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Safety and efficacy of holmium-166 radioembolization in hepatocellular carcinoma – the HEPAR Primary study

Running title: Holmium-166 radioembolization in HCC

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ABSTRACT

Safety and efficacy of ^{166}Ho-radioembolization was first determined in the HEPAR and HEPAR II studies, however excluding patients with hepatocellular carcinoma (HCC). The aim of this prospective clinical early phase II study was to establish the toxicity profile of ^{166}Ho-radioembolization in patients with measurable, liver-dominant HCC, BCLC stage B-C, Child-Pugh (CP) score ≤B7, ECOG 0-1 without curative treatment options.

The primary endpoint was rate of unacceptable toxicity defined as grade 3 hyperbilirubinemia (Common Terminology Cancer Adverse Events version 4.03) in combination with low albumin and/or ascites in the absence of disease progression or treatment-related serious adverse events (SAEs). Secondary endpoints included overall toxicity, response, survival, change in α-fetoprotein (AFP), and quality of life.

Thirty-one patients with BCLC stage B (71%) or C (29%) HCC were included, mostly multifocal (87%) bilobar (55%) disease. Common grade 1-2 clinical toxicity included fatigue (71%), back pain (55%), ascites (32%), dyspnea (23%), nausea (23%), and abdominal pain (23%), with no >10% grade 3-5 toxicity. Grade 3 laboratory toxicity (>10%) included AST and GGT increase (16%), hyperglycemia (19%), and lymphopenia (29%). Treatment-related unacceptable toxicity occurred in 3/31 patients. At three months, 54% of target lesions showed complete or partial response according to mRECIST. Median overall survival was 14·9 months (95% confidence interval (CI) 10·4 months-24.9 months). No significant changes in quality of life or pain were observed.

^{166}Ho-radioembolization safety was confirmed in HCC with <10% unacceptable toxicity. Efficacy data support further evaluation.

INTRODUCTION

The treatment landscape for patients with HCC consists of transplantation, resection, locoregional treatment options (including ablation, transarterial chemoembolization (TACE) and radioembolization), and systemic treatment options (targeted therapy and immunotherapy).(*1-3*) Despite therapeutic advances, prognosis remains poor. Only a minority of patients is eligible for curative treatment (e.g. transplantation, resection, and in some cases ablation). Yttrium-90 (^{90}Y) radioembolization is often used in selected patients with HCC without curative treatment options.(*4*)

Microspheres loaded with holmium-166 (^{166}Ho) are commercially available (QuiremScout® and QuiremSpheres®, Quirem Medical B.V., Deventer, the Netherlands) since 2015. The radioactive isotope ^{166}Ho is a high-energy beta-emitting isotope with a maximum energy of 1.85 MeV (50.0%) and 1.77 MeV (48.7%), comparable with 2.28 MeV for ^{90}Y, but with a half-life of 26.8 hours, which is approximately half that of ^{90}Y (i.e. 64 hours). The main advantage compared with ^{90}Y is the abundancy of gamma photons (81 keV, 6.7%) that can be used for single-photon emission computed tomography/computed tomography (SPECT/CT) imaging.(*5*) Furthermore, the lanthanide ^{166}Ho has paramagnetic properties, so MRI can also be used to image the distribution in the liver and quantify the absorbed dose in the tumors.(*6*) These unique characteristics improve pre- and post-therapeutic imaging options, enabling dosimetry-based individualized treatment planning. The mean diameter of ^{166}Ho-microspheres is 30 micrometer (µm) with a range of 15-60 µm, comparable with both types of ^{90}Y-microspheres. The density of ^{166}Ho-microspheres is 1.4 g/cm^3, which is comparable to the density of resin ^{90}Y-microspheres, but lower than glass ^{90}Y-microspheres.

Safety and efficacy of ^{166}Ho-radioembolization was first determined in the HEPAR and HEPAR II studies in patients with liver metastasis of different types of cancer origin, excluding HCC.(*7,8*) The aim of this clinical early phase II study was to establish the safety and toxicity profile of ^{166}Ho-radioembolization in patients with HCC.

MATERIALS AND METHODS

Study Population and Design

The HEPAR Primary study (NCT03379844) was a multicenter, interventional, non-randomized, non-comparative, open label, early phase II study in patients with BCLC stage B-C HCC, treated between 28 Jan 2018 and 18 Feb 2020. The study protocol was approved by the independent Medical Ethics Committee and was performed in accordance with Good Clinical Practice (GCP) and the declaration of Helsinki. All participants provided written, informed consent.

Main in- and exclusion criteria: ≥18 years with a life expectancy of at least six months, HCC according to criteria of the American Association for the Study of Liver Disease (AASLD)(*9*), measurable lesion(s) based on (modified) response evaluation criteria in solid tumors (RECIST 1.1 and mRECIST) criteria, liver-dominant disease (maximum five lung nodules all ≤1·0 cm, and mesenteric or portal lymph nodes all ≤2·0 cm), no curative treatment options, Child-Pugh (CP) ≤B7, Eastern Cooperative Oncology Group (ECOG) 0-1, no prior radioembolization, no main brach portal vein thrombosis (PVT).

Study Procedures

All patients were discussed in a multidisciplinary oncology board. Screening consisted of laboratory and physical examination, contrast-enhanced liver CT, liver MRI, hepatobiliary scintigraphy, and endoscopy of the upper gastrointestinal tract.

Patients received ondansetron 8 mg and dexamethasone 10 mg intravenously one hour before angiography. Ursodeoxycholic acid 300 mg twice daily was given for two months, prednisolone 10 mg daily for a month and 5 mg daily for the subsequent month (two months in total) to reduce the chance of radioembolization induced liver disease, besides pantoprazole 40mg daily for six weeks.(*10*)

A sheath was placed in the common femoral or radial artery and a microcatheter was placed in the tumor-feeding artery/arteries. C-arm CT was performed at each intended target position. Then, a scout dose of ^{166}Ho-microspheres was administered for treatment simulation (QuiremScout®, 250 MBq, approximately three million microspheres). The sheath stayed in situ, during SPECT-CT imaging. Patients received treatment via a microcatheter at exactly the same position during a second angiography the same day.

The intended average perfused volume absorbed dose was 60 Gy: A (MBq) = 3·781 x W (g), where A is the prescribed activity in MBq and W is the target liver mass in grams(1 mL = 1·04 gram).(*7,8*) Approximately 24 hours after treatment, MRI was acquired and patients were discharged. Three to five days after treatment, the patients came back for a post-treatment SPECT-CT. This SPECT-CT was delayed to prevent detector dead-time caused by the abundance of γ-photons.(*5*)

Post-treatment follow-up at three and six weeks, three and six months included blood and physical examinations, questionnaires, hepatobiliary scintigraphy (at three months), and MRI (at three and six months)(supplemental Table 1). Adverse events (AEs) were assessed according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Furthermore, European Organization for Research and Treatment of Cancer (EORTC) Quality of life C30 and HCC18 questionnaires, and Brief Pain Inventory Short forms (BPI) were obtained during screening, shortly after treatment and during follow-up.

Two independent radiologists, who were not involved in study proceedings, performed blinded and random response assessment. In case of discordant response assessment, a third radiologist was consulted to determine the final response category.

Quarterly interim safety analyses were presented to an independent Data Safety Monitoring Board (DSMB).

Endpoints

The primary endpoint was the rate of unacceptable toxicity using CTCAE methodology, which was defined as grade 3 hyperbilirubinemia in combination with ascites and low albumin in the absence of disease

progression (i.e. radioembolization induced liver disease) or any serious adverse event or serious device defect, possibly, probably or causally related to treatment. Secondary endpoints included treatment efficacy, liver function and quality of life. Dosimetric evaluation of pre- and post-treatment imaging fall outside the scope of this study.

Statistical Analysis

As a null hypothesis (H0) it was assumed that the probability of unacceptable toxicity (pT) was 10% and the alternative (H1) was pT is 25%. Unacceptable toxicity of 10% or less was considered acceptable and 25% or more was not. Consequently, a sample size of 30 patients was deemed appropriate. Power (85%) quantified the probability of stopping the study early if toxicity was unacceptably high (type II error, 15%), which was arguably of equal importance as wrongly stopping the study in the absence of true high toxicity (type I error, 15%), in line with previous reports.(*7*,*8*)

Results shown are based on the 'per protocol set', comprised of patients who received both scout and therapeutic ^{166}Ho-microspheres. Overall survival was calculated from the date of treatment until the date of death by any cause or end of registration January 1st, 2022. Kaplan-Meier curves and log-rank tests were used to evaluate overall survival. Comparison of responders (CR or PR) and non-responders (PD or stable disease) was performed using landmark analysis with first and second response assessment. Variables with a two sided p-value <0.05 were deemed significant. Statistical analyses were performed using RStudio version 1.2.5019.

RESULTS

From 15 Dec 2017 until 22 Jan 2020, 41 patients were included in the study. Eight patients failed screening: main branch PVT (n=2), rapid tumor progression (n=2), alternative treatment (n=1), dismal liver function (n=1), low GFR (n=1), or worsened ECOG (n=1). Two additional patients discontinued because of significant

lung shunt , and/or alternative treatment. A total of 31 patients were treated with a scout and therapeutic dose of ^{166}Ho-microspheres (Figure 1).

Baseline patient characteristics are given in Table 1. No cases with cavernous transformation were present. One patient previously underwent hemihepatectomy (right) followed by radiofrequency ablation of S3 and S2/3. One patient underwent resection of S6-7, then hemihepatectomy (right), followed by microwave ablation of S4, TACE and wedge resection of S2. One patient underwent resection of S5-6 and microwave ablation of S4a. One patient underwent resection of S4b/5. Finally, one patient previously underwent radiofrequency ablation of S6/7.

Treatment characteristics are summarized in Table 2. Unilobar treatment was performed in 20/31 (64%) of the patients, bilobar treatment (i.e. with at least one segment preserved) in 9/31 (29%) and 2/31 (6%) whole liver treatments. Seven patients received a dose adjustment (median –45%; range –24-56%), because of low hepatic function based on hepatobiliary scintigraphy (n=4) or a per-procedural deviation from planned treatment strategy (n=3). Median target volume absorbed dose was 56 Gy (range 27-90 Gy) and 23 patients received their intended dose. Twenty-eight patients received one-day treatment. Three patients were treated with an interval of seven days (n=1), 35 days (reversible renal dysfunction: n=1), and 168 days (malfunctioning aortic valve necessitating transarterial valve insertion first: n=1). Median treatment efficiency, prescribed versus net administered activity, was 95% (range 74-100%). Based on SPECT-CT imaging, median anticipated lung dose resulting from shunting was 1 Gy (range 0-16 Gy).

According to CTCAE, 120 laboratory adverse events were recorded, with no grade 4-5 events (Table 3). Furthermore, 168 clinical adverse events were observed, ranging from grade 1-5 (Table 4 and supplemental Tables 2 and 3). The vast majority of patients experienced a grade 1-2 increase in liver enzymes, with maximum grade 3 AST increase in 5/31 (16%) of the patients. However, the dynamic trajectory of these changes during six months follow-up did not show a clear peak or slope. Grade 2 or higher hematological toxicity rarely occurred, besides expected lymphopenia. Patients with diabetes mellitus type II (n=14)

experienced a high number of hyperglycemic adverse events, probably due to medication after treatment (i.e. steroids). Sixteen patients experienced grade 1 and one patient grade 2 back pain on the day of treatment as they had to hold supine position while undergoing a one-day procedure.

Nineteen serious adverse events occurred, of which four events in three patients were related to treatment (three possibly related and one definitely related). Two of these treatment-related events were from spontaneous bacterial peritonitis (both originated approximately 12 weeks after treatment). One patient deceased due to the infection after one day (treated with iv antibiotics) and the other patient recovered after five days (treated with iv and oral antibiotics). The third patient with BCLC stage B, multifocal HCC, ECOG 0, previously treated with resection and microwave ablation, suffered from radiation-induced cholecystitis and cholangitis one month after treatment, which developed into biliary fistula (grade 3 bilirubin increase), and finally stabilized after endoscopic intervention. His liver function and clinical performance gradually declined until his death one year after treatment. Unrelated serious adverse events occurred more often in BCLC stage C patients (5/9 (56%)) compared to BCLC stage B patients (4/22 (18%), p=0.036). Treatment approach (i.e. uni- vs. bilobar) or previous liver-directed surgery could not be identified as a predictor of toxicity.

Median MELD score was 9 (range 6-16) at baseline and worsened to 10 (range 7-20) at six months after treatment. During six months follow-up CP scores fluctuated (Figure 2). The three patients that experienced worsening of CP score with 3 or 4 points (besides the patient with biliary fistula) had proven progression of disease. These patients received unilobar treatments and showed no signs of radioembolization induced liver disease during the first three months after treatment. Two other patients died of progressive disease and hepatic failure within six months (considered unlikely related to treatment). Stratification per Child Pugh score or ECOG did not show any significant differences.

Twenty-nine patients were evaluable according to RECIST 1.1 three months (deceased (n=2)), and 20 patients six months after treatment (deceased (n=4), end of study because of disease progression (n=3),

lost-to-follow-up (n=3), no sufficient imaging quality (n=1)). Twenty-six patients were evaluable according to mRECIST at three months and 19 patients at six months.

Independent review of the MRI scans according to mRECIST resulted in 19% complete response (CR), 35% partial response (PR), 42% stable disease, and 4% progressive disease (PD) of the target liver lesions three months after treatment (Figure 3 and 4). Variable response specifically of the tumor thrombus in the portal vein in five patients was observed, with one CR, one PR, two stable disease and one lost-to-follow-up.

Five patients started sorafenib treatment and four patients received immunotherapy after study treatment. Median overall survival (OS) was 14.9 months (95% CI 10.4 months-24.9 months)(Figure 5). Median post-landmark OS of patients with either complete or partial response of the *total body* according to mRECIST at three months was 16.6 months (95% CI 8.72 months-NA), it was 13 months for non-responders (95%CI 8.95 months-NA, p=0.48). Median OS responders based on *target liver lesions* was not reached, for non-responders it was 12.8 months (95% CI 4.72-NA, p=0.046)(supplemental Figure 1).

Median AFP level was 20 µg/L (range 2.0-240,000 µg/L) at baseline, with median nadir 6.6 µg/L (range 2.0-120,000 µg/L; 67% decrease. At baseline, median liver function based on hepatobiliary scintigraphy was 5·3 %/min/m^2 (range 2.0-8.7) and three months after treatment it was 4.4 %/min/m^2 (range 1.8-9.2) (p=0.36).

No clinically relevant change in quality of life (supplemental Figure 2) or pain (supplemental Figure 3) was observed.

DISCUSSION

This first prospective study on ^{166}Ho-microspheres radioembolization in HCC confirmed safety. During and after ^{166}Ho-microspheres radioembolization, quality of life was maintained, pain and toxicity was mild and manageable. Furthermore, a pronounced anti-tumor effect was found.

A low activity scout dose of ^{166}Ho-microspheres can be used instead of the commonly used scout dose of technetium-99m (^{99m}Tc) macroaggregated albumin particles (^{99m}Tc-MAA), limited enough not to cause tissue damage.(*11*) In contrast with ^{99m}Tc-MAA, the scout dose of ^{166}Ho-microspheres is not administered as a bolus injection, but slowly. The extrahepatic (i.e. lung shunting) and intrahepatic dose distribution can be predicted more accurately in comparison with ^{99m}Tc-MAA.(*12,13*) A scout dose of ^{166}Ho-microspheres was superior with a median score of 4 vs. 2.5 for ^{99m}Tc-MAA ($p < 0.001$; visually assessed from 1-5), which was confirmed in a quantitative analysis. In contrast, in the SARAH trial, in which ^{99m}Tc-MAA was used as scout, only 52% 'optimal agreement' between pre-treatment ^{99m}Tc-MAA distribution and post-treatment resin ^{90}Y-microspheres distribution was found.(*14*)

The specific activity of ^{166}Ho-microspheres (i.e. ± 340 Bq/sphere) is higher than resin ^{90}Y-microspheres (i.e. ± 50 Bq/sphere) and lower than glass ^{90}Y-microspheres (i.e. ± 1250-2500 Bq/sphere). At lower specific activities a higher number of microspheres needs to be injected to reach the same absorbed dose. This is reflected in the relatively high incidence of adverse events related to the post-embolization syndrome in the current study (e.g. pain (22%), nausea (22%), fatigue (55%)). Moreover, differences in product characteristics will translate to different dose thresholds with regard to safety and efficacy, because of differences in dose distributions.(*15*) For Ho^{166} radioembolization in HCC, these dose thresholds need to be established for patient selection and treatment planning. In thirty-six patients with a total of 98 tumors from different metastatic origin, a significant difference was found between patients with complete or partial response (210 Gy; 95% CI, 161-274 Gy) and patients with progressive disease (116 Gy; 95% CI, 81-165 Gy).(*16*) Additionally, dose thresholds were confirmed in colorectal cancer, also looking at safety thresholds for non-tumorous liver tissue. The median parenchymal-absorbed dose was 37 Gy (range 12-55 Gy). The mean difference in parenchymal-absorbed dose for patients with CTCAE grade 0-2 versus CTCAE grade 3-5 was 12 Gy (95%CI 3.4-19.7, p=0.0070).(*17*) For HCC patients however, separate dose thresholds will need to be established,

including considerations with regard to treatment intent (i.e. palliative setting as in the current setting versus potential curative settings: radiation segmentectomy and lobectomy).(*18,19*)

These dosimetric considerations should be balanced with baseline patient characteristics, e.g. laboratory values, Child Pugh status, performance score, BCLC stage etc. Due to the relatively low number of patients in the current study, no definite conclusions could be drawn on patient selection. At the same time, differences in patient characteristics between studies also limit direct comparison. The SARAH, SIRveNIB and SORAMIC randomized controlled trials on resin ^{90}Y-microspheres radioembolization(*14,20-23*) and DOSISPHERE-01 study on glass ^{90}Y-microspheres radioembolization(*24*) included more advanced stage BCLC C, limiting toxicity and efficacy comparison. Nevertheless, 23% of adverse events grade 3 or higher, median overall survival of 14.9 months and a three-months response rate of 54% in the present study seems favorable. In the SARAH, SIRveNIB and SORAMIC trials, adverse events grade 3 or higher were observed in 27%, 28%, and 25% of the patients, respectively. Best overall response rate in the SARAH trial was 19%, reported best tumor response in the SIRveNIB trial was 23.1% and was not analyzed in the SORAMIC trial. The objective response rate was 35.7% in the patients in the DOSISPHERE-01 study treated based on a predefined average absorbed dose in the perfused volume, as was used in the present study.

One of the limitations of this study was the relatively limited number of patients included and the heterogeneous patient and disease characteristics, besides the fact that the study had a non-comparative design. In the current study, radioembolization treatment planning was performed according to a standard approach, regardless of tumor and functional liver dosimetry.(*25*) Single day treatment approach is beneficial from a patient perspective with regard to number of hospital visits, preparation and recovery.(*24,26*) However, a single day treatment strategy does not allow for dosimetry-based treatment planning since patient-specific treatment activity needs to be pre-ordered. Another limitation was the fact that the methods used for response evaluation ((m)RECIST) have inherent limitations (e.g. local vs. systemic evaluation, relation with OS), but contrast-enhancement on MRI may also be hampered by holmium-induced artifacts, since

^{166}Ho-microspheres cause loss of signal on the T1 MRI scans and makes it more difficult to measure viable tumor.(*6*)

Concomitant use of different therapies in patients with HCC is of special interest, for example adjuvant immunotherapy after resection or ablation to decrease the chance of recurrence.(*27*) But also the combination of immunotherapy with other local-regional treatment options, including TACE and radioembolization.(*28,29*) These combined approaches are expected to cause more toxicity, which may be seen as a clear call for more control. Radioembolization may offer that control by offering dosimetry-based individualized treatment planning. ^{166}Ho-microspheres radioembolization offers the unique combination of procedural control and individualized treatment by using a predictive scout dose of the exact same ^{166}Ho-microspheres and performing treatment planning based on accurate dosimetry.(*12*) However, dose thresholds for an effective tumor-absorbed dose and a safe functional liver-absorbed dose need to be established in larger series.

This interventional non-randomized study showed an acceptable low rate of ^{166}Ho- radioembolization-related serious toxicity (3 out of 31 patients; <10%) in patients with HCC. Furthermore, 54% of tumor lesions showed response (mRECIST) at three months after treatment. ^{166}Ho-radioembolization may be considered a safe and effective alternative treatment option in selected patients with BCLC B-C HCC.

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KEY POINTS

Question

Is holmium-166-radioembolization a safe treatment option for patients with hepatocellular carcinoma?

Pertinent findings

This interventional non-randomized study showed an acceptable low rate of homium-166 radioembolization-related serious toxicity (3 out of 31 patients; <10%) in patients with hepatocellular carcinoma. Furthermore, 54% of tumor lesions showed response (mRECIST) at three months after treatment.

Implications for patient care

Holmium-166-radioembolization may be considered a safe and effective alternative treatment option in selected patients with BCLC B-C HCC.

REFERENCES

1. Sangiovanni A, Colombo M. Treatment of hepatocellular carcinoma: beyond international guidelines. *Liver Int.* 2016;36 Suppl 1:124-129.

2. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *N Engl J Med.* 2020;382:1894-1905.

3. Johnston MP, Khakoo SI. Immunotherapy for hepatocellular carcinoma: Current and future. *World J Gastroenterol.* 2019;25:2977-2989.

4. Kallini JR, Gabr A, Salem R, Lewandowski RJ. Transarterial Radioembolization with Yttrium-90 for the Treatment of Hepatocellular Carcinoma. *Adv Ther.* 2016;33:699-714.

5. Elschot M, Nijsen JFW, Dam AJ, de Jong HWAM. Quantitative evaluation of scintillation camera imaging characteristics of isotopes used in liver radioembolization. *PLOS ONE.* 2011;6:e26174-e26174.

6. van de Maat GH, Seevinck PR, Elschot M, et al. MRI-based biodistribution assessment of holmium-166 poly(L-lactic acid) microspheres after radioembolisation. *Eur Radiol.* 2013;23:827-835.

7. Smits MLJ, Nijsen JFW, van den Bosch MAAJ, et al. Holmium-166 radioembolisation in patients with unresectable, chemorefractory liver metastases (HEPAR trial): a phase 1, dose-escalation study. *The Lancet Oncology.* 2012;13:1025-1034.

8. Prince JF, van den Bosch MAAJ, Nijsen JFW, et al. Efficacy of Radioembolization with (166)Ho-Microspheres in Salvage Patients with Liver Metastases: A Phase 2 Study. *J Nucl Med.* 2018;59:582-588.

9. Heimbach JK, Kulik LM, Finn RS, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology.* 2018;67:358-380.

10. Gil-Alzugaray B, Chopitea A, Iñarrairaegui M, et al. Prognostic factors and prevention of radioembolization-induced liver disease. *Hepatology.* 2013;57:1078-1087.

11. Braat A, Prince JF, van Rooij R, Bruijnen RCG, van den Bosch M, Lam M. Safety analysis of holmium-166 microsphere scout dose imaging during radioembolisation work-up: A cohort study. *Eur Radiol.* 2018;28:920-928.

12. Smits MLJ, Dassen MG, Prince JF, et al. The superior predictive value of (166)Ho-scout compared with (99m)Tc-macroaggregated albumin prior to (166)Ho-microspheres radioembolization in patients with liver metastases. *Eur J Nucl Med Mol Imaging.* 2019.

13. Elschot M, Nijsen JFW, Lam MGEH, et al. (^{99}m)Tc-MAA overestimates the absorbed dose to the lungs in radioembolization: a quantitative evaluation in patients treated with ^{166}Ho-microspheres. *Eur J Nucl Med Mol Imaging.* 2014;41:1965-1975.

14. Hermann AL, Dieudonné A, Ronot M, et al. Relationship of Tumor Radiation-absorbed Dose to Survival and Response in Hepatocellular Carcinoma Treated with Transarterial Radioembolization with (90)Y in the SARAH Study. *Radiology.* 2020:191606.

15. Pasciak AS, Abiola G, Liddell RP, et al. The number of microspheres in Y90 radioembolization directly affects normal tissue radiation exposure. *Eur J Nucl Med Mol Imaging.* 2020;47:816-827.

16. Bastiaannet R, van Roekel C, Smits MLJ, et al. First Evidence for a Dose-Response Relationship in Patients Treated with (166)Ho Radioembolization: A Prospective Study. *J Nucl Med.* 2020;61:608-612.

17. van Roekel C, Bastiaannet R, Smits MLJ, et al. Dose-Effect Relationships of (166)Ho Radioembolization in Colorectal Cancer. *J Nucl Med.* 2021;62:272-279.

18. Salem R, Padia SA, Lam M, et al. Clinical and dosimetric considerations for Y90: recommendations from an international multidisciplinary working group. *Eur J Nucl Med Mol Imaging.* 2019;46:1695-1704.

19. Levillain H, Bagni O, Deroose CM, et al. International recommendations for personalised selective internal radiation therapy of primary and metastatic liver diseases with yttrium-90 resin microspheres. *Eur J Nucl Med Mol Imaging.* 2021;48:1570-1584.

20. Vilgrain V, Pereira H, Assenat E, et al. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. *Lancet Oncol.* 2017;18:1624-1636.

21. Chow PKH, Gandhi M, Tan SB, et al. SIRveNIB: Selective Internal Radiation Therapy Versus Sorafenib in Asia-Pacific Patients With Hepatocellular Carcinoma. *J Clin Oncol.* 2018;36:1913-1921.

22. Ricke J, Bulla K, Kolligs F, et al. Safety and toxicity of radioembolization plus Sorafenib in advanced hepatocellular carcinoma: analysis of the European multicentre trial SORAMIC. *Liver Int.* 2015;35:620-626.

23. Ricke J, Klumpen HJ, Amthauer H, et al. Impact of combined selective internal radiation therapy and sorafenib on survival in advanced hepatocellular carcinoma. *J Hepatol.* 2019.

24. Garin E, Tselikas L, Guiu B, et al. Personalised versus standard dosimetry approach of selective internal radiation therapy in patients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): a randomised, multicentre, open-label phase 2 trial. *Lancet Gastroenterol Hepatol.* 2020.

25. Bastiaannet R, Kappadath SC, Kunnen B, Braat A, Lam M, de Jong H. The physics of radioembolization. *EJNMMI Phys.* 2018;5:22.

26. van Roekel C, Harlianto NI, Braat A, et al. Evaluation of the Safety and Feasibility of Same-Day Holmium-166 -Radioembolization Simulation and Treatment of Hepatic Metastases. *J Vasc Interv Radiol.* 2020;31:1593-1599.

27. Hack SP, Spahn J, Chen M, et al. IMbrave 050: a Phase III trial of atezolizumab plus bevacizumab in high-risk hepatocellular carcinoma after curative resection or ablation. *Future Oncol.* 2020;16:975-989.

28. Makary MS, Khandpur U, Cloyd JM, Mumtaz K, Dowell JD. Locoregional Therapy Approaches for Hepatocellular Carcinoma: Recent Advances and Management Strategies. *Cancers (Basel).* 2020;12.

29. Waidmann O. Recent developments with immunotherapy for hepatocellular carcinoma. *Expert Opin Biol Ther.* 2018;18:905-910.

Tables

Table 1: Baseline characteristics of the HEPAR Primary patients (total n=31).

	N (total n=31)	**%**
Gender		
Female	3	10
Male	28	90
Age (median (range))	73 (44-85)	
Cirrhosis on imaging	20	65
Underlying liver disease^		
Alcohol abuse	20	65
Hepatitis B	1	3
Hepatitis C	4	13
NASH	3	10
Hemochromatosis	2	4
None of the above	6	20
BCLC		
B	22	71
C	9	29
Bilirubin µmol/L (median (range))	12 (4-29)	
Albumin g/L (median (range))	38.5 (31-41.9)	
INR (median (range))	1.22 (0.94-1.94)	
Thrombocytes x10^9/L (median (range))	132 (75-464)	
Child Pugh score		
A5	19	61
A6	9	29
B7	3	10
MELD (median (range))	9 (6-16)	
ECOG performance status$		
0	18	58
1	13	42
Extrahepatic lesions		
None	27	87
Adrenal glands	4	13
Portal hypertension		
Thrombocytes <150	18	58
Varices		
Small	9	29
Large	2	6
Imaging	14	45
Portal vein thrombosis	6	19
- Tumor thrombus	4	13
- Non-tumor thrombus	1	3
- Mixed type	1	3
Bilobar disease*	17	55
Number of tumors		
1	4	13
2-3	4	13
3>	23	74
Tumor burden in % (median (range))	9.3 (0.5-46.8)	

Largest tumor diameter in mm (median (range))	56 (15[†]-195)	
Previous treatment[#]		
None	26	84
Resection	4	13
Ablation	4	13
TACE	1	1

[$] ECOG = Eastern Cooperative Oncology Group Performance Status

[^] Some patients had more than one underlying liver problem [†] Patient had more than 15 small lesions

* Only LIRADS-5 lesions were taken into account [#] Some patients had more than one previous treatment

Table 2: Procedure characteristics (results are given as median (range) or absolute numbers followed by percentages).

	N (Total n=31)	%
Liver volume (mL)	1941 (1036-3460)	
Treated fraction (%)	54 (16-100)	
Anticipated perfused volume average absorbed dose (n)		
Per protocol (60 Gy)	24	77
Dose adjustments	7	23
Actual perfused volume average absorbed dose (Gy)	50 (23-69)	
Treatment approach; all in one session (n)		
Unilobar	20	64
Bilobar (excluding some segments)	9	29
Whole liver	2	6
Number of injection positions (n)		
1	15	48
2	16	52
Interval scout-therapy (days)	0 (0-168)	
Prescribed activity (MBq)	3998 (1080-11451)	
Net administered activity (MBq)	3717 (1001-10420)	
Treatment efficiency (%)	95 (74-100)	
Lung shunt on SPECT-CT (Gy)	1 (0-16)	

Table 3: Laboratory adverse events according to CTCAE version 4.03. This table represents new and highest toxicity during six months follow-up. No laboratory adverse events grade 4 and 5 were observed.

CTCAE grade (v. 4.03)	**1**	**2**	**3**
AST increased	22/31 (71%)	2/31 (6%)	5/31 (16%)
Platelet count decreased	22/31 (71%)	1/31 (3%)	
INR increased	22/31 (71%)	2/31 (6%)	
AP increased	19/31 (61%)	5/31 (16%)	
Anemia	16/31 (52%)	5/31 (16%)	2/31 (6%)
ALT increased	15/31 (48%)	2/31 (6%)	
Hypoalbuminemia	14/31 (45%)	5/31 (16%)	1/31 (3%)
Prolonged APTT	13/31 (42%)	2/31 (6%)	
Hyponatremia	12/31 (39%)		3/31 (10%)
Hypokalemia	9/31 (29%)		
Hyperglycemia	9/31 (29%)	13/31 (42%)	6/31 (19%)
Creatinine increased	7/31 (23%)	1/31 (3%)	
Bilirubin increased	6/31 (19%)	4/31 (13%)	1/31 (3%)
GGT increased	5/31 (16%)	9/31 (29%)	14/31 (45%)
Hypoglycemia	3/31 (10%)		
Lymphopenia	1/31 (3%)	13/31 (42%)	9/31 (29%)

CTCAE = Common Terminology Criteria for Adverse Events version 4.03, AP= Alkaline phosphatase, GGT = γ-glutamyltransferase, AST = Aspartate trans aminotransferase, ALT = Alanine transferase, APTT = Activated Prothrombin Time, INR = International Normalized Ratio

Table 4: Clinical adverse events occurring >10% or grade 3-5 according to CTCAE version 4.03. This table represents new and highest toxicity during six months follow-up.

CTCAE grade (v. 4.03)	**1**	**2**	**3**	**4**	**5**
Back pain	16/31 (52%)	1/31 (3%)			
Fatigue	13/31 (42%)	4/31 (13%)			
Ascites	7/31 (23%)	2/31 (6%)	1/31 (3%)		
Dyspnea	7/31 (23%)				
Nausea	6/31 (19%)	1/31 (3%)			
Abdominal pain	4/31 (13%)	2/31 (6%)	1/31 (3%)		
Dizziness	4/31 (13%)				
Edema limbs	4/31 (13%)	1/31 (3%)			
Fever	4/31 (13%)				
Hepatic pain	4/31 (13%)				
Itch	3/31 (10%)	1/31 (3%)			
Abdominal infection			1/31 (3%)		
Allergic reaction			1/31 (3%)		
Arthritis			1/31 (3%)		
Atrial fibrillation			1/31 (3%)		
Bile duct stenosis			1/31 (3%)		
Biliary fistula			1/31 (3%)		
Cholecystitis			1/31 (3%)		
Endocarditis infective				1/31 (3%)	
Esophageal varices hemorrhage			2/31 (6%)		
Gastric hemorrhage			1/31 (3%)		
Hepatic failure					2/31 (6%)
Hip fracture			1/31 (3%)		
Intracranial hemorrhage					1/31 (3%)
Ischemia cerebrovascular					1/31 (3%)
Lung infection			1/31 (3%)		
Sepsis			1/31 (3%)		

CTCAE = Common Terminology Criteria for Adverse Events version 4.03

Figures

Figure 1: Flow diagram showing initial number of patients and those excluded for any given reason.

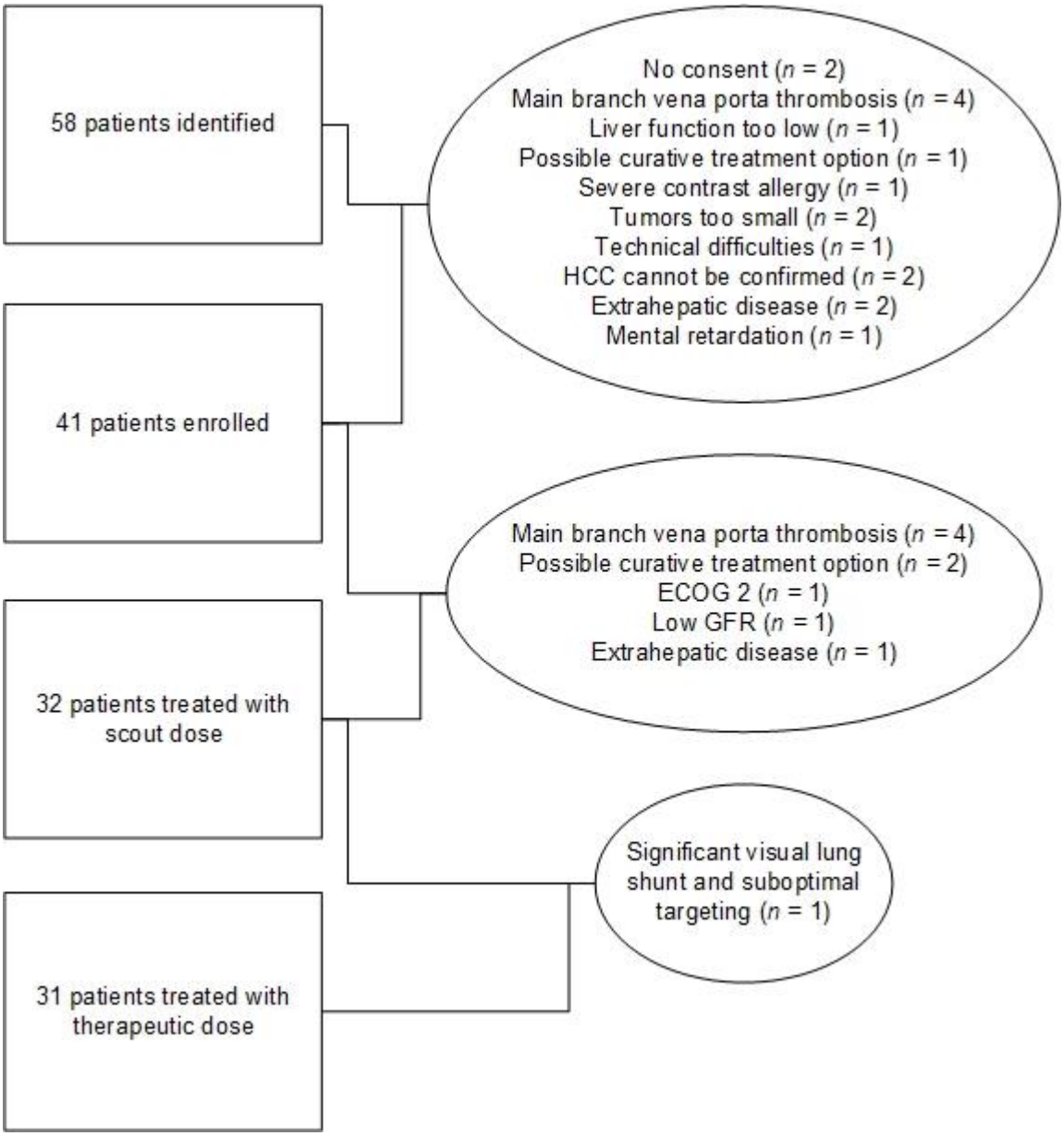


Figure 2: Child-Pugh score development over time.

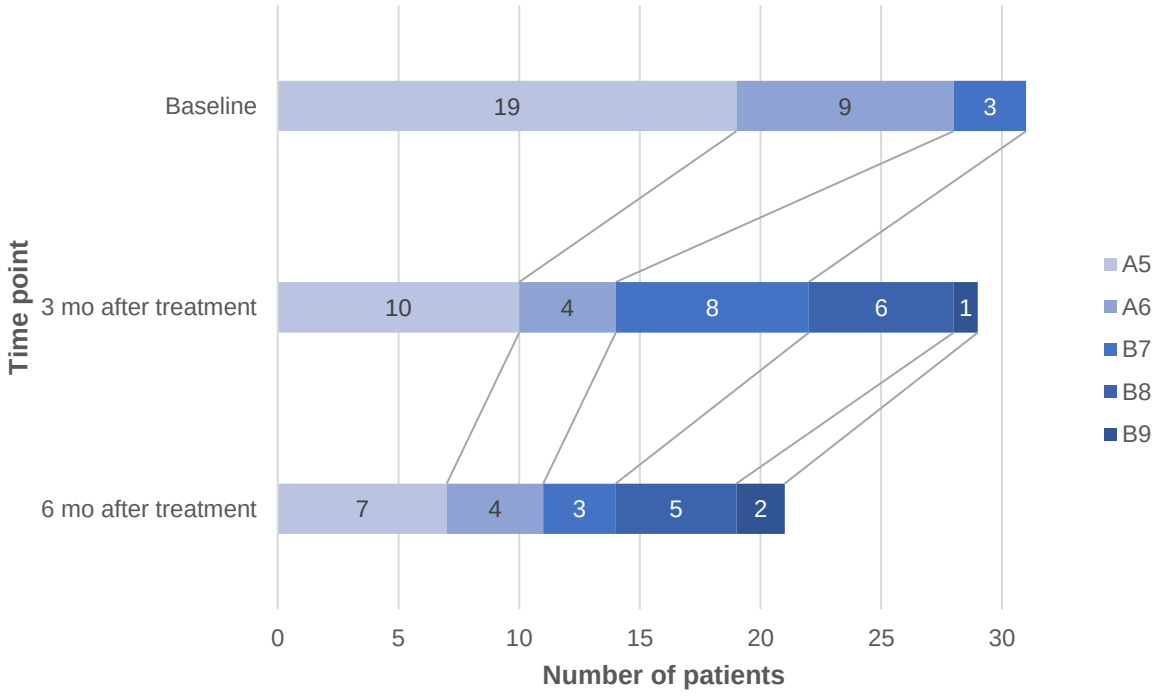


Figure 3: An 85 year old patient with hepatocellular carcinoma with no underlying liver disease and no previous treatment (ECOG 1, Child-Pugh A5, BCLC B) with a large hypervascular tumor spanning segments 4-8 (A, axial contrast-enhanced MRI) that had multiple tumor-feeding vessels from the right hepatic artery (B, DSA). He received a ^{166}Ho-microspheres scout procedure and SPECT (C), which showed good targeting of the tumor. The scout procedure proved highly predictive for post-treatment ^{166}Ho-microspheres distribution (D) and resulted in a complete response of the target liver lesions at three (E, axial contrast-enhanced MRI) and six months (F, axial contrast-enhanced MRI).

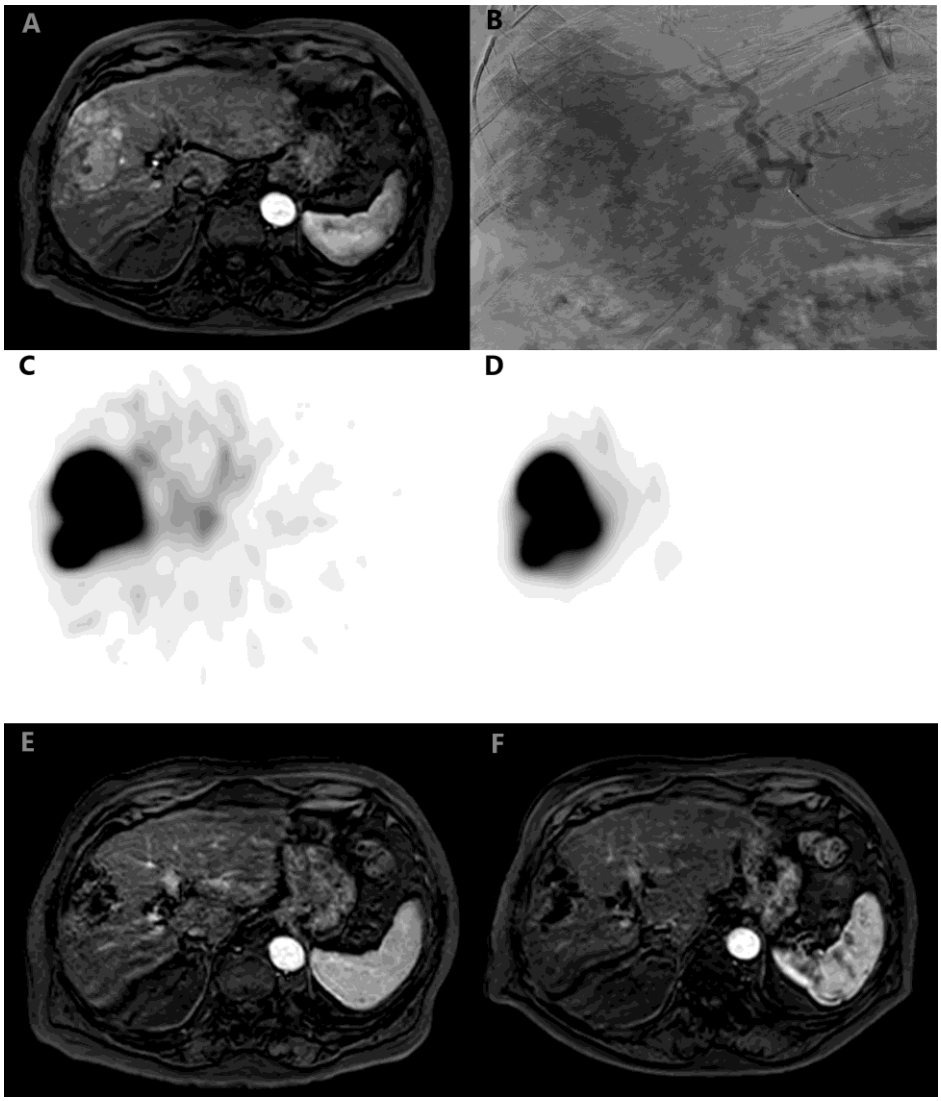


Figure 4: Response assessment of target liver lesions at three and six months after treatment with ^{166}Ho-microspheres radioembolization according to A) modified RECIST and B) RECIST 1.1.

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease. Some patients did not undergo imaging at three/six months follow-up because of death (n=2/8) or withdrawn consent (n=2/0). Some patients were not evaluable, because of absent arterial enhancement of the tumor or low quality imaging (e.g. artefacts, breathing motion) (n=3/2, they were considered to have PD).

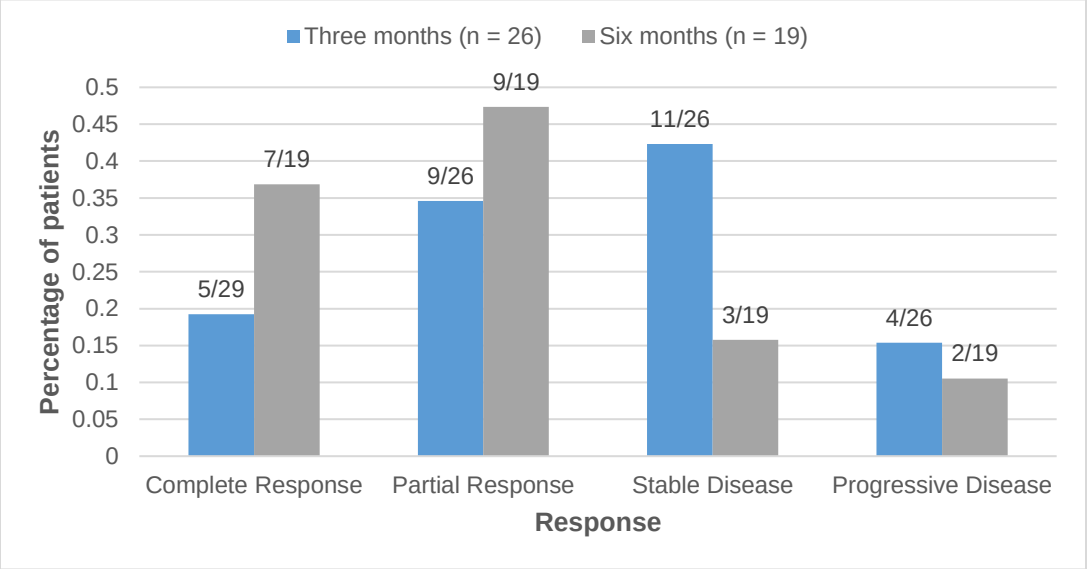
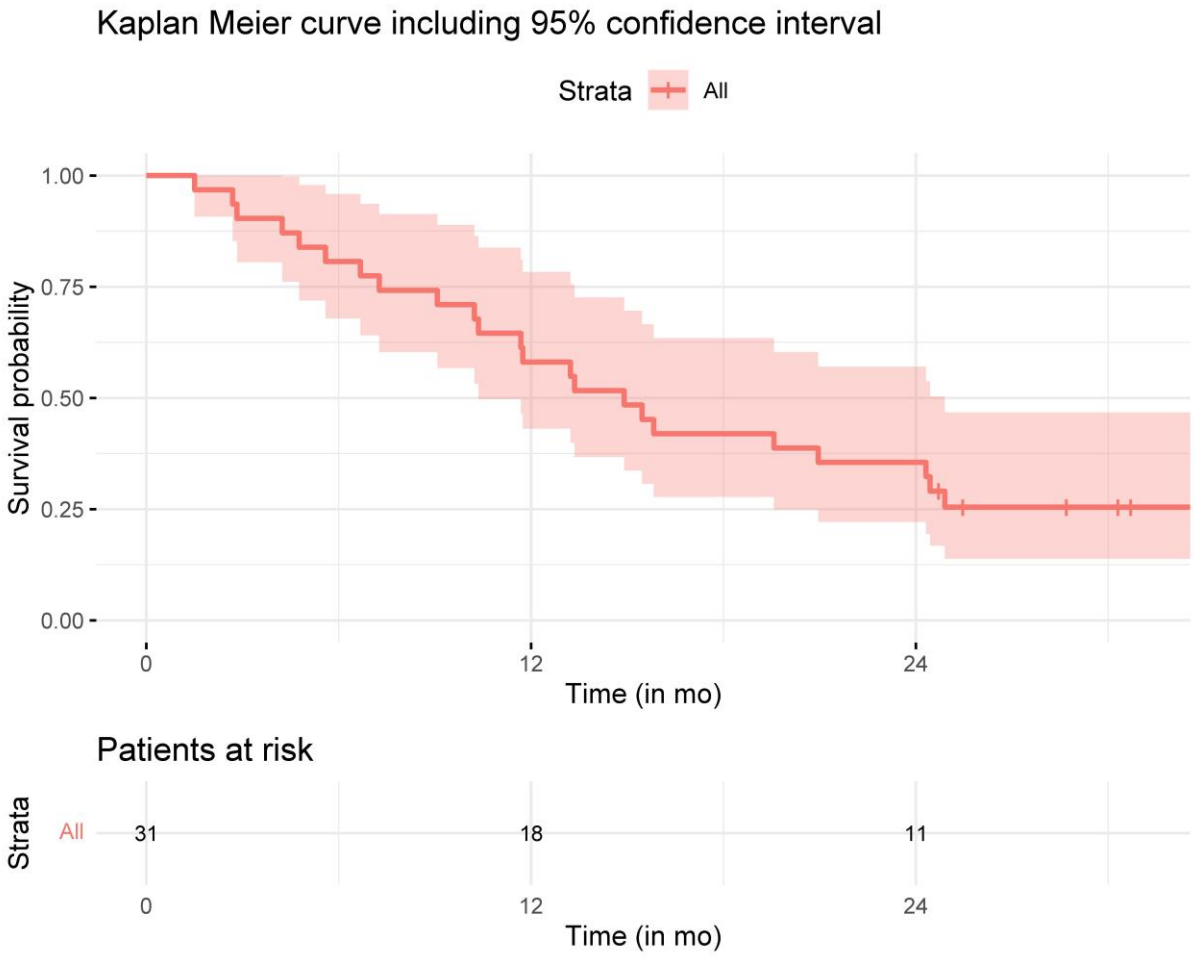


Figure 5: The overall survival of HEPAR Primary patients including 95% confidence interval.



Disclosure

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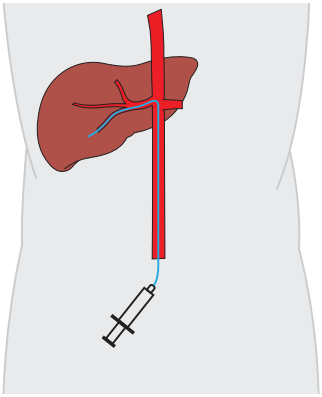
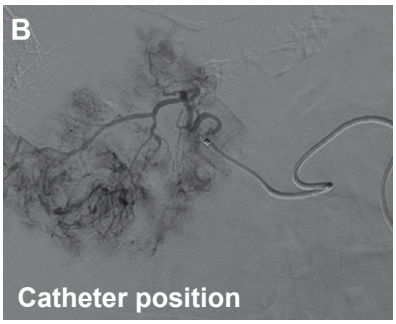
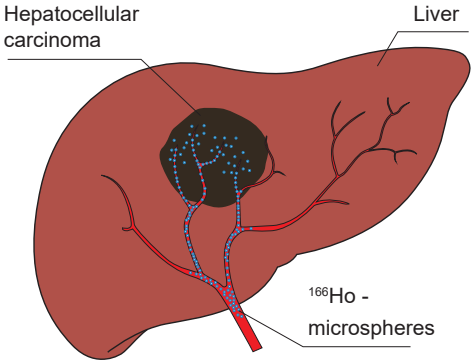
Graphical Abstract

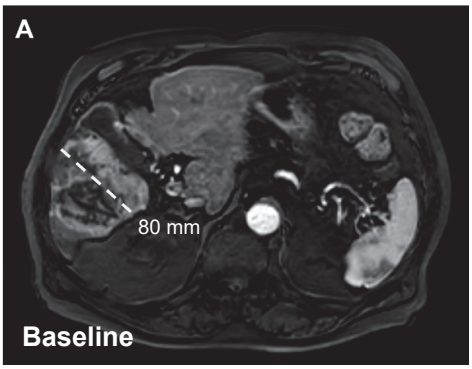


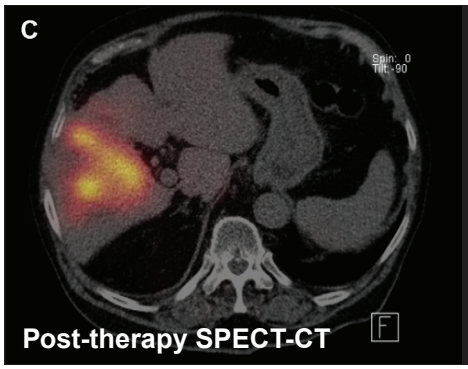


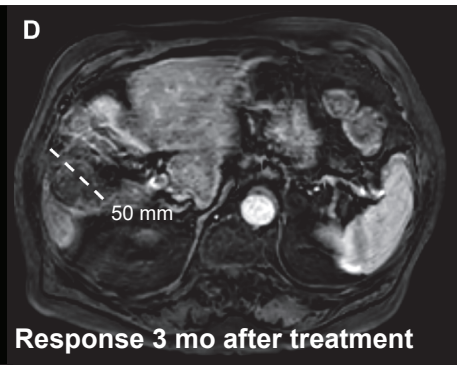


60 Gy to the target liver volume

- <10% serious adverse events
- 54% target liver lesion response
- 14.8 mo median overall survival







Supplementary data – Tables

Table 1: Study procedures per time point

Procedures	**Screening, treatment and follow-up period**						
	Screening	Prep. Angiography	Treatment	W3	W6	M3	M6
Informed consent	X						
In-/exclusion	X	X	X				
Demographic data	X						
Physical exam, vital signs and clinical performance status (ECOG)	X	X	X	X	X	X	X
EORTC QLQ C30 + HCC18 + BPI-SF	X	X	X	X	X	X	X
CT	X						
MRI	X		X (24 hours after treatment)			X	X
Oesophago-gastro-duodenoscopy (if not performed in past 6 months)	X						
Hepatobiliary scintigraphy	X					X	
SPECT/CT		X	X (3-5 days after treatment)				
Angiography		X	X				
Scout dose		X					
Therapeutic dose			X				
Laboratory examination	X	X	X	X	X	X	X
Monitoring of (S)AE's + concomitant med.	X	X	X	X	X	X	X

Table 2: New laboratory adverse events according to CTCAE version 4.03 per time point.

Time point	***Baseline***				***3 weeks***				***6 weeks***				***3 months***				***6 months***			
Number of patients	31				31				30				28				21			
CTCAE grade (v. 4.03)	**0**	**1**	**2**	**3**	**0**	**1**	**2**	**3**	**0**	**1**	**2**	**3**	**0**	**1**	**2**	**3**	**0**	**1**	**2**	**3**
ASAT increased	6	20	2	3	9	19	3		8	18	3	1	5	18	2	3	4	16	1	
Platelet count decreased	13	18			12	18	1		11	18	1		9	19			9	12		
Anemia	12	18	1		10	20	1		6	23		1	9	14	4	1	10	8	2	1
AF increased	14	16	1		12	18	1		10	17	3		9	16	3		7	13	1	
INR increased	16	15			14	16	1		10	20			11	16	1		7	13	1	
ALAT increased	20	9	2		18	13			22	8			19	8	1		13	8		
Hyperglycemia	11	9	8	3	13	5	9	4	7	7	12	4	13	6	9		2	12	7	
GGT increased	3	8	10	10	2	10	16	3	1	14	12	3	1	8	13	6	0	8	8	5
Hypoalbuminemia	25	6			20	9	2		18	9	3		12	14	1	1	8	11	2	
Prolonged APTT	24	5	2		26	4	1		23	7			17	11			11	10		
Hyponatremia	25	5		1	21	8		2	22	8			26	2			18	3		
Blood bilirubin increased	27	4			29	1	1		24	5	1		22	4	1	1	14	5	2	
Creatinine increased	29	2			29	2			27	3			23	4	1		18	3		
Hypokalemia	30	1			29	2			26	4			26	2			18	3		
Hypoglycemia	30	1			31				30				27	1			19	2		
Lymphocyte count decreased	26	1	4		11		12	8	10	1	15	4	17		8	3	15		6	

Table 3: New clinical adverse events according to CTAE version 4.03 per time point.

Time point	***Baseline***						***3 weeks***						***6 weeks***						***3 months***						***6 months***					
Number of patients	31						31						30						28						21					
CTCAE grade (v. 4.03)	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**
Back pain	14	16	1				30		1				29		1				27		1				21					
Pain	25	6					31						30						28						21					
Nausea	25	5	1				30	1					30						28						21					
Hepatic pain	28	3					31						30						27	1					21					
Chills	29	2					30	1					29	1					27	1					19	2				
Diarrhea	29	2					30	1					29	1					27	1					19	2				
Headache	29	2					31						30						27		1				21					
Hematoma	29	2					30	1					30						28						21					
Non-cardiac chest pain	29	2					31						29		1				28						21					
Vomitus	29	2					31						30						28						21					
Buttock pain	30	1					31						30						28						21					
Fatigue	29	1	1				14	13	4				17	13					17	9	2				15	4	2			
Fever	30	1					29	2					29	1					28						21					
Malaise	30	1					29	2					28	2					27	1					20	1				
Obstipation	30	1					31						30						28						21					
Shoulder pain	30	1					31						29	1					27	1					21					
Skin infection	30	1					31						30						28						21					
Urine discoloration	30	1					31						30						28						21					
Vasovagal reaction	30	1					31						30						28						21					
Abdominal infection	31						31						30						27			1			21					

Abdominal pain	30			1			26	4	1				28	2					26	1	1				21					
Allergic reaction	31						31						30						27			1			21					
Anorexia	30		1				30		1				29		1				25	3					21					
Anxiety	31						31						30						27	1					20	1				
Arthritis	31						31						30						27			1			21					
Ascites	31						31						28	1	1				21	5	1	1			14	5	2			
Atrial fibrillation	31						31						30						27			1			21					
Bile duct stenosis	31						31						30						27			1			20			1		
Biliary fistula	31						31						30						27			1			20			1		
Bone pain	31						30		1				29		1				28						20	1				
Cholecystitis	31						30			1			29			1			27			1			20			1		
Cough	31						31						29	1					27	1					21					
Dizziness	31						30	1					29	1					26	2					21					
Dry mouth	31						29	2					29	1					27	1					20	1				
Dyspnea	31						29	2					26	4					24	4					19	2				
Edema limbs	31						31						28	1	1				25	3					21					
Endocarditis infective	31						31						30						27				1		21					
Esophageal varices hemorrhage	31						30			1			28			2			28						21					
Extrapyrimidal disorder	31						31						30						27	1					20	1				
Flank pain	31						29	2					29	1					27	1					21					
Flu-like symptoms	31						30	1					30						28						21					
Fracture	31						31						29	1					28						21					
Gastric hemorrhage	31						31						29			1			28						21					
Hepatic failure	31						31						29					1	27					1	21					

Hip fracture	31						31						30						28						20			1			
Insomnia	31						31						30						27	1					20	1					
Intracranial hemorrhage	31						30					1	30						28						21						
Ischemia cerebrovascular	31						31						30						27					1	21						
Itch	31						30	1					29	1					26	1	1				20		1				
Joint infection	31						30		1				30						28						21						
Localized edema	31						31						29	1					27	1					21						
Lung infection	31						31						30						27			1			21						
Pain in extremity	30		1				31						30						27	1					21						
Pelvic pain	31						30		1				30						28						21						
Pleural effusion	31						31						30						27	1					20	1					
Sepsis	31						31						29					1	28						21						
Tremor	31						31						30						28						20	1					
Urethral infection	31						31						29		1				28						21						
Urinary retention	31						31						29		1				28						21						
Urinary tract infection	31						30		1				30						28						21						
Venous injury	31						31						30						28						20		1				

Supplementary data – Figures

Figure 1: The post 3 mo landmark overall survival of HEPAR Primary patients stratified in responders (complete and partial response) vs. non-responders (stable and progressive disease) based on target liver lesion response (log-rank test p=0.046) according to mRECIST.

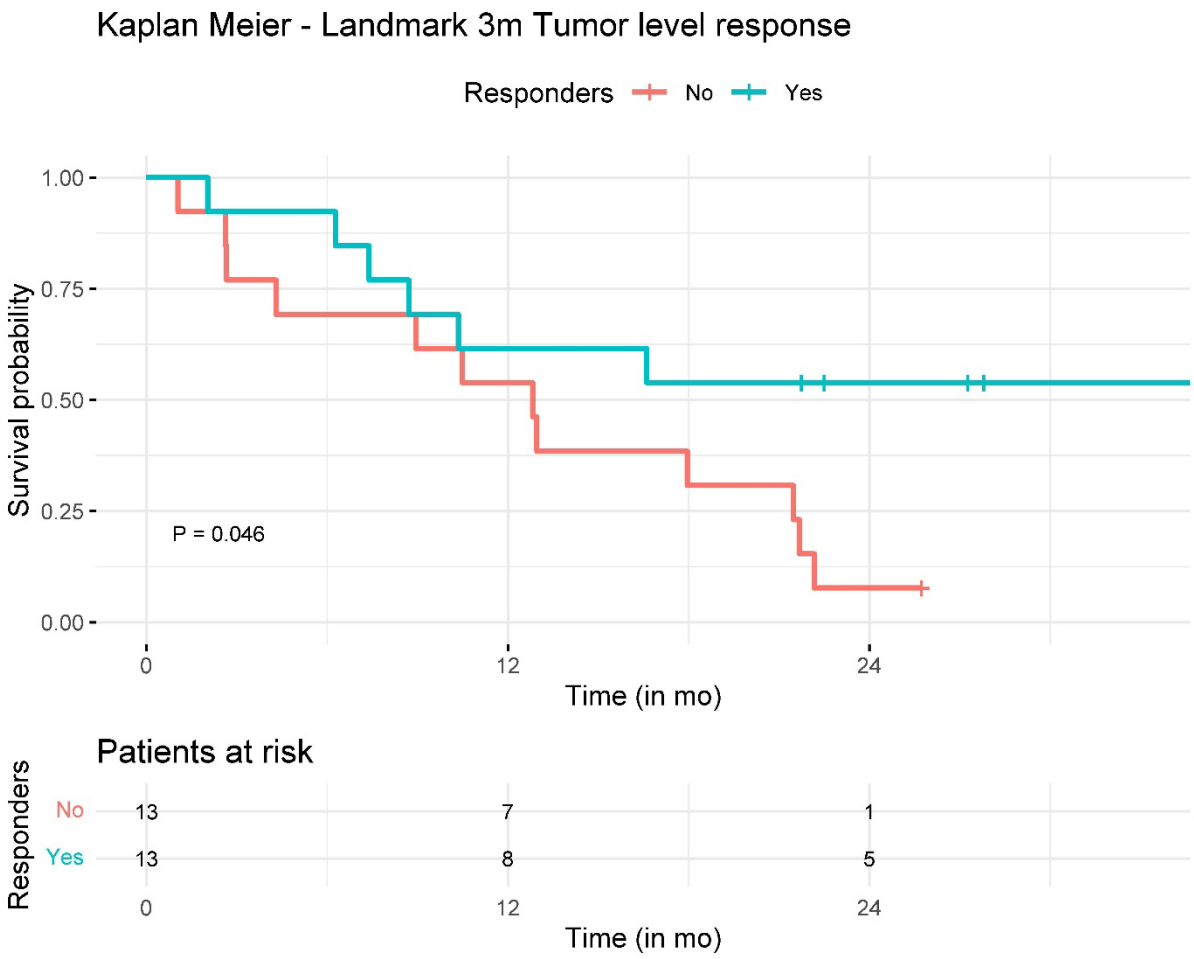
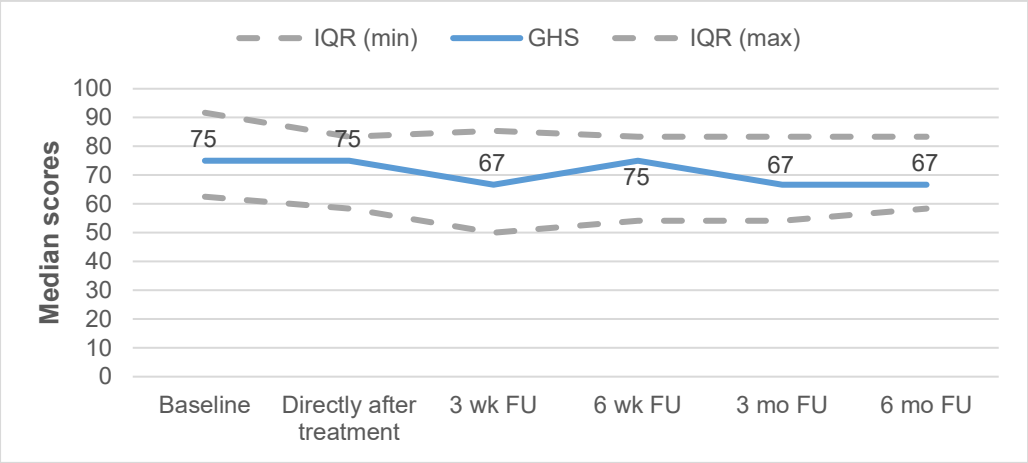
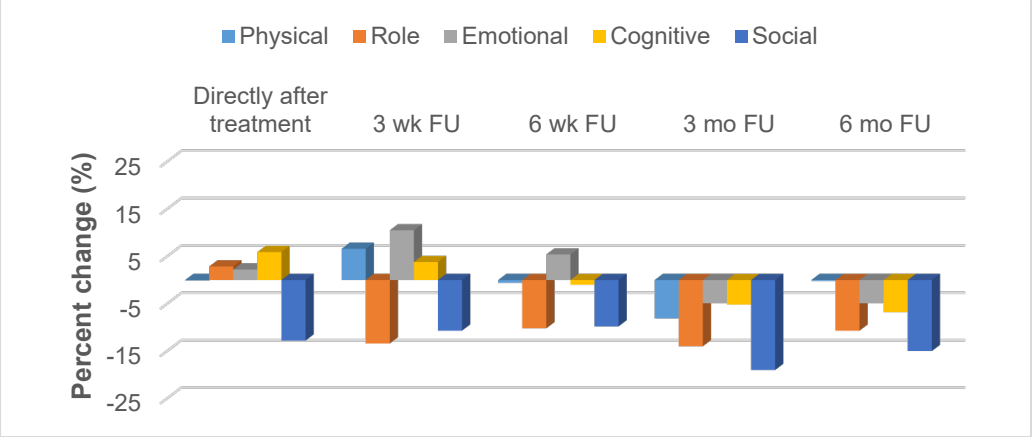


Figure 2: Quality of life of HEPAR Primary patients based on self-reported scores. A) Global Health status B) Functioning scales C) Symptom scores.

IQR = Interquartile range, GHS = Global health score





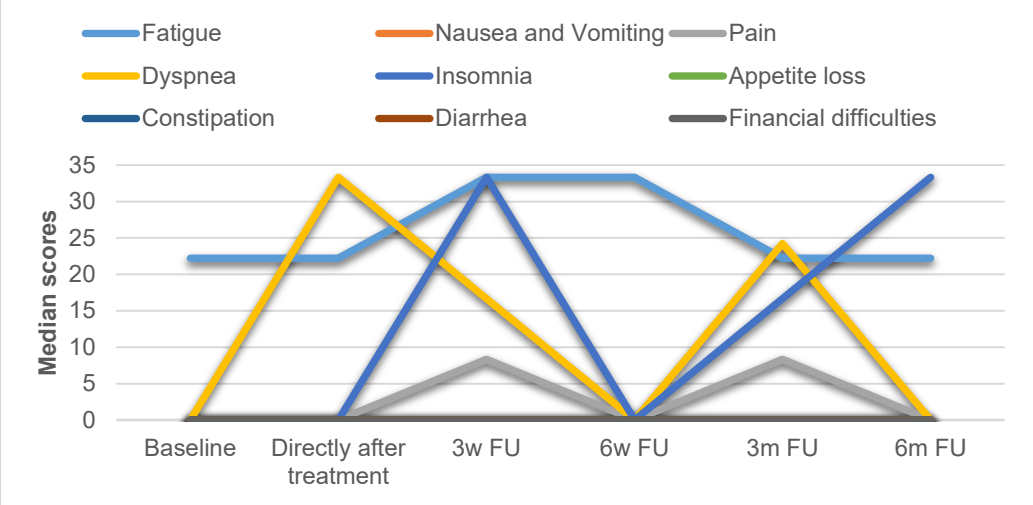


Figure 3: Mean scores of Pain Severity and Pain Interference based on self-reported scoring of HEPAR Primary patients at different time points. The numbers indicate the number of completed questionnaires at the different time points. No significant difference was found between baseline and any of the time points after treatment.