Hepatic Radioembolization in Neuroendocrine Neoplasms

Arthur J.A.T. Braat

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Colophon

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PhD thesis, Utrecht University – with a summary in Dutch

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ISBN: 978-94-028-1647-1
Cover Design: A.J.A.T. Braat & R. Sanders
Lay-out: R. Sanders
Printing: Ipskamp Printing B.V.

Hepatic Radioembolization in Neuroendocrine Neoplasms

Radioembolisatie van de lever in neuroendocrine neoplasmata

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor
aan de Universiteit Utrecht
op gezag van de rector magnificus, prof.dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op
vrijdag 20 september 2019
des middags te 4.15 uur

door

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geboren op 29 juni 1987
te Breda

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Chapter 1

General introduction

In the last couple of decades medical advances in the treatment of hepatic malignancies have rapidly developed, but surgical liver resection currently remains the primary modality for curation. Nevertheless, a lot of research is being performed on minimally invasive techniques directed towards the liver, to offer irresectable patients better chances of survival. Already described in 1966 by Dr. Michels, most hepatic malignancies solely, or mainly rely on arterial blood supply, whilst healthy liver parenchyma mostly relies on portal supply [1]. In 1994, Andrews et al. used this dual blood supply concept and they reported their initial results on a dose-escalation study using yttrium-90 (^{90}Y) loaded glass microspheres for the intra-arterial treatment of intrahepatic malignancies in 24 patients [2]. This was the beginning of the development of a new minimally invasive treatment, called Selective Internal Radiation Therapy (SIRT), a.k.a. radioembolization. Nowadays, radioembolization with either ^{90}Y-microspheres or holmium-166 (^{166}Ho)-microspheres is a well-established liver-directed treatment for patients suffering from different hepatic malignancies.

The hypervascular nature of liver malignancies leads to preferential blood flow from the artery towards the tumors. Microspheres injected in the hepatic artery will therefore preferentially lodge in the arterioles in and around the tumor. As the ^{90}Y or ^{166}Ho isotope decays, beta-particles are released that irradiate the tumor cells and damage tumor DNA, which leads to cell apoptosis and tumor reduction.

In the University Medical Center Utrecht, the collaboration between Nuclear Medicine, Radionuclide Pharmacy and Interventional Radiology resulted in a dedicated team of physicians, physicists, pharmacists and researchers interested in the development and refinement of radioembolization since the start of our clinical radioembolization program in 2009. Currently, the body of evidence on radioembolization in hepatic malignancies primarily resides with hepatocellular carcinoma (HCC) and liver metastases of colorectal carcinoma (mCRC). For patients with liver-only or liver-dominant disease suffering from HCC or mCRC, radioembolization is currently reimbursed in the Netherlands.

Liver-directed treatment of neuroendocrine liver metastases

At the time of diagnosis, 21-50% of neuroendocrine neoplasms (NEN) show disseminated disease, of which the liver is the most common affected site. At that stage, only 20-30% of NEN patients is eligible for surgical resection with curative intent. Liver metastases of NEN are usually hypervascular, like HCC. In theory, patients suffering from NEN liver metastases may benefit from an intra-arterial

treatment like radioembolization. Looking at the revised guideline of the European NeuroEndocrine Tumor Society (ENETS) from 2016, liver-directed treatments are often placed at the end of the treatment paradigm and reserved for patients with liver-dominant or liver-only disease, as depicted in **figure 1** [3]. In selected cases, it is advocated to apply liver-directed treatments earlier on in the disease to prevent hormone-related complaints or complications in functioning NEN. In another sub-selection of patients with liver-only disease, liver directed treatments may be considered instead of systemic treatments.

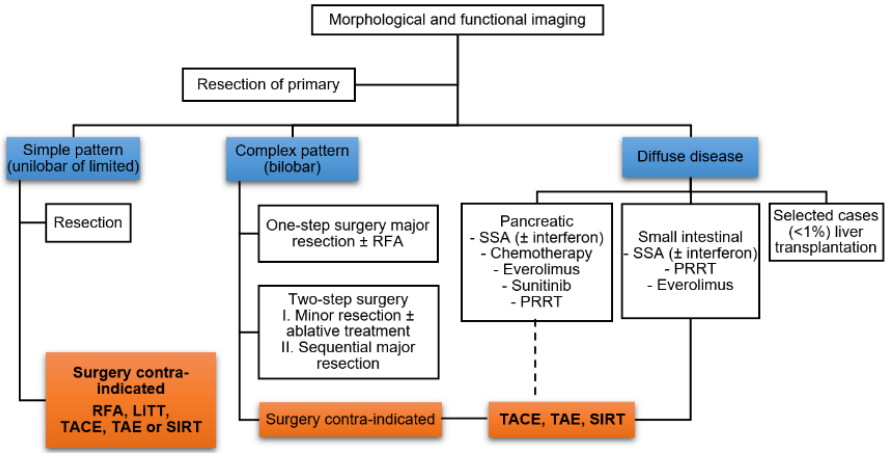

Figure 1. Flowchart from the most recent ENETS guideline (2016) on metastatic liver disease in grade 1 and grade 2 neuroendocrine tumors. Patterns defined by disease extent and locations within the liver. In orange boxes the place of liver-directed treatments in this guideline. RFA = radiofrequency ablation, LiTT = Laser-induced thermotherapy, TACE = trans-arterial chemoembolization, TAE = transarterial (bland) embolization, SIRT = selective internal radiation therapy, a.k.a. radioembolization, SSA = somatostatine analog, PRRT = peptide receptor radionuclide therapy.

The lack of large prospective trials on liver-directed embolizing therapies is the main reason for this conservative approach. Three embolizing therapies are often discussed; transarterial (bland) embolization (TAE), transarterial chemoembolization (TACE) and radioembolization. Common practice with TAE is a sequential whole liver approach (first one liver lobe and weeks-months later the other liver lobe), using relatively large particles ranging from 100-300 µm. During TAE the entire arterial supply of one lobe is completely embolized, resulting in devascularization / hypoxia of the tumors and healthy liver tissue (i.e. transient liver ischemia). TACE may be

performed in a lobar or selective approach, but combines complete embolization (like TAE) with chemotherapy embedded in the TACE particles. These particles are often smaller than bland particles (ranging from 50-150 µm) and can have different chemotherapeutics (most commonly used is doxorubicin). Contrarily to the other two liver-directed treatments, radioembolization uses smaller particles (around 30 µm) and does not aim for complete embolization of the arterial supply. In that sense the word 'radioembolization' is a misnomer, because arterial blood flow is (partially) maintained. The main reason not to aim for complete devascularization after radioembolization is the need for oxygen radicals to cause the radiation induced DNA damage. Once liver-directed treatments are considered in a NEN patient, the type of treatment depends on the physician's experience rather than evidence. As mentioned in the ENETS guideline, specifically radioembolization is deemed investigational, due to the sparse literature and lack of clinical trials on radioembolization in NEN [3]. Comparative data on the embolizing therapies is limited and up to now, no comparative prospective trials have been conducted. A retrospective analysis on USA data showed no specific preference for either one of the embolizing treatments, besides a suggested longer overall survival for patients treated with radioembolization compared to TACE [4]. Currently, one prospective randomized controlled trial is recruiting patients to compare TAE with TACE [5]. No large prospective trials comparing radioembolization to either TAE or TACE currently exist.

Basics of radioembolization

As radioembolization is a relatively complex treatment procedure, many aspects of the treatment need to be considered and a dedicated team should be involved in all treatment procedures. **Figure 2** illustrates the different steps in a radioembolization procedure, which will be discussed in more detail.

First off all, appropriate patient selection is needed to define appropriate candidates for radioembolization. Patients should have sufficient liver function, defined by the Child Pugh score (i.e. <B8), and a good or reasonable general performance, defined as an Eastern Cooperative Oncology Group (ECOG) performance score 0-2. Adequate morphological and functional imaging are paramount. Anatomical multiphase CT, especially the early arterial phase, allows the assessment of the arterial blood supply, and its variants, prior to the interventional procedure. As approximately 50% of patients has one or more anatomical variants, this significantly shortens procedure times. While functional imaging, in case of NEN, with either gallium-68

labelled somatostatine receptor binding ligands (e.g. ^{68}Ga-DOTATOC) or fluor-18-desoxyglucose (^{18}FDG), depending on the NEN grade, is essential in the detection and assessment of extrahepatic disease. If a patient has liver-only or liver dominant disease, with an appropriate general performance and liver reserve, patients may be considered for radioembolization.

Based on the imaging findings prior to actual treatment, patients subsequently undergo a treatment simulation session. The interventional radiologist performs a visceral angiography, gaining access to the arterial system via the femoral artery or radial artery. The microcatheter is proceeded to the hepatic arteries via the coeliac trunk or via arterial variants using digital subtraction angiography (DSA). Arterial blood supply to the liver and its metastases is visualized and inspected on the presence of potential culprit vessels (i.e. arteries supplying extrahepatic tissues, likely to cause complications, such as the right gastric artery), and parasitic vessels (i.e. extrahepatic arteries supplying intrahepatic tumors, such as the right phrenic artery). These culprit and/or parasitic vessels are embolized using coils or bland particles, if deemed necessary and technically possible. The additional use of a cone beam CT, by rotating the C-arm, allows perprocedural confirmation of the absence of potential culprit vessels and may confirm complete tumor coverage (i.e. excluding parasitic vessels). The interventional radiologist determines the microcatheter position(s) for the treatment injection(s), and a scout dose is administered. The scout dose is a small number of particles used to simulate the intrahepatic distribution of the actual microspheres and to exclude any extrahepatic deposition of activity. Either technetium-99m-macroagreggated albumin (^{99m}Tc-MAA) or ^{166}Ho-microspheres can be used. After the angiography procedure and administration of the scout dose, the patient is transferred to a SPECT/CT system. The SPECT/CT is currently the gold standard to exclude extrahepatic depositions of activity, prior to treatment. Additionally, the SPECT/CT is essential to determine the intrahepatic distribution of the future treatment.

Based on the technical feasibility, determined by the interventional radiologist during the angiography, and based on safety, determined by the nuclear medicine physician on the SPECT/CT, patients are planned for treatment. On the day of treatment, the patient undergoes a second visceral angiography and the previously determined injection positions are reproduced. In that exact position, the actual therapeutic dose of radioactive microspheres is administered. Finally, post-treatment imaging is performed to confirm the absence of extrahepatic depositions, to evaluate the distribution of the microspheres within the liver and to confirm treatment of all targeted tumors. Patients are discharged within 24

hours after treatment. They visit the outpatient clinic after 1 month for clinical and laboratory follow-up, and they return after 3 months for imaging evaluation.

Outline of this thesis

The broad aim of this thesis was to study radioembolization in NEN patients with liver metastases. To put this treatment in perspective, the many different variables of the treatment itself need to be discussed, before discussing the application of radioembolization in NEN. **Chapter 2** describes the many facets involved in a radioembolization treatment and the different considerations to be made prior to, during and after treatment. Proper patient selection is key. It directly influences the subsequent steps in the treatment (**Figure 2**). NEN patients often received prior surgical resections of the liver (e.g. hemihepatectomy) or biliary tract (e.g. Whipple procedure or pylorus preserving pancreaticoduodenectomy). The absence of the Sphincter of Oddi after a Whipple procedure may result in retrograde colonization of the biliary tract with enteral bacteria and could increase the risk of liver abscess formation. Dissection of important arteries (e.g. gastroduodenal artery) influences the arterial flow and may result in the formation of new collaterals. New collaterals may cause unwanted extrahepatic depositions, leading to the patient being excluded from treatment. As advances in radioembolization develop rapidly, especially technical aspects of the treatment need to be considered. With the introduction of the cone beam CT in the angiography suite, some say that a scout dose SPECT/CT becomes unnecessary. The increasing data on pre- and posttreatment dosimetry may lead to individualized treatment, for which many software packages are currently available. Literature on these and many other facets were discussed in **chapter 2**.

After the evaluation of the different aspects of radioembolization and moving towards personalized medicine in NEN, the concerns raised in the ENETS guideline from 2016 needed to be addressed. The main concern in the guideline was the absence of prospective data and the sparse literature on the subject. Therefore, all available literature on radioembolization in NEN was reviewed by performing a meta-analysis, as describe in **chapter 3**.

Based on our findings in the meta-analysis, the need for additional research on the correlation between radioembolization and important clinical parameters was needed. An international multicenter study was therefore conducted to address several knowledge gaps in a larger patient population, as reported in **chapter 4**.

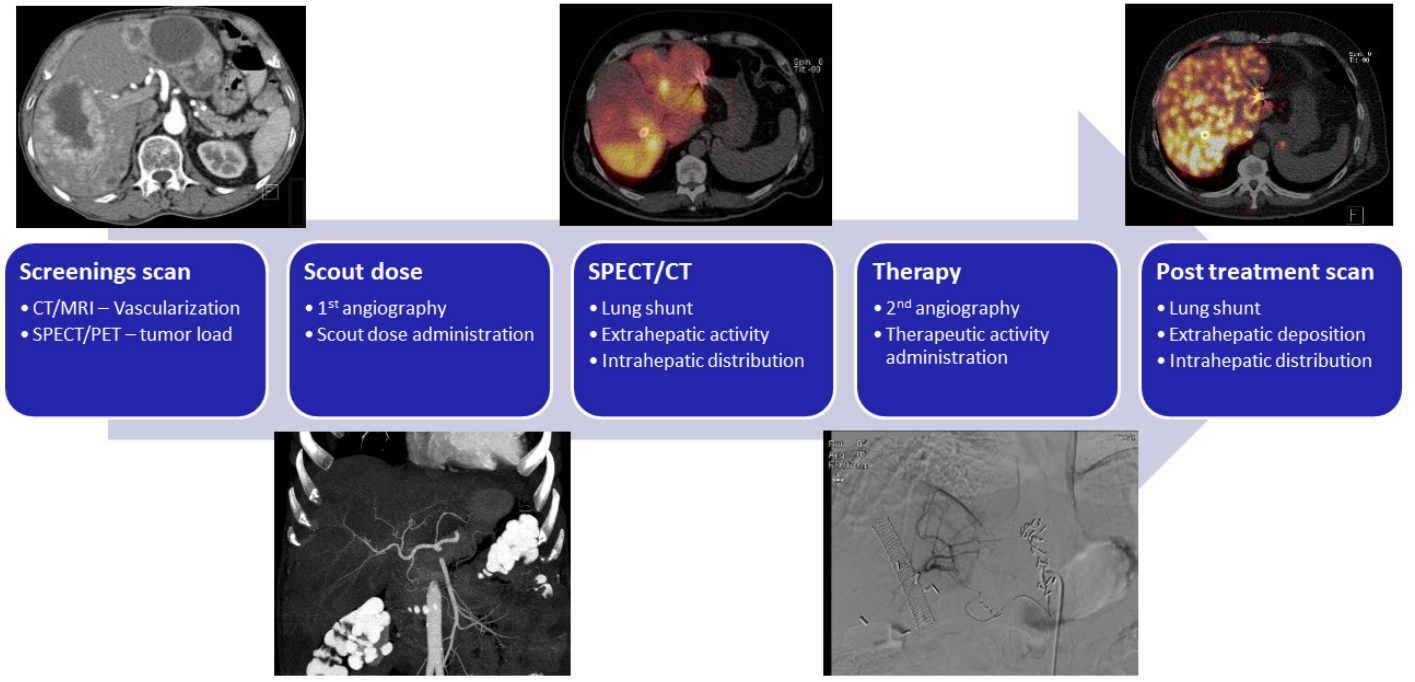

Figure 2. Flowchart of the different steps in a radioembolization treatment with the minimal acquired evaluations per step.

As most NEN patients have intra- and extrahepatic disease and the current ENETS guideline states that radioembolization should only be applied in liver dominant or liver only disease (**Figure 1**), combining a liver-directed treatment with a systemic treatment may be beneficial, especially in patients with more excessive liver disease. **Chapter 5** looks at the feasibility and safety of radioembolization after initial systemic radionuclide treatments in NEN patients. **Chapter 6** elaborates on the hypothesis that patients with residual liver disease after Peptide Receptor Radionuclide Therapy (PRRT) could benefit from a combined treatment. This chapter discusses the study protocol of the prospective HEPAR PLUS study, initiated in 2014. In January 2019, the recruitment of the HEPAR PLUS study was completed and its initial results are reported in **chapter 7.**

Currently, radioembolization resides at the end of the treatment paradigm for many different tumor types. In **chapter 8**, we elaborate on potential applications of radioembolization in earlier settings.

As emphasized in **chapters 2**, **4 and 8,** many recent technical developments will have major implications on the interpretation of currently available literature. Essential for a radioembolization treatment is a proper pre-treatment simulation. The commonly used ^{99m}Tc-MAA particles are insufficient to this end, as they physically differ from a microsphere, leading to differences in intrahepatic distribution [6, 7]. Ideally, one would use the same particle, which seems feasible when a small amount of ^{166}Ho-microspheres for pre-treatment simulation is used [8]. **Chapter 9** discusses the use and safety of a small amount of ^{166}Ho-microspheres for pre-treatment simulation in clinical practice, and its potential use for individualized treatment. Proper dosimetric calculations, based on the distribution of such a small number of ^{166}Ho-microspheres, injected as a scout dose, will be one of the steps towards actual individualized treatment. However, current methods to perform high-level dosimetry are complex and time-consuming. **Chapter 10** discusses the development of a new SPECT/CT protocol by combining two radioactive substances, ^{166}Ho and ^{99m}Tc. In theory, this scan protocol could provide (semi-)automated complex dosimetric evaluation.

Finally, this thesis is discussed in **chapter 11** and summarized in **chapter 12** (Dutch extended summary in **chapter 13**).

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Chapter 2

^{90}Y Hepatic Radioembolization: An Update on Current Practice and Recent Developments

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Journal of Nuclear Medicine 2015; 56:1079-1087

Abstract

Radioembolization is an established treatment modality that has been subjected to many improvements over the last decade. Developments are occurring at a high pace, affecting patient selection and treatment. The aim of this review is therefore to provide an overview of current practice, with a focus on recent developments in the field of radioembolization. Several practical issues and recommendations in the application of radioembolization will be discussed, ranging from patient selection to treatment response and future applications.

Introduction

As an established treatment modality for chemoresistant, unresectable hepatic malignancies, radioembolization has expanded its applications in recent years. Radioembolization is based on the administration of ^{90}Y-loaded microspheres in the arterial vasculature of the liver. Currently, two types of microspheres are Food and Drug Administration–approved and commercially available: resin microspheres (SIR-spheres; SirTex Medical) and glass microspheres (TheraSpheres; BTG International Ltd.). Because of preferential arterial flow, the microspheres occlude small tumor arterioles, thus selectively irradiating tumors. This review aims to give an overview of current developments in the field of ^{90}Y hepatic radioembolization.

Patient selection

Currently, radioembolization is indicated mainly in a palliative setting for primary and secondary hepatic malignancies, only when other (minimal) invasive or chemotherapeutic treatments have failed. Work-up for radioembolization includes clinical status, hematologic and biochemical status, anatomic assessment with CT/MR imaging, and, when appropriate, molecular imaging with SPECT/CT or PET/CT. The indications and contraindications (**Table 1**) need to be assessed by a multidisciplinary team (1,2). Unlike many treatment modalities, age is not a contraindication for radioembolization and has not been shown to alter prognosis (3,4). Sufficient liver function is of primary importance and is regarded as the greatest limitation (Child–Pugh score ≤ B7). Before considering radioembolization (when sufficient liver function is present), portal venous integrity, prior surgical treatments, and prior liver directed treatments need to be evaluated. Compromised portal venous integrity is most commonly caused by a portal vein tumor thrombus (PVT), resulting in a greater dependence of the liver parenchyma on its arterial supply (5). Theoretically, after embolization a compromised portal circulation could jeopardize liver function because of ischemia or infarction, induced by the arterial occlusion. However, radioembolization has a low embolic effect, and most of the arterial tree remains patent after treatment (6,7). Radioembolization in the setting of PVT is therefore safe and can sometimes lead to complete portal vein revascularization, even in main PVT (8). In contrast to transarterial chemoembolization (TACE), PVT is not considered a contraindication. Radioembolization is an emerging indication in early-advanced hepatocellular carcinoma (HCC) (Barcelona Clinical Liver Cancer [BCLC] C, liver-dominant, Eastern Cooperative Oncology Group [ECOG] 1–2, PVT) (8). On the basis of current evidence, application of radioembolization in patients

Table 1. Common Indications and Relative and Absolute Contraindications for Radioembolization

Indications	Relative contra-indications	Absolute contra-indications
Not amenable for surgical resection, liver transplantation or curative ablative therapies	Portal vein thrombosis of the main branch	Extensive and untreated portal hypertension
Not amenable for, refractory to, or not willing to receive chemotherapeutic alternatives	Abnormalities of the bile ducts or stents with an increased chance of infections. Exceptions: papillotomy and cholecystectomy	Extrahepatic deposition of ^{99m}Tc-MAA on SPECT/CT or contrast on C-arm CT
Compensated or early decompensated (Child-Pugh ≤ B7) liver cirrhosis	Serum bilirubin > 34.2 µmol/L (2 mg/dL)	Active hepatitis
Performance state (ECOG) ≤ 2	Leukocytes < 2 x 10^9/L and/or platelet count < 50 x 10^9/L	Life expectancy < 3 months
Liver-only or liver-dominant disease	Glomerular filtration rate < 35 mL/min	Unacceptable lung shunt*
Pre-operative indications: Downstaging, bridge to liver transplantation and hypertrophy induction of the future remnant liver.	Internationalized Normalized Ratio (INR) > 1.5	

**Lung absorbed dose < 30 Gy in a single session and < 50 Gy in multiple sessions.*

with a Child–Pugh score higher than B7 and main PVT should be weighed carefully, because of the limited potential survival benefit after radioembolization (4.5–5 months in Child–Pugh B patients and 2.5 months in Child–Pugh C patients vs. 2.7–4.0 months in untreated patients) (9–12).

Prior surgical liver resection is no contraindication for radioembolization. However, surgical procedures involving the biliary tract may be a risk factor for infectious complications. The incidence of hepatic abscesses after radioembolization in patients with a normal biliary tree, or in the presence of a bilidigestive anastomosis, is fortunately low—less than 1% (**Table 2**) (13)—as opposed to less than 5% in the general TACE population and 48%–86% after TACE in the presence of a bilidigestive anastomosis (14,15). An aggressive prophylactic antibiotic regimen is therefore not advised (16,17). Radioembolization in the presence of a bilidigestive anastomosis seems safe but needs further attention, as liver abscesses after TACE show a high mortality rate of 11%–50% (15,18). Currently, a bilidigestive anastomosis is considered to be a relative contraindication for radioembolization, but this view is based on the available TACE literature because there is only limited evidence for radioembolization.

Table 2. Current literature on liver abscesses and bilidigestive anastomoses after radioembolization

Study	Treatment	Total	BDA	Incidence	Comment
Atassi 2008[21]	Radioembolization	327	NR	0.3%	0.3% = 1 patient, who had a bilidigestive anastomosis
Cholapranee 2014[19]	Radioembolization + antibiotic prophylaxes*	16	11	0%	5/16 had biliary stents
	TACE + antibiotic prophylaxes*	13	5	23% of total	Not reported how many patients with liver abscesses had a bilidigestive anastomosis
Geisel 2014[23]	Radioembolization	168	9	0%	
Korkmaz 2014[25]	Radioembolization case report	1	0	NA	Liver abscess developed after radioembolization in absence of a bilidigestive anastomosis or stent
Mascarenhas 2010[113] 2011[24]	Radioembolization case report	1	0	NA	

**Levofloxacin 500 mg daily and metronidazole 500 mg twice daily starting 48 hr prior to the intervention and continued for 2 weeks after discharge. Additionally 1000 mg neomycin and 1000 mg erythromycin were given thrice on the day of the intervention. BDA = Bilidigestive anastomosis, NA = not applicable, NR = not reported.*

Hepatic vascularization and angiographic considerations

The standard hepatic arterial supply originates from a celiac trifurcation, from which the common hepatic artery arises. The common hepatic artery becomes the proper hepatic artery, after the gastroduodenal artery has branched off. The proper hepatic artery continues toward the hilar plate, where it splits into the right and left hepatic arteries (19). Anatomic variants of the hepatic arterial vasculature are common, and correct identification of these variants is essential as it may increase the risk of extrahepatic deposition (20). Information on arterial liver vascularization derived from preprocedural liver CT–angiography or MR imaging–angiography (e.g., with an early arterial phase) is paramount for successful angiography (19,21). Anatomic variants are frequently missed in clinical practice in the absence of a thorough evaluation of the arterial vascularization on multimodality imaging. This results in unnecessary additional angiography procedures and incomplete radioembolization treatments. The severity of an extrahepatic deposition of microspheres depends on the affected organ and the number of displaced

microspheres, and its location depends on the culprit vessel. Previously, so-called skeletonization of the hepatic arteries was advised to avoid extrahepatic depositions (2). In recent years, however, this has been debated. Skeletonization can be quite an endeavor, and new hepatic–enteric collaterals may develop after coil embolization (22). Moreover, numerous disadvantages are related to the angiography procedure itself: increased procedure complexity, additional radiation dose, potential vessel damage, and complications of coil deployment. At present, most experienced centers try to avoid coil embolization. Significant extrahepatic depositions are found mostly within the distribution of 3 distinct side-branches (**Table 3**): the gastroduodenal artery, cystic artery, and right gastric artery (20,21). In a recent case series of 134 patients, 68.7% did not undergo coil embolization of either the gastroduodenal artery or right gastric artery. After radioembolization with glass microspheres, 1% developed a gastric ulcer (23). On the other hand, in a case series of 247 patients treated with resin microspheres, 3.2% developed a biopsy-proven gastroduodenal ulcer, despite skeletonization (24). Potential culprit vessels need to be assessed and coiled individually. Thus, standard rigorous occlusion of all side-branches of the hepatic arteries (e.g., skeletonization) has been abandoned (23).

Table 3. The 3 Most Common Culprit Vessels (20,21,23,79,80)

Characteristic	Gastroduodenal artery	Cystic artery	Right gastric artery
Origin	Common hepatic artery	Right hepatic artery	Left hepatic artery (42%)
	Other (3%)	Other (2%)	Proper hepatic artery (40%)
			Gastroduodenal (10%)
			Common hepatic artery (3%)
Possible complication	Gastroduodenal ulcer	Radiation induced cholecystitis (0-7%)	Gastric ulcer
	Radiation induced pancreatitis		
Coil embolization?	Not needed when there is 1) hepatopetal flow, 2) distal placement of microcatheter (>4-5 cm), 3) no extrahepatic contrast on C-arm CT	Not needed; Microcatheter distal from origin is preferred	Not needed when there is distal placement of microcatheter (>4-5 cm) and no extrahepatic contrast on C-arm CT

If an extrahepatic deposition of activity is found on pretreatment simulation with ^{99m}Tc-macroaggregated albumin (^{99m}Tc-MAA) SPECT/CT, coil-embolizing the culprit vessel, a more distal position of the catheter, or superselective catheterization, can provide a safe treatment procedure, rendering 91%–96% of the prior selected patients eligible for radioembolization (25,26). To avoid the need for a second pretreatment angiography procedure, the use of catheter directed CT (e.g., C-arm cone-beam CT or hybrid angiography/CT) may prove indispensable. The culprit vessels can be identified during angiography and coil-embolized immediately (**Figure 1**) (27). Additionally, C-arm CT can assess tumor coverage during the angiography procedure. Unenhanced tumor regions can be detected, often leading to identification of additional supplying arteries, preventing incomplete treatment. The C-arm CT provides the interventional radiologist with valuable feedback during the angiography procedure and affects the treatment plan in up to 52% of the patients (28).

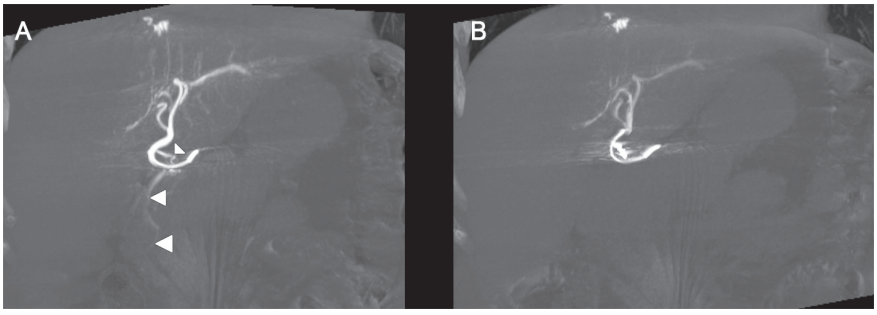

Figure 1. Coronal reconstructions of a C-arm CT in a patient prior to radioembolization.
During angiography the catheter was positioned in the proximal left hepatic artery. **a.** The C-arm CT illustrates arterial flow of contrast towards the pancreatic head / duodenal region, supplied by a supraduodenal artery (arrowheads), missed during digital subtraction angiography. Based on this additional finding, the artery was occluded. **b.** After coil embolization, contrast flow towards the gastrointestinal tract was resolved.

Pretreatment imaging and dosimetry

Pretreatment simulation is currently based on ^{99m}Tc-MAA SPECT/CT for assessment of extrahepatic depositions and lung shunting. Lung shunting is caused by arteriovenous anastomoses or shunts in the liver parenchyma or tumor, potentially resulting in radiation pneumonitis after radioembolization (29,30). The highest tolerable lung shunt absorbed dose was defined as 30 Gy after a single treatment

and up to 50 Gy after repeated treatments, in analogy with external-beam radiation therapy of the liver (31). The lung shunt fraction is usually calculated using the counts in a region of interest of the lungs, divided by the total counts in a region of interest of the lungs plus the liver (including tumor activity). However, this method is based on planar imaging and is operator- and institution-dependent. Overall, an absolute threshold (in Gy) is preferred over a relative one. Moreover, SPECT/CT leads to more accurate calculation of lung shunt absorbed dose than does planar imaging. Up to a 170% overestimation can occur when absorbed dose to the lung is calculated on planar imaging compared with SPECT/CT imaging (31,32). Elschot et al. determined the lung shunt dose on planar imaging and SPECT/CT using ^{99m}Tc-MAA (150 MBq) and ^{166}Ho-microspheres (250 MBq) (32). The true mean absorbed dose based on ^{166}Ho-SPECT/CT was 0.02 Gy. The absorbed dose was significantly overestimated by pretreatment planar imaging (^{99m}Tc-MAA, 5.5 Gy, and ^{166}Ho, 10.4 Gy) and by ^{99m}Tc-MAA SPECT/CT (2.5 Gy). At present, no alternative for ^{99m}Tc-MAA is commercially available.

In the absence of significant extrahepatic activity, the only true dosimetric limitation left is the total absorbed radiation dose in healthy liver parenchyma, also called the non-tumor dose. Little is known about the maximum tolerable non-tumor dose in radioembolization. It varies between patients depending on multiple variables, including distribution of radiation within the non-tumor volume. A non-tumor dose limit of less than 70 Gy has been proposed (non-tumor dose limit of less than 50 Gy in cirrhotic livers), although these limits seem quite arbitrarily defined and need to be confirmed in prospective studies (33). Nevertheless, pretreatment dosimetry is important to calculate the appropriate prescribed activity. Currently, 4 methods of calculating pretreatment activity are available for commercially available microspheres (**Table 4**) (33,34). For resin microspheres, the previously used activity calculation method was the empiric method. This method, which was based solely on tumor load, with no other patient-based factors, led to an unacceptable clinical and laboratory toxicity profile and was therefore abandoned (2,35). The second method, the body surface area method, is semi-empiric and has been used safely in many clinical trials. Its main limitation is the absence of target volume in the calculation method, which can result in undertreatment (small patient with large liver) or overtreatment (large patient with small liver) (35,36). Furthermore, it does not correct for the individual intrahepatic distribution differences, calculated by the so-called tumor-to-non-tumor ratio, which is to the disadvantage of patients with hyper- or hypovascular tumors. Theoretically, embedding the tumor-to-non-tumor ratio in the activity calculation method for patients with hypervascular

Table 4. Pre-treatment activity calculation methods

Method	Activity calculation equations
Empirical[52]	Tumor load ≤ 25% = 2.0 GBq whole-liver delivery, Tumor load 25-50% = 2.5 GBq whole liver delivery, Tumor load ≥ 50% = 3.0 GBq whole liver delivery
Body surface area[52]	$A(GBq) = (BSA - 0.2) + \left[\frac{tumor\ volume}{tumor\ volume + liver\ volume}\right]$ in which: $BSA = 0.20247 * height(m)^{0.725} * weight(kg)^{0.425}$
Partition[52]	$A(GBq) = \frac{D(Gy) * (\lceil \frac{T}{N} * Mass_{tumor}(kg) \rceil + Mass_{liver}(kg))}{49670 * (1 - Lung\ shunt\ fraction)}$ in which, based on MAA-SPECT/CT: $T/N = \frac{Activity_{tumor}\ (GBq)/Mass_{tumor}(kg)}{Activity_{liver}\ (GBq)/Mass_{liver}\ (kg)}$
Glass microspheres[53]	$A(GBq) = \frac{D(Gy) * Mass_{liver}(kg)}{50 * (1 - lung\ shunt\ fraction)}$ with an upper limit of lung shunt activity: $Lung\ shunt\ fraction(\%) * A(GBq) = 0.61\ GBq$

tumors will lead to a higher administered dose and higher tumor dose without compromising healthy liver tissue. The third calculation method, the so-called partition model, takes most relevant factors into account. Because the variables are acquired on ^{99m}Tc-MAA SPECT/CT before radioembolization, no additional procedures are needed (37,38). However, poorly defined tumors pose a problem for segmentation and quantification, and the overall complexity of the partition method renders its use less attractive in daily practice. For radioembolization using glass microspheres, an activity calculation method is advocated without the use of a tumor-to-non-tumor ratio (34). In analogy to the discussion surrounding activity calculation for resin microspheres, the partition model based on prior ^{99m}Tc-MAA SPECT/CT has been shown feasible for glass microspheres as well (8).

In daily practice, the body surface area method for resin microspheres and the volume-based calculation method for glass microspheres are the most commonly applied methods of calculating activity for radioembolization. Nonetheless, the partition model based on pretreatment ^{99m}Tc-MAA SPECT/CT should be preferred by nuclear physicians and interventional radiologists, because lesion based dosimetry on pretreatment ^{99m}Tc-MAA SPECT/CT has been shown to correlate with response and survival (39–43). The aim of radioembolization is to deliver the highest possible absorbed dose to tumor cells ("tumor dose") in order to induce apoptosis and tumor load reduction. The group of Garin et al. recently showed interesting results with the so-called partition method for treatment planning of glass microspheres.

Treatment planning was based on a target tumor dose of more than 205 Gy and a non-tumor dose of less than 120 Gy as calculated on ^{99m}Tc-MAA SPECT/CT. In 41 HCC patients with PVT (12/41 main branch), a median overall survival of 18 months was found. Patients with a tumor dose of more than 205 Gy had significantly longer progression-free survival and overall survival (8). The rationale of tumor dose–response correlations has been supported by clinical studies in different settings (39,44). One should bear in mind, however, that partition modeling is based on ^{99m}Tc-MAA SPECT/CT, which is influenced by many factors, including discrepancies between ^{99m}Tc-MAA and ^{90}Y-microsphere distribution (**Figure 2**). Several alternatives to ^{99m}Tc-MAA are currently under investigation, mainly to avoid discrepancies based on morphologic differences between ^{99m}Tc-MAA and ^{90}Y-microspheres and to improve lung shunt quantification (38).

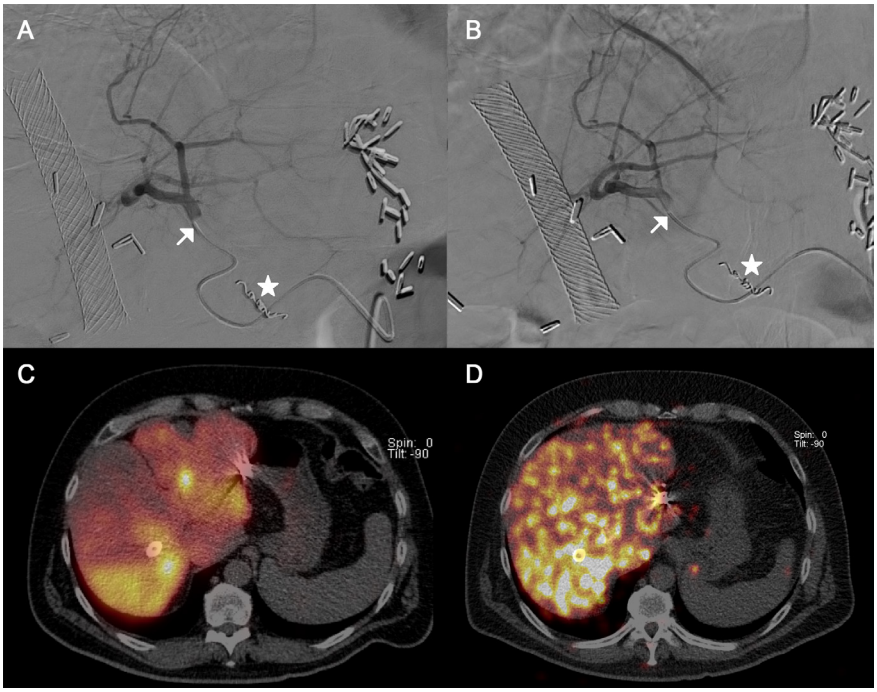

Figure 2. Patient with HCC recurrence in segment 7, who had previously undergone primary segmental resection with curative intent, cholecystectomy and biliary stent placement. Gastroduodenal artery was coil embolized (stars). Injection position in left hepatic artery for ^{99m}Tc-MAA (**a**) and ^{90}Y resin microspheres (**b**) Discrepancy of distribution between ^{99m}Tc-MAA SPECT/CT (**c**) and ^{90}Y PET/CT (**d**) can be acknowledged, with distribution in segment 4 being underestimated by ^{99m}Tc-MAA. These differences occurred even though the exact same 2-dimensional injection position was used in both angiographic procedures (arrows). Possible causes are the randomly shaped ^{99m}Tc-MAA versus spherical microspheres, bolus injection ^{99m}Tc-MAA versus intermittent injection ^{90}Y-microspheres, in plane (3-dimensional) catheter tip position differences, and a different number of particles injected during the scout dose, inducing differences in flow dynamics.

Because selective treatments are advocated to avoid extrahepatic deposition of activity, the prescribed activity needs to be split according to target volumes. A simple one-third (left lobe) and two-thirds (right lobe) split is used by some centers, but most centers use the pretreatment CT scan for splitting the prescribed activity according to their manual liver segmentation. The most accurate method was proposed by Kao et al., who split the dose according to artery-specific SPECT/CT-based liver segmentation, delineating an artery-specific target volume based on ^{99m}Tc-MAA distribution (37). C-arm cone-beam CT may also be used for that particular goal.

Treatment

During administration of resin microspheres, stasis of blood flow may occur, leading to incomplete injection of all intended microspheres. Stasis is caused by an embolic effect due to the higher number of resin microspheres (30–50 million) than of glass microspheres (4 million). The specific activity of resin microspheres (50 kBq/sphere) is approximately 50 times lower than that of glass microspheres (2,500 kBq/sphere), but this may vary by shelf-life. Although resin microspheres have a stable specific activity during a 24-h shelf-life, the specific activity (and number of microspheres) may vary for glass microspheres, having a maximum 2-wk shelf-life. It has been postulated that a more heterogeneous distribution of glass microspheres leads to a preferable toxicity profile but that, vice versa, a more homogeneous distribution of resin microspheres may lead to a preferable efficacy profile (45). The Northwestern University group in Chicago therefore advocated the use of so-called extended shelf-life glass microspheres (46). Microsphere characteristics are important to consider when analyzing dose–response relationships. It is not fully understood whether the antitumor effect is merely a radiation effect or a combination of an ischemic and radiation effect, especially in the case of resin microspheres. The embolic effect of resin microspheres sometimes leads to acute ischemic pain during injection. Recently, however, it was shown that when 5% glucose is used instead of sterile water for injection, there is less pain, less stasis, and more efficient administration. The flow dynamics during administration will be an important research topic in the coming years. Flow dynamics influence tumor targeting and the predictive value of a scout dose for dose distribution and treatment planning.

Posttreatment imaging and dosimetry

Initially, ^{90}Y-bremsstrahlung SPECT/CT was used after radioembolization to exclude extrahepatic activity deposition and to assess intrahepatic microsphere distribution. With 32 positrons per million decays, ^{90}Y PET/CT imaging has gradually taken over ^{90}Y-bremsstrahlung SPECT/CT, mainly because of new PET/CT scanners with time-of-flight technology. It allows more accurate quantification and dosimetry (47–49). Calculating tumor dose on posttreatment imaging may predict response (50–53). However, evidence was obtained in heterogeneous or small cohorts, mainly in HCC. Furthermore, the available studies differ in applied activity calculation method, used response criteria, and type of microsphere administered. Posttreatment imaging allows for detection of a heterogenic distribution of microspheres in the liver and in tumors, which correlates with partial or regional tumor response (49–51). In theory, after assessment of these parameters, additional radioembolization may be considered at an early stage, such as directly after administration of the treatment dose. However, the safety of repeated whole-liver radioembolization has not been firmly established yet (54,55).

Unfortunately, the true definition of the minimal effective tumor dose (and the maximum tolerated non-tumor dose) remains a challenge. The reported tumor dose thresholds were found to beindependent predictors of tumor response and survival, but lesion based analyses on posttreatment imaging show that these numbers range widely (50,53). In a follow-up study of 56 HCC patients with 98 tumors, including a quantitative assessment on ^{90}Y PET/CT after radioembolization with glass microspheres, lesion-based analysis yielded a mean tumor dose of 215 Gy (range, 17–555 Gy) in responders, defined as partial or complete response according to modified Response Evaluation Criteria in Solid Tumors (mRECIST), and a mean tumor dose of 167 Gy (range, 35–465 Gy) in non-responders (53). The true minimal effective tumor dose remains unknown and needs to be further investigated for each tumor type, tumor size, and microsphere type used.

Besides tumor dosimetry, ^{90}Y PET/CT allows early assessment of absorbed dose to healthy liver parenchyma: non-tumor dose. At present, a non-tumor dose of less than 70 Gy, or less than 50 Gy in cirrhotic livers, is assumed to be safe by the resin microsphere manufacturer (33). Nonetheless, a non-tumor dose above these limits has been described. Using pretreatment dosimetry, a non-tumor dose of less than 120 Gy on treatment planning was accepted for glass microspheres without additional toxicities (8). Like tumor dose, the maximum tolerated non-tumor dose needs to be refined for baseline liver function, treatment history, tumor characteristics, and type of microsphere used.

Clinical outcome and tumor response

In general, radioembolization is well tolerated. Mild clinical side effects usually occur within 4–6 weeks after radioembolization (e.g. abdominal pain, nausea, vomiting, fatigue, and fever) (2). More serious complications (1–3 months after radioembolization) include complications due to extrahepatic deposition of activity (e.g., gastric ulceration, pancreatitis, radiation pneumonitis) and liver decompensation. Excessive irradiation of healthy liver parenchyma leads to the most serious and life-threatening complication after radioembolization: radioembolization-induced liver disease. This is thought to be a venoocclusive disease/sinusoidal obstruction syndrome (56). Extensive sinusoidal congestion was acknowledged in liver biopsies, affecting the perivenular spaces with hepatic atrophy and necrosis around portal veins with fresh thrombus. In an early stage after radioembolization, serum markers show an induction of oxidative stress. Simultaneously, proinflammatory pathways are activated, resulting in endothelial injury with the activation of the coagulation cascade (57). Jaundice and ascites, in the absence of tumor progression or bile duct dilatation, are the main symptoms of radioembolization-induced liver disease (56,58). General risk factors for developing radioembolization-induced liver disease include prior chemotherapy, low tumor burden, high baseline bilirubin values, and cirrhotic liver disease (56,58). **Table 5** features the efficacy results of several landmark studies in the field of radioembolization.

In the intermediate and early-advanced stages of HCC (respectively, BCLC B and BCLC C), radioembolization has shown favorable outcomes compared with the currently preferred treatments (59,60). Compared with TACE, radioembolization has a similar or even better objective response rate and similar survival statistics (60). Moreover, as previously discussed, PVT and bilidigestive anastomoses are no absolute contraindication. Additionally, an ECOG performance score of at least 1 and a large tumor size (>10 cm) are currently considered a contraindication for TACE, in contrast to radioembolization (ECOG performance score 2, no tumor size limitation) (61). Radioembolization seems to effectively reduce the size of large tumors (**Figure 3**), and response rates of up to 91% have been described (8).

In BCLC B or BCLC C, not suitable for TACE, the current recommendation is systemic treatment with the multikinase inhibitor sorafenib. However, these patients might benefit more from radioembolization than from sorafenib. Recently, a large study (62) showed significantly better response rates and fewer adverse events after radioembolization than after sorafenib, even after correction of confounders

Tabel 5. Landmark Studies on Response and Survival in Liver Malignancies

Study	Design	Tumor	Treatment	N	Response criteria	CR*	PR*	SD*	PD*	TTHP†	MS†
Kolligs 2014[60]	Pilot RCT	HCC BCLC A-C CP ≤ B7	RE	13	RECIST 1.0	0	30.8	46.2	15.4	3.7	NA
			TACE	15		0	13.3	60.0	20.0	3.6	NA
Gramenzi 2014‡[62]	Retrospective cohort	HCC BCLC B-C CP ≤ B7	RE	63	mRECIST	14.3	53.9	14.3	17.5	3	13.2
						62.5		*18.8*	*18.7*	*3*	*11.2*
			sorafenib	73		0	9.5	41.9	48.6	5	14.4
						9.4		*37.5*	*53.1*	*3*	*13.1*
Al-Adra 2014[72]	Systematic review	ICC	RE	298	Pooled analysis	0	28	54	18	NA	15.5
Devcic 2014[111]	Systematic review	NET	RE	435	Pooled analysis	**50**		36	14	NA	28.5
Saxena 2014[97]	Systematic review	mCRC	RE	979	Pooled analysis	0	31	40.5	17.5	9	12

Legend: CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, TTHP = median time to hepatic progression, MS = median survival, RE = radioembolization, NA = not available, TACE = transarterial chemoembolization.
Italicized numbers are confounder-corrected results. Boldface numbers are data for CR and PR combined.

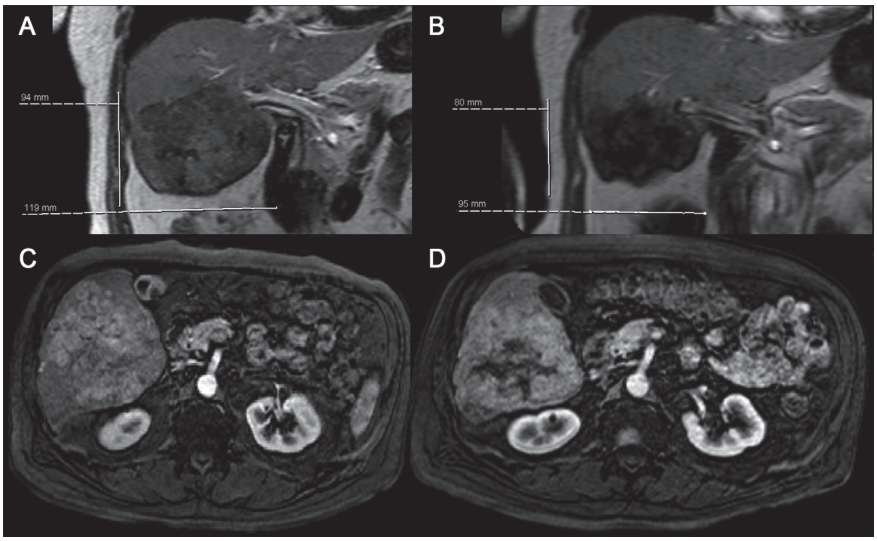

Figure 3. Patient with large HCC (12 cm) in the right lobe on T1-weighted MR sequences in coronal plane: before radioembolization (**a**); tumor shrinkage after radioembolization (**b**). T1 gadolinium enhanced MR image with fat suppression in an axial plane during arterial phase (20 seconds after injection), illustrating a hypervascular tumor (**c**); large area of necrosis in the tumor on the same sequence after radioembolization (**d**).

(**Table 5**); survival was similar. Patients are currently being recruited for the YES-P, SARAH, and SIRVENIB trials, in which sorafenib and radioembolization will be compared in a randomized controlled setting. The results of a phase II study in the Asia-Pacific trial indicate that combining both treatments seems beneficial, with manageable toxicities (63). This is currently under investigation in the SORAMIC trial (resin microspheres) and the STOP-HCC trial (glass microspheres). Patients who are ineligible or poor candidates for TACE are randomized into 2 groups: a group receiving sorafenib combined with radioembolization and a group receiving sorafenib alone. Even though radioembolization is currently not incorporated into the BCLC scheme and the results of the above-mentioned trials are pending, for selected patients radioembolization can be positioned between TACE and sorafenib (**Figure 4**).

In patients with focal or limited disease, ineligible for surgical resection or radiofrequency ablation, radioembolization using glass microspheres may provide an interesting alternative: radiation segmentectomy is meant to provide an ablating radiation dose (>200 Gy) by selective or superselective catheterization. By selective targeting, necrosis is induced in a limited portion of the liver, including the tumor, thus sparing radiation to healthy liver parenchyma. Vouche et al. described a high objective response rate (88%) and median overall survival (53.4 months)

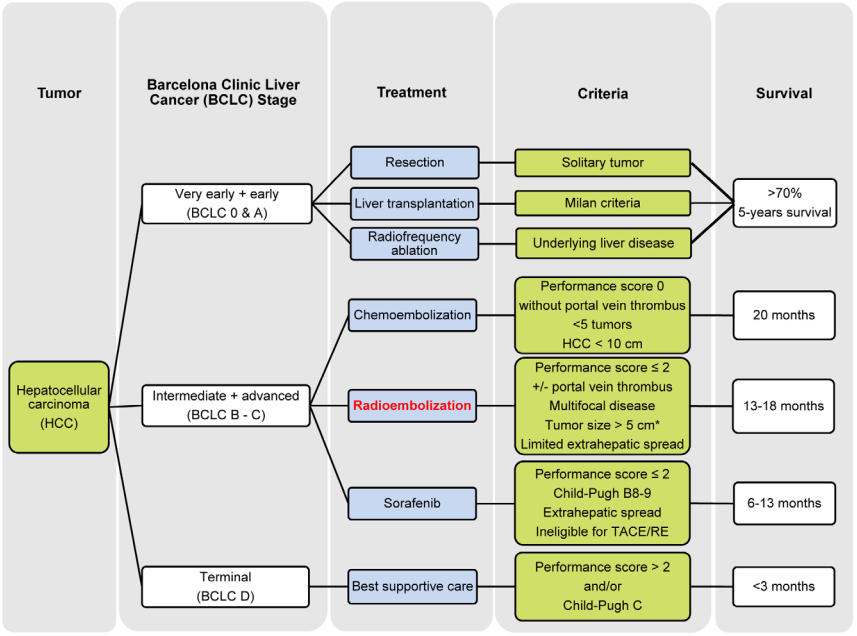

Figure 4. BCLC staging system with a proposal for radioembolization in the treatment paradigm. Radioembolization is placed between chemoembolization and sorafenib, based on eligibility criteria, featuring performance score (PS), liver function assessment (Child-Pugh-score), presence of portal vein tumor thrombus (PVT) and amount of extrahepatic disease. Due to the overlapping applicability of radioembolization in intermediate and advanced stage HCC, these stages have been combined in this proposal. *Size of tumors has been included in this BCLC scheme, however the exact size limits need to be investigated further. All tumors > 10 cm should be treated with radioembolization, due to an absolute contra-indication of TACE in these large tumors.

using this technique in solitary HCCs smaller than 5 cm (64). In their cohort, 33% of patients were amenable to liver transplantation after radiation segmentectomy. At pathologic examination of the native liver specimens, 100% necrosis and more than 90% necrosis were found in, respectively, 52% and 48% of patients (64). In HCC, the downstaging success rate with radioembolization is around 50% (range, 29%–67%), with a median time to downstaging of 3.1–4 months (65). In downstaging HCC, radioembolization is a suitable alternative to TACE, but downstaging should not be restricted to HCC alone (65).

The current European Society for Medical Oncology guideline on metastatic colorectal cancer states that in patients with liver-limited disease and unresectable liver metastases failing available chemotherapeutic regimens, radioembolization using resin microspheres prolongs time to tumor progression (66). Results in

heavily pretreated patients with chemoresistant metastatic colorectal cancer have been consistent over the years, making salvage treatment with radioembolization a widely accepted indication. According to a recent systematic review, treated patients have failed a median of 3 chemotherapeutic regimens before radioembolization (67). Left untreated, patients with chemorefractory liver metastases have a median survival of only 5–7 months (68–70). Nonetheless, in this population with an overall poor prognosis, after radioembolization a mean objective response rate of 31%, median progression-free survival of 9 months, and median overall survival of 12 months are obtained (**Table 5**) (67). Several ongoing randomized controlled trials are establishing the role of radioembolization for metastatic colorectal cancer (**Figure 5**). The addition of radioembolization to first-line chemotherapy regimens is being investigated in the SIRFLOX, FOXFIRE, and SIRstep trials (all using resin microspheres). After first-line failure, the EPOCH trial will randomize patients in second-line chemotherapy with or without radioembolization (glass microspheres).

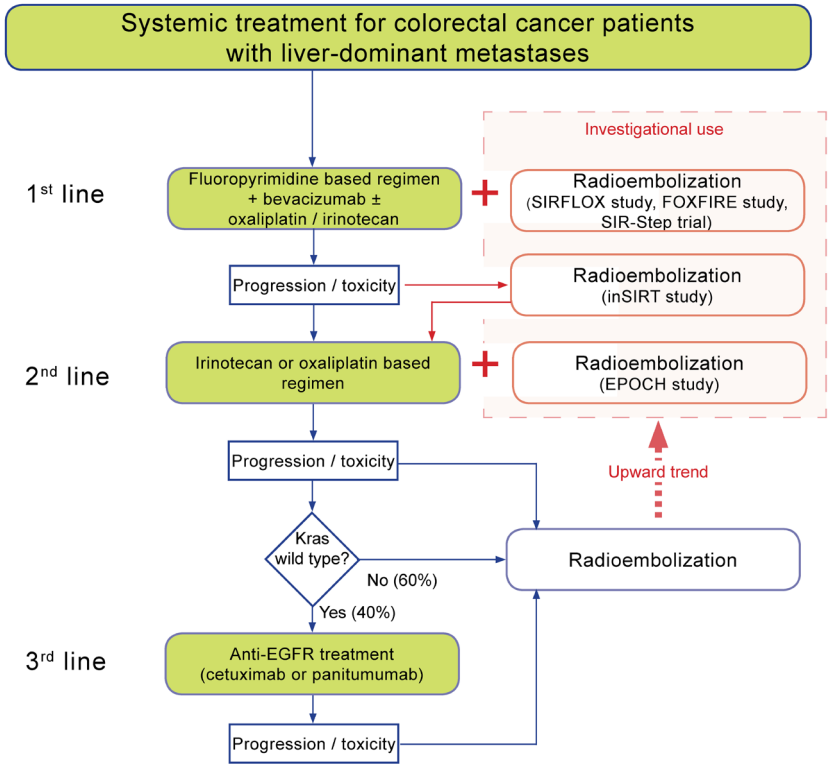

Figure 5. Schematic of evolving application of radioembolization in metastatic colorectal cancer and current trials. At present, radioembolization is mainly applied in a salvage setting; however, many clinical trials focus on bringing radioembolization to the forefront of the metastatic colorectal cancer treatment algorithm in first- or second line setting.

Another relatively new application of radioembolization before surgical resection is the induction of hypertrophy of the contralateral lobe by radioembolization of the diseased lobe. After portal vein embolization, 17.5% of patients are ineligible for surgical resection because of tumor progression, and in 4.8% of patients, hypertrophy induction of the future liver remnant is insufficient (71). Compared with portal vein embolization, induction of hypertrophy by radioembolization is similar but takes longer. A degree of hypertrophy of approximately 35% (8.9%–57%) can be obtained in 3–4 months (65). Theoretically, the main benefit of radioembolization is simultaneous tumor treatment, reducing the number of dropouts due to disease progression.

Unresectable intrahepatic cholangiocarcinoma, left untreated, has an overall survival of less than 8 months, and with gemcitabine and cisplatin overall survival is 11.7 months (72,73). After radioembolization, overall survival of 15.5 months can be reached (72). Repeated radioembolization can lead to local disease control for a longer period (**Figure 6**). Radioembolization before surgical resection, as in HCC and metastatic colorectal cancer, could be promising in intrahepatic cholangiocarcinoma as well. Downstaging occurs in 10%, and inducing contralateral hypertrophy seems feasible (65,72). In a small cohort combining radioembolization with chemotherapy, downstaging occurred in 22%, significant hypertrophy of the contralateral lobes was seen in all patients, and 18% were radically resected (74). In general, these results for intrahepatic cholangiocarcinoma are promising, but current literature is limited.

The heterogeneous group of neuroendocrine tumors has a lower incidence than the aforementioned tumors, though hepatic involvement in neuroendocrine tumors is common and is the greatest incriminating factor in survival (disease-free survival, 20 months with >4 hepatic metastases, versus 46 months with <4 hepatic metastases) (75). Most patients present with multifocal hepatic disease and are ineligible for resection or radiofrequency ablation (76). Conventional treatments (i.e., somatostatin analogs) and newer biologicals (i.e., sunitinib and everolimus) improve survival, but the objective response rate is poor. Because of the hypervascular nature of hepatic metastases, neuroendocrine tumors are prime candidates for radioembolization. In a meta-analysis including 414 patients, the pooled objective response rate was 50%, disease control rate was 86%, and overall survival was 28.5 months (**Table 5**) (77). Data reporting response rates based on the primary tumor origin and according to the World Health Organization histologic grading system are needed.

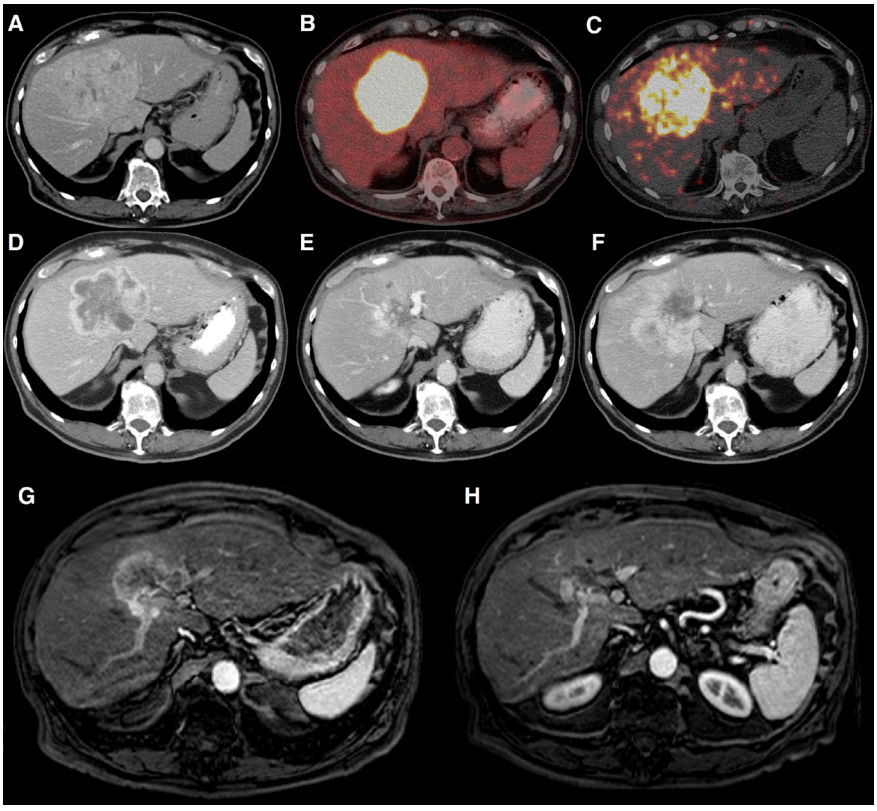

Figure 6. 82-year-old man with an intrahepatic cholangiocarcinoma with a long axis of 11.8 cm was referred for radioembolization. **a + b.** Venous phase CT and ^{18}FDG-PET/CT prior to radioembolization. **c.** Post-radioembolization ^{90}Y PET/CT showed accumulation of microspheres in and around the tumor. **d.** Venous phase CT after 6 months, E. Venous phase CT after 16 months, F. Tumor progression occurred 26 months after the first radioembolization on the venous phase CT, **g.** Arterial phase contrast enhanced MRI 5 months after the second radioembolization, **h.** Arterial phase contrast enhanced MRI 10 months after second radioembolization, 36 months after referral and initial radioembolization. The patient is still alive during the writing of this manuscript (40 months after first radioembolization).

Conclusion

Hepatic ^{90}Y radioembolization continues to develop rapidly. Clinical research is expanding indications in many different tumor types, overcoming technical angiographic challenges, fine-tuning the application of dosimetry, and optimizing quantitative imaging in daily practice.

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Chapter 3

The Efficacy of Hepatic ^{90}Y Resin Radioembolization for Metastatic Neuroendocrine Tumors: A Meta-Analysis

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Journal of Nuclear Medicine 2014; 55:1-7

Abstract

Background

^{90}Y resin radioembolization is an emerging treatment in patients with liver-dominant metastatic neuroendocrine tumors (mNETs), despite the absence of level I data. The aim of this study was to evaluate the efficacy of this modality in a meta-analysis of the published literature.

Methods

A comprehensive review protocol screened all reports in the literature. Strict selection criteria were applied to ensure consistency among the selected studies: human subjects, complete response data with time interval, resin microspheres, more than 5 patients, not a duplicate cohort, English language, and separate and complete data for resin-based ^{90}Y treatment of mNET if the study included multiple tumor and microsphere types. Selected studies were critically appraised on 50 study criteria, in accordance with the research reporting standards for radioembolization. Response data (Response Evaluation Criteria in Solid Tumors) were extracted and analyzed using both fixed and random-effects meta-analyses.

Results

One hundred fifty-six studies were screened; 12 were selected, totaling 435 procedures for response assessment. Funnel plots showed no evidence of publication bias ($P < 0.841$). Critical appraisal revealed a median of 75% of desired criteria included in selected studies. Very high between-study heterogeneity ruled out a fixed-effects model. The random-effects weighted average objective response rate (complete and partial responses, CR and PR, respectively) was 50% (95% confidence interval, 38%–62%), and weighted average disease control rate (CR, PR, and stable disease) was 86% (95% confidence interval, 78%–92%). The percentage of patients with pancreatic mNET was marginally associated with poorer response ($P < 0.030$), accounting for approximately 23% of the heterogeneity among studies. The percentage of CR and PR correlated with median survival ($R < 0.85$; $P < 0.008$).

Conclusion

This meta-analysis confirms radioembolization to be an effective treatment option for patients with hepatic mNET. The pooled data demonstrated a high response rate and improved survival for patients responding to therapy.

Introduction

Neuroendocrine tumors (NETs) are generally indolent tumors with a variable natural history of disease, arising from neuroendocrine cells throughout the body (1,2). They can be roughly divided into carcinoid and pancreatic cell tumors, and their incidence has inexplicably increased from 1.09 to 5.25 in 100,000 from 1973 to 2004 (3). The liver is the most frequent site of metastasis and the prognosis for metastatic disease is poor, with a median overall survival (OS) of 5–57 mo, often preceded by substantial morbidity such as the carcinoid syndrome (1–3).

There are various treatment options for patients with hepatic metastatic NETs (mNETs), aimed at improving quality of life, reducing symptoms, and increasing survival. The only potentially curative treatment option is surgery, which has a 10-y median OS of 42% but a median progression-free survival of only 21 mo, indicating that few patients are cured (4). Most patients are poor surgical candidates, presenting with diffuse or poorly differentiated disease (5). Inoperable patients may be evaluated for systemic therapies. Those with well-differentiated receptor-positive mNETs may be treated symptomatically with somatostatin analogs (octreotide), which have been shown to improve survival over placebo, whereas low- to intermediate-grade tumors may be treated with other systemic therapies such as streptozocin, doxorubicin, and dacarbazine, in addition to relatively newer agents including sunitinib and everolimus, both of which have been shown to improve survival over placebo (6–8). Those that are poorly differentiated or with a high Ki-67 proliferation index are typically treated with cytotoxic systemic therapies, which are usually platinum-based and may show a marked initial response, but it is usually not durable (9).

Liver-directed therapies have been widely adopted for liver dominant disease, but external-beam radiotherapy and percutaneous ablative therapies are rarely appropriate for multifocal disease. However, similar to primary hepatocellular carcinoma, mNETs typically derive nearly all of their blood supply from the hepatic artery, whereas normal liver parenchyma mainly uses the portal vein. Cytotoxic, radioactive, or ischemia-producing agents administered intraarterially thereby target tumors preferentially, limiting systemic and hepatic toxicity.

^{90}Y resin radioembolization has been shown to be an effective treatment for hepatic mNETs that is well tolerated, with low risk of grade 3 or higher early or late toxicity, and a superior quality of life profile (10–12). It involves injecting arteriole 30-mm-sized embolic resin (SIR-Spheres; Sirtex Medical Ltd.) or glass (TheraSphere; BTG Inc.) microspheres loaded with the ß-emitting radioisotope ^{90}Y into the tumor

hepatic arterial supply. The use of this therapy is largely institution-specific, as first-line therapy with or without other modalities, as second-line therapy after another modality has failed, or as salvage therapy in patients refractory to all other treatments. In the absence of level I data, the aim of this study was to evaluate the efficacy of radioembolization for liver mNETs in a meta-analysis of the published literature.

Materials and methods

Search Strategy and Study Selection

To cover all of the literature, we used a meticulous systematic review procedure of the following databases: Pubmed, EMBASE, Cochrane, Scopus, and CINAHL. The initial search only used the filters "English language" and "human studies", and the time frame included any study published before March 1, 2014. The search query included "90Y", "radioembolization", "liver metastases", "neuroendocrine tumor", "embolization", "selective internal radiation therapy", "internal radiation", "intraarterial radiation", "brachytherapy", "microspheres", and synonyms, derivations, permutations, and abbreviations of the above terms.

All articles with a relevant title or abstract were reviewed in full. Relevance was broadly defined to maximize the number of articles retrieved and yield from cross-referencing. All new articles retrieved from cross-referencing were also reviewed and cross-referenced. The following selection criteria were applied: human subjects, complete response data with time interval, at least 5 patients in the study group, not a duplicate cohort, English language, and if the study included multiple tumor or microspheres types it needed to have separate and complete data for hepatic mNET treated with resin microspheres.

For selected studies, the following data were retrieved: publication year, number of patients, type of radioembolic microsphere, radiographic criteria for response assessment, time after treatment to response assessment, percentage in each response category, degree of extrahepatic disease, prior therapy regimens, degree of liver tumor involvement, median overall survival, 1-y survival, activity administered, and primary site and histology of tumor. In mixed cohorts (i.e., patients with various tumor and microsphere types), only data for patients with hepatic mNET treated with resin microspheres were extracted.

Critical Appraisal

A critical appraisal of the selected studies evaluated whether they included the criteria listed in **Table 1**. The criteria were divided into major and minor, and studies scored 2 points for including major criteria and 1 point for minor criteria. Some of the above criteria were not applicable to each study, in which case points were not lost, but the total possible points was decreased accordingly. These criteria were developed in concordance with the research reporting standards for ^{90}Y radioembolization (13).

Table 1. Critical Appraisal According to Research Reporting Standards for Radioembolization

Criteria	Standard
Major (2 points)*	1) Study design, (2) inclusion criteria, (3) exclusion criteria, (4) description of statistics, (5) baseline clinical evaluation, (6) baseline imaging evaluation, (7) baseline laboratory evaluation, (8) primary neoplasm, (9) performance status, (10) tumor staging, (11) distribution of tumor, (12) prior treatments, (13) concomitant therapy, (14) radioembolic microsphere used, (15) details of dosimetry, (16) imaging used for follow-up, (17) method to assess tumor response, (18) time to follow-up, (19) tumor response, (20) overall survival, (21) laboratory value changes, (22) complications, (23) description of adverse events, (24) limitations, (25) conclusions
Minor (1 point)*	(1) Sponsorship/funding support, (2) participating centers, (3) institutional approval, (4) HIPAA compliance, (5) method of hepatic mNET diagnosis, (6) time elapsed from diagnosis of NET to radioembolization, (7) time elapsed from diagnosis of hepatic mNET to radioembolization, (8) absorbed dose to target area, (9) absorbed dose to any tissue, (10) details of flow stasis, (11) number of treatment sessions, (12) explanation of tumor targeting, (13) imaging after preparatory angiography, (14) formula to determine lung shunt fraction, (15) posttreatment imaging, (16) technical success, (17) Kaplan–Meier overall survival curve, (18) performance status, (19) uni- or multivariate analysis, (20) severe toxicity reported separately, (21) severe toxicity reported in standardized NCI-CTCAE format, (22) details of procedures with complications, (23) description of relevant vascular anatomy and missed findings with the occurrence of radiation pneumonitis, radiation cholecystitis, or gastrointestinal ulcers, (24) cost or cost effectiveness, (25) complications reported in standardized Society of Interventional Radiology format

**Total appraisal score was defined as all collected points divided by maximum points x 100.*
Legend: HIPAA = Health Insurance Portability and Accountability Act; NI-CTCAE = National Cancer Institue Common Terminology Criteria for Adverse Events.

Statistics

Twelve radioembolization articles were analyzed with both fixed-effects and random-effects meta-analyses; effect sizes were based on logit-transformed percentage of patients with disease response and control. Outcomes were per procedure. Effects of the following moderator variables were tested with a

mixed-effects model, using restricted maximum-likelihood estimation with Knapp–Hartung adjustment (14): percentage of patients with pancreatic and carcinoid mNETs and administered activity. As a check, covariate testing was performed with a 50,000-permutation test using the DerSimonian–Laird estimator. The median of the reported median survival times was estimated with a 1,000-sample bias-adjusted bootstrapped confidence interval. Statistical analyses were performed with R version 2.15.2 (www.r-project.org) using version 1.8.0 of the metafor package and version 2.3.0 of the meta package.

The critical appraisal scored each study as a percentage of total possible points. The denominator included all possible points (2 points for major criteria and 1 point for minor criteria), whereas the numerator included the total points accrued. The denominator was not the same across all studies, because some criteria were not applicable to each study.

Results

Studies Selected and Critical Appraisal

One hundred fifty-six relevant studies were reviewed in full, and 49 contained patients with hepatic mNETs treated with radioembolization. Application of the selection criteria narrowed down the selection to 12 studies (10,15–25). Most studies were excluded because they did not provide separate and complete Response Evaluation Criteria in Solid Tumors (RECIST) data specifically on hepatic mNETs treated with radioembolization. Rank-correlation tests for funnel plot asymmetry were not significant (percentage response, $P < 0.841$; percentage controlled, $P < 0.370$), demonstrating no evidence of publication bias (**Figure 1**).

From these 12 studies, 6 were retrospective, 3 were prospective, 1 was prospectively collected but retrospectively reviewed, and 2 didn't specify. The total number of procedures with response data was 435, in 414 patients. Most studies reported their response data per patient. The largest study in the cohort including 148 patients described their response data in terms of 168 procedures, because some patients had staged procedures to treat the entire liver or retreatment of the same territories (10). According to the critical appraisal system, the median score for all studies was 75% (range, 42%–81%). The median score for the major criteria was 83%, and for the minor criteria it was 45% (**Table 2**).

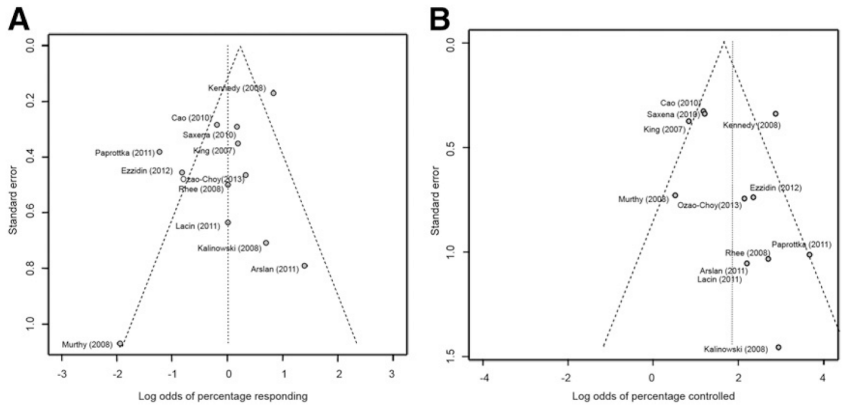

Figure 1. Funnel plots for included studies reporting on response (**a**) and disease control (**b**). No evidence of publication bias was found according to log-rank correlation (percentage response, p = 0.841; percentage controlled, p = 0.370).

Table 2. Critical Appraisal According to Research Reporting Standards for Radioembolization

Study	Study year	Major criteria score	Minor criteria score	All criteria weighted score*
Kennedy	2008	60%	33%	52%
Paprottka	2011	83%	47%	74%
Lacin	2011	79%	33%	67%
King	2007	88%	59%	79%
Cao	2010	80%	28%	66%
Kalinowski	2008	83%	58%	76%
Rhee	2008	75%	42%	66%
Saxena	2010	92%	50%	81%
Ezzidin	2012	88%	58%	78%
Arslan	2011	88%	39%	75%
Murthy	2008	88%	48%	76%
Ozao-Choy	2013	52%	19%	42%

**Total score for inclusion of minor and major criteria per study*

Patient Characteristics

From the 12 studies included, 8 specified the number of patients with extrahepatic metastases (median, 50%; range, 22%–63%). Eight specified the degree of liver replacement by tumor, with 4 having a median replacement of 44% (range, 32%–57%) and the other 4 reporting the percentage replacement in categories (**Table 3**).

Table 3. Baseline Patient Characteristics and Results for each Study Included in Meta-Analysis

Study	Kennedy	Paprottka	Lacin	King	Cao	Kalinowski	Rhee	Saxena	Ezzidin	Arslan	Murthy	Ozao-Choy
Study year	2008	2011	2011	2007	2010	2008	2008	2010	2012	2011	2008	2013
Number of procedures with response assessment	168	40	10	33	51	9	16	48	23	10	8	19
Pancreatic NETs*	19%	23%	30%	24%	27%	11%	20%	31%	61%	20%	75%	17%
Small bowel NETs*	82%	83%	NA	74%	82%	NA	81%	71%	NA	80%	25%	78%
Mean or median activity (GBq)	1.31	1.63	1.35	1.99	1.8	2.1	NA	1.94	3.4	1.49	1.23	NA
Extrahepatic disease	NA	NA	38%	59%	49%	22%	NA	48%	61%	50%	63%	NA
Liver replacement by tumor												
≤24% or ≤25%	NA	20%	NA	32%	35%	NA	NA	35%	13%	20%	NA	NA
25%-50% or 26%-50%	NA	70%	NA	41%	53%	NA	NA	38%	39%	80%	NA	NA
>50% or ≥50%	NA	10%	NA	27%	12%	NA	NA	27%	48%	0%	NA	65%
Mean	NA	NA	NA	32%	NA	57%	NA	32%	NA	NA	55%	NA
Prior therapies												
Surgery	NA	95%	38.5%	30.3%	33.3%	88.9%	40%	39.5%	17.3%	NA	25%	NA
Chemotherapy	NA	45%	NA	15.2%	37.3%	44.4%	NA	52%	34.7%	100%	87.5%	NA
Other intra-arterial therapies	NA	45%	23.1%	NA	9.8%	55.6%	0%	14.5%	NA	NA	100%	NA
Time of response assessment (months)†	3	3	1.5	4 – 60	1 – 61	3	6	1 - 63	3	4 - 28	2 – 15	1 – 2.5
Complete response‡	3%	0%	10%	18.2%	11.7%	0%	0%	14.5%	0%	30%	0%	10.5%
Partial response‡	66.7%	22.5%	40%	33.3%	27.5%	66.7%	50%	39.5%	30.4%	50%	12.5%	47%
Stable disease‡	25%	75%	40%	15.2%	27.5%	33.3%	43.7%	23%	60.9%	10%	50%	32%
Progressive disease‡	5.3%	2.5%	10%	33.3%	33.3%	0%	6.3%	23%	8.7%	10%	37.5%	10.5%
Median survival (months)	70	NA	18	NA	36	NA	28	35	29	NA	14	NA
One-year survival	NA	NA	85%	NA	86%	100%	NA	87%	NA	NA	NA	NA

**Percentages of pancreatic and small bowel NET do not necessarily add up to 100%, because of overlap in and/or inconsistent/incomplete recording of location and/or histology, †These studies provided a follow-up range, but did not explicitly state when RECIST was recorded. In most studies best response was given. ‡RECIST 1.0, except the Kennedy study, which used RECIST or WHO criteria. NA = not available*

Treatments before radioembolization included but were not limited to surgical resection; systemic cytotoxic, targeted, or hormonal treatment; radiofrequency ablation; percutaneous ethanol injection; intraarterial bland or chemoembolization; and external-beam radiation therapy, with some studies using up to 3 of these before radioembolization.

The most frequently specified were surgery in 9 studies (median, 39%; range, 17%–95%), cytotoxic chemotherapy in 8 studies (median, 45%; range, 15%–100%), and intraarterial chemoembolization in 6 studies (median, 34%; range, 10%–100%) (**Table 3**). Other details including age, sex, baseline laboratory values, Eastern Cooperative Oncology Group score, and time interval from NET diagnosis to ^{90}Y radioembolization are provided in **Table 4**

Response and Survival Assessment

Very high between-study heterogeneity (I-square, 65%–74%; P <0.0001) suggested that a fixed-effects model was not appropriate. For ^{90}Y radioembolization with resin microspheres only, objective radiographic response rates (defined as complete response plus partial response by RECIST) (26) ranged from 12% to 80%, with a random-effects weighted average of 50% (95% confidence interval, 38%–62%) (**Figure 2**). Disease control rates (defined as complete response, partial response plus stable disease) ranged from 62% to 100%, with a random-effects weighted average of 86% (95% confidence interval, 78%–92%) (**Figure 3**). For percentage responding, an increase in percentage of pancreatic mNET was marginally associated with a decrease in response rate (P = 0.030), accounting for approximately 23% of the heterogeneity among studies, whereas percentage carcinoid mNETs did not have a significant effect on response rate (P < 0.198). For percentage disease controlled, neither an increase in percentage of pancreatic mNET (P < 0.178) nor percentage of carcinoid mNET (P < 0.128) had a significant effect. Administered activity (median, 1.7 GBq; range, 1.2–3.4 GBq) did not correlate with either response or control rate.

Pooled survival data could not be provided for this cohort because 95% confidence intervals were not sufficiently provided. The median OS ranged from 14 up to 70 mo, with a median of 28.5 mo (95% confidence interval, 18–49.5 mo). The response rate correlated with median survival (R < 0.85; P < 0.008). Although a pooled analysis could not be calculated, the median and 1-y survival per individual study is listed in **Table 3**.

Table 4. Additional Baseline Patient Characteristics for each Study Included in Meta-Analysis

Study	Kennedy	Paprottka	Lacin	King	Cao	Kalinowski	Rhee	Saxena	Ezzidin	Arslan	Murthy	Ozao-Choy
Study year	2008	2011	2011	2007	2010	2008	2008	2010	2012	2011	2008	2013
Number of procedures with response assessment	168	40	10	33	51	9	16	48	23	10	8	19
Mean or median age (years)	58	62	53	61	61	59	61	60	58	49	56	62.5
Female patients	51%	29%	54%	35%	33%	78%	50%	40%	NA	50%	37%	39%
Male patients	49%	71%	46%	65%	67%	22%	50%	60%	NA	50%	63%	61%
Mean Albumin (g/l)	NA	72*	NA	NA	NA	NA	39	38	NA	NA	37	NA
Mean Alkaline Phosphatase (U/l)	NA	152	NA	NA	NA	NA	197	131	NA	NA	248	NA
Mean Aspartate Aminotransferase (U/l)	NA	34	91	NA	NA	NA	39	38	NA	NA	54.5	NA
Mean Alanine Aminotransferase (U/l)	NA	33	41	NA	NA	NA	45	49	NA	NA	37	NA
Mean Total Bilirubin (µmol/l)	NA	10.3	8.6	NA	NA	NA	12	18.8	NA	NA	6.8	NA
Mean Gamma Glutamyl Transferase (U/l)	NA	158	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Mean time from diagnosis to ^{90}Y treatment (months)	NA	27.4	NA	55.9	34.9	59	NA	NA	NA	30	NA	NA
Eastern Cooperative Oncology Group performance score 0	Median 0	74%	NA	NA	68%	NA	NA	50%	79%	NA	NA	NA
Eastern Cooperative Oncology Group performance score 1		17%	NA	NA	24%	NA	NA	25%		NA	NA	NA
Eastern Cooperative Oncology Group performance score 2		9%	NA	NA	6%	NA	NA	4%	21%	NA	NA	NA
Eastern Cooperative Oncology Group performance score 3		0	NA	NA	2%	NA	NA	0%	0%	NA	NA	NA

*Albumin reported as a whole protein. NA = Not available

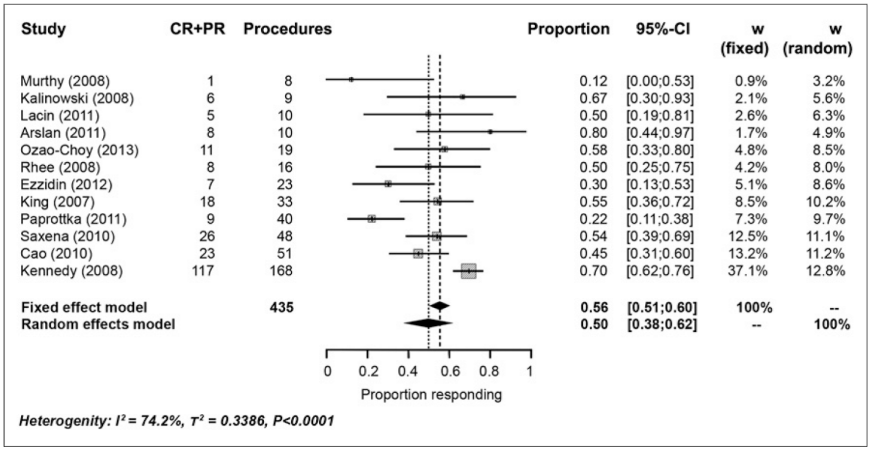

Figure 2. Response rates for included studies (year): complete response (CR) and partial response (PR). Weighted average response rate (W) according to random-effects model was 50%, with a 95% confidence interval (CI) of 38% - 62%. Fixed-effect model was ruled out because heterogeneity ($p < 0.0001$).

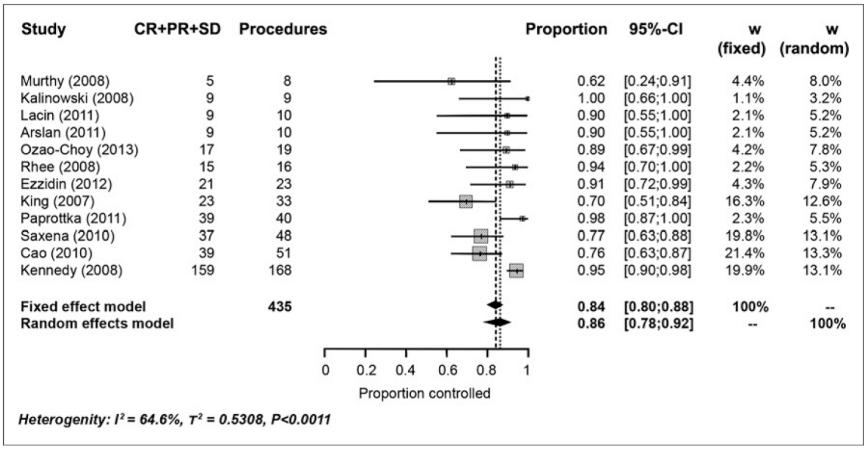

Figure 3. Disease control rates for included studies (year): complete response (CR), partial response (PR), and stable disease (SD). Weighted average disease control rate (W) according to random-effects model was 86%, with a 95% confidence interval (CI) of 78% - 92%. Fixed-effect model was ruled out because of heterogeneity ($p < 0.0001$).

Discussion

Radioembolization is an emerging and effective treatment for hepatic mNETs, with a superior toxicity profile (10–12). Multiple studies in the published literature have described outcomes of radioembolization for these patients. Twelve of these studies were included in our meta-analysis, with data pooled to evaluate overall efficacy. The pooled response rate of 50% and disease control rate of 86% by RECIST confirms the efficacy and validates the popularity of this treatment modality. The pooled response rates compare favorably with other therapies such assomatostatin analogs with or without interferon; older cytotoxic chemotherapeutics including dacarbazine, cisplatin, etoposide, streptozocin, and temozolomide; systemic radionuclide therapies such as peptide receptor radionuclide therapy; and newer targeted systemic therapies including everolimus and sunitinib (**Table 5**).

The response rates in individual reports varied from 12% to 80%, differences resulting in part from widely differing percentages of pancreatic mNETs in each study. Our meta-analysis found a decrease in response rate with increasing percentages of pancreatic mNETs, which is consistent with previous findings and probably reflects the more aggressive nature of pancreatic NETs. In a study using bland embolization and chemoembolization, only 35.2% of pancreatic mNETs responded radiographically, whereas 66.7% of carcinoid mNETs responded ($P < 0.0001$) (27). In addition, previous epidemiologic studies using the National Cancer Institute Surveillance Epidemiology and End Results cancer registry that included 49,012 NETs showed that pancreatic NETs are diagnosed at a higher stage than other NET primaries (28). Despite this relationship, carcinoid mNETs were not associated with a higher response rate in our meta-analysis, which may be due in part to incomplete and inconsistent histology reporting among the source studies.

The median OS averaged 28.5 mo and ranged 14–70 mo. This wide variation may also be explained in part by the percentage of pancreatic mNETs in these studies as pertaining to response rates. The Surveillance Epidemiology and End Results database indicates that pancreatic NETs exhibit the lowest 5-y survival, compared with all other NET primaries. Small bowel primaries have nearly a 2-fold-higher 5-y survival rate (68.1%) when compared with pancreatic mNETs, likely contributing to the high survival in the Kennedy study, which had one of the largest percentages of small bowel primaries (68%) (10,28). Previous studies found a survival advantage in metastatic carcinoid, compared with pancreatic mNETs, in patients treated with other liver-directed treatments (27,29–32), but studies on ^{90}Y radioembolization failed to find associations between primary tumor location and survival outcomes for hepatic mNETs (17,24). These studies, as well as our meta-analysis, may be underpowered to confirm this relationship.

Table 5. Overview of literature

Author (year)	Study design	Treatment	N	L	RAC	CR	PR	MS
Rinke (2009)	RCT	Octreotide	42	83%	WHO	0%	2.4%	NR
		Placebo	43	88%		0%	2.3%	73.7
Arnold (2005)	RCT	Octreotide	51	NA	>50%	0%	1%	35
		Octreotide + Inteferon	54			0%	1.9%	51
Ramanathan (2001)	Prospective	Dacarbazin	52 (50)	NA	>50%	8%	26%	19.3
Iwasa (2010)	Retrospective	Cisplatin + etoposide (PDNET)	21	81%	RECIST	0%	14.3%	5.8
Mirty (1999)	Retrospective	Cisplatin + etoposide (WDNET)	12	NA	WHO	0%	9%	17.6
		Cisplatin + etoposide (PDNET)	41			9.8%	31.7%	15
Turner (2010)	Prospective	5-FU + cisplatin + streptozocin	82	76%	RECIST	0%	32.9%	31.5
Olsen (2012)	Prospective	Temozolomide (PDNET)	28	86%	RECIST	0%	0%	3.5
Fine (2013)	Retrospective	CAPTEM (WDNET)	18	100%	RECIST	5.6%	55.6%	83
Strosberg (2011)	Retrospective	CAPTEM (WDNET)	30	NA	RECIST	0%	70%	NR
Pavel (2011)	RCT	Placebo + octreotide	213	92%	RECIST	0%	1.9%	NA
		Everolimus + octreotide	216	92%		0%	2.3%	
Yao (2010)	Prospective	Everolimus	115	95%	RECIST	0%	9.6%	24.9
		Everolimus + octreotide	45	93%		0%	4.4%	NR
Raymond (2011)	RCT	Placebo	85	94%	RECIST	0%	0%	NR
		Sunitinib	86	95%		2.3%	7%	NR
Imhof (2011)	Prospective	^{90}Y-DOTATOC	1109	NA	NA	0.6%	NA	94.6
Villard (2012)	Prospective	^{90}Y-DOTATOC	237	88%	RECIST	3.4%	16%	47.5
		^{90}Y-DOTATOC + ^{177}Lu-DOTATATE	249	76%		2.2%	20.9%	66.1
Kwekkeboom (2008)	Retrospective	^{177}Lu-DOTATATE	310	89%	SWOG	1.6%	27.7%	46
Claringbold (2012)	Prospective	^{177}Lu-DOTATATE + CAPTEM	34	94%	RECIST	14.7%	38.2%	NR
Berber (2002)	Prospective	Radiofrequency ablation	34	100%	NA	NA	NA	19.2
Gillams (2005)	Prospective	Laser thermal or radiofrequency ablation	25	100%	NA	NA	NA	29
Strosberg (2005)	Retrospective	TAE	84 (23)	100%	RECIST	0%	47.8%	36
Ruutiainen (2007)	Retrospective	TAE	23	100%	RECIST	0%	50%	39
		TACE	44	100%		0%	66%	44
Dong (2011)	Retrospective	TACE	123	100%	RECIST	0%	61.8%	65.6
Strosberg (2012)	Prospective	TAE + sunitinib	39	100%	RECIST	0%	72%	NR
Kratochwil (2011)	Prospective	Transarterial ^{90}Y- or ^{177}Lu-DOTATOC	15	100%	RECIST	6.7%	53.3%	NA
Limouris (2008)	Prospective	Transarterial ^{111}In-pentetreotide	17	100%	RECIST	5.9%	47.1%	32

N = number of patients, NA = not available, L = fractional liver involvement, RAC = response assessment criteria, CR = complete response, PR = partial response, MS = median survival, RCT = randomized controlled trial, PDNET = poorly differentiated NET, WDNET = well differentiated NET, CAPTEM = capecitabine + temozolomide, TAE = transarterial (bland) amebolization, TACE = Transarterial chemoembolization

It has been suggested that many factors, including prior surgery (33), size of target lesions (34), performance status (35, 36), baseline chemistry values (35), Ki-67 index (17), presence of extrahepatic disease (16), and inability to deliver a specified dose (34), influence patient outcomes for treatment of hepatic mNETs with ^{90}Y radioembolization. Unfortunately, despite publication reporting standards (13), publications do not conform to these standards and such clinical factors are often absent or incomplete, which limited the ability of this meta-analysis to analyze other factors potentially contributing to the pooled results. For instance, the study that included the largest database and reported some of the highest response and survival data provided little information on baseline patient characteristics (10). The critical appraisal resulted in a median score of only 75% among the 12 papers included. A higher median score of 83% was achieved when only major criteria were included, indicating that studies were slightly better at providing basic data but not sufficiently detailed to meet all criteria in the research reporting standards. Given the potential significance of these factors on outcomes, the importance of detailed reporting on patient characteristics, follow-up, treatment techniques, and outcomes cannot be stressed enough, and future authors need to become familiar with the reporting standards, which also need to be enforced by referees and editors.

This lack of comprehensive details, standardized follow-up, and inconsistency in reporting both objective response rates and survival in the source publications is the major limitation of this meta-analysis. For example, whereas 7 studies reported RECIST within 6 mo of treatment, the other studies only provided a follow-up range during which RECIST was recorded. These heterogeneous intervals may confound the response assessments. Other sources of uncertainty include large variability in the patient population of the 12 studies included in this meta-analysis—including wide variability in mNET histology, amount of extrahepatic disease and liver replacement by tumor, prior treatment regimens, and concurrent treatment regimens—as well as institution- and operator-specific variables that impact patient selection and treatment protocols (e.g., unilobar vs. bilobar treatment).

Besides the patient heterogeneity and reported details in the studies themselves, another potential limitation of any meta-analysis is publication bias. The studies included in meta-analyses are sometimes skewed toward smaller studies with unrealistically positive results. Critical appraisal of studies included in the present meta-analysis suggested they were well balanced. However, the large heterogeneity of the studies mandated use of a random-effects model, which has larger confidence intervals. In addition, inclusion of multi-institutional studies may

have resulted in inclusion of overlapping patients. However, given the limited data available in the source publications, it was not possible to identify and exclude all redundancies.

Conclusion

Hepatic radioembolization using ^{90}Y resin microspheres is an effective treatment option for hepatic mNETs. The pooled data demonstrated a weighted objective response rate of 50%, disease control rate of 86%, and improved OS for patients responding to therapy. Lower response rates and survival times were associated with mNETs of pancreatic cell origin, which may be due to their more aggressive nature and advanced stage at time of diagnosis. Future studies need to comply with consensus reporting standards to contribute meaningfully to our understanding of this disease and treatment modality.

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Chapter 4

Radioembolization with ^{90}Y resin microspheres of Neuroendocrine Liver Metastases: International Multicenter Study on Efficacy and Toxicity

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Cardiovascular Interventional Radiology 2019; 42: 413-425

Abstract

Background

Radioembolization of liver metastases of neuroendocrine neoplasms (NEN) has shown promising results; however, current literature is of limited quality. A large international, multicenter retrospective study was designed to address several shortcomings of the current literature.

Methods

Primary outcome parameters was radiologic response three and six months after treatment according to RECIST 1.1 and mRECIST. Secondary outcome parameters included clinical response, clinical and biochemical toxicities.

Results

244 NEN patients with different NEN grades were included. Radioembolization resulted in CR in 2%, PR in 14%, SD in 75%, and PD 9% according to RECIST 1.1 and in CR in 8%, PR in 35%, SD in 48%, and PD in 9% according to mRECIST. Objective response rates improved over time in 20% and 26% according to RECIST 1.1. and mRECIST, respectively. Most common new grade 3-4 biochemical toxicity was lymphocytopenia (6.7%). No unexpected clinical toxicities occurred. Radioembolization-specific complications occurred in <4%. In symptomatic patients, improvement and resolution of symptoms occurred in 44% and 35%, respectively. Median overall survival from first radioembolization was 3.7, 2.7 and 0.7 years for G1, G2 and G3 respectively. Objective response is independent of NEN grade or primary tumour origin. Significant prognostic factors for survival were NEN grade/Ki67 index, ≥75% intrahepatic tumour load, presence of extrahepatic disease and disease control rate according to RECIST 1.1.

Conclusion

Safety and efficacy of radioembolization in NEN patients was confirmed with a high disease control rate of 91% in progressive patients and alleviation of NEN-related symptoms in 79% of symptomatic patients.

Introduction

Neuroendocrine neoplasm (NEN) is a generic term for a class of rare tumours, consisting of an array of many different tumour types with steadily rising incidence. NEN can be divided by tumour grading, in accordance with the World Health Organization / European NeuroEndocrine Tumour Society (WHO/ENETS) grading system [1, 2]. At diagnosis, 21% of grade 1 neuroendocrine tumours (NET), 30% of grade 2 NET, and 50% of grade 3 NET (or neuroendocrine carcinoma = NEC) patients demonstrate distant metastases, of which the liver is the most commonly affected site [3, 4]. Once NEN patients are diagnosed with liver metastasis, only about 20-30% are eligible for surgical resection with curative intent, due to frequently present bilobar liver infiltration [3, 5]. With just a few randomized controlled trials providing evidence for efficacy of systemic therapeutic options in advanced NEN, and no randomized controlled trials comparing efficacy of locoregional interventions, apart from several guidelines, there is little evidence to guide the choice of treatment for these patients [6-10].

Radioembolization has gained interest due to reports on promising results with limited toxicities. However in current studies, NEN patients are often presented within a mixed population of non-NEN tumour types, and mostly in small numbers [11, 12]. Furthermore, many publications do not adequately report baseline characteristics, such as tumour grading and origin of the primary tumour, and if reported, these baseline characteristics are mostly not correlated to response or to survival [11, 12]. At the same time, large prospective studies and randomized controlled trials are notoriously difficult for NEN, due to its relatively rare occurrence, the large heterogeneity among NEN patients, and the heavily pre-treated population that presents for liver-directed therapies. In this international, multicenter, retrospective study we investigated efficacy and toxicity of a first radioembolization treatment in NEN with yttrium-90 (^{90}Y) resin microspheres (SIRSpheres®, Sirtex Medical, Sydney, Australia) and focussed on missing data in current literature.

Methods

All retrospective data were gathered in the period of July 2015 until October 2016 in eight participating hospitals in Europe and the USA (**Table 1**) by the first author to ensure consistent data gathering. The inclusion criteria were patients with histologically proven NEN, of any origin, with at least baseline and 3 ± 1.5 month follow-up cross-sectional imaging (i.e. contrast enhanced computed tomography = CT or magnetic resonance imaging = MRI). Additionally biochemical and

Table 1. Number of patients per participating center

Participating center	City and country	N
MD Anderson Cancer Center	Houston, United States of America	84
University Hospital Bonn	Bonn, Germany	50
Stanford University	Palo Alto, United States of America	41
Vanderbilt University	Nashville, United States of America	23
Jules Bordet Institute	Bruxelles, Belgium	18
Imperial College London	London, United Kingdom	15
University Medical Center Utrecht	Utrecht, The Netherlands	10
University Hospital Leuven	Leuven, Belgium	3

haematological laboratory data available after radioembolization with ^{90}Y resin microspheres were gathered. If available, imaging up to 6 ± 1 months after treatment was collected. Baseline and follow-up imaging had to be the same imaging modality (either CT or MRI). If patients received multiple radioembolization treatments, of one lobe or whole liver, only the first treatment was evaluated. This to obtain a comparable and reliable toxicity profile, as repeated radioembolization treatments are known to have more treatment related toxicities [13]. Baseline patient and tumour characteristics, angiography, and treatment specifics were gathered according to the reporting standards recommended for radioembolization [14]. Histological diagnosis of a NEN was confirmed on a surgical specimen or biopsy. Intrahepatic tumour load was visually estimated and the number of intrahepatic lesions was counted.

Prior to the actual radioembolization treatment, all patients received a treatment simulation during a preparatory angiography, in which the microcatheter position is determined for the actual treatment, followed by intra-arterial injection of technetium-99m macroaggregated albumin (^{99m}Tc-MAA). After the preparatory angiography, the patient is transported to the nuclear medicine department for planar imaging and SPECT or SPECT/CT. On planar imaging the lung shunt fraction (LSF) is calculated and based on the LSF the physician could consider a dose reduction for treatment. On SPECT(/CT), extrahepatic depositions of the radiopharmaceutical were excluded prior to treatment. Within weeks following the preparatory angiography and imaging, the patient received radioembolization treatment. Prophylactic intravenous octreotide infusion or prophylactic antibiotic treatment were given at the discretion of the treating physician and according to the institutes' guideline.

Study outcome parameters

The primary outcome parameter was imaging response after radioembolization of the liver disease only, defined according to Response Evaluation Criteria In Solid Tumours, version 1.1 (RECIST 1.1), and modified RECIST (mRECIST; in case multiphase imaging was available for hypervascular tumours) after three months.[15, 16] RECIST 1.1 was used, because it is currently the most commonly applied response criterion in NEN literature. mRECIST was used for comparison to other previously published articles, and mRECIST is advised for the assessment of hypervascular liver metastases. Imaging evaluation was performed by three experienced physicians. The largest diameter in axial plane of two representative intrahepatic target lesions was selected on baseline imaging; one in each lobe in the case of a whole liver treatment or one in different liver segments in case of a lobar treatment, thus representing the whole treated intrahepatic tumour load. Objective response rate (ORR) was defined as complete response (CR) plus partial response (PR). Disease control rate (DCR) was defined as CR, PR plus stable disease (SD).

Secondary outcome parameters included clinical response (improvement of symptoms) and clinical toxicities (adverse events) within three months, and within six months after treatment. Biochemical and haematological toxicities at 4-8 weeks, and at three months were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.[17] To assess overall survival (OS), date of death or date of last contact (when lost to follow up) was collected and as OS might be influenced by treatments following radioembolization, additional treatments following radioembolization were collected as well. Progression-free survival (PFS) analysis was not reliable in this retrospective series.

Statistical analysis

Survival curves were estimated using the Kaplan-Meier method and assessed with the log-rank test. The following variables were tested; tumour origin, NEN grade, Ki67 index, mitotic count, tumour differentiation, number of intrahepatic lesions, intrahepatic tumour load, resection of the primary tumour, presence of extrahepatic disease at time of treatment, LSF based on ^{99m}Tc-MAA, and elevated bilirubin levels at baseline. On the basis of current literature, the following variables were studied for their value in predicting longer OS: NEN grade, elevated bilirubin levels, intrahepatic tumour load, presence of extrahepatic disease, LSF, DCR according to RECIST after radioembolization.[18-21, 11, 22, 23] Continuous variables of intrahepatic tumour load (≥75% versus <75%)[20] and LSF (≤10% versus >10%)[18] were dichotomized in order to test the influence on OS from

radioembolization. Variables that were not significant in univariate Cox regression analyses were not excluded for multivariate analyses. Therefore, we started with all preselected variables and subsequently eliminated the variables by backward selection with a threshold P value of 0.20. Of all analyses 95% confidence intervals (95% CI) [lower – upper boundaries] were reported. P-values smaller than 0.05 were considered significant in all tests. The database was analysed using IBM SPSS statistics for Windows version 23.0 (IBM, Armonk, NY).

Results

Two hundred and forty-four patients were included in this retrospective analysis and treated between July 2004 and May 2016. Twenty-four patients received multiple radioembolization treatments (up to four treatments), of which only the first treatment was analysed. Patient demographics and baseline characteristics are shown in **table 2**. Prior to radioembolization, 91% had progressive disease, clinically (increase in symptoms or tumour marker) or on imaging. Most patients had diffuse liver metastases (**Table 3**).[3, 5] Median time to radioembolization after diagnosis was 4.0 years (range 75 days – 33 years).

At three months, all 244 patients had follow-up imaging and 47.5% had multiphase contrast enhanced imaging. At six months, follow-up imaging was available in 51.6% and multiphase contrast enhanced imaging in 28.7%. Pre-treatment and follow-up imaging was performed with contrast enhanced CT in 190 patients and with gadolinium enhanced MRI in 54 patients.

Treatments received after radioembolization are summarized in **table 4**. Follow-up period for available clinical data ranged from 51 days (patient lost to follow-up) to 12 years (patient alive at time of analysis). At time of analysis 128/244 (52.5%) patients had died.

Procedure details

No extrahepatic depositions of 99mTc-MAA were found. Median LSF was 5.6% (range 0.7%–33%), with just one patient having an LSF exceeding 20% (i.e. 33%), who received a whole liver treatment in one session without an activity reduction. He did not develop a radiation pneumonitis afterwards. Median net administered ^{90}Y activity was 1.8 GBq and mostly calculated by the body surface area (BSA) method (**Table 3**).

Table 2. Baseline characteristics

Performance score	N	%	Histopathology	N	%	Prior treatments	N	%
ECOG 0	115	47.2	**WHO/ENETS Grade**			Multiple treatments	232	95.1
ECOG 1	105	43.0	1	96	39.3	Surgical treatment only	8	3.3
ECOG 2	17	7.0	2	87	35.7	Treatment naive	4	1.6
ECOG 3	3	1.2	3	25	10.2	**Systemic treatments**		
Unknown	4	1.6	Unknown	36	14.8	Somatostatin analog	163	66.8
Primary tumour site			**Ki67 index**			Chemotherapy††	95	38.9
Unknown origin	34	13.9	<3%	50	20.5	Newer agents‡‡	86	35.2
Pancreas NF	76	31.2	3-20%	69	28.3	**Liver directed treatments**		
Functioning NEN*	9	3.7	>20	27	11.1	Bland embolization	13	5.3
Small bowel†	85	34.9	Unknown	98	40.1	Chemoembolization	11	4.5
Large bowel‡	24	9.8	**Mitotic count per 10 HPF**			RFA / MWA / CA	16	6.6
Lung/bronchus	13	5.3	<2	48	19.7	**Surgical treatments for liver metastases**		
Other°	3	1.2	2-20	25	10.2	Left hemihepatectomy	6	2.5
Primary tumour			>20	2	0.8	Right hemihepatectomy	2	0.8
Surgically resected	111	45.5	Unknown	169	69.3	Right posterior sectionectomy	2	0.8
In situ	99	40.6	**Differentiation**			Left lateral sectionectomy	1	0.4
Unknown primary	34	13.9	Well	55	22.5	Segmentectomy	11	4.5
Extrahepatic metastases			Moderate	11	4.5	Metastasectomy	12	4.9
No	83	34.0	Poor	6	2.5	**Other invasive treatments**		
Yes**	161	66.0	Unknown	172	70.5	Bilioenteric anastomosis	24	8.2
Lymph nodes	*115*	*47.1*				Biliary stenting	4	1.6
Bone	*44*	*18.0*				**Radionuclide treatments**		
Peritoneum	*31*	*12.7*				^{131}I-MIBG	2	0.8
Lungs	*15*	*6.1*				^{90}Y-PRRT	7	2.9
Other	*21*	*8.6*				^{177}Lu-PRRT	41	16.8

N = Number of patients, ECOG = Eastern Cooperative Oncology Group Performance Score, NF = non-functioning, NEN = neuroendocrine neoplasm, HPF = high power fields, RFA = radiofrequency ablation, MWA = microwave ablation, CA = cryoablation, MIBG = metaiodobenzylguanidine, PRRT = peptide receptor radionuclide therapy
**Different functioning NET: Gastrinoma 1.2%, Glucagonoma 1.2%, Insulinoma 0.4%, VIPoma 1.2%; † Including 5 gastric NEN; ‡Including 1 appendiceal NET; °Other primaries include thymus (0.4%), kidney (0.4%) and ovary (0.4%) NEN; **Most patients had a combination of involved organ systems, category 'Other' includes splenic, pancreatic, soft tissue, cardiac, renal, ovary, breast and gallbladder metastases. ††Approximately 30 different chemotherapeutic regimens without a distinct preference. ‡‡Newer drugs include, among others, tyrokinase inhibitors (e.g. pazopanib, sunitinib or sorafenib), mammalian target of rapamycin inhibitor (mTOR; e.g. everolimus), vascular endothelial growth factor inhibitor (e.g. bevacizumab).*

Table 3. Tumor characteristics and radioembolization related parameters

Intrahepatic tumour load	**N**	**%**
0%-25%	67	27.5
25%-50%	62	25.4
50%-75%	79	32.4
>75%	36	14.5
Intrahepatic lesions	**N**	**%**
<10	33	13.5
10-19	37	15.2
20-29	46	18.8
30-39	18	7.4
40-49	12	4.9
>50	98	40.2
Liver involvement*	**N**	**%**
Type I	1	0.4
Type II	11	4.5
Type III	232	95.1
Treatment planning	**N**	**%**
Median lung shunt fraction	-	5.6
Activity reduction applied	18	7.4
High lung shunt fraction†	*15*	*6.2*
Clinical reasons	*2*	*0.8*
Prior chemoembolization	*1*	*0.4*
Median activity reduction‡	-	20
Coil embolization	121	49.6
Prophylactic embolization	*101*	*41.4*
Parasitic vessel	*14*	*5.7*
For redistribution	*31*	*12.7*
Use of cone-beam CT	110	45.1

Activity calculation method[32]	**N**	**%**
Body surface area	206	84.4
50 Gy average liver absorbed dose	32	13.1
Partition model	6	2.5
Radioembolization treatment	**N**	**%**
Whole liver; single session	137	56.1
Whole liver; sequentially**	34	13.9
Right lobar	63	25.9
Left lobar	8	3.3
Selective	2	0.8
Administration complications††	**N**	**%**
No complications	201	82.5
Slow flow	25	10.2
Stasis	9	3.7
Reflux	4	1.6
Arterial dissection	2	0.8
Abdominal pain	2	0.8
Carcinoid crisis	1	0.4
Activities used		
Median ^{99m}Tc-MAA activity	179 MBq	
Median prescribed ^{90}Y activity	1.93 GBq	
Range	0.74 – 4.14 GBq	
Median net administered ^{90}Y activity	1.83 GBq	
Range	0.40 – 5.50 GBq	
Median residual activity ^{90}Y activity	74 MBq	
Range	0 – 2257 MBq	
Median % of prescribed dose	*3.93%*	
Range (% of prescribed dose)	*0% - 71%*	
N with >10% residual activity (%)	*38 (15.6%)*	

^{99m}Tc-MAA = technetium-99m macroaggregated albumin, MBq = megabecquerel, Gy = gray, GBq = gigabecquerel.
**classified according to Frilling et al.[7] and ENETS guideline[3], †High lung shunt fraction all between 10% - 20%, ‡In cases where activity reduction was applied, **Sequential treatment (first right lobe and then left lobe or other way around) with a median interval of 43 days (range 14 – 152 days). ††Per-procedural complications necessitating an early termination of activity administration.*

Efficacy

DCR of >90% was observed at three and six months follow-up (**Table 5**). Achieved response rates after treatment according to both RECIST 1.1 and mRECIST are not correlated to NEN grade (**Figure 1**). A similar figure arises when looking at the most common primary tumour origins. **Figure 2** depicts the changes in response assessments over time between the assessment at three versus six months, which improves in 20-26% of patients in time.

Table 4. Details on the treatments received after radioembolization

Therapy	N	%
No additional treatments after radioembolization	77	31.6
Additional treatments after radioembolization	160	65.6
Somatostatin analogs	89	36.5
Radioembolization	5	2.0
Peptide Receptor Radionuclide Therapy	35	14.3
^{188}Re-HEDP	1	0.4
Primary resection	6	2.5
Tumour debulking	6	2.5
Liver metastasectomy	2	0.8
Other surgery	4	4.9
Radiofrequency ablation	5	2.0
Bland embolization	8	3.3
Chemoembolization	12	4.9
External beam radiotherapy	19	7.8
Chemotherapy and tyrokinase inhibitors		
1 type of chemotherapy	50	20.5
2 types of chemotherapy	8	3.3
3 types of chemotherapy	9	3.7
4 types of chemotherapy	2	0.8
5 types of chemotherapy	1	0.4
Cyproheptadine	1	0.4
Lost to follow up directly after radioembolization	7	2.9

Of all patients, 60% had malignancy-related symptoms prior to radioembolization; mainly flushing (43%) and diarrhoea (40%). Clinical response defined as improvement and complete resolution of pre-treatment complaints occurred in 44% and 35%, respectively. 21% remained symptomatic after radioembolization.

Clinical toxicity

Complications related to the angiography procedure itself were arterial dissection in 2 patients (0.8%). During ^{90}Y resin microsphere administration, three patients experienced complaints necessitating early cessation of administration (**Table 3**).

Three and six months after radioembolization no clinical toxicities occurred in 32% and 55% of patients, respectively. Known radioembolization related adverse-events occurred in 56% within the first three months (fatigue 28%, abdominal pain 27% and nausea 23%) and persisted in 6% at six months (mainly abdominal pain).

Table 5. Radiological response

Assessment	1st*	2nd†	1st*	2nd†
Response assessment	RECIST 1.1		mRECIST	
Mean interval ± SD (days)	68 ± 34	187 ± 48	89 ± 78	189 ± 38
Number of patients	244	116	126	70
Complete response (%)	4 (1.7)	1 (0.9)	10 (7.9)	6 (8.6)
Partial response (%)	34 (14.0)	32 (27.6)	44 (34.9)	38 (54.3)
Stable disease (%)	185 (75.6)	73 (62.9)	61 (48.4)	38 (28.6)
Progressive disease (%)	21 (8.7)	10 (8.6)	11 (8.7)	6 (8.6)
Objective response rate (%)	38 (15.7)	33 (28.5)	54 (42.8)	44 (62.9)
Disease control rate (%)	223 (91.3)	106 (91.4)	115 (91.3)	64 (91.4)

*RECIST 1.1 = Response Evaluation Criteria In Solid Tumours version 1.1, mRECIST = modified RECIST, SD = standard deviation. *1st assessment around 3 months after radioembolization, †2nd assessment around 6 months after radioembolization.*

Unfortunately, clinical toxicities were not registered by the treating physician in 12% and 39% of patients, at three and six months respectively (missing data).

Radioembolization-specific complications occurred in <4%. Radiation-induced gastric ulcer occurred in seven patients (2.8%; all seven had endoscopy, four of which had histological confirmation with biopsy), radioembolization induced liver disease (REILD) in two patients (0.8%), radiation pneumonitis in one patient (0.4%; with a ^{99m}Tc-MAA LSF of 3.1%), liver abscess in one patient (0.4%) with bilioenteric anastomosis (without antibiotic prophylaxis) and cholangitis in one patient (0.4%) with bilioenteric anastomosis (without antibiotic prophylaxis).

Biochemical and haematological toxicity

New CTCAE grade 3-4 biochemical and haematological toxicities were limited, most common was lymphocytopenia in 6.7%. Grade 1-2 biochemical toxicities were encountered in up to 51%; however, grade 1-2 bilirubin elevation and/or decreased albumin levels occurred in 6%. Apart from an incidence of grade 1-2 lymphocytopenia in 52%, thrombocytopenia occurred in 17%, and a grade 1-2 anaemia or leukopenia occurred in <8%. Coagulation was unaffected as measured by the international normalized ratio (INR).

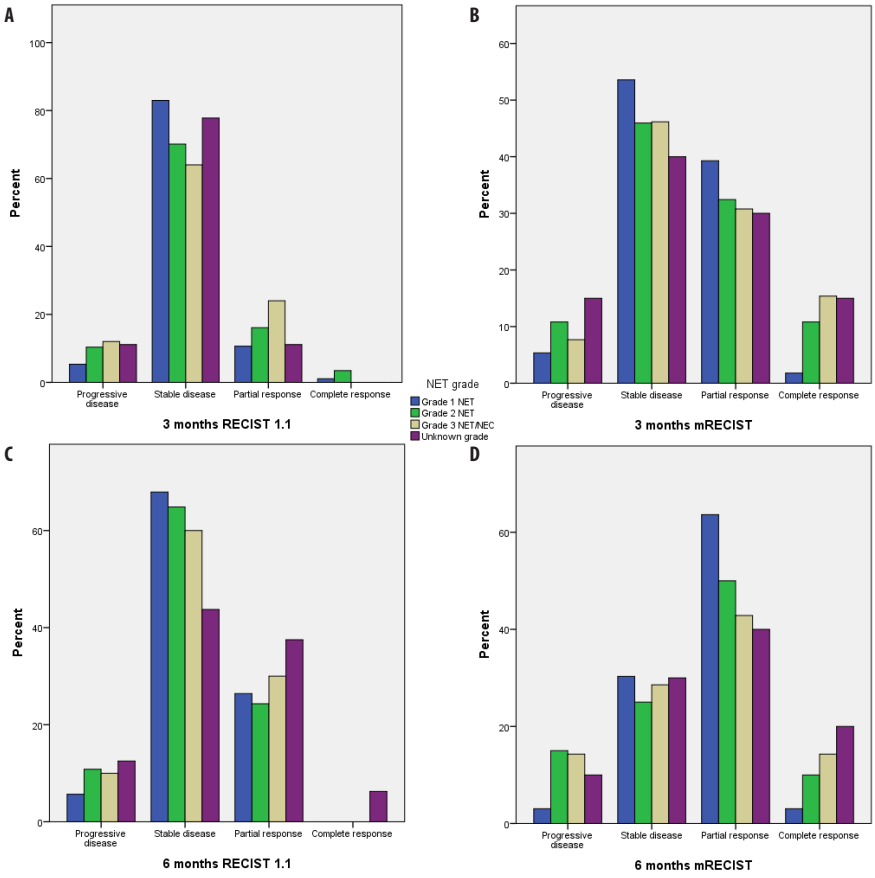

Figure 1. Distribution of response 3 months and 6 months after radioembolization according to RECIST 1.1 and mRECIST per NEN grade. **a.** RECIST 1.1 after 3 months (n=244), **b.** mRECIST after 3 months (n=126), **c.** RECIST 1.1 after 6 months (n=116), **d.** mRECIST after 6 months (n=70). mRECIST measured in patients with available multiphased contrast-enhanced imaging at baseline and follow-up. RECIST 1.1 shows mainly stable disease, whereas mRECIST shows more objective response in all NEN grades compared to RECIST 1.1.

Overall survival

Median OS after radioembolization for the entire population was 2.6 years (range: 51 days – 12 years) [95% CI 2.2–3.0 years]. Median OS in G1NET and G2NET was significantly longer than in G3NET/NEC in the Kaplan Meier analysis ($p<0.001$). Median OS was 3.1 years [95% CI 2.6–3.7] in G1NET, 2.4 years [95% CI 1.9–3.0] in G2NET and 0.9 years [95% CI 0.1–1.9] in G3NET/NEC (**Figure 3A**).

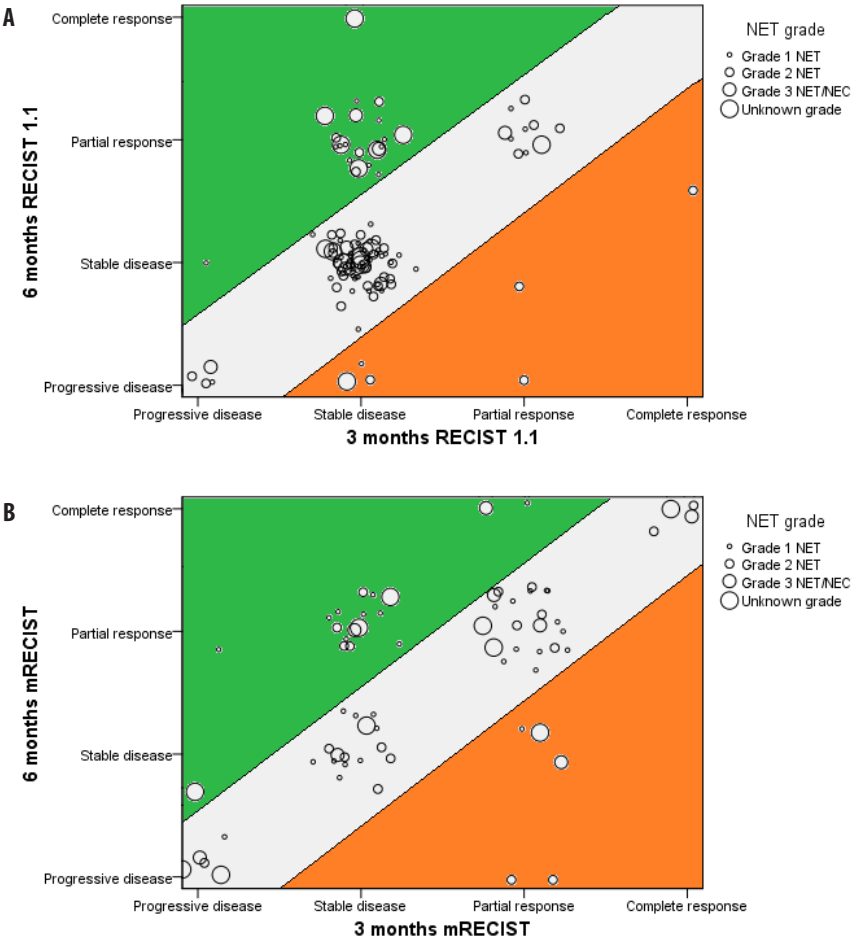

Figure 2. Changes in objective response in time. Response assessment 3 months (X-axis) and 6 months (Y axis) after radioembolization. **a.** Response assessment according to RECIST 1.1 in 116/244 patients, **b.** Response assessment according to mRECIST in 70/244 patients. Most patients show a durable response (grey area). Just several patients show a poorer response after 6 months compared to the 3 months assessment (orange area; A. 6/166 = 4%; B. 5/70 = 7%). Remarkably, in a relatively large number of patients an increase in objective response can be noticed after 6 months compared to the 3 months assessment (green area; A. 23/116 = 20%; B.18/70 = 26%).

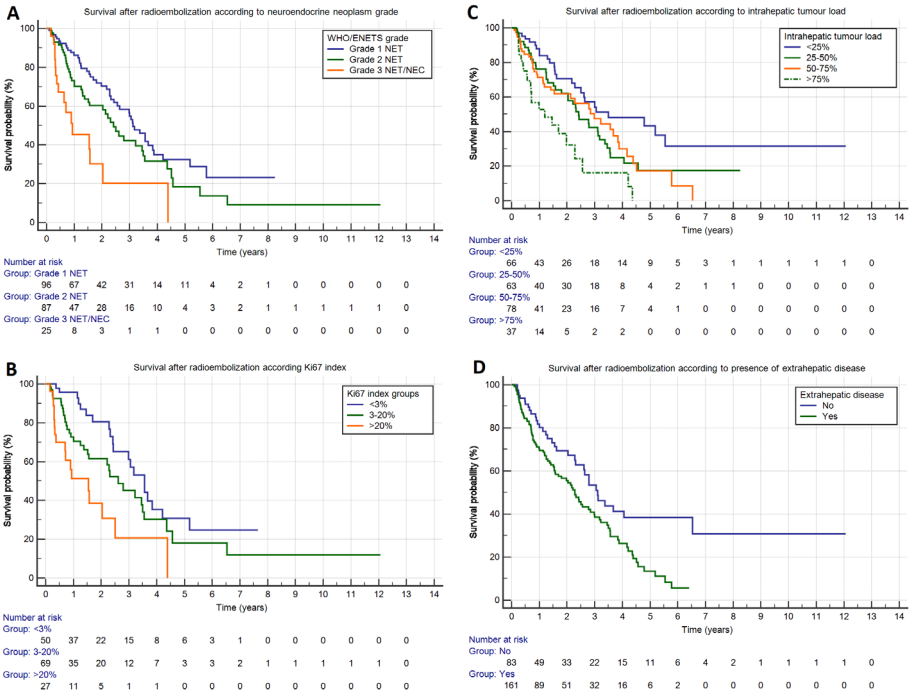

Figure 3. Kaplan-Meijer survival curves on the effect of four significant parameters influencing survival. **a.** Neuroendocrine neoplasm grade according to WHO/ENETS classification, **b.** Ki67 index, **c.** Intrahepatic tumor load, **d.** presence of extrahepatic disease.

Kaplan Meier analyses identified Ki67, intrahepatic tumour load ≥75% and presence of extrahepatic disease as significant negative prognostic factors for OS (all p<0.003; **Figure 3B-D**). In the Kaplan Meier analyses, OS was independent of tumour origin (also when stratified by tumour grade), tumour differentiation, mitotic count, number of intrahepatic lesions, resection of the primary tumour, LSF based on ^{99m}Tc-MAA, and elevated bilirubin levels at baseline.

DCR and ORR according to either RECIST 1.1 (p=0.001 and p=0.032, respectively; **Figure 4A+B**) or mRECIST (p=0.002 and p=0.007, respectively; **Figure 4C+D**) after three months showed a longer survival. The same was seen after six months (p<0.01 in all four categories). Patients experiencing improvement or resolution of pre-treatment symptoms had no significant improved OS (p=0.85).

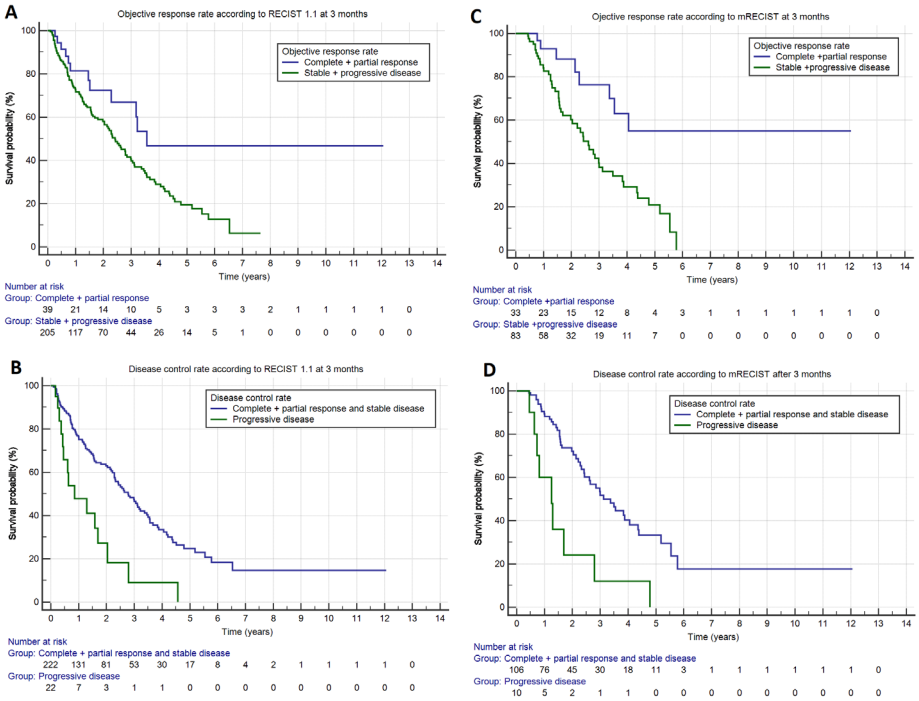

Figure 4. Kaplan-Meier survival curves on the effect of response 3 months after radioembolization on overall survival. Objective response rate and disease control rate according to the Response Evaluation Criteria In Solid Tumours, version 1.1 (RECIST 1.1; **a+b**) or modified RECIST (mRECIST; **c+d**).

In the multivariate analysis, DCR according to RECIST 1.1 at three months was predictive of a better OS (hazard ratio; HR 0.4; p<0.01). Whereas G3NET/NEC (HR 3.3; p<0.01), unknown NEN grade (HR 1.7; p=0.03), ≥75% intrahepatic tumour load (HR 2.2; p<0.01) and presence of extrahepatic disease (HR 1.7; p=0.04) were predictive of a worse OS (**Table 6**).

Table 6. Univariate and multivariate Cox proportional hazard models for known predictors of overall survival after radioembolization.

Parameter	Univariate			Multivariate		
	p-value*	HR	95% CI†	p-value*	HR	95% CI†
Grade 1 NET‡	-	1		-	1	
Grade 2 NET	0.10	1.4	0.94 – 2.14	0.08	1.4	0.93 – 2.24
Grade 3 NET/NEC	0.00*	3.3	1.84 – 5.94	0.00*	3.3	1.80 – 5.94
Unknown NEN grade	0.02*	1.8	1.10 – 3.04	0.03*	1.7	1.04 – 3.10
Intrahepatic load <75%‡	-	1		-	1	
Intrahepatic load ≥75%	0.00*	2.6	1.63 – 4.06	0.00*	2.2	1.35 – 3.54
No extrahepatic disease‡	-	1		-	1	
Extrahepatic disease	0.00*	1.8	1.21 – 2.69	0.04*	1.7	1.12 – 2.62
Lung shunt fraction ≤10%‡	-	1		-	1	
Lung shunt fraction >10%	0.14	1.4	0.90 – 2.09	0.31	1.3	0.81 – 1.94
Baseline bilirubin CTCAE 0‡	-	1				
Baseline bilirubin CTCAE ≥1	0.52	0.8	0.45 – 1.49			
PD RECIST 1.1‡	-	1		-	1	
DCR RECIST 1.1	0.00*	0.4	0.22 – 0.69	0.00*	0.4	0.23 – 0.73

*HR = Hazard ratio, 95% CI = 95% Confidence Interval, ECOG = Eastern Cooperative Oncology Group, NET = neuroendocrine tumour, NEC = Neuroendocrine carcinoma, NEN = Neuroendocrine neoplasm, PD = progressive disease, DCR = Disease Control Rate, RECIST 1.1 = Response Criteria in Solid Tumours version 1.1. *Deemed significant; p<0.05. †95% confidence interval; lower and upper boundaries shown. ‡Reference group. **Other primary tumour sites included lung, bronchus, thymus, kidney and ovary.*

Discussion

In this study, the efficacy of radioembolization of neuroendocrine liver metastases was confirmed with high DCR >90%, concordant between the two radiologic response assessment criteria (RECIST 1.1 and mRECIST), and a long median OS of 2.6 years (i.e. 31 months) for the entire study population. This is the first time a prolonged response for at least six months has been objectively demonstrated in patients with available imaging after 6 months and in approximately one-quarter of those patients, the optimal time to evaluate treatment might be later than 3 months (**Figure 2**). Additionally a high percentage of patients benefited from improvement (44%) or complete resolution (35%) of their malignancy-related symptoms, an important finding in this specific patient population.

Compared to a recent meta-analysis by Devcic et al. and other more recently published studies in the period of 2015 – 2016, radioembolization in NEN shows consistent results, with a median OS ranging between 24.7–39.0 months and a DCR of between 83%–94% according to either RECIST 1.1 or mRECIST, in line with

the 31 months [95% CI 26–36] and DCR of 91% according to either RECIST 1.1 or mRECIST in the presented population.[11, 20, 24, 18]

This study addressed several shortcomings of the current literature on radioembolization in NEN, by analyzing all available retrospective data. Current literature consists of small single center patient cohorts only, except for one large retrospective study by Kennedy et al. with 148 NEN patients.[25, 22] As stated by Devcic et al., including the study by Kennedy et al., most studies described a heterogeneous group of NEN patients and lacked proper baseline parameter description.[11] A major limitation of prior published cohorts was the lack of data referring to the NEN histopathologic characteristics, especially NEN grading according to the current WHO/ENETS classification, and its effect on tumour response and survival. ORR and DCR in this study are independent of the NEN grade (**Figure 1**) Ki67-index, mitotic index or tumor differentiation, and NEN grade is a prognostic factor for OS. Previously published data suggest a poorer response rate for patients with pancreatic NEN.[11] However, in accordance with three other studies, no significant difference in survival was observed between different origins of NEN ($p>0.3$).[18, 21, 20] The present study does confirm that the presence of extrahepatic disease is a significant factor for poorer survival.[22, 26, 27] Comparable to most other studies, a poorer OS with an intrahepatic tumour load ≥75% was found ($p<0.01$).[20]

Radioembolization has some benefits over other liver-directed treatments in NEN, of which trans-arterial (bland) embolization (TAE) and trans-arterial chemoembolization (TACE) are most commonly applied. To date, only one retrospective study addresses the differences.[23] In that study, radioembolization resulted in a similar hepatic PFS (15.7 months) compared to TAE (15.0 months), while achieving a significantly longer hepatic PFS compared to TACE (8.1 months). However, a significantly higher number of patients experienced abdominal pain after TAE compared to either radioembolization or TACE. On the other hand, radioembolization showed more biochemical toxicities compared to TAE and TACE. However, the total number of severe toxicities between radioembolization, TAE and TACE were similar.[23] The percentage of total clinical toxicities in the radioembolization group of that study (85%) were higher than the current study (56%), while severe biochemical toxicities were similar (7.5% versus 7%).[23] Compared to TAE and TACE, lately some concerns have been risen on the late onset cirrhosis after radioembolization [28]. With our limited follow-up of 6 months, we could not investigate this phenomenon. Other radioembolization induced complications were limited (<4%). REILD and gastric ulceration were

consistent with other studies in different disease groups..[29] One patient received a whole liver treatment without dose reduction, while having a LSF of 33%. On planar imaging a lot of free pertechnetate could be acknowledged and ^{99m}Tc-MAA is known to significantly overestimate LSF.[30] Based on these findings, LSF was recalculated on SPECT/CT, which was 7.8%, and patient was treated without a dose reduction.

This study has several limitations because of its retrospective design. Some histopathological characteristics could not be obtained for some patients, because the WHO/ENETS classification was not reported by pathologists before its introduction in 2011. Retrospective review of medical records did not allow comprehensive CTCAE grading of clinical toxicities and incorporated a reporting bias by the treating physician. PFS could not be measured reliably in this retrospective series since follow-up imaging intervals were not standardized across all centers. Follow-up was limited to six months after treatment in this cohort as most patients went on to receive subsequent treatment even before intrahepatic PD was documented according to either RECIST 1.1 or mRECIST, while some other patients were lost to follow-up after the first or second response assessment. Patients lost to follow-up and subsequent treatments prior to intrahepatic PD after radioembolization made imaging and toxicity follow-up beyond six months unreliable. If patients received a new treatment within the six-month follow-up, patients were excluded to avoid contamination of toxicity and imaging response data. Not all centers acquired post-treatment imaging, making dosimetric evaluation impossible and half of patients had no multiphasic imaging after treatment to assess response according to mRECIST. In recent years a lot has changed in treatment of NEN patients, so treatment sequencing is different in the patients evaluated in this study, making these results more difficult to interpret. Additionally, radioembolization was performed relatively late in the treatment regimen of patients, negatively influencing the reported OS after radioembolization.

Prospective randomized controlled studies on radioembolization in NEN are desperately needed, although it should also be recognized that clinical experience, captured in high quality retrospective study cohorts, is indispensable in this difficult-to-study heterogeneous patient population. Currently, treatment algorithms typically place radioembolization after failure of systemic treatments.[3] However, in NEN patients with disease limited or 'dominant' to the liver, radioembolization might be a more appropriate choice prior to, or in combination with first-line systemic treatment. Future studies need to address the sequencing of radioembolization along or amongst other treatment (systemic) options, like

peptide receptor radionuclide therapy (PRRT) or chemotherapy consisting of capecitabin + temozolomide (CAPTEM) in first- or second-line, and have longer follow-up after treatment [31, 32]. Technical advances in radioembolization should lead to better treatment planning and dosimetry in eligible patients, which may improve ORR and OS.[33-35] Currently literature on dosimetry in NEN is limited. Based on ^{99m}Tc-MAA SPECT/CT a mean tumour absorbed dose of >190 Gy with ^{90}Y resin microspheres has been suggested to predict tumour response with high specificity.[36] Dosimetry is of particular importance for future studies. The combination of a relatively favourable prognosis with lifestyle-limiting symptomatic disease in NEN patients favours quality of life as an important endpoint.[37-39] Quality of life indices should definitely be included in future studies as well.

Conclusion

In a broad spectrum of NEN and at different moments of the disease, radioembolization is safe, effective and can relieve symptoms, even in heavily pre-treated, progressive patients with high intrahepatic tumour load. In one-fourth of patients, objective response might improve after the commonly used 3 months evaluation scan.

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Chapter 5

Radioembolization with ^{90}Y resin microspheres of neuroendocrine liver metastases after initial PRRT

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Submitted for publication

Abstract

Background

Peptide receptor radionuclide therapy (PRRT) and radioembolization are increasingly used in neuroendocrine neoplasms (NEN) patients. However, concerns have been raised on cumulative hepatotoxicity. The aim of this sub-analysis was to investigate hepatotoxicity of yttrium-90 resin microspheres radioembolization in patients who were previously treated with PRRT.

Methods

Patients treated with radioembolization after systemic radionuclide treatment were retrospectively analysed. Imaging response according to RECIST 1.1 and clinical response after 3 and 6 months were collected. Clinical, biochemical and haematological toxicities according to CTCAE v4.03 were also collected. Specifics on prior PRRT, subsequent radioembolization treatments, treatments after radioembolization and overall survival (OS) were collected.

Results

Forty-four patients were included, who underwent a total of 58 radioembolization procedures, of which 55% whole liver treatments, at a median of 353 days after prior PRRT. According to RECIST 1.1, a disease control rate of 91% was found (CR 2%, PR 14%, SD 75% and PD 9%) after 3 months. Clinical response was seen in 65% of symptomatic patients. Within 6 months, clinical toxicities occurred in 26%. Biochemical and haematological toxicities CTCAE grade 3-4 occurred in ≤10%, apart from lymphocytopenia (42%). Radioembolization related complications occurred in 5% and fatal radioembolization induced liver disease (REILD) in 2% (one patient). A median OS of 3.5 years [95% confidence interval 1.8 – 5.1 years] after radioembolization for the entire study population was found.

Conclusion

Radioembolization after systemic radionuclide treatments is safe and no increased occurrence of hepatotoxicity (REILD) was found.

Introduction

With the introduction of radiolabelled somatostatin analogs (SSA), a.k.a. Peptide Receptor Radionuclide Therapy (PRRT), especially with ^{177}Lu-DOTATATE, treatment of neuroendocrine neoplasms (NEN) has evolved and results in long progression-free survival (PFS) and overall survival (OS) in WHO/ENETS grade 1 and 2 gastropancreatic neuroendocrine tumours. The main accelerator of this development was the recent publication of the NETTER-1 trial, combining ^{177}Lu-DOTATATE with long-acting SSA versus high dose SSA alone, resulting in a significantly prolonged PFS (not reached in the ^{177}Lu-DOTATATE arm versus 8 months in high dose SSA arm).[1] Because of the long PFS after PRRT in these patients, improving quality of life or postponing deterioration of quality of life becomes even more important. The additional analysis of the NETTER-1 study also showed a delayed time to deterioration of quality of life compared to the control arm.[2] Objective response rates according to Response Evaluation Criteria In Solid Tumors (RECIST 1.1) assessments were limited, with only 1% complete response (CR) and 17% partial response (PR).[1]

Transarterial radioembolization (a.k.a. selective internal radiation therapy or SIRT) has gained particular interest in the treatment of liver metastases of neuroendocrine neoplasms (NELM). Radioembolization with yttrium-90 (^{90}Y) resin microspheres (SIRSpheres®, Sirtex Medical, Sydney, Australia) has a high intrahepatic success rate and a limited toxicity profile. In patients treated with radioembolization, tumor reduction or stable disease according to RECIST 1.1 occurrs in 16% and 75%, respectively, and according to modified RECIST (mRECIST) in 43% and 48%, respectively.[3] Radioembolization alleviates NEN related symptoms (like flushing and diarrhoea) in 44% of symptomatic patients and resolves NEN related complaints in 35% of symptomatic patients.[3] Clinical toxicity is often related to the post-embolization syndrome and is limited to within the first 6 months after treatment. Biochemical and haematological toxicities higher than grade 2 according to the Common Terminology Criteria of Adverse Events version 4.03 (CTCAE) rarely occur (<7%).[3]

Combining PRRT and radioembolization seems logical in NEN patients with bulky hepatic disease or those with predominant liver tumour burden and extrahepatic disease, since PRRT results in less objective response in bulky liver disease compared to small volume (miliary) liver disease.[4] However, in part based on unpublished anecdotes, concerns have been raised on the potential cumulative hepatotoxicity of PRRT and radioembolization.[5, 6] Hepatotoxicity is suggested

to be more prone to occur by combining PRRT and radioembolization, however evidence and patient specific parameters are lacking. We performed a sub-analysis of our previously reported study, to determine the efficacy and toxicity profile in NEN patients who received radioembolization after PRRT.[3]

Methods

All retrospective data were gathered in the period of July 2015 until October 2016 in eight participating hospitals in Europe and the USA. The inclusion criteria were previously reported [3]: patients with histologically proven NEN (surgical specimen or biopsy), of any origin, with at least baseline and 3 ± 1.5 month follow-up cross-sectional imaging (i.e. contrast enhanced computed tomography = CT or magnetic resonance imaging = MRI, same modality at baseline and follow-up) and (for this sub-analysis) previous PRRT (e.g. ^{90}Y- or ^{177}Lu-DOTATATE/TOC) was used as an additional inclusion criteria. Details on previous PRRT treatments were gathered (number of cycles and cumulative administered activity) and time interval between PRRT and radioembolization. Medical record files were reviewed for clinical complaints registered by the treating physician. Biochemical and haematological laboratory data after radioembolization with ^{90}Y resin microspheres were gathered. If available, imaging up to 6 ± 1 months after treatment was collected. Baseline patient and tumour characteristics, angiography, and treatment specifics were gathered according to the reporting standards recommended for radioembolization [7]. Intrahepatic tumour load was visually estimated and the number of intrahepatic lesions was counted.

Prior to the actual radioembolization treatment, all patients received a treatment simulation during a preparatory angiography, in which the microcatheter position was determined for the actual treatment, followed by intra-arterial injection of technetium-99m macroaggregated albumin (^{99m}Tc-MAA). After the preparatory angiography, the patient was transported to the nuclear medicine department for planar imaging and SPECT or SPECT/CT. On planar imaging, the lung shunt fraction (LSF) was calculated, and based on the LSF, the physician could consider a dose reduction for treatment. On SPECT(/CT), extrahepatic depositions of the radiopharmaceutical were excluded prior to treatment. Within weeks following the preparatory angiography and imaging, the patient received radioembolization treatment. Prophylactic intravenous octreotide infusion or prophylactic antibiotic treatment were given at the discretion of the treating physician and according to the institutes' guideline. Ethics approval was obtained according to local regulations at the participating centers.

Study outcome parameters

The primary outcome parameter was hepatic response, according to RECIST 1.1, and mRECIST after 3 and 6 months.[8, 9] Objective response rate (ORR) was defined as complete response (CR) plus partial response (PR). Disease control rate (DCR) was defined as CR, PR plus stable disease (SD).

Secondary outcome parameters included clinical response (improvement of symptoms) and clinical toxicities (adverse events) within 3 and 6 months after radioembolization. Biochemical and haematological toxicities at 4-8 weeks, and at 3 months were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.[10] Radioembolization induced liver disease (REILD) was classified according to terminology defined by Braat et al.[11] To assess overall survival (OS), date of death or date of last contact (when lost to follow up) was collected. Because OS might be influenced by treatments following radioembolization, additional treatments following radioembolization were collected as well. Progression-free survival (PFS) analysis was not reliable in this retrospective series since follow-up imaging intervals were not standardized across all centres.

Statistical analysis

Scatter-plots were made to identify potential correlations between clinical, biochemical and haematological toxicities, and the interval between the last PRRT cycle and radioembolization and cumulative administered PRRT activity. Survival curves were estimated using the Kaplan-Meier method and assessed with the log-rank test. The following variables were tested: radiological response after treatment, tumour grade, intrahepatic tumour load and presence of extrahepatic disease at time of treatment, based on our previously published results.[3] P-values smaller than 0.05 were considered significant in all tests. The database was analysed using IBM SPSS statistics for Windows version 23.0 (IBM, Armonk, NY).

Results

All patients were treated between December 2006 and May 2016. A total of 58 radioembolization treatments in 44 patients with NELM were included; mean age 60±11 years, male 24/44 (54%). Patient demographics and baseline characteristics are shown in **table 1**. Prior to radioembolization, all patients had progressive disease prior to radioembolization and after PRRT, clinically (increase in symptoms) and/or biochemically (increase in tumour marker) and/or on imaging. Most patients had diffuse liver metastases with 96% having more than 10 lesions and 93% classified as diffuse, type III pattern.[12, 13] At the time of analysis, 24/44 (54%) patients had died.

Table 1. Baseline characteristics at time of first radioembolization

Age (Years)		
Mean	59	
Range	34-80	
Gender	**N**	**%**
Male	24	55
Female	20	45
Performance score	**N**	**%**
Eastern Cooperative Oncology Group 0	21	48
Eastern Cooperative Oncology Group 1	18	41
Eastern Cooperative Oncology Group 2	5	11
Extrahepatic metastases	**N**	**%**
No	9	21
Yes	35	79
WHO/ENETS Grade	**N**	**%**
1	13	30
2	22	50
3	3	7
Prior treatments†	**N**	**%**
Surgery	21	48
Somatostatin analog	28	64
Chemotherapy	16	36
Liver directed therapy	3	7
Unknown	6	13
Lung shunt fraction		**%**
Median		3.3
Range		0.9 – 33
Primary tumour site	**N**	**%**
Pancreas (non-functioning)	18	40
Small bowel*	11	25
Large bowel	7	16
Lung/bronchus	3	7
Unknown origin	3	7
Functioning NEN**	2	5
Administered ^{90}Y activity	**GBq**	
Median	1.7	
Range	0.4 – 5.5	

**including one gastric NEN; **one gastrinoma and one glucagonoma,*
†Besides the reported systemic radionuclide treatments and radioembolization treatments.

PRRT details

Of the 44 patients (**Table 2**), one patient received ^{131}I-MIBG (strictly speaking, the molecular target is the norepinephrine transporter, which is a catecholamine pump, and not a peptide receptor, but for the purpose of this study regarded as 'PRRT') with a cumulative activity of 14.8 GBq in two cycles, three patients received ^{90}Y-DOTATOC therapy with a median cumulative activity of 15.2 GBq (range 10 – 37 GBq) in a median of two cycles (range: 2 – 5 cycles), and 31 patients received ^{177}Lu-DOTATATE with a median cumulative activity of 30.8 GBq (range: 10 – 61.6 GBq) in a median of four cycles (range: 3 – 9 cycles). The remaining nine patients received a combination of different therapeutic radiopharmaceuticals. One patient received one ^{131}I-MIBG cycle of 11 GBq followed by two ^{90}Y-DOTATOC cycles with a cumulative activity of 18.6 GBq. The last eight patients received a median of two ^{90}Y-DOTATOC cycles (range 1- 5 cycles; median cumulative activity 15.2 GBq; range 7.4 – 32.3 GBq) followed by a median of one ^{177}Lu-DOTATATE cycle (range 1 – 4 cycles; median cumulative activity of 14.8 GBq; range 7.4 – 23.3 GBq).

Table 2. Systemic radionuclide treatment details prior to radioembolization in 44 patients

Systemic treatment	N	Number of cycles		Cumulative activity (GBq)	
		Median	Range	Median	Range
^{131}I-MIBG only	1	2	NA	14.8	NA
^{90}Y-DOTATOC only	3	2	2–5	15.2	10–37
^{177}Lu-DOTATATE only	31	4	3–9	30.8	10–61.6
^{131}I-MIBG + ^{90}Y-DOTATOC	1	1+1	NA	11+18.6	NA
^{90}Y- + ^{177}Lu-PRRT	8	2+1	1–5 + 1–4	15.2+14.8	7.4-32.3 + 7.4–23.3
Total	44	4	2 - 9	30.4	10 – 61.6

N = number of patients, NA = not applicable

Radioembolization procedure details

Median time to radioembolization from diagnosis was 4.6 years (range 1.3 – 12.9 years) and median time to radioembolization from last cycle of PRRT was 353 days (range 4 days – 6.3 years). No extrahepatic depositions of ^{99m}Tc-MAA were found on SPECT/CT (median ^{99m}Tc-MAA activity: 200 MBq; range 40 MBq–434 MBq). Median LSF was 3.3% (range 0.9%–33%). One patient had an LSF exceeding 20% (i.e. 33%), who subsequently received a whole liver treatment in one session without activity reduction. He did not develop radiation pneumonitis afterwards. Median net

administered ^{90}Y activity was 1.67 GBq (range 0.4–5.5 GBq), mostly calculated by the body surface area (BSA) method. Most procedures were whole liver treatments (32/58, 55%), followed by lobar treatments (25/58, 43%) and one patient received a segmental treatment as a fourth radioembolization procedure (1/58, 2%) (**Table 3**).

Table 3. Treatment approaches per number of radioembolization treatments (58 procedures in total)

Radioembolization approach	First	Second	Third	Fourth
One session whole liver treatment	20	2	1	
Sequential whole liver treatment*	9			
Lobar treatment	15	8	2	
Selective treatment				1

**Right lobe first and left lobe second with an interval of 4 – 6 weeks, or vice versa*

Imaging and clinical response

An ORR of 16% and DCR of 91% was observed at 3 months according to RECIST 1.1. Analysis according to mRECIST after 3 months was available in six patients, with CR in four patients, PR and SD in one patient each. At 6 months follow-up response assessment according to RECIST 1.1 was available for three patients, showing persistent SD in two patients and persistent PR in one patient. At 6 months no multiphase imaging was available for response assessment according to mRECIST.

Malignancy-related symptoms were present at treatment in 23/58 (40%) of procedures prior to radioembolization. Abdominal pain (35%) and flushing (30%) were most frequently reported. Clinical response occurred in 65% of these patients, with 7/23 (30%) having improvement of pre-treatment complaints and 8/23 (35%) experiencing complete resolution of pre-treatment symptoms after radioembolization. Only 8/23 (35%) remained symptomatic after radioembolization.

Clinical toxicity

No complications related to the angiography procedure itself occurred. During administration, one patient experienced abdominal pain necessitating early cessation of administration. Reflux and stasis of contrast during microsphere administration occurred once.

At 3 and 6 months after radioembolization, no clinical toxicities occurred in 37/58 (64%) and 32/58 (55%) of procedures. Within 3 and 6 months, known radioembolization related adverse-events occurred in 15/58 (26%) and 5/58 (9%),

respectively, mainly transient abdominal discomfort. The treating physician did not register clinical toxicities in 6/58 (10%) and 21/58 (36%) of procedures, at 3 and 6 months respectively (missing data or death). In the scatter-plot analyses, no correlation was found between the clinical toxicities and interval between PRRT and radioembolization, and the cumulative PRRT activity.

Biochemical and haematological toxicity

At baseline, most patients already had a variety of biochemical toxicities according to CTCAE v4.03 (**Table 4**). The most common newly developed CTCAE grade 3-4 biochemical and haematological toxicities were γ-glutamyl transpeptidase (γGT) elevation (10%) and lymphocytopenia (42%). New grade 1 and 2 hyperbilirubinemia occurred in 5% and 5%, respectively (**Figure 1A**). New grade 3 hyperbilirubinemia occurred in one patient who developed REILD (**Figure 1A**). Grade 1-2 toxicities of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), hypoalbuminemia or a combination of these measurements were encountered in up to 75% (**Table 4**). At 3 months, new grade 1 and 2 hypoalbuminemia occurred in 13% and 13%, respectively. At 3 months, ALP elevation was the most common new biochemical toxicity, with one CTCAE grade increase compared to baseline in 47% (**Figure 1B**). The most common new haematological toxicity was CTCAE grade 1 - 4 lymphocytopenia (**Table 4**). In case other haematological toxicities occurred, these were all limited to one CTCAE grade increase compared to baseline (**Table 4**). Coagulation was unaffected as measured by the International Normalized Ratio. Dynamics in bilirubin, ALP, AST and ALT after radioembolization are depicted in **figure 1**. In the scatter-plot analyses, no correlation was found between the biochemical and haematological toxicities, the interval between PRRT and radioembolization, and cumulative PRRT activity.

Radioembolization related toxicities

Radiation-induced gastric ulceration occurred in two patients (3%), due to accidental extrahepatic deposition of microspheres, both confirmed by endoscopy (one biopsy proven). Radiation pneumonitis occurred in one patient (2%), who had a ^{99m}Tc-MAA based LSF of 3.1%. The exact cause of the radiation pneumonitis was unknown. One patient developed a liver abscess (2%), successfully treated by antibiotics and a percutaneous drain, and one patient developed cholangitis (2%), successfully treated with antibiotics. Both patients had a bilioenteric anastomosis and underwent radioembolization without prophylactic antibiotics.

Table 4. Absolute percentage of biochemical and haematological toxicities

	Baseline			4-6 weeks			3 months		
CTCAE grade	0	1+2	3+4	0	1+2	3+4	0	1+2	3+4
Alkaline phosphatase	47%	51%	2%	25%	75%		25%	75%	
γGT	15%	47%	38%	5%	41%	54%	3%	31%	66%
AST	75%	23%	2%	64%	36%		55%	45%	
ALT	79%	21%		78%	22%		76%	22%	2%
Bilirubin	95%	5%		90%	8%	3%	87%	10%	3%
Albumin	73%	27%		64%	36%		55%	45%	
LDH	61%	37%	2%	56%	44%		69%	28%	3%
Haemoglobin	27%	73%		29%	71%		25%	75%	
Leucocytes	75%	25%		77%	23%		75%	23%	2%
Lymphocytes	45%	32%	23%	18%	54%	26%	25%	33%	42%
Platelets	82%	17%	2%	69%	29%	2%	70%	28%	3%
INR	100%			100%			100%		

CTCAE = Common Terminology Criteria for Adverse Events version 4.03, ALP = alkaline phosphatase, γGT = γ-glutamyl transpeptidase, AST = aspartate aminotransferase, ALT = alanine aminotransferase, LDH = lactate dehydrogenase and INR = International Normalized Ratio.

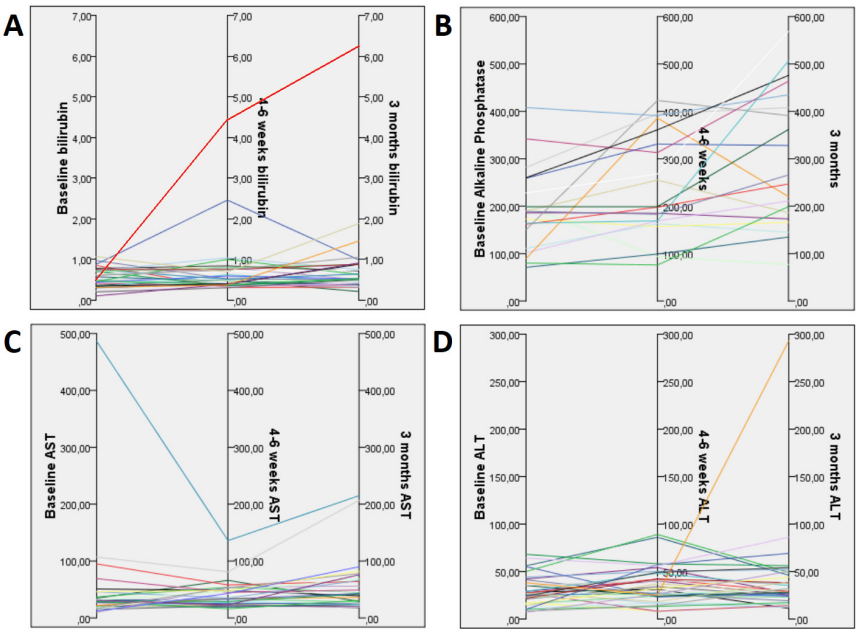

Figure 1. Biochemical toxicities in the first three months after radioembolization.
a. Bilirubin measurements in mg/dl; **b-d**. Alkaline phosphatase, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in U/l. One patients developed a grade 5 REILD with deteriorating bilirubine levels (**a**) and increasing ALT values at 3 months (**d**). One patient had isolated AST elevation prior to radioembolization (**c**) potentially related to prior treatment with everolimus.

Two patients developed REILD according to the treating physician; the first patient had a grade 2 NEN of unknown origin with progressive liver disease, stable lymph node metastases in the mesentery and stable bone metastases and Child-Pugh A5 at the time of radioembolization. This patient was previously treated with SSA and seven cycles of ^{177}Lu-DOTATATE, with a cumulative activity of 55.4 GBq. Whole liver radioembolization in one session with 2.7 GBq was performed 4.6 years after the last cycle of ^{177}Lu-DOTATATE. The patient developed ascites within three months after treatment with CTCAE grade 1-2 elevation of ALP, γGT, AST, ALT, without elevation of bilirubin or lactate dehydrogenase (LDH). Ascites decreased without medical intervention, and thus this was retrospectively classified as grade 2 REILD. Six months after radioembolization, the patient received one additional cycle of ^{177}Lu-DOTATATE (5.5 GBq), because progressive extrahepatic disease (bone metastases), without evidence of REILD.

The second patient had a grade 3 pancreatic NEN (Ki67 30%) with progressive liver disease and lymph node metastases and Child-Pugh B7 at the time of radioembolization. The patient was previously treated with a surgical resection of the primary tumour via a Whipple procedure at diagnosis, two types of chemotherapy (cisplatin + etoposide and dacarbazine monotherapy) and three cycles of ^{177}Lu-DOTATATE with a cumulative activity of 20.1 GBq. Sequential whole liver radioembolization (right lobe first and left lobe six weeks later) with a cumulative activity of 5.0 GBq (partition model calculation) was performed 3.2 years after the last cycle of ^{177}Lu-DOTATATE. The patient developed abdominal discomfort and ascites within six weeks after treatment with new CTCAE grade 3 hyperbilirubinemia and new CTCAE grade 2 ALP elevation at six weeks. Pre-existent CTCAE grade 1 hypoalbuminemia and CTCAE grade 3 γGT did not deteriorate. Biochemical toxicities persisted after three months and clinical toxicities persisted till the patient died 20 weeks after radioembolization (REILD grade 5).

In retrospect, one other patient developed clinical and biochemical evidence of REILD, but was not reported by the treating physician. The patient had grade 3 REILD, based on grade 2 bilirubin elevation after 4 weeks (at baseline already grade 1) and development of ascites, 3 months after radioembolization, without evidence of tumour progression. Bilirubin levels returned to grade 1 within 3 months (**Figure 1A**) and ascites resolved after 6 months with additional diuretics (spironolactone and furosemide). Treatments received after radioembolization were unknown (lost to follow-up).

Treatments after both PRRT and radioembolization

A total of 34/44 patients (77%) received additional treatment, mostly systemic, after PRRT and radioembolization, apart from the reported additional radioembolization procedures in 10 patients (**Table 3**). Long-acting SSA therapy was continued in 18/44 patients (41%). In 19/44 patients (43%), additional PRRT treatments were given. All additional PRRT treatments were ^{177}Lu-DOTATATE with a median of one treatment cycle (range 1-7 cycles). Median cumulative activity of the additional PRRT treatments was 9.2 GBq (range 5.5 – 41.5 GBq). Other treatments were less common and consisted of systemic chemotherapy (27%), surgery (9%) or additional liver-directed therapies (9%; bland-embolization and radiofrequency ablation).

Overall survival

Median OS after radioembolization for the entire population was 3.5 years; range: 51 days (lost to follow-up) – 7.6 years [95% CI 1.8–5.1 years] (n=44). Median OS for grade 1 NET was 3.6 years [95% CI 2.7–4.3] (n=13). Median OS for grade 2 NET was 2.8 years [95% CI 0.6 – 4.6] (n=22), and for grade 3 NET/NEC was 136 days (range 115 – 504 days; n= 3). Patients with an unknown tumour grade had a median OS of 262 days (range 73 – 644 days; n=6).

Kaplan-Meier analyses confirmed intrahepatic tumour load >75% as a significant negative prognostic factors for OS (p=0.007; **Figure 2A**). Presence of extrahepatic disease resulted in a poorer OS as well; median OS 3.2 years [95% CI 1.1–5.3] versus 6.2 years [95% CI 5.5–7.0] (p=0.001; **Figure 2B**). In the Kaplan-Meier analyses, OS was independent of DCR (p=0.7) or ORR (p=0.7) according to RECIST 1.1.

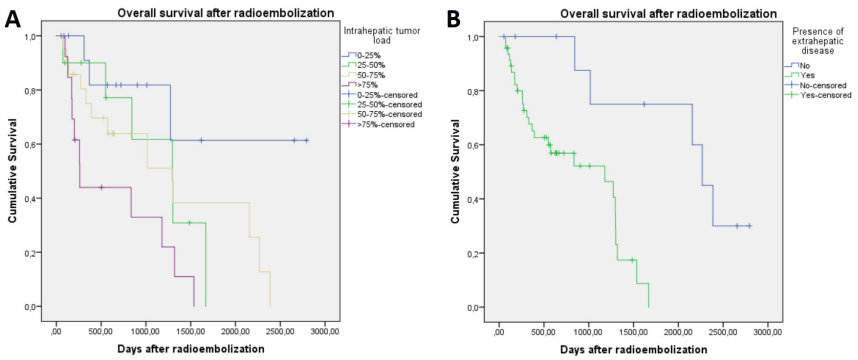

Figure 2. Kaplan-Meier survival curves of two factors with a negative impact on overall survival.
a. Intrahepatic tumour load. Patients with >75% tumour load have a significant shorter overall survival compared to patients with <75% tumour load (p=0.007). **b.** Presence of extrahepatic disease at time of radioembolization. Patients with extrahepatic disease have a significant shorter overall survival compared to patients without extrahepatic disease (p=0.001)

Discussion

In this study, radioembolization of progressive NELM after initial PRRT resulted in a DCR of 91% at 3 months according to RECIST 1.1, clinical response in 65% of symptomatic patients and a long median OS of 3.4 years (41 months) for the entire study population. Tumour grade (grade 3 NET/NEC and unknown grade) according to WHO/ENETS classification, intrahepatic tumour load >75%, and the presence of extrahepatic disease prior to treatment were negative prognostic markers for OS. Expected clinical toxicities within 6 months occurred in about one-quarter of patients, mainly consisting of abdominal discomfort, in line with previous reports. [3] Biochemical and haematological toxicities CTCAE grade 3-4 were limited (≤10%), apart from lymphocytopenia in 42% of procedures. Radioembolization-related complications within 6 months after treatment were limited as well (5%), with one case of fatal REILD (grade 5) and one case of moderate REILD (grade 3; requiring additional diuretics because of abdominal discomfort due to ascites). Our data showed no correlation between treatment toxicities and the time interval between PRRT and radioembolization. Additionally, there seemed to be no correlation between toxicities and cumulative activity of previous PRRT.

Previously reported studies on hepatotoxicity after radionuclide treatments are limited, are all retrospective studies, consist of small populations, and are difficult to interpret. Looking at hepatotoxicity following PRRT, the NETTER-1 study reported no hepatotoxicity.[1] However in 2015, Riff et al. reported an increased hepatotoxicity rate after PRRT (n=17) compared to standard-of-care (n=76). [5] In their small population, they mainly described the development of ascites in 10/17 patients (59%), of whom 8/10 (80%) were presumed to be related to PRRT, and 6/10 (60%) required medical therapy. Unfortunately, the time to ascites development after PRRT, the number of PRRT treatment cycles, and cumulative activity of PRRT was not reported. The authors suggested a correlation between radioembolization prior to PRRT and post-PRRT hepatotoxicity. In their PRRT group, post-PRRT hepatotoxicity was seen in 70% of patients previously treated with radioembolization prior to PRRT, compared to 42% in patients treated with PRRT alone. However, the correlation was not statistically significant.

More recently in 2017, Su et al. described long-term hepatotoxicity in 54 patients after whole liver and lobar radioembolization with ^{90}Y glass microspheres in NET patients.[6] In their cohort, time to development of a cirrhosis-like morphology on imaging studies was 1.8 years (0.7 - 7.2 years). This occurred in 22/39 patients after whole liver radioembolization and in 4/15 patients after

lobar radioembolization. Eight out of the 22 patients treated with a whole-liver radioembolization and one of the four patients after a lobar treatment had signs of hepatic decompensation. Of these patients, decompensation could be attributed solely to the radioembolization treatment in just two patients, since they had no additional treatments after radioembolization. The other seven patients underwent additional (hepatotoxic) treatments after radioembolization, mainly systemic chemotherapy. Most of the patients had cirrhosis-like changes on imaging in the years following radioembolization, however, the majority of these patients did not exhibit corresponding clinical symptoms.[6] Interestingly, the authors reported no differences in cumulative prescribed activity, whole liver radioembolization or repeated radioembolization between patients with either asymptomatic or symptomatic cirrhosis-like changes. Unfortunately, treatments prior to radioembolization were not reported.

To our knowledge, just one study discusses the occurrence of hepatotoxicity in NEN after radioembolization with ^{90}Y-resin-microspheres. Tomozawa et al. reported their findings in 52 patients with more than 1 year follow-up.[14] None of the patients had prior systemic radionuclide treatments or whole liver treatments in one session, and 29 out of 52 patients received bilobar treatment. At 1 year follow-up 25% had PR, 67% had SD and 8% had PD according to RECIST 1.1. Mainly CTCAE grade 2 biochemical toxicities were found and CTCAE grade 3 biochemical toxicities were found in just 8%. Cirrhosis-like morphology or portal hypertension on imaging was found in 15 patients (29%). However, other treatments following radioembolization were not reported and influence of other (hepatotoxic) treatments remains to be determined.[14]

In 2012, Ezziddin et al. reported on the safety of radioembolization after previous ^{177}Lu-DOTATATE treatment. In 23 patients a limited number of adverse events <10% (CTCAE version 3.03 grade 3 or 4) was reported with an objective response rate of 30% (after 3 months according to RECIST 1.0) and long OS of 29 months following radioembolization.[4] These results seem quite comparable to our results. However, 35% of the cohort reported by Ezziddin et al. did develop a CTCAE v3.03 grade 1 or 2 ascites, which is a higher occurrence of ascites compared to our data (5%). Unfortunately, both the cumulative administered activity of ^{177}Lu-DOTATATE and the time interval between ^{177}Lu-DOTATATE and radioembolization was not reported.

Two major issues currently exist in the literature. First, there is no accepted standardized definition for radiation-induced hepatotoxicity. Especially, since the adoption of radioembolization, the definition of REILD in the literature has been

vague and variable. We recently proposed a new classification system to define REILD, which could be applied to all patients, in line with the CTCAE system. [11] However this proposed system has yet to be adopted and differs from the definitions reported in the other studies. In the paper by Riff et al., hepatotoxicity was defined as CTCAE grade ≥2 biochemical or clinical toxicities related to the liver (e.g. ascites), while in the study of Su et al., hepatotoxicity, e.g. cirrhosis-like changes, was based on chronic imaging findings by the radiologist only. Lack of standardized definition of hepatotoxicity prevents valid comparison of studies.

Second, there is no established quantitative relationship between radiation absorbed dose and hepatotoxicity for radionuclide therapies. Hepatic decompensation or cirrhosis-like changes on imaging are thought to be related to the radiation absorbed dose in healthy liver parenchyma. However, there are no conclusive dosimetric data to support this theory, and neither PRRT nor radioembolization has validated voxel-based dosimetric methods available. The previously mentioned studies only suggested this phenomenon, without providing quantitative dosimetry. In the report by Riff et al., only patients who underwent ^{90}Y-labelled PRRT mono-therapy (6/7 patients) or a combination of ^{90}Y- and ^{177}Lu-labelled PRRT developed ascites. In the single patient treated with ^{177}Lu-DOTATATE only, no hepatotoxicity occurred. ^{90}Y-labelled PRRT results in a higher radiation absorbed dose in healthy liver tissue compared to ^{177}Lu-labelled PRRT, 0.5 – 1.0 Gy/GBq and 0.1-0.3 Gy/GBq, respectively. [15-19] These findings seem to support the hypothesis of a relationship between radiation absorbed dose in healthy liver tissue and the development of hepatotoxicity.

In the study by Su et al., the cumulative amount of activity was reported, but again, no quantitative dosimetry was performed, and no correlation was found between the development of cirrhosis-like changes on imaging and the cumulative amount of activity administered. Toxicity thresholds are also likely to be dependent on underlying hepatic reserve, which can be compromised by prior exposure to cytotoxic chemotherapy, radiation, viral hepatitis, and toxins such as alcohol. In addition, unlike the homogeneous absorption of radiation from external beam radiotherapy, radionuclide therapies, and especially radioembolization, result in highly heterogeneous radiation dose deposition on a cellular level due to heterogeneous intrahepatic distribution of microspheres. Distribution depends on many factors, including hypervascularity of the tumours, which directly influences the balance between tumour radiation absorbed dose and healthy liver tissue absorbed dose, and (progression free) survival.[20]

Besides the relatively short follow-up period and retrospective nature of our study, the lack of dosimetric data is the main limitation of our study. Unfortunately, not all recruiting centers acquired post-treatment ^{90}Y-bremsstrahlung SPECT or ^{90}Y PET imaging, making post-treatment dosimetric evaluation impossible. However, our study does describe the longitudinal medical history of the treated patients. Even after a combination of PRRT and radioembolization, there seems to be room for additional radioembolization treatments (performed in 10/44 patients; up to 4 treatments in total; **table 3**) or even ^{177}Lu-DOTATATE (performed in 19/44 patients; up to 7 cycles, amounting to 41.5 GBq). This also emphasizes the need for accurate dosimetric data on radioembolization and PRRT in NEN patients in future studies, not only looking at tumour absorbed dose and objective response, but also at healthy tissue absorbed dose and hepatotoxicity.

Furthermore, PFS could not be measured reliably in this retrospective series since follow-up imaging intervals were not standardized across all centres. Follow up was limited to 6 months after treatment in this cohort as most patients went on to receive subsequent treatment, even before intrahepatic PD was documented according to either RECIST 1.1 or mRECIST, while some other patients were lost to follow-up after the first- or second-response assessment. Patients lost to follow-up and subsequent treatments prior to intrahepatic PD after radioembolization made imaging and toxicity follow-up beyond 6 months unreliable.

Beside the need for accurate dosimetric data in radioembolization, prospective randomized controlled studies in NEN are clearly needed. Currently, treatment algorithms and guidelines typically place radioembolization after failure of systemic treatments, including PRRT, despite much higher reported rates of hepatic response.[12] However, in NEN patients with disease limited or 'dominant' to the liver, radioembolization might be a more appropriate choice prior to, or in combination with other systemic treatment, like PRRT or systemic chemotherapy.[21, 22] However, this deserves to be studied in carefully designed prospective trials and future studies need to address the sequencing of radioembolization amongst these other treatment options.

Conclusion

Radioembolization after systemic radionuclide treatments is safe and no increased occurrence of hepatotoxicity (REILD) was found.

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Chapter 6

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)

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BMC Gastroenterology 2018; 18: 84

Abstract

Background

Neuroendocrine tumours (NET) consist of a heterogeneous group of neoplasms with various organs of origin. At diagnosis 21% of the patients with a Grade 1 NET and 30% with a Grade 2 NET have distant metastases. Treatment with peptide receptor radionuclide therapy (PRRT) shows a high objective response rate and long median survival after treatment. However, complete remission is almost never achieved. The liver is the most commonly affected organ in metastatic disease and is the most incriminating factor for patient survival. Additional treatment of liver disease after PRRT may improve outcome in NET patients. Radioembolization is an established therapy for liver metastasis. To investigate this hypothesis, a phase 2 study was initiated to assess effectiveness and toxicity of holmium-166 radioembolization (^{166}Ho-RE) after PRRT with lutetium-177 (^{177}Lu)-DOTATATE.

Methods

The HEPAR PLUS trial ("Holmium Embolization Particles for Arterial Radiotherapy Plus ^{177}Lu-DOTATATE in Salvage NET patients") is a single centre, interventional, non-randomized, non-comparative, open label study. In this phase 2 study 30 – 48 patients with >3 measurable liver metastases according to RECIST 1.1 will receive additional ^{166}Ho-RE within 20 weeks after the 4th and last cycle of PRRT with 7.4 GBq ^{177}Lu-DOTATATE. Primary objectives are to assess tumour response, complete and partial response according to RECIST 1.1, and toxicity, based on CTCAE v4.03, 3 months after ^{166}Ho-RE. Secondary endpoints include biochemical response, quality of life, biodistribution and dosimetry.

Discussion

This is the first prospective study to combine PRRT with ^{177}Lu-DOTATATE and additional ^{166}Ho-RE in metastatic NET. A radiation boost on intrahepatic disease using ^{166}Ho-RE may lead to an improved response rate without significant additional side-effects.

Introduction

In accordance with the most recent WHO/ENETS criteria, grade 1 and 2 neuroendocrine tumours (G1-/G2NET) are regarded as well- to moderately-differentiated tumours and grade 3 NET (G3NET) as poorly-differentiated NET or neuroendocrine carcinomas (NEC) [1, 2]. At diagnosis, 21% of all G1NET, 30% of all G2NET and 50% of all G3NET have distant metastases, of which the liver is most commonly affected [3, 4]. A correlation between the organ of origin and the likelihood of metastasis exists. For example, rectal NET has a slim chance of distant metastasis (5%) compared with pancreatic or colonic NET (respectively 64% and 53-86%) [3, 5]. Considering these numbers, many patients will be ineligible for curative treatment, which currently only includes surgical resection of the primary tumour.

Most G1-/G2NET have membrane receptors for somatostatin, allowing for targeted therapies, of which somatostatin-analogs are the most commonly used (e.g. octreotide). Treatment with somatostatin-analogs, chemotherapeutics and kinase inhibitors show only limited objective response rates in G1-/G2NET [6-12]. In addition, systemic therapies give rise to systemic side effects. In the last decade, the treatment of G1-/G2NET with peptide receptor radionuclide therapies (PRRT) has increased. High objective imaging response rates (CR+PR 29%-58%) [13-17], clinical and biological response rates and a long median survival (95-128 months after diagnosis, 46 months after treatment) [13, 14] can be achieved after PRRT. (**Figure 1**)

All studies include high percentages of patients with liver metastases and show a dismal prognosis with increasing liver involvement (**Table 1**). As surgical resection techniques develop, some forms of hepatic involvement can be treated surgically. However, as three different patterns of hepatic metastases are described in NET, patients with the most common 'diffuse pattern' are not eligible for surgical resection (**Table 2**) [4]. Besides, most systemic therapies have a limited objective response rate. This indicates a need for improved treatment of extensive liver disease. In accordance with the ENETS guideline published in 2012, the treatment of choice in patients with NET liver metastases with a 'diffuse' or unresectable 'complex pattern', consists of systemic treatment followed by liver directed treatment [4]. Hepatic radioembolization (RE) is one of the liver directed treatments and it is an established minimal invasive treatment of patients with liver malignancies. RE has been demonstrated to be effective and well tolerated in primary, as well

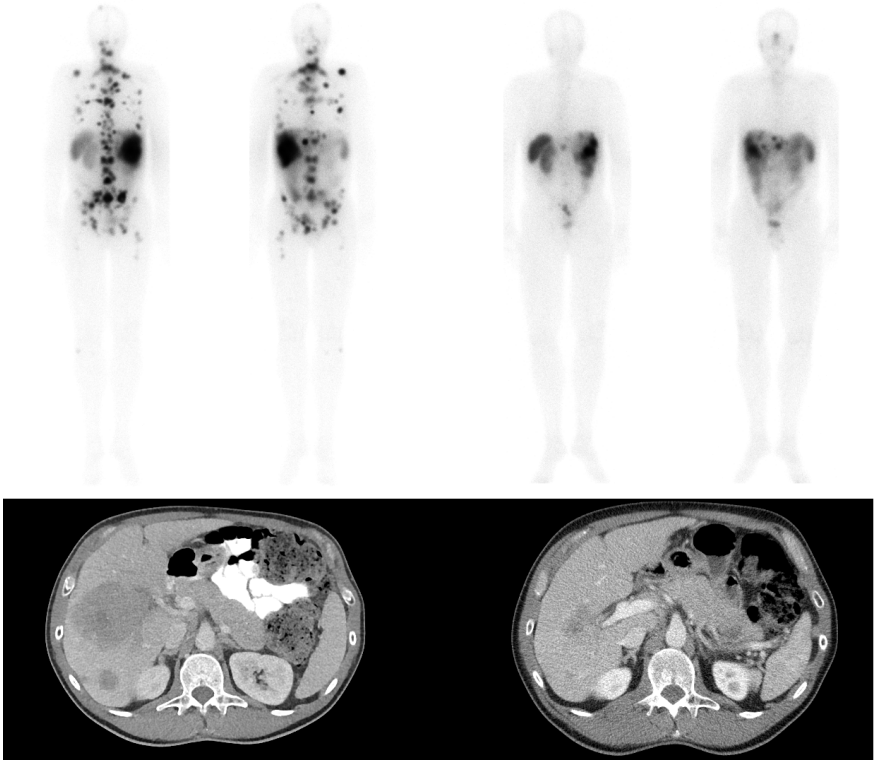

Figure 1. Example of ^{177}Lu-DOTATATE in NET. Upper row: planar whole body ^{111}In-pentetreotide scintigraphy. Lower row: venous phased CT of the liver. On the left baseline imaging and on the right imaging after ^{177}Lu-DOTATATE treatment.

Table 1. Liver involvement as a poor prognostic factor in different therapeutic studies.

Author	Treatment	N	Liver involvement	Median survival (months)	5-year survival	p-values
Chamberlain (2000) [46]	Surgical resection	85	0%-25%	-	90%	
			25%-50%	-	83%	
			50%-75%	47	80%	
			>75%	24	-	
Yao (2001) [47]	Surgical resection	16	≤4 liver metastases	46	-	< 0.05
			>4 liver metastases	20	-	
Gupta (2005) [48]	TAE *or* TACE	123	0%-25%	86	-	
			25%-50%	30	-	< 0.10
			50%-75%	39	-	< 0.17
			>75%	20	-	< 0.05
Kwekkeboom (2008) [14]	PRRT	310	None	>48	-	
			Moderate	>48	-	
			Extensive	25	-	< 0.01

TAE = transarterial (bland) embolization, TACE = transarterial chemoembolization, PRRT = peptide receptor radionuclide therapy

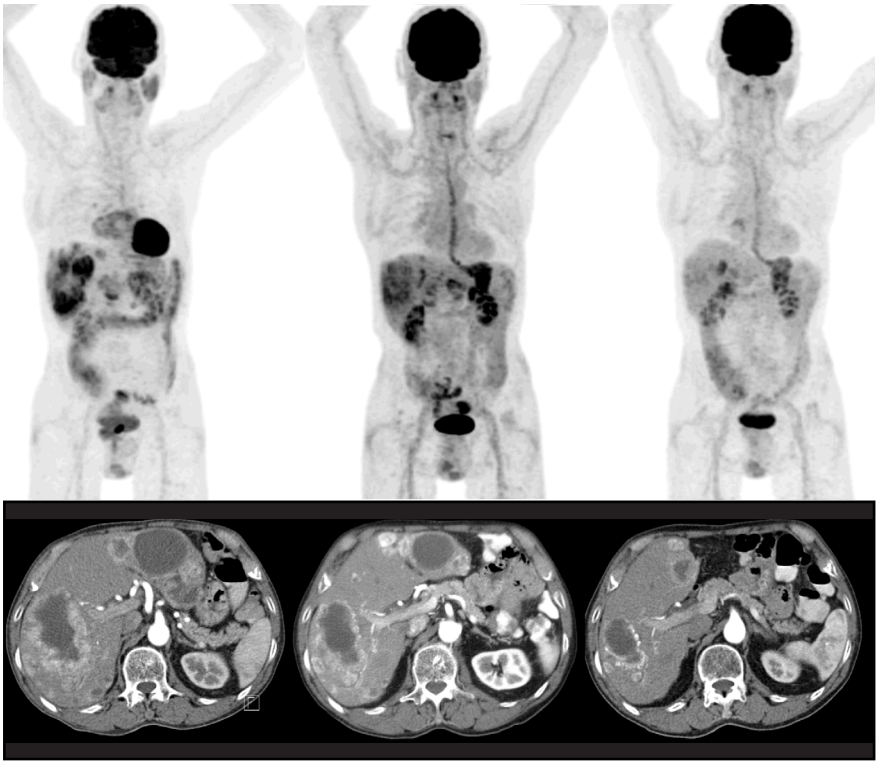

Figure 2. Example of ^{166}Ho-radioembolization in NET. A patient with a grade 2 small intestinal NET according to the WHO-criteria, treated in the prior HEPAR 2 trial. On the left, the ^{18}FDG-PET and venous phased CT at baseline. In the middle, the imaging studies 3 months after ^{166}Ho-RE with partial metabolic ^{18}FDG-PET response and some tumour reduction on CT. On the right, follow-up imaging studies 6 months after ^{166}Ho-RE with significant partial metabolic response and significant tumour reduction on CT.

as secondary liver malignancies. A recent meta-analysis by Devcic et al. showed an average objective response rate (CR+PR) of 50% and an average disease control rate of 86% in a heterogeneous group of NET treated with RE [18]. ^{166}Ho-RE is quite similar to ^{90}Y-RE, but its distinct advantages will be discussed later on. **Figure 2** shows an example of ^{166}Ho-RE in a NET patient.

Table 2. NET Liver involvement patterns.[4]

	Involvement	Incidence
Simple pattern	One lobe or two adjacent lobes	20-25%
Complex pattern	Primarily one lobe and smaller satellites contralaterally	10-15%
Diffuse pattern	Multifocal disease	60-70%

In the current clinical setting, RE is used for liver dominant or liver isolated disease, often in a salvage setting. In this study, it is hypothesized that improved outcome can be obtained by escalating the treatment of liver metastases, the most significant prognostic factor for NET patients, additional to treatment of all extrahepatic disease in G1-/G2NET patients, by combining systemic PRRT with RE. In the presented study, patients with metastasized NET will receive PRRT in 4 cycles of 7.4 GBq with ^{177}Lu-DOTATATE, followed by ^{166}Ho-RE in the University Medical Centre Utrecht, the Netherlands, using ^{166}Ho-microspheres. The following paragraphs will address the details of the study.

Methods

Study design

The HEPAR PLUS study is a single centre, interventional, non-randomized, non-comparative, open label study. In this phase 2 study all patients will receive additional ^{166}Ho-RE after ^{177}Lu-DOTATATE. Overall, 30 - 48 patients with metastasized NET will be investigated for efficacy and toxicity.

Subjects

Patients with NET and liver metastasis, who completed 4 cycles of 7.4 GBq ^{177}Lu-DOTATATE, will receive additional ^{166}Ho-RE within 20 weeks of the last/fourth cycle of ^{177}Lu-DOTATATE. At time of recruitment, all included patients have no need for conventional treatment options like surgery or chemotherapy. In the Netherlands, ^{177}Lu-DOTATATE is often a first- or second-line treatment. Previous treatments prior to ^{177}Lu-DOTATATE were no exclusion criterion. Detailed inclusion and exclusion criteria are listed in **table 3**.

Time schedule

Recruitment will take place between Augustus 2014 and January 2019. First participant was enrolled in November 2014.

Medical Device

^{166}Ho-microspheres are produced by incorporating non-radioactive ^{165}Ho and its acetylacetonate complex (^{165}HoAcAc) in a poly(L-lactic acid) matrix to form microspheres with an average diameter of 30 µm. By neutron-activation in a nuclear facility, the prescribed amount of radioactive ^{166}Ho-microspheres are produced [19, 20]. The radionuclide ^{166}Ho has a half-life of 26.8 hours, is a beta-emitter ($E_{\beta max}$ = 1.85 MeV) and a gamma emitter (E_{γ} = 81 keV). Due to their additional photon emitting properties, ^{166}Ho-microspheres can be visualized and quantified using SPECT imaging [21, 22].

Table 3. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Patient must have given a written informed consent	Brain metastases or spinal cord compression, unless irradiated > 4 weeks prior to ^{166}Ho-RE and stable for at least 1 week without steroids
≥ 18 years of age	Serum bilirubin > 1.5 x upper limit of normal
Confirmed histological diagnosis NET	Glomerular filtration rate <35 ml/min
Prior treatment with 4 cycles of 7.4 GBq ^{177}Lu-DOTATATE within 20 weeks before ^{166}Ho-RE	Alkaline phosphatase, alanine aminotransferase or aspartate aminotransferase > 5 x upper limit of normal
Life expectancy > 12 weeks	Leucocytes < 2.0 x 10^9/l and/or platelet count < 50 x 10^9/l
WHO performance score 0 – 2	Significant cardiac event within 3 months of inclusion
≥ 3 measurable liver lesions according to RECIST 1.1	Patients suffering from diseases with an increased chance of liver toxicity
Negative pregnancy test for women of childbearing potential	Patients declared incompetent or suffering from psychic disorders making comprehensive judgment impossible
No nursing activities for women of childbearing potential	Severe bile duct abnormalities: papillotomy, cholecystectomy, biliary stents and bilidigestive anastomosis are allowed
Acceptable method of contraception	Body weight > 150 kg
	Severe contrast allergy
	Liver tumour involvement >70% on CT

Recruitment

All patients have previously been treated with four cycles of ^{177}Lu-DOTATATE. After the fourth cycle patients are eligible for study inclusion. The study physician (AJATB) and principal investigator (MEGHL) inform all patients; thereafter informed consent will be obtained. On the informed consent form, participants can indicate whether they wish to receive a summary of the trial results, once the trial is completed.

Statistical analysis

This single arm open label study will have a sequential design. Stopping boundaries are determined such that an overall one-side alpha of at the most 0.05 is maintained in case the true tumour response is 20%. Early termination at a response interim analysis (after 30, 36 or 42 patients) is determined by pre-defined boundaries on the number of partial and complete responses according to RECIST 1.1 (**Table 4**). A superiority or futility boundary may be reached or crossed before 30 patients are reached, but the study will continue to at least 30 patients to allow estimation of the key secondary endpoints. The sequential design with boundaries as given in **table 4** will have a power of 90% to reach a positive tumour response decision in case the true target lesions tumour response is 40%. The exact overall one-sided type I error is 4.5%.

Table 4. Stopping boundaries for early termination at interim analyses.

Analysis	Sample Size	Lower boundary	Upper boundary
1	30	5	11
2	36	6	13
3	42	7	14
4	48	15	16

Interim analysis of toxicity with descriptive statistics (N, mean, median, etc.) will be performed for every 3 patients. All analysis will be performed in the Full Analysis Set (FAS), including all patients who received at least the scout dose procedure (see below). The Per Protocol Set (PPS) will include all patients who complied with the protocol up to at least 3 months. PPS analyses will be used for the primary endpoint. For the assessment of the primary objective at least 30 patients should have a 3 months follow-up CT-scan. If patients do not reach the 3 months follow-up CT-scan or receive a new treatment prior to the evaluation moment, a new patient will be included for the PPS analysis.

Monitoring

All safety interim analyses will be presented to our Independent Data Monitoring Commission (IDMC), consisting of one interventional radiologist, one nuclear medicine physician, one gastroenterologist and one biostatistician. All IDMC members are not involved in the trial and have no conflicting interests. Additionally, safety analysis will be performed every 3 months during the recruitment of the first 30 patients, after patient 36, patient 42 and patient 48, and evaluated by the IDMC.

Severe adverse (device) events will be reported to the Ethics Committee of the University Medical Center Utrecht and IDMC within 8 days. In accordance with Dutch regulations on research with medical devices, a summary of all severe adverse (device) events will be reported to the Dutch Health Care Inspectorate (in Dutch: Inspectie GezondheidsZorg en Jeugd in oprichting; IGJ) every 3 months.

Data management

All patient data collected in this trial, will be coded. All coded data will be entered in to an, in-house developed, electronic case report forms (e-CRF) in a secure digital environment. All collected data is monitored and validated by an independent, external data monitor approximately every 3-4 months. In accordance with Dutch regulations, all collected data will be stored for a duration of 15 years. Trial data is only accessible to the study physician, principal investigator and external data monitor.

Ethical considerations

The study protocol has been approved by the Ethics Committee and the institutional radiation protection committee of the University Medical Centre Utrecht, the Netherland. This study will be performed in accordance with the Declaration of Helsinki (current version October 2013), the Medical Research Involving Human Patients Act (WMO, the Netherlands) and the requirements of International Conference on Harmonization (Good Clinical Practice). In accordance to regulations, all future protocol amendments need Ethics Committee approval. Unexpected harm to the participant during the trial, is covered by the institutions' insurance for clinical trials.

Funding

This phase 2 study is funded by the Department of Radiology and Nuclear Medicine of the University Medical Center Utrecht. No external funding received.

Treatment

Screening

After obtaining informed consent, all study proceedings will occur in the University Medical Center Utrecht, Utrecht, The Netherlands. A screening visit will take place at the outpatient clinic prior to the first angiography. The study physician and principal investigator will check in- and exclusion criteria, perform a physical examination (including blood pressure, temperature and heart rate) and assess the WHO performance status of the patient. All patients are asked to fill out the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-GINET21 questionnaires. Additional tests include relevant laboratory testing (haematology, coagulation profile and serum chemistry) including a tumour marker (when present/measurable in the patient), electrocardiogram (ECG) and a contrast-enhanced CT. All contrast enhanced CT's will be assessed by RECIST 1.1 criteria [23].

Angiography

Patients are admitted for 3 days (2 nights) starting the day prior to the angiography. After physical examination and relevant laboratory testing, patients are pre-hydrated to prevent kidney damage, and started on proton pump inhibitors for 6 weeks (pantoprazole once a day 40 mg). Premedication one hour prior to the angiography consists of one dose of corticosteroids, antihistamines and anti-emetics (respectively dexamethasone 10 mg, clemastine 1 mg and ondansetron 8 mg), at the same time a tranquilizer is offered to the patient (oxazepam 10

mg). If the patient is familiar with a mild to moderate contrast allergy, additional corticosteroids and antihistamines will be given prior to the angiography according with national guidelines of the Central Accompaniment Institution (CBO in Dutch) [24].

A skilled and trained interventional radiologist will perform all angiographies of the upper abdominal vessels. A catheter is introduced via one of the femoral arteries by the Seldinger technique. After identifying all arteries supplying the liver, additional branches of these arteries that supply other organs than the liver are coiled, if needed. This usually involves the gastroduodenal artery (GDA) and right gastric artery (RGA).

Scout dose

Once successful identification of the supplying arteries and occlusion of additional branches has been performed, a scout dose of 250 MBq ^{166}Ho-microspheres will be administered [20, 25]. Due to the photon emission of ^{166}Ho, distribution of the microspheres, lung shunting and extrahepatic depositions can all be assessed using SPECT/CT. Planar imaging and SPECT/CT will be performed following the angiography and evaluated qualitatively as well as quantitatively. Extrahepatic deposition of activity is a contra-indication for treatment. Lung shunting will be assessed by planar imaging and SPECT/CT and should not exceed the maximum tolerable lung absorbed dose (i.e. 30 Gy).

Treatment

If the pre-treatment assessment is successful, patients return to the angiography suite for the treatment angiography combined with the ^{166}Ho-RE. This will take place on the same day as the pre-treatment angiography and scout dose procedure (see **Figure 3**). Based on the results of the dose escalation study (i.e. HEPAR I trial), a whole liver absorbed dose of 60 Gy was determined to be safe. A whole liver absorbed dose of 60 Gy leads to the following equation for activity calculation:

$$A_{^{166}Ho}(MBq) = 3781 \left(MBq * \frac{Gy}{J}\right) * liver\ weight\ (kg)$$

As mentioned above, additional information derived from the scout dose SPECT/CT can change treatment planning, either performing a one session whole liver treatment or two session sequential whole liver treatment. A significant lung shunt dose (>30 Gy) will lead to a reduction in treatment activity.

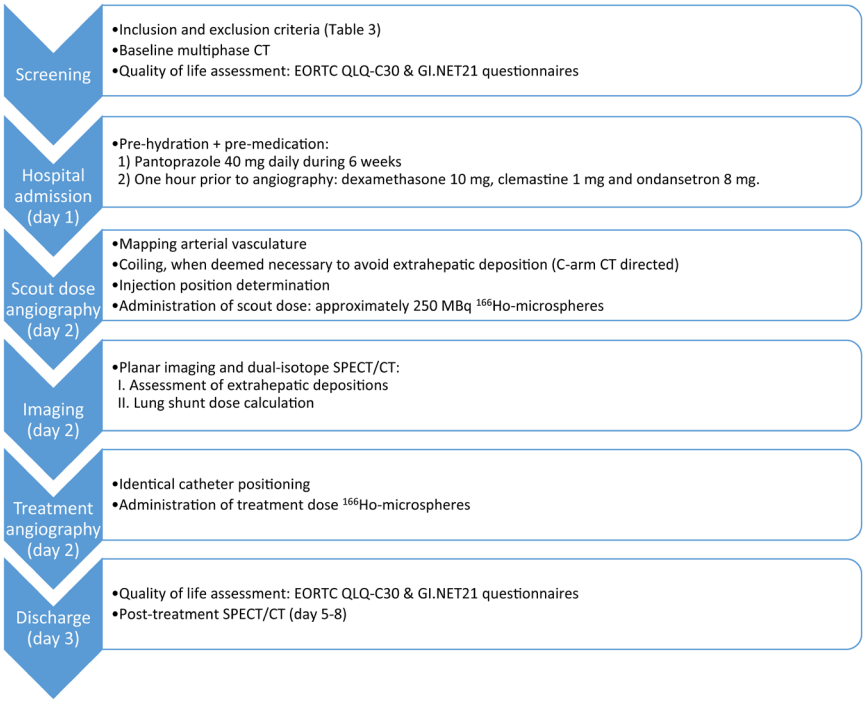

Figure 3. Study protocol depicting the time line and study proceedings between inclusion and hospital discharge.

Radiation exposure rate

The radiation exposure rate of the patient will be measured from 1-meter distance at t=0 hours and t=24 hours after the ^{166}Ho-RE.

Follow-up

Follow-up visits

During 12 months after treatment, patients are followed at the outpatient clinic. The visits will take place after 3 weeks, 6 weeks, 3 months, 6 months, 9 months and 12 months (closing visit). During these visits patients will undergo a physical examination, laboratory testing, WHO performance status assessment and will be monitored for (serious) adverse (device) events. Prior to the 3 weeks, 6 weeks and 3 months visits, patients are asked to fill out the EORTC questionnaires (QLQ-C30 and QLQ-GI.NET21). Prior to the 3, 6, 9 and 12 months visits, a CT will be performed for response assessment according to the RECIST 1.1 criteria.

Primary objectives

Two distinct objectives are the focus of our study. Tumour response on CT at 3 months of follow-up will be the first primary objective. This is defined as complete response (CR = disappearance of all lesions) or partial response (PR = ≥30% decrease in the sum of the longest diameters of the target lesions, compared to baseline measurements). The second primary objective is to establish the safety and toxicity profile of treatment with ^{166}Ho-RE as an additional treatment after ^{177}Lu-DOTATATE, using the Common Terminology Criteria for Adverse Events (CTCAE version 4.03) [26].

Secondary objectives

Three secondary objectives have been defined. Anti-tumour effect will be assessed by relevant tumour markers (when available), expressed as a percentage of the pre-treatment values. Furthermore, Quality of Life (QoL) will be assessed using the EORTC questionnaires (QLQ-C30 and QLQ-GI.NET21) during the first 3 months after treatment. The impact of treatment on QoL will be compared to tumour response and other parameters.

Additionally, biodistribution and dosimetry will be evaluated using a dual isotope fusion SPECT/CT protocol. After the standard scout dose SPECT/CT and treatment dose SPECT/CT (i.e. ^{166}Ho-SPECT), 50 MBq of ^{99m}Tc-phytacis (CIS bio, France) will be administered. Subsequently a dual-isotope SPECT/CT will be acquired, simultaneously providing a ^{166}Ho-SPECT for assessment of microsphere distribution and a ^{99m}Tc-phytacis SPECT for the assessment of truly functional liver parenchyma.

Safety profile

The phase 1 study on ^{166}Ho-RE (HEPAR I trial) [20] and its subsequent phase 2 study (HEPAR 2 trial) [27], demonstrated similar treatment-related effects as the current commercially available ^{90}Y-microspheres. Common adverse events up to grade 1 or 2 of the CTCAE v4.03 included: fever, nausea, vomiting, abdominal discomfort, and fatigue, often called the post-embolization syndrome. These complaints were generally self-limiting within 4-6 weeks. More serious adverse events of RE in general were rare (< 1%) and included RE-induced liver disease (REILD) [28] and inadvertent extrahepatic distribution of activity [29].

Escape medication

The protocol ensures all patients are pre- and post-hydrated in order to minimize the chance of renal insufficiency caused by the vascular contrast agent, jodixanol (Visipaque®). After ^{166}Ho-RE standard escape medication includes paracetamol up

to 4000 mg / day and ondansetron up to 24 mg, as respectively oral analgesic and intravenous anti-emetic. If persisting nausea occurs, additional metoclopramide up to 120 mg / day will be used. In case of diarrhoea, patients will receive loperamide up to 16 mg / day. In this specific patient group, some patients might experience excessive release of NET-related hormones that could cause a 'carcinoid syndrome' or 'carcinoid crisis'. These complaints can be prevented (to some extent) with octreotide intravenously, steroids and hydration.

Withdrawal of individual patients

Patients may be withdrawn from the study if a serious adverse event occurs. Patients will be withdrawn from the study if 1) the investigator considers it in the best interest of the patient that he/she be withdrawn (e.g. progressive disease), 2) the patient withdraws consent or 3) the patient is unable to comply with the protocol procedures.

Discussion

Liver metastases significantly limit patient survival (**Table 1**). In the current study, the beneficial effect of additional ^{166}Ho-RE within 12 weeks after systemic ^{177}Lu-DOTATATE will be investigated. Combining these treatments may lead to an improved response rate for liver metastases, with acceptable and suppressible side effects, which may eventually lead to prolonged survival. Although the latter question is not an objective of the current phase 2 study, if significant efficacy and limited toxicity are shown, a subsequent phase 3 study might be initiated.

To date, Ezziddin et al. published the only report describing RE with ^{90}Y-microspheres after PRRT with ^{177}Lu-DOTATATE in a retrospective study [30]. They described a population of 23 patients in which RE was performed in a salvage setting. Patients had progressive or functionally uncontrolled disease after PRRT. Three months after RE, 30% had PR and 61% had stable disease without any serious toxicity, comparable with other reports on ^{90}Y-microspheres in NET patients. The authors concluded that salvage RE after PRRT shows a toxicity profile similar to RE alone, despite the high cumulative activity administrated. Less than 15% experienced a CTCAE grade 3 toxicity (abdominal pain, fatigue, fever, nausea and vomiting) and one patient developed a gastroduodenal ulcer. The interval between PRRT and RE was not mentioned, but patients were only referred for RE in case they had progressive disease (i.e. salvage setting). In their study, a cumulative liver dose of 2 – 12 Gy was described after PRRT. Due to the hypervascular nature of NET, the absorbed dose on healthy liver parenchyma due to RE is (far) below the presumed

toxicity limit of healthy liver tissue (i.e. 70 Gy; and 50 Gy in cirrhotic livers with ^{90}Y resin microspheres) [31]. Thus, in theory, combining RE and PRRT can be safe. Nonetheless, concerns arise when implementing RE shortly after PRRT, due to the cumulative radiation dose and the short interval, potentially provoking REILD [28]. On the other hand in a recent case report, Filippi et al. described their treatment combination a patient with one hepatic metastasis, mesenteric metastasis and several bone metastases, diagnosed on a ^{68}Ga-DOTATATE-PET/CT [32]. The hepatic metastasis was downstaged with a lobar RE procedure, followed by 4 cycles of PRRT to treat extrahepatic lesions (a mesenteric metastasis and several bone metastases). Restaging after 3 months with a ^{68}Ga-DOTATATE-PET/CT showed a nearly complete remission of the extrahepatic metastases and an incomplete remission of the hepatic metastasis, thus another additional lobar RE procedure was performed to treat the hepatic lesion, with success [32]. They reported no significant adverse events of the combined treatments, complete symptomatic control and a survival of 42 months [32]. Additionally, they reported an absorbed dose on healthy liver parenchyma after the RE procedures of just 18 Gy and 20 Gy [32]. An example that the combination of RE and PRRT with short intervals can be safe.

In contrast to other studies, ^{99m}Tc-macroaggregated albumin (^{99m}Tc-MAA) will not be used as a scout dose for treatment planning. Instead, a small number of ^{166}Ho-microspheres will be used as a scout dose (approximately 250 MBq). This may overcome known limitations of ^{99m}Tc-MAA: 1) differences in flow dynamics caused by the randomly shaped ^{99m}Tc-MAA particles (90% between 10-90 µm) versus the spherically shaped ^{166}Ho-microspheres (30 ± 5 µm), 2) differences in scanning protocols of pre- and post-procedural imaging (i.e. ^{99m}Tc-SPECT vs ^{90}Y PET versus ^{166}Ho SPECT for both procedures), 3) employing a similar injection technique during both angiographies (i.e. bolus ^{99m}Tc-MAA versus intermittent injection of ^{166}Ho microspheres), and 4) overestimation of the lung shunt using ^{99m}Tc-MAA.

As shown by Elschot et al., in patients treated with ^{166}Ho-RE, using ^{99m}Tc-MAA as well as ^{166}Ho-microspheres as pre-treatment imaging scout dose, ^{166}Ho-SPECT/CT was the most accurate in predicting the lung absorbed dose after ^{166}Ho-RE [33]. On ^{166}Ho-SPECT/CT a median lung shunt dose of 0.02 Gy was calculated. This was significantly overestimated in lung shunt dose calculations based on ^{99m}Tc-MAA planar scintigraphy (5.5 Gy), ^{166}Ho planar scintigraphy (10.4 Gy) and ^{99m}Tc-MAA SPECT/CT (2.5 Gy). An example of severe overestimation by ^{99m}Tc-MAA compared to ^{166}Ho-microsperes is shown in **figure 4**. In the present study biodistribution / extrahepatic deposition assessment and lung shunt dose calculation will solely be evaluated by ^{166}Ho-SPECT/CT.

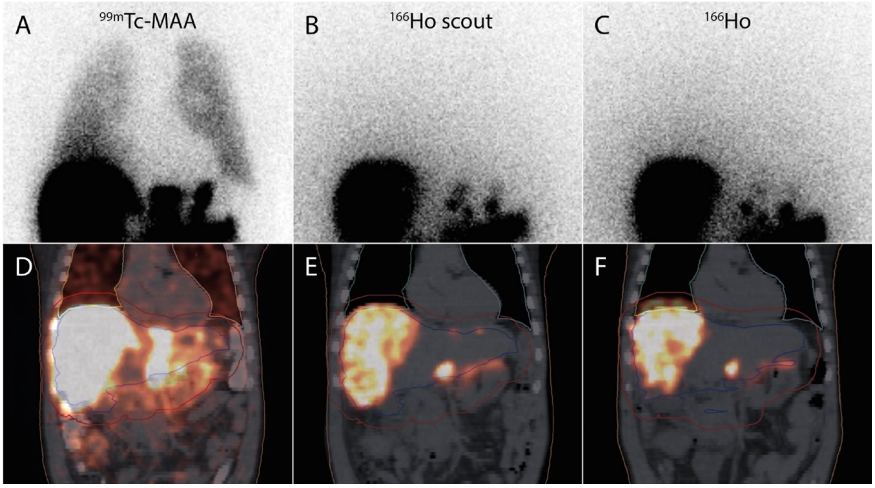

Figure 4. Example of lung shunt fraction overestimation by ^{99m}Tc-MAA. A patient with multiple liver metastases of a cholangiocarcinoma treated in the prior HEPAR 2 trial. Note the (visual) significant overestimation of ^{99m}Tc-MAA on planar imaging compared to the ^{166}Ho-scout dose and ^{166}Ho-treatment dose. Quantification of the lung shunt fraction on planar and SPECT/CT imaging confirmed the visual assessment: **a.** ^{99m}Tc-planar = 13.4%, **d.** ^{99m}Tc-SPECT = 6%, all ^{166}Ho-SPECT imaging (**e and f**) with the scout dose and with the treatment dose showed a lung shunt fraction of <1%.

The safety of administrating 250 MBq of beta-emitting ^{166}Ho-microspheres as a scout dose has been studied by Prince et al. [25] They predicted the amount of extrahepatic activity and radiation absorbed dose, using ^{99m}Tc-MAA SPECT/CT of 160 patients prior to ^{90}Y-RE. Based on a prior study by Kao et al, they defined a dose exceeding 49 Gy as clinically significant [25, 34, 35]. Simulating the use of 250 MBq ^{166}Ho-microspheres as a scout dose, only 1.3% of the patients had an extrahepatic deposition that could potentially be harmful (i.e. exceeded a mean dose of 49 Gy) [25]. Additionally, C-arm CT's will be acquired at each injection position, prior to scout dose administration, to minimize the chance of extrahepatic depositions and partial tumour coverage, and to avoid extra angiography procedures [36, 37].

As mentioned in the 'secondary objectives' section, the application of the dual isotope SPECT/CT protocol will enable us to derive all relevant dosimetric parameters for treatment dose calculation. ^{99m}Tc-phytacis, like other radiocolloids, is extracted from the blood pool by the reticuloendothelial cells of the liver [38]. Solely the functional liver parenchyma is depicted, due to absence of reticuloendothelial cells in tumours. Validation of this dual-isotope protocol will be performed in a side-study. Previous studies by Lam et al. have shown the prognostic value of the

combination of ^{99m}Tc-MAA and ^{99m}Tc-sulphur colloid imaging, showing a tumour dose-response correlation and healthy liver dose-toxicity correlation [39, 40].

As an additional advantage, holmium is one of the 14 lanthanide elements, making ^{166}Ho-microspheres MRI-compatible for treatment imaging. In short, using estimated R2* value changes from multi-gradient echo data, the holmium concentration per voxel could be determined [41, 42]. Conversion into units of activity enables dosimetric calculations. A prior study by Smits et al. has shown its feasibility in clinical practice and its comparability to SPECT-based dosimetry [21]. Using a similar MR-sequence, real-time imaging of the ^{166}Ho-microspheres during administration may become a future application [43]. However, the use of MRI is beyond the scope of this study, to minimize the study impact for patients.

In contrast to RE, PRRT's main limitation is absorbed kidney dose. To reduce the dose, the most important preparatory measure is intravenous amino acid infusion prior, during and after ^{177}Lu-DOTATATE administration. To overcome the disadvantage of the unavoidable kidney dose, intra-arterial administration of ^{177}Lu-DOTATATE in patients with liver only disease could be a future application [44]. Several studies show a decreased absorbed kidney dose and an increased uptake in the liver metastases in most patients after intra-arterial administration. In a study by Pool et al, kidney absorbed dose decreased by 13% in addition to a 2.9-fold increase in liver metastases uptake [45]. In theory, a combination of intra-arterial PRRT and RE could be superior in patients with liver only disease.

Limitations of the study protocol are the small study cohort, non-comparative design, single center design and relatively short clinical follow-up for NET patients.

Conclusion

Combining PRRT and RE could lead to improved treatment response and additional survival benefit: PRRT can be used to treat intra- and extrahepatic disease, whereas RE leads to an additional radiation boost on intrahepatic disease, the most incriminating factor in NET-patients' survival. Based on this hypothesis, the HEPAR PLUS trial will include all patients treated with ^{177}Lu-DOTATATE with significant intrahepatic disease.

Acknowledgements

The authors thank Tjitske Bosma (clinical research coordinator, University Medical Centre Utrecht) for her contribution to the study design and coordination, Remmert de Roos for his assistance in the production of the microspheres.

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Chapter 7

Additional ^{166}Ho-radioembolization of neuroendocrine tumor liver metastases after ^{177}Lu-DOTATATE; a single center, interventional, non-randomized, non-comparative, open label, phase II study (HEPAR PLUS)

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Submitted

Abstract

Background

Peptide receptor radionuclide therapy (PRRT) results in a long median (progression free) survival in patients with neuroendocrine neoplasms (NEN). The liver is the most commonly affected organ in metastatic disease and is the most incriminating factor for patient survival. Additional treatment of liver disease with holmium-166-radioembolization (^{166}Ho-radioembolization) may improve outcome. A phase 2 study was initiated to investigate the safety and efficacy of additional ^{166}Ho-radioembolization after PRRT.

Methods

The HEPAR PLUS study was a single center, interventional, non-comparative, open label, phase 2 study. Thirty patients with at least 3 measurable liver metastases according to RECIST 1.1 received additional ^{166}Ho-radioembolization within 20 weeks after the fourth and last cycle of PRRT (total of 4 x 7.4 GBq ^{177}Lu-DOTATATE). Primary objective was objective response rate (ORR), either complete or partial response, according to RECIST 1.1 three months after ^{166}Ho-radioembolization. Secondary endpoints included toxicity, based on Common Terminology Criteria for Adverse Events (CTCAE v4.03), biochemical response and quality of life.

Findings

Hepatic ORR was 43% and patient-based ORR was 40% at three months. CTCAE grade 3-4 toxicities included abdominal pain (10%), fatigue (3%), nausea (3%), alkaline phosphatase (10%), gamma-glutamyl transpeptidase (61%), and lymphocytopenia (48%). Quality of life assessments showed a (non-significant) decrease after six weeks, which fully recovered at three months.

Interpretation

A radiation boost on intrahepatic disease using ^{166}Ho-radioembolization leads to a high objective response rate without significant additional side-effects or reduction in quality of life.

Introduction

At diagnosis, 21% of all grade 1 neuroendocrine tumors (NET), 30% of all grade 2 NET and 50% of all grade 3 NET / neuroendocrine carcinomas have distant metastases, of which the liver is the most commonly affected organ.[1,2] Considering these numbers, many patients will not be eligible for curative treatment (i.e. surgery). Most NET overexpress membrane bound somatostatin receptors, typically the subtype 2 receptor, allowing for targeted therapies, of which somatostatin-analogs are the most commonly used (e.g. octreotide). Treatment with somatostatin-analogs, chemotherapeutics and kinase inhibitors shows only limited objective response rates (ORR) in G1-/G2NET [3-9]. In addition, systemic therapies give rise to systemic side effects. In the last decade, systemic treatment of neuroendocrine neoplasms (NEN) with lutetium-177-octreotate (^{177}Lu-DOTATATE; Lutathera®, Advanced Accelerator Applications, France) has gained much attention. In the phase 3 NETTER-1 trial in gastro-intestinal grade 1 and 2 NET a long progression free survival (PFS) and overall survival (OS) was shown; respectively 8.4 months (PFS) and 27.4 months (OS) in the control arm (i.e. high dose 60 mg octreotide LAR) versus PFS and OS not reached in the ^{177}Lu-DOTATATE arm (including low dose 30 mg octreotide LAR).[10,11] In that trial, ^{177}Lu-DOTATATE was favoured in almost all specified subgroups.[10] Furthermore, improvement or delayed deterioration of quality of life was more pronounced in the ^{177}Lu-DOTATATE arm.[12] However, ORR at three months was limited to 18% in the ^{177}Lu-DOTATATE group.

All metastatic NEN studies include high percentages of patients with liver metastases. With increasing tumor load, survival rates decline.[13] After ^{177}Lu-DOTATATE, patients with bulky (liver) disease (≥1 lesion; ≥30 mm maximal diameter) seem to have less benefit from treatment.[14] This indicates a need for improved treatment of extensive or bulky liver disease. In accordance with the ENETS guideline published in 2016, the treatment of choice in patients with NET liver metastases with a 'diffuse' or unresectable 'complex pattern', consists of systemic treatment first, followed by liver directed treatment after progression.[2] Hepatic radioembolization (a.k.a. selective internal radiation therapy or SIRT) is an established liver directed treatment, which has demonstrated to be effective and well tolerated in progressive NEN liver metastases.[15,16] In the current clinical setting, radioembolization is reserved for liver dominant disease in a salvage setting, after failure of systemic treatment options. In this study, it is hypothesized that improved outcome can be obtained by boosting the treatment of liver metastases after initial ^{177}Lu-DOTATATE treatment. The first results from the phase II HEPAR PLUS study that evaluated the efficacy and safety

of combining PRRT with radioembolization using holmium-166 loaded particles (QuiremSpheres® by Quirem Medical B.V., The Netherlands) in G1/G2NET patients with bulky liver disease, will be presented.

Methods

Patients

Eligible patients had histologically confirmed grade 1 or 2 NET (Ki67-index ≤20%) with residual and irresectabel liver metastases. They were treated with four cycles of 7.4 GBq ^{177}Lu-DOTATATE. After completion of the fourth ^{177}Lu-DOTATATE cycle, patients were discussed in the institutions' multidisciplinary tumor board and included in the study. Three measurable liver metastases according to the Response Evaluation Criteria In Solid Tumors, version 1.1 (RECIST 1.1) on the screening CT (acquired after the ^{177}Lu-DOTATATE treatment and prior to the ^{166}Ho-radioembolization), was the most important inclusion criterion.17 Presence of extrahepatic disease was no exclusion criterion, under the assumption that it was sufficiently treated by prior ^{177}Lu-DOTATATE. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance score of ≤2. Detailed inclusion and exclusion criteria are listed in **Table 1**. Informed consent was obtained from all participants. Simultaneous use of somatostatin analogs was accepted, unchanged and continued without interruption during the study. No other simultaneous anti-cancer treatments were allowed.

Study design

The HEPAR PLUS study ("Holmium Embolization Particles for Arterial Radiotherapy Plus ^{177}Lu-DOTATATE in Salvage NET patients"; Clinicaltrials.gov: NCT02067988) was a phase 2, single center, interventional, non-randomized, non-comparative, open label study. In this phase 2 study all included patients received additional ^{166}Ho-radioembolization within 20 weeks after the fourth cycle of ^{177}Lu-DOTATATE (7.4 GBq per treatment cycle, interval six - ten weeks; cumulative administered activity approximately 29.8 GBq). Details on the study protocol were previously published.13 After the screening visit, study proceedings were executed during a hospital admission of three days. The first day, blood tests were drawn and pre-hydration for the angiography was initiated. During pre-treatment visceral angiography on the second day, a small number of ^{166}Ho-microspheres (scout dose; 250 MBq; ±3 million microspheres) were administered for treatment simulation. Directly after the first angiography, a single photon emission computed tomography / computed tomography (SPECT/CT) was acquired to assess extrahepatic depositions, lung shunting and intrahepatic distribution of microspheres. In the afternoon, during

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Patient must have given written informed consent	Brain metastases or spinal cord compression, unless irradiated > four weeks prior to ^{166}Ho-radioembolization and stable for at least one week without steroids
≥ 18 years of age	Serum bilirubin > 1.5 x upper limit of normal
Confirmed histological diagnosis NET, grade 1 or 2 (Ki67 ≤20%)	Glomerular filtration rate < 35 ml/min
Prior treatment with 4 cycles of 7.4 GBq ^{177}Lu-DOTATATE, last cycle within 20 weeks before ^{166}Ho-radioembolization	Alkaline phosphatase, alanine aminotransferase or aspartate aminotransferase > 5 x upper limit of normal
Life expectancy > 12 weeks	Leucocytes < 2.0 x 10^9/l and/or platelet count < 50 x 10^9/l
ECOG performance score 0 – 2	Significant cardiac event within three months of inclusion
≥ 3 measurable liver lesions according to RECIST 1.1	Patients suffering from diseases with an increased chance of liver toxicity
Negative pregnancy test for women of childbearing potential	Patients declared incompetent or suffering from psychic disorders making comprehensive judgment impossible
No nursing activities for women of childbearing potential	Severe bile duct abnormalities: papillotomy, cholecystectomy, biliary stents and bilidigestive anastomosis are allowed
Acceptable method of contraception	Body weight > 150 kg
	Severe contrast allergy
	Liver tumor involvement >70%, measured on screening CT

a second angiography (i.e. sheet was left in situ), the therapeutic dose of ^{166}Ho-microspheres was administered (**Figure 1**).[13] Based on the results of the dose escalation and efficacy studies (i.e. HEPAR I and II studies), a whole liver absorbed dose of 60 Gy was determined to be safe.[18,19] A whole liver absorbed dose of 60 Gy leads to the following equation for activity calculation:

$$Prescribed\ activity_{^{166}_{Ho}}(MBq) = 3781 \left(MBq * \frac{Gy}{J}\right) * liver\ weight\ (kg)$$

Based on the microspheres distribution on pre-treatment scout dose SPECT/CT, a one session whole liver treatment or two session sequential whole liver treatment (>three months interval) was chosen. All angiography procedures were performed by an experienced interventional radiologist and nuclear medicine physician (both >five years experience in radioembolization treatments). The day after treatment, patients were discharged.

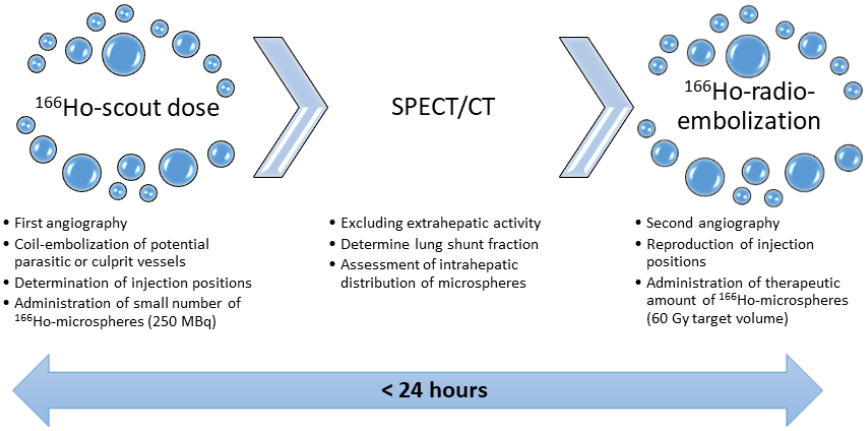

Figure 1. Radioembolization treatment schedule for patients in one day

Study Oversight

This phase 2 study was funded by the Department of Radiology and Nuclear Medicine of the University Medical Center Utrecht. No external funding was received. Quirem Medical supplied the microspheres at cost price. The Medical Ethics Committee and the institutional radiation protection committee of the University Medical Center Utrecht, the Netherlands, approved the study protocol. This study was performed in accordance with the Declaration of Helsinki, the Medical Research Involving Human Patients Act (WMO, the Netherlands) and the requirements of International Conference on Harmonization (Good Clinical Practice). In accordance to regulations, all protocol amendments received additional Ethics Committee approval. All interim safety analyses (every three months) were presented to an Independent Data and Safety Monitoring Commission (IDMC), consisting of one interventional radiologist, one nuclear medicine physician, one gastroenterologist and one biostatistician. All IDMC members were not involved in the study and had no conflicting interests.

End points and assessment

Primary endpoint of the study was objective tumor response of the treatment volume on multiphase contrast enhanced CT at three months, defined as complete response (CR = disappearance of all lesions) or partial response (PR = ≥30% decrease in the sum of the longest diameters of the target lesions, compared to baseline measurements) according to RECIST 1.1. Blinded and random response assessment according to RECIST 1.1 and modified RECIST (mRECIST) was performed

by two independent radiologists, who were not involved in study proceedings. The preferred response criterion in hypervascular liver metastases (i.e. mRECIST) was included in this study.[15] Besides response assessment of the treated liver volume, total hepatic and overall (i.e. patient based) response was also assessed. In case of discordant response assessment by the two radiologists, the mean decrease of the sum of largest diameters of the combined target lesions was calculated and the patient was reclassified in consensus.

Secondary endpoints included assessment of the toxicity profile using the Common Terminology Criteria for Adverse Events (CTCAE version 4.03) for the entire follow-up period.[20] Tumor marker response based on serum chromogranin A values (CgA), expressed as a percentage of the pre-treatment values, was also assessed. Biochemical responders were defined as a decrease of CgA ≥50% and biochemical progression as any CgA increase. Quality of Life (QoL) was assessed using EORTC questionnaires QLQ-C30 and QLQ-GI.NET21 during the first three months after treatment: at baseline, one day, three weeks, six weeks and three months after treatment.

Statistical analysis

This single arm open label study had a sequential design. Early termination of the study was based on pre-defined boundaries on the number of partial and complete responses according to RECIST 1.1.[13] The sequential design with predetermined boundaries had a power of 90% to reach a positive tumor response decision in case the true target lesions tumor response was 40%. The exact overall one-sided type I error was 4.5%.[13] All analysis were performed in the Full Analysis Set (FAS), including all patients who received at least the scout dose procedure (see below). The Per Protocol Set (PPS) included all patients who complied with the protocol up to at least three months. PPS analyses was used for the primary endpoint and QoL assessment.

Results

From November 2014 through November 2018, 34 patients were included in the study. Three patients were excluded from study participation (**Figure 2**). One patient had less than three measurable liver metastases according to RECIST 1.1 criteria on the screening CT, and two patients received their last ^{177}Lu-DOTATATE treatment >20 weeks previously and were therefore excluded. Thirty-one patients were treated, but one patient died within three months after ^{166}Ho-radioembolization, due to a hypoglycaemic crisis caused by an overproducing insulinoma. This patient did not reach the primary endpoint and was replaced. Finally, 30 patients were available for the primary endpoint analysis (**Figure 2**).

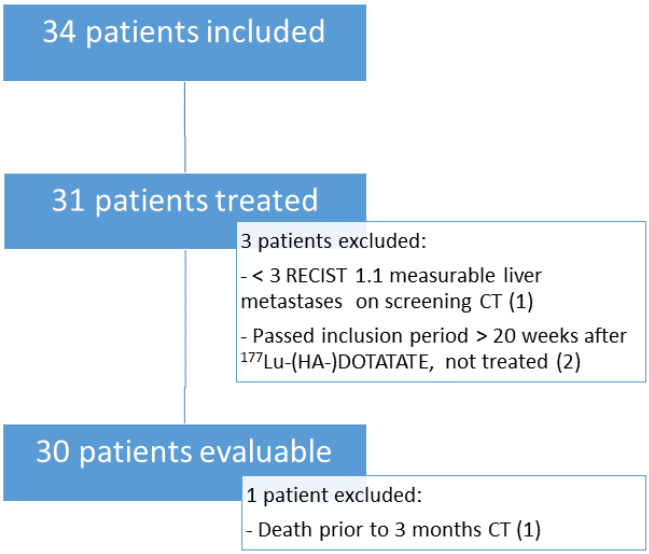

Figure 2. Flowchart of patient inclusion

Baseline characteristics are shown in **Table 2**. As per PPS, 12 patients (40%) had a grade 1 NET and 18 patients (60%) had a grade 2 NET. Extrahepatic disease was present in 24 patients (80%) at study inclusion. Two patients (7%) had progressive intrahepatic disease according to RECIST 1.1 after initial ^{177}Lu-DOTATATE treatment, and all other patients had either stable disease (SD) or a PR according to RECIST 1.1 after initial ^{177}Lu-DOTATATE. Mean serum chromogranin A level was 4240 µg/L (range 41 – 40.000 µg/L). One patient (3%) had a previous pylorus preserving pancreaticoduodenectomy with bilidigestive anastomosis for a pancreatic head NET, and was treated under antibiotic prophylaxis according to study protocol (metronidazole and levofloxacin).[13]

Efficacy

All patients were evaluable according to RECIST 1.1 at three months, and in 26 patients liver metastases were also evaluable according to mRECIST at three months (four patients had hypovascular disease). Objective response within the treatment volume was achieved in 13 patients (43%, all PR) according to RECIST 1.1 and in 18 patients (60%; 10% CR and 50% PR) according to mRECIST (**Table 3**). A case example is shown in **Figure 3**. The remaining patients all had SD within the treatment volume.

Table 2. Baseline characteristics

	PPA		FSA*	
Number of patients	30		34	
Age in years	62 ± 8		62 ± 8	
	N	**%**	**N**	**%**
Gender				
Male	22	73%	26	76%
Female	8	27%	8	24%
ECOG Performance score				
0	17	57%	20	59%
1	12	40%	13	38%
2	1	3%	1	3%
Primary tumor				
Pancreas†	9	30%	11	32%
Ileum/Jejunum	8	27%	9	26%
Unknown	6	20%	7	21%
Colon/Caecum/Rectum	4	13%	4	12%
Bronchus/Lung	3	10%	3	9%
NET grade				
1	12	40%	12	35%
2	18	60%	22	65%
Fraction liver involvement‡				
<25%	8	27%	8	24%
>25%	22	73%	26	76%
Extrahepatic disease				
Yes	24	80%	27	79%
No	6	20%	7	21%
Mean serum Chromogranin A level (µg/l)	4240		4584	
Treatment				
Whole liver one session	17	57%	18	53%
Whole liver sequential	6	20%	6	18%
Lobar treatment**	7	23%	7	21%
Mean activity administered (MBq)	7030		6971	

Legend: PPA = per protocol analysis, FSA = full set analysis.
One patient in the full set analysis was treated, but did not reach the primary endpoint, mentioned for completion of data presentation. Three patients in the full set analysis were excluded prior to treatment (Figure 1**). †One glucagonoma, two insulinomas, one ACTH-producing tumor and the others were afunctional pancreatic NET. ‡Fractional liver involvement was calculated by manual delineation of the liver and all tumor lesions on the screening CT-scan. **Two patients still in study follow-up, whom could opt for complementary lobar treatment as per protocol.*

Table 3. Response assessment according to RECIST 1.1 and mRECIST at three months

RECIST 1.1	Treatment volume			Non-treatment liver volume	Extrahepatic disease	Patient-based
	#1	#2	Mean			
Complete response	0%	0%	0%	0%	0%	0%
Partial response	40%	43%	43%	0%	0%	40%
Stable disease	60%	57%	57%	30%	63%	47%
Progressive disease	0%	0%	0%	7%	13%	13%
Not applicable*				63%	24%	

mRECIST	Treatment volume			Non-treatment liver volume
	#1	#2	Mean	
Complete response	10%	10%	10%	0%
Partial response	47%	43%	50%	0%
Stable disease	30%	30%	27%	20%
Progressive disease	0%	0%	0%	0%
Not applicable*	13%	17%	13%	80%

RECIST 1.1 = Response Evaluation Criteria In Solid Tumors, version 1.1, mRECIST = modified RECIST, #1 = blinded assessment by radiologist number 1, #2 = blinded assessment by radiologist number 2, Mean = mean summed decrease of all target lesions defined by blinded radiologists.
**Not applicable, measurable or present.*

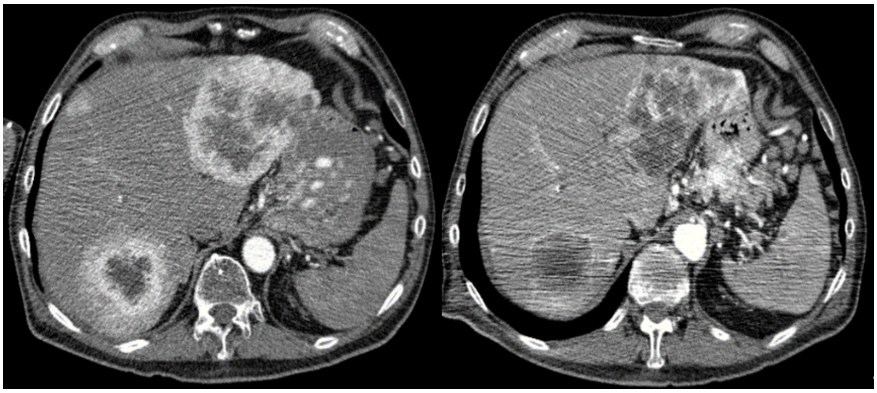

Figure 3. Example of an objective response after additional holmium-166-radioembolization treatment in an elderly man with an ACTH-producing, grade 2 pancreatic neuroendocrine tumor. A. After initial PRRT cycles, residual bulky, hypervascular, bilobar liver disease was found. Fourteen weeks after his last PRRT cycle, the patient received additional whole liver holmium-166-radioembolization. B. Three months after the study treatment, almost complete tumor necrosis could be acknowledged on his arterial phased CT (partial response according to mRECIST), with a 69% decrease in chromogranin A levels (i.e. biochemical responder).

Eleven patients were initially treated in a lobar fashion, of whom two patients had progressive disease (PD) in the non-treated lobe. Hepatic objective response (i.e. whole liver), according to RECIST 1.1, was achieved in 12 patients (40%; all PR). In the remaining 18 patients, 16 patients (53%) had SD and two patients had PD (7%, due to the aforementioned PD in the non-treated lobe).

Extrahepatic disease was stable at three months in 21 patients (70%) and progressive in four patients (13%) according to RECIST 1.1. One of the progressive patients had no extrahepatic disease at baseline (i.e. after ^{177}Lu-DOTATATE treatment), but developed new bone metastases at follow-up. No extrahepatic disease was present in five patients (17%).

Patient-based response assessment showed objective response in 12 patients (40%; all PR), SD in 14 patients (47%), and progressive disease in 4 patients (13%), according to RECIST 1.1. PD in the patient-based assessment was based on tumor growth in non-treated lobes, progression of extrahepatic disease, or new extrahepatic disease.

Mean chromogranin A levels decreased from 4240 µg/l (range 41 – 40,000 µg/l) to 2368 µg/l (range 49 – 24,000 µg/l). Median decline was 29% (range -81% – +229%). Biochemical response (i.e. >50% decline) was seen in 9 patients (30%) and biochemical progression (i.e. any increase) in two patients (7%), who also had extrahepatic progression on imaging studies.

Toxicity

Most common clinical toxicity was CTCAE grade 1-2 abdominal pain or fatigue in 65% and 58% of patients, respectively. All reported clinical toxicities are described in **Table 4**.

Overall, CTCAE grade 3 toxicities were limited to three patients, of whom two patients (7%) suffered from abdominal pain (CTCAE grade 3), and one patient (3%) experienced abdominal pain, fatigue and nausea (all CTCAE grade 3). In the first three months, one patient had a related serious adverse event (SAE; grade 4), who developed radioembolization-induced liver disease (REILD; ascites and hepatic encephalopathy), requiring additional medication and hospitalization.[21] Four months after ^{166}Ho-radioembolization this patient died (i.e. grade 5 toxicity).[21]

Biochemical toxicities related to ^{166}Ho-radioembolization, e.g. liver enzymes, are depicted in **Figure 4**. Highest biochemical toxicity scores were seen six weeks after treatment, mainly alkaline phosphatase and gamma-glytamyl transpeptidase with CTCAE grade 3-4 in 10% and 61%, respectively. These numbers steadily decreased

afterwards (**Figure 4**). The patient suffering from REILD was the only patient with a CTCAE grade 4 bilirubin elevation and a CTCAE grade 3 aspartate aminotransferase elevation after treatment. No other CTCAE grade 3-4 biochemical toxicities occurred.

Haematological toxicities related to ^{166}Ho-radioembolization were limited to lymphocytopenia (48%). Most patients had a pre-existing lymphocytopenia due to the previous PRRT treatments, which temporarily deteriorated after additional ^{166}Ho-radioembolization, without clinically significant consequences.

Table 4. All clinical toxicities reported within the first three months as per Full Analysis Set (n=31)

Related toxicity	CTCAE grade					Unrelated toxicity	CTCAE grade		
	0	1	2	3	4		0	1	2
Hepatic failure†	30				1	Constipation	27	3	1
Abdominal pain	8	9	11	3		Insomnia	30		1
Fatique	12	10	8	1		Urinary retention	30		1
Nausea	11	12	7	1		Coughing	30		1
Back pain	22	7	2			Pruritis	30		1
Vomiting	18	7	6			Sweating	28	3	
Malaise	24	6	1			Shivering	29	2	
(sub)febrile	27	3	1			Diarrhea	29	2	
Weight loss*	29	2				Oedema	29	1	
						Joint pain	30	1	
						Headache	30	1	
						Cramps	30	1	

†Radioembolization induced liver disease (REILD).

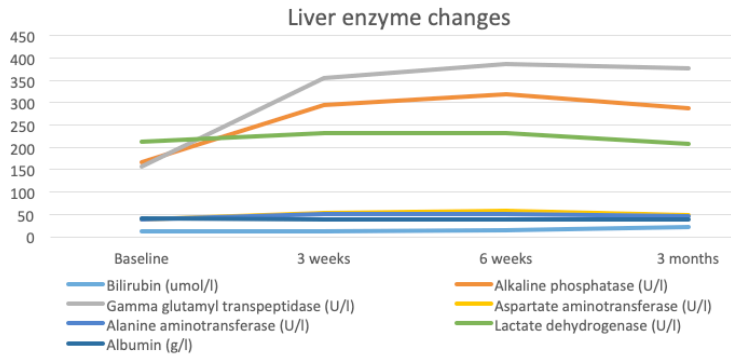

Figure 4. Changes in liver enzymes in the first 3 months after holmium-166-radioembolization.

Quality of life

All questionnaires at all time points were completed by all 30 patients, except two questionnaires at the three months time point; both patients were admitted in an external hospital, one due to REILD and the other due to a somatostatine analogue related cholecystitis. QLQ-C30 questionnaire analyses of functioning scales and symptoms scales are depicted in **Figure 5**. Apart from a significant decrease after three weeks in the role functioning scale, which normalized after three months, non-significant temporary decreases were noticed after ^{166}Ho-radioembolization. A temporary significant increase in the fatigue scale was noticed, in line with the findings from the clinical toxicity data (**Figure 5**). Additional GI.NET21 scales showed similar results, with non-significant temporary changes (**Figure 5**).

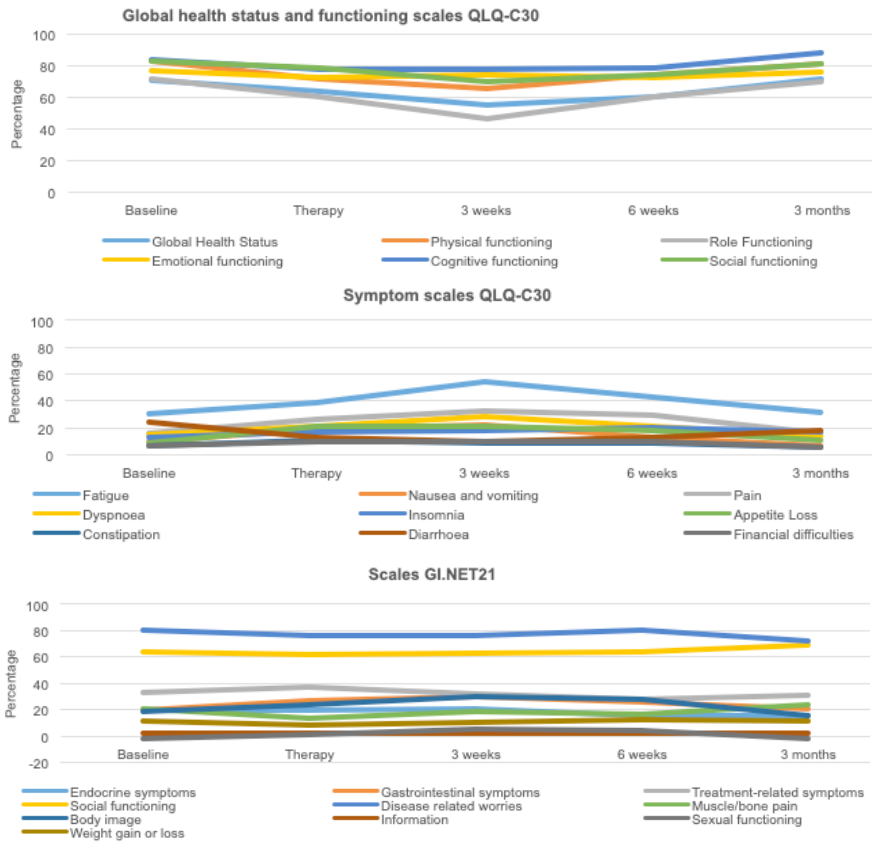

Figure 5. Results of all EORTC questionnaires at baseline, one day, three weeks, six weeks and three months after treatment. For GI.NET21, both questions concerning the treatment-related symptoms scale addressed the use of somatostatin analogs (SSA): in patients not receiving SSA, these results were censored.

Discussion

This first prospective study on the combination of four cycles of PRRT with 7.4 GBq ^{177}Lu-DOTATATE and ^{166}Ho-radioembolization showed that additional tumor reduction can be obtained in patients with residual bulky liver disease. The combination of these treatments is safe, with only mild to moderate side effects during the first three months after ^{166}Ho-radioembolization. Additionally, patients did not report changes in their quality of life. Adding a radiation boost to bulky liver metastases after systemic radionuclide treatment may potentially improve progression free and overall survival in these difficult to treat patients. To investigate this hypothesis, a subsequent randomized phase 3 study should be initiated.

The hepatic and patient-based objective response was more than 40%. Compared to the NETTER-1 study on PRRT, with a patient-based objective response of 18%, more tumor reduction can be obtained with the addition of ^{166}Ho-radioembolization. However, the results of the present study are difficult to compared with the NETTER-1, because of a significantly higher fraction of grade 2 NET (present study 60% versus NETTER-1 34%) and all patients had (excessive) liver disease. Nevertheless, in the present study patient-based objective response was better in an overall poorer population.

Radioembolization is known to be safe and effective in patients suffering from NEN liver metastases.[15,16] Due to the hypervascular nature of NET, the absorbed dose on healthy liver parenchyma is relatively low. Nonetheless, concerns have been raised on the implementation of radioembolization shortly after PRRT, because of the cumulative radiation and the short interval, potentially provoking REILD.[22] To date, besides our study, two retrospective studies discussed the combination of PRRT and radioembolization. Ezziddin et al. described their results of radioembolization with ^{90}Y resin microspheres after PRRT with ^{177}Lu-DOTATATE in a retrospective study.[23] Twenty-three patients with progressive or functionally uncontrolled disease received radioembolization in a salvage setting. Three months after radioembolization, 30% had PR and 61% had SD without any serious toxicity. The authors concluded that salvage RE after PRRT shows a toxicity profile similar to radioembolization alone, despite the high cumulative activity administered. Unfortunately, the interval between PRRT and radioembolization was not mentioned.

Our group retrospectively analysed 244 patients with progressive NEN liver metastases receiving ^{90}Y resin microspheres radioembolization.[24] In a subgroup analysis of 44 patients who received 56 radioembolization procedures after

previous PRRT (median interval 353 days; range 4 days – 6.3 years) an ORR of 16% and stable disease in 75% was observed, according to RECIST 1.1. The toxicity profile was similar to patients who did not previously received PRRT, with one fatal REILD, short-term clinical toxicities in 9-26% and absolute CTCAE grade 1-2 biochemical toxicities in 75%. Cumulative PRRT activity was quite variable (7.4 – 61.6 GBq). Importantly, during long-term follow-up, subsequent treatments were initiated in 77% and 43% of patients even received additional PRRT cycles after the initial PRRT and radioembolization treatments.[24]

Both studies described NEN patients with progressive intrahepatic disease after PRRT, in contrast to the prospective design of the present study, adding radioembolization as a radiation boost to the liver after PRRT. However, the studies do confirm the (short-term) safety of radioembolization after previous PRRT treatments.

One patient developed REILD, three months after ^{166}Ho-radioembolization. After treatment he had PR according to RECIST 1.1. Initially, the patient did not have complaints, besides fatigue. Symptoms consistent with REILD started six weeks after ^{166}Ho-radioembolization, when he developed hyperbilirubinemia (47 pmol/l) and ascites. Even though diuretics and high dose prednisolone were started, his clinical condition deteriorated and he eventually developed hepatic encephalopathy. In hindsight, his hypovascular disease led to a relatively high absorbed dose on his healthy liver tissue. Combined with the simultaneous methotrexate treatment for his rheumatoid arthritis, which is known to be liver toxic, this probably resulted in the development of REILD. The occurrence of REILD in NEN patients treated with radioembolization (and PRRT) in general is uncommon (<1%).[15,24]

Long-term hepatotoxicity of both PRRT and radioembolization in NEN patients is debated in literature. However, literature is sparse and just three retrospective case studies correlated PRRT and/or radioembolization to hepatotoxicity.[25-27]. The NETTER-1 trial did not report any hepatotoxicity.[10] Riff et al. reported an increased hepatotoxicity rate after PRRT with ^{90}Y-labelled ligands (n=17).[25] Ascites developed in 10/17 patients (59%), of whom 8/10 (80%) were possibly related to PRRT, and 6/10 (60%) required medical therapy. The authors suggested a correlation between previous radioembolization and post-PRRT hepatotoxicity, however, no significant correlation was reported. Su et al. described 54 patients who received radioembolization with ^{90}Y glass microspheres.[26] Time to development of a cirrhosis-like morphology on imaging studies was 1.8 years (0.7 - 7.2 years), occurring in 26/54 patients. Seventeen patients were asymptomatic, and in just two out of

nine patients with clinical signs of hepatic decompensation, their symptoms could be solely attributed to radioembolization.[26] Tomozawa et al. reported 52 patients treated with ^{90}Y resin microspheres.[27] CTCAE grade 3 biochemical toxicities were found in just 8%. Cirrhosis-like morphology or portal hypertension on imaging was found in 15 patients (29%). Unfortunately, all three retrospective studies missed important data and no clear definition for hepatotoxicity was reported, making these results difficult to interpret. None of these three studies reported specifically on hepatotoxicity after the combination of PRRT and radioembolization. In the previously mentioned studies by Ezzidin et al. and Braat et al. on the other hand, no short-term toxicities were noticed and radioembolization did not interfere with additional radionuclide treatments later on.[23,24] Nonetheless, long-term follow-up in these patients is needed.

Another important issue is the radiation dose to healthy liver tissue. None of the aforementioned studies discussed this. Increasing the radiation absorbed dose to healthy liver tissue will result in loss of hepatocyte function, thereby increasing the likelihood of inducing REILD. To calculate proper dose estimates, adequate imaging of the activity distribution is needed. Imaging with ^{90}Y remains difficult, due to its pure beta emission and low positron emission (32 per million decays). However, with its additional gamma emission, ^{166}Ho allows more accurate dose calculations on healthy liver tissue. Not only the post-treatment imaging provides more accurate dose estimations, but recent studies have also shown the superior predictive value of the ^{166}Ho scout dose in both lung shunting and intrahepatic distribution, thus improving pre-treatment prediction as well.[28,29] More accurate pre-treatment dosimetry will be essential to improve radioembolization in NEN patients even further and is expected to result in better treatment efficacy and reduced toxicity.

This study has several limitations. The study was conducted in patients with residual liver disease after initial PRRT treatment in a single arm, non-randomized setting. The studied population was confounded by a selection bias, because patients received four cycles of PRRT by protocol. This was decided to study treatment outcomes in a homogeneous population. Furthermore, the majority of patients had a grade 2 NET (60%). In NETTER-1, most patients had grade 1 NET, making comparison difficult.[10] Patients were treated with ^{166}Ho-radioembolization using therapeutic activity as calculated by a single compartment activity calculation method, as investigated in the initial dose escalation study.[18,30,31] However, using a patient tailored activity calculation method (e.g. partition modelling or voxel-based modelling), treatment accuracy, both in terms of efficacy and toxicity,

could be increased.[13,32-34] The data of this study may be used for finding the right thresholds for a safe normal liver absorbed dose and an effective tumor absorbed dose. These optimized dosimetry-based planning methods should be included in a future phase 3 randomized controlled study. Lastly, only short-term toxicity was reported. Long-term toxicity will be further studied.

In conclusion, combining PRRT and ^{166}Ho-radioembolization is safe and leads to a high objective tumor response. The combination of these treatments may potentially lead to additional survival benefit for patients with residual bulky liver disease after PRRT. This should be further studied.

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Chapter 8

Hepatic radioembolization as a bridge to liver surgery

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Frontiers in Cancer Imaging and Diagnosis 2014; 4:199

Abstract

Treatment of oncologic disease has improved significantly in the last decades and in the future a vast majority of cancer types will continue to increase worldwide. As a result, many patients are confronted with primary liver cancers or metastatic liver disease. Surgery in liver malignancies has steeply improved and curative resections are applicable in wider settings, leading to a prolonged survival. Simultaneously, radiofrequency ablation (RFA) and liver transplantation (LTx) have been applied more commonly in oncologic settings with improving results. To minimize adverse events in treatments of liver malignancies, locoregional minimal invasive treatments have made their appearance in this field, in which radioembolization (RE) has shown promising results in recent years with few adverse events and high response rates. We discuss several other applications of RE for oncologic patients, other than its use in the palliative setting, whether or not combined with other treatments. This review is focused on the role of RE in acquiring patient eligibility for radical treatments, like surgery, RFA, and LTx. Inducing significant tumor reduction can downstage patients for resection or, through attaining stable disease, patients can stay on the LTx waiting list. Hereby, RE could make a difference between curative of palliative intent in oncologic patient management. Prior to surgery, the future remnant liver volume might be inadequate in some patients. In these patients, forming an adequate liver reserve through RE leads to prolonged survival without risking post-operative liver failure and minimizing tumor progression while inducing hypertrophy. In order to optimize results, developments in procedures surrounding RE are equally important. Predicting the remaining liver function after radical treatment and finding the right balance between maximum tumor irradiation and minimizing the chance of inducing radiation-related complications are still challenges.

According to recent estimations, an increase in the global cancer burden is expected from 12.7 million new cases in 2008 to 22.2 million by 2030 (1). As these numbers grow, so does the number of patients with liver malignancies. As primary liver cancer, hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide. In metastatic liver disease, the incidence of colorectal carcinoma (CRC) is high. It is the third most common cancer worldwide (2). At the time of diagnosis, 14.5% of the patients present with synchronous metastatic liver disease, of which 76.8% is limited to the liver. Another 12.8% develops metachronous liver metastases within 5 years after initial diagnosis (3). Many other tumor cell types, including neuroendocrine tumors (NET), cholangiocarcinoma (CC), and others, frequently present as liver-dominant disease (4). By the time that the disease has spread to the liver it is often difficult to treat with low response rates and a dismal survival. For example, in patients with CRC presenting with synchronous liver metastases, without palliative chemotherapy survival is only 5–7 months. With palliative chemotherapy survival increases to 22 months (5–7). In patients with unifocal HCC (<5 cm) a 5-year survival of 7% and a median survival of 18 months is seen without resection. After surgical resection this increases to a 33% and 47 months, respectively (8).

These numbers indicate a clear need for improvement of current treatment strategies for liver malignancies. In recent years, trans-arterial yttrium-90 (^{90}Y) radioembolization (RE) has gained rapid interest in the management of liver malignancies. High response rates and a favorable toxicity profile make this an elegant therapy, even in patients with underlying cirrhotic liver disease. Compared to trans-arterial chemoembolization (TACE), which is commonly used in patients with HCC, RE results in similar response rates, a comparable overall survival (OS) and less adverse events (9–12). Currently, many phase 2–3 clinical studies on RE are recruiting patients for efficacy evaluation and toxicity screening in patients with primary liver malignancies compared to current treatments [YES-P (13), SARAH (14), and SIRVENIB (15)] or combined with current treatments [SORAMIC (16) and STOP-HCC (17)]. In secondary liver malignancies, RE is investigated in phase 2–3 trials for efficacy evaluation and toxicity combined with chemotherapeutic regimes. Simultaneously, determining the place of RE in the treatment algorithm as a first-line, second-line, or salvage therapy [SIRFLOX (18), EPOCH (19), FOXFIRE, and SIR-step (20)]. At this point, RE is mostly used as an end of line treatment modality. However, RE can also be applied in a pre-operative setting before hepatic surgery, before ablative treatments such as radiofrequency ablation (RFA), or before a combination of those. In this review, the possible merits of RE in the pre-surgical setting will be discussed.

Surgical eligibility depends on many factors, currently rendering 10–30% of HCC patients and 5–9% of CRC patients eligible for primary surgical resection (5, 6, 21–23). When deemed ineligible for radical treatments, providing sufficient tumor reduction, called downstaging, might allow for radical treatments. Once downstaging has occurred, selected patients could be eligible for liver transplantation (LTx). However, availability of liver donors is limited and minimizing the chance of tumor progression while on the waiting list is needed, since disease progression and death occur in 10–23% of the patients while being listed (24, 25). Prevention of disease progression during this waiting period is called a bridge to transplantation, and will be discussed in our second section. Once patients are eligible for resection (not for transplantation), a sufficient postoperative liver reserve is needed to avoid post-operative complications and death due to hepatic failure. Inducing hypertrophy of the future remnant liver (FRL) by portal vein embolization (PVE) is an accepted method to minimize the chance of post- operative hepatic failure. After PVE, it takes about 3–6 weeks to induce adequate hypertrophy and around 17.5% of the patients experience tumor progression during this time interval, making them ineligible for resection (26). In unilobar RE, hypertrophy of the non-treated lobe has been described. Maybe using RE instead of PVE to achieve hypertrophy could help overcome this problem of tumor progression.

Using RE in the pre-operative setting, when patients may still be treated with curative intent, requires special attention to issues of efficacy and toxicity. After a short introduction to RE treatment itself, the role of RE in downstaging disease and as a bridge to LTx will be discussed. The role of RE in optimizing the future liver remnant will also be discussed, as well as issues of dosimetry and treatment accuracy.

Radioembolization

Radioembolization is a liver-directed treatment using radioactive microspheres. It is based on the dual blood supply of the liver (i.e., the portal vein and the hepatic artery). The contribution of the portal vein and hepatic artery to the blood flow of the normal liver parenchyma is circa 70% and 30%, respectively (27). For liver malignancies, the hepatic artery is the primarily blood supply (28). RE uses these perfusion differences between tumors and non-tumorous tissue to its advantage. The administered microspheres mainly lodge in the tumor arterioles, leading to a high tumor absorbed dose and a limited absorbed dose to the healthy liver parenchyma. This is even more the case for hypervascular tumors such as HCC and NET. In RE treatment planning these and several other factors play an important role.

Adequate patient selection is required first of all. Performance score (ECOG 0–2), adequate liver function (Child Pugh score A or B; bilirubin levels <2 mg/dl), liver-dominant, or liver-limited disease and a life expectancy of >3 months are of particular importance (22,29). When patients comply with these initial criteria, angiography follows. Injection positions for RE are planned during angiography, necessary precautions are taken to prevent extrahepatic deposition of microspheres, and the distribution of the microspheres is simulated by injecting ^{99m}Tc-macroaggregated albumin (^{99m}Tc-MAA). This is followed by planar scintigraphy and SPECT(/CT) imaging to detect possible extrahepatic deposition in abdominal organs and the lungs.

Once extrahepatic depositions have been excluded, treatment activity may be calculated. Different methods apply for the different microspheres commercially available. Resin microspheres (SIR-Spheres®, SIRTeX Medical Limited, Lane Cove, NSW, Australia) and glass microspheres (TheraSphere®, BTG International Ltd., Canada) are both FDA approved. Both have different activity calculation methods defined by the manufacturer (**Table 1**). One method is advocated for glass microspheres, while three methods can be used for resin microspheres; the so-called empirical, body surface area (BSA) and partition method (**Table 1**).

After RE treatment, ^{90}Y-brehmsstralung SPECT or ^{90}Y-PET is conducted to evaluate the distribution of the microspheres, excluding extrahepatic depositions. Post-treatment imaging can also be used for dosimetry. RE is generally a safe therapy, with relatively

Table 1. Dose calculation methods.

Microspheres		Dose calculation method
SIR-spheres User manual(30)	Empirical	Tumor load ≤ 25% = 2 GBq whole-liver delivery, Tumor load 25-50% = 2,5 GBq whole liver delivery, Tumor load ≥ 50% = 3 GBq whole liver delivery
	Body surface area (BSA)	$A(GBq) = (BSA - 0.2) + \left[\frac{tumor\ volume}{tumor\ volume + liver\ volume}\right]$ in which: $BSA = 0.20247 * height(m)^{0.725} * weight(kg)^{0.425}$
	Segmentation	$A(GBq) = \frac{D(Gy) * ([T/N * Mass_{tumor}] + Mass_{liver})}{49670 * (1 - \frac{Lung\ shunt\ raction\ (\%)}{100})}$ in which: $T/N = \frac{Activity_{tumor}/Mass_{tumor}}{Activity_{liver}/Mass_{liver}}$ based on MAA-SPECT/CT
Theraspheres User manual(31)		$A(GBq) = \frac{D(Gy) * Mass_{liver}(kg)}{50 * (1 - \frac{Lung\ shunt\ fraction(\%)}{100})}$ with an upper limit of lung shunt dose: $Lung\ shunt\ fraction(\%) * A(GBq) = 0.61\ GBq$

A = desired activity of microspheres, D = nominal dose to the liver, T/N = tumor to non-tumor ratio.

few side effects. Most patients will experience a limited degree of acute side effects (<30 days after RE) at a constitutional (fatigue and fever), gastrointestinal (nausea, emesis, abdominal pain, and ulcer), or hepatic level (biochemically). Some might develop late radiation effects, like RE-induced liver disease (REILD), which may occur in up to 5% of patients treated with RE (29, 32, 33).

Downstaging

Undoubtedly, surgery with curative intent is the most effective treatment strategy for a patient with liver malignancy. Literature has shown improved survival in HCC and CRC (liver metastases) after resection of all liver tumors (34, 35). Surgical eligibility depends on many factors, currently rendering 10–30% of the HCC patients and 5–9% of the CRC patients eligible for primary metastasectomy (5, 6, 21–23). Several contra-indications for surgical resection are in order: multiple bilobar tumors, inadvertent tumor localizations (near proximity to large blood vessels), inability to create sufficient resection margins (>10 mm), or an inadequate residual liver volume (liver remnant) (36, 37). Due to improvements in surgical techniques, the number of liver metastases in CRC has become less important and does not influence prognosis (36–38). Patients with ≥4 liver metastases in CRC show a significantly poorer survival after resection with a 5-year survival of 23% compared to patients with 1–3 liver metastasis with a 5-year survival of 44% (39). In HCC, there is a direct relation between the amount of tumors and survival. In solitary HCC, a 5-year survival of 56% is seen and in all patients with multiple HCC's survival is shorter than 3 years after resection (40–42).

As an alternative, RFA is a well-accepted treatment modality with good response rates in primary and secondary liver malignancies (43). Like surgical resection, near proximity to large vessels ("heatsink" effect; incomplete ablation) poses a problem (44, 45). Furthermore, the tumor must be reachable with the RFA-probe. RFA is adequate for tumors smaller than 3 cm to obtain complete necrosis, so tumor size should not exceed 3 cm (46). In a meta-analysis for HCC, surgical resection as primary treatment is superior to RFA with regard to recurrence rates, but surgical resection has more complications (47). For CRC results for RFA are similar to surgical resection (48).

In patients originally ineligible for resection/RFA, will downstaging followed by radical treatment [resection, RFA, and orthotopic liver transplantation (OLT)] truly lead to survival prolongation? A recent article by Ramanathan et al., described a 14-year experience of multiple treatments for HCC's (25). Their population was analyzed retrospectively and divided in three groups. The first two groups were treated with an intention to transplantation down the road (goal: downstaging). The first group underwent transplantation eventually (Group 1, *n*=139) and the second group did not receive transplantation, due to progressive disease (PD) (Group 2, *n*=93). The third

group had contra-indications for transplantation (Group 3, *n*=484). Used treatments included TACE, transarterial chemoinfusion (TACI), RFA, resection, sorafenib, RE, or a combination. RE was not frequently used and rarely as downstaging modality in the first two groups (Group 1: 0/139, Group 2: 6/93, and Group 3: 55/484). The 5-year survival in the third group was only 4.4%. The second group showed a 5-year survival of 35%, which was significantly worse than the transplantation-group, with a 5-year survival of 72.5% (25). This puts the need for downstaging in perspective. Once significant tumor reduction has occurred, patients with HCC can be treated with radical treatments leading to prolonged survival.

In patients with larger tumors (i.e., >3 cm; ineligible for RFA) or with tumors ineligible for resection, downstaging might be achieved by chemotherapy or biologicals, such as tyrokinase inhibitors. These systemic agents, however, are commonly accompanied by (serious) adverse events. In order to gain a controlled and local tumor reduction, downstaging with RE seems a logical sequel. In contrast to surgery and RFA, tumor size and tumor localization pose less of a problem for RE. The role of RE for downstaging has predominantly been described in patients with HCC. No randomized controlled trials have been performed on downstaging patients using RE. Nonetheless, approximately 50% (range 29–67%) of the patients with HCC will be downstaged successfully (**Table 2**) (11, 49–52).

Successful downstaging led to either resection, RFA, or OLT in three studies, in which approximately 1/3 of the downstaged patients were transplanted (10–23%

Table 2. Response assessment and downstaging in HCC patients.

Author	Year	N	mRECIST %		WHO %		EASL %		Downstaging success rate	Median time to response / downstaging*	Resection or RFA	OLT
			CR	PR	CR	PR	CR	PR	%	Months (range)	%†	%†
Kulik(49)	2006	34	-	-	-	50	-	-	67	4 (1.9-16.3)	34	23
Lewandowski(11)	2009	43	-	-	0	61	47	39	58	3.1 (1.8-8.7)	42	21
Ibrahim(51)	2012	8	-	-	13	63	37	50	50	-	-	37
Iñarrairaegui(50)	2012	21	-	-	-	-	-	-	29	-	19	10
Tohme(52)	2013	20	37	19	-	-	-	-	33	-	-	100•
Vouche(53)	2014	102	47	39	-	-	-	-	-	-	-	32

*N = number of patients, - = Data not available, *in both studies defined as WHO PR, †Percentage of total population, •All patients received a liver transplantation (study design).*

of the total population) and 2/3 underwent resection or RFA (19–42% of the total population) (11, 49, 50). Two other studies focused on downstaging followed by OLT. Ibrahim et al. described eight patients with a caudate lobe HCC treated with RE. Four patients were downstaged successfully (50%) and three of them received OLT (37% of the total population) (51). Vouche et al. treated 102 patients ineligible for RFA or resection with RE, which led to OLT in 33 patients (32%); however, downstaging success rate was not described (53). The remaining study by Tohme et al. had a different study design, in which they retrospectively reviewed 20 transplanted patients that received RE as sole treatment as a bridge-to-transplant. Of these patients, 33% was downstaged according to imaging (52).

Out of six studies on downstaging prior to radical treatment, two studies described a median time to response, defined as partial response (PR) according to the World Health Organization (WHO) response criteria, of 3.1–4.2 months, significantly shorter than TACE with a median time to response of 10.9 months (11, 49). In concordance with literature on RE in a palliative setting, **Table 2** shows a high PR rate and even complete response (CR) rate for HCC treated with RE. According to WHO, CR and PR was seen in 0–13 and 50–61%, respectively (11, 49, 51). By the European Association for the Study of the Liver criteria (EASL), CR and PR were even better 37–47% and 39–50%, respectively (11, 51). The most recent articles have implemented modified Response Evaluation Criteria In Solid Tumors (mRECIST), which looks at tumor size as well as enhancing patterns. With mRECIST good results were shown with a CR and PR of 37–47% and 19–39%, respectively (52, 53). These numbers are also comparable to the numbers shown in an earlier published meta-analysis by Vente et al. (54).

In HCC, downstaging with RE seems feasible. Moreover, comparable response rates have been described for other liver malignancies. In metastatic CRC reported response rates ranged from 18 to 46%, in metastatic NET around 63% and in metastatic breast carcinoma they ranged from 26 to 91% (55–57). Like RE in HCC patients, randomized controlled trials are needed to better define the role of RE in downstaging patients with primary or secondary liver malignancies.

As discussed above, high response rates can be observed after RE in many different tumor types. RE as monotherapy can induce CR, for example in up to 47% of HCC (see **Table 2**). The question is, how accurate are the current imaging modalities and its response criteria after RE therapy? Data of explanted livers show interesting results after RE in patients with HCC, who were downstaged for transplantation with RE. A correlation between radiologic response on follow-up imaging and the

Table 3. Explanted data of HCC patients.

Author	Year	Number of OLT	Degree of necrosis %			Comments on correlation imaging and histopathology
		(% total population)	100%	50-99%	0-50%	
Kulik(49)	2006	7 (24)	71	NA	NA	No correlation between imaging and histopathology
Riaz(58)	2009	35 (100) Based on 38 lesions	61	24	15	EASL complete response and WHO partial response correlated well with complete necrosis
Ibrahim(51)	2011	3 (37)	33	66	0	
Tohme(52)	2013	20 (100)	25	30	45	4 of 5 patients with 100% necrosis had complete response according to mRECIST
Vouche(53)	2014	33 (32)	52	48	0	Limitation of mRECIST; in complete response 50% only partial necrosis

NA = not available

degree of necrosis found in the explanted specimen has been suggested (**Table 3**) (52, 58). In the study of Riaz et al., CR by EASL and PR by WHO correlated well with complete necrosis in their population of 33 transplantations, 1 surgical resection, and 1 autopsy. No enhancement of the lesions on imaging corresponded with complete necrosis in these cases. When using response criteria EASL had a 100% positive predictive value (PPV) and specificity, whereas WHO PR had a PVV and specificity of 78 and 71%, respectively (58). On the other hand, in an earlier study by Kulik et al. no correlation was described with WHO criteria. It was incorrect in five of the six explanted specimens and correct in the seventh resection specimen. However, all incorrect interpreted lesions (5/7) showed contrast enhancement on imaging (49). More recently, mRECIST has been introduced in HCC instead of WHO and EASL. Tohme et al. showed that four of the five patients (80%) with CR by mRECIST had complete necrosis in their explanted livers (52). In contrast, the more recent study by Vouche et al. found that only 7 of 14 patients (50%) with CR by mRECIST had complete necrosis at pathology (53).

These discordant results highlight the limitations of current response criteria and its inability to consistently predict the degree of necrosis in treated liver malignancies. There is no primary role for ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) in HCC, due to its low sensitivity of 50–55% in an overall HCC population (59, 60). Well-differentiated HCC's show no to minimal FDG-uptake, while high to intense FDG-uptake can be seen in poorly differentiated/aggressive HCC's (59–61).

With this knowledge, individual prognostication seems possible (62). In the case of HCC and RE, currently two studies investigated the value of FDG-PET. Sabet et al. performed an FDG-PET before and after whole-liver RE in 33 patients. OS was best in FDG-negative HCC's (13 months), followed by FDG-positive HCC's that showed a metabolic response (defined as a SUV_{max} decrease of at least 20%; 10 months). Patients with FDG-positive HCC's without metabolic response had the worst prognosis (OS 5 months) (63). Kucuk et al. investigated pre-treatment FDG-PET as a prognostication method in 19 patients. A longer progression free survival (PFS) was seen in the group with evident FDG-positive HCC's prior to RE, compared to low FDG-positive or FDG-negative HCC's prior to RE (20, 12, and 5 months, respectively). The author stated that the evident FDG-positive HCC's responded better to RE (64).

FDG-PET could be of better value to predict response in mCRC or metastases from other primary cancers than the conventional response criteria (65). A correlation between CEA and FDG-PET/CT has been described in a few studies (66–68). The metabolic response observed by PET-CT is based on a reduction in tumor load, and therefore, a decline in CEA. This does not always correlate with the response assessed on anatomical imaging (66,68). Zerizer evaluated 25 patients with metastatic colon cancer to the liver with CECT and PET/CT. PFS at 2 years and decline in tumor markers were the primary end-points. Response on PET/CT was highly correlated with tumor markers (p <0.0001) and prediction of PFS, while response on CT was not significantly correlated (68).

More PET/CT studies with histopathological correlation or correlation with patient outcome are needed. Hypothetically, if non-invasive imaging and its response criteria could better predict the degree of necrosis, patients could be stratified in time frames, giving clinicians better means to triage patients eligible for OLT.

Bridge to transplantation

Initially, the long-term results of OLT for HCC were disappointing with high recurrence rates and low survival. Early 30-day mortality was 21.3% after transplantation with septicemia and graft failure as leading causes and 5-year survival was 15.2% with a median disease-free survival of 5.2 months (69). In 1996, a landmark study by Mazzaferro et al. defined selection criteria for HCC patients, the so-called Milan criteria (70). With the Milan criteria, a subgroup of HCC patients could be identified, consisting of patients with a single nodule up to 5 cm or <3 nodules <3 cm without extrahepatic manifestation and no vascular invasion, who achieve similar results after OLT as patients who receive OLT in end-stage cirrhosis without HCC.

Many have since adopted the Milan criteria and confirmed its success with a 5-year survival of >70% (71,72). In contrast, with increasing experience, multiple authors addressed the Milan criteria as being too restrictive. Careful selection of patients remains a matter of debate, the fact of the matter being the limited availability of liver donors worldwide (71–73).

Once eligible for OLT, patients are placed on a waiting list. Availability ranges from days to months. The incidence of disease progression while listed is 10–23% and death during evaluation is around 11% (24,25). Since liver donors are scarce, bridging the period of listing is essential. This clinical setting is called "bridge to transplantation." Many of the aforementioned modalities maybe used in this particular setting. Regional control as a bridge to transplant by using either RE, TACE, RFA, resection, chemotherapy, or a combination of these modalities is usually safe, without affecting post-transplant survival (16). Both RE and TACE show promising results in gaining regional control. As a bridge to transplantation, time and quality of life play an important role.

Lewandowski et al. compared RE (n=43) with TACE (n=43) as a bridge to transplantation (11). In their study, the median time to progression was defined as the interval between PD by WHO response criteria and the time of treatment. The median time to progression for TACE vs. RE was 19.6 vs. 48.6 months, respectively (p=0.008). According to the EASL criteria, the 1-year progression rate was 40% for TACE vs. only 8% for RE (p=0.01). Given its durable response in HCC, RE might, therefore, be the preferred choice as a bridge to transplantation. Moreover, the group treated with TACE was hospitalized for 3 days on average and received a median of two treatments per patient. In contrast, the RE group was treated on an outpatient basis and received a median of one treatment per patient (11). As quality of life plays an increasingly important role in medical decision-making, these logistical benefits definitively favor RE over TACE in this setting. In the developing field of RE even single session outpatient procedures have been described, in which all procedures take 1 day in total (74). Additionally, after treatment with ≤3 GBq ^{90}Y-microspheres no contact restrictions are necessary for patients and their families (75). Al together these results are very promising, but need to be reproduced in larger patient populations including quality of life investigations.

Transplantation may not be restricted to HCC alone. Other primary liver malignancies have shown promising results as well, like CCs and hepatic epitheloid hemangioendotheliomas (76). When it comes to secondary malignancies that are limited to the liver, well-differentiated NET have been investigated for OLT too. Primary treatment of a NET includes resection of the primary tumor. Dissemination

usually occurs at a later stage and is often limited to the liver only. In NET, 60–70% of patients present with diffuse, multifocal liver metastases, ineligible for radical treatments (77). When NET patients present with limited liver metastases, surgical resection results in only 10–25% curative resections with a 5-year recurrence rate of around 80% (78).

Orthotopic liver transplantation may provide the best curative treatment option for patients with metastatic NET, similar as to OLT in HCC. Both producing NET and non-producing NET are eligible for OLT and selection criteria for NET include the Milan criteria of 2007 (78), which are adopted by the European Neuroendocrine Tumor Society guideline of 2012 (77). Logically, the Milan Criteria for NET are different from the Milan criteria for HCC. They include only histologic confirmed well-differentiated tumors, liver tumor load <50%, age <50 years and stable disease for at least 6 months prior to OLT. With a 5-year survival up to 90% (range 33–90%) OLT seems promising in NET patients matching these criteria. However, tumor recurrence after transplantation may eventually pose a problem with a 5-year disease-free survival rate ranging from 20 to 77% (79).

Radioembolization as a bridge to transplantation in NET may have some benefit. As mono-treatment, the largest study to date on RE in NET patients (n=148) reported a response rate of 63% and a disease control rate (defined as CR + PR + stable disease) of 86%, combined with a median survival of 70 months (56). With such efficacy, RE may provide effective bridging in NET patients. No studies have been performed to investigate this hypothesis. Currently in other secondary liver malignancies, OLT has no place in the treatment algorithm. Some have used OLT in CRC, but within 2 years essentially all patients developed disease recurrence (76).

Future remnant liver

As surgical techniques evolve, more patients will be candidates for extensive liver surgery. Resections of liver segments or complete lobes are well tolerated. However, careful patient selection is crucial to avoid liver failure due to limited hepatic reserve after resection. According to current standards, the FRL should account for more than 25% of the total liver volume (TLV). In patients with underlying chronic liver diseases (like cirrhosis) this should be more than 40% of TLV (80). Both cut-off values are based on volumetric measurements on radiologic imaging, computed tomography, or magnetic resonance imaging (CT or MRI).

Once patients are screened for resection and FRL is deemed inadequate, PVE of the tumor-bearing lobe is often considered to gain hypertrophy of the FRL, the

non-embolized lobe. After PVE, adequate hypertrophy can be accomplished in 3–6 weeks, and extensive resections can be permitted (80). In cirrhotic livers and patients formerly treated with chemotherapy (especially platinum compounds), hypertrophy of the FRL after PVE may be insufficient (81,82). After PVE, hypertrophy of the FRL may range from 8.5% up to 69% (82). Several clinics have noticed a similar phenomenon of hypertrophy of the non-treated lobe after RE (83–88). **Table 4** summarizes findings of mainly retrospective studies on the degree of hypertrophy (DoH) of the non-treated lobe. DoH is defined as the FRL volume minus the FRL volume before treatment, divided by the FRL volume before treatment. A DoH of approximately 35% has been observed at 3–4 months after RE (range 8.9–57%). Garlipp et al. compared RE (n=35) with PVE (n=141). In their population, PVE resulted in significantly more hypertrophy of the non-treated lobe compared to RE after 1 month (61.5 vs. 29%) (88). The main limitation of this study was the follow-up interval of 1 month. This might have been too short to observe sufficient hypertrophy.

We have learned from studies with living donor LTx that the liver has a steady pace in regeneration. In a study by Klink et al., after donation of a right liver lobe, the remaining left lobe had a mean volume of 36.1% of the TLV (baseline) (89). After 1 month, FRL was 54.8% of the pre-transplantation TLV (53.6% DoH). After 3 months, 80% of the pre-transplantation TLV was restored (146% DoH) and after 12 months the post-transplantation volume was equal to or even more than 100% of the initial TLV (267% DoH) (89). This shows the value of a longer interval between the induction of hypertrophy and surgery.

Vouche et al. showed a similar dynamic pattern in RE (**Table 4**) with a DoH of 7% at 1 month, 35% at 3 months, and 45% at 9 months (87). In comparison, Corrêa et al. showed that PVE resulted in a 50% DoH occurring in the first 90 days (approximately 3 months) and 75% by 230 days (approximately 8 months) in patients who were not eligible for resection after PVE. The study by Corrêa et al. included patients who experienced PD during the time interval between PVE and surgical resection. This corresponded with 26% of the total population treated with PVE (90).

Resection should be performed shortly after PVE, since significant tumor progression may be seen in the PVE lobe and tumor progression can affect the FRL. Comparable to the previously mentioned study by Corrêa et al. and other studies, a study by de Baere et al. showed a high rate of patients with tumor progression after PVE, rendering them ineligible for resection (81,90). De Baere et al. treated 106 patients with PVE and showed a DoH of the FRL of 69% obtained within 27–52 days

Table 4 Hypertrophy after radioembolization.

Author	Year	Patients	Follow up period	Volume measurement	Degree of hypertrophy contralateral lobe	Degree of atrophy treated lobe
Jakobs(83)	2008	32	139 days	CT/MRI	8.9%	21.2%
Gaba(84)	2009	20	3 months	CT/MRI	40%	52%
Ahmadzadehfar(85)	2012	24	44-66 days	MRI	57%	6%
Edeline(86)	2013	34	3 months	CT	29%	23%†
Vouche(87)	2013	83	1 month 3-6 months >9 months	CT/MRI	7% 35% 45%	2% 21% 32%
Garlipp(88)*	2014	35 141†	46 days 33 days†	MRI	29% 61.5%†	NA

*NA = not available, *Only prospective study, †RE vs PVE, PVE results are marked. †Result corrected for tumor volume changes after RE.*

(mean 31±5 days). Subsequently, successful hemihepatectomies were performed in 88%, but 12% were deemed inoperable due to tumor progression, extrahepatic spread, or liver metastasis in the hypertrophic lobe (81). In a recent analysis by Vyas et al., 17.5% of the patients experienced tumor progression and 4.8% had failure of hypertrophy prior to surgery in a pooled population of 1532 patients undergoing PVE (26).

Although at a slower rate, RE can induce substantial hypertrophy in the non-treated lobe while treating the tumor at the same time. This may lead to less tumor progression during the interval between RE and surgery. Unfortunately, no prospective trials have yet been performed to investigate this hypothesis.

Another way to prevent tumor progression is to simply perform surgery sooner, before the tumor has the chance to progress. There are some studies suggest that FLR volume is a suboptimal predictor of post-operative liver failure. Ideally, we should look at FRL *function* to predict the chance of success (91,92). This especially becomes relevant in patients with underlying liver disease, in whom some parts of the liver might have a better function than other parts. There are different methods for assessing liver function. First assessment of liver function is usually done by measurements of liver enzymes (aminotransferase levels and alkaline phosphatase) and products indicative of liver synthesis such as albumin, bilirubin, and prothrombin time in blood. However, liver enzymes are markers of liver injury and products of hepatic synthesis function can be affected by different extrahepatic factors such as nutrition, hemolysis, antibiotic use, and systemic illness.

The most well-known and applied dynamic quantitative liver function tests are the indocyanine green clearance (ICG) and galactose elimination capacity. ICG is a tricarbocyanine dye, cleared from the plasma by hepatocytes and excreted into the bile. The ICG clearance test is considered the most accurate test to evaluate the hepatic functional reserve before surgery and to predict post-operative mortality (93). The carbohydrate galactose is metabolized nearly exclusively in the liver. The elimination rate of galactose from the blood depends on the phosphorylation of galactose by galactokinase. Both these dynamic tests, in which multiple blood samples need to be taken, have been shown to predict post-operative complications and mortality (94,95). However, they are not able to tell the surgeon how much of the liver can be resected safely or whether there are regional differences in liver function.

In order to appreciate regional differences in liver function, you have to make them visible. In the past years, two different nuclear medicine imaging techniques for assessment of liver function have been developed: ^{99m}Tc-galactosyl human serum albumin(^{99m}Tc-GSA) and ^{99m}Tc-IDA. ^{99m}Tc-GSA scintigraphy measures the binding of ^{99m}Tc-GSA to its receptor (the asialoglycoprotein receptor), which is expressed on functional hepatocytes only. Liver function measured by ^{99m}Tc-GSA scintigraphy correlates well with conventional liver function parameters, including the ICG clearance test (96,97). ^{99m}Tc-GSA has been shown to be of value for pre-operative risk assessment of partial hepatectomy (97,98). One major limitation is the availability of ^{99m}Tc-GSA, as it is only available for clinical use in Japan.

Hepatobiliary scintigraphy (HBS) using ^{99m}Tc-iminodiacetic acid analogs (^{99m}Tc-IDA), has been used since the 1970s for the scintigraphic evaluation various biliary diseases. After uptake by organic anion transporter peptides expressed on the hepatocytes, IDA analogs are excreted in the bile by ATP-dependent export pumps, without undergoing biotransformation (99). Therefore, IDA agents are ideal tracers for the biliary tract. More recent, HBS with IDA analogs has been used to evaluate liver function. Liver uptake of IDA analogs can be influenced by high plasma levels of bilirubin (100). Of all IDA analogs, ^{99m}Tc-mebrofenin has the strongest resistance to displacement by high bilirubin concentrations and it also has the highest hepatic extraction fraction. For these reasons, ^{99m}Tc-mebrofenin is the most favorable IDA analog. Erdogan et al. have shown that the hepatic uptake rate of ^{99m}Tc-mebrofenin correlates well with the ICG clearance rate and is an efficient method for determining liver function (101). The same group from Amsterdam later showed that pre-operative HBS is more valuable in estimating the risk of post-operative liver failure than CT volumetry in patients with underlying

liver disease (102). They provided a FRL function cut-off value for the prediction of post-operative liver failure. Because HBS is a pure functional test, this cut-off-value is the same for patients with or without underlying liver disease. Therefore, it can be used in patients with a pre-operative unknown quality of liver parenchyma (99) (**Figure 1**).

With the use of SPECT-CT and CECT, assessment of liver function at a segmental level becomes possible. Combining the functional data from the SPECT and the anatomical information of the CECT will enable an even more accurate estimation of the post-operative liver function in the future.

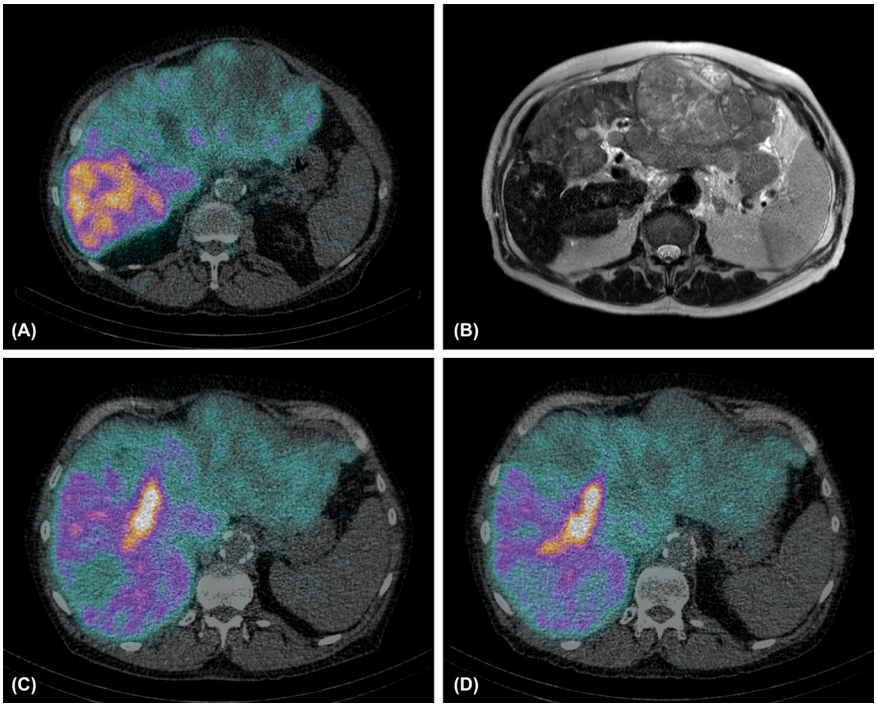

Figure 1. Axial HBS SPECT-CT image through the abdomen of a patient with hemochromatosis and multifocal HCC. Notice the regional uptake differences in cirrhotic and tumorous tissue (**a**). Corresponding MRI T2 weighted image (**b**). Same patient before (**c**) and after (**d**) RE of the left lobe including segment 4. Image (**c**) is from the same HBS SPECT/CT as image (**a**), but shown in a different axial plane. The decrease of ^{99m}Tc-mebrofenin uptake after treatment is best visible in segment 4. The area of high uptake is biliary excretion in a dilated bile duct.

There have been few studies on the effect of PVE on liver function compared to liver volume. In a study of 24 patients by De Graaf et al., FRL volume and function were assessed 3–4 weeks after PVE. FRL function increased significantly more than FRL volume (103). Using ^{99m}Tc-GSA, other studies also describe that the increase in function is more pronounced than the increase in volume (91,92). These findings suggest that the time between PVE and surgery may be shortened, thereby leaving less time for tumor progression.

Discussion

In the previous sections, we described RE as an interval treatment modality for downstaging, bridge-to-transplant and future remnant hypertrophy. Although level 1 evidence is lacking, preliminary results show promising accuracy of RE for these particular indications.

Downstaging is feasible in patients with HCC as shown by several authors (11, 49–53), but it should not be limited to HCC alone, since response rates of other liver malignancies by RE are similar or even higher, including a long-lasting effect. As described in our review, gaining surgical eligibility leads to survival prolongation. If patients are treated with an intention to downstage and when sufficient tumor reduction has occurred, selected cases might even be eligible for OLT, which is the most promising curative treatment for several primary and secondary liver malignancies at this time, as discussed in our review. If patients are not eligible for OLT and the future liver remnant is deemed insufficient, the later making the patient ineligible for resection as well, inducing hypertrophy is paramount. In achieving sufficient hypertrophy RE might be preferred over PVE, because RE has the advantage of the combination of hypertrophy induction and local disease control. Success of a combination of simultaneously downstaging and inducing hypertrophy has already been described in a case report by Gulec et al. (104).

Use of RE for downstaging, bridge-to-transplant and attaining an adequate FRL seems very promising; however, several related procedures need refinement too. Current imaging modalities and their response criteria are incapable of predicting the degree of tumor necrosis in lesions treated by RE (49,53). A better determination of the degree of necrosis could assist clinicians in personalizing treatment algorithms and might even define the timing of applying treatment (alternations). In improving related imaging for these indications, hepatobiliary scintigraphy is taking the lead. By determining liver function instead of liver volume, eligibility for surgical resection could be attained sooner by evaluating function gain in

the FLR, since functional and volume gain do not go hand in hand. Furthermore, hepatobiliary scintigraphy takes an underlying liver disease into account, like cirrhosis, which is not uncommon in patients with HCC.

At the same time, dosimetry is crucial to optimize RE in these settings. Theoretically, the higher the tumor absorbed dose, the more effective. This rationale was supported by (pre-)clinical studies in different settings (105–108). However, although the surrounding normal liver cells are affected less, high activity levels can result in loss of healthy liver parenchyma. Thus, the goal is to find the right balance between maximum tumor absorbed dose and preservation of healthy tissue in each individual patient. As briefly pointed out in our introduction on RE, multiple activity calculation methods are being used. When using resin microspheres three activity calculation methods have been described (**Table 1**). The empirical method that was solely based on tumor load has been abandoned due to an unacceptable toxicity profile and the lack of any patient-individualized factors (29,109). The BSA-method (semi-empirical) has been used safely in many clinical trials and is recommended in patients with concurrent or previous chemotherapy by the manufacturer (30). It is easy to use in daily practice and has strong historical data (77). However, this method has been criticized in literature in many aspects, mostly based on not taking liver volume into consideration. As a result, under- (small patient + large liver) or overtreatment (large patient + small liver) can occur (109,110). Additionally, the BSA-method does not take the tumor-to-non-tumor ratio (T/N ratio) into account, which is to the disadvantage of patients with hypervascular tumors who could withstand higher administered activities. The third calculation method, the partition model, embeds many of these relevant factors. It takes into account the T/N ratio, tumor volume, and liver volume. All variables in this equation can be acquired from the ^{99m}Tc-MAA-SPECT/CT prior to RE, so no additional procedures are needed (111). Only poorly delineated tumors pose a problem for quantification. The complexity of the partition method makes its use less attractive in daily practice. In daily practice, the BSA-method is most commonly applied method for dose calculation (111). Nonetheless, the partition model based on the 99mTc-MAA-SPECT/CT findings should be preferred by clinicians (111).

In the case of glass microspheres, the manufacturer advocates one activity calculation method (**Table 1**), in which the T/N ratio has not been included (31). Like the discussion surrounding activity calculation for resin microspheres, treatment based on prior ^{99m}Tc-MAA-SPECT/CT has been shown feasible for glass microspheres and seems very promising (108). One should bear in mind though that the result of the ^{99m}Tc-MAA-SPECT/CT is influenced by many factors, causing discrepancies

between ^{99m}Tc-MAA-particles distribution and ^{90}Y-microspheres distribution on which dose calculation is based, when applying the partition method (summarized in **Table 5**).

As mentioned in our short introduction to RE, ^{90}Y-brehmsstralung SPECT/CT or ^{90}Y-PET/CT is acquired post-treatment to evaluate the distribution of the microspheres. At the same time, both modalities can be used for post-treatment dosimetry. Currently, ^{90}Y-PET/CT is favored over ^{90}Y-brehmsstralung SPECT/CT by many RE-centers (114–119). Calculating the administered tumor absorbed dose on post-treatment imaging gives insight into the expected response. Several studies showed that the tumor absorbed dose was correlated to the objective response (115,117,120,121). Additionally, heterogeneity of the absorbed dose within the tumor can be assessed, which correlates with the partial / regional tumor response (115,119,120).

In downstaging and bridge to transplant, dosimetry should optimize the tumor absorbed dose, while delivering an acceptable to minimal dose on healthy liver tissue. Applying the partition method based on the ^{99m}Tc-MAA-SPECT/CT is

Table 5. Factors causing ^{99m}Tc-macroaggregated albumin (^{99m}Tc-MAA) and ^{90}Y-microspheres (^{90}Y-MS) distribution discrepancy (27, 110, 112, 113)

Procedural aspects	
Catheter positioning	Similar positioning in both angiographies
	Equal proximity to bifurcations
Injection rate	Bolus or rapid (^{99m}Tc-MAA) versus intermitted delivery (^{90}Y-MS)
Particle aspects	
Particle flow dynamics	Randomly formed ^{99m}Tc-MAA versus spherical ^{90}Y-MS
Administered amount	^{99m}Tc-MAA ± 150.000 particles versus ^{90}Y-MS ± 4 – 50 million particles
Technical aspect	
Patient positioning	Registration mismatch between scans
Shortcomings imaging	Variability in delineation of tumors
	Threshold definition of tumor versus non-tumor
Scanning modality	^{90}Y-Brehmstralungs-SPECT/CT versus ^{90}Y-PET/CT
Breathing artefacts	Registration difficulties between scans
Patient factors	
Primary tumor	Ability of tumor delineation on imaging
Vascular	Artery spasms during delivery
	Stasis of flow during ^{90}Y-MS administration

preferable and when possible, superselective catheterization of the tumor-bearing lobe can be considered to further improve tumor dose and healthy liver dose differences. By doing so, minimizing radiation induced complications and preserving healthy liver tissue, which is badly needed after surgical resection. However, the vast majority of the current studies did not use dose calculations based on the ^{99m}Tc-MAA-SPECT/CT, so optimal dose calculation might not have been reached and downstaging success rates could be even higher (11,49–53). Additionally, minimizing lung shunting and preserving lung function before an intensive liver transplant procedure or large surgical resection, may become an additional aspect to consider. In LTx, perioperative death occurs in 5.3–7.0%, mostly due to multiple organ failure (including respiratory insufficiency) and approximately 42.1% of all patients develop pulmonary complications (pneumonia and pleural effusion) after LTx (122,123). In current studies performing RE as a bridge to transplantation, none specifically mentioned pulmonary complications after OLT (11,49–53).

In the induction of FRL hypertrophy, the underlying mechanism of liver hypertrophy remains a mystery (82). Since the embolic effect of RE is less substantial than in PVE, remnant hypertrophy after RE might largely be based on an irradiation induced effect in the treated liver lobe. This causes fibrosis, leading to increased portal pressure and eventually to shunting of portal venous blood away from the irradiated fibrotic lobe to the untreated contralateral lobe by preferential flow (83,84,86). This effect and its results do not arise as rapidly as in PVE, as described by Vouche et al. and Corrêa et al. (87,90). After PVE, a more macroscopic occlusion creates a sudden shunt of portal venous blood to the untreated lobe. In some cases, repeated RE resulting in a higher cumulative dose led to an increase in hypertrophy of the untreated lobe (50). Only Edeline et al. found no correlation between the absorbed dose and hypertrophy in their study (86). That study was soon followed by a multivariate analysis of Vouche et al., in which the absorbed dose was no significant variable (87). Nonetheless, no studies have been performed solely to investigate this phenomenon and its relation to dose.

Apart from assessing FRL function with HBS, HIDA could be a very interesting modality when it comes to RE. At present, there have been no studies evaluating the effect of RE therapy on liver function apart from laboratory toxicity. In the future, scintigraphy can be used to learn us more about changes in liver function after RE, for example in relationship to microsphere distribution and dose. Another area of research could be time to functional recovery after RE, which in turn could potentially be helpful in determining when to perform repeat RE treatment if needed.

Conclusion

Trans-arterial treatment of liver malignancies with RE is an emerging treatment modality. RE is predominantly performed in patients with no curative options, mostly in a salvage setting. Potentially curative settings in which RE may be applied include downstaging patients to resectable disease, a bridge to transplantation and induction of remnant liver hypertrophy. RE involves a combination of tumor reduction and disease control, minimizing the chance of tumor progression during the time interval prior to liver surgery with curative intent. This may eventually lead to prolonged survival, although prospective controlled trials are needed to test this hypothesis. Imaging is indispensable for patient selection and dosimetry-based treatment planning to use the full potential that RE has to offer in patients with liver malignancy, especially when liver surgery with curative intent might still be an option.

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Chapter 9

Safety analysis of holmium-166 microsphere scout dose imaging during radioembolisation work-up: A cohort study

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European Radiology 2018; 28: 920-928

Abstract

Background

Radioembolization is generally preceded by a scout dose of technetium-99m-macroaggregated albumin to estimate extrahepatic shunting of activity. Holmium-166 microspheres can be used as a scout dose (±250 MBq) and as a therapeutic dose. General toxicity of a holmium-166 scout dose (^{166}Ho-SD) and safety concerns of an accidental extrahepatic deposition of ^{166}Ho-SD were investigated.

Methods

All patients who received a ^{166}Ho-SD in our institute were reviewed for general toxicity and extrahepatic depositions. The absorbed dose in extrahepatic tissue was calculated on SPECT/CT and correlated to clinical toxicities.

Results

In total, 82 patients were included. No relevant clinical toxicity occurred. Six patients had an extrahepatic deposition of ^{166}Ho-SD (median administered activity 270 MBq). The extrahepatic depositions (median activity 3.7 MBq) were located in duodenum (3x), gastric fundus, falciform ligament and the lesser curvature of the stomach, and were deposited in a median volume of 15.3 ml, which resulted in an estimated median absorbed dose of 3.6 Gy (range 0.3 – 13.8 Gy). No adverse events related to the extrahepatic deposition of the ^{166}Ho-SD occurred after a median follow-up of 4 months (range 1 – 12 months).

Conclusion

These results support the safety of a 250 MBq ^{166}Ho-SD in a clinical setting.

Introduction

Before yttrium-90 (^{90}Y) radioembolization (RE) is performed, a scout dose is used to predict intra- and extrahepatic distribution of activity and check for potential contraindications (i.e. excessive lung shunt and extrahepatic depositions). Technetium-99m macro aggregated albumin (^{99m}Tc-MAA) is commonly used, however its predictive value is discussed throughout literature [1; 2]. In patients treated with holmium-166 (^{166}Ho) microspheres a scout dose using 250 MBq ^{166}Ho is used as an alternative, which is superior in calculating the lung shunt fraction compared to ^{99m}Tc-MAA [1]. This may be due to the fact that identical ^{166}Ho microspheres are used for the scout dose procedure and the RE treatment.

The beta and gamma emitting properties of ^{166}Ho (respectively $E_{\beta max}$ = 1.85 MeV and E_{γ} = 81 keV) may theoretically cause concerns on the safety of using ^{166}Ho microspheres as a scout dose. An earlier study concluded that ^{166}Ho microspheres can safely replace ^{99m}Tc-MAA in the majority of cases [3]. However, these data were based on ^{99m}Tc-MAA data of extrahepatic depositions, theoretically translated to ^{166}Ho microspheres; if these extrahepatic ^{99m}Tc-MAA depositions would have been ^{166}Ho microspheres, just 5,9% of patients would have excessive absorbed doses in extrahepatic tissues [3]. This toxicity assessment was performed because of a lack of events after ^{166}Ho microspheres scout dose procedures.

Since then, a ^{166}Ho microsphere scout dose (^{166}Ho scout dose) has been used in several clinical trials. Several events of extrahepatic ^{166}Ho scout dose were observed that warrant a re-evaluation of the previous theoretically based safety assumptions. To assess the safety of the ^{166}Ho scout dose in clinical practice, the general toxicity of a ^{166}Ho scout dose was studied. Additionally, the absorbed dose in extrahepatic tissue in all patients with an extrahepatic ^{166}Ho scout dose deposition was calculated and clinical record forms for potential complications due to these extrahepatic depositions were reviewed.

Methods and materials

Patient population

All patients that have been treated with ^{166}Ho microspheres since the start of its clinical use were included from November 2009 till January 2016. All patients included in this study participated in a prospective trial with ^{166}Ho microspheres (**Table 1** [4-7]) and written informed consent was obtained for all patients at study inclusion. All data was gathered prospectively. Results of 15 patients treated with ^{166}Ho radioembolization in the HEPAR trial were published before [4]. This prior

Table 1. Trials with ^{166}Ho-microspheres

Trial	N	FU period	MAA*	Description
HEPAR [4]	15	12 months	Yes	Phase 1 trial
HEPAR 2 [5]	42	12 months	Yes	Phase 2 trial
HEPAR PLUS [6]	13	12 months	No	Additional ^{166}Ho radio-embolization after PRRT in NET
SIM [7]	11	3 months	No	Surefire Infusion System vs. standard micro-catheter use during ^{166}Ho radio-embolization in CRLM

*FU = follow up, PRRT = Peptide Receptor Radionuclide Therapy, NET = Neuroendocrine Tumours, CRLM = Colorectal Liver Metastasis. *Use of ^{99m}Tc-MAA prior to the ^{166}Ho scout dose and actual treatment*

article dealt with development of the ^{166}Ho microspheres as a therapeutic agent, whereas this manuscript provides additional information solely on the toxicity of the ^{166}Ho scout dose of those patients. The scout dose with ^{166}Ho microspheres was aimed at 250 MBq in all study protocols and administered intra-arterially. The 250 MBq was divided amongst the injection positions according to the targeted liver volume. All patients received the scout dose administration in the morning prior to the therapeutic ^{166}Ho dose administration in the afternoon on the same day. In patients with an extrahepatic deposition, additional volume, activity and dose quantification on imaging studies were performed and discussed separately (details in the next sections). Clinical record forms were evaluated for any adverse events during or after the ^{166}Ho scout dose procedure and prior to the radioembolization treatment with ^{166}Ho microspheres. They were scored according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.1. Angiography procedures were performed by experienced interventional radiologists (>3 years) and SPECT/CT readings by experienced nuclear medicine physicians (>3 years).

Imaging and reconstruction

Our phantom and all patients were scanned on a Symbia T16 SPECT/CT scanner (Siemens Healthcare, Erlangen, Germany) within one hour of the injection of the ^{166}Ho scout dose. Similar to ^{99m}Tc-MAA, lung shunt fraction (LSF) was determined by drawing regions-of-interest (ROI) of the lungs and the liver on anterior and posterior planar imaging of the thorax and abdomen and calculating the fraction of the total administered dose using the geometric mean:

$$Geometric\ mean = \sqrt{(counts_{anterior} * counts_{posterior})}$$

SPECT data of the liver were acquired using a medium-energy general purpose collimator, on a 128 x 128 matrix (pixel size, 4.8 x 4.8 mm) with 120 angles (20

s per projection) over a noncircular 360° orbit and photonpeak energy window centred around 81 keV with a width of 15%. Low-dose CT data (110 kVp, 40 mAs, adaptive dose modulation with Siemens CARE Dose 4D) were acquired and reconstructed to a voxel size of 1.27 x 1.27 x 5 mm using a smoothing kernel (B08s; Siemens Healthcare). After a CT-derived attenuation map was created (Syngo MI Applications; Siemens Healthcare). Quantitative SPECT images were reconstructed with 10 iterations, 8 subsets using the Utrecht Monte Carlo System (UMCS), an in-house-developed Monte Carlo simulator, incorporating Monte Carlo based scatter correction, attenuation correction, and modelling of photon interaction with the collimator and detector [8-10].

Phantom Equipment

To estimate the accuracy of our measurement a National Electrical Manufacturers Association (NEMA) NU2 image quality (IQ) phantom was used. It contains 6 spheres of sizes varying between 0.5 and 26.5 mL suspended in a water-filled background compartment of 9.7 L. All spheres were filled with a ^{166}Ho acidic solution of known activity concentration and scanned identically to the protocol used for the ^{166}Ho scout dose SPECT/CT, as described previously [8].

Activity and volume analysis of a deposition

Activity and volume estimation was done similar to the earlier study using additional in-house-developed software (Volumetool) [3; 11]. Manual delineation of the extrahepatic deposition was performed by taking a large enough margin around the extrahepatic deposition to include all displaced counts due to breathing, patient motion and partial volume effects (excluding intrahepatic activity). The extrahepatic activity was estimated by summation of all voxels (in units of Bq), without the use of a threshold, within the manual delineated extrahepatic deposition, preventing underestimation of the extrahepatic activity (and thus of absorbed dose).

The threshold for volume delineation was determined in our phantom study and was defined as a percentage of the maximum voxel value. The threshold was applied to the same manual delineation in our case series to determine the extrahepatic deposition volume. A threshold was chosen to approximate or underestimate the volume (but not overestimate). This resulted in an overestimation of the extrahepatic tissue absorbed dose, which should decrease the possibility of a type II error: a failure to reject the null hypothesis "Use of ^{166}Ho scout dose is safe".

Dose calculation

The following formula was used to calculate the absorbed dose in the extrahepatic tissue:

$$D(Gy) = 15.87\left(\frac{mJ}{MBq}\right) * \frac{Extrahepatic\ activity\ of\ ^{166}Ho\ (MBq)}{Extrahepatic\ volume\ of\ ^{166}Ho(cm^3) * 1.06\left(\frac{g}{cm^3}\right)}$$

In which 15.87 mJ/MBq is the total energy absorbed in tissue from the total decay of 1 MBq of ^{166}Ho assuming soft tissue density of 1.06 g/cm3 [12]. The mean penetration of the beta emission of ^{166}Ho (2.5 mm) is small, so all energy was assumed to be absorbed within the extrahepatic deposition [3].

Results

A total of 90 patients were included in the trials. After the initial ^{99m}Tc-MAA procedure in the HEPAR and HEPAR-2 trial, 8 patients were excluded. Five patients were excluded based on earlier ^{99m}Tc-MAA findings (excessive lung shunt or extrahepatic deposition) and three due to technical reasons (dissection resulting in a permanent stenosis or new collaterals). A total of 82 patients with moderate to extensive bilobar disease received a ^{166}Ho scout dose at our institute (**Table 2**). A mean scout dose of 244 MBq was administered (median 251 MBq; range 103 – 313 MBq). Six patients (7.9%) had an extrahepatic deposition, which will be discussed in detail in the next section. **Table 3** provides all the adverse events after the scout dose administration (prior to therapeutic dose administration) and adverse events related to the pre-treatment angiography procedure. No adverse events that were possibly, probably or definitively related to the ^{166}Ho scout dose occurred.

Extrahepatic depositions ^{166}Ho scout dose

Six patients had an extrahepatic deposition of the ^{166}Ho scout dose (**Figure 2–7**). One HEPAR, three HEPAR 2, one HEPAR PLUS and one SIM candidate [4-7]. Baseline characteristics can be found in **Table 4**. Median LSF (of these patients) was 13.3% (range 9.4% – 17.6%). Median follow up was 4 months (range: 1 – 12 months).

Patient 2 and 4, respectively depicted in **figure 3** and 5, were excluded from treatment, as the culprit vessels remained unidentified, so treatment was deemed unsafe. After focused reviewing of the old DSA images several years later, probable culprit vessels were identified. In patient 2 the right gastric artery was the probable culprit vessel, as its origin was exactly at the tip of the microcatheter during the ^{166}Ho scout dose injection (**Figure 3**). In patient 4 an intrahepatic collateral was the culprit vessel, which fed the region of the coil embolized gastroduodenal artery (**Figure 5**).

Table 2. Baseline characteristics of patients receiving a ^{166}Ho scout dose

Age (years)	
Mean	62.2
Standard deviation	10.5
Range	38 – 88
Primary tumour (n)	
Colorectal carcinoma	43
Neuroendocrine tumour	16
Orbital melanoma	8
Cholangiocarcinoma	5
Breast cancer	5
Pancreatic adenocarcinoma	2
Appendix carcinoma	1
Gastric cancer	1
Thymoma	1
Scout dose	
Mean prescribed dose (MBq)	265
Range	105 – 326
Mean net administered dose (MBq)	242
Range	103 – 313
Mean lung shunt fraction (%)	13.2
Range	1.1 – 24.9
Treatment planning	
Whole liver, one session	80
Whole liver, sequentially	2

Table 3. Adverse events surrounding scout dose administration

Adverse event	**CTCAE***	**N**	**%**
Back pain†	1	5	6.3
	2	3	3.8
Abdominal pain‡	1	2	2.5
Dissection		2	2.5
Stenosis RHA		1	1.3
Allergic reaction to iodine contrast		1	1.3

*RHA = right hepatic artery, *Common Terminology Criteria for Adverse Events version 4.03. †Back pain related to angiography suite table or SPECT/CT table. ‡Abdominal pain occurred after coiling of a phrenic artery, before ^{166}Ho scout dose administration*

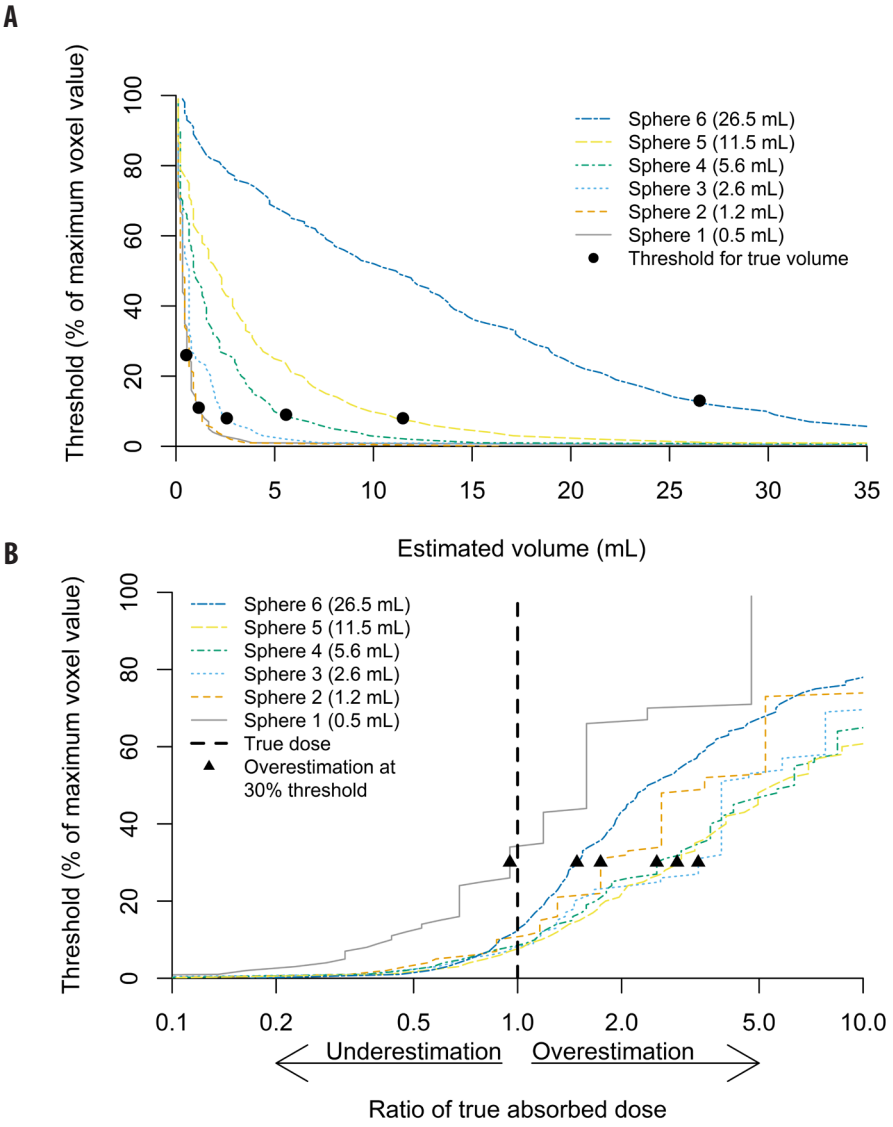

Figure 1 a. Graph featuring results of threshold-based volume estimation of six ^{166}Ho-filled spheres in NEMA NU-2 Image Quality phantom (0.5 - 26.5 mL). **b**. Threshold-estimated absorbed doses relative to their true value in phantom spheres, using 30% threshold and known ^{166}Ho acidic solution concentration. Underestimation of affected tissue volume in vivo will occur, subsequently leading to overestimation of absorbed tissue dose (up to 4 times in sphere 3 of 2.6 ml). A slight underestimation of absorbed dose will only occur in small volume extrahepatic depositions (<1 ml).

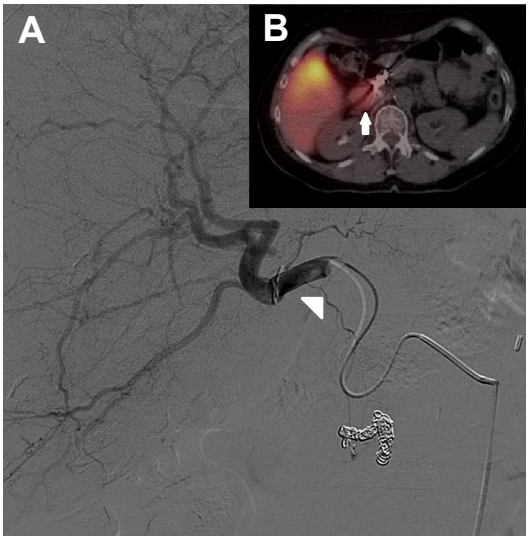

Figure 2. A 63-year-old female with an intrahepatic cholangiocarcinoma. **a.** Digital subtraction angiography (DSA) image with injection position in right hepatic artery. **b.** ^{166}Ho scout dose SPECT/CT with duodenal extrahepatic deposition (arrow). On DSA, posterior superior pancreatico-duodenal artery was the culprit vessel (arrow), which in 15% of cases originates from common hepatic artery or main hepatic artery [26]. However, it can also arise from right hepatic artery [27], as illustrated here.

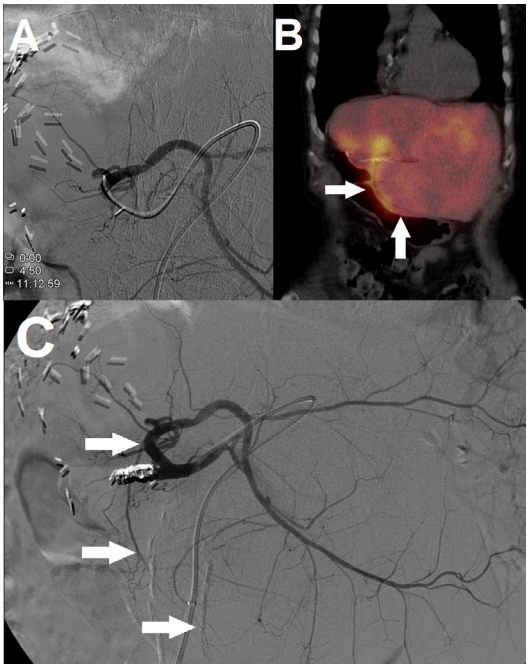

Figure 3. An 80-year-old female with colorectal cancer liver metastases was initially treated with a resection of her sigmoid carcinoma and simultaneous right hemihepatectomy. **a.** Digital subtraction angiography (DSA) with injection position during ^{166}Ho scout dose pre-treatment angiography. **b.** SPECT/CT after administration of ^{166}Ho scout dose with large extrahepatic deposition in lesser curvature of the stomach (arrows). **c.** DSA showing the right gastric artery arising from right hepatic artery as culprit vessel (arrows).

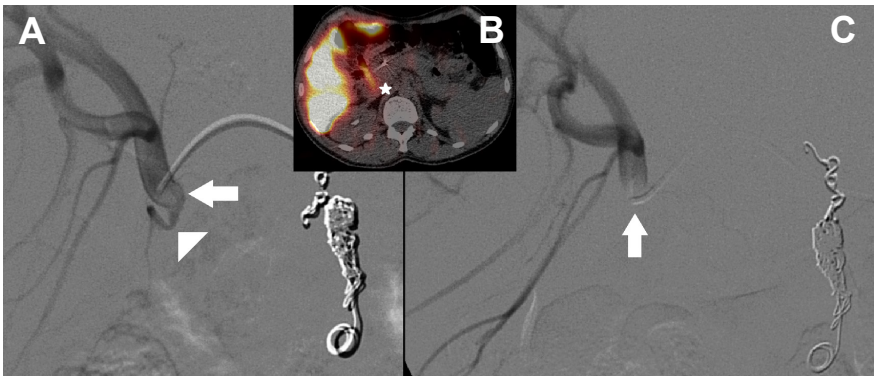

Figure 4. A 63-year-old male with colorectal cancer liver metastases. **a.** Digital subtraction angiogram (DSA) of injections position of ^{166}Ho scout dose procedure. **b.** ^{166}Ho scout dose SPECT/CT with extrahepatic deposition in duodenum (star). **c.** DSA of injection position of ^{166}Ho therapy. Note the difference in positioning of microcatheter (arrows). During ^{166}Ho scout dose procedure the microcatheter pointed downwards, instead of horizontally (arrows). On the same DSA of ^{166}Ho scout dose procedure the culprit vessel, supraduodenal artery, can be acknowledged (arrowhead).

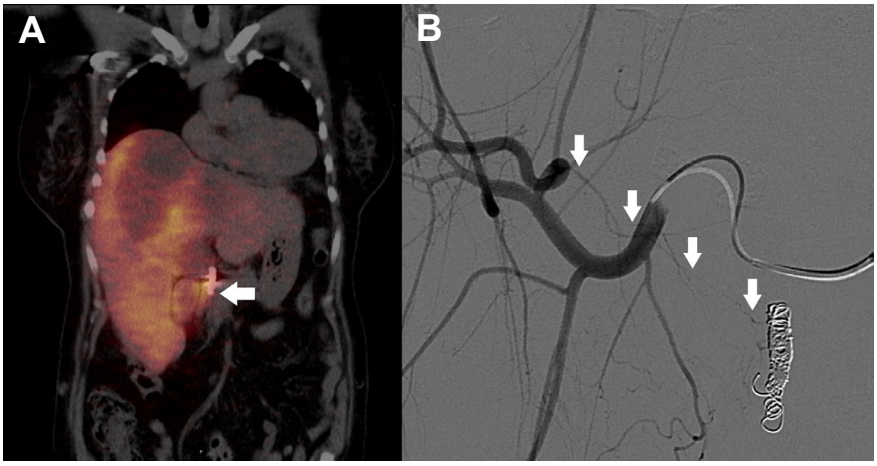

Figure 5 A 62-year-old female with liver metastases of a pancreatic adenocarcinoma. **a.** SPECT/CT after administration of ^{166}Ho scout dose. Extrahepatic deposition in the duodenum (arrow). **b.** Digital subtraction angiography shows flow redistribution in intrahepatic collateral (arrows), directly following coil embolization of gastroduodenal artery. Development of new hepatico-enteric collaterals after previous coil embolization has been described before [28].

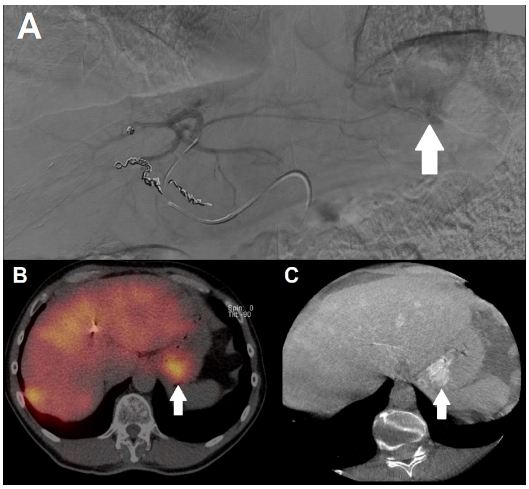

Figure 6. A 56-year-old male with a primary rectal neuroendocrine tumour, liver and bone metastases. **a.** Digital subtraction angiography of ^{166}Ho scout dose procedure. **b.** Corresponding ^{166}Ho scout dose SPECT/CT. **c.** Corresponding C-arm CT. All images show extrahepatic deposition and contrast blush in gastric fundus (arrows). After coiling of accessory left gastric artery, extrahepatic deposition on SPECT/CT and contrast blush on C-arm CT disappeared (images not shown). Accessory left gastric artery originated distally from left hepatic artery, running through ligamentum venosum towards gastric fundus [29].

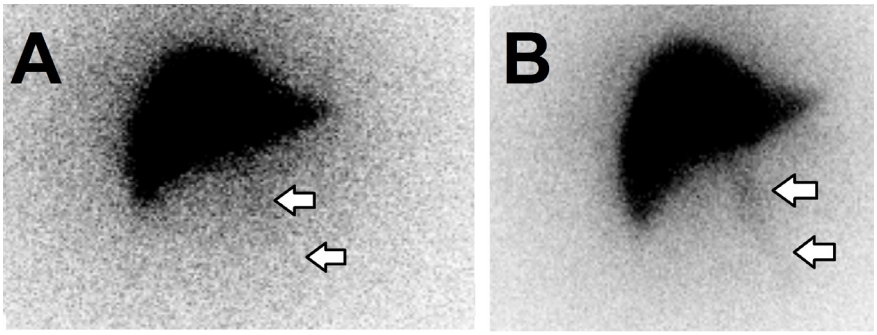

Figure 7. A 60-year-old male with colorectal liver metastases. **a.** Planar ^{166}Ho image of scout dose, depicting a faint extrahepatic deposition in falciform ligament. **b.** Post-treatment planar ^{166}Ho image, depicting similar extrahepatic deposition in falciform ligament (SPECT/CT images not shown).

Dosimetry and follow-up

Result phantom study

A threshold of 30% of the maximum voxel value was chosen based on our phantom study because it provided an underestimation of the volume in all spheres (**Figure 1A**). Using this threshold, the absorbed dose in only the smallest sphere (0.5 ml) was underestimated (**Figure 1B**; due to simultaneous underestimation of the activity). This was deemed irrelevant from a clinical point of view, because the earlier

published study with ^{99m}Tc-MAA data had no depositions smaller than 1 ml in a larger patient population [3].

Patient data

Based on the ^{166}Ho scout dose SPECT/CT, the absorbed dose on extrahepatic tissues by the scout dose was assessed (**Table 4**). Calculations in these patients showed a median extrahepatic deposition volume of 15.3 ml (range 9.2 – 35.5 ml) and median absorbed dose of 3.6 Gy (range 0.3 – 13.8 Gy). The maximum absorbed dose to extrahepatic tissues was 13.8 Gy. The used method conservatively underestimated the volume of the deposition to reduce the risk of underestimating the absorbed dose. Although extrahepatic depositions of ^{166}Ho occurred, the resulting absorbed doses were estimated to be at most 14 Gy.

The extrahepatic deposition in patient 1, depicted in **Figure 2**, was also seen on the prior ^{99m}Tc-MAA SPECT/CT and the culprit vessel was unidentified at the time of treatment (only identified after focused retrospective reviewing). Patient 1 was treated at that time, because she had no other therapeutic options and had very aggressive disease. Within several days, the patient developed abdominal pain (maximum CTCAE grade 4) and the post-treatment SPECT/CT showed the same extrahepatic deposition in the duodenum. Using the same quantitative SPECT-reconstruction method for the post-treatment imaging, a radiation absorbed dose in the duodenum of 134.5 Gy was calculated. Endoscopy revealed an inflamed duodenal wall, which fitted a radiation induced (non-erosive) duodenitis. No severe complication (e.g. perforation) occurred. Her duodenitis recovered after six weeks and she passed away four months after treatment due to progressive disease.

The extrahepatic deposition in the falciform ligament in patient 6, depicted in **figure 7**, was deemed irrelevant and the patient was treated the same day without ice packing of the abdominal skin. No clinical complications occurred (e.g. radiation dermatitis) during follow-up. Using the same quantitative SPECT-reconstruction method for the post-treatment imaging, a radiation absorbed dose in the falciform ligament of 33.5 Gy was calculated. Four months after the treatment, the patient started a new chemotherapeutic regimen due to progressive disease and was lost to follow-up.

Table 4. Patients with an extrahepatic deposition of a ^{166}Ho scout dose

Patient (figure)	Age	Primary tumour	Location	Culprit vessel	Treated	Target volume*	Activity (MBq)	Estimated Dose (Gy)
1 (2)	63	Intrahepatic cholangiocarcinoma	Duodenum	Posterior superior pancreatico-duodenal artery	Yes	13.9	1.3	1.4
2 (3)	80	Sigmoid carcinoma	Lesser curvature of the stomach	Right gastric artery	No	35.5	33.1	13.8
3 (4)	63	Colon carcinoma	Duodenum	Supraduodenal artery	Yes	15.4	2.3	2.2
4 (5)	62	Pancreas adenocarcinoma	Duodenum	Intrahepatic collateral	No	15.3	3.7	3.6
5 (6)	56	Neuroendocrine tumour	Gastric fundus	Accessory left gastric artery	Yes	9.6	7.4	11.7
6 (7)	60	Colon carcinoma	Falciform ligament	Falciform artery	Yes	9.2	0.2	0.3

Extrahepatic deposition (in ml) was based on the 30% threshold of the phantom study (see **figure 1)*

Discussion

As shown in this study, no clinical adverse events occurred that were related to the use of a ^{166}Ho scout dose. Common adverse events related to the angiography table or procedure were seen and are similar to those seen in ^{99m}Tc-MAA related procedures. In patients with extrahepatic depositions of the scout dose, a maximum of 14 Gy in extrahepatic tissues was calculated. Although the calculated 14 Gy was overestimated due to the overestimation of the deposited activity and underestimation of the extrahepatic deposition volume, this absorbed dose was far below the limit of 49 Gy as suggested by Kao et al [13; 14]. These clinical results of the ^{166}Ho scout dose confirm the previously published safety assumptions based on theoretical evaluation using ^{99m}Tc-MAA data [3]. However, the limit of 49 Gy suggested by Kao et al. is based on just 2 patients [13; 14]. Additionally, the absorbed dose in extrahepatic tissue is being discussed in literature, as the limits could be even higher depending on the extrahepatic tissue type. In six porcine models, absorbed doses greater than 50 Gy (up to 92 Gy) in the gastric fundus showed mucosal haemorrhage or small (healed) superficial ulcers without a severe complication (e.g. perforation) [15]. Nonetheless, dose limitations for different tissue types need to be investigated further.

Based on the HEPAR and HEPAR 2 data, using a ^{99m}Tc-MAA procedure prior to the ^{166}Ho scout dose procedure, the use of ^{166}Ho scout dose alone for radioembolization assessment was deemed safe. Along with the suspected limited extrahepatic tissue dose and its safety, both supported by this study, we have skipped the ^{99m}Tc-MAA procedure in more recent studies with ^{166}Ho microspheres, namely the SIM and HEPAR PLUS study [6; 7].

Using ^{166}Ho microspheres as a scout dose could benefit patients. The variation in intrahepatic distribution between the scout dose and treatment dose is expected to be minimal, due to the identical morphology of the microspheres. This is important for accurate intrahepatic dosimetry, especially when using the so-called 'partition calculation method' or voxel-based dosimetry, which is based on SPECT/CT of the scout dose distribution [16]. Currently, it is known that a large intrahepatic variability between ^{99m}Tc-MAA and ^{90}Y microspheres exists, probably influenced by many factors, including tumour type and burden, particle flow dynamics and catheter positioning, but also particle morphology [2; 16; 17]. Additionally, unlike ^{99m}Tc-MAA and free pertechnetate, ^{166}Ho does not freely circulate in vivo. No unwanted uptake of activity in the stomach wall, kidneys, thyroid and lungs occurs. Due to its identical particle morphology and the absence of freely circulating ^{166}Ho, a ^{166}Ho

scout dose is superior in lung shunt fraction calculation compared to ^{99m}Tc-MAA [1]. As shown by Elschot et al. with SPECT/CT data, ^{99m}Tc-MAA may overestimate the lung shunt fraction up to 170% when compared to ^{166}Ho microspheres. Yu et al. also showed a significant overestimation of the lung shunt fraction by ^{99m}Tc-MAA using standard planar scintigraphy compared to SPECT/CT [18]. Considering their data, most patients with a lung shunt fraction of >20% on planar ^{99m}Tc-MAA imaging are wrongfully refused for radioembolization treatment, which can be overcome by the use of ^{166}Ho scout dose.

The use of ^{166}Ho microspheres scout dose imaging is safe, could lead to more reliable pre-treatment imaging and subsequently to improved individualized treatment planning. Another benefit of holmium is its large magnetic susceptibility (typical for most lanthanides), which may enable MRI-based dosimetry [19] and MR-guided treatments [20] in the future. Once MRI-based dosimetry is adequately developed, the scout dose may eventually be replaced for the stable, non-radioactive ^{165}Ho microspheres.

The main limitation of this study was the fact that safety analysis was limited by the number of events. However, theoretical and clinical analysis concordantly showed an acceptable low risk of toxicity. An additional limitation was the use of a pre-treatment angiography procedure with ^{99m}Tc-MAA prior to the ^{166}Ho scout dose procedure in the HEPAR and HEPAR 2 trials, resulting in a selection bias as 5 patients were excluded based on ^{99m}Tc-MAA findings. Four patients were excluded based on a ^{99m}Tc-MAA extrahepatic deposition and one patient was excluded based on a ^{99m}Tc-MAA lung shunt of 26.5%. Additionally, microcatheter positioning was altered based on the ^{99m}Tc-MAA-SPECT/CT in another patient, to prevent an unwanted gallbladder deposition.

The calculation of absorbed dose is prone to the same limitations as described in the earlier publication [3]; The 30% threshold was based on a homogenous activity distribution in the spheres of our phantom versus a more heterogeneous accumulation of activity in extrahepatic depositions. Additionally, the phantom study is an ideal situation without breathing artefacts or patient movements.

In none of the six patients with an extrahepatic deposition of ^{166}Ho microspheres C-arm CT's were performed prior to injection of the scout dose. Without the use of C-arm CT's, up to 6.5% of the cases still have an extrahepatic deposition on the SPECT/CT, when DSA is negative [21].

The introduction of improved pre-treatment CT imaging and C-arm CT during the radioembolization procedures has probably contributed to a decrease in the number (and probably also extent of) of extrahepatic depositions [16]. The use of the C-arm CT has improved the detection of potential culprit vessels during the angiography procedure. The use of scout dose SPECT/CT is therefore debated in literature [22-24]. Nonetheless, once both DSA and C-arm CT are negative, the use of ^{166}Ho microspheres for the detection of extrahepatic depositions becomes even safer.

Additionally, the 81 keV gamma-emitting properties of ^{166}Ho make dual-isotope imaging with ^{99m}Tc compounds possible. We have developed a dual-isotope protocol using ^{166}Ho scout dose and ^{99m}Tc stannous phytate, respectively for microspheres distribution and healthy liver parenchyma delineation [25]. Using this combination, dose-volume-histograms of healthy liver parenchyma can be easily calculated and allows the physician to calculate the maximum, safe to use therapeutic dose in a patient. The main advantage is the quick insight in the dose to healthy liver parenchyma, which is the main limiting factor in all radioembolization treatments.

Conclusion

This study clinically supports the previously stated hypothesis that the use of ^{166}Ho microspheres as a scout dose (250 MBq) prior to radioembolization is a safe alternative for ^{99m}Tc-MAA.

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Chapter 10

Simultaneous ^{166}Ho/^{99m}Tc dual isotope SPECT with Monte Carlo-based down-scatter correction for automatic liver dosimetry in radioembolization

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Submitted for publication

Abstract

Background

Intrahepatic dosimetry is paramount to optimize radioembolization treatment accuracy using radioactive holmium-166 microspheres (^{166}Ho). This requires a practical protocol that combines quantitative imaging of microsphere distribution with automated and robust delineation of the volumes of interest. To this end, we propose a dual isotope SPECT protocol based on ^{166}Ho therapeutic microspheres and technetium-99m (^{99m}Tc) stannous phytate, which accumulates in healthy liver tissue. This protocol may allow accurate and automatic estimation of tumor absorbed dose and healthy liver absorbed dose. The current study focuses on a Monte Carlo based reconstruction framework that inherently corrects for scatter cross talk between the ^{166}Ho and ^{99m}Tc imaging., To demonstrate the feasibility of the method it is evaluated with realistic phantom experiments and patient data.

Methods

The Utrecht Monte Carlo System (UMCS) was extended to include detailed modeling of crosstalk interactions between ^{99m}Tc and ^{166}Ho. First, ^{99m}Tc images were reconstructed including energy window-based corrections for ^{166}Ho-downscatter.. Next, ^{99m}Tc-downscatter in the 81 keV ^{166}Ho window was Monte Carlo simulated to allow quantitative reconstruction of the ^{166}Ho images. The accuracy of the ^{99m}Tc downscatter modeling was evaluated by comparing measurements to simulations. In addition the ratio between ^{99m}Tc and ^{166}Ho yielding the best ^{166}Ho dose estimates was established and the quantitative accuracy was reported.

Results

^{99m}Tc contributes twice as many counts to the 81 keV window than ^{166}Ho, and four times as many counts to the 140 keV window, thus a ^{166}Ho/^{99m}Tc ratio of 5:1 yielded a high accuracy in both ^{166}Ho and ^{99m}Tc reconstruction. Phantom experiments revealed that the accuracy of quantitative ^{166}Ho activity recovery was reduced by 10% due to the presence of ^{99m}Tc. Twenty iterations of the dual-isotope SPECT/CT was considered feasible for clinical practice. Applicability of the proposed protocol was shown in a proof-of-concept case.

Conclusion

A novel ^{166}Ho/^{99m}Tc dual-isotope protocol for automatic dosimetry, compensates accurately for downscatter and allows for the addition of ^{99m}Tc without compromising ^{166}Ho SPECT image quality.

Introduction

Radioembolization has rapidly developed over the past decade. Conventionally the injected activity is calculated used either body surface area based (BSA) or target volume based activity calculation methods for the commercially available resin and glass yttrium-90-loaded microspheres, (respectively SirSpheres® from Sirtex Medical and Therasphere® from BTG International). These methods are applied under the assumption that microsphere distribution is homogenous in the treated volume. However, due to patient characteristics and especially the heterogeneity of the microsphere distribution, these methods are too simplistic to allow for reliable dosimetry. In recent years, more and more centers have adopted the partition model, defining a tumor and non-tumor compartment, and allowing more personalized activity calculation by comparison to minimal required tumor dose and maximum allowable healthy liver dose from literature. Although much more accurate, the downside of the partition model is the delineation of the compartments, which is usually done manually. This can be cumbersome and hampers clinical widespread adoption. An automatic protocol could solve this. For radioembolization treatments with holmium-166-loaded (^{166}Ho) microspheres (Quiremspheres®, Quirem Medical), we propose a dual isotope SPECT/CT protocol using pretreatment ^{166}Ho scout dose as treatment simulation and technetium-^{99m} stannous phytate (a radiocolloid) for healthy liver tissue delineation.[1] ^{99m}Tc-stannous phytate only accumulates in Kupfer cells by phagocytosis of the stannous phytate particle. As Kupfer cells are absent in tumorous tissue, this radiopharmaceutical has been used for many decades for the detection of liver disease and liver malignancies. The main advantage of simultaneous SPECT acquisition of both the treatment simulation with ^{166}Ho microspheres and healthy liver tissue segmentation with ^{99m}Tc-colloid is the absence of miss registration, due to patient related factors. This manuscript will focus on the technical challenges concerning image acquisition and reconstruction with this dual isotope protocol, mainly being the detection of cross talk of the two isotopes. Accurate quantitative reconstruction of ^{166}Ho SPECT has been demonstrated in previous work by Elschot et al. [2], but the presence of ^{99m}Tc during the acquisition causes a significant contamination in the ^{166}Ho energy window. Vice versa, the ^{99m}Tc photo peak window is contaminated due to downscatter from high energy ^{166}Ho emissions. This crosstalk interaction is illustrated in **figure 1**, depicting an energy spectrum of both ^{166}Ho and ^{166}Ho+^{99m}Tc. The Utrecht Monte Carlo System (UMCS) was extended to be able to correct for these cross talk interactions.

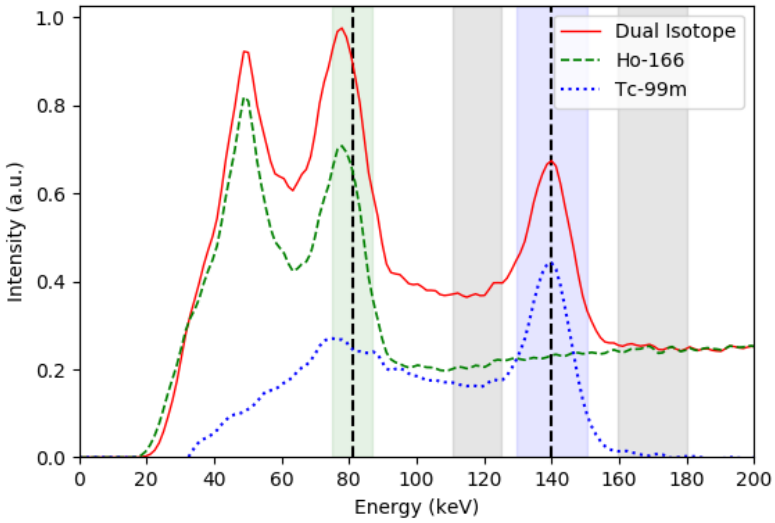

Figure 1. ^{166}Ho-only spectrum of a patient scan (dashed green line), dual-isotope spectrum of the same patient after administration of ^{99m}Tc (solid red line), difference between the two spectra, representing ^{99m}Tc-only (dotted blue line). Recorded energy windows are shaded. Both isotopes contribute a significant amount of scatter to one another's photo peak window.

Materials and methods

Implementation of the photon modelling

In previous work, Elschot et al. demonstrated an iterative OSEM reconstruction method (Utrecht Monte Carlo System, UMCS) for quantitative ^{166}Ho SPECT, which includes the Monte Carlo based modeling of photon contributions from the full ^{166}Ho energy spectrum, including bremsstrahlung [2]. In short, besides Compton and photo-electric effects in the patient, fast simulation of all collimator and crystal effects was accomplished by incorporating a look-up-table of Point Spread Functions (PSF), which was generated that MCNP6 simulations, a general purpose Monte Carlo radiation transport code [3]. For this work, this method was extended to include the effect of ^{99m}Tc-downscatter in the 81 keV photopeak window of ^{166}Ho in a similar fashion. The PSF as detected in the 81 keV (15% width) energy window depends on the energy of the photons before the detection and the distance to the collimator. To represent this, multiple PSFs were simulated for the Siemens Symbia Medium Energy collimator at source-detector distances of 1 cm, 5 cm, 12 cm, 24 cm and 40 cm. PSFs for intermediate distances are interpolated at runtime. In order to restrict computation time, 8 specific energies are applied to cover the full energy spectrum. Each photon is associated with a PSF, determined by its

energy as illustrated in **table 1**. These PSFs represent photons that have an initial energy outside the 81 keV window and require a collimator or detector interaction (e.g. partial energy deposition, lead x-ray emission) to generate a detection. In addition to the PSFs for these indirect detections, a separate PSF was generated to represent photons that are 'directly' detected, i.e., photons that have an energy in the 81 keV window (e.g. after scattering in the patient). These events are weighted by the detection probability, determined by the energy of the photon relative to the energy window and the energy resolution of the gamma camera.

Table 1: UMCS photon energies and their associated PSF (denoted by the pre-simulated source energy) for detection in the 81 keV (15% width) energy window.

Photon Energy (keV)			Associated PSFs
60	-	88	81
88	-	106	95
106	-	129	118
129	-	154	140
154	-	226	170
226	-	462	300
462	-	992	713
992	-	2000	1379

Image reconstruction and validation

Image reconstruction with UMCS of a dual isotope acquisition was performed in three consecutive steps:

- ^{99m}Tc reconstruction: crosstalk of ^{166}Ho in the 140 keV ^{99m}Tc photo peak window was corrected for during iterative reconstruction by addition of an upper scatter window (170 keV, k-factor 0.93, excluding window-widths).
- ^{99m}Tc downscatter: using the ^{99m}Tc reconstruction projection images of ^{99m}Tc downscatter into the 81 keV ^{166}Ho photo peak window were Monte Carlo simulated as described above.
- ^{166}Ho reconstruction: crosstalk from ^{99m}Tc was corrected for by adding the simulated ^{99m}Tc downscatter projections during iterative reconstruction of ^{166}Ho.

Evaluation

The cross talk simulation and performance of the image reconstructions were assessed by conducting and comparing phantom studies. A ^{99m}Tc line source centered between two 40 x 40 x 10 cm^3 slabs of PMMA scatter material and a 6.3L cylindrical phantom, filled with 50 MBq ^{99m}Tc, were scanned on a Siemens Symbia T16 SPECT/CT, recording the clinically used energy windows of both ^{99m}Tc (140 keV, 15% width) and ^{166}Ho (81 keV, 15% width), along with two scatter windows centered at 118 keV and 170 keV (widths 12%). The recorded projections of both phantoms were compared with simulated projections of a digital phantom (of equal shape and activity, based on the attenuation CT image of the setup) to assess quantitative accuracy of the ^{99m}Tc-downscatter simulations (i.e., the extent to which ^{99m}Tc contaminates the 81-keV ^{166}Ho photo peak window). Projections of the ^{99m}Tc line source were used to validate the shape of the PSFs corresponding to ^{99m}Tc-downscatter in the 81 keV energy window.

Determination of the ^{166}Ho – ^{99m}Tc activity ratio

To define a practical balance between the amount of administered ^{166}Ho and ^{99m}Tc, an anthropomorphic torso phantom was measured. Within the 1200 ml water filled liver compartment of the phantom, a 130 ml insert was placed containing a 53 MBq ^{166}Ho solution. Two scans were performed: in the first scan the phantom contained ^{166}Ho only, for the second scan 35 MBq ^{99m}Tc was added to the liver compartment. The data was reconstructed with our protocol and analyzed for quantitative accuracy for both the ^{166}Ho only and the dual isotope scan. A clinically acceptable ^{166}Ho / ^{99m}Tc activity ratio was defined, based on the results of the latter phantom study and on a visual interpretation and consensus reading by two nuclear medicine physicians and a medical physicist.

Quantitative assessment

The quantitative reconstruction accuracy of a ^{166}Ho activity distribution is dependent on the size of the distribution and is further influenced by the presence of ^{99m}Tc. The NEMA Image Quality (IQ) phantom was used to determine the sphere size based activity recovery for three different ^{99m}Tc background concentrations. The six spheres in the NEMA IQ phantom (diameters: 10, 13, 17, 22, 28 and 37 mm, volumes: 0.52, 1.15, 2.6, 5.6, 11.5, 26.5 ml) were filled with a 0.8 MBq/ml ^{166}Ho solution and three acquisitions were performed with varying ^{99m}Tc activity concentrations in the background compartment (0, 6 and 11 kBq/ml). The phantom was partially filled with agar-agar to reduce the total volume of the background compartment (5.5 L instead of the conventional 9.7L), in order to obtain a ratio between the total

activity and the activity concentration that resembles a clinical situation more closely. Images of the ^{166}Ho activity distribution were reconstructed using the dual isotope reconstruction protocol described above. The radii of the VOIs of the NEMA phantom spheres were also increased by 1 cm, to limit spill-out due to the partial volume effect, to assess its effect on ^{166}Ho activity recovery. Activity Recovery Coefficients (ARCs) were computed for all spheres and for each iteration in the reconstruction (100 iterations using 8 subsets of 15 projections) to investigate the influence of the number of iterations on the quantitative accuracy of the reconstruction protocol.

Proof of concept in clinical setting

If a patient is a candidate for radioembolization, first a visceral angiography is performed to assess the arterial blood supply of the liver and tumors. During the same angiography, positioning of the microcatheter for a radioembolization treatment is determined by the interventional radiologist. To simulate the actual radioembolization treatment, a scout dose of 250 MBq ^{166}Ho-microspheres is administered in the pre-determined microcatheter positions. Subsequently, a SPECT/CT is acquired to assess treatment safety (i.e. excluding extrahepatic depositions of activity) and assess the intrahepatic distribution of the particles for treatment dosimetry. As part of a prospective clinical study (HEPAR PLUS), informed consent for the acquisition of the proposed dual-isotope SPECT/CT in a patient was obtained [4]. After a regular ^{166}Ho scout dose procedure (with 250 MBq), a ^{166}Ho-only SPECT/CT was acquired. Subsequently ten minutes after intravenous injection of 50 MBq ^{99m}Tc-stannous phytate, a dual isotope SPECT/CT was acquired. The imaging protocol of the dual-isotope SPECT/CT was based on the results of our phantom study.

Results

Projection images of the ^{99m}Tc line source in the 81 keV and 140 keV energy windows were simulated and compared with the measured projection images (**Figure 2**). Comparing the number of counts in the 81 keV window (C81) with the number of counts in the 140 keV window (C140), the simulation underestimated C81 / C140 by 8% (0.59 simulated versus 0.64 measured).

Quantitative accuracy of the ^{99m}Tc forward projections in the 140 keV and the 81 keV window was also assessed using the cylindrical phantom. A homogeneous activity distribution was imposed inside the digital phantom, matching the total activity as measured in a dose calibrator (**figure 2**). The simulated projections overestimated

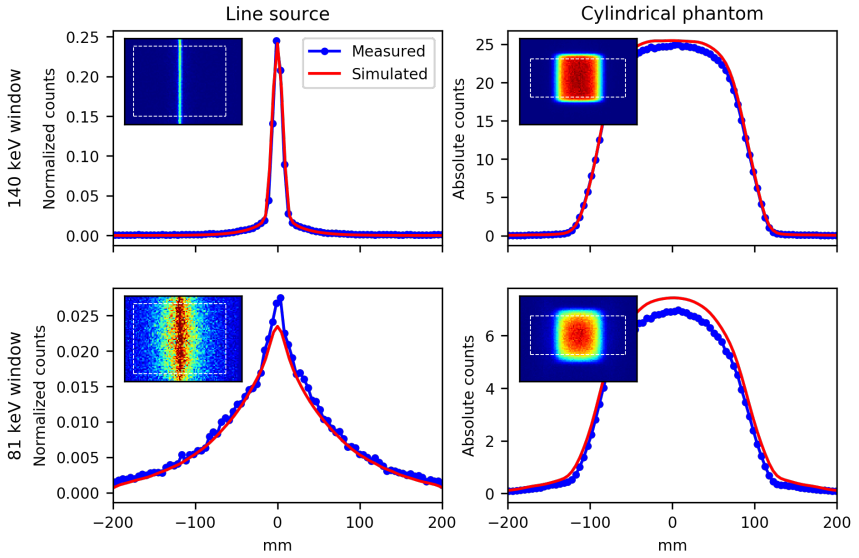

Figure 2. Line profiles of a ^{99m}Tc line source (images on the left) and ^{99m}Tc cylindrical phantom (images on the right), with the corresponding projections in the upper left corners. Both recorded in the 140 keV energy window (top) and the 81 keV energy window (bottom). The line profiles were obtained by summing along the length of the line source as indicated by the dashed box. All profiles were scaled to normalize the summed intensity in the 140 keV window, for the measurement and simulation independently. The projection images were averaged over all angles (120 angles over a 360 degree rotation), and subsequently averaged over the length of the phantom as indicated by the dashed markers, resulting in the line profiles

the counts in the 140 keV energy window by 3.5%, and the counts in the 81 keV window by 10.7%. Since no cross-calibration was performed between the dose-calibrator and the scanner, the simulated projections were intrinsically quantitative (i.e. unscaled).

The SPECT/CT of the anthropomorphic phantom (**figure 3**) showed that, for an equal amount of activity, ^{99m}Tc contributes approximately twice as many counts to the 81 keV window than ^{166}Ho, and approximately four times as many counts to the 140 keV window. These numbers depend on the distribution of the isotopes, acquisition angle and on the geometry of the patient. Based on the results of the anthropomorphic phantom study and the consensus reading, a clinical activity ratio of 5:1 (250 MBq ^{166}Ho : 50 MBq ^{99m}Tc) was chosen. Thus, counts contributing to the 81 keV window are mostly due to ^{166}Ho (5:2), while at the same time the intensity in the 140 keV window is approximately balanced between ^{166}Ho and ^{99m}Tc (5:4). The quantitative accuracy of the ^{166}Ho only reconstruction was 7% (overestimated). Addition of ^{99m}Tc in the liver compartment further reduced the accuracy to 14%.

The reconstructed ^{166}Ho images of the NEMA IQ phantom were analyzed by defining Volumes of Interest (VOIs) over the spheres that matched the actual sphere sizes, **Figure 3**. **Figure 4** shows the ARCs for the six spheres in which the expected activity is based on the dose-calibrator measurements (used as ground truth).

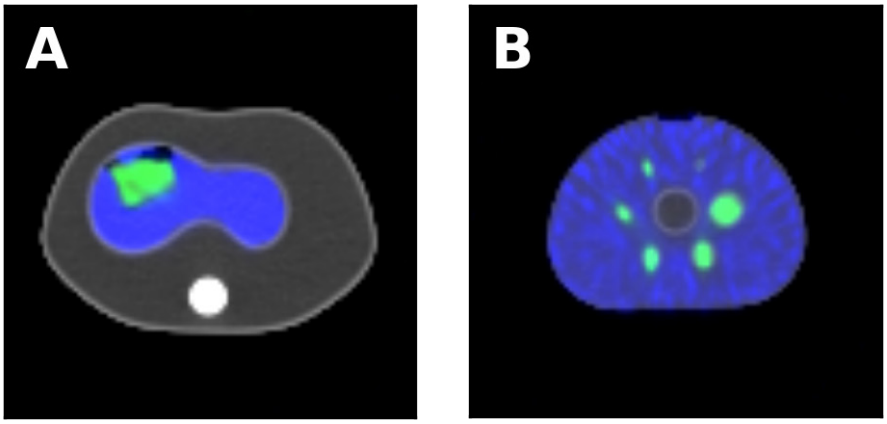

Figure 3. Dual isotope SPECT reconstructions (^{166}Ho in green, ^{99m}Tc in blue) fused with the accompanying CT images (grayscale). A) Anthropomorphic torso phantom with the 1200 ml liver compartment filled with a 34 kBq/ml ^{99m}Tc solution. A 130 ml insert, filled with a 409 kBq/ml ^{166}Ho solution, was placed inside of the liver compartment. The remaining volume of the phantom was filled with water. B) NEMA Image Quality phantom, background filled with a 11 kBq/ml ^{99m}Tc activity concentration. The spheres were filled with a 0.8 MBq/ml ^{166}Ho solution.

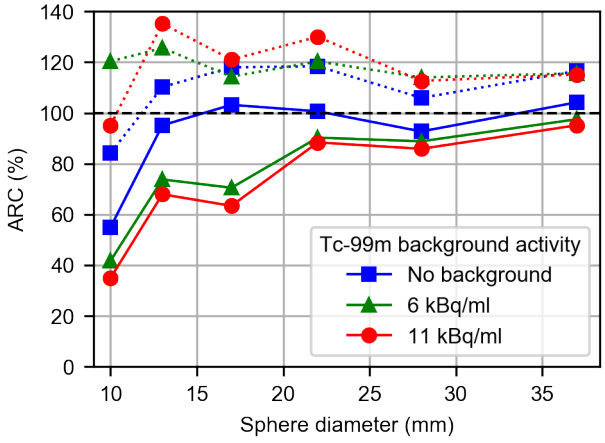

Figure 4. Recovered activity as a fraction of the known injected activity for ^{166}Ho filled spheres in the NEMA Image Quality phantom, after 20 iterations (8 subsets). Three subsequent acquisitions were performed with ^{99m}Tc background activity concentrations of 0, 6 and 11 kBq/ml (squares, triangles and circles respectively). Mean activity concentrations were measured in volumes of interest (VOIs) matching the actual sphere sizes (solid lines), and in VOIs with diameters increased by 20 mm (dashed lines).

In this phantom study, activity recovery was highest for the ^{166}Ho only images, i.e. addition of ^{99m}Tc decreased the activity recovery. However, when the radii of the VOIs were increased by 1 cm adding ^{99m}Tc increased the apparent ^{166}Ho activity.

Figure 4 shows the rate of convergence for three different sphere sizes and the dependence on ^{99m}Tc background activity concentration. All ARCs were normalized to the ARC after 100 iterations (not shown in **figure 5**). Based on these results, 20 iterations were found to provide an acceptable degree of convergence for all but the smallest spheres.

Visual interpretation of the ^{166}Ho-only SPECT/CT and the ^{166}Ho reconstruction of the dual isotope SPECT/CT in the patient setting showed no differences, as shown in **figure 6**.

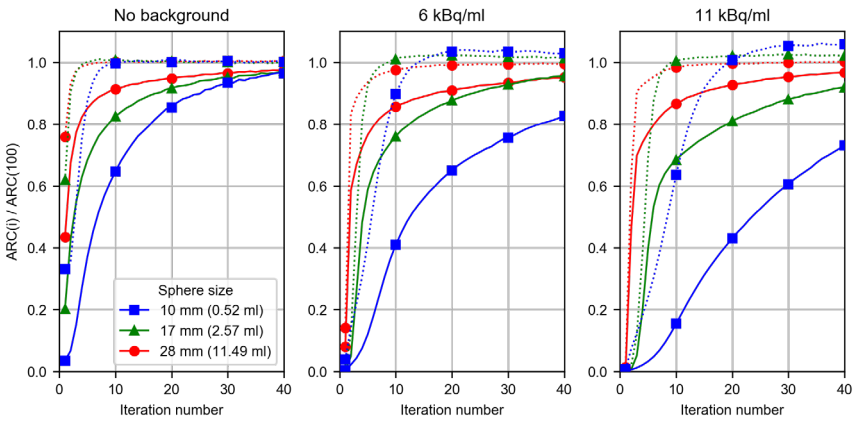

Figure 5. Recovered activity fraction as a function of the number of UMCS-OSEM iterations (8 subsets), normalized to the activity recovery after 100 iterations, ^{166}Ho filled spheres in the NEMA Image Quality phantom with various background concentrations of ^{99m}Tc. Solid lines: VOIs matching actual sphere sizes. Dotted lines: VOIs 20 mm larger diameter than the sphere sizes. For clarity, results of only 3 out of the 6 NEMA IQ phantom spheres are shown.

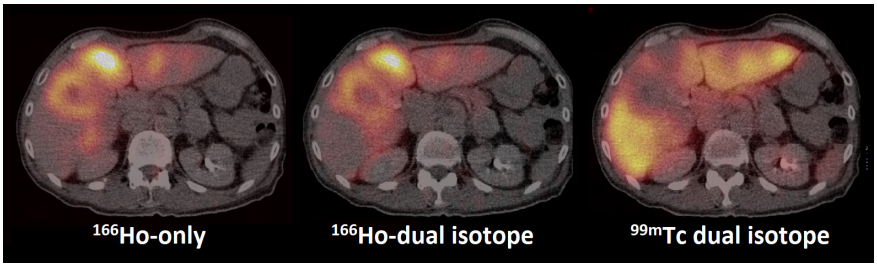

Figure 6. Fused ^{166}Ho-only SPECT/CT (left), ^{166}Ho-reconstruction SPECT/CT from dual isotope acquisition (middle) and corresponding ^{99m}Tc-stannous phytate reconstruction SPECT/CT from a dual isotope acquisition (right) in a patient. Visual assessment of the images by two nuclear medicine physicians shows no differences and the ^{99m}Tc stannous phytate SPECT/CT shows a negative correlation (no uptake in tumor tissue, only uptake in healthy liver tissue).

Discussion

A quantitative reconstruction framework for dual isotope scanning of ^{166}Ho with ^{99m}Tc seems feasible for clinical use. With an appropriate reconstruction method, 250 MBq ^{166}Ho scout dose and 50 MBq ^{99m}Tc-stannous phytate can be used for simultaneous treatment simulation and healthy liver tissue delineation.

Based on a previous publication by Lam et al in 2013, the combination of a pre-treatment simulation SPECT/CT with ^{99m}Tc-MAA and physiological healthy liver tissue delineation with ^{99m}Tc sulphur colloid SPECT/CT seemed feasible [5]. ^{99m}Tc labeled radiocolloids only accumulate in healthy liver tissue via phagocytosis of the colloid particle by Kupfer cells [6]. As Kupfer cells are absent in tumorous tissue, this allows an easy differentiation between tumorous and healthy liver tissue. In the study protocol by Lam et al, healthy liver tissue was delineated on the ^{99m}Tc- sulphur colloid SPECT/CT using a 10% threshold of the maximum pixel value, and on the ^{99m}Tc-MAA SPECT/CT liver tissue below a 10% threshold was simplified to zero (i.e. 'non-irradiated functional liver tissue'). By subtraction of both images with the according thresholds, four different compartments (based on physiological data) could be defined; irradiated tumor, irradiated healthy liver tissue, non-irradiated healthy liver tissue and tumor necrosis. In the population of 122 patients treated with ^{90}Y-loaded microspheres, clinical toxicity data was correlated to the absorbed dose in healthy liver tissue [5].

However, the combination of ^{99m}Tc-MAA and ^{99m}Tc sulphur colloid is impractical, mainly because of the separate acquisition of the two SPECT/CT's. The main advantage of having simultaneous SPECT acquisition of both the treatment

simulation with ^{166}Ho microspheres and healthy liver tissue segmentation with ^{99m}Tc-colloid in the current protocol is the absence of miss registration of the SPECT's.

The advantage of the ^{99m}Tc-colloid SPECT is the potential to improve image segmentation [5]. Inter-observer differences caused by manual delineation may be avoided, which is known to results in variations and additional errors in dosimetry [5]. Research on (semi-)automated segmentation of dual-isotope SPECT images is being conducted.

The importance of dosimetry has been emphasized after the negative results of large prospective trials, that used simplified single compartment activity calculations methods [7-10]. In the SIRFLOX, FOXFIRE and FOXFIRE Global studies colorectal carcinoma patients receiving first-line chemotherapy were randomized to receive additional radioembolization. Treatment activity was calculated based on a modified BSA-method [7]. In the combined analysis of those three studies, the primary endpoint of overall survival was not reached. Several other smaller studies in colorectal carcinoma patients have shown a clear tumor absorbed dose – tumor response correlation and overall survival correlation [11, 12]. To our knowledge, dosimetric analysis of the data of the SIRFLOX, FOXFIRE and FOXFIRE Global has not been performed, which is of paramount importance to make a proper judgement on the value of radioembolization in the first-line setting, combined with chemotherapy [7, 8]. In the SARAH trial, radioembolization was compared to sorafenib in advanced hepatocellular carcinoma (HCC) and treatment activity calculation was again based on the BSA-method [9, 10]. The SARAH trial did not reach its primary endpoint of overall survival benefit either. However in a post-hoc dosimetric analysis, performed in a subset of patients, a clear tumor absorbed dose – overall survival correlation was found [13, 14]. Patients receiving a tumor absorbed dose of ≥100 Gy had a significant longer median overall survival of 14.1 months (95% confidence interval 9.6-19) compared to patients receiving <100 Gy (6.1 months; 95% confidence interval 4.9-6.8; $p<0.0001$) [13].

Furthermore, ^{99m}Tc-MAA is known to be a poor predictor of intrahepatic distribution of microspheres [15, 16]. To bring pre-treatment dosimetry to a higher level, a more predictive particle is needed. In previous studies, the use of a small amount of ^{166}Ho microspheres with an activity of 250 MBq, was determined to be safe and superior to ^{99m}Tc-MAA [16-21].

There are several limitations to our reconstruction protocol. In the current protocol, patient breathing was not accounted for. Patient breathing is known to result in

an underestimation of actual activity depositions and blurs SPECT/CT images [22]. This issue may be resolved by applying breath gating during image acquisition, although this feature is currently not supported on our SPECT/CT imaging devices. The acquisition time is similar to the widely applied ^{99m}Tc-MAA SPECT, however the post-processing computation time is approximately 3 minutes per iteration on a regular desktop PC for ^{166}Ho. Based on our findings, 20 iterations were clinically acceptable in a daily workflow. The results of this technical study are very promising, however this dual-isotope protocol needs additional research on its applicability in the clinical setting.

By optimization of treatment prediction via the use of identical particles for both pre-treatment simulation as well as treatment itself, radioembolization can become more individualized. The presented dual-isotope protocol may allow physicians and physicists to acquire all relevant dosimetric parameters in a single SPECT/CT acquisition.

Additionally, (semi-)automated voxel-based dosimetric assessment for treatment activity calculation will become available, instead of using the current widely applied single compartment calculation methods (BSA-method or MIRD), with their known major limitations [9, 23]. Common errors made in current dosimetric analyses, mainly based on miss registration, can be reduced by simultaneous acquisition.

The future success of radioembolization depends on the balance between treatment efficacy, defined by the tumor absorbed dose, and treatment toxicity defined by healthy liver tissue absorbed dose. Maximizing the healthy liver tissue absorbed dose will increase the tumor absorbed dose compared to the current single compartment models, and is likely to improve treatment outcomes. Even though the maximum threshold for the healthy liver tissue absorbed dose still needs to be defined for ^{166}Ho microspheres, future patients should be treated according to the acceptable healthy liver tissue absorbed dose threshold, introducing individualized activity planning for radioembolization treatment.

Conclusion

A realistic quantitative reconstruction framework for dual isotope scanning of ^{166}Ho and ^{99m}Tc was successfully developed and seems feasible for clinical practice. This dual isotope protocol may resolve several technical issues in radioembolization dosimetry.

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Chapter 11

Future directions and discussion

The aim of this thesis was to gain more insight into the application of radioembolization in the treatment of neuroendocrine liver metastases. To start off, one should be familiar with the many aspects of a radioembolization procedure. In general, one should be familiar with the differences of the three commercially available products, as described in **table 1**. Besides the materials used, the biggest difference between the particles is the specific activity (i.e. Bq per microsphere), resulting in a different number of particles used for treatment. In theory, a specific product may be more appropriate for a specific indication than another. When fewer particles are used, the administration becomes easier because of a limited embolic effect. The limited embolic effect reduces the chance of inducing stasis or reflux, avoiding extrahepatic complications. Besides, fewer particles allows for treatment of smaller liver volumes with a sufficient absorbed dose because of the higher specific activity. The downside of having a limited number of particles is its heterogeneous distribution within the liver, especially present in patients with bulky, hypervascular liver tumors, which may cause suboptimal tumor coverage in terms of dose distribution. Another essential difference is the isotope used. Two products use yttrium-90 (^{90}Y) as a pure beta-emitting isotope. ^{90}Y is a commonly used therapeutic isotope, but unfortunately has poor characteristics for imaging. ^{90}Y bremsstrahlung SPECT lacks resolution and is blurry because of scatter. The alternative, ^{90}Y PET, is very noisy and difficult to interpret because of the limited number of positrons (i.e. 32 per million decays). As the field moves towards personalized imaging and dosimetry, a clinical need for a more useful isotope for both imaging and therapy exists. Holmium-166 (^{166}Ho) is an available alternative, with similar beta-particle energy. However, its additional gamma-emission of 81 keV allows for more accurate SPECT imaging and, being a lanthanide, can be used for magnetic resonance imaging (MRI). Adequate imaging is of vital importance in radioembolization. Currently, in most centers it is only used to predict and determine treatment safety (i.e. excluding extrahepatic depositions and lung shunting). However, to reach actual treatment personalization, more parameters need to be derived, including intrahepatic evaluation of dose distribution. A major advantage of ^{166}Ho-microspheres is the use of identical particles for pre-treatment simulation and treatment, as discussed in **chapter 9**.

Table 1. Characteristics of the different commercially available microspheres

Microsphere	TheraSphere®	SIR-Spheres®	Quirem-spheres®
Radionuclide (T½ in hours)	^{90}Y (64.1)	^{90}Y (64.1)	^{166}Ho (26.8)
$E_{\beta max}$ in MeV (yield)	2.28 (99.9%)	2.28 (99.9%)	1.77 (48.7%), 1.85 (50.0%)
E_{γ} in keV	2x 511 (<0.1%)	2x 511 (<0.1%)	80.6 (6.7%)
Microspheres	Glass	Resin	Poly(L-)lactic acid
Density (g/ml)	3.3	1.6	1.4
Diameter (μm)	25 ± 10	32 ± 10	30 ± 5
Scout dose	^{99m}Tc-MAA	^{99m}Tc-MAA	^{166}Ho (or ^{99m}Tc-MAA)
Scout dose particle amount	1-2 million	1-2 million	3 million (1-2 million)
Relative pressure for infusion	High	Low	Low
Relative embolic potential	Low	High	Moderate
Activity per microsphere (Bq)	1,250-2,500	50	330-450
Therapy dose particle amount	1.2 - 5 million	50 million	10-20 million
Contrast injection during infusion	Possible	Alternately	Possible
Imaging modality	SPECT/CT or PET/CT	SPECT/CT or PET/CT	SPECT/CT and/or MRI

The publication of new and large prospective studies in recent years [1, 2] has emphasized the importance of the knowledge on the technical aspects of radioembolization [3, 4]. This was for example illustrated by the SARAH-trial. In this prospective, randomized, controlled, phase 3 SARAH trial, included patients had locally advanced hepatocellular carcinoma (HCC), defined as Barcelona Clinic for Liver Cancer (BCLC) stage C, or recurrent HCC after surgical resection or thermal ablation (ineligible for additional surgical resection, thermal ablation or liver transplantation), or failing two rounds of chemoembolization. After randomization, patients were treated with radioembolization with either ^{90}Y resin microspheres or systemic treatment with sorafenib (tyrokinase inhibitor) [2]. In the radioembolization arm, patients received the conventional work-up (with visceral angiography, treatment simulation with ^{99m}Tc-MAA and SPECT/CT imaging). If treatment was deemed safe, patients were treated and the used therapeutic activity was calculated according to the so-called body surface area (BSA) method. In the sorafenib arm, patients received sorafenib 400 mg twice daily. Treatment suspension and dose reductions (to 400 mg daily) were allowed (according to previous finding in the SHARP study [5]). Primary endpoint of the trial was overall survival (OS) by any cause. Secondary endpoints included progression free survival (PFS), objective response and disease control on imaging studies according to Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1), quality of life scored by EORTC QLQ-C30 and QLQ-HCC18 questionnaires, and adverse

events reported according to the Common Terminology Criteria for Adverse Events (CTCAE version 4). From December 2011 till March 2015, 459 patients were available for the intention-to-treat analysis. Both treatment arms were comparable at baseline. In 2017, the negative results were published, showing no benefit in OS in the radioembolization arm compared to the sorafenib arm (8.0 months versus 9.9 months; hazard ratio 1.15; 95% confidence interval 0.94-1.41) [2]. No difference in PFS was found (radioembolization 4.1 months versus sorafenib 3.7 months). Objective response rate on imaging showed a higher disease control rate in the sorafenib arm (78% versus 68%; p=0.0346). On the other hand, quality of life (QoL) assessments showed a significantly better global health status subscore in the radioembolization arm (p=0.0048), and radioembolization was overall better tolerated. Thus the authors concluded; *"In conclusion, in patients with locally advanced or intermediate-stage hepatocellular carcinoma after unsuccessful transarterial chemoembolization, overall survival did not significantly differ between the two groups. Quality of life and tolerance might help when choosing between the two treatments"* [2].

Radioembolization is a complex treatment with many variables. Firstly, most of the participating centers in France had very limited experience with radioembolization, resulting in 18.6% of patients being excluded for radioembolization based on a failed scout dose procedure [2]. This may be partially explained by the use of ^{99m}Tc-MAA as a treatment surrogate, which is known to overestimate lung shunting. This occurred in 6.2% of patient [6]. Secondly, the method to calculate therapeutic activity for the actual radioembolization treatment was based on a simplified approach, not differentiating between tumor and non-tumor tissue [4]. Thirdly, retreatments (47.1%) needed to be performed because of incomplete administration of the therapeutic activity. These limitations emphasize the need for sufficient expertise of all involved physicians. As emphasized in **chapter 2**, improved patient selection and accurate individualized therapeutic activity calculation are paramount for radioembolization success.

Personalized radioembolization in neuro endocrine neoplasms?

Unfortunately, the three limitations applicable to the SARAH trial were also applicable to current literature on radioembolization in neuroendocrine neoplasms (NEN). As noted throughout the thesis, current literature is sparse. The initially conducted meta-analysis in **chapter 3** showed promising results in the tumor reductive capabilities of radioembolization, but many patient-related characteristics and

procedure related aspects were missing, and presented data were based on mixed populations, making the results difficult to interpret. The subsequently conducted international retrospective study in **chapter 4** investigated the histopathological features of NEN patients and their relation with radioembolization. Interestingly, on the contrary to what we found in the meta-analysis, there was no significant difference in tumor reduction between the origins of NEN (gastro-intestinal, pancreatic, lung, etc.). Also the objective response rate between different NEN grades did not significantly differ. The latter being of interest, since it is often assumed that higher NEN grades, i.e. tumor cells that are more often in a proliferative state, are more sensitive to radiation [7]. However, radioembolization is different from external beam radiotherapy, from which this assumption is adopted. Based on the physical half-life of the isotope incorporated in the therapeutic particle (^{90}Y half-life is 64 hours; ^{166}Ho half-life is 26.8 hours), radioembolization results in a longer and continues irradiation of tumor cells, compared with high dose rate external beam radiation therapy. Clinical data on Peptide Receptor Radionuclide Therapy (PRRT) with ^{177}Lu-DOTATATE (^{177}Lu half-life is 6.7 days) supports this theory, being effective in both low and intermediate grade NEN [8]. The study also showed an increasing objective response rate over time in 20% of all patients according to RECIST 1.1 (complete + partial response from 9% at three months to 27% at six months), and in 26% according to mRECIST (complete + partial response from 36% at three months to 60% at six months).

All studies presented in this thesis used a simplified single compartment method to calculate treatment activity. Contrary to PRRT, which has an effective half-life influenced by both the physical half-life of the isotope and its biological half-life with washout, radioactive microspheres used in radioembolization are 'permanently implanted'. Radiation exposure to tissue is solely depended on the physical half-life of the used isotope (^{90}Y or ^{166}Ho). As a result, prospective dosimetry in NEN using radioembolization will be easier to accomplish compared with PRRT (because of the necessity for multiple time point imaging to determine the biological half-life of PRRT). Ideally, patients should receive prescribed activity optimization based on the pre-treatment simulation. Looking back at the previously mentioned SARAH trial, in the post hoc analysis of the investigators, taking all the technical considerations into account and looking more closely at the dosimetric calculations, there was a significant tumor reductive effect and overall survival benefit in properly dosed patients compared to the sorafenib group [9]. Patients receiving a tumor absorbed dose of ≥100 Gy had a significant longer median overall survival of 14.1 months (95% confidence interval 9.6-19 months) compared with patients receiving <100

Gy with an overall survival of 6.1 months (95% confidence interval 4.9-6.8 months; p<0.0001) [9]. In accordance with other literature, it confirms the importance of prospective dosimetry. Fortunately, in HCC patients the DOSISPHERE trial was initiated (ClinicalTrials.gov Identifier: NCT02582034), randomizing patients eligible for SIRT between different methods of therapeutic activity calculation (standard single compartment method versus partition modelling). The trial completed enrollment in December 2018 and its results are eagerly awaited. Unfortunately, no such trial currently exists for the NEN population.

Combining systemic treatments with liver-directed treatments

As most NEN patients suffer from both intra- and extrahepatic disease, radioembolization is currently limited to selected patients with liver-only or liver-progressive disease. Combining radioembolization with a systemic treatment seems to be a logical step forward. The first attempt to this end was the combination of systemic chemotherapy with capecitabine and temozolomide (CAPTEM) [10]. In this study by Soulen et al., 21 patients with grade 2 NEN (Ki67 3-20%) and liver dominant disease were treated. Therapeutic activity was calculated according to the BSA method. During the initial CAPTEM cycle, a pretreatment angiography and simulation was performed. The actual radioembolization treatment was performed at the second CAPTEM cycle. In case of bilobar disease, patients were treated in a sequential fashion (first lobe in the second CAPTEM cycle and the second lobe in the third or fourth CAPTEM cycle). In their study, an intrahepatic objective response rate according to RECIST 1.0 of 74% was reached (of which 14% complete response), and an objective response in extrahepatic disease was seen in 55%. Median time to intrahepatic progression or any progression was not reached (median follow-up time 22 months). These results show a potential synergistic effect of a systemic treatment and a liver-directed treatment in NEN.

In the Netherlands and some other European countries, the first or second systemic treatment of choice currently is PRRT, based on the findings of the NETTER-1 trial. The phase 3 randomized controlled NETTER-1 trial on PRRT with ^{177}Lu-DOTATATE in grade 1 and 2 NEN patients showed significantly longer progression free survival (PFS) in all analyzed subgroups, compared to high dose somatostatin analogs [8]. In a post-hoc analysis on the efficacy of PRRT on liver disease, patients with different liver involvement showed no difference in PFS [11]. However, in patients with bulky disease, PFS was shorter than in patients with non-bulky disease (28.4 months in bulky disease versus PFS not reached in non-bulky disease). Bulky disease was defined as ≥1 lesion larger than 30 mm maximum diameter. Of all the bulky

disease, 70% was located in the liver [11]. These findings confirm the main problem in NEN, being liver disease. There seems to be a need for an additional treatment of residual bulky liver disease. On the short term, additional radioembolization does not seem to come with any additional toxicities, as described by our subgroup analysis in **chapter 5,** and the initial HEPAR PLUS results in **chapter 7**. Long-term hepatotoxicity of both PRRT and radioembolization are fiercely discussed in scientific literature, however no proper data has been presented yet, as described in **chapter 5**. Long-term efficacy and toxicities of radioembolization are still awaited, as the HEPAR PLUS follow-up period hasn't been concluded yet. Based on our long-term clinical follow up data in **chapter 5**, there seem to be no restrictions for follow-up treatment with either PRRT or chemotherapy. Importantly, significant additional tumor reduction can be obtained by adding radioembolization to PRRT. Based on the quality of life assessments in the HEPAR PLUS study, the additional radioembolization treatment wasn't considered to be an additional burden on the long run. For now, the combination of PRRT and radioembolization seems feasible and safe in well-selected patients. However, its effect on progression free survival and overall survival should be investigated in a randomized controlled phase 3 trial in patients with bulky liver disease (i.e. PRRT + ^{166}Ho radioembolization versus PRRT alone).

A proposed protocol for such a phase 3 trial may include randomization of patients with a gastro-intestinal pancreatic NET, grade 1 or 2, with residual bulky liver disease after PRRT. This particular group of patients is the main reason to add an additional treatment, as shown by the post-hoc analysis of the NETTER-1 study [11]. In that post-hoc analysis, the investigators show that a staggering 80 out of 117 patients from the PRRT arm had bulky disease. Again emphasizing the clinical need for an added treatment. The primary endpoint of such a trial should be focused on intrahepatic PFS and secondary endpoints could focus on OS, overall PFS, and long-term toxicity. Objective response rates could also be assessed, like the HEPAR PLUS trial, however to date no proper response assessment criteria exist. RECIST 1.1 is known to underestimated treatment response in many tumor types, especially in radioembolization, but is currently the most accepted response assessment method by oncologists. Modified RECIST could be a valuable alternative, however it isn't generally adopted, not validated enough in NEN and only applicable in hypervascular tumors. Functional imaging in NEN could offer a quantitative method of response assessment, but again limited literature exists on this subject with either somatostatin receptor ligands or ^{18}FDG, and no proper validation studies have been performed yet.

As mentioned earlier in this discussion, the most important aspect in radioembolization is the application of accurate dosimetry. Only experienced radioembolization centers capable of performing high-level radioembolization dosimetry should participate, to avoid unjustified negative results. Even though the post-hoc analysis of the SARAH trial was positive, harm had already been done. The same goes for the SIRFLOX, FOXFIRE and FOXFIRE global trials in metastatic colorectal carcinoma and the previously discussed CAPTEM + radioembolization trial by Soulen et al. in grade 2 NEN, where no proper dosimetry was performed [1, 3, 10]. *'Adequate radioembolization activity dose is as important as adequate chemotherapy dose'* [3]. Radioembolization dosimetry should not be restricted to simple partition modeling, but voxel-based modeling should be advocated with the proposed dual-isotope protocol as described in **chapter 10**.

Future perspectives

The predictive value of the currently used ^{99m}Tc-MAA particles as a pre-treatment simulation is disappointing, primarily caused by the difference in physical characteristics compared to the therapeutic microspheres [6, 12]. To this end, the clinical feasibility of ^{166}Ho-microspheres as a scout dose was investigated in **chapter 9.** Recently, our group confirmed the superiority of a ^{166}Ho-microspheres scout dose for treatment planning in a qualitative, as well as a quantitative analysis [13]. Using the data derived from the pre-treatment assessment with a ^{166}Ho-microspheres scout dose and the dual isotope scan protocol as described in **chapter 10**, a big improvement in personalized dosimetry can be made. At the moment, this dual isotope protocol is being validated in the HEPAR PLUS cohort. Important dosimetric thresholds for ^{166}Ho-microspheres, like minimal tumor absorbed radiation dose and, more importantly, tolerable healthy liver tissue absorbed radiation dose will be investigated. With these results, a new clinical study to validated these thresholds and test the feasibility of this scan protocol in clinical practice is a logical next step toward individualized treatment in NEN patients.

The potential to improve the treatment of neuroendocrine liver metastases isn't restricted to liver-directed therapies alone. Combined knowledge on PRRT with ^{177}Lu-DOTATATE and radioembolization, led to a new idea in NEN, in which the radiopharmaceutical ^{177}Lu-DOTATATE is injected intra-arterially. Intra-arterial injection of ^{177}Lu-DOTATATE results in a higher first-pass extraction of the radiopharmaceutical, hypothetically leading to a higher tumor uptake, and potentially to a higher objective response rate. The first study to test this

hypothesis, the non-randomized ARETAIEION study, did show a significantly improved objective response rate of 75%, compared to literature [14]. As NEN are very heterogeneous, the results of that study cannot be directly translated to the general NEN population in clinical practice. In a new prospective study, the LUTIA study (ClinicalTrials.gov Identifier: NCT03590119), another approach was chosen to exclude the NEN heterogeneity, by applying intra-patient randomization. By treating one hepatic lobe via the hepatic artery (first-pass), the other lobe will be treated via the normal systemic circulation (second pass, resembling intravenous administration). The added effect of intra-arterial injection of ^{177}Lu-DOTATATE can subsequently be compared within each patient separately. The study is currently enrolling patients. Combining both intra-arterial ^{177}Lu-DOTATATE treatment and ^{166}Ho-microspheres radioembolization could even further improve control on hepatic NEN disease.

As final future perspective, an upgrade of the currently proposed dual isotope protocol as described in **chapter 10** needs additional investigation. ^{99m}Tc-stannous phytate is limited to Kupfer cells in healthy liver tissue via phagocytosis of the particle. It helps us to delineate healthy liver tissue, however it does not provide any insight into the actual liver function of the patient. Instead of ^{99m}Tc stannous phytate, the use of ^{99m}Tc with a type of iminodiacetic acid (^{99m}Tc-mebrofenin, a.k.a. hepatobiliary scintigraphy) may be considered, a bilirubin conjugate, which is processed by hepatocytes and subsequently excreted via the biliary tract. It has shown to be indicative of hepatic function [15]. Trends in actual hepatocyte function before and after radioembolization is especially relevant in patients treated in a pre-operative setting, as described in **chapter 8.** Initial results of our group report the discrepancies between liver volume on CT and liver function on hepatobiliary scintigraphy before and after radioembolization, which is of paramount importance prior to surgical resection [16]. The technical details as described in **chapter 10** will still be applicable on the dual isotope SPECT/CT images. However, for the calculation of the linear clearance rate of ^{99m}Tc-mebrofenin, planar imaging is used, which will require additional research on the influence of ^{166}Ho on the quantification of planar ^{99m}Tc imaging. Additionally, SPECT/CT imaging time of ^{99m}Tc-mebrofenin is limited, due to its rapid biliary clearance, thus optimization of activities injected and acquisition time is required. It is expected that the combination of ^{166}Ho scout dose and ^{99m}Tc-mebrofenin will allow (semi-)automated voxel-based dosimetry and predict hepatocyte loss after radioembolization, all in one scan protocol.

As described in this thesis, current literature on radioembolization in NEN is sparse and should be interpreted with caution. But radioembolization in NEN remains promising, even though the treatment used in current literature is far from optimized. In the end, optimizing and combining treatments to gain better control of hepatic disease in NEN, is expected to benefit our patients. As the OS of our patients increases, like it has done the past decades, our goal should be to achieve long PFS with minimally invasive treatments and limited side effects. With these goals in mind, radioembolization could become a very important part of NEN patient care.

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Chapter 12

Summary

Neuroendocrine Neoplasms (NEN) is a generic term for a class of rare tumours, consisting of an array of many different tumor types. Similar to the trends noticed internationally, in the Dutch population the incidence of gastro-intestinal pancreatic NEN has increased from 298 per 100.000 per year in 2000 to 828 per 100.000 per year in 2016, according to the Dutch Cancer Registry (NKR hosted by IKNL). On the one hand, the disease has gotten more attention in the last decades and on the other hand more and more accurate diagnostic modalities have become available to detect the disease.

Unfortunately at time of diagnosis, 21% of grade 1 NET, 30% of grade 2 NET and 50% of grade 3 NET or NEC patients have disseminated disease, of which the liver is the most common affected site. Once a NEN patient is diagnosed with liver metastases, only about 20-30% is eligible for surgical resection with curative intent. Ineligibility for surgery is mainly due to bilobar involvement of the liver. Additionally, patients with liver metastases of functioning (hormone-producing) NEN suffer of debilitating complaints, like frequent diarrhea and flushing, with a direct impact on their quality of life. This emphasizes the clinical need for new therapeutic approaches of NEN liver disease.

Radioembolization is a well-established liver-directed treatment for patients suffering from hepatic malignancies. **Chapter 2** describes the radioembolization treatment procedure in detail. With increasing evidence on treatment efficacy the last couple of years and the relatively low toxicity profile, the application of radioembolization is steadily expanding. Besides the body of clinical data, **Chapter 2** emphasizes the other side of the radio-embolization procedure, namely its many rapid technical developments in nuclear medicine imaging and the interventional radiology, e.g. angiography suite.

Compared to other malignancies, NEN are relatively rare, thus literature on radioembolization in NEN is sparse. **Chapter 3** describes a meta-analysis on all available literature on radioembolization in NEN. Overall, the available articles reported very promising results on objective response rates and median overall survival. However, proper data on patient characteristics and its correlations to treatment outcome were lacking. Effect on hormone related symptoms isn't described at all.

Chapter 4 reports the results of an international retrospective study, in an attempt to address these gaps in available literature. Treatment efficacy was confirmed and moreover, the majority of patients suffering of a functional NEN had reduction or resolution of their hormone related complaints. The study did not reveal a

difference in treatment efficacy for NEN of different origins, but did emphasize the prognostic value of the NEN grade, fractional liver involvement and presence of extrahepatic disease.

Especially in the USA, fear exists to combine radioembolization with previous systemic radionuclide treatments. Mainly scientific anecdotes state that combining both radionuclide treatments increases the likelihood of hepatotoxicity. In **chapter 5** the subgroup analysis of the retrospective study is discussed, focusing on the patients who received radioembolization after previous peptide receptor radionuclide treatment (PRRT) with, amongst others, ^{177}Lu-DOTATATE. This subgroup analysis showed a comparable treatment efficacy and toxicity profile of radioembolization and no additional short-term toxicities. **Chapter 5** also discusses all available literature on this subject.

Chapter 6 outlines the hypothesis for the first prospective trial (HEPAR PLUS): the combination of PRRT with ^{177}Lu-DOTATATE with ^{166}Ho radioembolization. In short, we hypothesized that PRRT could be used to treat intra- and extrahepatic disease and in patients with residual bulky liver disease after PRRT, ^{166}Ho radioembolization can be added as a treatment boost to the liver disease.

Chapter 7 reports the first results of the prospective HEPAR PLUS trial, showing an additional tumor reductive effect in patients with residual bulky liver disease after PRRT. The combination of PRRT and radioembolization is deemed safe and effective. Patients report a temporary non-significant decrease in quality of life, which is fully recovered after 3 months.

Chapter 8 discusses new indications for radioembolization in an upfront, curative setting, instead of the common salvage setting where it currently resides. Based on available literature, radioembolization could have several benefits in pre-operative, pre-ablative or pre-transplantation patients.

Chapter 9 discusses the safety of a small amount of ^{166}Ho microspheres (^{166}Ho scout dose) as a treatment simulation prior to the actual radioembolization procedure, as an alternative to the currently used ^{99m}Tc-MAA particles. Using an identical particle for treatment planning, with similar intravascular flow dynamics, will lead to a more effective radioembolization treatment by increasing the accuracy of the dosimetry, thus benefitting both physician and patients.

Chapter 10 elaborates on the technical aspects and challenges of SPECT/CT imaging with both ^{166}Ho and ^{99m}Tc (a.k.a. dual isotope imaging). This technical manuscript shows that the combination of both isotopes for simultaneous acquisition of a pre-

treatment simulation using ^{166}Ho scout dose and healthy liver tissue delineation using ^{99m}Tc stannous phytate is feasible. This dual isotope SPECT/CT protocol could provide all necessary data for sophisticated individualized dosimetry.

In **chapter 11** the findings of this thesis are discussed and future directions for research are proposed.

Chapter 13

Uitgebreide samenvatting

Neuroendocriene tumor (NET) is een generieke term voor een groep zeldzame tumoren, welke bestaat uit vele verschillende tumor-subtypen. Vergelijkbaar met internationale trends, is de incidentie van deze ziekte in Nederland van 298 per 100.000 personen per jaar in 2000 naar 828 per 100.000 personen per jaar in 2016 gestegen, als gekeken wordt naar gastro-intestinale (maag en darm) en pancreas (alvleesklier) NET in de Nederlandse Kankerregistratie (IKNL). Enerzijds komt dit door toegenomen bewustzijn over het bestaan van NET, anderzijds door de verbetering in de detectie van NET binnen de huidige diagnostiek.

NET worden beschreven op basis van histologische karakteristieken. De belangrijkste parameters zijn de mitotische index en Ki67-index, welke beide een weerspiegeling zijn van de groeisnelheid van de NET, en de tumor differentiatie van de NET is voorspellend voor ziekte agressiviteit. De World Health Organization (WHO) of European NeuroEndocrine Tumor Society (ENETS) classificatie onderverdeelt neuroendocrine neoplasmata (NEN) in vier groepen met toename van de ziekte-agressiviteit per graad: graad 1 tot en met graad 3 zijn goed tot matig gedifferentieerde NET, met per gradering een toegenomen groeisnelheid. Daarentegen wordt een NEN, een neuroendocriene carcinoom (NEC) genoemd als het een snel groeiende, agressieve, slecht gedifferentieerde tumor betreft.

Bij diagnose is 21% van de graad 1 NET, 30% van de graad 2 NET en 50% van de graad 3 NET of NEC uitgezaaid, waarbij de lever meestal als eerste uitzaaiïngen bevat. Als een NET patiënt eenmaal uitzaaiïngen in de lever heeft, komt slechts 20-30% van de patiënten in aanmerking voor eventuele curatieve resectie van de ziekte en is de prognose significant slechter dan voor NET patiënten zonder uitzaaiïngen in de lever. De meeste NET patiënten zijn geen kandidaat voor curatieve resectie, vanwege de uitgebreide betrokkenheid van de lever. Een deel van de patiënten heeft een hormoonproducerende oftewel functionerende NET, die zorgt voor invaliderende klachten zoals frequente diarree en opvliegers (flushing). De gedachte is dat deze hormoon-gerelateerde klachten voornamelijk veroorzaakt worden door uitzaaiïngen in de lever. Deze klachten hebben een directe negatieve impact op de kwaliteit van leven van NET patiënten. Deze factoren benadrukken de klinische behoefte voor nieuwe behandelmogelijkheden van de NET uitzaaiïngen in de lever.

Radioembolisatie is een levergerichte therapie voor de behandeling van verschillende levertumoren. De behandeling maakt gebruik van miljoenen radioactieve bolletjes (microsferen) met een grootte van ongeveer 30 micrometer. De microsferen worden via een slangetje in de leverslagader gespoten, waarbij de microsferen vastlopen in de haarvaten in en rondom de levertumoren. Zodoende worden de levertumoren lokaal bestraald.

Hoofdstuk 2 beschrijft de radioembolisatie procedure in detail. Door de toename van wetenschappelijke bewijs over de effectiviteit en de relatief beperkte bijwerkingen (toxiciteit) van radioembolisatie, wordt deze behandeling steeds vaker toegepast in patiënten met levertumoren. **Hoofdstuk 2** beschrijft de klinische onderbouwing van deze behandeling en benadrukt tegelijkertijd het belang van de snelle technische ontwikkelingen. Belangrijke technische ontwikkelingen zijn gaande binnen zowel de nucleaire geneeskunde als de interventie radiologie. Een belangrijk onderdeel hiervan is de berekening van de (per individu verschillende) benodigde hoeveelheid radioactiviteit voor een behandeling, 'dosimetrie' genaamd.

Vergeleken met andere maligniteiten, zijn NET relatief zeldzaam en is de beschikbare literatuur over radioembolisatie in NET beperkt. In **hoofdstuk 3** wordt een meta-analyse van alle beschikbare literatuur over radioembolisatie in NET besproken. Deze meta-analyse laat zien dat een goede tumorafname op beeldvorming en een lange gemiddelde overleving kan worden bereikt. Helaas is de beschikbare literatuur beperkt en bestaat deze uit voornamelijk gemengde patiënt populaties. Belangrijke parameters, zoals de verschillende NET karakteristieken van de behandelde patiënten en het effect van de behandeling op hormoon-gerelateerde klachten worden niet beschreven.

In **hoofdstuk 4** worden de resultaten van een internationale retrospectieve studie besproken, welke in opzet was bedoeld om de kennis hiaten over radioembolisatie bij NET patiënten in kaart te brengen. Deze studie bevestigde de eerder beschreven effectiviteit van de behandeling en de relatief beperkte toxiciteit. In patiënten met klachten van een hormoon-producerende NET leidde de radioembolisatie behandeling in een groot deel van de patiënten tot verlichting of volledig verdwijnen van de hormoon-gerelateerde klachten. Ook bleek de effectiviteit van radioembolisatie niet voorbehouden aan één subtype NET of tumorgraad. In deze studie werd de negatieve invloed van een aantal factoren op de overleving bevestigd.

Peptide Receptor Radionuclide Therapie (PRRT) is een systemische behandeling voor NET, waarbij gebruik wordt gemaakt van lutetium-177 (^{177}Lu)-DOTATATE, wat uiterst effectief is gebleken in een grote internationale studie. Helaas heerst met name in de Verenigde Staten een - op voornamelijk wetenschappelijk anekdotes gebaseerde - angst om radioembolisatie te combineren met PRRT, vanwege een eventueel verhoogde kans op levertoxiciteit. **Hoofdstuk 5** bespreekt de subgroep-analyse van de bovengenoemde internationale retrospectieve studie, waarbij specifiek werd gekeken naar patiënten behandeld met radioembolisatie na

eerdere systemische radionuclide therapie (met name PRRT) in het verleden. Deze aanvullende analyse gaf vergelijkbare resultaten met de niet-voorbehandelde groep ten aanzien van effectiviteit en toxiciteit, en rapporteerde geen verhoogde kans op korte termijn levertoxiciteit. **Hoofdstuk 5** bediscussieert ook alle beschikbare literatuur aangaande de combinatie van radioembolisatie en PRRT.

In **hoofdstuk 6** presenteren we het studie protocol van de eerste prospectieve studie (HEPAR PLUS) over de combinatie van PRRT met ^{177}Lu-DOTATATE en radioembolisatie met holmium-166 (^{166}Ho) microsferen. In een notendop is de hypothese dat met PRRT zowel de ziekte binnen als buiten de lever wordt behandeld, en dat bij NET patiënten met resterende uitzaaiïngen in de lever na PRRT, een aanvullende behandeling (boost) met radioembolisatie resulteert in een betere behandeling van de uitzaaiïngen in de lever.

Hoofdstuk 7 presenteert de eerste resultaten van de HEPAR PLUS studie. De eerste interim analyse toont significant meer tumorafname op beeldvorming, wat een toegevoegde waarde van de combinatie van de behandelingen impliceert. De aanvullende radioembolisatie behandeling wordt veilig geacht en leidt slechts tot een tijdelijke, niet-significante daling van de kwaliteit van leven, welke volledig hersteld is 3 maanden na de behandeling.

Hoofdstuk 8 bediscussieert de huidige plaats van radioembolisatie binnen de oncologische zorg. Hoewel deze op dit moment vaak als laatste therapeutische optie wordt benut, kan radioembolisatie in de toekomst verschillende mogelijke voordelen hebben in geselecteerde patiëntengroepen, bijvoorbeeld in een preoperatieve, pre-ablatieve of pre-transplantatie setting.

In **hoofdstuk 9** wordt de veiligheid van het gebruik van een kleine hoeveelheid ^{166}Ho microsferen (^{166}Ho scout dose) als simulatie van de daadwerkelijke behandeling besproken. Het gebruik van een identiek partikel, met vergelijkbare intravasculaire verdeling als het behandelpartikel, is theoretisch beter voor de planning van de behandeling. Voor behandelaars en patiënten lijkt dit voordelig, met als resultaat een betere en geïndividualiseerde radioembolisatie behandeling op basis van betere dosimetrie en met een hogere effectiviteit tot gevolg.

Hoofdstuk 10 weidt uit over de technische aspecten van het gelijktijdig afbeelden van een ^{166}Ho scout dose en technectium-^{99m} (^{99m}Tc) fytaat. Het gelijktijdig scannen van twee verschillende isotopen wordt ook wel 'dual isotope' beeldvorming genoemd. Dit technische manuscript beschrijft het gebruik van de ^{166}Ho scout dose voor de simulatie van een radioembolisatie behandeling in combinatie met het gebruik van ^{99m}Tc-fytaat voor het onderscheid tussen gezond lever weefsel

en tumor weefsel. Het 'dual isotope' scan protocol blijkt bruikbaar voor klinische toepassing en door het gebruik van dit protocol kunnen alle benodigde relevante parameters voor geïndividualiseerde dosimetrie worden verkregen in één scan.

In **hoofdstuk 11** worden alle bevindingen uit dit proefschrift bediscussieerd en worden potentiële toekomstige onderzoeksvoorstellen besproken.

Chapter 14

List of publications

Will ^{177}Lu-DOTATATE Treatment Become More Effective in Salvage Meningioma Patients, When Boosting Somatostatin Receptor Saturation? A Promising Case on Intra-arterial Administration. **Braat A.J.A.T.**, Snijders T.J., Seute T., Vonken E.P.A.. *Cardiovasc Intervent Radiol. 2019 doi: 10.1007/s00270-019-02262-1*

First Experience With ^{177}Lu-PSMA-617 Therapy for Advanced Prostate Cancer in the Netherlands. van Kalmthout L.W.M., **Braat A.J.A.T.**, Lam M.G.E.H., van Leeuwaarde R.S., Krijger G.C., Ververs F.A.A., Mehra N., Bins A., Hunting J., de Keizer B. *Clin Nucl Med. 2019. doi: 10.1097/RLU.0000000000002561.*

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Chapter 15

Curriculum Vitae

Arthur Johannes Anthonius Theodorus Braat was born on the 29th of June in Breda, the Netherlands. After spending his childhood years in Terheijden, he started high school at 'het Onze Lieve Vrouwe Lyceum' in Breda.

After some persuasion from his father (back then a general practitioner in his home town), he applied for medical school. From 2005 until 2011 he attended medical school. During that period, in 2009 he travelled to Australia for his pediatrics rotation at the Women's and Children's Hospital in Adelaide. With a special interest in pediatric intensive care and pediatric oncology. After his rotation he and a friend, Thomas Klein Nulent (a.k.a. BARRIE), travelled throughout Australia.

In the last year of medical school, he was convinced he would become a plastic surgeon. During his final year he did both his scientific and last rotation with dr. Arnold Schuurman at UMC Utrecht. During that last year, students had to pick an additional rotation in another specialization. His sister Manon (back then a Radiology resident at UMC Utrecht), persuaded him to pick a Nuclear Medicine rotation. Only by telling him: "Nuclear Medicine is your cup of tea".

Fully trusting his sister and not really knowing what he had chosen, he went on to meet Monique Hobbelink. And the rest is, as they say, history.

During his residency, he was active as a member of the Junior Dutch Society of Nuclear Medicine for four years. After completing his Nuclear Medicine residency at UMC Utrecht, he became faculty at UMC Utrecht in 2017 with a special interest in radionuclide treatments of all sorts. As part of this particular interest, he started his PhD during his residency under supervision of Marnix Lam. Now finally, everybody can read what he has been up to the last couple of years in Europe and USA. Radionuclide treatments will have his interest for the years to come.

He married his girlfriend Steffie Kremer on the 9th of July 2016 and their first child Juliëtte has born on the 8th of January 2019.

Chapter 16

Postscriptum

Het leukste hoofdstuk volgens velen en meestal het meest gewaardeerd. Niet alleen door mij als promovendus, maar ook door degenen die mij de afgelopen jaren hebben geholpen in dit traject.

Beste Eerste Promotor, Beste Marnix, dank voor het vertrouwen, steun en begeleiding de afgelopen jaren. Initieel als co-promotor, deels vanuit Californië, en nu als promotor, heb je enorm veel tijd gestoken in mijn begeleiding. Gepaard met een goede dosis humor en de benodigde kritische noot, heb ik dat zeer gewaardeerd de afgelopen jaren. Hopelijk kunnen we deze fijne samenwerking nog jaren voortzetten als collega's.

Beste Tweede promotor en co-promotor, beste Hugo en Rob, dank voor jullie hulp van de afgelopen jaren, zowel in de kliniek, als voor onderwijs en wetenschap. Hopelijk kunnen we deze fijne samenwerking nog jaren voortzetten als collega's.

Beste Leden van de Leescommissie, Prof. Dr. Roel Goldschmeding, Prof. Dr. Max Viergever, Prof dr. Menno Vriens, Prof. Dr. Roel Benninck en Prof. dr. Willem Mali, bedankt voor alle tijd die jullie hebben vrijgemaakt om dit proefschrift te beoordelen.

Beste Nucleair Geneeskundigen, Beste Monique, Henny, Marnix, Bart en Nelleke. Dank voor de fijne tijd en de gelegenheid te mogen promoveren tijdens mijn opleiding. Ik ben nog steeds blij onderdeel te mogen zijn van onze kleine groep. Met onze kleine groep weten we toch veel voor elkaar te krijgen, met heel veel humor. Op naar de volgende jaren en successen.

Beste MNW'ers en front-office Radiologie medewerkers, dank voor jullie geduld, flexibiliteit, humor, plezier in jullie werk en steun de afgelopen jaren. Niet alleen het dagelijkse werk, maar ook dit proefschrift was zonder jullie niet mogelijk geweest.

Beste Tjitske en Shanta, zonder jullie was dit moment nooit gekomen. Dank voor alle ondersteuning en advies voor het uitvoeren van wetenschappelijk onderzoek. Zonder jullie was de HEPAR PLUS nooit zo soepel verlopen en was ik binnen de berg bureaucratie allang de weg kwijtgeraakt. Dank voor al jullie inzet en toewijding.

Beste Gerard, Tessa, Remmert, John en Janneke, dank voor jullie inzet en toewijding voor onze mooie kliniek en dank voor de ondersteuning van al onze wetenschappelijke projecten. Zonder jullie is het allemaal niet mogelijk.

Beste Verpleegkundigen van de Stralingsunit, iedere keer weer wordt een beroep gedaan op jullie beschikbaarheid. Dank voor jullie flexibiliteit, meedenken en hoge kwaliteit! Niet alleen wij als artsen waarderen jullie enorm, ook onze patiënten zijn altijd zeer over jullie te spreken.

Beste Interventie Radiologen, Beste Rutger, Evert-Jan, Gèrard, Rob en Irene, dank voor jullie hulp bij alle patiënten behandelingen. Mede dankzij jullie is dit proefschrift gerealiseerd en ben ik blij dagelijks met jullie te mogen samenwerken.

Beste Staf Radiologie van het UMC Utrecht, dank voor de prettige samenwerking van de afgelopen jaren, mogen er nog vele mooie jaren volgen.

Beste Menno, Inne, Gerlof, Rachel, Mark en Nick, dank voor de prettige samenwerking!

Beste mede-auteurs, mede-promovendi, toekomstige promovendi en studenten, dank voor jullie werk en ik zie uit naar jullie successen.

Lieve Manon, lieve paranimph, allereerst dank voor het goede advies destijds! Anders was ik geen nucleair geneeskundige geworden, was ik niet je collega geworden en was dit proefschrift nooit ontstaan. Ook al denkt iedereen dat wij elkaar vaak zien en spreken, laat ik die gedachte uit de wereld helpen; ik zie mijn eigen zus slechts 1x per week op de werkvloer = de stafvergadering. Dank voor al je steun en hulp.

Beste Asbjørn, beste paranimph, begonnen in hetzelfde schuitje van full-time werken en promoveren tegelijkertijd. Dank voor de goede borrels en gedachtewisselingen van de afgelopen jaren. Mogen we nog regelmatig borrelen en op naar je eigen verdediging!

En dan de lieve families, dank voor alle gezelligheid.

Lieve Huub en Monique, lieve vader en moeder, dank voor alle leuke dingen de afgelopen jaren. Dank voor al jullie geduld en steun. Niet alleen voor de steun rondom dit traject, maar ook voor alle hulp in het huis. Ik hoop dat met het afronden van dit proefschrift, ik vaker op bezoek kan komen in la douce France met Steffie en de kleine.

Lieve Yvonne en Manon, dank voor jullie geduld en flexibiliteit. Het was niet altijd even makkelijk en ik weet dat ik afgelopen jaren weinig tijd heb gehad om leuke dingen samen te doen, maar hopelijk komt daar nu verandering in. Dank voor al jullie steun.

Lieve Kremers (Berry, Judith, Philip en Marjolein, Sophie en Mark, Floris en Varja), dank voor alle gezelligheid en steun de afgelopen jaren.

Lieve Steffie, nu toch al weer ruim 3 jaar getrouwd en 10 jaar samen, hoe hou je het met me uit? Ik ben je enorm dankbaar voor al je geduld, flexibiliteit en liefde. Ik weet dat het soms niet makkelijk is geweest; dan weer een deadline, dan weer een tripje, dan weer een praatje. Gelukkig was je zelf niet vies van een beetje werken. Toen bedachten we ook nog even een klushuisje te kopen! Maar eind goed, al goed. Ik beloof je dat ik onze weekenden niet meer zal spenderen aan werk en alle tijd voor ons en ons gezin zal maken. En een beetje klussen ;-)

Last, but most important; Lieve Juliëtte, lieve dochter. Je eerste indruk van je vader was waarschijnlijk niet de beste, tijdens de kraamweek meer tijd aan zijn promotie gespendeerd dan aan jou. Nu gaan we een leuke tijd tegemoet!