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Local Treatment of Unresectable Colorectal Liver Metastases: Results of a Randomized Phase II Trial

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Abstract

Background: Tumor ablation is often employed for unresectable colorectal liver metastases. However, no survival benefit has ever been demonstrated in prospective randomized studies. Here, we investigate the long-term benefits of such an aggressive approach.

Methods: In this randomized phase II trial, 119 patients with unresectable colorectal liver metastases (n < 10 and no extrahepatic disease) received systemic treatment alone or systemic treatment plus aggressive local treatment by radiofrequency ablation ± resection. Previously, we reported that the primary end point (30-month overall survival [OS] > 38%) was met. We now report on long-term OS results. All statistical tests were two-sided. The analyses were according to intention to treat.

Results: At a median follow up of 9.7 years, 92 of 119 (77.3%) patients had died: 39 of 60 (65.0%) in the combined modality arm and 53 of 59 (89.8%) in the systemic treatment arm. Almost all patients died of progressive disease (35 patients in the combined modality arm, 49 patients in the systemic treatment arm). There was a statistically significant difference in OS in favor of the combined modality arm (hazard ratio [HR] = 0.58, 95% confidence interval [CI] = 0.38 to 0.88, P = .01). Three-, five-, and eight-year OS were 56.9% (95% CI = 43.3% to 68.5%), 43.1% (95% CI = 30.3% to 55.3%), 35.9% (95% CI = 23.8% to 48.2%), respectively, in the combined modality arm and 55.2% (95% CI = 41.6% to 66.9%), 30.3% (95% CI = 19.0% to 42.4%), 8.9% (95% CI = 3.3% to 18.1%), respectively, in the systemic treatment arm. Median OS was 45.6 months (95% CI = 30.3 to 67.8 months) in the combined modality arm vs 40.5 months (95% CI = 27.5 to 47.7 months) in the systemic treatment arm.

Conclusions: This phase II trial is the first randomized study demonstrating that aggressive local treatment can prolong OS in patients with unresectable colorectal liver metastases.

Surgery is the gold standard of treatment in patients with resectable colorectal liver metastases, with reported five-year survival rates ranging from 40% to 60% (1–3). Only 20% to 30% of patients with CRC metastases confined to the liver are candidates for surgery (2,4). In others, extensive tumor burden within the liver or poor anatomical position of the tumors close to critical vascular or biliary structures precludes resection. In these patients, systemic therapy is offered with the goal of improving survival or potentially converting patients into resection candidates (5,6). Although the outcome of systemic therapy is still being improved and promising biological agents are being incorporated into treatment protocols, the realistic goal of systemic treatment remains palliative (7–10). It is for this reason that more aggressive local therapeutic approaches are being pursued in patients with unresectable colorectal liver metastases.

Radiofrequency ablation (RFA) is a treatment modality that is being increasingly used (11). In patients with unresectable colorectal liver metastases, total tumor clearance from the liver can often still be obtained by RFA or a combination of RFA plus resection (12–14). The efficacy of this approach is controversial because data on the effect on overall survival compared with the standard of care, systemic treatment, are lacking (11–18). To deliver compelling evidence on the beneficial effect of such an aggressive approach, a European intergroup randomized phase III study (European Organisation for Research and Treatment of Cancer 40004 CLOCC trial, ClinicalTrials.gov, No. NCT00043004) was initiated. The trial was designed with overall survival (OS) as the primary end point.

Patients with unresectable colorectal liver metastases were randomly assigned to systemic treatment alone (standard arm) or systemic treatment plus local treatment by RFA with or without additional resection (experimental arm). Because of slow accrual, the study was amended to a randomized phase II trial. Previously published results of this phase II study showed that the primary end point, being a 30-month overall survival (OS) rate greater than 38% in the combined modality arm, was met (61.7%) (19).

At the time of primary analysis with a median follow-up time of 4.4 years, median progression-free survival (PFS) was statistically significantly different between both arms, being 16.8 months in the combined modality arm and 9.9 months in the systemic treatment–only arm (P = .025) (19). After an extended follow-up of 9.7 years, we now report on the definitive impact on overall survival.

Methods

Study Design and Patients

Patients with unresectable colorectal liver–limited metastases were randomly assigned to systemic treatment alone (standard arm) or systemic treatment plus local treatment by RFA ± resection (experimental arm). The primary end point of this phase II study was a 30-month OS rate higher than 38% in the combined modality arm. Using a Fleming design, 76 patients were required in the experimental arm to reject a 30-month OS rate of 38% or lower under the alternative hypothesis of a 30-month OS

rate of 53% with 90% power, using a one-sided test with a type I error of 10%.

Secondary end points were progression-free survival (PFS), overall survival (OS), and health-related quality of life. From April 2002, patients were recruited from 22 centers in Europe. The trial was prematurely closed for poor accrual because of physician's preferences in treatment modalities in June 2007, with 60 patients in the experimental arm and 59 patients in the control arm.

Eligible patients were age 18 to 80 years with a World Health Organization performance of less than 2 and who presented with nonresectable colorectal liver metastases without extrahepatic disease. Nonresectability was defined as no possibility to completely resect all tumor lesions, as judged by a multidisciplinary team with at least a hepatobiliary surgeon and radiologist on board. Patients were eligible only when all liver lesions could be fully treated by either RFA alone or combined treatment that consisted of resection of resectable lesions and RFA of the remaining unresectable lesions. To allow complete treatment of all liver lesions, the number of liver metastases had to be less than 10. Full inclusion and exclusion criteria have been previously reported (19). The trial was approved by the medical ethics committees of all participating centers. Written informed consent was obtained from all patients prior to random assignment. Random assignment (1:1) was done at the EORTC headquarters with the minimization technique and was stratified according to center, previous systemic treatment for liver metastases, previous adjuvant treatment, and route of random assignment (before or during surgery).

Procedures

Patients assigned to the combined modality therapy received complete treatment of all liver metastases either by RFA alone or by RFA in combination with resection. The optimal strategy to obtain adequate local treatment was decided upon by the hepatobiliary surgeon and the multidisciplinary team. RFA procedures were carried out according to the guidelines of the manufacturer of the ablation device used during open surgery, laparoscopically, or percutaneously. Quality control for RFA and surgery required specialized liver surgeons and radiologists to assess the suitability of patients for ablation and full documentation of the lesions treated. From April 2002 to October 2005, systemic treatment in both study arms consisted of 5-FU/LV/oxaliplatin. After October 2005, bevacizumab was added when it became accepted as the standard of care in most participating centers. Treatment of 5-FU/LV/oxaliplatin consisted of the FOLFOX 4 regimen while bevacizumab was administered at 5 mg/kg body weight once every two weeks. Detailed systemic treatment regimens were reported previously (19).

In the systemic treatment arm only, no additional local treatment options were allowed except for resection when unresectable disease was converted to resectable disease by systemic treatment. In both study arms, treatment was started within four weeks of random assignment and systemic

treatment after RFA was planned within four to eight weeks after the procedure.

Systemic treatment in both arms was administered for six months unless there was disease progression or unacceptable toxicity. After protocol treatment, any further systemic treatment was at the discretion of the multidisciplinary team.

Patients were assessed for PFS and OS every six weeks during protocol treatment, every three months after treatment for a period of two years, and every six months thereafter. Disease progression was assessed using contrast-enhanced CT scan by the local radiologist according to RECIST 1.0. Recurrence at the RFA site was defined by the appearance on CT imaging of one or more new lesions along the margin of the ablated lesion or at least a 20% increase in the longest diameter of the RFA-treated lesion.

Statistical Analysis

Follow-up duration was computed from the time of random assignment to the date of last follow-up. Patients who died were censored at the date of death. PFS was defined as the time interval between the date of random assignment and the date of progression (or recurrence) of the disease or death, whichever occurred first. OS was defined as the time interval between the date of random assignment and the date of death. Patients who were still event free at the last visit were censored at the date of last follow-up.

The updated analyses of PFS and OS are intent-to-treat analyses. Overall PFS and OS were estimated by the Kaplan-Meier method and compared by a two-sided log-rank test. The level of statistical significance was set to .05.

Additional sensitivity univariate analyses of OS, adjusting for baseline factors, that is, number of liver metastases (≤4 vs >4) and synchronicity (synchronous vs metachronous), were performed to correct for a potential prognostic effect on the results. OS was compared between arms using a two-sided log-rank test stratified for the baseline factor. Possible heterogeneity of the results in these subgroups was tested by means of a Cochran's Q test. A graphical display of the results is provided using Forest plots. To determine any possible influence of secondary treatments on OS, survival duration after initial disease progression was analyzed in progressive patients (for whom death was not the first recorded event, 55 and 43 patients in the systemic treatment and in the combined modality arms, respectively). Survival duration after initial disease progression was computed as the time interval between the date of first progression and the date of death. Patients who were still alive at the last visit were censored at the date of last follow-up. Survival duration after initial disease progression was estimated by the Kaplan-Meier method and compared between treatment arms by a two-sided log-rank test.

The analysis of the time to hepatic progression and to extrahepatic progression was performed using the competing risk methodology in the intent-to-treat population as exploratory analyses. The cumulative incidence of the event of interest (including the occurrence of the event and a simultaneous progression at another site) was estimated and compared by means of a Gray test (20). In these analyses, death in absence of hepatic or extrahepatic progression, respectively, was considered the only competing risk.

Results

A total of 119 patients were randomly assigned to either systemic treatment alone or combined modality treatment (systemic plus local treatment). Patient and tumor characteristics appeared balanced between both arms (Table 1).

In the combined modality arm (n = 60), three patients were ineligible, two had more advanced disease than allowed per protocol, and one showed liver metastases that were considered resectable at baseline (Figure 1). Of the 60 patients randomly assigned to combined modality, two patients did not receive any local treatment because of patient refusal (n = 1) or ineligibility (n = 1); for one patient, no treatment data are available. Local treatment in the 57 remaining patients consisted of RFA only in 30 patients, RFA plus resection in 26 patients, and resection only in one patient (Table 2). In 51 patients, local treatment was combined with planned systemic treatment. Six patients did not receive any systemic treatment because of fast disease progression (n = 2), patient death (n = 1), or postoperative complications (n = 3).

In the systemic treatment arm (n = 59), all patients started systemic therapy. One patient was considered ineligible; this patient showed resectable disease on the initial CT scan and was resected after the start of systemic treatment. Six additional patients underwent liver resection as intended by the protocol because unresectable disease was converted by systemic treatment into resectable disease. In the systemic treatment arm, the median number of systemic treatment cycles was 10 (range = 1–12), in the combined modality arm 8.5 (range = 0–12).

After a similar long-term follow-up in both arms at a median of 9.7 years, 92 of 119 (77.3%) patients had died, 53 of 59 (89.8%) patients in the systemic treatment arm and 39 of 60 (65.0%) patients in the combined modality arm (Table 3). Nearly all patients died due to progressive disease (PD), 49 patients in the systemic treatment arm and 35 patients in the combined modality arm. Only five patients were lost to follow-up, two patients in the systemic treatment arm and three patients in the combined modality arm.

Patients in the combined modality arm had a statistically significantly longer OS as compared with the patients in the systemic treatment arm (HR = 0.58, 95% CI = 0.38 to 0.88, P = .01) (Figure 2). Three-, five-, and eight-year OS rates were 56.9% (95% CI = 43.3% to 68.5%), 43.1% (95% CI = 30.3% to 55.3%), and 35.9% (95% CI = 23.8% to 48.2%) in the combined modality arm and 55.2% (95% CI = 41.6% to 66.9%), 30.3% (95% CI = 19.0% to 42.4%), and 8.9% (95% CI = 3.3% to 18.1%) in the systemic treatment arm. The median overall survival was 45.6 months (95% CI = 30.3 to 67.8 months) for the combined modality arm and 40.5 months (95% CI = 27.5 to 47.7 months) for the systemic treatment arm.

As previously reported, PFS was statistically significantly prolonged in the combined modality arm as compared with the systemic treatment arm (HR = 0.57, 95% CI = 0.38 to 0.85, P = .005) (Figure 3). Median PFS was improved from 9.9 months (95% CI = 9.1 to 12.9 months) to 16.8 months (95% CI = 11.0 to 21.9 months).

After this long-term follow-up, 45 patients in the combined modality arm had recurrent disease or had died compared with 57 patients in the systemic treatment arm. In the combined modality arm, apart from the three patients who were lost to follow-up without progression, 12 patients did not experience any recurrence or death. The minimum follow-up in these 12 patients was 7.9 years. In the systemic treatment arm, one patient was lost to follow-up without progression and only one patient did not experience any progression after a follow-up duration of 10.8 years.

Table 1. Baseline characteristics

Patient and tumor characteristics	Local plus systemic treatment (n = 60) No. (%)	Systemic treatment (n = 59) No. (%)
Age, y		
Median (range)	64 (31–79)	61 (38–79)
Sex		
Male	37 (61.7)	42 (71.2)
Female	23 (38.3)	17 (28.8)
WHO performance status		
0	47 (78.3)	47 (79.7)
1	13 (21.7)	12 (20.3)
No. of liver metastases		
1	15 (25.0)	7 (11.9)
2	6 (10.0)	4 (6.8)
3	8 (13.3)	7 (11.9)
4	9 (15.0)	8 (13.6)
5	6 (10.0)	10 (16.9)
6	3 (5.0)	9 (15.3)
7	6 (10.0)	8 (13.6)
8	3 (5.0)	2 (3.4)
9	4 (6.7)	4 (6.8)
Median	4.0	5.0
Synchronicity of liver metastases		
Metachronous metastases	37 (61.7)	31 (52.5)
Synchronous metastases*	23 (38.3)	28 (47.5)
Time from surgery for primary cancer to random assignment, d		
Median (range)	290 (28–1802)	308 (30–2754)
T stage of primary cancer		
pT2	9 (15.0)	4 (6.8)
pT3	42 (70.0)	48 (81.4)
pT4	9 (15.0)	6 (10.2)
Unknown	0 (0.0)	1 (1.7)
N stage of primary cancer		
pN0	17 (28.3)	21 (35.6)
pN1	22 (36.7)	24 (40.7)
pN2	20 (33.3)	12 (20.3)
Unknown	1 (1.7)	2 (3.4)
Adjuvant chemotherapy for primary cancer†		
No	50 (83.3)	49 (83.1)
Yes	10 (16.7)	10 (16.9)
Prior chemotherapy for metastatic disease†		
No	51 (85.0)	51 (86.4)
Yes	9 (15.0)	8 (13.6)
Previous liver surgery for CRC metastases		
No	51 (85.0)	49 (83.1)
Yes	9 (15.0)	10 (16.9)
Route of random assignment†		
Before surgery	46 (76.7)	44 (74.6)
During surgery	14 (23.3)	15 (25.4)

*Liver metastases detected within three months after primary cancer diagnosis.
CRC = colorectal cancer; WHO = World Health Organization.
†Stratification factors.

Three-, five-, and eight-year PFS rates in the combined modality arm were 27.7% (95% CI = 16.9% to 39.5%), 24.2% (95% CI = 14.1% to 35.7%), and 22.3% (95% CI = 12.7% to 33.7%), respectively (Figure 3). In the systemic treatment arm, three-, five-, and eight-year PFS rates were 11.9% (95% CI = 5.2% to 21.5%),

5.9% (95% CI = 1.6% to 14.4%), and 2.0% (95% CI = 0.2% to 9.0%), respectively. Among patients who experienced progression, six and three patients in the combined modality arm and in the systemic treatment arm, respectively, were still alive during the last follow-up. In the systemic treatment arm, the six patients who underwent liver resection because nonresectable disease was converted by systemic treatment into resectable disease all developed recurrence.

The liver as first site of recurrence (with or without extrahepatic disease) was observed in 28 of 60 (46.7%) patients in the combined modality arm and in 46 of 59 (78.0%) of those in the systemic treatment arm. In the combined modality arm, in 56 patients treated with radiofrequency ablation, nine patients (16.1%) experienced a first liver recurrence at a site treated by RFA. Extrahepatic progression only as first progression was observed in 25.0% of patients (15/60) in the combined modality arm and 13.6% of patients (8/59) who received systemic treatment alone (Table 3).

Furthermore, given the small sample size, it was impossible to completely eliminate the possibility of small imbalances in baseline characteristics, for example, in the number of lesions or synchronicity. To correct for a potential prognostic effect of baseline factors on the results, we conducted additional sensitivity analyses. The results of the sensitivity analyses of OS adjusting for the number of liver metastases (≤4 vs >4) and synchronicity (synchronous vs metachronous) show that the difference in OS between both arms remains statistically significant. No heterogeneity in the results in patients with four or fewer liver metastases vs more than four liver metastases or in patients with synchronous vs metachronous liver metastases was observed (Supplementary Figures 1 and 2, available online).

To determine any possible influence of secondary treatments on OS, survival after initial disease progression was analyzed. Median survival after disease progression was 21.0 months (95% CI = 16.2 to 30.5 months) in the systemic treatment arm only and 19.5 months (95% CI = 14.3 to 32.3 months) in the combined modality arm (HR = 0.86, 95% CI = 0.56 to 1.31, P = .48) (Supplementary Figure 3; Supplementary Table 1, available online). With death in absence of hepatic progression considered the only competing risk, the cumulative incidence of hepatic progressions at one, three, and five years were 31.0% (95% CI = 19.1% to 42.9%), 58.6% (95% CI = 45.9% to 71.3%), and 62.1% (95% CI = 49.6% to 74.6%) in the combined modality arm vs 51.7% (95% CI = 38.9% to 64.6%), 86.2% (95% CI = 77.3% to 95.1%), and 88.2% (95% CI = 79.8% to 96.6%) in the systemic treatment arm (P < .001) (Figure 4). The cumulative incidence of extrahepatic progressions at one, three, and five years was 24.1% (95% CI = 13.1% to 35.1%), 55.2% (95% CI = 42.4% to 68.0%), and 60.4% (95% CI = 47.8% to 72.9%) for the combined modality arm and 20.9% (95% CI = 10.4% to 31.5%), 45.5% (95% CI = 32.6% to 58.5%), and 60.2% (95% CI = 47.4% to 73.1%) for the systemic treatment arm (P = .73) (Figure 5). With regard to local recurrence after RFA, in total 11 lesions (in nine patients) out of 170 RFA-treated lesions showed a local recurrence at the RFA site as first progression. In addition, three lesions (in two patients) recurred after initial progression at another site.

Discussion

In this randomized phase II trial, we found that a combination of aggressive local treatment plus systemic treatment, as compared with systemic treatment alone, improved both progression-free survival and overall survival in patients with unresectable colorectal liver metastases. The addition of local
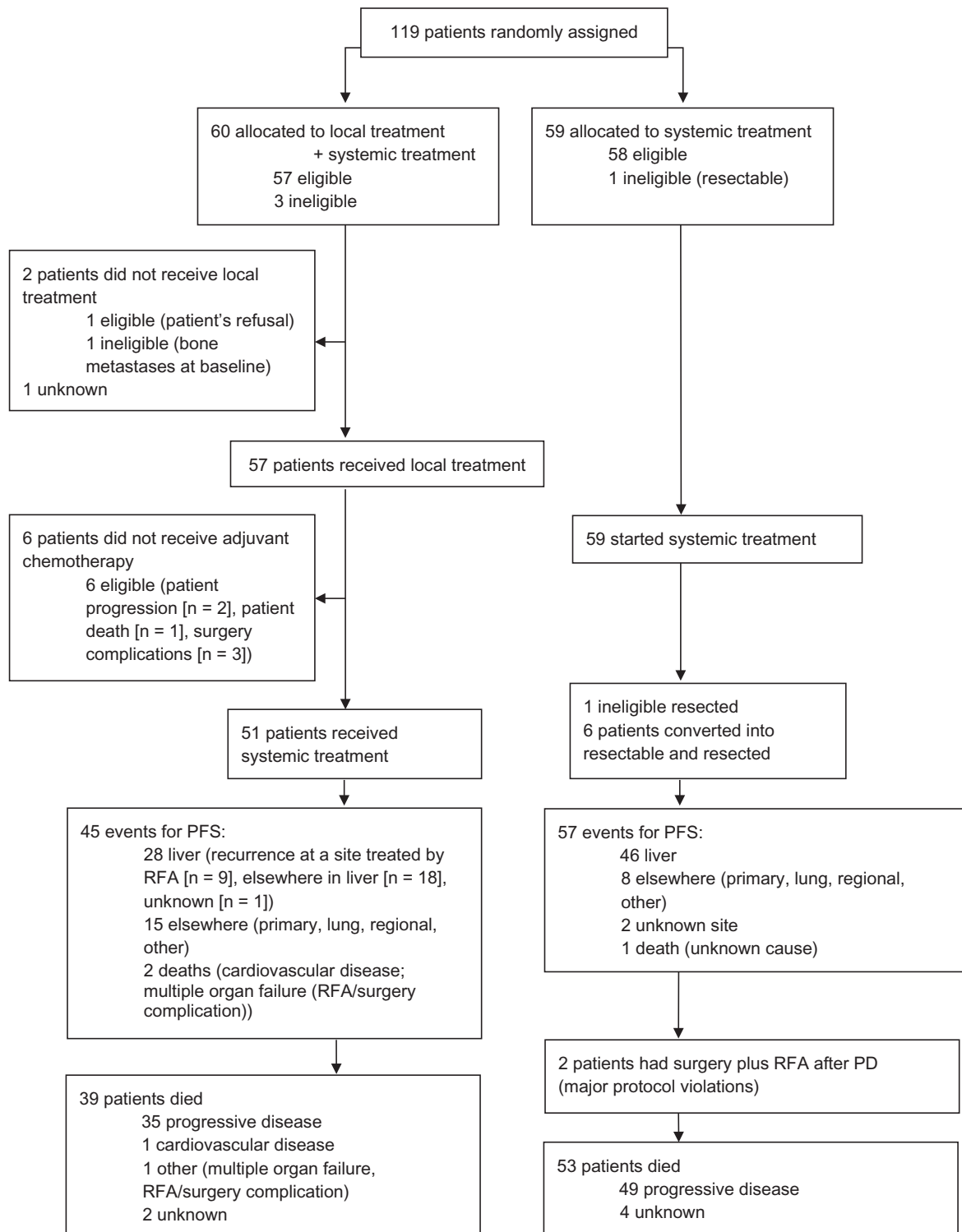
Figure 1. CONSORT flow diagram. PD = progressive disease; PFS = progression-free survival; RFA = radiofrequency ablation.

treatment using RFA was clinically beneficial and was associated with a statistically significant improvement in overall survival (P = .01). Patients were followed for a minimum of 7.8 years, and only five patients (4.2%) were lost to follow-up. Almost all deaths were due to progressive disease.

The current analysis, after a median follow up time of 9.7 years, extends the initial analysis on the primary end point of 30-month overall survival. At 30 months, overall survival in the experimental arm (61.7%) and the control arm (57.6%) was comparable, both being higher than expected. At the time of original study design (late 1990s), figures on overall survival of patients with liver-limited colorectal metastases were scarce, which has led to a very conservative estimation of overall survival (21,22). At the time of the initial analysis, a statistically significant

Table 2. Local treatment received in the combined treatment arm

| | Method | | |
	RFA only (n = 30) No. (%)	RFA plus resection* (n = 27) No. (%)	Total (n = 57) No. (%)
Radiofrequency/surgery			
Means of radiofrequency administration			
At laparotomy	25 (83.3)	26 (96.3)	51 (89.5)
Laparascopically	1 (3.3)	0 (0.0)	1 (1.8)
Percutaneously	4 (13.3)	0 (0.0)	4 (7.0)
No RFA performed	0 (0.0)	1 (3.7)*	1 (1.8)
Worst margin for resected† tumors per patient (n = 27), cm			
≥1	NA	10 (37.0)	–
<1	NA	16 (59.3)	–
Residual tumor	NA	1 (3.7)	–
Worst margin for tumors treated by radiofrequency per patient (n = 56), cm		(n = 26)	(n = 56)
≥1	8 (26.7)	5 (19.2)	13 (23.2)
<1	16 (53.3)	17 (65.4)	33 (58.9)
No margin	4 (13.3)	1 (3.8)	5 (8.9)
Unknown	2 (6.7)	3 (11.5)	5 (8.9)
Treatment of at least one liver metastasis unsuccessful			
No	29 (96.7)	26 (96.3)	55 (96.5)
Yes	1 (3.3)‡	1 (3.7)	2 (3.5)

*One patient was ineligible; all lesions were resected at baseline, no RFA done. RFA = radiofrequency ablation.
†Resection consisted of one segment or wedge resection(s) (n = 16) or resection of two or more liver segments (n = 11).
‡For this patient, one lesion could not be successfully treated by RFA because of its close proximity to the stomach.

Table 3. Site of first progression and main cause of death

Disease and survival status	Local plus systemic treatment (n = 60) No. (%)	Systemic treatment (n = 59) No. (%)
Site(s) of first progression		
Any hepatic progression*	28 (46.7)	46 (78.0)
Site treated by radiofrequency	9 (15.0)	
Extrahepatic only	15 (25.0)	8 (13.6)
Unknown site		2 (3.4)†
Death before first progression	2 (3.3)	1 (1.7)
Survival status		
Lost to follow-up	3 (5.0)	2 (3.4)
Alive at last contact‡	18 (30.0)	4 (6.8)
Dead	39 (65.0)	53 (89.8)
Main cause of death		
Progressive disease	35 (58.3)	49 (83.1)
Cardiovascular disease	1 (1.7)	0 (0.0)
Other	1 (1.7)§	0 (0.0)
Unknown	2 (3.3)	4 (6.8)

*Any hepatic progression with or without extrahepatic disease.
†One patient in the systemic treatment arm died from progressive disease as first event.
‡All patients were followed for a minimum of 7.8 years.
§Sepsis and multiple organ failure (radiofrequency ablation/surgery complication).

difference was observed for PFS between both treatment arms. Longer follow-up, as presented in this study, was needed before this statistically significant difference in PFS was translated into a statistically significant and clinically relevant difference in overall survival. The currently observed results on overall survival in the control arm correspond more closely to the recent studies in metastatic colorectal cancer (7–10,23–27).

This trial has limitations. This is a phase II trial with a sample size lower than the sample size initially planned for a phase III trial. A larger sample size would have offered better protection against possible risks of imbalances between treatment arms and a better reassurance on the external validity of the results. Also, overall survival was a secondary end point of the phase II trial. However, the patients' baseline characteristics appeared well balanced between treatment arms, and despite the reduced power to detect a difference in long-term outcomes, statistical significance was reached reflecting the clear difference observed in OS between both arms.

Our results demonstrate for the first time in a randomized trial that aggressive local ablative treatment of colorectal liver metastases can improve overall survival. Even for resection of extensive colorectal liver metastases, such compelling evidence for survival benefit was still lacking. In the present study, we selected patients with colorectal liver metastases that were judged unresectable by experienced liver surgeons. Over 90% of the patients were included in tertiary referral centers. Patients were classified unresectable by the multidisciplinairy team either because of extensive bilobar involvement of the liver or unfavorable location of lesions that precluded hepatic resection as the sole treatment option. The latter also applied to some isolated lesions situated in the middle of the three hepatic veins involving their origin. The criteria on resectability as used in the present study still apply in the current era of advanced liver surgery for colorectal metastases. It is important, however, to highlight the role of specialized multidisciplinary teams and experienced liver surgeons in assessing the suitability of unresectable patients for RFA treatment.

The intention to treat all liver lesions underlines the curative intent of our approach. It should be stressed that to obtain complete tumor treatment a combined approach of RFA with resection was often required (45.6%). Using this approach, complete tumor treatment was achieved in all patients except two. In one patient undergoing resection residual tumor was found in the resection margin, and in one patient undergoing RFA treatment one lesion could not be successfully treated due to its close proximity to the stomach.

After eight years, 36% of the patients treated with the combined modality approach were still alive. This number approximates the 40% eight-year overall survival in the recently published Eloxatin Peri-Operative Chemotherapy (EPOC) study, in which patients with one to four resectable colorectal liver metastases (median number of lesions = 1) were treated by resection plus systemic treatment (28).

Data on progression-free survival after 9.7 years of median follow-up are consistent with earlier results published after a median follow up of 4.4 years (19). Initial analysis at that time showed a median PFS of 16.8 months (95% CI = 11.7 to 22.1 months) in the arm assigned to combination treatment and 9.9 months (95% CI = 9.3 to 13.7 months) in the arm assigned to systemic treatment only (HR = 0.63, 95% CI = 0.42 to 0.95, P = .025).
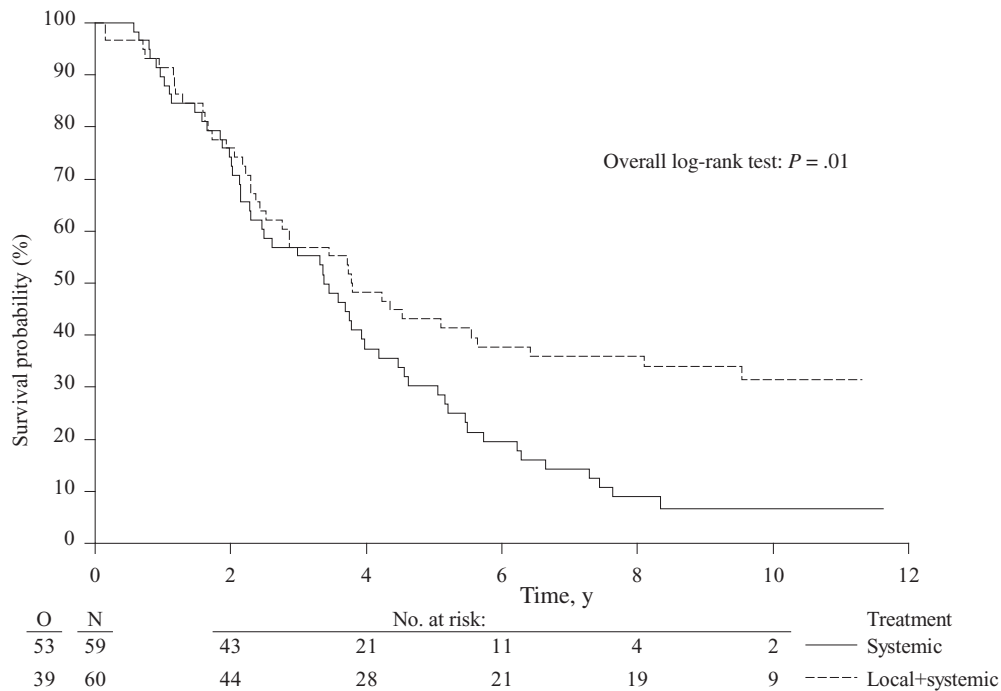
Figure 2. Kaplan-Meier curves for overall survival in patients with unresectable colorectal liver metastases treated by systemic treatment alone or combined modality treatment by systemic treatment plus aggressive local treatment by radiofrequency ablation ± resection (P = .01). P value was calculated using a two-sided log-rank test.

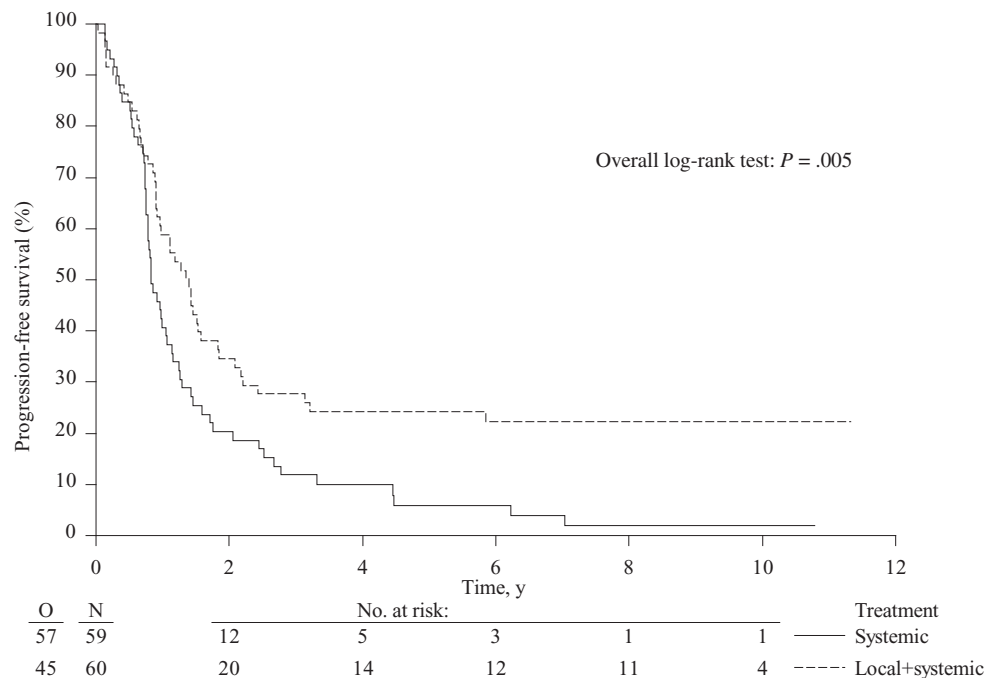**Figure 3.** Kaplan-Meier curves for progression-free survival in patients with unresectable colorectal liver metastases treated by systemic treatment alone or combined modality treatment by systemic treatment plus aggressive local treatment by radiofrequency ablation ± resection (P = .005). P value was calculated using a two-sided log-rank test.

In the current analysis, we calculated the cumulative incidence of hepatic progression, which was statistically significantly different between both treatment arms. In contrast, the cumulative incidence of extrahepatic progression was similar for both treatment arms. These data stress the effect of aggressive liver treatment on PFS and ultimately on overall survival. While extrahepatic recurrence was not affected by local liver treatment as might be expected, the effect of maximal treatment of liver metastases translated into superior PFS for liver recurrence and into a better long-term overall survival.
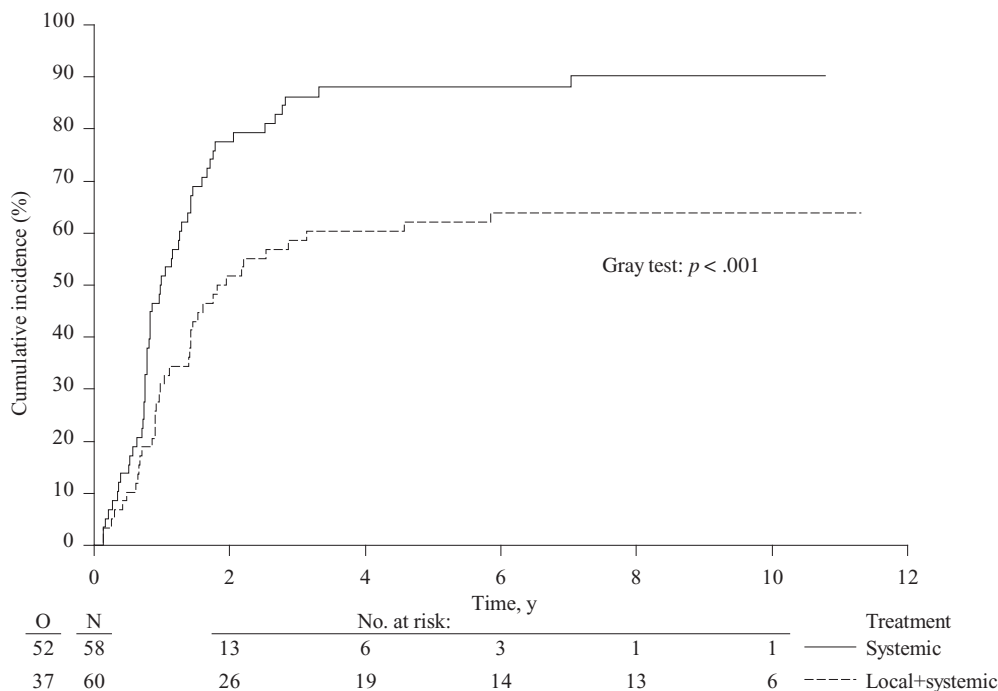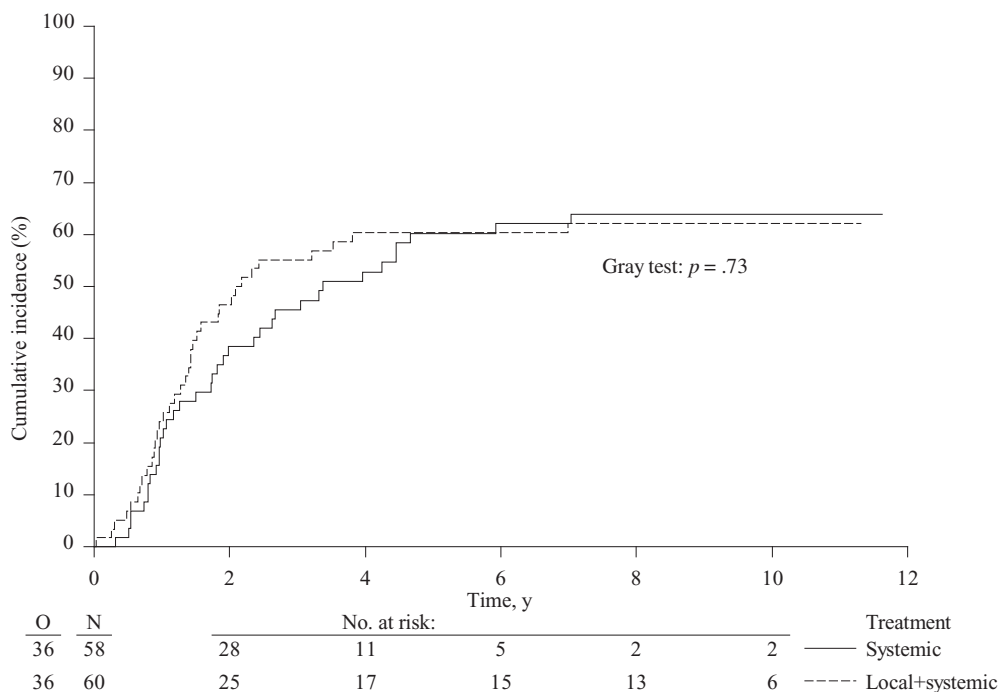
Figure 4. Cumulative incidence of hepatic progressions in patients with unresectable colorectal liver metastases treated by systemic treatment alone or combined modality treatment by systemic treatment plus aggressive local treatment by radiofrequency ablation ± resection (P < .001). P value was calculated using a two-sided Gray test.

Figure 5. Cumulative incidence of extrahepatic progressions in patients with unresectable colorectal liver metastases treated by systemic treatment alone or combined modality treatment by systemic treatment plus aggressive local treatment by radiofrequency ablation ± resection (P = .73). P value was calculated using a two-sided Gray test.

In the systemic treatment arm, resection of liver metastases was allowed when unresectable disease was converted to resectable disease later in the treatment. Seven patients (11.9%) underwent resection, six per protocol, and one was resectable from the start of systemic treatment. Compared with figures in the literature for patients with liver-only disease, this percentage is relatively low and may reflect the unfavorable anatomic locations of the lesions at random assignment, which is not influenced by systemic treatment (5,6).

As reported earlier, the percentage of patients undergoing salvage treatment was comparable between both arms (19). The choice of salvage treatment, however, varied between both treatment arms. In the systemic treatment arm, a higher percentage of patients received systemic treatment, whereas in the combined modality arm salvage treatment more often consisted of local treatment by surgery or RFA. Because differences in overall survival reflect the differences in PFS, variation in salvage treatment did not seem to influence the ultimate course of the disease between both treatment arms. Indeed, further analysis showed that survival after recurrence was not statistically significantly different between both arms.

With the availability of local ablative techniques, the treatment options for surgeons in more advanced disease of colorectal liver metastases have increased. Despite the limitations of this study, these data strongly suggest that the combined modality of aggressive local tumor treatment in combination with systemic treatment can change the outcome of these patients considerably with a clear benefit on overall survival. This encourages the early integration of local ablative techniques alone or in combination with surgical resection in patients with unresectable colorectal liver metastases, as should be discussed in a multidisciplinary team setting.

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TR was responsible for the design of the trial. TR, CP, FvC JP, IBR, JAL, and WB contributed patients to the study and reviewed the report. TR, MAL, MD, EVC, BN, and GP contributed to the trial management and reviewed the report. MM analyzed the trial data and contributed to the writing of the report together with TR and GF. All authors approved the final version of the report.

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