ELSEVIER

Seminars in
NUCLEAR
MEDICINE

Holmium-166 Microsphere Radioembolization of Hepatic Malignancies

Margot T.M. Reinders, MSc, Maarten L.J. Smits, MD, Caren van Roekel, MD, and Arthur J.A.T. Braat, MD

Holmium microspheres have recently become available in the European market as the third type of microspheres for radioembolization of unresectable liver malignancies. Holmium microspheres come with a dedicated administration system, and since these microspheres contain holmium-166 (^{166}Ho) instead of yttrium-90, unique dosing and imaging possibilities have become available as well. In addition, a scout dose of ^{166}Ho microspheres (Conformité Européenne mark is now granted and not pending anymore) can be used instead of ^{99m}Tc-macroaggregated albumin during the preparatory angiography procedure. So far, two prospective phase I and phase II clinical studies have been performed on ^{166}Ho radioembolization in a population of liver metastases from mixed origins. These studies showed that a mean whole-liver dose of 60 Gy is safe and induces tumor response. Ongoing trials investigate the effect of ^{166}Ho radioembolization in patients with neuroendocrine tumor metastases, hepatocellular carcinoma, and colorectal cancer metastases. Data derived from these studies will be used to refine the dosing schedule of 60 Gy to the whole liver and determine the optimal level of activity for each patient. This paper discusses several basics and provides an overview of relevant dosing aspects, technical aspects of performing holmium radioembolization, as well as a summary of completed and ongoing clinical studies and the upcoming developments regarding these microspheres.
Semin Nucl Med 49:237-243

Radioembolization

Radioembolization is a therapy during which radioactive microspheres are injected into the hepatic artery via a microcatheter. The treatment principle relies on the fact that hepatic malignancies are mainly fed by arterial blood, so the microspheres will lodge in small tumor arterioles and irradiate tumors, while relatively sparing the healthy liver tissue. Before treatment with radioembolization, patients undergo a visceral angiography to map tumor-perfusing vessels and a scout dose is administered to assess the presence of pulmonary and gastro-intestinal shunts.

Currently, three different types of radioactive microspheres are commercially available. Yttrium-90 (^{90}Y) has become the most commonly used radionuclide that is available in two forms, as a glass microsphere containing ^{90}Y, known as TheraSphere (BTG, London, UK) and as a resin microsphere coated with ^{90}Y brought to the market as SIR-Spheres (Sirtex Medical Limited, North Sydney NSW, Australia). Nowadays microspheres containing holmium-166 (^{166}Ho) are commercially available as QuiremSpheres (Quirem Medical BV, Deventer, the Netherlands) across Europe and provide an alternative to ^{90}Y microspheres with potential superior characteristics for imaging.

Before QuiremSpheres became commercially available, ^{166}Ho microspheres were developed at the University Medical Center Utrecht, the Netherlands. Quirem Medical became a spin-off company from the University Medical Center Utrecht and now commercializes, manufactures, and distributes QuiremSpheres. In April 2015, QuiremSpheres received Conformité Européenne (CE) mark approval for the

Abbreviations: CE, Conformité Européenne; ^{166}Er, Erbium-166; FDA, Food and Drug Administration; HCC, hepatocellular carcinoma; ^{165}HoCl, Holmium-165-chloride; ^{165}HoAcAc, Holmium-165 acetylacetone; ^{166}Ho, Holmium-166; ^{177}Lu-DOTATATE, Lutetium-177-dotatate; MRI, magnetic resonance imaging; PET/CT, positron emission tomography/computed tomography; PLLA, poly-L-lactic acid; SPECT/CT, single-photon emission computed tomography/computed tomography; ^{99m}Tc-MAA, technetium-99m-macroaggregated albumin; ^{90}Y, Yttrium-90

University Medical Center Utrecht (UMCU), Utrecht, Netherlands.

Address reprint requests to Margot T.M. Reinders, MSc, University Medical Center Utrecht (UMCU), Heidelberglaan 100, 3584 CX Utrecht, Netherlands. E-mail: m.t.m.reinders@umcutrecht.nl

https://doi.org/10.1053/j.semnuclmed.2019.01.008
0001-2998/

treatment of unresectable liver tumors and they are currently available in Europe and a few selected countries outside Europe.

Holmium Microspheres—Specifications and Activity Calculation

^{166}Ho microspheres are made of poly-L-lactic acid. The poly-L-lactic acid constitutes a matrix which contains holmium-165. Of the holmium-165, a fraction is activated to ^{166}Ho by neutron activation in a nuclear reactor. The final product is quality checked prior to shipment to the customer. The activity of the final product is patient specific and matches the activity at reference time as ordered by the customer.

^{166}Ho microspheres are delivered with the following specifications and differ on several aspects compared to the other commercially available microspheres (Table 1). Microsphere size of the three products is quite comparable. ^{166}Ho microspheres have a mean diameter of 30 μm (range 15-60 μm), compared to a median diameter of 32.5 μm (range 20-60 μm) of resin microspheres and a mean diameter of 20-30 μm of glass microspheres.[1,2] The density of ^{166}Ho microspheres is 1.4 g/cm^3, compared to 1.6 g/cm^3 and 3.3 g/cm^3 for resin and glass microspheres, respectively. The density of ^{166}Ho microspheres is the closest to that of blood, which could positively influence the intravascular flow dynamics of the microspheres and therefore its biodistribution.

^{166}Ho emits low-energy gamma rays (81 keV, 62%) besides beta radiation (maximum energy: 1.85 MeV, 50% and 1.77 MeV, 48.7%) when it emits an electron to reach its steady state as decay product Erbium-166. With the emitted low gamma rays, visualization of the microspheres is possible by single-photon emission computed tomography/computed tomography (SPECT/CT). As both holmium and erbium are lanthanides, visualization of the microspheres is possible by magnetic resonance imaging (MRI) of the paramagnetic metal (see section "Imaging").

The maximum beta particle range in soft tissue of ^{166}Ho is approximately 9 mm with a mean of 2.5 mm, whereas the beta particles of ^{90}Y reach up to 11 mm with a mean of 2.5 mm.[1,2] Furthermore, the half-life of ^{166}Ho- and ^{90}Y-microspheres differ significantly, 26.8 and 64.1 hours, respectively. Due to the shorter half-life and differences in energy spectra, more activity is needed when using ^{166}Ho microspheres to attain the same radiation-absorbed dose compared to ^{90}Y microspheres. As a result, approximately 90% of the radiation is released within the first 4 days after delivery compared to eleven days with ^{90}Y microspheres.[1]

Activity calculation for ^{166}Ho microspheres is currently based on the Medical Internal Radiation Dose model assuming a homogeneous distribution of the microspheres and no lung shunt (although it is known that homogenous distribution is an oversimplification). Based on the findings of the phase 1 dose escalation study, the recommended whole-liver average absorbed dose is 60 Gy.[3] Using the target volume (or liver weight), one can easily calculate the amount of activity required for treatment using the following formula:

$$A_{Ho166}\,[MBq] = 3781\,[MBq/kg] \times LW\,[kg]$$

If treatment is planned based only on specific segments, the required activity should be calculated based on the weight of the specific liver segment, as a fraction of the total liver weight.

Liver (segmental) weight of the patient should be determined based on (cone-beam) CT or MRI using a software program of choice.

QuiremSpheres Delivery Set and Customer Kit

The QuiremSpheres Delivery Set contains the tubing to the catheter and to the V-vial. The V-vial is the vial containing the radioactive microspheres. The QuiremSpheres Customer Kit, which contains the administration box, vial holder, needle guide, bag hook, light-emitting diode light, and waste

Table 1 Microsphere Characteristics

	SIR-Spheres	TheraSphere	QuiremSpheres
Matrix	Resin	Glass	Poly-L-lactic acid
Diameter (mean)	32 μm	25 μm	30 μm
Diameter range	30-60 μm	20-30 μm	15-60 μm
Density	1.6 g/ml	3.3 g/mL	1.4 g/mL
Isotope	^{90}Y	^{90}Y	^{166}Ho
β-energy	2.28 MeV	2.28 MeV	1.81 MeV
γ-energy	-	-	81 keV (6.7%)
Half-life	64.1 h	64.1 h	26.8 h
Number of microspheres (for 3 GBq activity)	50 million	4 million	30 million
Amount of mg per dose	1370 mg	110 mg	600 mg
Activity per microsphere	50 Bq	1250-2500 Bq	67-400 Bq
Imaging techniques	Bremsstrahlung SPECT/PET	Bremsstrahlung SPECT/PET	SPECT/MRI
Surrogate particle/ Scout dose	^{99m}Tc-MAA	^{99m}Tc-MAA	^{99m}Tc-MAA/^{166}Ho microspheres

container, together with the QuiremSpheres Delivery Set composes the administration system for QuiremSpheres. The vial holder features lead-shielding and the needle guide is made of tungsten to protect against the gamma-rays.

Comparable to the administration systems of the other vendors, during the assembly of the administration system all air is removed from the tubing by flushing the system with saline. Alternating administration of QuiremSpheres and contrast agent is recommended, like with ^{90}Y-resin microspheres, and in theory, it could be administered simultaneously during the procedure. To allow the operator to look at the sediment layer of microspheres, the V-vial is backlit with a light-emitting diode light. The activity remaining in the V-vial after several saline flushes (±20 cc) of the V-vial is negligible according to the manufacturer and therefore application of a final air bolus is not recommended. An air bolus requires needle manipulation and would pose unnecessary risk of radioactive contamination of the box or operator.

After administration, the tube to the V-vial and the tube to the stopcock may be cut and discarded together with the V-vial, microcatheter, and draping, separately from the rest of the tubing to minimize radioactive waste.

Radioembolization Procedure With ^{166}Ho

Contraindications for radioembolization with ^{166}Ho microspheres are similar as for ^{90}Y radioembolization. Patients need a good quality contrast-enhanced multiphased CT scan to be able to visualize hepatic vasculature and precisely localize the tumors before treatment. Prior to the administration of the therapeutic activity, patients undergo a safety procedure. During a preparatory angiography, the anatomy is confirmed, injection positions are determined, and administration of a scout dose, either ^{99m}Tc-macroaggragated albumin (^{99m}Tc-MAA) or a small number of ^{166}Ho-particles, is performed. Currently, ^{99m}Tc-MAA is used as a scout dose, consisting of approximately 150,000 randomly shaped particles.[4] In the case of ^{166}Ho microspheres, a scout dose can be used consisting of ^{166}Ho microspheres with limited radioactivity (approximately 250 MBq) and limited embolization effect (60 g; approximately 3 million particles). Since the ^{166}Ho scout dose microspheres are of identical shape and size to the ^{166}Ho microspheres used for therapy, it is expected that it better predicts the intra- and extrahepatic distribution than ^{99m}Tc-MAA. This has indeed been confirmed for prediction of lung shunting and intrahepatic biodistribution.[5] The scout dose is sufficient in activity to be visualized using SPECT/CT, but low enough to be clinically safe.[6]

The safety procedure enables the treatment team to predict the intrahepatic distribution of the microspheres and visualize possible extrahepatic deposition. Like with ^{90}Y particles, uncorrectable extrahepatic depositions in gastrointestinal organs, such as duodenum, stomach, and pancreas, or lungs (if calculated absorbed dose is >30 Gy), is a contraindication for treatment. By using a scout dose, the need for (additional) coil-embolization, different injection positions, or the use of an antireflux catheter can be assessed. The ^{166}Ho scout dose can be used to better assess the safety profile and future toxicity for the patient. This could potentially lead to a more efficacious therapy as the maximum amount of radioactivity delivered to the tumor can be optimized, while ensuring that the radiation-absorbed dose to healthy liver tissue remains within safe limits, thus limiting toxicity. So far, the ^{166}Ho scout dose has been used in clinical studies only and is not yet commercially available, QuiremScout is now granted CE mark approval.

Following a successful safety procedure, patients can undergo the treatment procedure with the therapeutic amount of ^{166}Ho activity. Similar to therapy with ^{90}Y resin microspheres, pulsatile administration of the microspheres is performed with alternately visual checks for potential stasis.

Radiation Safety

The radiation exposure for personnel should be reduced as much as possible based on the As-Low-As-Reasonably-Achievable principles. During treatment, measurements performed at University Medical Center Utrecht indicated that the additional radiation exposure to staff due to the ^{166}Ho microspheres procedure is negligible compared to the scattered X-rays from the X-ray tube prior and throughout the procedure.

Certain precautionary measures should be taken in order to prevent radioactive contamination. As for the ^{90}Y procedures, it is recommended to use a new microcatheter for each injection position and a fluid-absorbing drape should be placed both on the trolley carrying the administration system and underneath the connection between the microcatheter and the administration system. A fluid-absorbing drape on the floor of the angiography suite, covering the working area, can be considered. Detailed regulations concerning treatment administration and releasing the angiography suite after a treatment with ^{166}Ho microspheres may vary between centers and countries. Unforeseen radioactive contaminations by ^{166}Ho microspheres might be more easily detected than contamination by ^{90}Y microspheres, because of the primary gamma photon emitted by ^{166}Ho.

Depending on the amount of administered therapeutic activity and the timing of release, patients can be released after treatment with contact restrictions (eg, sleeping separately from their partners, avoiding contact with children and pregnant women), because of the additional γ-particle emission of ^{166}Ho. These restrictions are based on reduction of radiation by distance and time and in consensus with the instructions by the Nuclear Regulatory Commission for patients with permanent implants.[7,8]

Imaging

SPECT/CT Imaging

The characteristics of ^{166}Ho allow for visualization with SPECT/CT and MRI. SPECT has proven to increase the

accuracy of extrahepatic deposition detection with ^{99m}Tc-MAA compared to planar imaging. Detection of potential extrahepatic depositions is considered to be the most important reason for scout dose treatment simulation and thus SPECT/CT is considered mandatory by most expert centers.[9] ^{166}Ho scout dose is able to detect extrahepatic depositions.[6] ^{166}Ho emits gamma photons and bremsstrahlung photons that can be detected by the gamma cameras of a SPECT system, but that interact with the patient and the detector, causing image-degrading effects. Proper collimator selection and reconstruction parameters improve image quality and reduce scatter. Acquisition of SPECT images takes approximately 30 minutes, which has the disadvantage of breathing-motion artifacts. To prevent additional noise on SPECT/CT, caused by a number of high energy γ's of ^{166}Ho, the use of a medium-energy or high-energy collimator is recommended. Using multienergy window imaging (81 keV energy window ±15% and additional scatter windows) along with common iterative reconstruction methods of known gamma camera manufacturers, images with high resolution and quality can be acquired. For quantitative imaging, more sophisticated reconstruction methods are paramount, because of the different decay products of ^{166}Ho. These can be predicted by Monte Carlo simulation that simultaneously compensates for attenuation, scatter, and collimator-detector response and therefore improves quantification, for example, lung shunt calculation.[5,10,11] Secondly, because ^{166}Ho decays to the stable isotope Erbium-166, imaging should be performed within 6 days after administration as otherwise there are no gamma photons to detect anymore. On the other hand, when the activity is above 1420 MBq detector dead time may play a role in imaging quality, depending on the SPECT-system used.[11] To account for dead time (or saturation) and calibration factor, the manufacturer provides calibration products to determine the maximum ^{166}Ho activity level that can be accurately measured by the SPECT system available in an institute. The benefit of ^{166}Ho is its superior imaging capabilities with both SPECT as well as MRI compared to the current imaging acquired with ^{90}Y. ^{90}Y (bremsstrahlung) photons can be captured by SPECT as well, but due to the broad spectrum of energies released by the ^{90}Y photons and relatively low yield, image quality is limited and often results in blurred images, which makes quantitative imaging more challenging. On the other hand, ^{90}Y PET imaging has emerged as a new image modality. There are two major issues in ^{90}Y PET/CT imaging: the low true-coincidence rate and the high singles rate due to bremsstrahlung X-rays. The first issue may result in noisy images, long scan times, and background noise from scintillator-decay. The singles-count rate from bremsstrahlung is much higher than the positron emission rate and may cause saturation of the detector, leading to a limited quantitative accuracy.[12] However, this latter issue has not been found in recent investigations.[13]

Magnetic Resonance Imaging

MR imaging of ^{166}Ho microspheres is independent of radioactivity. In addition, it has higher resolution and can easily be combined with anatomical scans without the burden of breathing-motion as acquisition takes only several seconds. However, MRI is not suitable for tissues that contain air, such as the lungs and gastrointestinal organs or tissues containing metal, for example, staples, surgical clips and/or coils. The linear relationship between T2* times and holmium concentration was shown in rabbit livers and phantoms.[14-17] The feasibility of MR quantification of ^{166}Ho microspheres has been validated in humans using SPECT as a reference standard.[18,19] Currently, MRI protocols are being optimized for clinical application.

Clinical Research

An overview of finished and several ongoing studies with ^{166}Ho radioembolization in the Netherlands is presented in Table 2.

Performed Studies

Holmium Embolization Particles for Arterial Radiotherapy

The Holmium Embolization Particles for Arterial Radiotherapy (HEPAR) trial was a dose-escalating study that was published in 2012 by Smits et al to find the maximum tolerated radiation dose in patients with unresectable, chemorefractory liver metastases from different primary cancers.[3] It was concluded that ^{166}Ho radioembolization is feasible and safe based on the inclusion and treatment of 15 patients who received whole-liver absorbed doses of either 20, 40, 60, or 80 Gy. Dose-limiting toxicity was defined as an adverse event exceeding grade two as described by the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 3.0) and was possibly or probably related to the ^{166}Ho radioembolization. In the first cohort of three patients, one patient had a pulmonary embolism; therefore, three more patients were added to the first cohort. No serious adverse events were seen in the second and third cohort, whereas two of three patients had dose-limiting toxicities in the fourth (80 Gy) cohort. Therefore, it was decided that the maximum tolerated radiation dose is 60 Gy and would be used in the following phase II trial.

HEPAR II

In the phase II trial (HEPAR II), efficacy was the main aim for which 48 patients with progressive liver metastases of various primaries were included.[20] Data from HEPAR and HEPAR II patients were used to acquire CE mark approval for ^{166}Ho microspheres in 2015. For quantification of the microsphere distribution, all patients underwent SPECT/CT and MR imaging. To follow-up on efficacy, all patients also underwent contrast-enhanced CT and ^{18}F-FDG-PET/CT scans at 3, 6, 9, and 12 months after treatment. These scans were then rated by three radiologists independently and blinded for time of imaging. The HEPAR II trial recruited 38

Table 2 Overview of Clinical Studies With ^{166}Holmium in the Netherlands

Trial	Status	Study Design	Tumor Types	Number of Patients	Intervention
HEPAR I	Finished	Dose-finding study	Liver metastases, mixed primaries	15	^{166}Ho radioembolization
HEPAR II	Finished	Efficacy study	Mainly liver metastases, mixed primaries	38	^{166}Ho radioembolization
HEPAR +	Recruitment finished	Efficacy study	Neuroendocrine liver metastases	30	i.v. ^{177}Lu-DOTATATE + ^{166}Ho radioembolization
SIM	Recruiting	Within-patient RCT	Colorectal liver metastases	25	^{166}Ho radioembolization, anti-reflux- vs. standard catheter
HEPAR Primary	Recruiting	Two-center, efficacy study	Hepatocellular carcinoma (intermediate-advanced stage)	30	^{166}Ho radioembolization
Hora Est	Recruiting	Multicenter, dose-finding study	Hepatocellular carcinoma (early stage)	10-30	RFA + ^{166}Ho radioembolization

patients with different primary tumors, of which 37 patients were evaluable for the primary endpoint. Of these 37 patients, 73% showed complete response, partial response, or stable disease 3 months after treatment. Adverse events were comparable to known adverse events with ^{90}Y radioembolization (mainly abdominal pain and fatigue). Health-related quality of life (QoL) patient reported outcomes showed a decrease in QoL at 1 week after the procedure, but had returned to baseline values at 6 weeks follow-up, consistent with the rate of reported adverse events and in line with the expected postembolization syndrome.[20]

Ongoing Studies in the Netherlands

SIM Study

Microspheres for radioembolization are normally injected via a standard end-hole microcatheter. There are, however, several more advanced microcatheters available that claim to have an antireflux effect and lead to an increased tumor dose.[21,22] One of these catheters is the Surefire Infusion System, which is currently investigated in the SIM study (full name: "Surefire Infusion System vs Standard Microcatheter Use during ^{166}Ho Radioembolization").[23] The SIM study investigates whether the use of an antireflux catheter increases the tumor to nontumor activity concentration ratio compared to a standard end-hole microcatheter. Twenty-five patients with unresectable, chemorefractory, liver-dominant, bilobar colorectal metastases will receive ^{166}Ho radioembolization and via within-patient randomization, the use of standard or antireflux catheter will be randomly assigned to the infusion site (left or right hepatic artery).[24] The primary endpoint, differences in tumor to nontumor activity ratios between the two microcatheters used, will be determined on the post-treatment SPECT/CT scans. Secondary endpoints entail the differences between catheters in mean absorbed doses of radioactivity in tumorous and healthy liver tissue, tumor response, and predictive value of ^{166}Ho and infusion efficiency. Additionally, dose-response relationships (both on anatomical and metabolic imaging), clinical toxicity, and overall survival will be assessed for all patients.

HEPAR PLUS Study

The most incriminating factor for survival for a patient with a metastatic neuroendocrine tumor is the presence of liver metastases.[25] The recently published randomized controlled trial on systemic radionuclide treatment with ^{177}Lu-DOTATATE has shown promising long-term results; however, the objective response rate 3 months after treatment is 18%.[26] Recently completed its recruitment, another phase II trial called ^{166}HEPAR Plus ^{177}Lu-dotatate in Salvage NET patients, a.k.a. HEPAR PLUS trial, aims to further decrease hepatic tumor burden by applying an additional radiation boost on liver metastases.[27] In the HEPAR PLUS trial, 30 patients with residual neuroendocrine liver metastases

(>3 liver metastases, measurable according to RECIST 1.1) after four cycles of systemic intravenous ^{177}Lu-DOTATATE were treated with ^{166}Ho radioembolization, within 20 weeks after the fourth cycle of ^{177}Lu-DOTATATE.[25] Primary objective is response rate, assessed 3 months after ^{166}Ho radioembolization on multiphased CT, rated by independent radiologists according to RECIST 1.1 and mRECIST. Furthermore, treatment combination safety, QoL, biodistribution, dosimetry, and adverse events are evaluated as secondary endpoints.

HEPAR Primary Study

The multicenter phase II trial "HEPAR Primary: ^{166}Ho radioembolization in Hepatocellular Carcinoma (HCC) patients' started recruiting patients earlier this year (2018).[28] The main objective is to establish the safety and toxicity profile of ^{166}Ho radioembolization in unresectable advanced HCC patients (either BCLC B or C). Secondary endpoints include efficacy, tumor marker response, QoL through questionnaires, biodistribution/dosimetry based on SPECT/CT as well as MR imaging and hepatobiliary scintigraphy for the assessment of hepatic function pre- and post-treatment.

HORA EST

In the HORA EST study (full name: HOlmium radioembolization as adjuvant treatment to Radiofrequency Ablation for Early STage HCC: a dose-finding study), patients with early-stage HCC receive holmium radioembolization as adjuvant treatment after radiofrequency ablation.[29] The rationale is to decrease the local recurrence rate. This is a phase I dose-finding study, to determine the treatment area dose that will result in delivery of a radiation-absorbed dose of $\geq$120 Gy to the target area in at least 90% of patients. Secondary endpoints include toxicity, local tumor recurrence, and QoL. The Leiden University Medical Center has started recruitment for this study.

Future Perspectives

The field of Nuclear Medicine and radioembolization in particular is subject to constant and rapid change. For instance, indications have expanded from last-resort therapy to downstaging prior to surgery or to induce contralateral hypertrophy prior to surgery akin to portal vein embolization.[30,31] The use of a ^{166}Ho scout dose might pave the road for more personalized medicine since one can reliably determine the dose to the healthy liver and tumors prior to treatment. Future efforts should be aimed at personalizing radioembolization therapy. Several research groups worldwide have shown promising data on tumor absorbed dose—tumor response correlations.[32] The data gathered from the patients treated in prospective trials thus far at a whole-liver dose of 60 Gy will help to understand how dosing might be optimized for future patients. Based on these results, future phase III randomized controlled studies will include more sophisticated dosimetric models.

Part of the work to improve personalized dosimetry is focused on the fact that ^{166}Ho allows dual-isotope imaging with ^{99m}Tc-labelled radiopharmaceuticals. Promising preliminary results have been obtained with a dual-isotope protocol with the ^{166}Ho scout dose and a ^{99m}Tc-labelled colloid, in which ^{166}Ho simulates the treatment distribution and the radiocolloid (semi-)automatically delineates the healthy liver tissue.[33] Via several postprocessing methods, fast voxel-based dosimetry (within several hours) and automated dose-volume histograms can become widely available. One of the main benefits of the dual-isotope protocol is the simultaneous acquisition of both scans, thus avoiding patient-related artifacts (eg, motion) and imaging registration issues (acquisition time is identical).

Looking at prospective clinical data, the results of the HEPAR PLUS study are expected in the first half of 2019, which will bring new insights in the treatment of NET patients and the combination of ^{166}Ho radioembolization with ^{177}Lu-DOTATATE treatment. The results of HEPAR PLUS are expected to further establish the role of radioembolization within the complex treatment paradigm of NET. Ongoing clinical research will provide us with new knowledge on biodistribution/dosimetry and personalized patient treatment.

In conclusion, ^{166}Ho microspheres are a valuable alternative to ^{90}Y microspheres for clinical use. The main potential advantages of ^{166}Ho microspheres lie in the imaging characteristics and better dosimetry using a scout dose of ^{166}Ho microspheres.

References

1. SIRTeX. SIR-Spheres Microspheres. Instructions for use. 2016. Available from: https://www.sirtex.com/media/155127/pi-ec-12.pdf
2. BTG. TheraSphere yttrium-90 glass microspheres instructions for use. Available from: https://www.btg-im.com/BTG/media/TheraSphere-Documents/PDF/10093509-Rev8_English-searchable.pdf
3. 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. Lancet Oncol 13:1025-1034, 2012
4. Van de Wiele C, Maes A, Brugman E, et al: SIRT of liver metastases: Physiological and pathophysiological considerations. Eur J Nucl Med Mol Imaging 39:1646-1655, 2012
5. 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 41:1965-1975, 2014
6. Braat AJAT, Prince JF, van Rooij R, et al: Safety analysis of holmium-166 microsphere scout dose imaging during radioembolisation work-up: A cohort study. Eur Radiol 28:920-928, 2018
7. Prince JF, Smits MLJ, Krijger GC, et al: Radiation emission from patients treated with holmium-166 radioembolization. J Vasc Interv Radiol 25:1956-1963, 2014. e1
8. U.S. Nuclear Regulatory Commission. Release of patients administered radioactive materials. Regul Guide 8:39, 1997
9. Ahmadzadehfar H, Muckle M, Sabet A, et al: The significance of bremsstrahlung SPECT/CT after yttrium-90 radioembolization treatment in the prediction of extrahepatic side effects. Eur J Nucl Med Mol Imaging 39:309-315, 2012
10. Elschot M, Smits MLJ, Nijsen JFW, et al: Quantitative Monte Carlo-based 90Y SPECT reconstruction. J Nucl Med 54:1557-1563, 2013

11. Elschot M, Nijsen JFW, Dam AJ, et al: Quantitative evaluation of scintillation camera imaging characteristics of isotops used in liver radioembolization. PLoS One 6:11, 2011.
12. Pasciak AS, Bourgeois AC, McKinney JM, et al: Radioembolization and the dynamic role of 90Y PET/CT. Front Oncol 4, 2014
13. Willowson KP, Tapner M, Bailey DL: A multicentre comparison of quantitative (90)Y PET/CT for dosimetric purposes after radioembolization with resin microspheres: The QUEST phantom study. Eur J Nucl Med Mol Imaging 42:1202-1222, 2015
14. Nijsen JFW, Seppenwoolde JH, Havenlth T, et al: Liver tumors: MR imaging of radioactive holmium microspheres—Phantom and rabbit study. Radiology 231:491-499, 2004
15. Seevinck PR, Seppenwoolde JH, Zwanenburg JJM, et al: FID sampling superior to spin-echo sampling for T2*-based quantification of holmium-loaded microspheres: Theory and experiment. Magn Reson Med 60:1466-1476, 2008
16. Seevinck PR, van de Maat GH, de Wit T, et al: Magnetic resonance imaging-based radiation-absorbed dose estimation of 166Ho microspheres in liver radioembolization. Int J Radiat Oncol Biol Phys 83:e437-e444, 2012
17. Seevinck PR, Seppenwoolde JH, de Wit T, et al: Factors affecting the sensitivity and detection limits of MRI, CT, and SPECT for multimodal diagnostic and therapeutic agents. Anticancer Agents Med Chem 7:317-334, 2007
18. 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 23:827-835, 2013
19. Smits MLJ, Elschot M, van den Bosch MAAJ, et al: In vivo dosimetry based on SPECT and MR imaging of 166Ho-microspheres for treatment of liver malignancies. J Nucl Med 54:2093-2100, 2013
20. 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 59:582-588, 2018
21. Pasciak AS, McElmurray JH, Bourgeois AC, et al: The impact of an antireflux catheter on target volume particulate distribution in liver-directed embolotherapy: A pilot study. J Vasc Interv Radiol 26:660-669, 2015
22. Arepally A, Chomas J, Kraitchmann D, et al: Quantification and reduction of reflux during embolotherapy using an antireflux catheter and tantalum microspheres: Ex vivo analysis. J Vasc Interv Radiol 24:575-580, 2013
23. Van den Bosch, MAAJ: Surefire infusion system vs. standard microcatheter use during holmium-166 radioembolization (SIM). Clinical Trials. gov Identifier: NCT02208804. 2014; Available from: https://clinicaltrials.gov/ct2/show/NCT02208804?term=surefire+holmium&rank=1
24. van den Hoven AF, Prince JF, Bruijnen RCG, et al: Surefire infusion system versus standard microcatheter use during holmium-166 radioembolization: Study protocol for a randomized controlled trial. Trials 17:520, 2016
25. Braat AJAT, Kwekkeboom DJ, Kam BLR, et al: Additional hepatic (166) Ho-radioembolization in patients with neuroendocrine tumours treated with (177)Lu-DOTATATE; a single center, interventional, non-randomized, non-comparative, open label, phase II study (HEPAR PLUS trial). BMC Gastroenterol 18:84, 2018
26. Strosberg J, El-Haddad G, Wolin E, et al: Phase 3 trial of (177)Lu-dotatate for midgut neuroendocrine tumors. N Engl J Med 376:125-135, 2017
27. Lam MGEH: Holmium-166-radioembolization in NET after lutetium-177-dotatate; an efficacy study (HEPAR Plus). ClinicalTrials.gov Identifier: NCT02067988. 2014; Available from: https://clinicaltrials.gov/ct2/show/NCT02067988?term=NCT02067988&rank=1
28. Lam MGEH: HEPAR primary: Holmium-166-radioembolization in hepatocellular carcinoma patients. ClinicalTrials.gov Identifier: NCT03379844. 2017; Available from: https://clinicaltrials.gov/ct2/show/NCT03379844?term=NCT03379844&rank=1
29. Burgmans MC: Holmium radioembolization as adjuvant treatment to RFA for early stage HCC: Dose finding study (HORA EST HCC). ClinicalTrials.gov Identifier: NCT03437382. 2018; Available from: https://clinicaltrials.gov/ct2/show/NCT03437382?term=hora+est&rank=1
30. Palard X, Edeline J, Rolland Y, et al: Dosimetric parameters predicting contralateral liver hypertrophy after unilobar radioembolization of hepatocellular carcinoma. Eur J Nucl Med Mol Imaging 45:392-401, 2018
31. Goebel J, Sulke M, Lazik-Palm A, et al: Factors associated with contralateral liver hypertrophy after unilateral radioembolization for hepatocellular carcinoma. PLoS One 12:0181488, 2017
32. Kappadath SC, Mikel J, Balagopal A, et al: Hepatocellular carcinoma tumor dose response after (90)Y-radioembolization with glass microspheres using (90)Y-SPECT/CT-based voxel dosimetry. Int J Radiat Oncol Biol Phys 102:451-461, 2018
33. Braat AJAT, Van Rooij R, Van den Bosch MAAJ, et al: Improved dosimetry in radioembolization using a dual isotope SPECT/CT protocol with 166Ho-microspheres and 99m Tc-stannous phytate: A proof of concept. J Nucl Med 57:1423, 2016