Randomized Phase III Study to Assess Efficacy and Safety of Adjuvant CAPOX with or without Bevacizumab in Patients after Resection of Colorectal Liver Metastases: HEPATICA study[1,2]

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Nikol Snoeren[*], Richard van Hillegersberg[*], Sander B. Schouten[*], Andre M. Bergman[†], Erikv van Werkhoven[‡], Otilia Dalesio[‡], Rob A.E.M. Tollenaar[§], Henk M. Verheul[¶], Joost van der Sijp[#], Inne H.M. Borel Rinkes[*] and E.E. Voest[†,**], on behalf of the Hepatica study group

[*]Department of Surgical Oncology, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands; [†]Department of Medical Oncology, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, the Netherlands; [‡]Department of Biometrics, The Netherlands Cancer Institute/Antoni van Leeuwenhoek, Plesmanlaan 121, 1066 CX Amsterdam, the Netherlands; [§]Department of Surgery, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, the Netherlands; [¶]Department of Medical Oncology, VU Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, the Netherlands; [#]Department of Surgery, MC Haaglanden, Lijnbaan 32, 2512 VA, Den Haag; [**]Department of Medical Oncology, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands

Abstract

Bevacizumab is a humanized monoclonal antibody targeting vascular endothelial growth factor (VEGF). Recurrence after resection of colorectal liver metastases (CRLMs), presumably caused by VEGF-mediated outgrowth of micrometastases, might decrease when VEGF is inhibited. This study examines the efficacy and safety of adding bevacizumab to an adjuvant regimen of CAPOX in patients undergoing radical resection for their CRLMs. Patients with resected CRLMs were randomized after surgery to receive CAPOX and bevacizumab (arm A) or CAPOX alone (arm B) as adjuvant treatment. CAPOX was given in both arms for a total of eight cycles. Bevacizumab was administered for 16 cycles. The primary end point was disease-free survival (DFS). Secondary outcomes were overall survival (OS), toxicity, and quality of life (QoL). In total, 79 patients were randomized. At the time of analysis, 23 events were encountered in arm A and 20 in arm B. One-year DFS rate was 79% [95% confidence interval (CI): 68%-93%] and 68% (95% CI: 55%-85%) for arm A and B, respectively ($P = .89$). Toxicity was evaluated for 75 patients. No significant differences in toxicity between the two arms were found. QoL scores were higher in arm A, of which emotional functioning and global QoL scores were significant. Adding bevacizumab to a CAPOX regimen in patients undergoing a resection for their CLM is safe and showed higher QoL scores compared with CAPOX alone. Because of premature closure of the study, conclusions about the effect on DFS of additional VEGF inhibition in this setting could not yet be made.

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Introduction

Long-term survival of patients with resectable colorectal liver metastases (CRLMs) has been achieved in patients who could undergo radical resection, with 5-year survival rates of 30% to 60% when treated with surgery alone [1–4]. Unfortunately, the majority of patients will experience a recurrence after resection. To improve treatment outcome, the combination of surgery with chemotherapy for patients with resectable (CRLM) was examined in three randomized controlled trials [5–7]. These studies demonstrated a marginal benefit compared with surgery alone. Therefore, novel approaches are needed to improve the prospect of patients with liver metastases amendable to surgery. An analysis of resected livers revealed that micrometastases are present in 30% to 70% of patients undergoing curative resections for CRLM [8–11]. The outgrowth of these subclinical tumor cells is assumed to be one of the major factors responsible for the high recurrence rates. It is shown that, immediately after liver resection, proangiogenic growth factors such as vascular endothelial growth factor (VEGF) are upregulated to support liver regeneration. VEGF is a ligand playing a central role in tumor growth, (tumor) blood vessel development, and endothelial cell survival [12–14]. Neutralizing the VEGF and VEGF receptor (VEGFR) signaling pathways has improved treatment outcome in a number of diseases [15,16]. Bevacizumab, a humanized monoclonal antibody targeting VEGF-A, is now considered an integral part of first-line chemotherapy for patients with metastatic colorectal cancer. It has been shown that micrometastases are susceptible to antiangiogenic treatment because they depend on the local production of VEGF. Supportive evidence comes from preclinical research where treatment with an angiogenesis inhibitor inhibited the growth of colorectal liver metastases [17–19]. Given the fact that the residual liver most likely contains micrometastasis and that liver resections induce a growth factor response, including increased concentrations of VEGF, we argued that the addition of bevacizumab to standard postresection chemotherapy might lower the recurrence rate in patients undergoing resection for their CRLM. To test this hypothesis, we performed a randomized controlled study in this patient population.

Material and Methods

Patients

Patients older than 18 years were eligible if they had radically resected, histologically proven CRLM. Eligible patients needed to have an Eastern Cooperative Oncology Group score below two and adequate bone marrow, hepatic, and renal functions. For detailed inclusion and exclusion criteria, see the published protocol for this study [20].

Treatment

Four to eight weeks after surgery for CRLM, treatment with either capecitabine, oxaliplatin (CAPOX), and bevacizumab or CAPOX alone was started. All treatment cycles were administered at intervals of 3 weeks. Treatment of patients in arm A consisted of oral capecitabine (1000 mg/m^2 twice daily) on day 1 through day 14, oxaliplatin 130 mg/m^2 infusion on day 1, and bevacizumab 7.5 mg/kg infusion on day 1 for a duration of 8 cycles followed by bevacizumab alone (7.5 mg/kg every 3 weeks) for another 8 cycles. Patients assigned to arm B received capecitabine (1000 mg/m^2 twice daily) on day 1 through day 14 and oxaliplatin 130 mg/m^2 infusion on day 1 for 8 cycles. Treatment was continued until 16 cycles in arm A and 8 cycles in arm B were completed or until there was progression of disease or unacceptable toxicity.

Amendment of the Trial

The study protocol was amended in November 2009 based on the input of participating centers because of slow accrual rate. The amendment allowed three preoperative cycles of CAPOX. It also allowed radiofrequency ablation of tumors smaller than 4 cm and of a maximum of three tumors when the liver volume was insufficient to resect all tumor tissue but only in combination with surgery. Both were added as stratification factors.

Study Design

The HEPATICA study was designed as a phase III, two-arm, multicenter, randomized, controlled study comparing adjuvant CAPOX and bevacizumab (arm A) versus CAPOX alone (arm B) in patients with resected CRLM in terms of disease-free survival (DFS), overall survival (OS), toxicity, and quality of life (QoL). This study was conducted in 28 centers in the Netherlands and 2 centers in Sweden. Randomization was done centrally by a minimization technique with stratification according to the number of liver metastases (<4 or ≥4), metachronous or synchronous metastases, prior adjuvant chemotherapy, blood transfusion, and treatment site. The study and its amendments were approved by the Central Committee of Human-Related Research and by the local ethics committees of all participating centers. Written informed consent was required from all patients before study entry.

Primary End Point

The primary end point of this study was DFS. In November 2009, the eligibility criteria were modified to allow neoadjuvant treatment and radiofrequency ablation for a group of patients with high risk of recurrence, and the sample size was recalculated. It was calculated that to detect a difference between the groups with a hazard ratio (HR) of 0.67, 300 patients should be recruited in 3 years, with 1 year of further follow-up.

Secondary End Points

Secondary end points were OS, toxicity, and QoL. Toxic effects were assessed according to the US National Cancer Institute Common Toxicity Criteria, version 3.0, before each cycle of treatment. QoL was measured using the QLQ-C30 questionnaire of the European Organization for Research and Treatment of Cancer (EORTC) before the start of adjuvant treatment and, thereafter, every 6 months for 2 years after surgery. The QLQ-30 measures the QoL separated by function and symptom areas [21]. Next to the five functional scales (physical functioning, role functioning, cognitive functioning, emotional functioning, social functioning) and a scale for global QoL, there are three symptom scales (fatigue, nausea/vomiting, and pain) and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties).

Data Collection

An independent data and safety monitoring committee monitored recruitment, serious adverse events, and data quality at least every 2 months. Relevant information was included in regular study reports and was made available to the independent data and safety monitoring committee. Data forms were entered in a database by a double data entry procedure. Computerized and visual consistency checks were performed on newly entered forms; queries were issued in case of inconsistencies. Verification of all data (100%) was done for 1 of the 2 first subjects at each site; 1 of subjects 3 to 10; and, thereafter, 1 subject per 10 randomized or treated subjects.

Funding of the Trial

This was an investigator-initiated study supported in part by the Dutch Cancer Society, Roche, and Sanofi Aventis. The funding source

had no role in the design, conduct, data collection, data analysis, or interpretation of the study or the results.

Statistical Analysis

DFS time was calculated from randomization until recurrence of disease or death, whichever occurred first. Patients alive without recurrence of disease were censored at last follow-up. OS was calculated until death of any cause. All patients were included in the efficacy analysis (intention-to-treat principle). For two patients who withdrew their consent, only data prior to withdrawal could be used. Univariable Cox proportional hazards regression models were used to estimate the HRs of all clinicopathological factors and treatment arms. Toxicity was analyzed for all patients who received at least one cycle of treatment. QoL was evaluated using a mixed-effect modeling procedure (SAS Proc Mixed), allowing to retain patients with missing values in the analysis. A first-order autoregressive covariance structure was used so that correlations between measurements declined exponentially with the time between them. Treatment and baseline value were entered as covariates. Patients with missing baseline values were removed from the model but still taken into account in the calculation of mean per time point. F tests were used to assess the interaction effect of treatment and time. Analyses were performed using SAS version 9.2 and R version 2.15.0.

Premature Closure of the Trial

Because of the slow accrual of the study which would have extended the total accrual time to 8 years and the outcome of the National Surgical Adjuvant Breast and Bowel Project C-08 and AVANT study, which demonstrated no benefit of the addition of bevacizumab to an oxaliplatin-based adjuvant regimen after resection of stage II and III colorectal cancer, the steering committee decided to close the HEPATICA study prematurely in October 2010 [22,23].

Results

Patients

Seventy-nine patients were randomized in the study. Forty patients were allocated to arm A (CAPOX + bevacizumab), and 39 patients were allocated to receive treatment according to arm B (CAPOX alone) (Figure 1). Baseline characteristics are depicted in Table 1. Two patients (one in arm A, and one in arm B) withdrew their consent after randomization. These patients were censored at the first day. There were two patients (in arm B) who did not receive treatment because of progression discovered just before start of treatment. Both patients were retained in the analysis and counted as having progression.

Treatment

Twenty-two patients (56.4%) in arm A completed the full 16 cycles. Ten patients were not able to complete all cycles because of toxicity. Two patients had recurrent disease before the end of chemotherapy (Supplemental Table 2). In arm B, 22 (57.9%) patients completed the full 8 cycles according to the study protocol. Two patients were diagnosed with recurrent disease before start of chemotherapy. Three patients discontinued treatment because of recurrence of their cancer during treatment, and eight patients discontinued treatment because of toxicity. One patient received bevacizumab in arm B (major protocol violation).

Survival

At the time of analysis, January 2013, 23 events occurred in arm A and 20 in Arm B. Median follow-up time was 36 months. The 1-year DFS estimate was 79% [95% confidence interval (CI): 68%-93%] and 68% (95% CI: 86%-93%) for arm A and B, respectively (log-rank P = .89). Two-year DFS probabilities were 55% (95% CI: 41%-74%) and
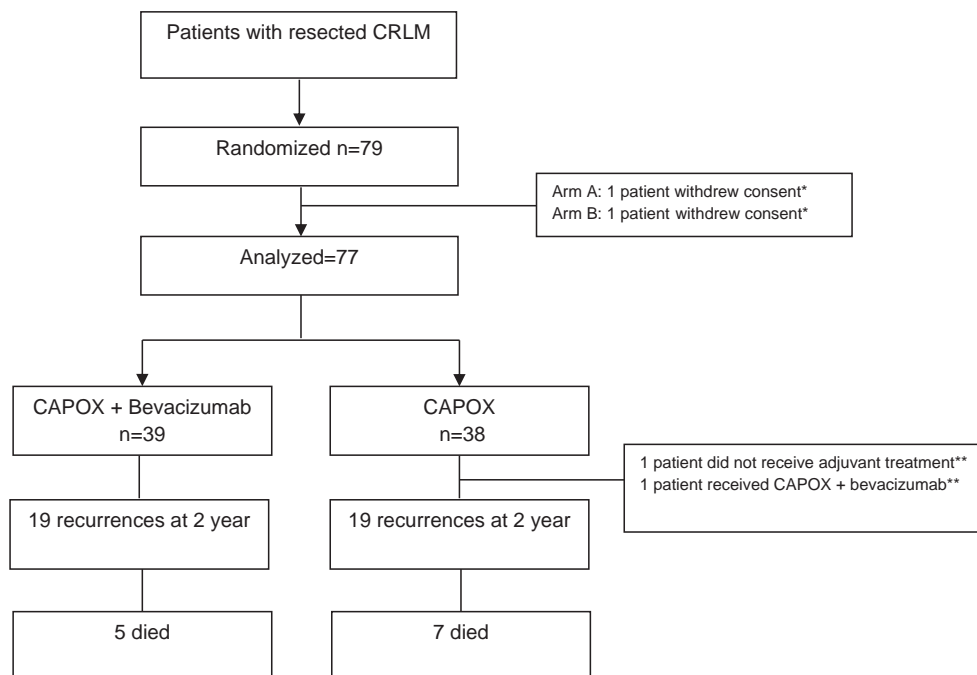
* Patients could not be included in analysis
** Patients were kept in analysis according to the intention to treat principle

Figure 1. Trial profile.

Table 1. Patient Baseline Demographics

	Randomized Treatment		
	Arm A: CAPOX + Bev	Arm B: CAPOX	Total
Total	39 (51%)	38 (49%)	77
Age at randomization			
Median	62	61	61
Interquartile range	57-70	53-63	55-66
Performance status			
WHO 0	17 (44%)	13 (34%)	30 (39%)
WHO 1	6 (15%)	11 (29%)	17 (22%)
NA	16 (41%)	14 (37%)	30 (39%)
Histological grade			
Well differentiated	2 (5%)	4 (11%)	6 (8%)
Moderately differentiated	27 (69%)	28 (74%)	55 (71%)
Poorly differentiated	6 (15%)	1 (3%)	7 (9%)
Unknown	4 (10%)	5 (13%)	9 (12%)
N status			
N0	18 (46%)	15 (39%)	33 (43%)
N1	12 (31%)	12 (32%)	24 (31%)
N2	7 (18%)	6 (16%)	13 (17%)
NX	2 (5%)	5 (13%)	7 (9%)
Location of primary tumor			
Colon	13 (33%)	17 (45%)	30 (39%)
Rectum	14 (36%)	13 (34%)	27 (35%)
Rectosigmoid	12 (31%)	8 (21%)	20 (26%)
Radical resection			
R0	38 (97%)	36 (95%)	74 (96%)
R1	1 (3%)	0 (0%)	1 (1%)
Unknown	0 (0%)	1 (3%)	1 (1%)
NA	0 (0%)	1 (3%)	1 (1%)
Radiotherapy primary			
No	27 (69%)	28 (74%)	55 (71%)
Yes	12 (31%)	10 (26%)	22 (29%)

Table 2. Univariable Cox Models for DFS

	Events	Subjects	HR	95% CI	P Value
Randomized treatment					
Arm A: CAPOX + bev	23	40	1		.88
Arm B: CAPOX	20	39	0.96	(0.53-1.75)	
Gender					
Male	32	52	1		.18
Female	11	25	0.63	(0.32-1.24)	
Age at randomization (continuous)					
Per 10 years	43	77	0.78	(0.56-1.08)	.14
Age at randomization (grouped)					
34-65	31	55	1		.41
65-75	11	22	0.75	(0.38-1.49)	
Location of primary tumor					
Colon	16	30	1		.32
Rectum	18	27	1.40	(0.71-2.75)	
Rectosigmoid	9	20	0.786	(0.34-1.76)	
Histological grade					
Well differentiated	4	6	1		.44
Moderately differentiated	32	55	0.65	(0.23-1.84)	
Poorly differentiated	4	7	0.50	(0.12-2.00)	
Unknown	3	9	0.31	(0.07-1.39)	
N status					
N+	23	37	1		.10
N0	15	33	0.58	(0.30-1.12)	
Presentation of the liver metastases					
Metachronous	22	39	1		.81
Synchronous	21	38	1.08	(0.59-1.96)	
Adjuvant chemotherapy					
No	37	69	1		.29
Yes	6	8	1.60	(0.67-3.85)	
Blood transfusion received					
Yes	6	15	1		.48
No	37	62	1.75	(0.74-4.17)	
Number of liver metastases					
<4	34	624	1		.48
≥4	9	15	1.30	(0.62-2.72)	
Log CEA tumor marker					
Per IQR	19	40	1.40	(0.75-2.63)	.29

IQR, interquartile range.
  Including two patients censored at withdrawal of consent.

54% (95% CI: 40%-73%) for arm A and B, respectively (log-rank P = .73). Univariable Cox regression analysis was performed (Table 2). Five patients died in arm A and 7 in arm B. Two-year OS rate was 94% for both arms (P = .43). Survival curves for DFS and OS are depicted in Figure 2. In Supplemental Table 3, the sites of recurrences are depicted.

Toxicity

Toxicity was evaluated for 75 patients (Table 3). In general, toxicities were comparable between the two arms. In total, there were two grade 5 toxicities. In arm A, one patient died of terminal kidney failure 3 years after randomization. In arm B, one patient experienced a grade 5 toxicity of mucositis. This patient died from respiratory failure after aspiration of blood as a complication of mucositis probably caused by capecitabine. This patient received one cycle of CAPOX.

Quality of Life

Fifty-eight patients were evaluated for QoL. Compliance with completing QoL questionnaires compared with baseline dropped to 59% at 6 months, 43% at 12 months, 41% at 18 months, and 29% at 24 months (Supplemental Table 4). Patients receiving CAPOX + bevacizumab (arm A) had a higher mean score in all QoL functional scales at baseline except from emotional functioning (Supplemental Table 5) and a lower mean score in all QoL symptom scales at baseline except for insomnia. In the functional scales, all scores were higher during the 2 years in arm A compared with arm B, of which global QoL and emotional functioning reached significance at the .05 level. Both these scores were higher than the 10-point cutoff for clinical significance at 18 and 24 months compared with baseline (Supplemental Figure 1). There were no significant differences in symptoms between patients receiving CAPOX + bevacizumab and CAPOX alone (Supplemental Table 5).
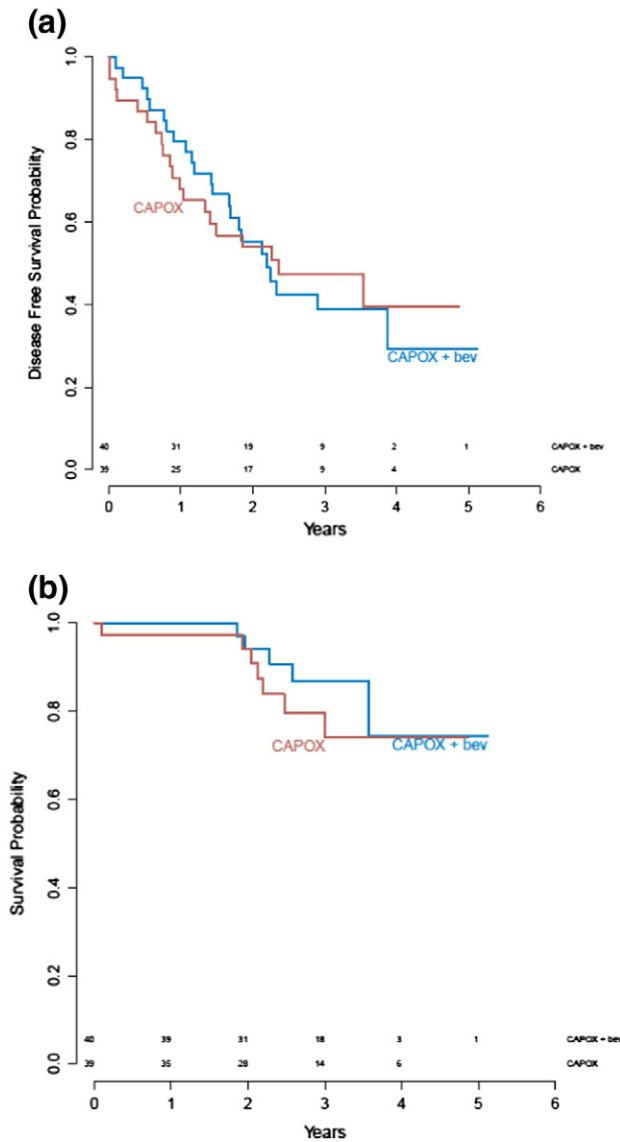
Discussion

Although this study did not reach its intended accrual, several relevant observations were made. The DFS rate is comparable to larger studies with resected colorectal liver metastases in combination with systemic therapy, although we did include more patients with synchronous metastases and patients with four or more metastases unlike the EORTC 40983 study [6]. Furthermore, in the first 18 months, survival rate in our study was better for treatment with CAPOX-B when compared with CAPOX alone. We speculate that the addition of bevacizumab may have a temporary growth-delaying effect on the outgrowth of metastases. Although, in the C08 and AVANT studies, both large, randomized, and well-executed studies, there was no DFS or OS benefit for the addition of bevacizumab after resection of colorectal cancer, there is an important difference between the HEPATICA study and the beforementioned studies [22,24]. In the HEPATICA study, patients were included with established metastases, whereas the two other studies included patients without apparent metastases after resection of the primary tumor. In the metastatic setting, studies have shown benefit of treatment with bevacizumab [25].

Another aspect of the HEPATICA study was assessment of toxicity and QoL. There were no differences in toxicities between both regimens, and remarkably, patients in the treatment arm scored higher on QoL.

There is extensive experience with both the CAPOX and CAPOX-B regimens that supports the notion that toxicity is not significantly

(a)

(b)

Figure 2. Kaplan-Meier curves depicting (a) DFS and (b) OS probability for patients receiving CAPOX and CAPOX + bevacizumab.

Table 3. Number of Patients with Toxicities of Common Toxicity Criteria grade 3, 4, or 5

	Arm A: CAPOX + Bev	Arm B: CAPOX	Total
Total	39 (52%)	36 (48%)	75
Allergic reaction/hypersensitivity	1 (2.6%)	0 (0.0%)	1 (1.3%)
Cardiac ischemia/infarction	1 (2.6%)	0 (0.0%)	1 (1.3%)
Hypertension	9 (23.1%)	6 (16.7%)	15 (20.0%)
Hypotension	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other cardiac symptoms	2 (5.1%)	1 (2.8%)	3 (4.0%)
Fatigue (malaise, asthenia)	3 (7.7%)	2 (5.6%)	5 (6.7%)
Fever	0 (0.0%)	1 (2.8%)	1 (1.3%)
Weight loss	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other constitutional symptoms	0 (0.0%)	0 (0.0%)	0 (0.0%)
Alopecia	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hand-foot syndrome	3 (7.7%)	1 (2.8%)	4 (5.3%)
Injection site reaction/extravasation	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nail changes	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other skin symptoms	0 (0.0%)	0 (0.0%)	0 (0.0%)
Diarrhea	7 (17.9%)	8 (22.2%)	15 (20.0%)
Mucositis/stomatitis	1 (2.6%)	1 (2.8%)	2 (2.7%)
Nausea	1 (2.6%)	0 (0.0%)	1 (1.3%)
Vomiting	1 (2.6%)	1 (2.8%)	2 (2.7%)
Other gastrointestinal symptoms	2 (5.1%)	3 (8.3%)	5 (6.7%)
Hemorrhage/bleeding	0 (0.0%)	1 (2.8%)	1 (1.3%)
Febrile neutropenia	0 (0.0%)	2 (5.6%)	2 (2.7%)
Infection	2 (5.1%)	3 (8.3%)	5 (6.7%)
Dizziness	0 (0.0%)	0 (0.0%)	0 (0.0%)
Neuropathy-sensory	7 (17.9%)	8 (22.2%)	15 (20.0%)
Other neurological symptoms	0 (0.0%)	2 (5.6%)	2 (2.7%)
Abdominal pain, cramping	1 (2.6%)	1 (2.8%)	2 (2.7%)
Headache	0 (0.0%)	1 (2.8%)	1 (1.3%)
Other pain	0 (0.0%)	1 (2.8%)	1 (1.3%)
Cough	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dyspnea	1 (2.6%)	0 (0.0%)	1 (1.3%)
Hiccoughs (hiccups, singultus)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pneumonitis/pulmonary infiltrates	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other pulmonary symptoms	0 (0.0%)	0 (0.0%)	0 (0.0%)
Thrombosis/embolism	4 (10.3%)	2 (5.6%)	6 (8.0%)
Other vascular symptoms	1 (2.6%)	1 (2.8%)	2 (2.7%)
Any of above toxicities worst grade	21 (53.8%)	18 (50.0%)	39 (52.0%)

respectively, 822 and 209 patients. Patients were randomized to receive either irinotecan, 5-fluorouracil, and leucovorin or irinotecan, 5-fluorouracil, leucovorin, and bevacizumab, suggesting that the addition of bevacizumab did not add to patients' treatment burden [29].

Another important observation is that we did not observe increased numbers of metastatic lesions in the bevacizumab arm. Based on preclinical studies, this was a serious concern because it was shown that, within 7 days after cessation of anti-VEGF treatment, accelerated tumor growth occurred as a result of rapid revascularization [30,31]. In a regenerating liver, the physiological state after liver resections, this may even be more relevant because angiogenesis is constantly active. The preclinical concept of accelerated tumor growth when bevacizumab treatment was interrupted was supported by a small series of patients with colorectal liver metastases receiving perioperative chemotherapy in combination with bevacizumab [32]. Furthermore, preclinical studies showed that, in certain conditions, treatment with a VEGF/VEGFR inhibitor can cause a hypoxic and protumorigenic inflammatory state leading to increased invasiveness [32,33]. In our study, patients already had established metastases which define a population at high risk for microscopic residual disease; we could not determine accelerated recurrence. This indicates that, in this setting, the preclinical studies did not have a clinical correlate and warrant further investigation.

A recent meta-analysis concluded that the addition of chemotherapy to surgery is beneficial [33]. The timing of chemotherapy however remains unclear. Fifty-seven percent of patients completed all cycles of chemotherapy in our study. This is in line with other

different with the exception of specific bevacizumab-related toxicities such as hypertension and proteinuria. A reduced liver capacity may result in temporary impairment of liver function and altered clearance of chemotherapeutic agents [26]. The toxicity profile in this study does not seem to indicate excessive toxicity compared with the toxicity seen in patients treated without liver resections [27,28]. In general, patients in the treatment arm scored higher on QoL, of which the functional scales global QoL and emotional functioning reached significance. Compliance dropped to 41.3% at 18 months; however, it was not different between the 2 arms. A possible explanation for the reported higher QoL in the bevacizumab arm might be attributed to the addition of a new agent to a known regimen, suggesting superior treatment, positively affecting patients' mood and influencing the way patients experience their QoL.

There are not many studies reporting the QoL when adding bevacizumab to chemotherapy. Kabbinavar et al. examined the time to deterioration of health care–related QoL using the colorectal cancer subscale or Trial Outcome Index score, examining two studies with,

postsurgery adjuvant studies and is sometimes used as an argument to advocate preoperative chemotherapy because patients are more fit to undergo chemotherapy and more likely to complete all cycles. However, there are also arguments against preoperative chemotherapy. In the EORTC 40983 study, 12 patients had progressive disease during preoperative chemotherapy, potentially preventing subsequent surgery, and 24% could not receive postoperative chemotherapy. Moreover, postoperative complications were significantly higher in the chemotherapy group (25% vs 16%, $P = 0.04$) [6]. In contrast, the new Eloxatin for Peri-Operative chemotherapy trial, not included in this meta-analysis, showed a detrimental effect of the addition of cetuximab to perioperative chemotherapy for resectable or suboptimal resectable disease [34]. This underpins the complexity of the choice of treatment and optimal timing of adjuvant treatment.

Our study has encountered significant problems in recruitment, ultimately leading to a premature closure of the trial. Unfortunately, this is a frequent phenomenon in studies investigating peri- or postoperative treatment of patients with colorectal liver metastases [5–7]. Institutions have developed their own programs for hepatic surgery, chemotherapy, or local interventions, hampering joint efforts to resolve clinical problems. Patient numbers are generally small, and the time needed to include sufficient patients is long. We therefore hope that ongoing studies using anti-VEGF therapy in stage IV patients with resectable liver metastases such as a study initiated by the Yonsei University (NCT01632722) will provide a solid outcome and result in clinical guidance. In conclusion, no definite answers could be provided as to whether patients with established metastases in the liver might benefit from antiangiogenic treatment after liver surgery and differ from patients receiving adjuvant treatment after resection of the primary tumor. This study does however show that it is safe to add bevacizumab to an adjuvant regimen of CAPOX in patients undergoing radical resection for their CRLM.

Participating centers

The principal investigators of the local hospitals are mentioned below. Investigators are of the Department of Surgery (S), Oncology (O), or Gastroenterology (G).

Academic Medical Center Amsterdam: O. R. C. Busch (S), D. J. Richel (O); Amphia Hospital Breda: A. Rijken (S), O. J. L. Loosveld (O); Atrium Medical Center Heerlen: J. Wals (O); Deventer Hospital: M. S. L. Liem (S), A. L. T. Imholz (O); Diakonessenhuis Utrecht: C. I. Perre (S), D. ten Bokkel Huinink (O); Gelre Hospital Apeldoorn: E. J. Hesselink (S), J. M. Smit (O); Jeroen Bosch Hospital Den Bosch: K. Bosscha (S), J. F. M. Pruijt (O); Leiden University Medical Center: R. Tollenaar (S), A. J. Gelderblom (O); Maastricht University Medical Center: C. H. C. Dejong (S), R. L. H. Jansen (O); Maxima Medical Center Veldhoven: R. Roumen (S), G. Vreugdenhil (O); Meander Medical Center Amersfoort: B. van Ooijen (S), C. Rodenburg (O); Medical Center Alkmaar: C. H. Smorenburg; Medical Center The Hague: J. R. M. van der Sijp (S), H. M. Oosterkamp (O); Medical Center Leeuwarden: J. P. E. N. Pierie (S), M. B. Polée (O); Medical Spectrum Twente Enschede: J. M. Klaase (S), M. C. J. C. Legdeur (O); Onze Lieve Vrouwe Gasthuis Amsterdam: P. J. Borgstein (S), B. de Valk (O); Saint Elisabeth Hospital Tilburg: J. M. G. H. van Riel (O); Slingeland Hospital Doetinchem: E. W. Muller (O); Antoni van Leeuwenhoek Hospital: F. van Coevorden (S), A. Cats (G); Tergooiziekenhuizen Blaricum/Hilversum: H. P. van den Berg; University Medical Center Groningen: R. J. Porte (S), K. P. de Jong (S), G. A. P. Hospers (O); University Medical Center Utrecht: R. van

Hillegersberg (S), E. E. Voest (O); VieCuri Venlo: A. J. van der Wouw (O); VU Medical Center Amsterdam: M. P. van den Tol (S), E. Boven (O); Westfriesgasthuis Hoorn: J. W. D. de Waard (O); Haga Hospital The Hague: J. E. A. Portielje (O); Röpcke-Zweers Ziekenhuis-Saxenburg Groep Hardenberg: E. A. Runhaar (O); Gelderse Vallei Ede: C. Sietses (S), E. Balk (O).

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