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Holmium-166 Radioembolization in Hepatocellular Carcinoma: Feasibility and Safety of a New Treatment Option in Clinical Practice

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Abstract

Purpose To investigate clinical feasibility, technical success and toxicity of ^{166}Ho-radioembolization (^{166}Ho-RE) as new approach for treatment of hepatocellular carcinomas (HCC) and to assess postinterventional calculation of exact dosimetry through quantitative analysis of MR images.

Materials and Methods From March 2017 to April 2018, nine patients suffering from HCC were treated with ^{166}Ho-RE. To calculate mean doses on healthy liver/tumor tissue, MR was performed within the first day after treatment. For evaluation of hepatotoxicity and to rule out radioembolization-induced liver disease (REILD), the Model for End-Stage Liver Disease (MELD) Score, the Common Terminology Criteria for Adverse Events and specific laboratory parameters were used 1-day pre- and posttreatment and after 60 days. After 6 months, MR/CT follow-up was performed.

Results In five patients the right liver lobe, in one patient the left liver lobe and in three patients both liver lobes were treated. Median administered activity was 3.7 GBq (range 1.7–5.9 GBq). Median dose on healthy liver tissue was 41 Gy (21–55 Gy) and on tumor tissue 112 Gy (61–172 Gy). Four patients suffered from mild postradioembolization syndrome. No significant differences in median MELD-Score were observed pre-, posttherapeutic and 60 days after ^{166}Ho-RE. No deterioration of liver function and no indicators of REILD were observed. One patient showed a complete response, four a partial response, three a stable disease and one a progressive disease at the 6 months follow-up.

Conclusion ^{166}Ho-RE seems to be a feasible and safe treatment option with no significant hepatotoxicity for treatment of HCC.

Keywords Holmium · Microspheres · Radioembolization · SIRT · Liver · Hepatocellular carcinoma · HCC · Radioembolization-induced liver disease · REILD · RILD · Cirrhosis

Introduction

With 810,000 deaths and 854,000 new cases per year primary liver cancer is the fourth most common cause of cancer-related mortality after lung, colorectal and stomach cancer and the sixth most commonly diagnosed cancer worldwide in 2015 [1, 2]. Hepatocellular carcinoma (HCC) represents about 90% of liver cancers [3]. The treatment options of HCC depend on the tumor stage as well as the underlying liver function. Depending on Barcelona-Clinic Liver Cancer (BCLC) stage, selective internal radiation therapy (SIRT) could be used as bridging treatment until

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transplantation (BCLC-A), as an alternative to TACE or systemic therapy (BCLC-B or C) or for downstaging to transplantation (BCLC-B/C) [3–6]. Until 2015, Yttrium-90 (^{90}Y) was the only commercially available radionuclide for radioembolization. In 1999, Holmium-166 (^{166}Ho) loaded microspheres suitable for SIRT were described for the first time by Nijsen et al. [7]. Since then, many animal studies have proven safety, low toxicity and efficacy of ^{166}Ho containing microspheres [8–11]. In contrast to ^{90}Y microspheres, the in vivo biodistribution of ^{166}Ho microspheres is able to be visualized after radioembolization because ^{166}Ho emits low-energy gamma photons and has paramagnetic properties which allows dosimetry through quantitative analysis of the single photon emission computed tomography (SPECT) and magnetic resonance (MR) images [12]. Previous studies reported a good correlation between the MR and SPECT assessed whole liver mean absorbed radiation dose with a correlation coefficient of 0.927 [13]. This quantitative evaluation of adequate dose after radioembolization could enable personalized treatments. After promising results of the phase I HEPAR trial in patients with unresectable and chemorefractory liver metastases, ^{166}Ho containing microspheres with a diameter of 30 ± 5 µm (QuiremSpheres®) received the European CE mark for quality and safety in April 2015 [14]. In March 2017, this treatment was applied for the first time worldwide outside of a clinical study at our Department. To date, there are no data available regarding safety and toxicity of this novel therapy for hepatocellular carcinoma (HCC), especially in patients with liver cirrhosis. Therefore, we aimed to study feasibility, technical success and toxicity of ^{166}Ho-radioembolization (^{166}Ho-RE) in patients suffering from HCC within the clinical routine. Additionally, we wanted to evaluate the new possibility to calculate the exact dosimetry through quantitative postinterventional analysis of the MR images, early complications and therapy outcome of this novel treatment option in a "real world setting" (during routine clinical practice with no strict inclusion and exclusion criteria).

Materials and Methods

Study Design and Patients

All patients who underwent ^{166}Ho-RE between March 2017 and April 2018 at our hospital were retrospectively identified by analysis of a prospectively maintained service database. Decision to perform a radioembolization was taken by an interdisciplinary tumor board including at least one experienced surgeon, interventional radiologist, internal oncologist, radiooncologist, nuclear medicine physician and pathologist. Selected patients had a confirmed diagnosis of HCC according to European Association of the Study of the Liver (EASL) criteria and were staged according to BCLC criteria [3, 6]. Contraindications for ^{166}Ho-RE were chosen accordingly to these applied for ^{90}Y-RE [15]. Previous treatments like resection, thermal ablation or TACE just like single lobe or whole liver disease were no exclusion criteria.

Procedure

At a median time of 14 days (range 7–20 days) before treatment, a Technetium-99 m human serum albumin angiography (^{99m}Tc-HSA, ROTOP-HSA microspheres B20, ROTOP Pharmaka, Dresden, Germany) was performed and vessels arising from the hepatic artery near the injection position such as the gastroduodenal artery were coil-embolized to avoid extrahepatic embolization. Pulmonary shunting was ruled out using a SPECT (ForteTM JetStream®, Philips, Best, The Netherlands) and if lung shunting exceeded 20% treatment was canceled. Standard clinical and liver-specific laboratory parameters were collected 1-day pretreatment, 2 days posttreatment, weekly up to 4 weeks and after 60 days. MR (MAGNETOM Verio 3T® or MAGNETOM Vida 3T®, Siemens, Erlangen, Germany) including contrast (Gd-EOB-DTPA, Primovist®, Bayer Pharma, Leverkusen, Germany) and non-contrast images as well as T1-weighted multi-gradient echo images was performed 1 day before and 1 day after the intervention. To calculate the required ^{166}Ho activity, a maximum whole liver dose of 60 Gy was aimed according to the published maximum tolerated radiation dose of the HEPAR trial and adjusted to the targeted liver mass, using the following formula as described by Smits et al.: $A(\mathrm{MBq}) = \text{liver dose (Gy)} \times 63\ (\mathrm{MBq/J}) \times \mathrm{LW}$ (A = administered activity, liver dose = aimed whole liver absorbed dose, LW = liver weight) [14, 16]. According to the literature, we used a sequential approach for whole liver radioembolization and the activity was split to avoid liver-related significant adverse events [35]. To reduce postembolization syndrome and avoid pain, all patients received anti-emetics (ondansetron 4 mg, GlaxoSmithKline, München, Germany) and analgesic (piritramide 3 mg, Janssen-Cilag GmbH, Neuss, Germany) as an intravenous dose during the procedure according to the expert guidance of Sangro et al. [17]. ^{166}Ho-radioembolization with QuiremSpheres® (Quirem Medical, Deventer, Netherlands) was performed according to the standard technical procedure of transarterial radioembolization as described by the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) [18]. Due to German laws, patients had to stay on the ward for 72 h after treatment. On this ward, they did not need any special isolation comparable to patients treated with ^{90}Y-SIRT. Mean dose on healthy liver

tissue (whole liver inclusive the tumor) as well as mean dose on tumor tissue were calculated as MR-based dosimetry using the T1-weighted multi-gradient echo sequences (pre- and posttreatment) and Q-Suite™ (v1.2, QuiremSpheres®) (Fig. 1) [12, 19, 20]. Q-Suite™ is a software to calculate the exact dose of ^{166}Ho using R_2^* values from the multi-gradient echo sequences and subtracted the pretreatment R_2^* values from the posttreatment R_2^* values to determine the microsphere-induced change in $R_2^*(\Delta R_2^*)$. By means of the formula ^{166}Ho-microspheres = $\Delta R_2^*/r_2^*$ ($r_2^* = 103\ s^{-1}\ mL^{-1}\ mg$ for ^{166}Ho-microspheres with holmium content of 18.9%), the amount of ^{166}Ho-microspheres could convert into units of activity [12]. This algorithm was described and validated by Seevinck et al. and van de Maat et al. [13, 20]. The multi-gradient echo sequences were acquired during breath-hold with an in-plane resolution of 4 × 4 × mm and a slice thickness of 5 mm. If sequential treatments of the left and right liver lobes were performed dosimetry was calculated separately for both treatments. Depending on patients' current state of health, we additionally evaluated MR or contrast-enhanced abdominal CT (Somatom Force®, Somatom Definition AS+®, Siemens, Erlangen, Germany) after 2 and 6 months as follow-up.

Definitions

To assess overall toxicity, Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 by the US National Cancer Institute were used (Table 3). Adverse events exceeding grade 2 were defined as major complications. CTCAE were evaluated 1 day after radioembolization. Specific hepatotoxicity was assessed with the appearance of radioembolization-induced liver disease (REILD) 60 days after treatment which was described by Sangro et al. [21]. It is based on external radiation-induced liver disease (RILD) and is characterized by clinical presentation of jaundice, ascites and a bilirubin increase of over 50 µmol/l 4–8 weeks after treatment [21]. To find out if hepatotoxicity has any effects on the severity of chronic liver disease, we additionally evaluated the Model for End-Stage Liver Disease (MELD) 1 day before, 1 day and

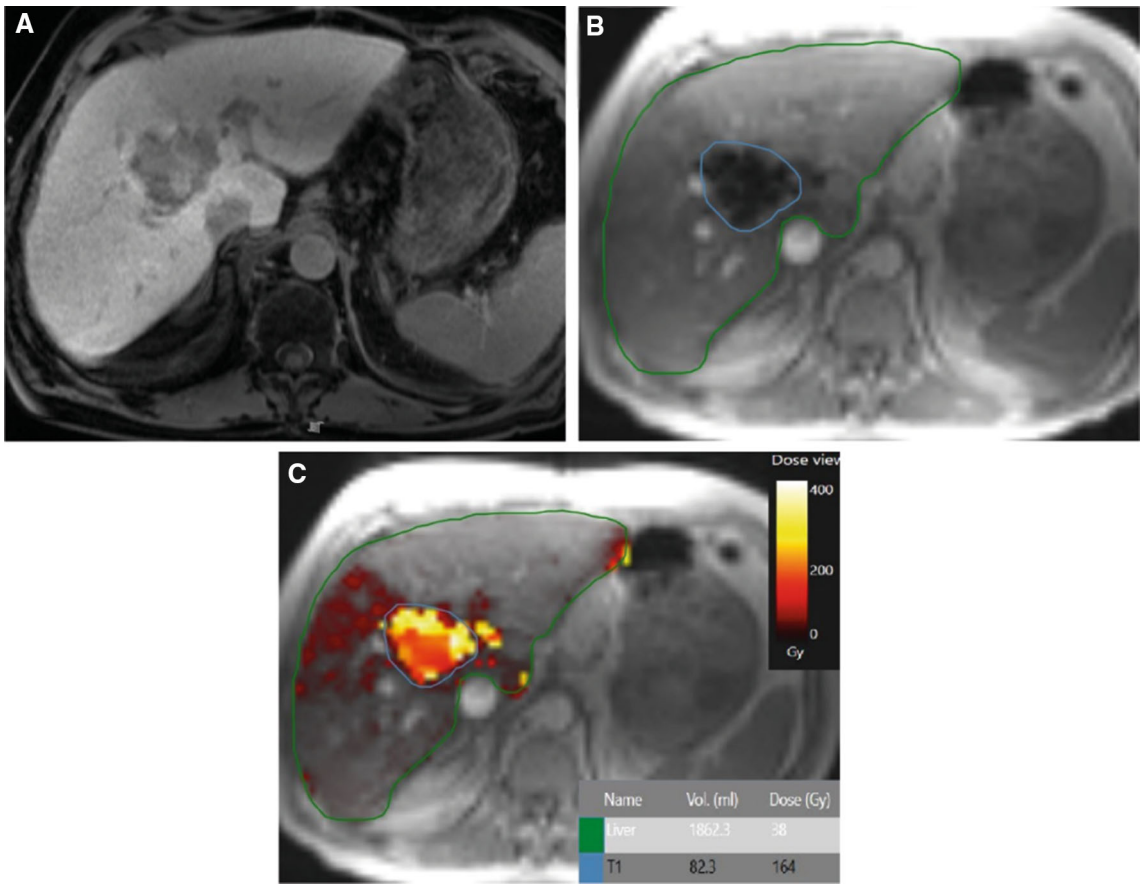

Fig. 1 75-year-old male patient with hepatocellular carcinoma (HCC). **A** Contrast-enhanced T1-weighted MR showing HCC with washout in the right liver lobe, **B** T1-weighted multi-gradient echo image after ^{166}Ho-RE with segmentation of the liver (green outline) and the tumor (T1, blue outline), **C** T1-weighted multi-gradient echo image fused with the calculated dose image. Visually, scale bar is in Grays

60 days after treatment [22]. The procedure was performed by a board-certified radiologist with more than 10 years' experience in performing radioembolization and a board-certified nuclear medicine physician and images were evaluated by board-certified radiologists. To evaluate tumor response, the modified RECIST (mRECIST) criteria for HCC were applied which were recommended by the European Association for the Study of the Liver [3, 23].

Statistical Analyses

Data were collected in an Excel database (Excel 2016; Microsoft Corporation, Redmond, WA, USA), and statistical analyses were performed with SPSS software version 23 (SPSS, Chicago, IL, USA). Data are reported as medians with ranges. To compare the three MELD-Scores, we used the Friedman test for related samples. A p value under 0.05 was considered as statistically significant.

Results

From March 2017 to April 2018, 63 radioembolizations in 49 patients were performed in our hospital. In ten patients, QuiremSpheres® were used and nine out of these ten patients were treated because of HCC. The other patients were treated with ^{90}Y radionuclides. Three Patients had a bilobar disease, and the left and right liver lobes were treated separately after a median time of 34 days (range 27–35 days); one patient had a left-lobar disease, and the other five patients had a right-lobar disease and were treated in one session. Patients' characteristics are shown in Table 1. During interventions, no procedure-related complications were observed and planned activity could completely be administered in all patients. Median administered activity was 3.7 GBq (range 1.7–5.9 GBq). Due to technical problems of the MR scanner, two patients could not get his posttreatment MR in time (1 day after). Consecutively, calculation of MR-based dosimetry was not possible in these cases and dosimetry values are calculated for 7 patients. The calculated median dose on whole liver tissue was 41 Gy (range 21–55 Gy), and the median dose on tumor tissue was 112 Gy (range 61–172 Gy) per treatment. Table 2 gives an overview on dose data. A mild postradioembolization syndrome occurred in four patients 1 day after radioembolization (CTCAE grade 1–2) and moderate ascites (CTAE grade 1–2) was found in two patients 1 day after RE. With no observed major complications (CTCAE grade 3–5), the overall toxicity was low. The complete recorded adverse events after RE are outlined in Table 3. No patient developed a REILD at the 60 days follow-up. The median MELD-Score 1 day before RE was 8 (range 7–13), and with a median MELD-Score of 8 (range 6–11) 1 day after RE and a median MELD-Score of 8 (range 6–14) 60 days after RE, the hepatotoxicity of ^{166}Ho-RE showed no significant effect on the severity of chronic liver disease ($p = 0.14$). To evaluate tumor response 2 and 6 months after radioembolization, MR was performed in six patients and CT in three patients (CT was performed because of inadequate breath-hold). According

Table 1 Patient characteristics

Characteristic	Value ($n = 9$)
Age in years (median, range)	73 (64–78)
Sex	
Male	8 (89%)
Female	1 (11%)
Cirrhosis	
Present	7 (78%)
Absent	2 (22%)
Etiology of cirrhosis	
Alcohol abuse	5 (71%)
HCV	1 (17%)
Unknown	1 (17%)
Child–Pugh classification	
A	4 (57%)
B	3 (43%)
ECOG	
0	6 (67%)
1	2 (22%)
2	1 (11%)
BCLC classification	
B	6 (67%)
C	3 (33%)
Prior liver treatments	
Resection	4 (45%)
Resection and TACE	2 (22%)
None	3 (33%)
Treatment approach	
Right lobe	5 (56%)
Left lobe	1 (11%)
Whole liver	3 (33%)

Table 2 Dose data

Parameter	Median	Range
Administered ^{166}Ho activity (GBq)	3.7	1.7–5.9
Calculated[a] whole liver dose (Gy)	41	21–55
Calculated[a] tumor dose (Gy)	112	61–172

[a]MR-based absorbed dose

Table 3 Follow-up

	1 day before RE (n = 9)	1 day after RE (n = 9)	60 days after RE (n = 9)
Presence of REILD[a]	–	–	0
MELD-Score (median, range)	8 (7–13)	8 (6–11)	8 (6–14)
Numbers of CTCAE: all (grade 3–4 events)			
Nausea	–	3 (0)	–
Abdominal pain	–	2 (0)	–
Fatigue	–	3 (0)	–
Vomiting	–	3 (0)	–
Fever	–	1 (0)	–
Ascites	–	2 (0)	–
Liver abscesses	–	0	–
Bilirubin	–	1 (0)	–
Response[b] on MR/CT			
Partial response	–	–	5 (56%)
Stable disease	–	–	3 (33%)
Progressive disease	–	–	1 (11%)

[a]Jaundice, ascites and a bilirubin increase of over 50 µmol/l

[b]According to mRECIST

–: not evaluated

to mRECIST, criteria six patients showed a partial response, three patients had a stable disease and one patient a progressive disease after 2 months. After 6 months, one patient showed a complete response, four patients a partial response, three patients a stable disease and one patient a progressive disease. Consequently, tumor response which includes complete response (CR) and partial response (PR) is 60% and the disease control rate (DCR) which includes CR, PR and stable disease is 90%. No death occurred within 2 months after treatment.

Discussion

Radioembolization with ^{166}Ho loaded microspheres represents a new opportunity for intraarterial radiation therapy and could contribute to improve the treatment of HCC. In our study, ^{166}Ho-RE was successfully performed in all patients. Patients' preparation, pretherapeutic examinations and treatment itself are very similar to ^{90}Y-RE and therefore easy to perform for physicians who are familiar with ^{90}Y-RE, [14, 24].

Dosimetry

Up to now with ^{90}Y, there is no way to perform an accurate in vivo dosimetry in clinical routine to monitor the success of RE although it has been proven that the outcome for HCC after RE depends on radiation dose that is actually delivered to tumor tissue but otherwise that hepatotoxicity is dose related [21, 25–28]. ^{166}Ho has different characteristics from ^{90}Y, and with 26.8 h, the physical half-life of ^{166}Ho is significantly shorter than that of ^{90}Y (64.1 h). Consequently, a nearly threefold higher activity must be applicated to achieve the same dose in the target tissue compared to ^{90}Y resulting in an equal dose deposition but over a significantly shorter time [7]. This has several radiobiological implications for both the target and the surrounding healthy liver tissues. Currently, there are no data available if this could change hepatotoxicity after RE in patients with cirrhosis. Undoubtedly, the cirrhotic liver has a reduced functional reserve resulting in an increased risk of liver failure. In particular, radiobiological experiences from percutaneous radiotherapy and from ^{90}Y-based RE have been leading to the recommendation that the whole liver dose after ^{90}Y-RE in patients with cirrhosis should be kept below 50 Gy [29, 30]. For these reasons, the necessity of dosimetry is becoming increasingly important. Contrary to ^{90}Y, ^{166}Ho emits low-energy gamma photons and has paramagnetic properties which allows the visualization of the microspheres after treatment in SPECT and MR [12, 16]. In clinical routine, MR dosimetry could have a slight advantage against SPECT because it uses the paramagnetic nature of the microspheres, and therefore, the posttreatment imaging time point is of minor relevance. We were able to perform MR dosimetry after ^{166}Ho-RE in

seven cases. With a median dose on whole liver tissue of 41 Gy in our patient cohort, the absorbed dose is slightly lower than the reported median dose of 51 Gy after ^{166}Ho-RE in patients with liver metastases and well below 50 Gy which should not be exceeded [29, 30]. The reason for not reaching the aimed whole liver absorbed dose of 60 Gy is that the calculation is based on the concept that all administered activity is homogeneously absorbed by the liver, but especially in good vascularized tumors, the major deposition of activity is in the tumor, and therefore, the amount of activity is significantly lower in the healthy liver parenchyma. Until now, there are no data regarding tumor dose which can be reached after ^{166}Ho-RE. In our study, we found a median dose within the tumor tissue of 112 Gy, ranging from 61 to 172 Gy. Comparing our tumor tissue dose with reported doses of up to 500 Gy after ^{90}Y-RE of HCC, it seems that the rate we achieved in this study is significantly lower [26, 31]. However, in contrast to dose achieved by us the values given in the literature are frequently not the average doses within the whole volume of the tumor but only maximum values of doses within the tumor, usually located in the peripheral margin of the target tissue [31, 32]. Campbell et al. described that the average dose within the tumor periphery ranges from 200 to 600 Gy, but the average dose in the necrotic tumor center ranges from 3.7 to 6.8 Gy. In contrast to these doses, Q-Suite^{TM} enables to calculate the dose to the complete tumor volume, and therefore, the published high dose values could not reached in our cohort [32]. A comparable study was published by Ng et al. [33] in which calculation of the hole tumor dose was performed in five cases (three HCC, two metastases). For the three evaluated HCC-patients, the median tumor dose was 122.7 Gy which is slightly higher than our calculated 112 Gy, but even with our lowest tumor dose of 61 Gy, we are higher than the reported lowest dose of 40 Gy that is necessary to achieve a sufficient tumor response [34]. However, our results show how important personalized dosimetry can be for the outcome after RE especially because the absorbed dose correlates with response and toxicity [25, 28]. Therefore, the limiting factor to obtain better response rates after radioembolization is the dose exposure of healthy liver parenchyma which can result in developing a REILD.

Toxicity

REILD is pathophysiological equivalent to hepatic veno-occlusive disease (VOD) and leads to hepatic congestion which is ultimately resulting in liver failure, hepatorenal syndrome and death [21, 35, 36]. Gulec et al. [34] described that doses up to 99.5 Gy to healthy liver tissue are tolerated with no clinical veno-occlusive disease or liver failure. Considering that our highest liver dose was 55 Gy, it is consistent that we found no indicators of a REILD. To evaluate the overall toxicity, the most common adverse events were recorded according to CTCAE. With no grade 3–5 event and only four patients with moderate postradioembolization syndrome, our overall toxicity is below comparable studies after ^{90}Y-RE of HCC with reported rates up to 18% of adverse events (CTCAE grade 3–5) [37, 38]. The severity of chronic liver disease evaluated with the MELD-Score is one of the most relevant factors for determination of urgency for the transplantation list, and additionally, the progression of MELD-Score was found to be highly predictive in toxicity risk of the liver [39, 40]. Because bridging or downstaging to liver transplantation is an indication for radioembolization, it is important to find out if hepatotoxicity after ^{166}Ho-RE affects the MELD-Score [4]. In our cohort, there was no significant difference in MELD-Score between the pre-, posttherapeutic and 60 days scores after RE. Ettorre et al. [5] reported similar findings after ^{90}Y-RE in patients with HCC prior to liver transplantation. Therefore, it seems that ^{166}Ho-RE has no short-term effect on the MELD-Score and consequently no effect on the liver function too.

Response

Up to now, there are many studies regarding outcome and survival for patients with HCC after ^{90}Y-RE, but there are no data so far for tumor response in patients with HCC after ^{166}Ho-RE [37, 41–44]. Due to our short follow-up, a comparison between the reported long-term data of 37–60% disease control rate for ^{90}Y-RE in patients with HCC is not very reasonable particularly because the reported median time to progression for HCC ranges from 7.9 to 10.0 months [37, 45]. However, our short-term data could useful to give a first impression regarding tumor response. After ^{90}Y-RE, the reported response rates range from 25 to 50% which is less than the 56% tumor response rate in our cohort [45]. As described by literature, high response rates do not improve the overall survival but especially if RE is chosen for bridging to transplantation patients may benefit of the early response rates of ^{166}Ho-RE [3–6]. Additional to the good response rate, no death occurred in our cohort. Compared with a mortality rate of 3–6.8% at 30–90 days, we are at least in the same range [37, 41, 42].

Limitations

The main limitation of this study was the small number of patients and certainly, a 2 months follow-up is too short to get any conclusions about outcome regarding overall survival. To produce a higher level of evidence, prospective randomized controlled studies are necessary.

Conclusion

In summary, radioembolization with ^{166}Ho seems to be a feasible and safe treatment option which is easy to perform for attending physicians who are familiar with ^{90}Y-RE. No significant hepatotoxicity was found after ^{166}Ho-RE. The possibility of accurate dosimetry calculations in clinical routine after treatment could improve outcome regarding tumor response and the overall safety of the procedure. Bigger sample sizes and longer follow-ups are needed to prove the comparability with established radiotracers.

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Compliance with Ethical Standards

Conflict of interest R.-T. Hoffmann participates as proctor, advisory board member and received speaker's honoraria from Sirtex and Terumo. The other authors declare no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by local ethics committee. In addition, it is a retrospective study, and for this type of study, formal consent is not required.

Informed Consent Informed consent was obtained from all individual participants included in the study.

Consent for Publication Consent for publication was obtained for every individual person's data included in the study.

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