow-up evaluation (FU4), the CRLM of this patient were considered resectable (Figs. 2 and 3).

Conversion rate

Of 127 patients with CRLM assessed as potentially resectable at baseline evaluation, 71 (56%), 24 (19%), and 4 (3%) patients were converted to resectable status after systemic induction therapy at FU1, FU2, and FU3, respectively. The CRLM were considered permanently unresectable in 13 (10%) and 5 (4%) patients at FU1 and FU2, respectively. Thirty-six (78%) of 46 patients considered to have permanently unresectable CRLM at

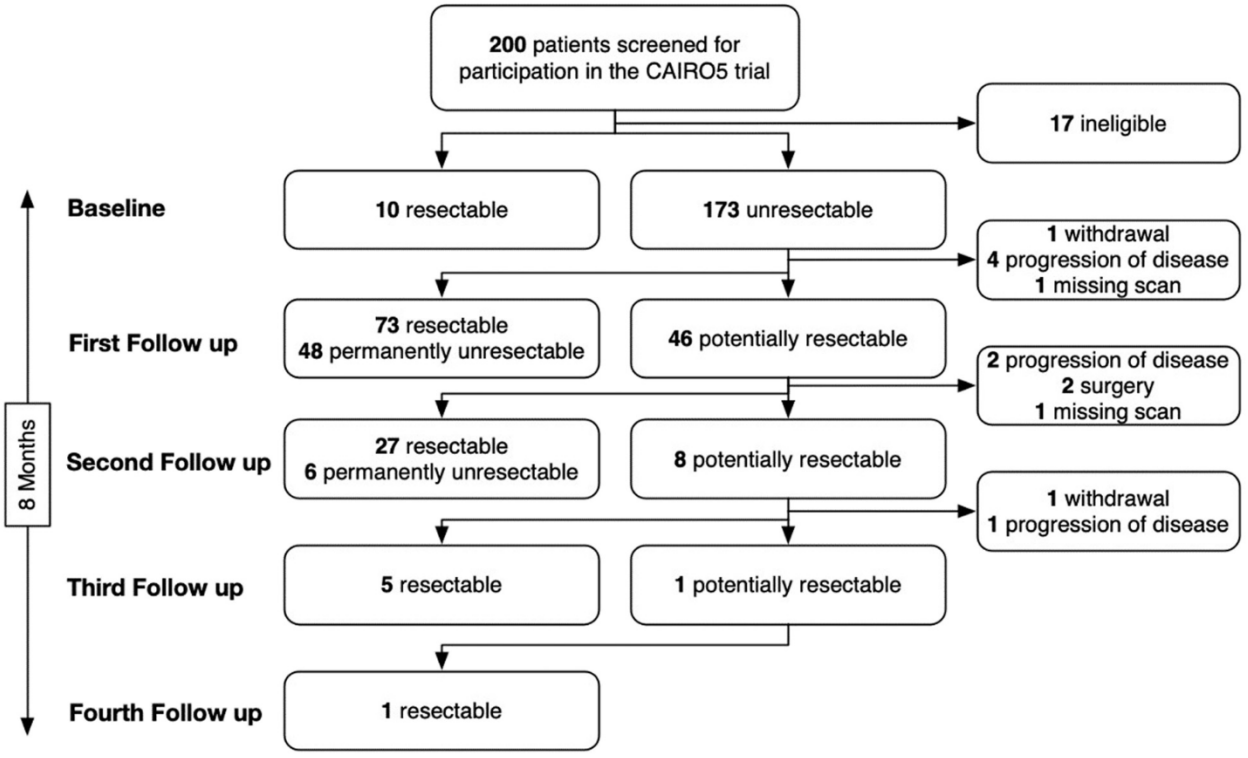

Figure 2. Flowchart with numbers of patients assessed to be resectable, potentially resectable, or permanently unresectable at baseline, and follow-up evaluations and reasons for patients not to be re-evaluated.

baseline, remained permanently unresectable during follow-up assessment, whereas 2 (4%), 3 (7%), 1 (2%), and 1 (2%) patients converted from permanently unresectable disease to resectable disease at FU1, FU2, FU3 and FU4, respectively (eFig. 1).

Time to panel conclusion

Overall, the median time to panel conclusion was 7 days (IQR 5 to 11 days). At baseline and follow-up evaluations, the median times to panel conclusion were 6 days (IQR 4 to 9 days) and 9 days (IQR 6 to 13 days), respectively.

Intersurgeon variation in panel evaluations

Overall, any form of intersurgeon disagreement was observed in 206 (52%) baseline and follow-up evaluations, with major disagreement (resectable vs permanently unresectable) in 42 (11%) evaluations. Any intersurgeon disagreement was lower at baseline compared with follow-up panel evaluations; 80 (43.7%) vs 126 (58.6%), respectively, $p = 0.003$. Major intersurgeon disagreement was lower at baseline compared with follow-up panel evaluations; 3 (1.6%) vs 39 (18.1%), respectively, $p < 0.001$.

For all panel evaluations at FU1, FU2, and FU3, a vast majority of panel evaluations resulted in any form of disagreement among the selected panel surgeons. The rates of panel disagreement per time of evaluation are presented in Table 1.

Over time, the number of evaluations with panel disagreement increased. In the first 199 panel evaluations, panel disagreement existed in 91 (46%) evaluations compared to 115 (58%) in the second group, defined by the last 199 panel evaluations ($p = 0.021$).

Adherence to panel conclusion

Of 10 patients with CRLM considered resectable at baseline and who did not receive systemic therapy in the CAIRO5 study, 2 patients underwent R0 resection, while 5 patients first started systemic treatment on decision of the local surgeon or MDT, and in 3 patients extrahepatic metastases were found on additional imaging.

A total of 106 (61%) patients with initially unresectable CRLM (73 patients at FU1, 27 at FU2, 5 at FU3, and 1 patient at FU4) were assessed as having resectable CRLM at follow-up evaluation. In 93 (88%) of these patients, resection of CRLM was attempted. Complete local treatment of CRLM by resection ($n = 51$) or resection in combination with ablative therapy ($n = 29$) or ablative therapy

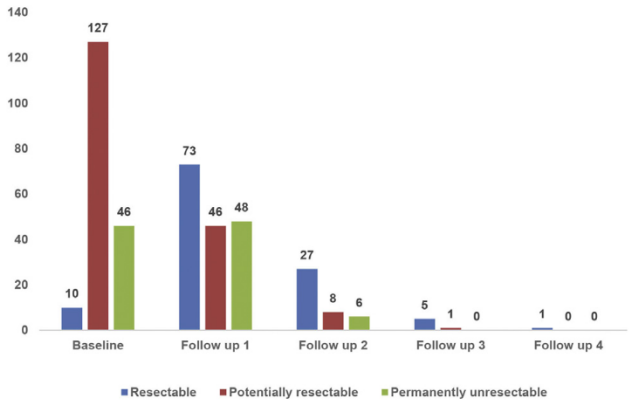

Figure 3. Distributions of panel conclusions at baseline and during follow-up.

only (n = 4) was performed in a total of 84 (79%) patients. Reasons for nonadherence to the panel decision are presented in Table 2. In 38% of resections and/or local ablative treatments, the final procedure was carried out exactly the same as the treatment plan suggested by the panel.

Characteristics of the intervention in patients who underwent resection and/or local ablative treatment

Of 84 patients who underwent a procedure with curative intent, 21 (25%) patients required preoperative portal vein embolization. Twenty-seven (32%) patients underwent a right hemihepatectomy, 21 (25%) had a segmentectomy or local resection plus ablative treatment, 17 (21%) had a segmentectomy or local resection, 7 (8%) had a left hemihepatectomy, another 7 (8%) had an extended right hemihepatectomy, 4 (5%) patients were treated with a local ablative procedure only, and 1 patient underwent an extended left hemihepatectomy. Twenty-two (26%) 2-stage procedures and 11 (13%) laparoscopic procedures were performed (Table 3).

In patients who underwent resection (n = 51), R0, R1, and R2 resections were achieved in 41 (80%), 9 (18%), and 1 (2%) cases, respectively. In patients who underwent resection in combination with local ablative treatment (n = 29), R0, R1, and R2 resections were achieved in 22 (76%), 6 (21%), and 1 (3%) cases, respectively.

Outcome in relation to panel agreement

Of 106 patients evaluated to have resectable CRLM, 52 (49%) patients had assessments with panel agreement; in 54 (51%) patients, panel disagreement occurred. In patients with panel agreement and resectable CRLM, resections (n = 26) and/or ablative treatment (n = 19) were undertaken in 45 of 52 (87%) patients; 39 of 54 (72%) patients received resections (n = 25) and/or ablative treatments (n = 14) when there was panel disagreement at evaluation (p = 0.069). In patients with panel agreement, R0 resection (n = 22) and/or ablative treatment (n = 17) was achieved in 39 of 52 (75%) patients, compared with 28 (19 resections and 9 resections with ablative therapy) of 54 (52%) patients when disagreement occurred (p = 0.013).

In panel evaluations with major panel disagreement and resectable outcome, 9 of 18 (50%) patients did not receive a liver resection. The reasons for nonresection in this group included: intraoperative unresectability in 3 patients, insufficient future liver remnant in 2, decision over-ruled by the local MDT or surgeon in 3, and decision of the patient in 1.

Further analysis was done, excluding 13 patients in whom no surgery was initiated for reasons of extrahepatic disease, decision of the local MDT, or condition of the patient. Of the remaining 93 patients, 47 (51%) had an assessment with panel agreement. R0 resection (n = 22) and/or local ablative treatment (n = 17) was achieved in 39 of 47 (83%) patients with panel agreement, compared with 28 (19 resections and 9 resections with ablative therapy) of 46 (61%) patients with panel disagreement (p = 0.018) (Table 4).

DISCUSSION

This study demonstrates successful implementation and feasibility of the CAIRO5 national DCCG Liver Expert

Table 1. Inter-surgeon Variation in Panel Evaluations

	Panel agreement		Minor disagreement*		Major disagreement†	
Time of evaluation	**n**	**%**	**n**	**%**	**n**	**%**
Overall	193	48	163	41	42	11
Baseline	103	56	77	42	3	2
Follow-up 1	69	41	74	45	24	14
Follow-up 2	19	47	10	24	12	29
Follow-up 3	1	17	2	33	3	50
Follow-up 4	1	100	0	0	0	0

*In 1 panel evaluation, at least 1 panel surgeon judged "potentially resectable"; at least 1 other surgeon judged "permanently unresectable or "resectable."
†In 1 panel evaluation, at least 1 panel surgeon judged "resectable"; at least 1 other surgeon judged "permanently unresectable."

Table 2. Adherence to Panel Conclusion and Panel Treatment Plan in Resectable Patients at Follow-Up Evaluation

Panel conclusion adherence	Total (n = 106)
Resection and/or local ablative treatment, n (%)	
Yes	84 (79)
No	22 (21)
Reason no resection and/or local ablative treatment, n	
Perioperatively unresectable (open-close)	6
Patient condition	4
Decision local surgeon/multidisciplinary team	4
New intra- and/or extrahepatic metastases	4
Second stage not executed due to insufficient liver remnant	3
Patient decision	1
Final resection similar to panel treatment plan, n (%)	
Yes	32 (38)
No	52 (62)
Reason resection not similar to panel conclusion, n	
Final resection more extensive	12
Final resection less extensive	16
1-stage converted to 2-stage resection	8
2-stage converted to 1-stage resection	7
Local ablative treatment instead of wedge/segment resection	8
Wedge/segment resection instead of local ablative treatment	1

Table 3. Procedure Characteristic

Procedure	Total (n = 84) n	%
Portal vein embolization		
Yes	21	25
No	63	75
Surgical and/or ablative treatment		
Surgical procedure	51	60
Surgical + local ablative treatment	29	35
Local ablative treatment	4	5
Procedure type		
Left hemihepatectomy	7	8
Extended left hemihepatectomy	1	1
Right hemihepatectomy	27	32
Extended right hemihepatectomy	7	8
Segmentectomy/local resection	17	21
Segmentectomy/local resection + local ablative treatment	21	25
Only local ablative treatment	4	5
Two-stage procedure		
Yes	17	20
ALPPS	5	6
No	62	74
Laparoscopic procedure		
Yes	11	13
No	70	83
Unknown	3	4
Radicality		
R0	63	75
R1	15	18
R2	2	2
Local ablative treatment only	4	5

ALPPS, associating liver partition and portal vein ligation for staged hepatectomy.

Panel in clinical practice. The median time to panel conclusion of 7 days was considerably faster than the preconceived maximum of 14 days, allowing efficient assessment by multiple experienced liver surgeons in these very complex patients.

Despite resectability assessments by a panel of experienced liver surgeons, a high level of intersurgeon disagreement per assessment was observed, as shown in earlier studies.[17-19,21] This underlines the complexity of defining (un)resectability. However, with consensus on baseline criteria for (un)resectability, we noted significantly less intersurgeon variation compared with follow-up evaluations, which underscores the value of well-defined resection criteria. Our data support the evaluation of CRLM patients by a panel of liver surgeons rather than by an individual surgeon or MDT in order to achieve a more reproducible and more balanced decision per patient. The true value of the panel can be assessed when further clinical, translational, and outcomes data are available. The high R0 resection rate and/or ablative treatment rate after patients were considered resectable, confirms the feasibility of resectability assessment by the panel. The difference in successful local treatment (R0 resection and/or ablative treatment) between patients with evaluations with panel agreement vs panel disagreement shows that resectability is more difficult to predict in this subgroup of patients and calls for the definition of more stringent resectability criteria. The design of this panel enables further prospective analysis of these subgroups, incorporating follow-up data on clinical outcomes and translational research data on clinical characteristics and biomarkers, in order to provide improved selection criteria for (un)resectability. The increase over time of panel evaluations with disagreement, confirms that lack of resection criteria remains an important issue today and that the outcomes of these future analyses are as vital as when the CAIRO5 study started in 2014.

Table 4. Outcomes in Relation to Panel Agreement in Patients with Colorectal Cancer Liver Metastases Considered Resectable by the Panel after Systemic Therapy

	Total patients with resectable CRLM (n = 106)		Panel agreement (n = 52)		Panel disagreement (n = 54)		
Outcome	**n**	**%**	**n**	**%**	**n**	**%**	**p Value**
Resection without ablative treatment							
R0	41	39	22	42	19	35	—
R1	9	8	3	6	6	11	
R2	1	1	1	2	0	0	
Resection with ablative treatment							
R0	22	21	13	25	9	17	—
R1	6	6	1	2	5	9	
R2	1	1	1	2	0	0	
Local ablative treatment only	4	4	4	8	0	0	—
Perioperatively unresectable	6	6	2	4	4	7	—
2nd stage not done, insufficient liver remnant	3	3	0	0	3	6	—
No operation	13	12	5	10	8	15	—
Resection and/or ablative treatment	84	79	45	86	39	72	
No resection and/or ablative treatment	22	21	7	14	15	28	0.069
R0 resection and/or ablative treatment	67	63	39	75	28	52	0.013
R1 or R2 or incomplete or no resection	39	37	13	25	26	48	

CRLM, colorectal cancer liver metastases.

In 62% of patients, the final resection carried out was different than the surgical plan proposed by the panel. We assign this high rate to the fact that the surgical plan itself was not mandatory. Other explanations could be that most hospitals perform an additional preoperative MRI because of better diagnostic performance and the finding of new lesions.[27-29] Furthermore, intraoperative adjustment of the surgical plan is a well-known phenomenon because intraoperative ultrasonography is still known to be the gold standard in revealing the total extent of disease.[30-32] We did not note much resistance from local MDTs or surgeons regarding the proposed treatment plans by the panel. Two patients with potentially resectable CRLM, as assessed by the panel, did not finish further panel evaluations because the local surgeon or MDT decided to proceed with surgical resection. In 4 patients considered resectable by the panel, the resection was not executed due to disagreement of the local surgeon or MDT.

In the absence of formal international consensus on resectability criteria for CRLM, baseline criteria for unresectability were defined by consensus among Dutch liver surgeons for the purpose of more uniform selection of CRLM patients for multimodality treatment, according to state-of-the-art management of CRLM in a governed, auditable, and reproducible manner, allowing improved reproducibility and minimal selection bias in the CAIRO5 study, as well as a better interpretation of patient outcomes.[23]

Our criteria imply that more patients are exposed to perioperative systemic treatment in the CAIRO5 study than in routine Dutch practice, since (neo)adjuvant systemic therapy is not recommended in the Dutch treatment guidelines for patients with resectable CRLM due to the lack of survival benefit in the EPOC trial.[33] This will have contributed to the high conversion rate of 61%. However, there was general consensus that the administration of induction systemic treatment is ethical and appropriate in the relatively high-risk patient group qualifying for the CAIRO5 study, moreover because some studies suggest a survival benefit of systemic therapy in patients with high risk CRLM.[34-36]

This study has some limitations. Evaluation of the panel is by observational design, which may introduce bias. However, a randomized selection for evaluation by the panel was considered unethical. Furthermore, the panel evaluation of patients was performed only by radiologic imaging, without considering patient's clinical condition and possible comorbidity. Notwithstanding these facts, the CAIRO5 eligibility criteria included the most relevant assessments of performance status and organ functions to allow the safe administration of systemic treatment and surgery, while the final decision for

implementation of the panel decision remained with the treating physician.

CONCLUSIONS

This study analyzed prospective evaluation of patients with unresectable CRLM, as defined by uniform criteria, using an online expert panel of radiologists and liver surgeons. The high inter-surgeon variation reflects the complexity in defining treatment strategies for CRLM and supports the use of a panel rather than a single-surgeon decision. Our results demonstrate that the DCCG CAIRO5 Liver Expert Panel is feasible and provides a platform for prospective initial and follow-up assessments on resectability in patients with advanced CRLM on a national level.

Author Contributions

Study conception and design: Punt, Van Gulik

Acquisition of data: Huiskens, Bolhuis, Engelbrecht, De Jong, Kazemier, Liem, Verhoef, De Wilt, Punt, Van Gulik, Analysis and interpretation of data: Huiskens, Bolhuis, Engelbrecht, De Jong, Kazemier, Liem, Verhoef, De Wilt, Punt, Van Gulik

Drafting of manuscript: Huiskens, Bolhuis, Engelbrecht, De Jong, Kazemier, Liem, Verhoef, De Wilt, Punt, Van Gulik

Critical revision: Huiskens, Bolhuis, Engelbrecht, De Jong, Kazemier, Liem, Verhoef, De Wilt, Punt, Van Gulik

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APPENDIX

Additional members of the Dutch Colorectal Cancer Group who co-authored this article are as follows:

MJ Van Amerongen, MD, Department of Radiology, Radboud UMC, Nijmegen, The Netherlands

Cornelis HC Dejong, MD, PhD, Department of Surgery, Maastricht University Medical Center, Maastricht, The Netherlands; Universitätsklinikum Aachen, Aachen, Germany

Michael F Gerhards, MD, PhD, Department of Surgery, OLVG Hospital, Amsterdam, The Netherlands

Dirk Grunhagen, MD, PhD, Department of Surgery, Erasmus Medical Center, Rotterdam, The Netherlands

Linda Heijmen, MD, PhD, Leiden University Medical Center, Leiden, The Netherlands

John J Hermans, MD, PhD, Department of Radiology, Radboud UMC, Nijmegen, The Netherlands

Astrid Keijser, MSc, Netherlands Comprehensive Cancer Center, Utrecht, The Netherlands

Joost M Klaase, MD, PhD, Department of Surgery, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Krijn P Van Lienden, MD, PhD, Department of Radiology, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

Quintus I Molenaar, MD, PhD, Department of Surgery, Regional Academic Cancer Center Utrecht, University Medical Center Utrecht and St Antonius Hospital Nieuwegein, The Netherlands

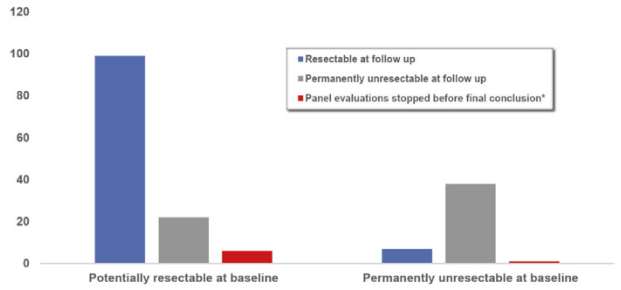
Gijs A Patijn, MD, PhD, Department of Surgery, Isala Hospital, Zwolle, The Netherlands

Arjen M Rijken, MD, PhD, Department of Surgery, Amphia Hospital, Breda, The Netherlands

Theo M Ruers, MD, PhD, Department of Surgery, Netherlands Cancer Institute, Amsterdam, The Netherlands

Rutger-Jan Swijnenburg, MD, PhD, Department of Medical Oncology, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

Harm van Tinteren, MD, PhD, Department of Biostatistics, Netherlands Cancer Institute, Amsterdam, The Netherlands



eFigure 1. Distributions of panel conclusions at follow-up according to panel conclusion at baseline. *Patients with missing panel evaluations because of progression were scored as permanently unresectable.