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Efficacy of radioembolization with holmium-166 microspheres in salvage patients with liver metastases: a phase 2 study.

Efficacy of Ho-166 radioembolization.

Authors

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ABSTRACT

Rationale

Radioembolization of liver malignancies with holmium-166 (^{166}Ho) microspheres has been shown safe in a phase 1 dose-escalation study. The purpose of this study was to investigate the efficacy of ^{166}Ho radioembolization.

Methods

In this prospective single-arm study, 56 patients were enrolled, all with liver metastases refractory to systemic therapy and ineligible for surgical resection. The primary outcome was tumor response of two target lesions on triphasic liver CT scans, 3 months after therapy using Response Evaluation Criteria In Solid Tumors 1.1. Secondary outcomes included overall tumor response, time to imaging progression, overall survival, toxicity, quality of life, and quantification of the microspheres on single-photon emission computed tomography and magnetic resonance imaging.

Results

Between May 2012 and March 2015, 38 eligible patients were treated, one of whom was not evaluable. In 27/37 (73%) patients, the target lesions showed complete response, partial response or stable disease (disease control) at three months (95% confidence interval [CI], 57 to 85%). The median overall survival was 14.5 months (95% CI, 8.6 to 22.8 months). For colorectal cancer patients (*n*=23), the median overall survival was 13.4 months (95% CI, 8.2 - 15.7 months). Grade 3 or 4 toxic events after treatment (according to CTCAE v4.03 criteria) included abdominal pain (in 18% of patients), nausea (8%), ascites (3%), fatigue (3%), gastric stenosis (3%), hepatic failure (3%), liver abscesses (3%), paroxysmal atrial tachycardia (3%), thoracic pain (3%), upper gastrointestinal hemorrhage (3%), and vomiting (3%). On single-photon emission computed tomography, ^{166}Ho could be quantified with high accuracy and precision, with a mean overestimation of 9.3±7.1% in the liver.

Conclusion

Radioembolization with ^{166}Ho microspheres induced a tumor response with an acceptable toxicity profile in salvage patients with liver metastases.

INTRODUCTION

Hepatic radioembolization involves the injection of radioactive microspheres into the hepatic arteries, with the aim to embolize and irradiate liver malignancies. The most often used microspheres contain the radioactive isotope yttrium-90 (^{90}Y) that can be quantified on bremsstrahlung single-photon emission computed tomography / computed tomography (SPECT/CT) or positron-emission tomography (PET)/CT, but only after a full treatment dose (*1*). Pretreatment imaging can be performed with technetium-99m macro-aggregated albumin (^{99m}Tc-MAA) (*2–4*). Microspheres containing holmium-166 (^{166}Ho) emit gamma rays (81 keV) and can be visualized on SPECT/CT with high sensitivity, which enables quantification at lower activities, such as after a scout dose (*5*). A scout dose with ^{166}Ho microspheres enables individualized treatment dosimetry (*6,7*).

A previous phase 1 dose-escalation study showed that administration of ^{166}Ho radioembolization with a projected average liver absorbed dose of up to 60 Gy was safe (*8*). In this phase 2 study, the efficacy was investigated.

MATERIALS AND METHODS

Study Design

The Holmium Embolization Particles for Arterial Radiotherapy II (HEPAR II) study was a single-arm, single-center study (Clinicaltrials.gov: NCT01612325).

Patients were eligible if diagnosed with metastatic liver lesions of any primary origin and limited disease outside the liver as determined on ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET/CT (the sum of lesion diameters had to be <50% the sum of lesions inside the liver), were unable or unwilling to undergo (further) chemotherapy and/or surgery (salvage patients), had an estimated life expectancy of >3 months, had adequate liver, renal, and bone marrow function, and had a World Health Organization performance score of ≤2 (see the study protocol (*9*)).

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local research ethics committee. All patients provided written informed consent. An independent monitor verified all data. All data mentioned in this manuscript are available upon request (imaging_research@umcutrecht.nl).

Microspheres

Non-radioactive ^{165}Ho microspheres were manufactured (University Medical Center Utrecht, Utrecht, the Netherlands), neutron irradiated to obtain radioactive ^{166}Ho microspheres (Reactor Institute Delft, Delft, the Netherlands) and subsequently dispersed in water for injection containing 2% pluronic F-68 and 10% absolute ethanol as described previously (*10*). After 8 patients were treated, ethanol was replaced by an isotonic phosphate buffer (116 mM, pH 7.4) to improve the microsphere stability, and additional quality controls were implemented.

Treatment

A preparatory angiography was performed at a median of 7 days (range 2 – 21 days) before treatment. Extra-hepatic vessels (gastroduodenal, right gastric, or pancreatic arteries) were coil

embolised if distal or near to the injection position(s). Tumor feeding arteries (phrenic or segmental hepatic arteries, e.g. from the left gastric artery) were coil embolised if necessary. A scout dose of ^{99m}Tc-MAA (150 MBq, Technescan LyoMAA®; Mallinckrodt Medical B.V., Petten, the Netherlands) was administered to assess the safety of subsequent administrations. If more than 20% of the particles shunted to the lungs, treatment was cancelled. On the day of treatment, ^{166}Ho microspheres were administered first as a scout dose (aimed ^{166}Ho activity of 250 MBq, 60 mg, 0.04 mL, 3 million microspheres) and second as a treatment dose (variable ^{166}Ho activity, 0.54 g, 0.39 mL, 30 million microspheres), with SPECT/CT and MR image acquisition after both injections. Treatment was planned as a single treatment session unless there were too many injection positions (>3). The total amount of radioactivity was adjusted to the targeted liver mass measured on CT (aimed absorbed dose, 60 Gy or 3.8 GBq/kg liver tissue, including the ^{166}Ho scout dose) and was contained in a fixed amount of microspheres. The prepared activities exceeded the prescribed activities by around 10% to account for losses during preparation and administration. Before treatment, patients received proton pump inhibitors (pantoprazole 40 mg for 6 weeks), anti-emetics (ondansetron i.v. 8 mg), and steroids.

Assessments

The primary outcome was the disease control rate of target lesions after 3 months according to Response Evaluation Criteria in Solid Tumors, version 1.1, on triphasic liver CT (*11*). Secondary outcomes included overall tumor response, response on ^{18}F-FDG-PET/CT (not presented here), time to imaging progression, overall survival, toxicity, quality of life, and quantification of the microspheres on SPECT and MRI.

After treatment, follow up included visits after three, six, and nine weeks, and from then on every three months. Response imaging was performed every three months using triphasic liver CT and ^{18}FDG-PET/CT. Patients were followed until intrahepatic progressive disease occurred, with a maximum of 12 months.

Three independent readers scored the primary outcome (FJW, RCGB, MNGJAB). The outcome was determined by the majority vote (≥2) or imputed as 'not evaluable' (e.g., when all reviewers had a different outcome). Response was dichotomized into progression or disease control, i.e. complete response, partial response, or stable disease. For a conservative estimation, progressive disease was imputed for patients who were 'not evaluable' or missing (not) at random (see Sterne et al. for definitions).(*12*) Only if data was missing completely at random, did we enter data as 'not available'.

Adverse events were registered and laboratory tests performed every visit and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 (*13*). The maximum severity of adverse events after treatment was reported. Quality of life was assessed using the European Organization for Research and Treatment of Cancer score and liver metastases questionnaires at baseline, six weeks, and every three months. After 11 patients were treated, an extra questionnaire one week after treatment was added to better reflect patients' transient symptoms.

^{166}Ho microspheres were quantified on SPECT/CT with in-house developed Monte Carlo reconstructions (UMCS), using in-house developed software (Volumetool) (*5*,*14*). MR quantification was based on the impact of holmium on T2* relaxation times, utilizing multi-gradient echo sequences and performed on in house developed software, similar to earlier reports but using adjusted acquisition parameters (*15*,*16*). Acquisition parameters for SPECT/CT and MR can be found in a Zenodo repository (*9*). Both quantifications were compared with the injected amount of microspheres (corrected for residual microspheres). Values of prepared and residual radioactivity were obtained from a dose calibrator (assumed uncertainty 10%, VDC-404, Veenstra Instruments, Joure, Netherlands) (*5*).

Statistical Analysis

For efficacy, an exact group sequential design was used to define stopping boundaries beforehand. The design had an exact type I error of 4.5% (one sided) if the true disease control rate was 20% and power of 90% if the true disease control rate was 40%. Futility boundaries were also employed

to be able to stop the study if the disease control rate was considerably lower than the 40% expected in the power calculation (*17*). We aimed to include 30 to 48 patients with interim analyses scheduled when the primary outcome became available for 30, 36, and 42 patients. The stopping boundaries after analysis of the first 30 patients were 5 (for futility) and 11 (for efficacy; see Supplemental Fig. 1 for all boundaries). Inclusion continued while waiting for the first patients to reach the time of first follow up.

For toxicity, a continuous sequential analysis was used based on an expected proportion of severe toxicity events of 25%, a limit of 50%, and a type I error of ≤5% (one-sided) (*18*). Severe toxicity was defined as all CTCAE events ≥ grade 3 and all Serious Adverse Events as defined by the local research ethics committee, but only if they were not caused by baseline concomitant diseases, intercurrent disease, or disease progression. Safety monitoring was performed every three months by both an independent data monitoring committee and the Dutch Health Care Inspectorate ("Inspectie voor de Gezondheidszorg").

Descriptive statistics were calculated as medians and (interquartile) range, means and standard deviations, or percentages and frequencies. Patients were followed until January 20, 2016. Analyses for survival and time to progression were performed by the Kaplan-Meier method on a per protocol set. Differences between groups were tested using the log-rank test. Survival time was measured from administration of ^{166}Ho microspheres to end of follow up or death. Confidence intervals for proportions (e.g., of response data) were displayed as the Adjusted Wald (*19*). Two-sided *P* values were calculated (with the exception of the efficacy analysis, as mentioned above). Analyses were performed using R statistical software (R version 3.2.1 for Windows).

RESULTS

Patients

From May 2012 until March 2015, 56 patients were enrolled, 38 of whom received treatment with ^{166}Ho microspheres (Fig. 1). Of the treated patients, 23/38 (61%) had colorectal cancer. Overall, the study population had been diagnosed with a malignancy a median of 28 mo prior (range 4 – 95 mo) and with liver metastases a median of 18 months prior (range, 3 – 92 mo, Table 1).

Treatment and Efficacy

Of 38 patients, two were treated in two separate sessions for both liver lobes (both three weeks later with a target absorbed dose of 60 Gy for both the right and left liver lobe). Two other patients received right lobar treatment, all others received whole liver treatment in one session. The median liver absorbed dose was 51 Gy (range, 26 – 69 Gy, Table 1).

At the first interim analysis, the stopping boundary for efficacy was surpassed and study inclusion was stopped. One patient was not evaluable because this patient did not receive IV contrast during CT acquisition at three months. Of the evaluable 37 patients, two patients had clinical progressive disease before three months and one extra patient was imputed as having progressive disease because of a protocol deviation (namely, concomitant treatment within 3 months). All other patients were evaluable at three months as planned.

The target lesions showed disease control on CT imaging in 27/37 (73%) evaluable patients after three months (95% confidence interval [CI], 57 - 85%, Table 2) . The proportion of specific agreement between the three readers was 88% for the assessment of disease control or progression of target lesions at three months after treatment. Disease control in the liver (assessing also new lesions and progression of non-target lesions) was achieved in 18/37 (49%) of patients (95% CI, 33 – 64%) after three months. The median time to progression in the liver was 3 months (95% CI, 3 to 6 months, see Supplemental Fig. 2).

The median overall survival was 14.5 months (95% CI, 8.6 to 22.8 months, Supplemental Fig. 3A). The overall survival analysis was based on 29 deaths (76%) after a median follow up of 13.3 months (range 2.5 to 39.3 months). Colorectal cancer patients showed whole liver disease control in 10/22 (45%) patients on CT imaging after 3 months (95% CI, 27 - 65%). One patient did not receive IV contrast. Their median overall survival was 13.4 months (95% CI, 8.2 - 15.7 months, Supplemental Fig. 3B). The median overall survival of colorectal cancer patients with disease control of their target lesions after 3 months was 14.1 months (95% CI, 8.2 – ∞ months). Colorectal cancer patients with progression of their target lesions had a median survival of 7.1 months (95% CI, 3.3 to ∞ months, p = 0.44, Fig. 2).

Toxicity

The continuous interim analysis showed an acceptable toxicity profile, with 10/38 (26%, 95% CI, 25% - 42%) of patients experiencing severe toxicity as defined in the protocol (i.e., related to therapy and either CTCAE ≥ grade 3 or a Serious Adverse Events). The most common adverse events during follow up were gastrointestinal complaints as part of the post radioembolization syndrome: nausea, abdominal pain, and fatigue (Tables 3 and 4).

Two deaths occurred within 3 months after treatment. One patient had rapid recurrence of gastric cancer that compromised oral intake. The other patient, with rectal cancer, developed hepatic failure, for which expedited diagnostic studies were performed that showed intrahepatic and extrahepatic disease progression. Neither permitted autopsy.

Quality of Life

Quality of life was mostly affected by ^{166}Ho radioembolization in the short term (within 1 week), after which it returned to baseline values. The median global health status decreased from 83 (interquartile range 67 – 83) at baseline to 42 (25 – 71) after one week and it recovered after six weeks (67 [56 – 83]). The most affected functional scales were physical, role, and social functioning (Fig. 3A, all

scores in Supplemental Table 1). The worst symptoms were comparable to the most common adverse events: fatigue, eating, pain, and emotional problems, all of which peaked after one week (Fig. 3B).

Imaging

After treatment, recovered ^{166}Ho activity on SPECT/CT was slightly overestimated by a mean of 9.3±7.1%. The scout dose of ^{166}Ho microspheres was recovered with a mean overestimation of 6.4±6.0%. A median of 0.02% (range, 0 – 0.7%) of the administered ^{166}Ho activity was present in the lungs after treatment. This was in agreement with the median lung shunt after the scout dose of ^{166}Ho microspheres: 0.01% (range, 0 – 0.3%). After ^{99m}Tc-MAA injection, a median lung shunt of 3.2% (range, 0.01 – 19.3%) was measured; no patients were excluded from treatment based on their lung shunt.

MR quantification showed lower accuracy and precision, mainly due to unexpected noise in the images related to the adjusted acquisition parameters used for imaging. On average, 51±18% to 67±17% (depending on the applied noise threshold) of all Ho was recovered in the liver.

DISCUSSION

In this cohort of salvage patients with metastatic liver lesions, the target lesions of 73% of the patients showed disease control after three months, which is an indicator of efficacy. For colorectal cancer patients, disease control in the liver was achieved in 45% after three months, while reported disease control rates when applying best supportive care are around 10% (*20*,*21*).

The reported median survival of 13.4 months (95% CI, 8.2 - 15.7 months) in colorectal liver metastases patients after treatment with ^{166}Ho microspheres fits in the previously reported range of 8.3 to 15.2 months after ^{90}Y radioembolization (*22*). In one of the few prospective studies in salvage patients treated with ^{90}Y glass microspheres, Benson et al. (n = 61) reported a median overall survival of 8.8 months.

Radioembolization with ^{166}Ho microspheres was associated with a number of adverse events of grade 3 or higher, most of which were transient and manageable: abdominal pain and nausea were most common (18% and 8%). In the aforementioned prospective study by Benson et al., the rates of grade 3 or 4 adverse events were slightly lower or comparable to this study, while fewer patients had abdominal pain in the retrospective cohort study by Kennedy et al.: the occurrence of grade 3 or 4 (abdominal) pain was 18% in this study versus 13% and 6% in the study by Benson et al. and Kennedy et al. respectively, the occurrence of nausea 8% versus 1% and 1%, the occurrence of vomiting 3% versus 3% and 2%, and the occurrence of fatigue 3% versus 3% and 6% (*23*,*24*).

A strength of this study was the conservative analysis of efficacy; patients with missing data were imputed as having progressive disease. And disagreement between the three readers of the primary outcome was also conservatively considered as progressive disease.

A limitation of this study was that the confidence intervals for the primary outcome were not adjusted for the interim analysis because no valid methodology is known; the reported intervals are probably narrower than they should be.

Personalized dosimetry can increase the efficacy of radioembolization. Garin et al. showed that selected patients can safely get an intensification of their treatment with ^{90}Y microspheres (based on pretreatment ^{99m}Tc-MAA dosimetry) (*4*). Patients with a higher absorbed dose (>205Gy) to the tumor(s) showed a longer time to progression. By combining pretreatment ^{99m}Tc-MAA and ^{99m}Tc-labeled sulfur colloid, Lam et al. were able to calculate both the absorbed dose to tumors and to the healthy liver parenchyma. These absorbed doses correlated with the response and toxicity respectively (*2*).

An advantage of ^{166}Ho microspheres is that the absorbed dose to the lungs can be more accurately predicted with a scout dose compared with the commonly used ^{99m}Tc-MAA.(*6*) This is important, because the prescribed activity is reduced in up to 40% of patients (based on ^{99m}Tc-MAA) to reduce the probability of radiation pneumonitis (*25*). Furthermore, a scout dose using the exact same ^{166}Ho microspheres is expected to improve the ability to predict the distribution of the treatment dose (i.e. dosimetry), which can be limited when using ^{99m}Tc-MAA (*26*,*27*). The presence of gamma emission does increase radiation exposure to some extent, but only patients treated with more than 7 GBq of ^{166}Ho and released within 6 hours after treatment (instead of 24 hours) would require contact restrictions, in all other cases, patients can be released without contact restrictions (*28*).

In conclusion, this single-arm phase 2 study showed that radioembolization with ^{166}Ho microspheres induced a response in salvage patients with metastatic liver malignancies.

DECLARATION OF INTERESTS

MGEHL is a consultant for BTG and Mirada. He received honoraria from Sirtex.

JFWN and BAZ are inventors on the patents related to the ^{166}Ho microspheres which are assigned to University Medical Center Utrecht Holding BV (patent numbers US 6373068 B1 and US 2005/0201940 A1).

JFWN is co-founder and chief scientific officer (0.5FTE) of Quirem Medical BV. He has a minority share in the company Quirem Medical BV. He is inventor on the following patent families: USA Patent No. 6373068 B1, 8632751, EP07112807.8, 10190254.2, and P112614NL00.

MLJS had accommodation expenses reimbursed by Quirem Medical BV.

BAZ received honoraria from GSK Netherlands, he also received honoria, consulted for, received research funding from and had expenses reimbursed by Novartis Pharm Inc. SN reports personal fees from Mapi Group consultancy, outside the submitted work.

All other author(s) declare that they have no competing interests.

The department of Radiology and Nuclear Medicine of the UMC Utrecht receives royalties from Quirem Medical BV.

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FIGURES

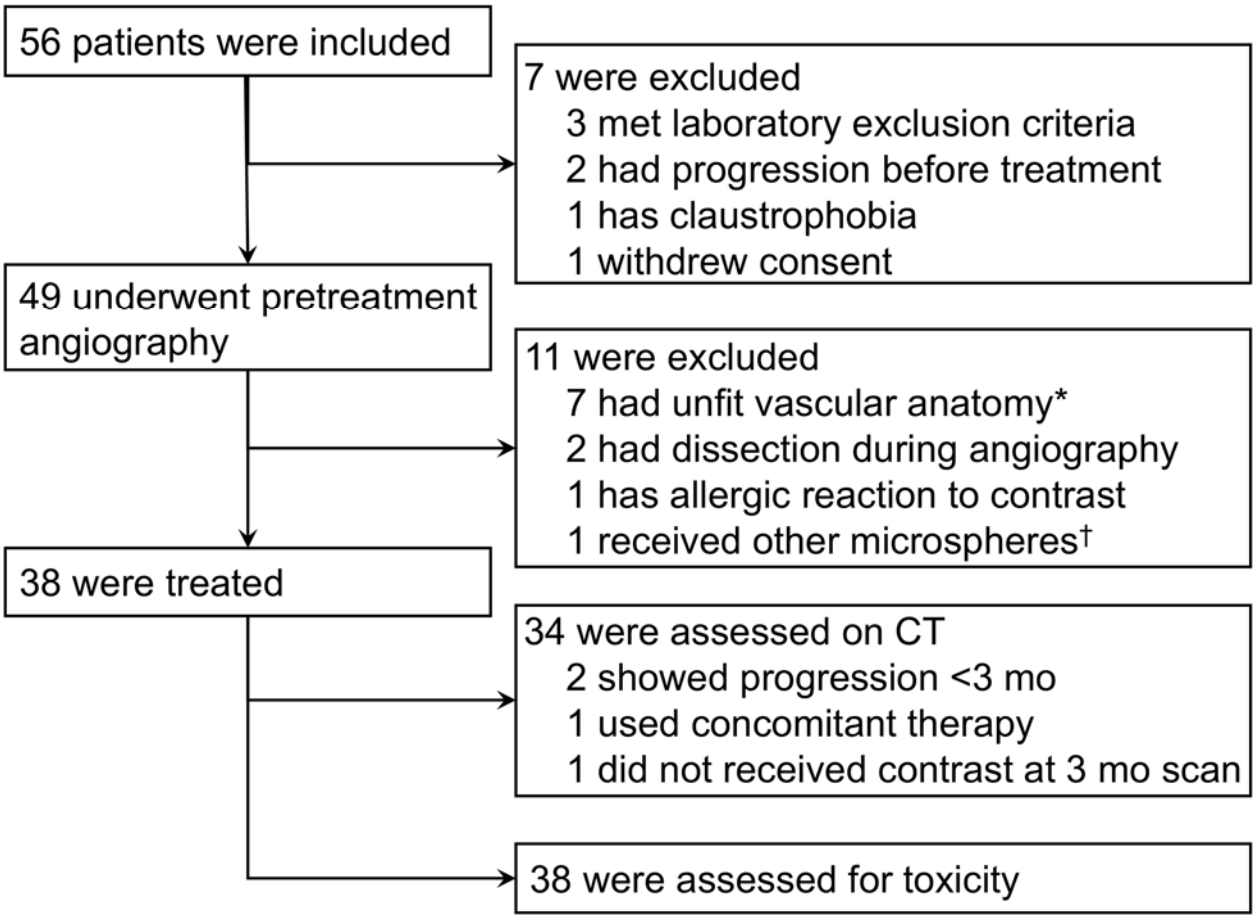

Figure 1. Flowchart of study. * Metastases could not be adequately targeted, extrahepatic tissue was also targeted, or too many injection positions. † Laboratory experiments indicated a need to optimize the microspheres production process, treatments were halted until it was complete.

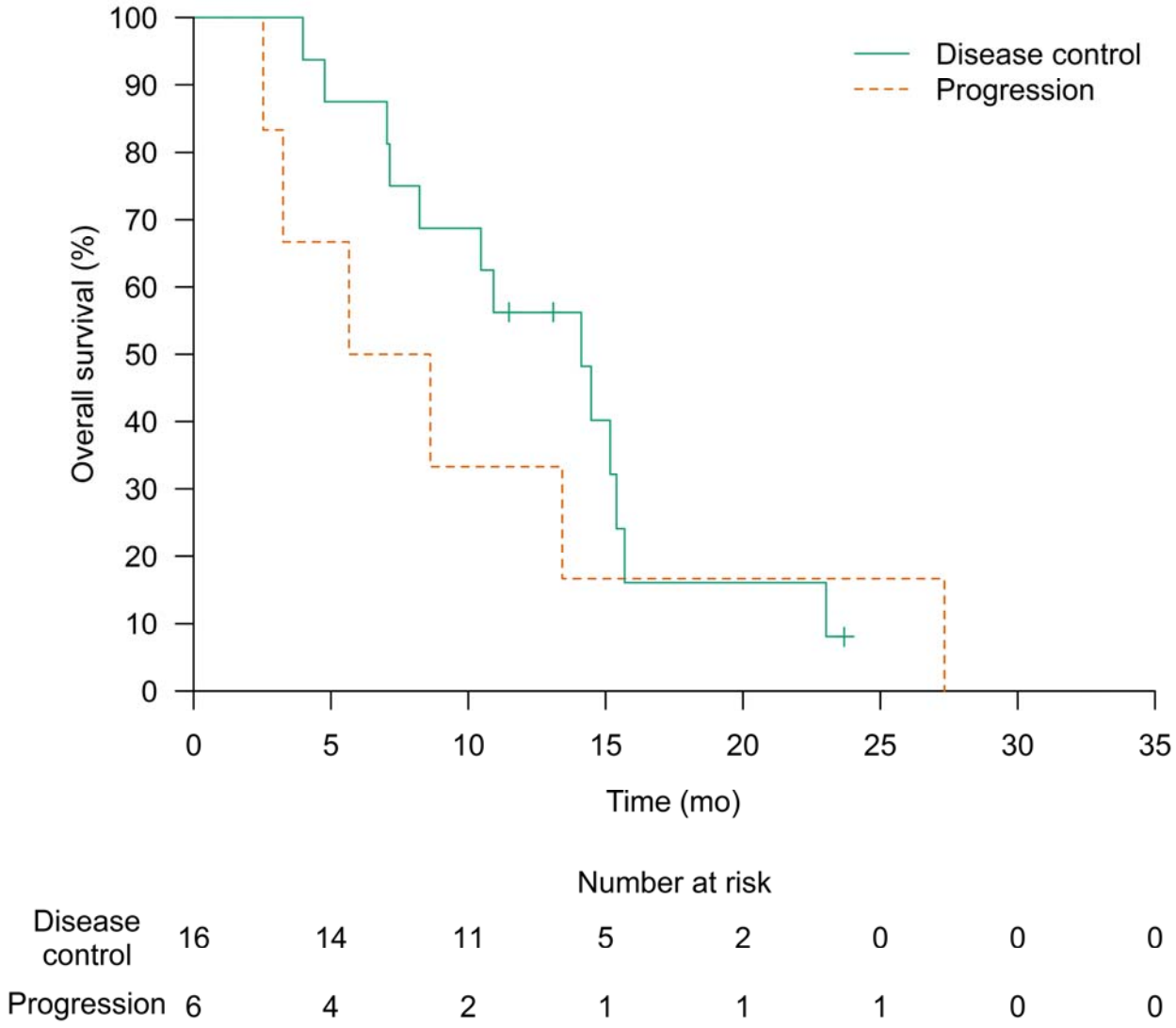

Figure 2. Kaplan-Meier estimate of median overall survival was 14.1 months (95% CI, 8.2 – ∞ months) for patients with colorectal disease and disease control of target lesions at 3 months and 7.1 months (95% CI, 3.3 to ∞ months) for patients with progressive target lesions at 3 months (p = 0.44). One patient missing (see Fig. 1).

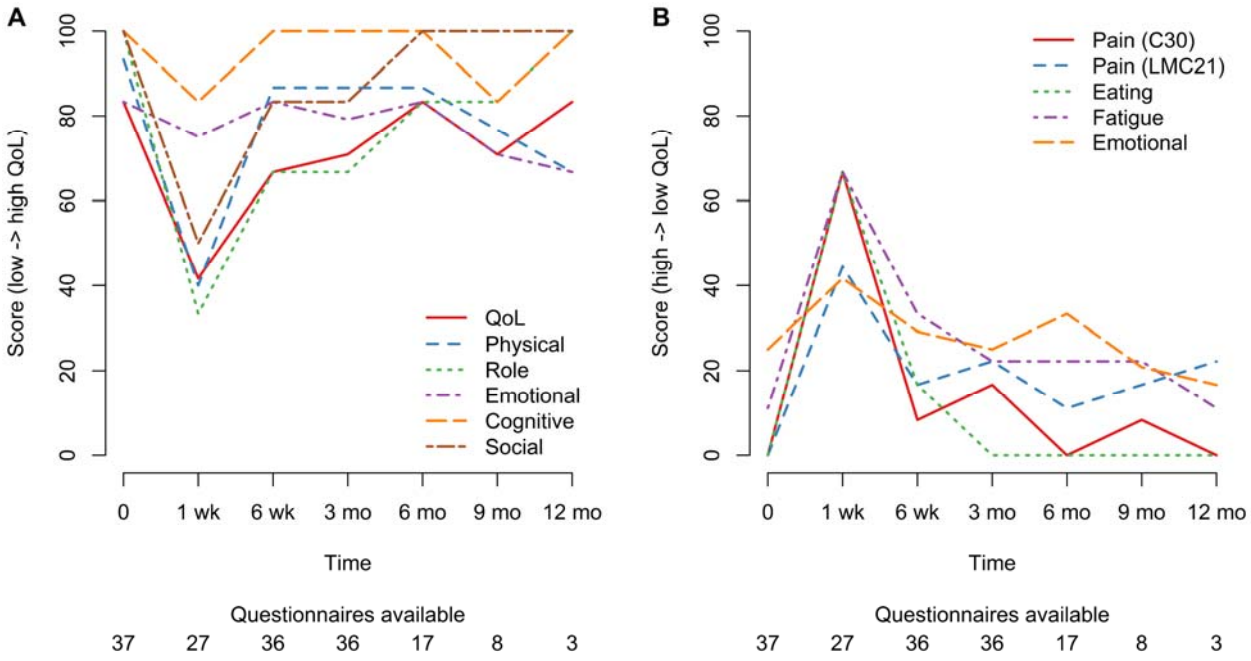

Figure 3. Quality of life (QoL, A, higher is better QoL) and symptom scores (B, higher is lower QoL), median per time point.

TABLES

Table 1. Baseline and treatment characteristics of treated patients (n=38)

Characteristic	Value	Characteristic	Value
Age (years)	66 (41–84)	Extrahepatic disease on ^{18}F-FDG-PET/CT	
Sex		Lung	8/10 (80%)
Male	22 (58%)	Lymph node	4/10 (40%)
Female	16 (42%)	Skeletal	2/10 (20%)
WHO performance status		Liver mass (kg)	2.0 (1.2–4.0)
0	32 (84%)	Tumor load on CECT.	
1	5 (13%)	0%-25%	30 (79%)
2	1 (3%)	25%-50%	6 (16%)
Primary malignancy		>50%	2 (5%)
Colorectal	23 (61%)	Targeted liver lobe(s)	
Breast	4 (11%)	Whole liver	36 (95%)
Cholangiocarcinoma	4 (11%)	Right lobe	2 (5%)
Neuroendocrine tumor	2 (5%)	Left lobe	0 (0%)
Uveal melanoma	2 (5%)	Treatment sessions	
Other*	3 (8%)	1	36 (95%)
Time since diagnosis (months)	28 (4-95)	2	2 (5%)
Occurrence of liver metastases		Specific activity (MBq/mg) †	11,26 (4,95–21,34)
Synchronous	19 (50%)	Infused activity (MBq) †	6,412 (2,213–13,189)
Metachronous	19 (50%)	Administration of treatment dose (% of prepared)	96% (41%-99%)
Time since liver metastases (months)	28 (3-92)	Adequate administration of activity (>90%) ‡	26/37 (70%)
Chemotherapy (colorectal)		Average absorbed liver dose (Gy)	51 (26-69)
N	23 (100%)	Predicted lung shunt (^{99m}Tc-MAA)	3.2% (0.01%–19.3%)
Capecitabine	22 (96%)	Actual lung shunt (^{166}Ho)	0.02% (0%–0.7%)
Oxaliplatin	21 (91%)		
Bevacizumab	14 (61%)		
Irinotecan	11 (48%)		
5-Fluorouracil	6 (26%)		
Leucovorin	5 (22%)		
Panitumumab	4 (17%)		
Cetuximab	1 (4%)		
Dabrafenib	1 (4%)		
Tegafur-uracil	1 (4%)		

Data are n (%), n/N (%), median (range), or as specified. CECT = contrast enhanced CT. WHO = World Health Organization

* Pancreatic cancer, gastric cancer, and thymoma.

† All injections combined (including scout dose), at respective time of injection.

‡ §In other patients, stasis occurred or the infusion was stopped because of pain.

Table 2. Response on Contrast Enhanced CT			
Category of response	**Target lesions**	**Liver specific**	**Abdomen**
3 months			
Complete response	-	-	-
Partial response	5 (14%)	5 (14%)	5 (14%)
Stable disease	22 (59%)	13 (35%)	9 (24%)
Progressive disease*	10 (27%)	19 (51%)	23 (62%)
Total	37 (100%)	37 (100%)	37 (100%)
6 months			
Complete response	1 (3%)	1 (3%)	1 (3%)
Partial response	2 (5%)	2 (5%)	2 (5%)
Stable disease	10 (26%)	4 (11%)	3 (8%)
Progressive disease*	25 (66%)	31 (82%)	32 (84%)
Total	38 (100%)	38 (100%)	38 (100%)
9 months			
Complete response	1 (3%)	1 (3%)	1 (3%)
Partial response	1 (3%)	-	-
Stable disease	2 (5%)	1 (3%)	1 (3%)
Progressive disease*	34 (89%)	36 (95%)	36 (95%)
Total	38 (100%)	38 (100%)	38 (100%)
12 months			
Complete response	-	-	-
Partial response	-	-	-
Stable disease	2 (5%)	-	-
Progressive disease*	36 (95%)	38 (100%)	38 (100%)
Total	38 (100%)	38 (100%)	38 (100%)

Date are n (%). Timing was at a median of 90 days (range, 76 – 104 days) after treatment at three months, 181 days (152 – 195) at six months, 278 days (252 – 312) at nine months and 369 days (368 – 369) at 12 months.

* Not evaluable and/or missing patients imputed as progressive disease

Table 3. Adverse events - clinical				
Adverse Event	**Any time**	**≤1 week**	**>1 week**	**Grade 3 or 4**
Nausea	74% (28)	71% (27)	34% (13)	8% (3)
Abdominal Pain	71% (27)	68% (26)	47% (18)	18% (7)
Fatigue	66% (25)	26% (10)	61% (23)	3% (1)
Vomiting	66% (25)	58% (22)	18% (7)	3% (1)
Back Pain	34% (13)	24% (9)	11% (4)	0
Anorexia	26% (10)	13% (5)	21% (8)	0
Edema limbs	18% (7)	0	18% (7)	0
Fever	18% (7)	11% (4)	11% (4)	0
Constipation	16% (6)	5% (2)	11% (4)	0
Dizziness	16% (6)	11% (4)	11% (4)	0
Allergic reaction	13% (5)	13% (5)	5% (2)	0
Arthralgia	13% (5)	3% (1)	11% (4)	0
Dyspnea	13% (5)	0	13% (5)	0
Shoulder pain	13% (5)	5% (2)	11% (4)	0
Ascites	11% (4)	0	11% (4)	3% (1)
Chills	11% (4)	0	11% (4)	0
Dysgeusia	11% (4)	3% (1)	11% (4)	0
Gastric stenosis	3% (1)	0	3% (1)	3% (1)
Hepatic failure*	3% (1)	0	3% (1)	3% (1)
Liver abscesses	3% (1)	0	3% (1)	3% (1)
Paroxysmal atrial tachycardia	3% (1)	0	3% (1)	3% (1)
Thoracic pain	3% (1)	3% (1)	3% (1)	3% (1)
Upper gastrointestinal hemorrhage	3% (1)	0	3% (1)	3% (1)

Adverse events with incidence of >10% or CTCAE grade 3 or 4, after treatment, regardless of relation with ^{166}Ho radioembolization.

* We suspected a mix of disease progression and radioembolization induced liver disease. This patient is also included in the parameter 'Ascites'.

Table 4. Adverse events – laboratory examinations				
Laboratory examination	**Grade 1-2**	**Grade 3**	**Grade 4**	**NA**
Gamma-glutamyl transferase	6	28	4	0
Lymphocytopenia	15	6	1	0
Bilirubin	12	0	1	0
Alkaline phosphatase	32	6	0	0
Aspartate aminotransferase	35	3	0	0
Alanine aminotransferase	28	2	0	0
Lactate dehydrogenase	27	0	0	0
Hemoglobin	26	0	0	0
Ammonia	22	0	0	0
Albumin	20	0	0	0
Platelet count	19	0	0	0
Erythrocytes	15	0	0	0
Sodium	15	0	0	2
Leukocytes	14	0	0	0
Creatinine	12	0	0	0
Potassium	9	0	0	2
Total protein	9	0	0	4
Calcium (ionized)	8	0	0	3
Magnesium	6	0	0	4
Phosphorus	6	0	0	3
Urea	6	0	0	3
Chloride	5	0	0	4
Bicarbonate	4	0	0	4

Maximum CTCAE grade of adverse event during follow up after treatment is shown, some of which are pre-existent. NA = not available.

SUPPLEMENTAL TABLES AND FIGURES

Table S1 Quality of life							
Scale	**Baseline** (*n*=37)	**1 week** (27)	**6 weeks** (36)	**3 months** (36)	**6 months** (17)	**9 months** (8)	**12 months** (3)
QLQ-C30							
QoL	83 (67 - 83)	42 (25 - 71)	67 (56 - 83)	71 (58 - 83)	83 (67 - 92)	71 (54 - 88)	83 (58 - 92)
Physical Functioning	93 (87 - 100)	40 (20 - 83)	87 (67 - 93)	87 (67 - 100)	87 (73 - 93)	77 (63 - 95)	67 (57 - 83)
Role Functioning	100 (83 - 100)	33 (0 - 42)	67 (50 - 100)	67 (62 - 100)	83 (67 - 100)	83 (62 - 100)	100 (67 - 100)
Emotional Functioning	83 (75 - 92)	75 (54 - 96)	83 (67 - 100)	79 (67 - 92)	83 (67 - 92)	71 (62 - 83)	67 (67 - 79)
Cognitive Functioning	100 (83 - 100)	83 (67 - 100)	100 (83 - 100)	100 (83 - 100)	100 (67 - 100)	83 (75 - 100)	100 (83 - 100)
Social Functioning	100 (67 - 100)	50 (33 - 83)	83 (67 - 100)	83 (67 - 100)	100 (83 - 100)	100 (62 - 100)	100 (67 - 100)
Fatigue	11 (0 - 22)	67 (44 - 100)	33 (22 - 56)	22 (11 - 56)	22 (0 - 33)	22 (8 - 56)	22 (11 - 50)
Nausea and vomiting	0 (0 - 0)	33 (17 - 67)	0 (0 - 17)	0 (0 - 17)	0 (0 - 0)	0 (0 - 17)	0 (0 - 8)
Pain	0 (0 - 0)	67 (33 - 83)	8 (0 - 33)	17 (0 - 33)	0 (0 - 17)	8 (0 - 42)	0 (0 - 33)
Dyspnea	0 (0 - 33)	0 (0 - 33)	0 (0 - 33)	0 (0 - 33)	0 (0 - 67)	33 (0 - 33)	67 (33 - 67)
Insomnia	0 (0 - 33)	33 (0 - 67)	17 (0 - 33)	17 (0 - 33)	33 (0 - 33)	33 (25 - 42)	33 (17 - 33)
Appetite loss	0 (0 - 0)	33 (33 - 100)	0 (0 - 33)	0 (0 - 33)	0 0 - 33)	0 (0 - 8)	0 (0 - 0)
Constipation	0 (0 - 0)	33 (0 - 67)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)
Diarrhea	0 (0 - 33)	0 (0 - 0)	0 (0 - 0)	0 (0 - 33)	0 (0 - 33)	17 (0 - 33)	0 (0 - 17)
Financial difficulties	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 17)
QLQ-LMC21							
Eating	0 (0 - 17)	67 (38 - 83)	17 (0 - 33)	0 (0 - 33)	0 (0 - 33)	0 (0 - 17)	0 (0 - 8)
Fatigue	11 (0 - 33)	67 (44 - 94)	33 (19 - 44)	22 (6 - 39)	22 (11 - 33)	22 (11 - 53)	11 (6 - 44)
Pain	0 (0 - 11)	44 (22 - 67)	17 (0 - 33)	22 (0 - 33)	11 (0 - 33)	17 (11 - 39)	22 (11 - 22)

Emotional problems	25 (17 - 42)	42 (17 - 58)	29 (17 - 42)	25 (17 - 42)	33 (17 - 33)	21 (17 - 44)	17 (17 - 33)
Weight loss	0 (0 - 0)	0 (0 - 0)	0 (0 - 8)	0 (0 - 0)	0 (0 - 33)	0 (0 - 33)	0 (0 - 0)
Taste	0 (0 - 0)	0 (0 - 67)	0 (0 - 33)	0 (0 - 33)	0 (0 - 0)	0 (0 - 8)	0 (0 - 0)
Dry mouth	0 (0 - 33)	0 (0 - 50)	0 (0 - 33)	0 (0 - 33)	0 (0 - 33)	33 (0 - 67)	33 (17 - 33)
Sore mouth/tongue	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 17)
Peripheral neuropathy	33 (0 - 33)	0 (0 - 33)	33 (0 - 67)	33 (0 - 33)	0 (0 - 33)	0 (0 - 33)	33 (17 - 33)
Jaundice	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)
Contact with friends	0 (0 - 0)	33 (0 - 67)	0 (0 - 8)	0 (0 - 33)	0 (0 - 33)	0 (0 - 33)	0 (0 - 33)
Talking about feelings	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 33)	0 (0 - 0)	17 (0 - 33)	0 (0 - 17)
Sex life	0 (0 - 33)	17 (0 - 67)	33 (0 - 33)	33 (0 - 33)	0 (0 - 33)	50 (8 - 67)	0 (0 - 33)

Median score (interquartile range). QLQ-C30: quality of life questionnaire – common 30, QLQ-LMC21: quality of life – colorectal liver metastases 21

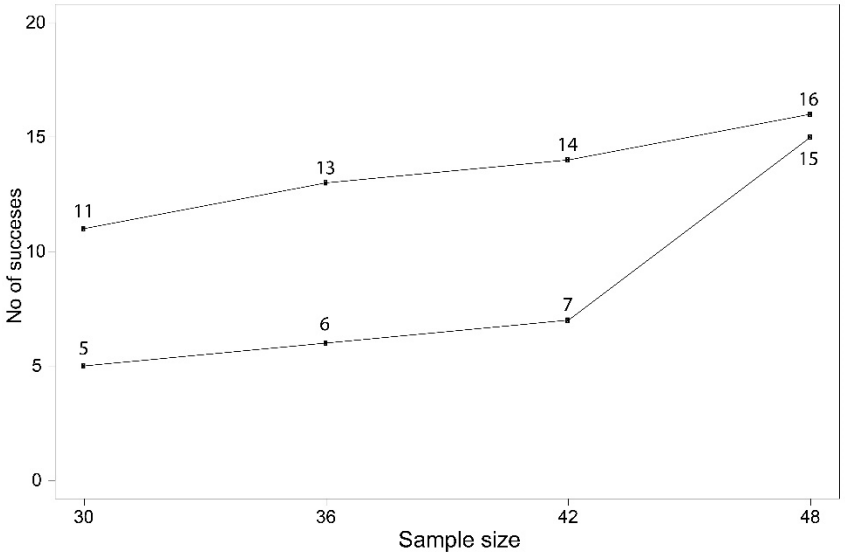

Figure S1. Stopping boundaries for futility and efficacy based on an exact sequential study design that aimed for a type I error ≤5%. The exact power of this design was 90%. Efficacy was seen at first interim analysis, when 24 out of 30 patients showed a response.

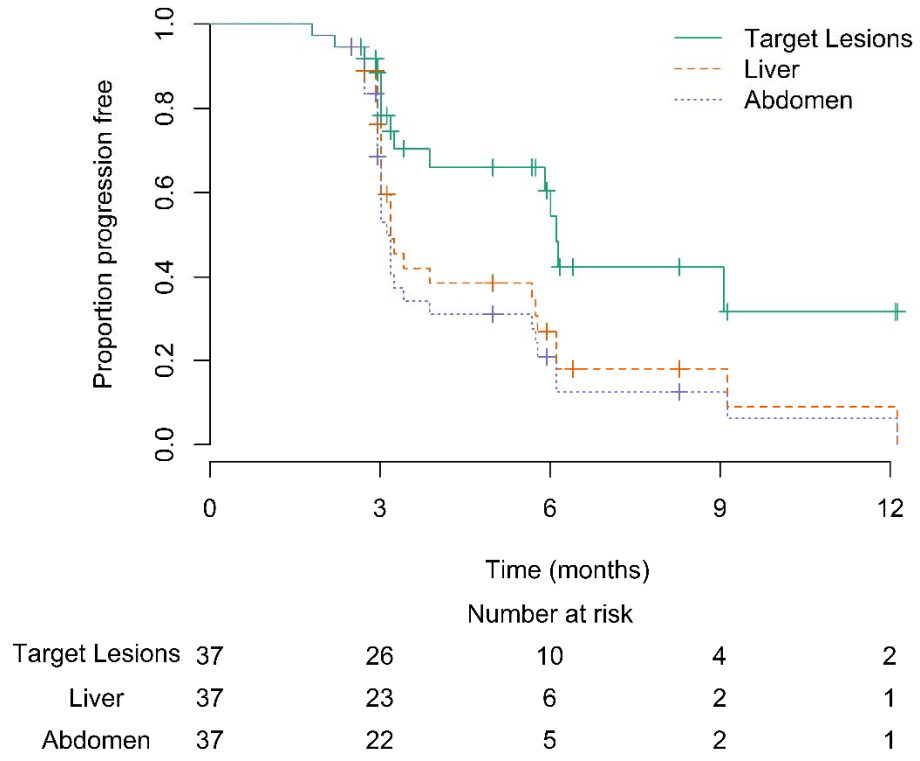

Figure S2. Kaplan-Meier estimate of median time to progression was 6 mo (95% CI, 6 mo - ∞) for target lesions, 3 mo (95% CI, 3 – 6 mo) for liver specific and 3 mo (95% CI, 3 – 6 mo) for whole body.

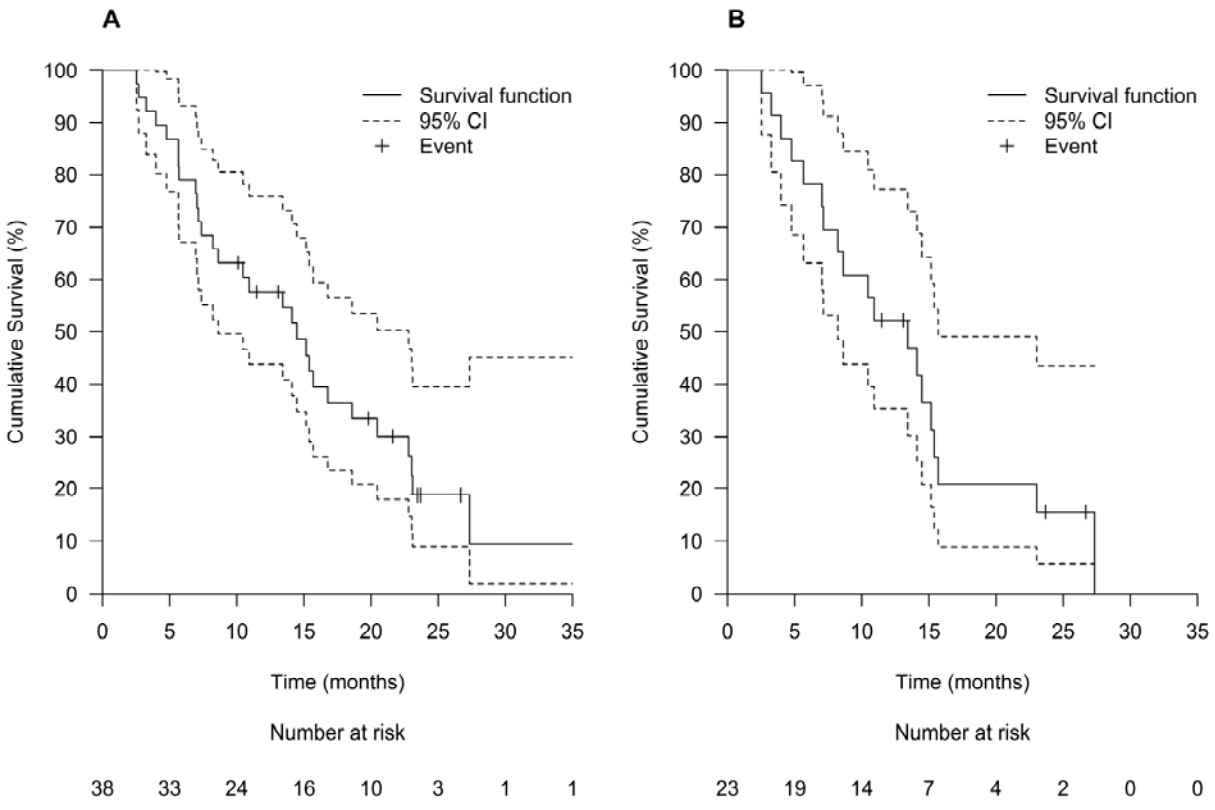

Figure S3. Kaplan-Meier estimate of median overall survival was 14.5 months (95% CI, 8.6 to 22.8 months) for all patients (A) and 13.4 months (95% CI, 8.2 – 15.7 months) for colorectal cancer patients (B)