Survival Benefit of Repeat Local Treatment in Patients Suffering From Early Recurrence of Colorectal Cancer Liver Metastases

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Abstract

Repeat local treatment should be considered in patients suffering from early recurrence of colorectal cancer liver metastases (CRLM). A multimodality approach, consisting of neoadjuvant systemic therapy followed by repeat local treatment of CRLM, appeared favorable in patients with recurrence within 4 months. The optimal sequence and the role of systemic therapy in patient selection should be further clarified in prospective studies.

Background: A uniform treatment strategy for patients suffering from early recurrence after local treatment of CRLM is currently lacking. The aim of this observational cohort study was to assess the potential survival benefit of repeat local treatment compared to systemic therapy in patients suffering from early recurrence of CRLM. Patients and Methods: Patients who developed recurrent CRLM within 12 months after initial local treatment with curative intent were retrospectively identified in Amsterdam University Medical Centers between 2009-2019. Differences in overall and progression-free survival among treatment strategies were assessed using multivariable Cox regression analyses. Results: A total of 135 patients were included. Median overall survival of 41 months [range 4-135] was observed in patients who received repeat local treatment, consisting of upfront or repeat local treatment after neoadjuvant systemic therapy, compared to 24 months [range 1-55] in patients subjected to systemic therapy alone (adjusted HR = 0.42 [95%-CI: 0.25-0.72]; P = .002). Prolonged progression-free survival was observed after neoadjuvant systemic therapy followed by repeat local treatment, as compared to upfront repeat local treatment in patients with recurrent CRLM within 4 months following initial local treatment of CRLM (adjusted HR = 0.36 [95%-CI: 0.15-0.86]; P = .021). Conclusion: Patients with early recurrence of CRLM should be considered for repeat local treatment strategies. A multimodality approach, consisting of neoadjuvant systemic therapy followed by repeat local treatment, appeared favorable in patients with recurrence within 4 months following initial local treatment of CRLM.

Clinical Colorectal Cancer, Vol. 20, No. 4, e263–e272 © 2021 The Author(s). Published by Elsevier Inc.
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Keywords: Hepatectomy, Ablation, Systemic therapy, Treatment strategy, Survival analysis

Introduction

Local treatment of colorectal cancer liver metastases (CRLM), including resection and local ablative techniques for smaller lesions, is the only treatment with curative intent. 1,2 Long term survival is improving, with 5- and 10-year overall survival rates of up to 55.2% and 27.5%, respectively. 3,7 Unfortunately, about half of these
patients develop recurrence in the liver remnant after successful local treatment of CRLM.\(^{8,10}\) Technical developments in liver surgery and increasing efficacy of systemic therapy regimens have broadened the indication for repeat local treatment of CRLM. Since 1960 repeat hepatic resections have been performed in highly selected patients. High survival rates and low morbidity after repeat local treatment were reported.\(^{11,12}\) Until then, prior resection had often been considered a contraindication for repeat local treatment of recurrent CRLM and patients were offered palliative systemic therapy instead.\(^{15,16}\) Nowadays, repeat local treatment is considered a safe and effective treatment for patients with recurrence of CRLM.\(^{17,18}\)

Although repeat surgery or ablation for recurrent CRLM has become widely adopted, no randomized controlled trials have been conducted and potential contraindications are unclear. Several prognostic factors for overall survival have been identified to aid selection of patients who may benefit from repeat local treatment of CRLM. A short disease-free survival after initial local treatment is considered an independent prognostic factor for overall survival.\(^{17,18}\) The benefit of repeat local treatment for early recurrence of CRLM may be questioned, as patients with short disease-free interval are known to have a more aggressive tumor biology which is related to worse prognosis.\(^{19-23}\) New metastases are likely to develop in these patients, so it is reasoned that patients may benefit more from systemic therapy for early recurrence of CRLM.

At present, the optimal treatment strategy for patients with early recurrence of CRLM is frequently debated in multidisciplinary team meetings, as no evidence-based or uniformly adopted treatment protocol is available and comparative studies are scarce. Therefore, we aimed to study the potential survival benefit of repeat local treatment compared to systemic therapy in patients with early recurrence of CRLM.

**Patients and Methods**

**Study Population**

In this observational cohort study, patients with CRLM were retrospectively identified from electronic health records, based on International Classification of Diseases (ICD-10) codes for colorectal cancer and liver metastasis in Amsterdam University Medical Centers (Amsterdam UMC), two tertiary referral hospitals in the Netherlands. Medical files of patients diagnosed with recurrence of CRLM from January 01, 2009 until March 01, 2019 were reviewed. Patients with early recurrence of CRLM, defined as recurrent metastases in the liver remnant within 12 months after initial local treatment with curative intent, were selected for this study. Eligibility criteria were prior history of resection or local ablation techniques, including radiofrequency ablation and microwave ablation (or irreversible electroporation for unselectable central lesions close to blood vessels or bile ducts) by an open, laparoscopic or percutaneous approach. Patients treated with stereotactic ablative radiotherapy were not included. Patients with tumor re-growth at lesion borders (ie, local recurrence) after ablative techniques without onset of new metastases did not qualify for this study, as these lesions were considered residual disease. In accordance with the Dutch national guidelines, neoadjuvant systemic therapy prior to initial local treatment of CRLM was only administered to patients initially unsuit-
Local recurrence of the primary tumor, at the lesions borders after ablative techniques, or elevated CEA levels without substrate on diagnostic imaging were not considered events in the progression-free survival analysis. Progression in patients with systemic therapy was defined according to response evaluation criteria in solid tumors and start of second line systemic therapy regimen.24

Data Collection
Demographic and clinicopathological data were extracted from prospectively maintained electronic patient files. Patient's age at initial local treatment of CRLM was reported. Tumor localization and stage were based on radiology and pathology reports. Diagnosis of liver metastases during pre-operative work-up or at time of primary resection was defined as synchronous disease. Number of metastases and largest diameter were reported for initial and recurrent CRLM. The anatomy of the liver was based on Couinaud's classification.25 Presence of liver metastases in both the left and right liver lobe (or caudate lobe) were considered bilobar disease. In clinical practice, imaging was not always planned after exactly 3 months. Very early recurrence of CRLM was therefore defined as recurrent CRLM within 4 months following initial local treatment with curative intent.

Statistics
Logistic regression analysis was used to explore differences in demographic and clinicopathological features of patients receiving repeat local versus systemic treatment for early recurrence of CRLM. Age at initial local treatment of CRLM, which was a continuous variable without normal distribution, was compared between groups using Mann-Whitney U test. All variables identified by univariable analysis with a P-value <.1 were included in multivariable analysis by forward selection procedure. A Pearson correlation coefficient of more than 0.7 between two variables was considered relevant to correct for multicollinearity in multivariable analysis.

Kaplan-Meier curves were shown to illustrate overall and progression-free survival over time. Median overall survival was reported with interquartile ranges [IQR]. Cox regression analyses were performed to estimate the difference in overall and progression-free survival among treatment strategies. Disease-free interval after initial local treatment of CRLM with curative intent was examined as potential effect modifier by adding the variable and the interaction with treatment strategy in the model. Patient and tumor characteristics, including sex, age, localization, stage and lymph node status of the primary tumor, onset of initial metastases, interval of initial metastases with resection of primary tumor, number, distribution and size of largest lesion of initial and recurrent metastases, disease-free interval and presence of extrahepatic disease were analyzed for potential confounding. Unadjusted hazard ratio’s (HR) and adjusted hazard ratio’s (aHR) were reported, with 95%-confidence intervals [95%-CI]. A P-value of less than .05 was considered statistically significant.

Results
A total of 281 patients were identified with recurrent CRLM in Amsterdam UMC between 2009 and 2019. Of these patients, 221 (78.6%) developed an early recurrence in the liver remnant within 12 months of initial treatment of CRLM with curative intent. In 86 (38.9%) cases, one of the exclusion criteria was met, resulting in a study population of 135 patients (Figure 1).

Patient and Tumor Characteristics
The majority of patients were men, presented with a left-sided primary tumor and synchronous multiple liver metastases (Table 1). Patients underwent initial local treatment of CRLM at a median age of 63 years [range 26-87]. Patients were diagnosed with recurrent CRLM after a median follow-up of 5 months [range 1-12]. Sixty-five of these patients (48.1%) were diagnosed with recurrent metastases within 4 months following initial treatment with curative intent. Out of a total of 135 patients with early recurrence, 100 patients (74.1%) were treated with repeat local treatment, whether or not combined with systemic therapy, and 35 (25.9%) with systemic therapy alone.

Confounding by Indication
Patients were more frequently treated with systemic therapy alone, in case of invasion of the primary tumor into the subserosa, bilobar distribution of initial and recurrent CRLM, and multiple (>1) recurrent CRLM (Table 1). In multivariable analysis, distribution of initial and recurrent metastases and multiple recurrent CRLM were considered independent predictive factors for treatment with systemic therapy alone, instead of repeat local treatment of CRLM.

Systemic Therapy
Sixty patients received systemic therapy for early recurrence of CRLM, either as neoadjuvant systemic therapy followed by repeat local treatment or in a palliative setting. Repeat local treatment followed neoadjuvant systemic therapy in 25/60 (41.7%) cases. These patients underwent a median of 4 cycles [range 3-16] prior to repeat local treatment of CRLM. Patients treated with systemic therapy alone received a median of 7 cycles [range 1-26] before progression of disease. The chemotherapy regimen consisted of doublet fluoropyrimidine-based therapy in the far majority of patients (71.3%), in particular capcitabine and oxaliplatin combined with bevacizumab.

Overall Survival
The median overall survival of the entire study population was 36 months [IQR 23-64], with three- and five-year survival rates of 48.4% and 26.0%, respectively. Median follow-up from date of recurrence was 27 months [IQR 18-41], in which 73/135 (54.1%) patients died. Patients who underwent repeat local treatment, consisting of either upfront or repeat local treatment after neoadjuvant systemic therapy, had a median overall survival of 41 months [IQR 29-not reached] compared to 24 months [IQR 15-32] in patients receiving systemic therapy alone (HR = 0.38 [95%-CI: 0.23-0.63]; P < .001). A disease-free interval of 4 months or less was not considered an effect modifier in the association between treatment strategy and overall survival (P = .102), which means that the effect of repeat local treatment on overall survival for patients with recurrence within 4 months is like those suffering from later
## Table 1  Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total n = 135</th>
<th>Repeat local treatment n = 100</th>
<th>Systemic therapy n = 35</th>
<th>Univariable analysis P-value</th>
<th>Multivariable analysis P-value</th>
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<tbody>
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<td><strong>Demographics</strong></td>
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<tr>
<td>Median [range]</td>
<td>63 [26-87]</td>
<td>63.5 [26-87]</td>
<td>63 [34-81]</td>
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<td>Sex, n (%)</td>
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<tr>
<td>men</td>
<td>93</td>
<td>67 (67.0)</td>
<td>26 (74.3)</td>
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<td>women</td>
<td>42</td>
<td>33 (33.0)</td>
<td>9 (25.7)</td>
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<td>Side, n (%)</td>
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<td>Left-sided</td>
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<td>11 (31.4)</td>
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<td>Localization, n (%)</td>
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<td>Lymph node status, n (%)</td>
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<td>76</td>
<td>55 (56.1)</td>
<td>21 (61.8)</td>
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<td><strong>Initial liver metastases</strong></td>
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<td>Onset, n (%)</td>
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<td>Metachronous</td>
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<td>Synchronous</td>
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<td>Interval with primary, n (%)</td>
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<td>≤12 mo</td>
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<td>31 (88.6)</td>
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<td>&gt;12 mo</td>
<td>16</td>
<td>12 (12.0)</td>
<td>4 (11.4)</td>
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<tr>
<td>Number, n (%)</td>
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<td>.018</td>
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<tr>
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<td>33</td>
<td>30 (30.0)</td>
<td>3 (8.6)</td>
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<tr>
<td>&gt;1</td>
<td>102</td>
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<td>32 (91.4)</td>
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<td>Distribution, n (%)</td>
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<tr>
<td>Monolobar</td>
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<td>48 (48.0)</td>
<td>4 (12.1)</td>
<td>.001</td>
<td>.03</td>
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<td>52 (52.0)</td>
<td>29 (87.9)</td>
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<tr>
<td>Size largest diameter, n (%)</td>
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<td></td>
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<tr>
<td>≤5 cm</td>
<td>101</td>
<td>76 (80.9)</td>
<td>25 (78.1)</td>
<td>.739</td>
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<tr>
<td>&gt;5 cm</td>
<td>25</td>
<td>18 (19.1)</td>
<td>7 (21.9)</td>
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<td><strong>Recurrent liver metastases</strong></td>
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<tr>
<td>Disease-free interval, n (%)</td>
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<tr>
<td>≤4 mo</td>
<td>65</td>
<td>44 (44.0)</td>
<td>21 (60.0)</td>
<td>.106</td>
<td></td>
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<tr>
<td>&gt;4 mo</td>
<td>70</td>
<td>56 (56.0)</td>
<td>14 (40.0)</td>
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</table>

(continued on next page)
recurrence (between 5-12 months) (Figure 2). Number of recurrent CRLM (solitary versus multiple) was considered a relevant confounder, so this variable was included in the model. Repeat local treatment for early recurrence of CRLM remained an independent prognostic factor for overall survival (aHR = 0.42 [95%-CI: 0.25-0.72]; P = .002).

**Sequence**

In 25/60 (41.7%) patients initially assigned to systemic therapy, local treatment was performed after non-progression of disease. Median overall survival was significantly better in this group of patients, i.e., 40 months [95%-CI: 30.4-49.6] compared to 24 months [95%-CI: 11.4-36.6] for patients receiving systemic therapy alone (HR = 0.39 [95%-CI: 0.19-0.80]; P = .010). Distribution of initial CRLM, size of largest lesion of initial and recurrent CRLM, and presence of extrahepatic disease were relevant confounders. Based on the number of events, distribution of initial CRLM and presence of extrahepatic disease (ie, the strongest confounders) were included in the model. Local treatment after neoadjuvant systemic therapy remained favorable as compared

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**Table 1 (continued)**

<table>
<thead>
<tr>
<th></th>
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<th>Multivariable analysis P-value</th>
</tr>
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<tbody>
<tr>
<td>Number, n (%)</td>
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<tr>
<td>1</td>
<td>60</td>
<td>55 (55.0)</td>
<td>5 (14.3)</td>
<td>&lt;.001</td>
<td>.036</td>
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<tr>
<td>&gt;1</td>
<td>75</td>
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<td>30 (85.7)</td>
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<td>Distribution, n (%)</td>
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<tr>
<td>Monolobar</td>
<td>93</td>
<td>80 (80.8)</td>
<td>13 (37.1)</td>
<td>&lt;.001</td>
<td>.007</td>
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<tr>
<td>Bilobar</td>
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<td>22 (62.9)</td>
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<td>Size largest diameter, n (%)</td>
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<tr>
<td>≤5 cm</td>
<td>125</td>
<td>91 (93.8)</td>
<td>34 (97.1)</td>
<td>.462</td>
<td></td>
</tr>
<tr>
<td>&gt;5 cm</td>
<td>7</td>
<td>6 (6.2)</td>
<td>1 (2.9)</td>
<td></td>
<td></td>
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<tr>
<td>Extrahepatic disease, n (%)</td>
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<tr>
<td>Absent</td>
<td>110</td>
<td>84 (84.8)</td>
<td>26 (74.3)</td>
<td>.166</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>24</td>
<td>15 (15.2)</td>
<td>9 (25.7)</td>
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</tbody>
</table>

* Fisher’s exact test, variable not included in multivariable analysis
* Correlation between variables; distribution of initial metastases was included in multivariable analysis
to systemic therapy alone (aHR 0.44 [95%-CI: 0.19-1.00]; P = .05).

Most patients (19/25; 76.0%) who underwent repeat local treatment after neoadjuvant systemic therapy had experienced recurrent CRLM within 4 months following initial treatment with curative intent. These patients were often offered neoadjuvant systemic therapy based on oncological aspects due to development of ‘very early’ recurrence. Overall, repeat local treatment was performed after neoadjuvant systemic therapy in 19/44 (43.2%) patients suffering from recurrent CRLM within 4 months, as compared to 6/56 (10.7%) patients with recurrent CRLM after 4 months (P < .001). Survival curves were therefore stratified for three treatment strategies in patients with recurrence within 4 months: systemic therapy alone, upfront repeat local treatment, and neoadjuvant systemic therapy followed by repeat local treatment (Figure 3). No significant difference in overall survival was observed among treatment strategies, though a multimodality approach consisting of neoadjuvant systemic therapy followed by repeat local treatment appeared favorable (Table 2).

**Progression-free Survival**

Progression of disease occurred in 112/135 (83.0%) patients after a median follow-up of 9 months [IQR 6 - 16] from the time of recurrence. Progression-free survival did not differ significantly between patients treated with repeat local treatment or systemic therapy for recurrent CRLM (HR = 0.88 [95%-CI: 0.58-1.35]; P = .569). One-year progression-free survival rates of 32.9% and 34.4% were obtained, respectively.

In patients with recurrence within 4 months following initial treatment of CRLM, a combined treatment strategy consisting of neoadjuvant systemic therapy followed by repeat local treatment was superior compared to upfront local treatment of CRLM, resulting in a median progression-free survival of 12 months [IQR 8-22] vs. 6 months [IQR 5-10], respectively (HR = 0.50 [95%-CI: 0.26-0.95]; P = .035) (Figure 4). Distribution and largest size of initial metastases, and number and largest size of recurrent metastases were considered relevant confounders, so were included in the model. Prolonged progression-free survival was observed in patients who underwent a combined treatment strategy, consisting of neoadjuvant systemic therapy followed by repeat local treatment, as compared to upfront local treatment of recurrent CRLM (aHR = 0.36 [95%-CI: 0.15-0.86]; P = .021).

**Discussion**

This study shows a potential overall survival benefit of repeat local treatment in patients suffering from early recurrence of CRLM after initial treatment with curative intent. Patients undergoing repeat local treatment (after neoadjuvant systemic therapy) showed better.
overall survival compared to patients solely treated with systemic therapy for early recurrence of CRLM. In sub-analysis of patients with recurrent CRLM within 4 months, no significant difference in overall survival was observed among treatment strategies. However, a multimodality approach consisting of neoadjuvant systemic therapy followed by repeat local treatment appeared favorable in these patients, in particular due to the prolonged progression-free survival compared to patients subject to upfront local treatment of CRLM.

Many studies evaluated the benefit of repeat hepatectomy without considering disease-free interval. Moreover, previous studies lacked comparison to systemic treatment, or distinction between intra- and extrahepatic disease, even though patients with extrahepatic recurrence patterns are believed to have an impaired prognosis.

Outcomes of the current study resemble those of previous reports on the potential benefit of repeat local treatment in patients with...
Treatment strategy for early recurrent CRLM

early recurrence of CRLM. Watanabe et al. showed favorable overall survival in patients treated with repeat hepatectomy for recurrence within 6 months.\textsuperscript{44} Similar overall survival rates after repeat local treatment and chemotherapy were reported in patients with recurrence within 6 months by Inoue et al., even though a few patients with extrahepatic metastases were included for analysis.\textsuperscript{45} In addition, Viganò et al. and Hashimoto et al. showed improved overall survival rates after repeat hepatectomy as compared to non-repeat hepatectomy in patients with intrahepatic recurrences within 6 and 12 months, respectively.\textsuperscript{45,46} However, even though a survival benefit of neoadjuvant systemic therapy prior to metastasectomy was observed by Viganò et al. for the entire study population, the potential benefit of neoadjuvant systemic therapy was not discussed in sub-analysis of patients with recurrences confined to the liver remnant. In accordance with the current findings, Dijkstra et al. showed no significant survival benefit of neoadjuvant systemic therapy in patients undergoing repeat local treatment for recurrent CRLM.\textsuperscript{47}

Perioperative systemic therapy for recurrent CRLM is often administered at the clinician’s discretion and regimens may differ among centers as no uniform treatment protocol exists. High variety in three-year overall survival rates after repeat hepatectomy have therefore been reported, ranging from 0 to 100% in patients with early recurrence of CRLM.\textsuperscript{21,23,48} Besides differences in systemic therapy regimens, these variations in survival rates may also be explained by differences in the definition and the etiology of early recurrent disease. Definitions for early recurrence of CRLM range from 4 to 12 months following initial treatment with curative intent.\textsuperscript{21,23,38,42} In addition, the etiology of early recurrent CRLM is often debated, as these lesions may represent new onset metastases or previously occult metastases.\textsuperscript{25} To reduce potential bias, patients with tumor regrowth at lesion borders after ablative techniques were excluded from the current analysis as patients with residual disease should qualify for upfront repeat local treatment.\textsuperscript{46,49}

The current study assessed the potential benefit of repeat local treatment in patients with recurrent CRLM within 12 months, as a disease-free interval of more than 12 months is considered an independent prognostic factor for overall survival after repeat hepatectomy.\textsuperscript{12,17,18} To reduce potential bias, patients with recurrence after 12 months were therefore excluded from this study. Current findings may support clinicians in deciding on the most optimal treatment strategy when faced with patients with early recurrence of CRLM.

Several limitations of the study need to be addressed. First, patients were retrospectively identified in this relatively small observational cohort study. Motivation for selection of repeat local or systemic treatment strategies could therefore have been biased. To overcome this potential bias, confounding by indication was analyzed and a multivariable analysis with correction for relevant confounders was performed. Nevertheless, residual bias may have resulted in selection of more favorable patients for repeat local treatment strategies. Second, the limited number of patients in subgroups hampered in-depth analysis on the potential survival benefit of patients treated with neoadjuvant systemic therapy followed by repeat local treatment as compared to those treated with systemic therapy alone. Last, the prognostic value of R1-

resections was not included in the present analysis, since ablative techniques were frequently used. Also, CEA levels and \textit{RAS/BRAF} mutation status were lacking in the majority of patients due to pre-operative work-up in regional hospitals. These published independent prognostic factors for overall survival may have influenced the outcome of this study. In addition, the potential effect of a third or fourth repeat local treatment of recurrent disease were not taken into account, which may explain the difference in overall survival without difference in progression-free survival. Nevertheless, this comparative study may give guidance in proper treatment selection for patients suffering from early recurrence of CRLM. Moreover, it may be a first step in the development of a widely adopted treatment protocol for these patients, even though a randomized controlled study should be performed to establish a standardized treatment protocol to overcome potential selection bias for repeat local treatment strategies.

This study emphasizes the importance of exploring feasibility of local treatment strategies, even in patients with very early recurrence of CRLM. Eligibility for repeat local treatment strategies of recurrent CRLM is however subject to several prognostic factors, including performance status, the initial aggressiveness of the tumor, and anesthesiological and surgical risk. When these criteria are met, repeat local treatment for patients suffering from early recurrence of CRLM merits consideration.

Conclusion

High overall survival rates were observed after repeat local treatment in patients suffering from early recurrence of CRLM, in particular compared to patients treated by systemic therapy alone. Patients with recurrence within 12 months should therefore be considered for repeat local treatment strategies. A combined regimen, consisting of neoadjuvant systemic therapy followed by repeat local treatment, may benefit patients with recurrence within 4 months following initial treatment of CRLM, although the optimal sequence remains to be further clarified in future prospective studies.

Clinical Practice Points

Treatment strategy in patients suffering from recurrence of colorectal cancer liver metastases (CRLM) is frequently debated during multidisciplinary team meetings, in particular in those suffering from recurrence within 6 months following initial treatment with curative intent. Previous studies have evaluated the benefit of repeat hepatectomy in patients with recurrent CRLM. A disease-free interval of more than 12 months was established an independent prognostic factor for overall survival. However, many studies lacked consideration of a shorter disease-free interval, comparison to systemic treatment or distinction between intra- and extrahepatic recurrent disease. This study showed, by analyzing overall and progression-free survival in patients suffering from recurrence within 12 months, that patients should be considered for repeat local treatment of CRLM. A multimodality approach, consisting of neoadjuvant systemic therapy followed by repeat local treatment of CRLM, appeared favorable in patients with recurrence within 4 months. These findings may support clinicians in deciding on the most optimal treatment strategy when faced with patients...
with early recurrence of CRLM, although the optimal sequence remains to be further clarified in future prospective studies.

Disclosures
No financial or non-financial compensation was granted to conduct this research. Three co-authors (GK, HJV and MRM) received financial compensation for work outside the submitted work, including grants, personal fees and non-financial support.

Acknowledgments
Not applicable

Supplementary materials

CRediT authorship contribution statement

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