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High resection rates of colorectal liver metastases after standardized follow-up and multimodal management: an outcome study within the COLOFOL trial

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Abstract

Background: Outcome after colorectal liver metastases (CRLM) resection has improved over time, despite increased resection rates. Hence, it's crucial to identify all patients possible to treat with curative intent. The objectives of this study were to map recurrence pattern, treatment strategy and survival depending on treatment and follow-up strategy.

Methods: In the COLOFOL-trial, patients with radically resected stage II-III colorectal cancer were randomized to high-frequency (6, 12, 18, 24 and 36 months; HF) or low-frequency (12 and 36 months; LF) follow-up. In this study, all CRLM within 5 years were identified and medical files scrutinized. Overall survival (OS) was analysed in uni- and multivariable analyses. Primary endpoint was 5-year OS.

Results: Of 2442 patients, 235 (9.6%) developed metachronous CRLM of which 123 (52.3%) underwent treatment with curative intent, resulting in 5-year OS of 58%. Five-year OS for patients with CRLM was 43% after HF versus 24% after LF. The survival benefit was confirmed for HF 8 years from resection of the primary tumour, HR 0.63 (CI 0.46–0.85).

Conclusion: A high proportion of metachronous CRLM was possible to treat with curative intent, yielding high survival rates. More intense follow-up after colorectal cancer resection might be of value in high-risk patients.

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Introduction

The liver is the most common site of metastases in colorectal cancer (CRC) and approximately 25% of all patients develop colorectal liver metastases (CRLM) at some point in time. As higher incidences of CRLM have been reported historically, it is possible that earlier detection of the primary tumours and modern use of adjuvant chemotherapy could decrease recurrence rates further.[1,2] Improved preoperative staging also enables more metastases to be detected synchronously, subsequently lowering the proportion of metachronous metastases, which affect about 10% of all patients. Long term survival for patients after resection and/or ablation of CRLM is constantly improving, and 5-year OS survival rates over 50% have been reported in national cohorts, despite increasing resection rates.[3,4] Survival in palliative chemotherapy has also improved, but 5-year OS rates are still reported to be below 10%.[5,6] This indicates the importance of

[##] The COLOFOL study group.

identifying all patients with CRLM possible to treat with curative intent.

The benefit of intense follow-up programs for early detection of recurrences is debated. The main goal of follow-up programs is early detection of recurrences, with subsequently improved possibilities of curative treatment due to less severe tumour stage. Several studies have been performed to evaluate the impact of intensity of postoperative imaging and measurement of serum carcinoembryonic antigen (CEA), without convincing proof of any survival benefit from more intense follow-up regimens.[7–9] Among them, the COLOFOL trial randomized 2509 patients radically treated for CRC (stage II-III) to either high- or low-frequency follow-up. This did not show any differences in 5-year overall mortality or cancer specific mortality between the randomization groups.

Prognostic factors for mortality in metastatic disease have been well described, with the conclusion that patient factors and primary tumour characteristics, such as lymph node status and vascular invasion together with metastatic pattern, are of great importance for prognosis.[10–14] Beyond patient selection, also choice of surgical technique and adding of preoperative and postoperative adjuvant chemotherapy is of relevance.[15–17] However, selection criteria for curatively intended treatment of CRLM are not fully established and have varied over time and between centers. At the same time, individual assessment in multidisciplinary boards including presence of liver surgeon expertise has been proven important.[18–20] The COLOFOL trial protocol stipulated that all recurrences detected at follow-up should be discussed in a multidisciplinary therapy board, in which the possibility for metastasectomy should be evaluated.

Based on a multimodal treated population diagnosed with CRC, the objectives of this study were to map liver recurrence pattern, treatment strategy and survival depending on treatment and follow-up strategy.

Methods

The COLOFOL trial was a prospective randomized multicenter trial, with 24 participating centers in Denmark, Sweden and Uruguay, comparing high- and low-frequency follow-up of patients radically treated for CRC (stage II-III) between 2006 and 2010. Eligible patients had to be 75 years or younger with a life expectancy based on co-morbidity of at least two years. The patients were further required to have at least one imaging procedure of liver and lungs before primary surgery to rule out synchronous metastases and a colonoscopy to rule out synchronous colorectal tumours. A total of 2509 patients were randomized to either high-frequency (at 6, 12, 18, 24 and 36 months) or low-frequency (at 12 and 36 months) examinations with multislice CT scan of the thorax and abdomen and measurement of CEA. Patients were followed prospectively for 5 years after primary tumour resection and primary outcomes were overall and cancer specific mortality.[7]

For the present study, patients registered in Denmark (8 study sites) and Sweden (15 study sites) with any kind of recurrences within 5 years after resection of the primary CRC were identified and medical files were scrutinized. For pragmatic reasons, the one participating center in Uruguay was not included. Data collected included patient- and primary tumour-characteristics, time to recurrence, metastatic distribution, detailed information on surgical and medical treatment, multidisciplinary assessment, intention- and outcome of treatment, surgical and/or ablative technique, and oncological treatment at any point in time, including palliation. Data on any 2nd and 3rd recurrences were also retrieved. Mortality was checked via the Danish and Swedish population registers where all deaths are continuously registered. Follow-up time after first recurrence was 5 years in all but one patient.[21]

To include all metastases detected in the scheduled 1-year control, the time frame was set to 0–13 months and defined as early metachronous metastases. Curatively intended treatment was defined as radically resected or ablated liver metastases, and when present, also radical treatment of extra-hepatic disease. The study was approved by Copenhagen and Frederiksberg Scientific committee (KF 01–194/04) in Denmark and the Regional Ethical committee in Uppsala (2004:M453 and amendment (2016-07-22)).

Statistics

Predictive factors for treatment with curative intent of all patients with liver metastases were analyzed by means of uni- and multivariable Poisson regression. Five-year overall survival (OS) was measured from date of detection of CRLM to death or end of follow-up within 5 years.

To compensate for the lead-time bias in comparison of survival between randomization arms (high- or low-frequency follow-up), analysis of conditional probability of survival was performed. Overall survival (OS) was measured from date of resection of the primary tumour to death or end of follow-up within 8 years, where patients entered the analysis at time of detection of liver recurrence. To reduce excessive effect of early deaths when few cases are at risk, not attributable to follow-up regimen, patients with liver metastases that died within one year of the primary tumour resection were excluded from the analysis.

OS was computed using the Kaplan–Meier method and group comparisons were analyzed by logrank test, uni- and multivariable Cox proportional hazards regression. The proportional hazards assumption was tested with Schoenfeld's residuals. To further explore any differences in survival, 5-year restricted mean survival (RMS) was calculated as complement to 5-year OS, to get a better impression on loss of life-time (in years) during the 5-year follow-up time. In the multivariable analyses, all collected variables from the univariable analyses were put in the analysis and kept in the model if they were independently statistically significant or had a p-value <0.20 and a confounding effect (*i.e.* effected other HRs with more than 10%).

To test difference of recurrence characteristics between high- and low-frequency follow-up groups Fisher's exact test or Wilcoxon rank sum test was used. P-values <0.05 were considered statistically significant. When appropriate, 95% confidence intervals (CI) are presented in parenthesis. All statistical analyses were carried out with Stata version 16.1 (Stata Corp, College Station, Texas, USA).

Results

Metastatic pattern

A total of 2442 patient were included in the study population and 471 (19.3%) patients were confirmed to have recurrent disease within 5 years after primary surgery. A total of 235 patients (9.6%) developed CRLM as 1st recurrence. Out of these, 148 (63.0%) patients had tumors confined to the liver whereof 78 (33.2%) patients had single metastases. Fifty-six percent of the metastases were detected within the first 13 months after operation of the primary tumour (Table 1).

Treatment with curative intent

Out of the total cohort of patients with liver metastases as 1st recurrence, 220 (93.6%) patients were assessed in a multidisciplinary tumour board. A total of 123 (52.3%) patients underwent surgical resection and/or ablation therapy with a curative intent, resembling 5.0% of all patients in the COLOFOL cohort. Out of the 78 patients with single metastasis, 72 (92.3%) were treated with curative intent compared to 5 out of 24 (20.8%) patients with more than 5 metastases. More than 5 metastases and concomitant metastases in other organs were the only risk factors for not being treated with curative intent in multivariable analysis (Supplementary Table 1). Although size was not an independent selection criterion in the multivariable analysis, 45/48 (93.8%) of the patients with largest sized liver metastasis 20 mm or smaller (without any other metastatic site) were treated with curative intent compared to 8/20 (40.0%) of all patients with largest sized liver metastasis ≥50 mm.

Out of all patients treated with curative intent, 93 (75.6%) patients were treated with resection only, 20 (16.3%) patients with ablation therapy only, and 9 (7.3%) patients with a combination of resection and ablation. One patient had complete remission after neoadjuvant chemotherapy and was not subject for surgical treatment. Out of these 123 patients, 106 (86.2%) were treated with chemotherapy at some point in time (after primary surgery and/or before or after liver surgery; Table 1). Out of the 112 patients not treated with curative intent, 96

Table 1 Liver recurrences and resection rates and chemotherapy for those with a curatively intended treatment of first liver recurrence

	CRLM as 1st recurrence n	Curatively intended treatment n ([a])	Adjuvant chemo after CRC n (%)	Chemo before or after liver surgery n (%)	Chemo at some time point n (%)
Total	235	123[b] (52)	68 (55)	73 (59)	106 (86)
Liver metastases only	148	112 (76)	60 (54)	64 (57)	96 (86)
No of tumours:					
≤ 1	78	72 (92)	39 (54)	39 (54)	61 (85)
2–4	44	34 (77)	18 (53)	20 (59)	29 (85)
≥ 5	24	5 (21)	2 (40)	5 (100)	5 (100)
Missing	2	1 (50)	1 (100)	0	1 (100)
Max size (mm):					
≤ 20	48	45 (94)	28 (62)	22 (49)	39 (87)
21–30	40	31 (78)	13 (42)	17 (55)	26 (84)
31–50	34	24 (71)	14 (58)	16 (67)	20 (83)
> 50	20	8 (40)	3 (38)	7 (88)	8 (100)
Missing	6	4 (67)	2 (50)	2 (50)	3 (75)
Liver + lung only	23	6 (26)	4 (67)	5 (83)	5 (83)
Liver + other/multiple	64	5 (8)	4 (80)	4 (80)	5 (100)
Time to recurrence					
<13 months	129	72 (56)	40 (56)	39 (54)	60 (83)
≥13–60 months	106	51 (48)	28 (55)	34 (67)	46 (90)
Low-frequency FU	113	56 (50)	37 (66)	32 (57)	49 (88)
High-frequency FU	122	67 (55)	31 (46)	41 (61)	57 (85)

Values in parenthesis are percentages of patients treated with curative intent unless indicated otherwise.
[a] Values in parenthesis are percentages of all 1st liver recurrences.
[b] 93 patients were treated with resection only, 20 patients with ablation therapy only and 9 patients with a combination of resection and ablation. One patient had complete remission after neoadjuvant chemotherapy and was not subject for surgical treatment. FU, Follow-up.

(85.7%) were treated with palliative chemotherapy. After curatively intended treatment, 77 (62.6%) patients developed a 2nd recurrence out of which 41 (53.2%) patients were subject for further treatment with curative intent. Out of these, 25 (61.0%) patients developed a third recurrence of which 7 (28.0%) patients were again treated with curative intent (Supplementary Table 2).

Survival

Survival data for all patients and the group treated with curative intent depending on metastatic pattern, time of detection, and follow-up regimen are presented in Table 2. The 5-year OS calculated from date of detection for all patients with liver metastases was 34% (CI 28%–40%) and median survival was 36.5 (CI 29.8–42.1) months. Patients treated with curative intent had a 5-year OS of 58% (CI 48%–66%) (median not reached) whereas patients treated with palliative intention or best supportive care had a 5-year OS of 7% (CI 3%–13%) (Table 2; Fig. 1) and median survival of 14.7 (CI 10.7–17.1) months. There was no difference in 5-year OS between early (<13 months) and late (≥13–60 months) detected metachronous metastases (33% and 34% respectively; $p = 0.60$).

In multivariable analysis, risk factors for death within 5 years after detection of liver metastases were: age ≥70 years (HR 1.89, CI 1.14–3.08); medium sized (21–30 mm compared to ≤20 mm) liver metastases (HR 1.79, CI 1.14–2.82); liver metastases ≥50 mm (HR 2.52, CI 1.55–4.11); ≥5 liver metastases (HR 3.18, CI 2.02–5.00); combined liver and lung metastases (HR 2.35, CI 1.35–4.08); and other synchronous or multiple locations of metastases (HR 2.67, CI 1.78–4.00). Rectal cancer was associated with a lower risk compared to colon cancer (HR 0.64 and HR 0.44 compared to left and right sided colon cancer respectively; Supplementary Table 3). The median follow-up time was 9.7 (IQR 8.5–10.3) years for patients alive at end of follow-up and 2.2 (IQR 0.9–4.4) years for those who died.

High/low frequency follow-up

The 5-year OS for patients after detection of liver metastases in the high-frequency follow-up randomization group was 43% (CI 34%–51%) and 5-year RMS was 3.2 years (CI 2.9–3.6) compared to 24% (CI 17%–32%) and 2.7 years (CI 2.4–3.0) in the low-frequency group (Table 2; Fig. 2A).

In the conditional probability of survival analysis with follow-up start at date of CRC resection, the patients randomized to

Table 2 Overall survival and 5-year restricted mean survival from date of first liver recurrence for all patients with liver metastases and for patients treated with curative intent

	All liver metastases			Curatively intended treated liver metastases		
	N	5-year OS % (range)	5-year RMS Years (range)	n	5-year OS % (range)	5-year RMS Years (range)
Total	235	34 (28–40)	3.0 (2.7–3.2)	123	58 (48–66)	4.2 (4.0–4.4)
Liver met only	148	47 (38–54)	3.6 (3.3–3.8)	112	60 (50–68)	4.2 (4.0–4.4)
No of tumours:						
≤ 1	78	55 (43–65)	3.9 (3.6–4.3)	72	60 (47–70)	4.2 (3.9–4.5)
2 – 4	44	48 (33–61)	3.7 (3.3–4.2)	34	62 (43–76)	4.3 (3.9–4.7)
≥ 5	24	21 (8–31)	2.2 (1.4–2.9)	5	60 (13–88)	4.7 (4.0–5.3)
Missing	2	–	–	1	–	–
Max size (mm):						
≤ 20	48	63 (47–74)	4.1 (3.7–4.5)	37	67 (51–78)	4.3 (3.9–4.6)
21–30	40	40 (25–55)	3.6 (3.1–4.1)	31	52 (33–67)	4.1 (3.7–4.6)
31–50	34	44 (27–60)	3.5 (3.0–4.0)	7	58 (36–75)	4.1 (3.7–4.6)
> 50	20	30 (12–50)	2.6 (1.7–3.5)	8	62 (23–86)	4.4 (3.4–5.4)
Missing	6	–		4		
Liver met + lung	23	13 (3–30)	2.6 (1.9–3.2)	6	17 (8–52)	3.7 (3.1–4.4)
Liver met + other	64	11 (5–20)	1.8 (1.4–2.2)	5	60 (13–88)	3.9 (2.5–5.2)
Detected within < 13 months	129	33 (25–41)	3.0 (2.7–3.4)	72	56 (43–66)	4.2 (3.9–4.4)
Detected ≥ 13–60 months	106	34 (25–43)	2.9 (2.5–3.2)	51	61 (46–73)	4.2 (3.8–4.5)
Low-frequency FU	113	24 (17–32)	2.7 (2.4–3.0)	56	46 (33–59)	3.9 (3.6–4.3)
High-frequency FU	122	43 (34–51)	3.2 (2.9–3.6)	67	67 (55–77)	4.4 (4.1–4.7)

Values in parenthesis are 95% confidence intervals. OS, overall survival; LM, liver metastases; RMS, restricted mean survival; FU, follow-up.

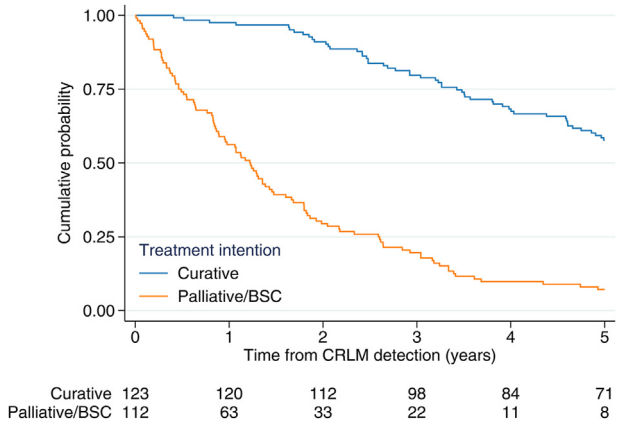

Figure 1 Overall survival after 1st liver recurrence following radical resection of colorectal cancer stage II and III, stratified on treatment intention. BSC, best supportive care.

high-frequency follow-up had significantly better 8-year OS ($p < 0.001$; Fig. 2B) and significantly lower HR for mortality within 8 years compared to low-frequency follow-up, i. e 0.61 (CI 0.44–0.86) in multivariable analysis (Table 3). When not excluding patients who died from CRLM during the first year after resection of the primary tumour (n = 9), the HR was 0.66 (CI 0.48–0.92) in favour to the high-frequency follow-up group in multivariable analysis.

The median follow-up time for patients alive at end of follow-up was 11.0 years (IQR 10.2–11.7) and 3.8 years (IQR 2.3–5.8) for those who died. There was no significant difference between the follow-up groups regarding extra-hepatic dissemination or number of liver tumours, but there was a significant difference in size of metastases with significantly larger tumours in the low-frequency follow-up group ($p = 0.039$; Supplementary Table 4).

Discussion

Fifty-two percent of all patients with liver recurrences and over 92% of patients with solitary liver metastases within 5 years after radical resection of CRC (stage II-III) were subject to liver resection or ablation with curative intent. Albeit the high proportion of operated cases, the long-term OS of about 60% is well in line with or better than previous reports. The combination of a higher proportion of operated patients and simultaneously a high 5-year OS in the whole group of patients with CRLM suggests that indications for treatment of CRLM with curative intent can be widened and underlines the importance of assessment in multimodal therapy boards that includes liver specialists.

Even though high rates of CRLM after radically treated colorectal cancer of about 25–35% are still frequently referred to,[22,23] the recurrence rate after radically treated CRC with modern use of adjuvant chemotherapy is clearly lower in modern retrospective reports.[6,24,25] Thorough preoperative work-up of CRC patients with high-resolution contrast-enhanced CT-scans enables more accurate screening for synchronous liver metastases enhancing the possibility of liver resection at time of primary disease. We perceive that the rate of about 10% metachronous CRLM in total, and 6% for recurrences confined to the liver – as found in this well-defined cohort of radically treated stage II-III CRC prospectively observed in standardized follow-up programs – reflect modern data on recurrent liver disease.

The fact that three quarters of all patients with metastases confined to the liver and 92% of solitary liver metastases were treated with resection and/or ablation therapy, is in accordance with the intention of the COLOFOL trial. Included patients were all 75 years or younger at time of inclusion, and had a life-expectancy of more than 2 years in respect of co-morbidity, aiming at being possible to treat with curative intent in case of recurrent disease. Notably, more than half of all patients with metachronous CRLM were treated with curative intent. Moreover, a large proportion of patients with a second or third recurrence after radically resected CRLM (53 and 61% respectively) underwent curatively intended treatment. These high resection numbers emphasize the benefit of standardized follow-up and individual evaluation. In this study, >90% of all patients were subject to assessment in a multidisciplinary tumour board after detection of first liver recurrence. Interestingly, only number of liver metastases ($\geq$5) and synchronous extra-hepatic spread were significantly associated with lower resection rates in multivariable analysis, whereas primary tumour stage and time of detection (within 13 months or later) did not affect the probability of curatively intended treatment or long-term survival. Thus, patients with previously regarded unfavorable prognostic factors are still likely to be subject for treatment of metastases when technically possible with good results. This further underlines the need for organ specialists in the MDT assessments.

The 5-year OS rates for patients with CRLM was high. One third of all patients with liver metastases and about 50% of patients with metastases confined to the liver were alive after 5 years, irrespective of treatment. In the group of patients treated with curative intent, the 5-year OS was about 60%, independent of extrahepatic spread. This figure is higher than for most national- and multicenter reports.[26] Although all patients in the COLOFOL trial were $\leq$75 years at inclusion and with limited co-morbidity, this points to a survival benefit of widened indications for treatment of CRLM with a curative intent. This is further emphasized by the poor OS of only 7% for palliatively treated patients. In contrast to these encouraging results, the 5-year OS was only 13% in patients with combined liver and lung metastases and still only 20% in the small group that went on to curatively intended treatment. The latter figure is lower compared to most published data and the reason for this is obscure. Earlier reports have stipulated better long-term survival for late metachronous metastases,[27] but in this study there was

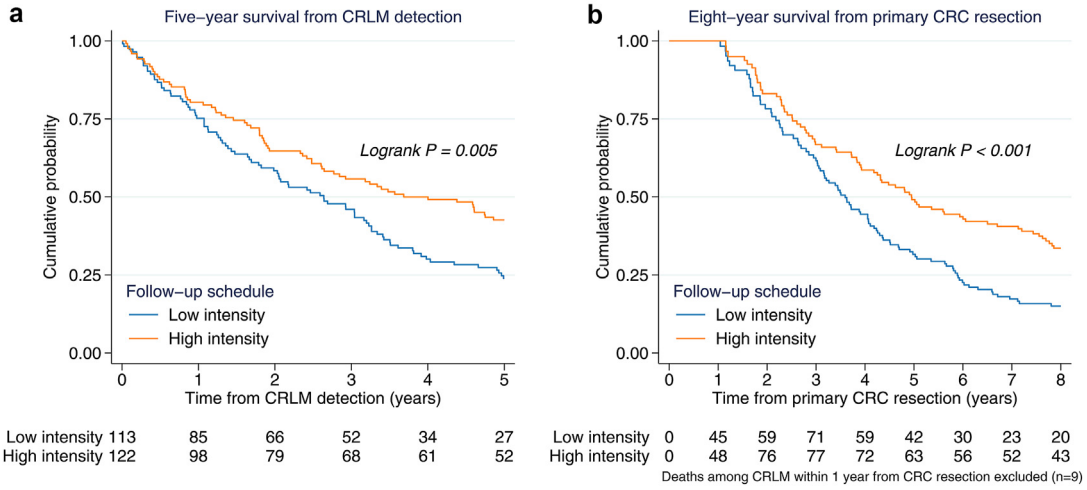

Figure 2 Overall survival for patients with liver recurrences following radical resection of colorectal cancer stage II and III, stratified on follow-up schedule. a) 5-year survival from date of detection and b) 8-year survival conditional on having survived the first year after resection of primary colorectal tumor. Time measured from date of resection of primary tumor and delayed entry of patients in the analyses at date of detection of liver metastases.

no survival difference between metastases detected during the 1st year of follow-up and later on.

In this study of patients that developed liver metastases as 1st recurrence, a survival benefit was noted in the subgroup randomized to high-frequency follow-up. This finding was not expected and is inevitably affected by a lead-time bias when analyzed from date of detection of CRLM, as metastases in the high-frequency follow-up group are potentially detected at an earlier stage. However, treatment delay has been identified as a risk factor for death for primary colorectal cancer,[28] and when long term survival (8 years) was analyzed from date of primary tumour resection, a significant survival benefit remained in the multivariable analysis. This result is supported by the finding that patients in the high-frequency follow-up group were more likely to undergo treatment with curative intent and had smaller tumours, which were independently associated with increased survival. Moreover, a higher proportion of patients detected in between scheduled examinations were noted in the low-frequency group, which was associated with a worse prognosis in the multivariable analysis. Theoretically, more patients with fast growing tumours with aggressive biology would be found and treated in the high-frequency follow-up group. However, second recurrences (at any site) after radical treatment of CRLM were more common in the low-frequency follow-up group.

Although a clear difference in survival between follow-up groups was noted in this study, the problem remains to identify the group of patients that will develop CRLM, already at the time of primary tumor resection. Moreover, one must consider that even if, as proposed in this material, an improved 5-year OS of about 20% for all patients with CRLM by high-frequency compared to low-frequency follow-up after the primary CRC surgery exists, it corresponds to a long-term survival benefit of less than 2% of the total study population and cost-benefit must be taken under consideration. Notably, we did not find any differences in survival in lung metastases depending on follow-up regimen[29] and the small difference in total numbers probably explains why no difference could be detected in the main study on the whole trial population. Taken together, although these findings have to be interpreted with caution, they evoke the hypothesis that high-frequency follow-up could be of benefit in patients with high risk of recurrence, such as LNR >0.25, T4 tumors, and/or extramural vascular invasion. This warrants a randomized trial, although with the challenging problem of selecting the right patients.

Biomarkers, including CEA and circulating tumor DNA (ctDNA) could be of additional value to identify a cohort with high risk of recurrences that theoretically would benefit from more intensive follow-up. However, a post-hoc analysis of the high-risk group with elevated CEA-levels, before or after primary surgery, has been performed within the COLOFOL trial population without any noted survival benefit from high-frequency follow-up.[30] Although detectable levels of ctDNA after CRC resection is associated with high rates of cancer recurrence, it may take several months before recurrent disease can be verified by imaging techniques and a potential survival benefit from early recurrence detection with ctDNA screening is yet to be proven. However, also preoperative ctDNA is associated with increased risk of recurrence and might be of value in defining a high-risk group.[31,32]

The most important strength of this study is the well-defined cohort of patients, all meticulously worked-up perioperatively and prospectively followed for five years postoperatively. This enables good possibilities to study incidence and treatment of metachronous liver metastases. Further, all medical records were

Table 3 Eight-year overall survival from primary tumor resection and uni- and multivariable Cox proportional hazards regression for patients with liver recurrences in the Colofol trial

	Number of patients (n = 226)[a]	8-year Overall survival (95% CI)	Univariable Cox regression		Multivariable Cox regression	
			HR (95% CI)	P	HR (95% CI)	P
Follow-up						
Low-frequency	111 (49%)	15% (9%–22%)	Ref.		Ref.	
High-frequency	115 (51%)	34% (25%–42%)	0.57 (0.42–0.78)	<0.001	0.61 (0.44–0.86)	0.004
Gender						
Males	136 (60%)	22% (16%–29%)	Ref.			
Females	90 (40%)	27% (18%–36%)	0.91 (0.66–1.24)	0.538		
Age						
0–59	55 (24%)	40% (27%–53%)	Ref.		Ref.	
60-69	98 (43%)	19% (12%–27%)	1.76 (1.16–2.66)	0.008	1.82 (1.16–2.84)	0.009
≥ 70	73 (32%)	19% (11%–28%)	1.87 (1.21–2.89)	0.005	2.04 (1.27–3.26)	0.003
BMI						
< 18.5	5 (2%)	0%	5.03 (1.96–12.9)	0.001	5.00 (1.72–14.6)	0.003
18.5–25	96 (42%)	27% (19%–36%)	Ref.		Ref.	
> 25	125 (55%)	23% (16%–30%)	1.14 (0.83–1.56)	0.420	0.93 (0.67–1.30)	0.680
Alcohol						
No alcohol	150 (66%)	26% (19%–33%)	Ref.			
Less than 3 drinks	42 (19%)	21% (10%–34%)	1.17 (0.79–1.74)	0.440		
3 or more drinks	10 (4%)	24% (5%–51%)	1.05 (0.49–2.27)	0.894		
Missing	24 (11%)					
Smoking						
No, occasionally	174 (77%)	25% (19%–31%)	Ref.			
Yes, daily	41 (18%	21% (11%–34%)	1.12 (0.76–1.66)	0.573		
Missing	11 (5%)					
Diabetes						
No	197 (87%)	25% (19%–31%)	Ref. [b]			
Yes	29 (13%)	22% (9%–38%)	0.97 (0.62–1.51)	0.877		
Primary tumour site						
Colon, other	92 (41%)	25% (17%–34%)	Ref.		Ref.	
Right side	49 (22%)	14% (6%–24%)	1.45 (0.98–2.15)	0.064	1.69 (1.10–2.60)	0.017
Rectum	85 (38%)	30% (20%–39%)	0.88 (0.62–1.25)	0.473	0.96 (0.67–1.39)	0.843
Stage						
Stage II	85 (38%)	35% (25%–45%)	Ref.		Not Included	
Stage III	141 (62%)	18% (12%–24%)	1.62 (1.16–2.25)	0.004		
T-stage						
T1-3	179 (79%)	27% (21%–33%)	Ref.		Ref.	
T4	47 (21%)	15% (7%–26%)	1.43 (0.99_2.06)	0.054	1.49 (1.00–2.21)	0.048
LNR						
Neg	80 (35%)	36% (25%–46%)	Ref.		Ref.	
> 0 – <0.1	33 (15%)	29% (15%–45%)	1.20 (0.73–1.99)	0.476	1.02 (0.61–1.72)	0.937
0.1 – < 0.25	41 (18%)	11% (4%–22%)	2.07 (1.34–3.21)	0.001	1.70 (1.07–2.69)	0.024
> 0.25	65 (29%)	17% (10%–27%)	1.68 (1.13–2.49)	0.010	1.58 (1.05–2.38)	0.030
Missing	7 (3%)					

Table 3 (*continued*)

	Number of patients (n = 226)[a]	8-year Overall survival (95% CI)	Univariable Cox regression		Multivariable Cox regression	
			HR (95% CI)	P	HR (95% CI)	P
Primary chemotherapy						
No	90 (40%)	33% (23%–43%)	Ref.			
Yes	136 (60%)	19% (13%–25%)	1.55 (1.12–2.14)	0.008		

Time measured from date of resection of the primary tumor and delayed entry of patients in the analyses at date of detection of liver metastases. Patient inclusion in the analysis was conditional on having survived the first year after the primary resection.
[a] Patients with liver metastases that died within one year of the primary tumour resection were excluded from the analysis (n = 9).
[b] The proportional hazard rates assumption was not fulfilled in the Cox proportional hazard regression and the hazard ratio should be interpreted as the mean over the 8-year period.

reviewed for all detected recurrences, although retrospectively. This study only comprises metachronous metastases and results are thus not generalizable to synchronous disease. Age and co-morbidity could influence the possibility of and outcome after curatively intended treatment. All patients in the COLOFOL trial were 75 years or younger at inclusion and had a life expectancy of more than 2 years, based on co-morbidity. Patients aged over 75 years are underrepresented in many liver resected cohorts, although relative survival for those selected do not seem to be inferior.[14,33]

A majority of all patients with liver recurrences after CRC were possible to treat with curative intent and with high survival rates. Specifically, 76% of all patients with recurrences confined to the liver were treated with curative intent with a 5-year OS of 60%. These impressive results were gained although follow-up was not extensive in neither randomization arm, which points out the importance of meticulous work-up and assessment in multidisciplinary boards. More intense follow-up might be of value in high-risk patients but needs further studies.

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This study was not preregistered in an independent, institutional registry. All methods and data are available to other researchers on request.

Conflict of interest

None to declare.

References

1. Manfredi S, Lepage C, Hatem C, Coatmeur O, Faivre J, Bouvier AM. (2006) Epidemiology and management of liver metastases from colorectal cancer. *Ann Surg* 244:254–259.
2. Engstrand J, Nilsson H, Stromberg C, Jonas E, Freedman J. (2018) Colorectal cancer liver metastases - a population-based study on incidence, management and survival. *BMC Cancer* 18:78.
3. Scherman P, Syk I, Holmberg E, Naredi P, Rizell M. (2021) Impact of patient, primary tumor and metastatic pattern including tumor location on survival in patients undergoing ablation or resection for colorectal liver metastases: a population-based national cohort study. *Eur J Surg Oncol* 47:375–383.
4. Booth CM, Nanji S, Wei X, Biagi JJ, Krzyzanowska MK, Mackillop WJ. (2016) Surgical resection and peri-operative chemotherapy for colorectal cancer liver metastases: a population-based study. *Eur J Surg Oncol* 42:281–287.
5. Stangl R, Altendorf-Hofmann A, Charnley RM, Scheele J. (1994) Factors influencing the natural history of colorectal liver metastases. *Lancet* 343:1405–1410.
6. Elferink MA, de Jong KP, Klaase JM, Siemerink EJ, de Wilt JH. (2015) Metachronous metastases from colorectal cancer: a population-based study in North-East Netherlands. *Int J Colorectal Dis* 30:205–212.
7. Wille-Jorgensen P, Syk I, Smedh K, Laurberg S, Nielsen DT, Petersen SH *et al*. (2018) Effect of more vs less frequent follow-up testing on overall and colorectal cancer-specific mortality in patients with stage II or III colorectal cancer: the COLOFOL randomized clinical trial. *JAMA* 319:2095–2103.
8. Primrose JN, Perera R, Gray A, Rose P, Fuller A, Corkhill A *et al*. (2014) Effect of 3 to 5 years of scheduled CEA and CT follow-up to detect recurrence of colorectal cancer: the FACS randomized clinical trial. *JAMA* 311:263–270.
9. Rosati G, Ambrosini G, Barni S, Andreoni B, Corradini G, Luchena G *et al*. (2016) A randomized trial of intensive versus minimal surveillance of patients with resected Dukes B2-C colorectal carcinoma. *Ann Oncol* 27:274–280.
10. Smith MD, McCall JL. (2009) Systematic review of tumour number and outcome after radical treatment of colorectal liver metastases. *Br J Surg* 96:1101–1113.
11. Mann CD, Metcalfe MS, Leopardi LN, Maddern GJ. (2004) The clinical risk score: emerging as a reliable preoperative prognostic index in hepatectomy for colorectal metastases. *Arch Surg* 139:1168–1172.
12. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. (1999) Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg* 230:309–318. discussion 318-321.
13. Sasaki K, Morioka D, Conci S, Margonis GA, Sawada Y, Ruzzenente A *et al*. (2018) The tumor burden score: a new "Metro-ticket" prognostic

tool for colorectal liver metastases based on tumor size and number of tumors. *Ann Surg* 267:132–141.
14. Scherman P, Syk I, Holmberg E, Naredi P, Rizell M. (2020) Influence of primary tumour and patient factors on survival in patients undergoing curative resection and treatment for liver metastases from colorectal cancer. *BJS Open* 4:118–132.
15. Kopetz S, Chang GJ, Overman MJ, Eng C, Sargent DJ, Larson DW *et al*. (2009) Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. *J Clin Oncol* 27:3677–3683.
16. Kawaguchi Y, Kopetz S, Panettieri E, Hwang H, Wang X, Cao HST *et al*. (2022) Improved survival over time after resection of colorectal liver metastases and clinical impact of multigene alteration testing in patients with metastatic colorectal cancer. *J Gastrointest Surg* 26:583–593.
17. Adam R, Hoti E, Bredt LC. (2010) Evolution of neoadjuvant therapy for extended hepatic metastases–have we reached our (non-resectable) limit? *J Surg Oncol* 102:922–931.
18. Homayounfar K, Bleckmann A, Helms HJ, Lordick F, Ruschoff J, Conradi LC *et al*. (2014) Discrepancies between medical oncologists and surgeons in assessment of resectability and indication for chemotherapy in patients with colorectal liver metastases. *Br J Surg* 101:550–557.
19. Folprecht G, Gruenberger T, Bechstein WO, Raab HR, Lordick F, Hartmann JT *et al*. (2010) Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. *Lancet Oncol* 11:38–47.
20. Basendowah M, Awlia AM, Alamoudi HA, Ali Kanawi HM, Saleem A, Malibary N *et al*. (2021) Impact of optional multidisciplinary tumor board meeting on the mortality of patients with gastrointestinal cancer: a retrospective observational study. *Cancer Rep (Hoboken)* 4:e1373.
21. Hansdotter P, Scherman P, Petersen SH, Mikalonis M, Holmberg E, Rizell M *et al*. (2021) Patterns and resectability of colorectal cancer recurrences: outcome study within the COLOFOL trial. *BJS Open* 5.
22. Manfredi S, Bouvier AM, Lepage C, Hatem C, Dancourt V, Faivre J. (2006) Incidence and patterns of recurrence after resection for cure of colonic cancer in a well defined population. *Br J Surg* 93:1115–1122.
23. Galandiuk S, Wieand HS, Moertel CG, Cha SS, Fitzgibbons RJ, Jr., Pemberton JH *et al*. (1992) Patterns of recurrence after curative resection of carcinoma of the colon and rectum. *Surg Gynecol Obstet* 174:27–32.
24. Malakorn S, Ouchi A, Hu CY, Sandhu L, Dasari A, You YN *et al*. (2021) Tumor sidedness, recurrence, and survival after curative resection of localized colon cancer. *Clin Colorectal Cancer* 20:e53–e60.
25. Osterman E, Glimelius B. (2018) Recurrence risk after up-to-date colon cancer staging, surgery, and pathology: analysis of the entire Swedish population. *Dis Colon Rectum* 61:1016–1025.
26. Dexiang Z, Li R, Ye W, Haifu W, Yunshi Z, Qinghai Y *et al*. (2012) Outcome of patients with colorectal liver metastasis: analysis of 1,613 consecutive cases. *Ann Surg Oncol* 19:2860–2868.
27. Landreau P, Drouillard A, Launoy G, Ortega-Deballon P, Jooste V, Lepage C *et al*. (2015) Incidence and survival in late liver metastases of colorectal cancer. *J Gastroenterol Hepatol* 30:82–85.
28. Hanna TP, King WD, Thibodeau S, Jalink M, Paulin GA, Harvey-Jones E *et al*. (2020) Mortality due to cancer treatment delay: systematic review and meta-analysis. *BMJ* 371:m4087.
29. Hansdotter P, Scherman P, Nikberg M, Petersen SH, Holmberg E, Rizell M *et al*. (2023) Treatment and survival of patients with metachronous colorectal lung metastases. *J Surg Oncol*.
30. Egenvall M, Martling A, Veres K, Horvath-Puho E, Wille-Jorgensen P, Hoirup Petersen S *et al*. (2021) No benefit of more intense follow-up after surgery for colorectal cancer in the risk group with elevated CEA levels - an analysis within the COLOFOL randomized clinical trial. *Eur J Surg Oncol* 47:2053–2059.
31. Reinert T, Petersen LMS, Henriksen TV, Larsen MO, Rasmussen MH, Johansen AFB *et al*. (2022) Circulating tumor DNA for prognosis assessment and postoperative management after curative-intent resection of colorectal liver metastases. *Int J Cancer* 150:1537–1548.
32. Nors J, Henriksen TV, Gotschalck KA, Juul T, Sogaard J, Iversen LH *et al*. (2020) IMPROVE-IT2: implementing noninvasive circulating tumor DNA analysis to optimize the operative and postoperative treatment for patients with colorectal cancer - intervention trial 2. Study protocol. *Acta Oncol* 59:336–341.
33. Booth CM, Nanji S, Wei X, Mackillop WJ. (2015) Management and outcome of colorectal cancer liver metastases in elderly patients: a population-based study. *JAMA Oncol* 1:1111–1119.

Appendix A. Supplementary data

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