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Original Research

# The role of tumour biological factors in technical anatomical resectability assessment of colorectal liver metastases following induction systemic treatment: An analysis of the Dutch CAIRO5 trial

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**Abstract** ***Background:*** Large inter-surgeon variability exists in technical anatomical resectability assessment of colorectal cancer liver-only metastases (CRLM) following induction systemic therapy. We evaluated the role of tumour biological factors in predicting resectability and (early) recurrence after surgery for initially unresectable CRLM.
***Methods:*** 482 patients with initially unresectable CRLM from the phase 3 CAIRO5 trial were selected, with two-monthly resectability assessments by a liver expert panel. If no consensus existed among panel surgeons (i.e. same vote for (un)resectability of CRLM), conclusion was based on majority. The association of tumour biological (sidedness, synchronous CRLM, carcinoembryonic antigen and $RAS/BRAF^{V600E}$ mutation status) and technical anatomical factors with consensus among panel surgeons, secondary resectability and early recurrence (<6 months) without curative-intent repeat local treatment was analysed by uni- and pre-specified multivariable logistic regression.
***Results:*** After systemic treatment, 240 (50%) patients received complete local treatment of CRLM of which 75 (31%) patients experienced early recurrence without repeat local treatment. Higher number of CRLM (odds ratio 1.09 [95% confidence interval 1.03–1.15]) and age (odds ratio 1.03 [95% confidence interval 1.00–1.07]) were independently associated with early recurrence without repeat local treatment. In 138 (52%) patients, no consensus among panel surgeons was present prior to local treatment. Postoperative outcomes in patients with and without consensus were comparable.
***Conclusions:*** Almost a third of patients selected by an expert panel for secondary CRLM surgery following induction systemic treatment experience an early recurrence only amenable to palliative treatment. Number of CRLM and age, but no tumour biological factors are predictive, suggesting that until there are better biomarkers; resectability assessment remains primarily a technical anatomical decision.


## 1. Introduction

Resectability assessments of CRLM are primarily based on technical anatomical features and are defined as the ability to perform a complete resection, while preserving a sufficient future liver remnant [1,2]. Improved surgical, liver augmentation and ablation techniques paraleled with the optimisation of induction systemic therapies have increased the number of patients with technically resectable disease [3–5]. However, up to 45% of patients have early disease recurrence within 6–8 months after local treatment of CRLM, which is often not amenable to repeat local treatment and is negatively associated with overall survival (OS) [6–12]. Additionally, resectability assessment is subject to large inter-surgeon variability due to lack of consensus on (un)resectability criteria [13–16]. These issues warrant studies on the potential added predictive value of currently clinically available tumour biological factors on clinically relevant outcomes after local treatment of CRLM.

Varying preoperative available factors have been reported to be associated with survival outcomes after CRLM resection such as number and size of CRLM, serum carcinoembryonic antigen (CEA), disease-free interval between primary tumour and CRLM [17–20], sidedness of primary tumour and $RAS/BRAF^{V600E}$ mutation status [21–24]. Combining these factors into prediction models are of limited clinical utility caused by

the relatively low discriminative power and limitations such as the lack of entry resectability criteria and retrospective nature of the data [25].

This analysis of patients who received local treatment of CRLM after induction systemic therapy in the CAIRO5 study [26] overcomes the limitations due to the prospective design, the clear entry resectability criteria and repeat resectability assessments by a liver expert panel. We evaluated the predictive value of technical anatomical and tumour biological factors on conversion to resectable CRLM, early recurrence and early recurrence without curative-intent repeat local treatment. Outcomes after local treatment of CRLM were compared according to the degree of consensus among panel surgeons in resectability assessments of CRLM.

## 2. Methods

### 2.1. Patient selection

Patients were selected from the phase 3 randomised controlled CAIRO5 trial of the Dutch Colorectal Cancer Group (DCCG) (NCT02162563), investigating first-line systemic regimens of chemotherapy (5-fluorouracil, oxaliplatin and/or irinotecan) plus targeted therapy (bevacizumab or panitumumab) in patients with initially unresectable CRLM. The design of the study has been published [26]. To allow a meaningful follow-up period, patients randomised between start of the study and until April 2021 were selected for this analysis.

### 2.2. Resectability assessment by the DCCG liver expert panel

Computed tomography (CT) scans of patients were evaluated at baseline for eligibility by a central liver expert panel, consisting of 15 liver surgeons and 3 abdominal radiologists. Given the lack of consensus on (un)resectability criteria, baseline resectability criteria were selected by consensus among Dutch liver surgeons to allow a homogeneous study population. CRLM were deemed unresectable at baseline if an R0 resection could not be achieved in a single procedure by surgical resection. Thereafter, patients were reassessed for resectability by the panel every two months during systemic treatment according to more liberal criteria allowing all established local treatments (i.e. ablation, two-stage surgery, portal vein embolisation). CT scans were uploaded in a program specially designed to share patient imaging in a privacy-respecting manner. Each CT scan with panel radiology report (including patient's age, number of treatment cycles, location and resection (yes/no) of primary tumour) was evaluated by three randomly selected panel surgeons, who voted individually on the following categories: resectable, potentially resectable after further induction systemic treatment or permanently unresectable. If no consensus (i.e. same category selected by all three surgeons) was obtained, two additional surgeons were consulted and panel conclusion was accepted by majority vote [13].

### 2.3. Selection of tumour biological and technical anatomical tumour features

The following tumour biological features were collected: $RAS/BRAF^{V600E}$ mutation, synchronous metastases (metastases <6 months after diagnosis of primary tumour [27]), histopathological nodal status and sidedness of primary tumour (right-sided was defined as tumours located proximal of the splenic flexure), serum CEA (ng/ml). Patient characteristics and technical anatomical tumour features were collected: age, gender and number, size and distribution (unilobar/bilobar) of CRLM, diaphragm involvement, involved liver segments and RECIST 1.1 defined response to induction treatment [28]. Resection margin (R0 was defined by the absence of microscopic tumour invasion of the resection margin), type of local CRLM treatment (e.g. resection and/or ablation) and type of curative-intent repeat local treatment (e.g. resection, ablation, cytoreductive surgery and hyperthermic intraperitoneal chemotherapy and/or radiotherapy) were collected. Major liver resections were defined as resection of at least three segments or an (extended) hemihepatectomy. Complete local treatment was defined as R0/R1 resection and/or ablation of all CRLM.

### 2.4. Outcomes

Relapse-free survival (RFS) was calculated from the date of last local liver treatment until progression or death or censored on last clinical visit date. Early recurrence was defined as disease progression or death occurring within six months after complete local treatment of CRLM [8,9]. Death and palliative or no local treatment within six months after recurrence were scored as an event for early recurrence without curative-intent repeat local treatment.

### 2.5. Statistical analysis

Continuous variables were displayed as median with interquartile range (IQR) and categorical variables as counts and percentages and differences were analysed using Pearson's chi-square test. Univariable and multivariable logistic regression were performed to analyse predictive factors for panel (dis)agreement at first follow-up and prior to local treatment, secondary resectability, early recurrence and early recurrence without curative-intent repeat local treatment. Based on the ten events per variable rule, a maximum of 32,

10 and 7 variables could be introduced in multivariable analyses for secondary resectability, early recurrence and early recurrence without repeat local treatment, respectively. Pre-specified variables for the multivariable analyses were age, sidedness, time to metastases, $RAS/BRAF^{V600E}$ mutation status, CEA, number and size of largest CRLM. Linear association between a variable and outcome will be tested by restricted cubic splines. $P \leq 0.05$ was considered statistically significant. Analyses were performed using R (version 4.0.3).

## 3. Results

After exclusion of 23 patients, 482 patients were analysed (Fig. 1). Baseline patient characteristics show a median age of 62 years (54–69), a median number of CRLM of 12 (7–22), synchronous disease in 421 (90%) patients and $RAS$ or $BRAF^{V600E}$ mutation in 266 (57%) patients (Table 1).

### 3.1. Secondary resectability of CRLM

After induction systemic treatment, the liver panel considered CRLM resectable in 324 (69%) patients (Fig. 1). In the pre-specified multivariable analysis, the probability for resectable CRLM was lower in patients with synchronous versus metachronous CRLM (odds ratio [OR] 0.18 [95% confidence interval [CI] 0.03–0.68], $p = 0.029$), $RAS$ mutation versus $RAS/BRAF^{V600E}$ wildtype (OR 0.38 [95% CI 0.21–0.69], $p = 0.002$), $BRAF^{V600E}$ mutation versus $RAS/BRAF^{V600E}$ wildtype (OR 0.10 [95% CI 0.03–0.30], $p < 0.001$), larger number of CRLM (OR 0.89 [95% CI 0.86–0.91], $p < 0.001$) and larger size of CRLM (OR 0.97 [95% CI 0.96–0.98], $p < 0.001$) (Table 1).

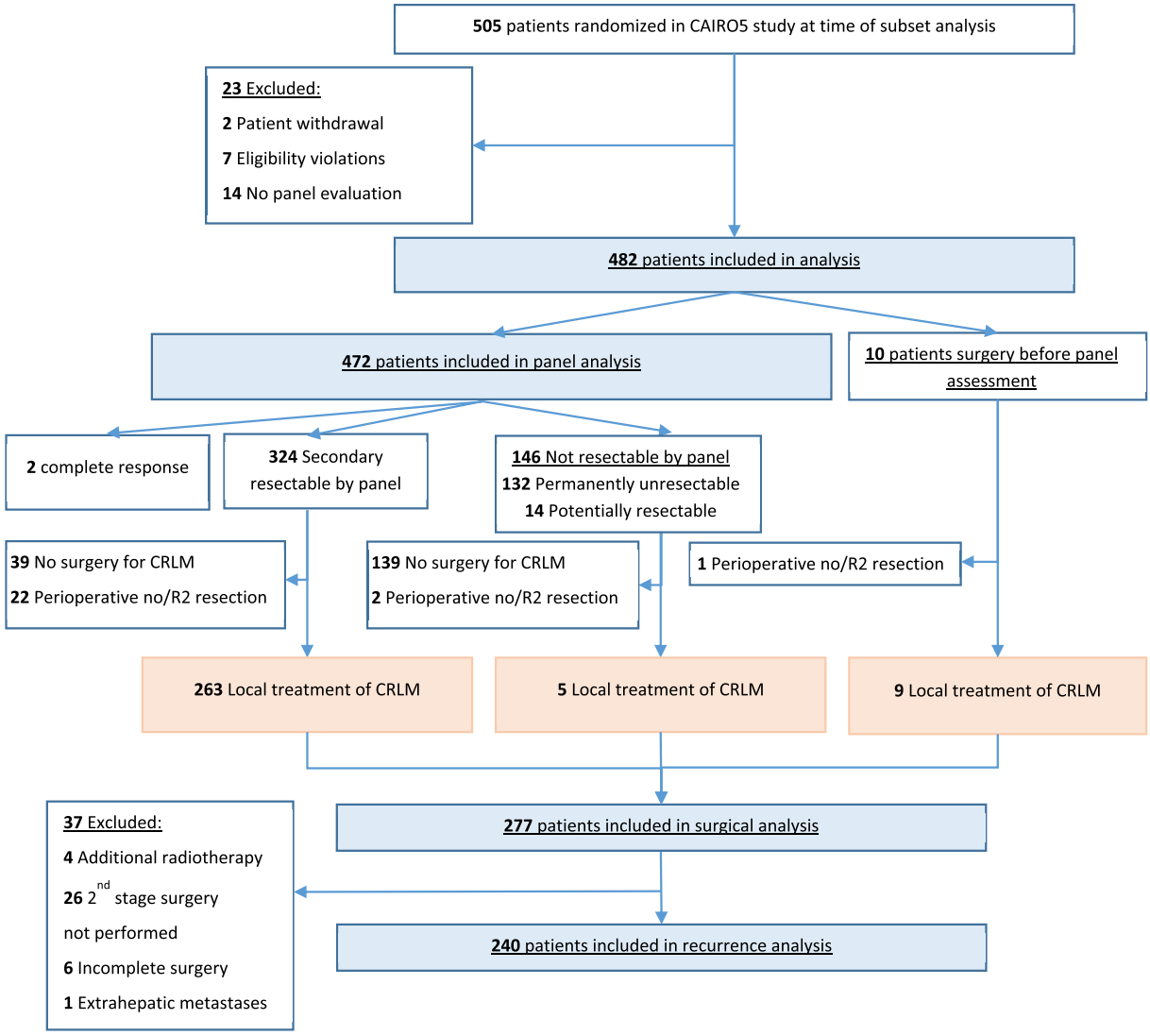


Fig. 1. Flowchart eligible patients for analysis.

Table 1
Univariable and multivariable logistic regression analysis to evaluate the association of baseline patient and tumour characteristics with probability to be assessed resectable after systemic treatment.

| Characteristic | Total cohort[a] | Resectability | | Univariable analysis | | | Multivariable analysis[b] | | |
|---|---|---|---|---|---|---|---|---|---|
| | N = 470 | Unresectable, N = 146 | Resectable, N = 324 | OR | 95% CI | *P*-value | OR | 95% CI | *P*-value |
| Age patient | 62 (54–69) | 61 (54–69) | 62 (54–70) | 1.00 | 0.98, 1.02 | 0.829 | 0.98 | 0.95, 1.01 | 0.156 |
| Sex | | | | | | | | | |
| Female | 182 (39%) | 65 (45%) | 117 (36%) | – | – | | | | |
| Male | 288 (61%) | 81 (55%) | 207 (64%) | 1.42 | 0.95, 2.11 | 0.084 | | | |
| Site of primary tumour | | | | | | | | | |
| Left colon or rectum | 344 (73%) | 92 (63%) | 252 (78%) | – | – | | – | – | |
| Right colon | 126 (27%) | 54 (37%) | 72 (22%) | 0.49 | 0.32, 0.75 | <0.001 | 0.71 | 0.39, 1.30 | 0.265 |
| Time to metastases | | | | | | | | | |
| Metachronous | 49 (10%) | 2 (1%) | 47 (15%) | – | – | | – | – | |
| Synchronous | 421 (90%) | 144 (99%) | 277 (85%) | 0.08 | 0.01, 0.27 | <0.001 | 0.18 | 0.03, 0.68 | 0.029 |
| Tumour nodal status | | | | | | | | | |
| Negative | 33 (7%) | 5 (3%) | 28 (9%) | – | – | | | | |
| Positive | 112 (24%) | 21 (14%) | 91 (28%) | 0.77 | 0.24, 2.11 | 0.636 | | | |
| No surgery before registration | 325 (69%) | 120 (82%) | 205 (63%) | 0.31 | 0.10, 0.75 | 0.017 | | | |
| Mutational status | | | | | | | | | |
| *RAS* & *BRAF* wildtype | 203 (43%) | 48 (33%) | 155 (48%) | – | – | | – | – | |
| *RAS* mutation | 239 (51%) | 80 (55%) | 159 (49%) | 0.62 | 0.40, 0.93 | 0.024 | 0.38 | 0.21, 0.69 | 0.002 |
| *BRAF* mutation | 28 (6%) | 18 (12%) | 10 (3%) | 0.17 | 0.07, 0.39 | <0.001 | 0.10 | 0.03, 0.30 | <0.001 |
| Serum CEA level, (ng/mL)—baseline | 45 (10–256) | 122 (17–409) | 28 (8–146) | 1.00 | 1.00, 1.00 | <0.001 | 1.00 | 1.00, 1.00 | 0.494 |
| Number of liver metastases | 12 (7–22) | 24 (14–42) | 10 (6–15) | 0.91 | 0.89, 0.93 | <0.001 | 0.89 | 0.86, 0.91 | <0.001 |
| Diameter of largest metastasis | 41 (27–65) | 57 (37–75) | 36 (26–57) | 0.98 | 0.98, 0.99 | <0.001 | 0.97 | 0.96, 0.98 | <0.001 |
| Diaphragm involved | | | | | | | | | |
| No | 257 (55%) | 59 (40%) | 198 (61%) | – | – | | | | |
| Yes | 178 (38%) | 71 (49%) | 107 (33%) | 0.45 | 0.29, 0.68 | <0.001 | | | |
| Unknown | 35 (7%) | 16 (11%) | 19 (6%) | 0.35 | 0.17, 0.74 | 0.005 | | | |
| Number of liver segments involved | 6 (5–8) | 8 (7–9) | 5 (4–7) | 0.51 | 0.43, 0.58 | <0.001 | | | |
| Distribution of liver metastases | | | | | | | | | |
| Unilobar | 25 (5%) | 3 (2%) | 22 (7%) | – | – | | | | |
| Bilobar | 445 (95%) | 143 (98%) | 302 (93%) | 0.29 | 0.07, 0.85 | 0.046 | | | |

Median (IQR); n (%). OR = Odds Ratio, CI = Confidence Interval.
[a] Two patients with complete response were excluded from this analysis.
[b] The variables to include in the multivariable analyses were pre-specified.

### 3.2. RFS and recurrences after local liver treatment

After a median follow-up of 36.5 months (95% CI 23.8–42.7) of patients who received local treatment, the median RFS was 6.9 months (95% CI 6.2–8.2) with 202 (84%) events (recurrence n = 198 and death without recurrence n = 4), including 104 (43%; 53% of recurrences) early recurrences or death (n = 4). The site of early recurrence was liver-only in 62 (62%) patients, lung-only in 12 (12%) patients, peritoneal-only in 5 (5%) patients, lymph node-only in 2 (2%) patients, colon-only in 1 (1%) patients and multi-organ recurrence in 18 (18%) patients. Among patients with early recurrence, 29 (28%) patients underwent curative-intent repeat local treatment.

### 3.3. Predictive factors for early recurrence and early recurrence without repeat local treatment

In the pre-specified multivariable analysis, number of CRLM prior to local treatment was the only independent predictive factor for a higher chance of early recurrence (OR 1.10 [95% CI 1.04–1.17], $p < 0.001$) (Table 2). Number of CRLM was linearly associated with the log-odds of early recurrence which was tested by restricted cubic splines, implying that there is no meaningful cut-off value. To provide more insight on these results, number of CRLM was analysed on a categorical scale: compared to 1–5 CRLM, 6–10 CRLM are not (OR 1.30 [95% CI 0.70–2.44], $p = 0.411$) and >10 CRLM are significantly associated with early recurrence (OR 3.16 [95% CI 1.58–6.51], $p = 0.001$). In the pre-specified multivariable analysis for early recurrence without repeat local treatment, age (OR 1.03 [95% CI 1.00–1.07], $p = 0.047$) and number of CRLM (OR 1.09 [95% CI 1.03–1.15], $p = 0.003$) were independent risk factors (Table 3). Age and number of CRLM was linearly associated with the log-odds of early recurrence without repeat local treatment, implying that there is no meaningful cut-off value. Compared to 1–5 CRLM, 6–10 CRLM are not (OR 1.83 [95% CI 0.92–3.70], $p = 0.089$) and >10 CRLM were significantly associated with early recurrence without repeat local treatment (OR 3.20 [95% CI

Table 2
Univariable and multivariable logistic regression analysis to evaluate the association of tumour biological and technical anatomical features at baseline and prior to local treatment, with early recurrence within 6 months following complete local treatment of colorectal liver metastases.

| Characteristic | | Univariable analysis | | | Multivariable analysis[a] | | |
|---|---|---|---|---|---|---|---|
| | Event rate | OR | 95% CI | *P*-value | OR | 95% CI | *P*-value |
| Age patient | 104/240 (43%) | 1.01 | 0.99, 1.04 | 0.321 | 1.02 | 0.99, 1.05 | 0.203 |
| Sex | | | | | | | |
| Female | 35/89 (39%) | – | – | | | | |
| Male | 69/151 (46%) | 1.30 | 0.76, 2.22 | 0.337 | | | |
| Fong risk score | | | | | | | |
| Low, <3 | 48/112 (43%) | – | – | | | | |
| High, ≥3 | 56/128 (44%) | 1.04 | 0.62, 1.73 | 0.889 | | | |
| Site of primary tumour | | | | | | | |
| Left colon or rectum | 78/185 (42%) | – | – | | – | – | |
| Right colon | 26/55 (47%) | 1.23 | 0.67, 2.25 | 0.502 | 0.99 | 0.49, 1.99 | 0.980 |
| Time to metastases | | | | | | | |
| Metachronous | 12/34 (35%) | – | – | | – | – | |
| Synchronous | 92/206 (45%) | 1.48 | 0.71, 3.24 | 0.309 | 1.44 | 0.65, 3.35 | 0.379 |
| Tumour nodal status | | | | | | | |
| Negative | 9/23 (39%) | – | – | | | | |
| Positive | 26/63 (41%) | 1.09 | 0.42, 2.98 | 0.858 | | | |
| No surgery before registration | 69/154 (45%) | 1.26 | 0.52, 3.20 | 0.610 | | | |
| Mutational status | | | | | | | |
| *RAS* and *BRAF* wildtype | 50/122 (41%) | – | – | | – | – | |
| *RAS* mutation | 50/111 (45%) | 1.18 | 0.70, 1.99 | 0.532 | 1.03 | 0.58, 1.84 | 0.915 |
| *BRAF* mutation | 4/7 (57%) | 1.92 | 0.41, 10.1 | 0.406 | 1.83 | 0.35, 10.5 | 0.472 |
| Serum CEA level, (ng/mL)—PTL | 104/239 (44%) | 1.00 | 1.00, 1.00 | 0.139 | 1.00 | 1.00, 1.00 | 0.142 |
| Response—PTL | | | | | | | |
| Response | 63/157 (40%) | – | – | | | | |
| No response (PD/SD) | 41/83 (49%) | 1.46 | 0.85, 2.49 | 0.169 | | | |
| Number of liver metastases—PTL | 104/239 (44%) | 1.10 | 1.04, 1.16 | <0.001 | 1.10 | 1.04, 1.17 | <0.001 |
| *Number of liver metastases—PTL, categorical*[b] | | | | | | | |
| *1–5* | *33/94 (35%)* | – | – | | – | – | |
| *6–10* | *35/87 (40%)* | *1.24* | *0.68, 2.28* | *0.477* | *1.30* | *0.70, 2.44* | *0.411* |
| *>10* | *36/58 (62%)* | *3.02* | *1.55, 6.04* | *0.001* | *3.16* | *1.58, 6.51* | *0.001* |
| Number of liver segments involved—PTL | 104/240 (43%) | 1.34 | 1.15, 1.57 | <0.001 | | | |
| Diameter of largest metastasis—PTL | 104/239 (44%) | 1.00 | 0.99, 1.01 | 0.968 | 1.00 | 0.99, 1.01 | 0.732 |
| Distribution of liver metastases—PTL | | | | | | | |
| Unilobar | 9/29 (31%) | – | – | | | | |
| Bilobar | 95/211 (45%) | 1.82 | 0.81, 4.38 | 0.158 | | | |

OR = Odds Ratio, CI = Confidence Interval, PTL = prior to local treatment.
[a] The variables to include in the multivariable analyses were pre-specified. Number of liver metastases was included in its original continuous form.
[b] A separate multivariable analysis was performed were the continuous number of liver metastases was replaced by the categorical variant.

1.53–6.87], $p = 0.002$), corresponding to an early recurrence without repeat local treatment rate of 22%, 32% and 45%, respectively.

### 3.4. Predictive factors for consensus in resectability assessments

In patients receiving local treatment following panel conclusion (n = 263), no consensus among panel surgeons was present in 138 (52%) patients at the evaluation prior to local treatment. Factors displaying more advanced disease were associated with no consensus prior to local treatment at univariable analysis: higher CEA (OR 1.00 [95% CI 1.00–1.01], $p = 0.036$), larger number of CRLM (OR 1.09 [95% CI 1.04–1.15], $p = 0.001$) and larger number of involved liver segments (OR 1.26 [95% CI 1.09–1.45], $p = 0.002$) (data not shown). Number of CRLM and involved liver segments were linearly associated with the log-odds of no consensus prior to local treatment, which was tested by restricted cubic splines, implying that there is no meaningful cut-off value of these parameters to decide whether patients may benefit from a panel evaluation.

### 3.5. Outcomes of local treatment according to consensus among panel surgeons

At the last panel evaluation prior to local treatment, patients with resectability consensus among panel surgeons compared to no consensus with panel conclusion by majority vote had a lower rate of major resections (45 [36%] versus 68 [49%] patients, $p = 0.041$) with no difference in complete local treatment rate between these groups (114 [91%] versus 119 [86%], $p = 0.284$). The

Table 3
Univariable and multivariable logistic regression analysis to evaluate the association of tumour biological and technical anatomical features at baseline and prior to local treatment, with early recurrence within 6 months without repeat local treatment with curative intent.

| Characteristic | | Univariable analysis | | | Multivariable analysis[a] | | |
|---|---|---|---|---|---|---|---|
| | Event rate | OR | 95% CI | *P*-value | OR | 95% CI | *P*-value |
| Age patient | 75/240 (31%) | 1.03 | 1.00, 1.06 | 0.033 | 1.03 | 1.00, 1.07 | 0.047 |
| Sex | | | | | | | |
| Female | 23/89 (26%) | – | – | | | | |
| Male | 52/151 (34%) | 1.51 | 0.85, 2.73 | 0.167 | | | |
| Fong risk score | | | | | | | |
| Low, <3 | 37/112 (33%) | – | – | | | | |
| High, ≥3 | 38/128 (30%) | 0.86 | 0.49, 1.48 | 0.577 | | | |
| Site of primary tumour | | | | | | | |
| Left colon or rectum | 54/185 (29%) | – | – | | – | – | |
| Right colon | 21/55 (38%) | 1.50 | 0.79, 2.80 | 0.208 | 1.12 | 0.53, 2.29 | 0.764 |
| Time to metastases | | | | | | | |
| Metachronous | 11/34 (32%) | – | – | | – | – | |
| Synchronous | 64/206 (31%) | 0.94 | 0.44, 2.12 | 0.881 | 1.02 | 0.45, 2.45 | 0.962 |
| Tumour nodal status | | | | | | | |
| Negative | 6/23 (26%) | – | – | | | | |
| Positive | 20/63 (32%) | 1.32 | 0.47, 4.10 | 0.614 | | | |
| No surgery before registration | 49/154 (32%) | 1.32 | 0.51, 3.85 | 0.580 | | | |
| Mutational status | | | | | | | |
| *RAS* and *BRAF* wildtype | 33/122 (27%) | – | – | | – | – | |
| *RAS* mutation | 39/111 (35%) | 1.46 | 0.84, 2.56 | 0.183 | 1.19 | 0.64, 2.22 | 0.574 |
| *BRAF* mutation | 3/7 (43%) | 2.02 | 0.38, 9.65 | 0.373 | 1.67 | 0.28, 8.86 | 0.550 |
| Serum CEA level, (ng/mL)—PTL | 75/239 (31%) | 1.00 | 1.00, 1.00 | 0.320 | 1.00 | 1.00, 1.00 | 0.340 |
| Response—PTL | | | | | | | |
| Response | 43/157 (27%) | – | – | | | | |
| No response (PD/SD) | 32/83 (39%) | 1.66 | 0.94, 2.93 | 0.077 | | | |
| Number of liver metastases—PTL | 75/239 (31%) | 1.08 | 1.03, 1.14 | 0.004 | 1.09 | 1.03, 1.15 | 0.003 |
| *Number of liver metastases—PTL, categorical*[b] | | | | | | | |
| *1–5* | *21/94 (22%)* | – | – | | – | – | |
| *6–10* | *28/87 (32%)* | *1.65* | *0.85, 3.23* | *0.138* | *1.83* | *0.92, 3.70* | *0.089* |
| *>10* | *26/58 (45%)* | *2.82* | *1.40, 5.80* | *0.004* | *3.20* | *1.53, 6.87* | *0.002* |
| Number of liver segments involved—PTL | 75/240 (31%) | 1.30 | 1.10, 1.53 | 0.002 | | | |
| Diameter of largest metastasis—PTL | 75/239 (31%) | 1.00 | 0.99, 1.01 | 0.929 | 1.00 | 0.99, 1.01 | 0.811 |
| Distribution of liver metastases—PTL | | | | | | | |
| Unilobar | 5/29 (17%) | – | – | | | | |
| Bilobar | 70/211 (33%) | 2.38 | 0.94, 7.31 | 0.090 | | | |

OR = Odds Ratio, CI = Confidence Interval, PTL = prior to local treatment.
[a] The variables to include in the multivariable analyses were pre-specified. Number of liver metastases was included in its original continuous form.
[b] A seperate multivariable analysis was performed were the continuous number of liver metastases was replaced by the categorical variant.

incidence of no early recurrence, early recurrence with local treatment and early recurrence without local treatment was not statistically different between patients with and without consensus (Fig. 2). The risk of early recurrence for patients with no panel consensus was increased at univariable analysis (crude OR 1.73 [95% CI 1.03–2.94], $p = 0.040$), but not after adjusting for age, primary tumour site, time to metastases, *RAS*/*BRAF*$^{V600E}$ mutation status, CEA, number and size of CRLM (adjusted OR 1.37 [95% CI 0.78–2.41], $p = 0.274$).

### 3.6. Benefit of resectability assessments by the panel

In 263 patients who received local treatment following the panel advice, 50 (19%) patients were at least once assessed by an individual panel surgeon as having permanently unresectable CRLM. In 127 patients who were judged as having permanently unresectable CRLM by the panel and without local treatment, 14 (11%) patients were at least once assessed as having resectable CRLM by an individual panel surgeon. Thus these patients would have potentially received local treatment if resectability was determined by an individual surgeon.

## 4. Discussion

In this study with patients with initially unresectable CRLM, age and number of CRLM but not tumour biological factors were associated with early recurrence without the possibility of repeat local salvage treatment, without taking the type of systemic treatment into account. Consensus among panel surgeons was present in less than half of the resectability assessments. This high

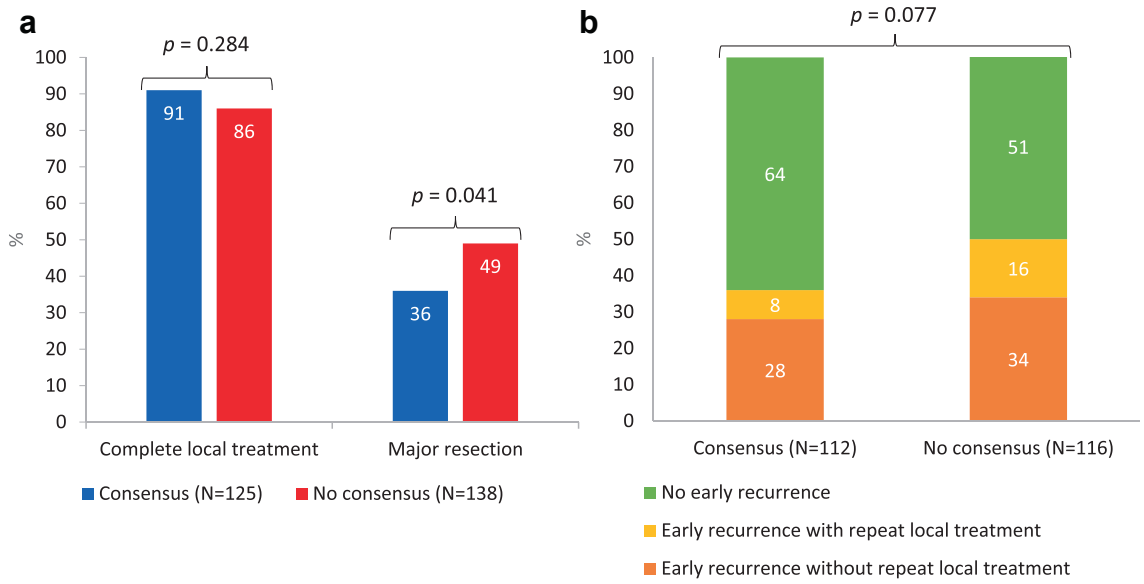


Fig. 2. Outcomes according to degree of consensus among panel surgeons in panel resectability assessments. (**a**) short-term resection outcomes in patients from 'surgical analysis', (**b**) first recurrence outcomes in patients from 'recurrence analysis'. All figures include only patients who received local treatment following the panel conclusion. Major liver resections were defined as resection of at least three segments or an (extended) hemihepatectomy.

inter-surgeon variability has been shown in previous retrospective surgical reviews, with reduced survival outcomes in patients in whom local treatment was considered feasible in retrospect [16,29,30]. Considering the absence of (a meaningful cut-off value of) predictive factors for consensus among panel surgeons and the selection of more patients for curative-intent local treatment, our data support the added value of evaluations by a panel rather than by just one or two (dedicated liver) surgeons in a multidisciplinary team and suggest that panel evaluations should be offered to all patients with initially unresectable CRLM. Patients with consensus or no consensus among panel surgeons prior to local treatment had comparable postoperative outcomes when adjusted for other risk factors in multivariable analysis. Hence, the panel does not lead to an increased selection of patients for local treatment with worse postoperative outcomes. This further supports the use of an expert panel.

Patients with CRLM are increasingly offered local treatment due to improved systemic and local treatments. The current study concerned patients with advanced CRLM and showed a rate of early recurrences without curative-intent repeat local treatment within 6 months after recurrence of over 30%. This warrants preoperative predictive factors to allow realistic patient expectations and to weigh individualised treatment decisions. As mentioned before, previous studies [8–10,12,21–24,31–33] suggested various factors to affect outcomes after local treatment of CRLM, but these retrospective studies are limited by inter-surgeon variability in assessing CRLM (un)resectability. Strengths of the current study are the prospectively selected cohort based on defined baseline unresectability criteria and that panel surgeons were blinded for tumour biological factors such as *RAS*/*BRAF* mutation status, resulting in a predominantly technical anatomical decision for resectability which reduced bias to a minimum.

Although number of CRLM was significantly associated with early recurrence without repeat local treatment options, this factor could not act as a resection criterion. This was concluded after no meaningful cut-off value could be defined due to the linear association and was further substantiated by showing that the majority of patients with the highest number of CRLM (>10) still received repeat local treatment after early recurrence. RFS was shown to have a weak association with OS after resection of CRLM [34]. As such, an optimal surrogate end-point for OS after local treatment of CRLM has yet to be defined. This study used early recurrence without curative-intent repeat local treatment as a novel and clinically relevant end-point in this patient group.

While older patients did not have a higher risk of early recurrence, age was a risk factor for early recurrence without repeat local treatment. This could either be caused by limitations in terms of technical abilities and/or patient physical condition or preference.

*RAS*/*BRAF*$^{V600E}$ mutations were reported to be correlated with more invasive spread, higher risk of positive surgical margins, tumour regrowth after ablation and worse RFS and OS [35]. We found a very strong association of *BRAF*$^{V600E}$ mutations, and to a lesser extent for *RAS* mutations, with a lower probability to convert to resectable disease. After systemic and subsequent local treatment, both *RAS* and *BRAF*$^{V600E}$

mutations lost their predictive value for early recurrence. These outcomes are in line with results from a previous phase 3 study [36]. In addition to the careful selection of patients undergoing local treatment including the assessment of tumour biology during systemic treatment, controlling micrometastatic disease by preoperative systemic treatment may result in counteracting the biological aggressiveness of the genetic mutation [36].

We acknowledge that our study has limitations. First, the number of variables tested for association with postoperative outcomes was limited by the number of events. Second, all patients underwent panel resectability assessments. However, to objectively assess the added value of a panel, the outcomes should be compared with a matched cohort without intercurrent resectability assessments by a panel. Lastly, since the number of patients with $BRAF^{V600E}$ mutations undergoing local treatment is relatively small in this study, results should be interpreted with caution.

The lack of predictive tumour biological factors as found by our study warrants further research on novel predictive factors, such as the consensus molecular subtypes, which are strongly related with prognosis and response on treatment in colorectal cancer [37], and specific oncogenic driver mutations such as *KRAS* A146, which is associated with larger tumour burden and worse outcome in patients with CRLM [38]. In addition, preoperative and postoperative sampling of liquid biopsies for circulating tumour DNA are reported to have a strong association with pathologic response on preoperative systemic treatment and survival outcomes after local CRLM treatment [39,40].

In conclusion, a higher age and number of CRLM but not tumour biological factors were independently associated with early recurrence without repeat local treatment options in patients who received local treatment of CRLM after systemic induction therapy. Outcomes of patients with no consensus and panel conclusion by majority vote are similar to patients with consensus among panel surgeons. As such, the use of a liver panel allows a meaningful selection of an increased number of patients who are eligible for local treatment. Thus far, with the current clinically available tumour biomarkers, resectability assessment remains primarily a technical anatomical decision.

## Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Author contribution statement

Participated in research design: KB, MJGB, CJAP, RJS.

Participated in the writing of the paper: KB, MJGB, AMM, CJAP, RJS.

Participated in the performance of the research: KB, MJGB, MvA, AK, TC, CHCD, MRWE, MFG, DJG, TMvG, JJH, KPdJ, GK, JMK, NFMK, WKGL, MSLL, KPvL, IQM, UPN, GAP, AMR, TMR, CV, JHWdW, AMM, CJAP, RJS.

Participated in data analysis: KB, MJGB, AMM.

Participated in data management: KB, MJGB, AK, CJAP, RJS.

Participated in the liver expert panel for resectability assessments: MvA, TC, CHCD, MRWE, MFG, DJG, TMvG, JJH, KPdJ, GK, JMK, NFMK, WKGL, MSLL, KPvL, IQM, UPN, GAP, AMR, TMR, CV, JHWdW, RJS.

All authors approved the manuscript and agree with its submission to European Journal of Cancer.

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## Conflict of interest statement

C.J.A.P. has an advisory role for Nordic Pharma. This funding is not related to the current research. The remaining authors declare no potential conflicts of interest.

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