We are IntechOpen,
the world's leading publisher of Open Access books
Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

154
Countries delivered to

Our authors are among the

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

BOOK CITATION INDEX
CLARIVATE ANALYTICS
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Radioembolization for the Treatment of Unresectable Hepatocellular Carcinoma

Hojjat Ahmadzadehfar, Amir Sabet and
Hans Jürgen Biersack

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/56291

1. Introduction

Nuclear medicine therapy is required to be highly specific and targeted since it always involves administration of unsealed sources of radioactivity. Radionuclides emitting ß particles are generally used for therapeutic purposes because of their ability to penetrate and depositing cytotoxic energy in tissues. There are several choices of ß emitters with respect to energy of the emission. Lower energy ß particles can travel a few cell diameters, or at most in the sub-millimeter range, whereas higher energy ß particles such as those emitted by yittrium 90 (90Y) have a greater tissue penetration with a range beyond the source of several millimeters. The physical half-life of the therapeutic radionuclide is also an important consideration and underlying principle for therapy planning. For therapeutic purposes, radionuclides are usually, except in thyroid treatment, attached to a drug or particle that controls the biodistribution. The ideal therapeutic radiopharmaceutical is one that remains attached to the parent drug or its metabolites, and is excreted rapidly through a known simple route[1].

1.1. Concepts and principles

Along with the significant progress in hepatobiliary surgery in the last 30 years, various innovative liver-directed treatments have been developed [2] including conformal radiation, hepatic arterial infusion chemotherapy (HAI), transarterial chemoembolization (TACE), radiofrequency ablation (RFA) and radioembolization (RE) with radionuclide microspheres [3].

Conformal and stereotactic radiation therapy techniques can be used to deliver high radiation doses in cases with focal involvement [4]; however, since hepatic primary neoplasms are often multifocal and irregular in shape, and potentially replacing large parts of the liver volume, only a small minority of patients are optimal candidates for such therapies[5].

Radioembolization (RE), also named selective internal radiation therapy (SIRT), is a promising catheter based liver-directed modality for patients with primary and metastatic liver cancer. RE provides several advantages over traditional treatment methods including its low toxicity profile[6, 7].

Its rationale arises from the anatomic and physiological aspects of hepatic tumors being exploited for the delivery of therapeutic agents. The prominent feature is the dual blood supply of liver tissue, from the hepatic artery and the portal vein. Observations on vascular supply to hepatic malignancies have demonstrated that metastatic hepatic tumors >3 mm derive 80–100% of their blood supply from the arterial rather than the portal hepatic circulation[8]. Normal liver tissue, in contrary, is predominantly fed by the portal vein (60-70%). Apart from RE with 90Y microspheres, being an approved therapy by the Food and Drug Administration (FDA), various other radionuclides has also been used or investigated for treatment of liver tumors including Phosphorus-32, Rhenium-188 and holmium-166[9-12]. In this chapter, however, we focus only on the therapeutic indications, usefulness and methods of treatment with ^{90}Y-microspheres.

1.2. Physical characteristics of ^{90}Y and microspheres

^{90}Y is a pure β emitter, produced by neutron bombardment of yttrium-89 in a reactor, with a limited tissue penetration (mean 2.5 mm, max 11 mm), and short half-life (64 h), making it an ideal transarterial liver-directed agent. The size of the microspheres ranges between 20-40 μm. The upper size limit of the microspheres allows delivery to the tumours via the hepatic artery, while the lower size limit prevents the microspheres from passing from the arterial circulation into the venous circulation. The microspheres remain trapped within the vasculature of the tumours and deliver a selective radiation dose to the tumour tissue [13].
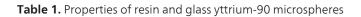
The mean tissue penetration of 2.5 mm of ß particles emitted from the selectively delivered yttrium allows an extremely high local tumour doses ranging from 50 to 150 Gy [14-17] to > 1000 Gy to the tumour tissue while sparing normal liver parenchyma. This is in contrast to traditional whole liver external beam radiation where radiation doses have to be limited to 30 Gy to prevent serious hepatic dysfunction [18].

Two 90Y microsphere products are commercially available: TheraSphere® (glass micro-spheres) and Sirsphere® (resin microsphere). There are some distinct differences in properties between the two products as shown in Table 1.

1.3. Patient selection criteria

The selection process of patients referred for RE involves several aspects to be taken into account. Patients considered for RE should have especially (1) unresectable hepatic tumour, (2) liver-dominant tumour burden, (3) a life expectancy of at least 3 months and (4) an ECOG perform-ance score of ≤2[19]. The general clinical condition, as described by the ECOG or Karnofsky performance score is an important aspect for patient selection prior to RE. Patients with a significantly reduced performance status are at higher risk of developing severe side effects, including radiation induced liver failure[20, 21] and generally have worse treatment outcome.

Y90 microspheres	SIR-Spheres	TheraSphere
Company	Sirtex Medical, Sydney, Australia	MDS Nordion, Ottawa, Ontario, Canada
material	resin-based	glass-based
Diameter	20–60 μm	20–30 μm
Activity per particle	50 Bq	2500 Bq
Number of microspheres per 3-GBq vial	40–80 X 106	1.2 X 106
Specific gravity	1.6 g/mL	3.2 g/mL
Maximal prescribed dose (GBq)	3	20
Relative embolic potential	Higher	Lower
Relative pressure for infusion	Lower	Higher
Contrast injection during infusion	possible	Not possible

Table 1. Properties of resin and glass yttrium-90 microspheres

These lead to questioning the rationale of posing the patient at such costly and potentially harmful treatment measure. Contraindications for RE include pretreatment angiogram indications of flow to the gastrointestinal tract which can not be corrected by coilc embolization techniques, an excessive shunting to the lungs that would result in > 30 Gy lung dose on a single administration as quantified by the tc-99m macroaggregated albumin (Tc-MAA) scan, excessive tumour burden with limited hepatic reserve, and biochemical evidence of reduced liver function as potentially indicated by elevated levels of bilirubin (widely suggested cut-off: 2 mg/dl), highly elevated liver enzymes (AST or ALT > 5x upper normal limit), significantly altered INR or PTT, or reduced serum albumin. Patients with prior radiotherapy involving the liver should be carefully reviewed on a case-by-case basis (Table 2) [7, 19].

1. Absent surgical (resection, liver transplantation) or ablative options (RFA)
2. Preserved liver function (intact liver synthesis)

a Bilirubin (< 2 mg/dl)
    b. Albumin (≥ 3 mg/dl)
    c. PT/PTT (no endogenous severe impairment)
    d. AST/ALT ≤ 5 x normal

3. Adequate general condition (ECOG performance score ≤ 2)
4. Liver-dominant tumor burden 5. Life-expectancy ≥ 3 months 6. Acceptable LSF (≤20% for resin and ≤30Gy for glass microspheres)

Table 2. Basic requirements for radioembolization

The renal status should be adequate to accommodate for any concurrent chemotherapy that is part of the treatment plan[22], as well as for the use of contrast agents during the diagnostic and the therapeutic angiogram. Hemodialysis patients may be treated with RE, however, dialysis has to be planned and timed before and after the intervention.

The decision to perform RE should be based on an interdisciplinary consent, ideally after discussion in an adequate tumor board with participation of specialists in surgery, gastroenterology, oncology, radiology, nuclear medicine and radiation therapy. Especially patients not fulfilling the common inclusion criteria should only be accepted as RE candidates after appropriate consent from such interdisciplinary tumor board.

1.4. Imaging modalities before radioembolization

The imaging includes a three-phase contrast computed tomography (CT) and/or gadolinium-enhanced magnetic resonance imaging (MRI) of the liver for assessment of tumour and non-tumour volume, main portal vein patency, and extent of extrahepatic disease.

18F-Fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG-PET/CT) is a very sensitive functional imaging modality for tumours with high glucose metabolism such as colorectal carcinoma, melanoma, head and neck tumors, and breast cancer. However, it is not a satisfactory imaging choice for pre- and post treatment evaluation of patients with HCC as these tumours except for their aggressive types, show no or a very low grade FDG uptake. This results in the suboptimal sensitivity of 18F-FDG-PET for HCC, ranging between 50% and 70% [23, 24]. Nevertheless, 18F-FDG-PET may provide prognostic information (metabolic grading) as patients with a negative FDG-PET have a better prognosis than those with high FDG uptake. Furthermore, addition of a metabolic imaging to the anatomical imaging modalities before performing RE leads to a more accurate follow up and therapy response assessment[25].

1.5. Angiogram with selective visceral catheterization and therapy simulation

Once a patient has been selected as a candidate for RE, an initial angiographic evaluation, known as test-angiogram, has to be performed as the first step, It is well known that the anatomy of the mesenteric system and the hepatic arterial bed has a high degree of variation, with "normal vascular anatomy" being present in only 60% of cases. Therefore, in order to perform any kind of therapeutic transarterial procedure in the liver in a safe and efficient manner it is essential to be acquainted with the hepatic arterial anatomy[26].

A feature of the neoplastic vasculature within tumours is the formation of arteriovenous anastomoses or shunts. Shunts allow microspheres to directly enter the venous return by bypassing the terminal arterioles in the tumour. This will deposit the shunted microspheres into the lung, resulting in radiation pneumonitis [22, 27].

Dystopic spread of microspheres to other extrahepatic visceral sites such as stomach, duodenum or pancreas, may also be associated with the risk of severe radiation damage leading to pain, ulceration and possibly perforation, pancreatitis, cholecystitis, skin necrosis and other non-target radiation complications[28].

Avoiding extrahepatic deposition of microspheres requires prophylactic embolization of all extrahepatic vessels including the gastroduodenal, right gastric and pancreaticoduodenal branches. If embolization is not possible, the catheter for treatment can alternatively be placed beyond the respective origins of these vessels. The angiogram must be accomplished with Tc-MAA injected into the hepatic artery similar to the application during microsphere treatment [19]. Scintigraphy should be performed within 1 hour of Tc-MAA injection to prevent false-positive extrahepatic activity due to free [99m]technetium (^{99m}Tc). The unwanted uptake of ^{99m}Tc-pertechnetate in the thyroid and stomach can be avoided using perchlorate. For this purpose patients should receive 600 mg perchlorate orally 30 minutes before angiography [29, 30].

It is of note that these vessels/organs can revascularize quickly, and therefore the embolization should be performed close to the intended time of RE, with a check arteriogram required before RE to ensure that such revascularization has not occurred[19].

Determining the possibility of lung damage due to liver-to-lung shunting is relatively simple as described by Lau et al.[31] Following infusion of 100-400 MBq Tc-MAA in the hepatic arterial branches, a whole body scan in anterior and posterior projections is sufficient to calculate the percentage of lung shunting and, consequently, the possibility of pulmonary side effects. The percentage of lung shunting can be determined from the total counts within regions of interest (ROIs) over both lobes of the lung and the liver, using the geometric mean of ventral and dorsal images. Depending on the shunt rate, a reduction of the total administered dose to the liver may be necessary. The highest tolerable dose to the lungs after treatment with RE is considered to be up to 30 Gy with a single injection, and up to 50 Gy for multiple injections[27]. The estimated dose (Gy) to the lungs is equal to A (GBq) x LSF x 50, assuming the total mass of both lungs to be 1 kg. Where A is the activity infused and LSF is the lung shunt fraction. The cumulative absorbed lung radiation dose can be calculated with the following equation [32] [33]:

$$\text{Cumulative absorbed lung radiation dose} = 50 \times \text{lung mass} \sum_{i=1}^{n} A_i \times \text{LSF}_i$$

Where A_i = activity infused, LSF_i = lung shunt fraction during infusion, n = number of infusions, and approximate vascular lung mass = 1 kg.

Another way is recommended by SIRTex Company as shown in table 3. According to SIRTex recommendations, the amount of microspheres delivered to the patient should be reduced if the lung shunting is more than 10% and RE should not be performed if there is a shunt more than 20% of the administered dose[22].

Percent Lung Shunting	Activity of SIR-Spheres microspheres
<10%	Deliver full amount of SIR-Spheres
10% to 15%	Reduce amount of SIR-Spheres by 20%
15% to 20%	Reduce amount of SIR-Spheres by 40%
>20%	Do not give SIR-Spheres microspheres

Table 3. The percent lung shunting may alter the activity that can be safely implanted commensurate with acceptable risk of radiation pneumonitis.

Extrahepatic hot spots in Tc-MAA images indirectly mark the possible locations of microspheres misplaced during therapy. However, detection and accurate localisation of extrahepatic hot spots using only two-dimensional planar scintigraphic images is not always possible, mainly due to the low spatial resolution. Furthermore, the localization of several different organs within a relatively small region of upper abdomen demands the analysis of tomographic images in order to accurately distinguish whether the Tc-MAA has accumulated in the liver or in some adjacent organ [30] as planar images cannot always make this distinction due to organ superposition.

If an extrahepatic tracer accumulation is detected by the Tc-MAA scan, angiogram and coil-embolization of aberrant arteries should be repeated prior to the RE until no extrahepatic accumulation is detectable[30]. In this setting, Tc-MAA SPECT/CT imaging has been shown to provide valuable additional information compared to planar and SPECT images and is the imaging modality of choice [30, 34, 35]. It significantly increases the sensitivity and negative predictive value of Tc-MAA scan compared to planar and SPECT alone[30, 34]. The sensitivity, specificity, positive predictive value and negative predictive value of SPECT/CT in the diagnosis of abdominal extrahepatic shunting has been found to be as high as100%, 93 %, 89 % and 100 % respectively [30].

2. Dose calculation and therapy planning

In addition to the selective distribution of the microspheres to the liver, the distribution within the liver plays a critical role in the planning of RE. The treatment should result in low radiation doses to normal liver tissue and a lethal dose to the tumor tissue. Abnormal high radiation doses to normal tissue may result in radiation induced hepatitis with potential risk of liver failure[36].

The required activity for treatment of each patient is to be calculated differently according to

whether glass or resin microspheres are to be used and their significant physical differences should be considered (Table 1). Selection of the optimal activity of microspheres for an individual patient is a complex and challenging task. There are some methods for dose calculation which are briefly introduced here.

2.1. Glass ^{90}Y microsphere activity calculation

TheraSphere® consists of insoluble glass microspheres, where ^{90}Y is an integral constituent of the glass. The mean sphere diameter ranges from 20 to 30 μm. Each milligram contains between 22,000 and 73,000 microspheres[37].

The dose determination for glass microspheres is based on a nominal average target dose (80-150 Gy/kg) and the patient's liver mass which determined from the CT or MRI data and assumes the uniform distribution of the microsphere throughout liver volume as [38]:

$$A(GBq)_{glass} = \frac{D(Gy) \times M(Kg)}{50}$$

In this equation, A is the activity, D the nominal target dose, and M is the mass of the targeted liver tissue.

It is recommended that the cumulative lung dose be kept to < 50 Gy to prevent radiation pneumonitis. The target dose for any given solid tumor is not known; however, it is believed that doses of 100–120 Gy balance response rates and hepatic fibrosis risk when glass microspheres are used[19].

When lung shunt fraction and residual activity in the vial after treatment are taken into account, the actual dose delivered to the target mass (Gy) becomes:

D (in Gy) = [A (in GBq)×50×(1 – [LSF – R])]/M (in kg)

where A is net activity delivered to the liver, D is the radiation absorbed dose to the target liver mass, M is target liver mass, LSF is lung shunt fraction, and R is percentage residual activity in the vial[21].

2.2. Resin ^{90}Y microsphere activity calculation

There are two methods for prescribed activity determination provided by the resin microsphere user's manual[22] (*1*) the empiric method and (*2*) the partition method.

2.2.1. The empiric method

The empiric method recommends a standard amount of activity which is varied only according to the size of the tumour within the liver. The recommended activity to be implanted for different degrees of tumour involvement of the liver is as follow:

Tumor <= 25% of the total mass of the liver by CT scan = 2 GBq whole-liver delivery

Tumor > 25% but < 50% of liver mass by CT scan = 2.5 GBq whole-liver delivery

Tumor > 50% of liver mass by CT scan = 3 GBq for whole-liver Delivery

2.2.2. The Body Surface Area (BSA) method

BSA method is a variant of the empiric method that is to adjust the activity implanted according to the size of the tumor within the liver and the size of the patient. The BSA method is calculated as follows:

First BSA is calculated from a weight/height chart

$$BSA(m^2) = 0.20247 \times height(m)^{0.725} \times weight(kg)^{0.425}$$

The activity of resin microspheres can be calculated with following formula:

Activity of resin microspheres in

$$GBq = (BSA - 0.2) + \left[\frac{volume\ of\ tumour}{volume\ of\ tumour + volume\ of\ normal\ liver} \right]$$

The BSA method is recommended for patients having concurrent systemic chemotherapy or for particularly small patients[22].

2.2.3. The partition model

This method involves implanting the highest possible activity to the tumour while maintaining radiation dose to sensitive tissues such as the lung and the normal liver. The partition model was developed from basic MIRD methodology to provide an estimate of the radiation dose separately to tumour and to normal liver. The partition model considers the liver and tumour to be effectively separate organs from the MIRD point of view. This model relies on accurate information relating to the degree of lung shunting, liver mass, tumour mass and tissue/normal (T/N) ratio.

Use of the partition model requires two measurements to be made:

1. measurement of the volume of tumour and normal liver determined from a CT or MRI scan and

2. measurement of the proportion of Tc-MAA activity that lodges in the tumour, normal liver and lung.

To determine the T/N the following equation should be used:

$$T\left|N = \frac{(A_{tumour}/M_{tumour})}{A_{liver}/M_{liver}}\right.$$

Where

A Tumor is the activity in tumor

M Tumor is the mass of tumor

A Liver is the activity in the normal liver

M Liver is the mass of the normal liver

The activity could be calculated as shown by the equation below:

$$A(GBq)_{resin} = \frac{D_{liver}(\{T:N \times M_{tumour}\} + M_{liver})}{49670(1 - LSF/100)}$$

Where

D_{liver} = nominal dose (Gy) to the liver

LSF = shunt fraction (%) of microspheres from liver to lung based on MAA scan

M_{liver} = total mass of liver (kg) from CT volume

The partition model has been described in detail in the SIRTex user manual[22].

The activity prescribed can be reduced if the hepatic function is compromised. There is no consensus guideline regarding the needed rate of reduction in the activity if a patient's liver

function or estimated reserve is only just good enough to be a candidate. Generally, more experienced users reduce dose by 30% for patients with poorer liver function who are still candidates for this approach according to established eligibility criteria[19]. The amount of 90Y should be also reduced according to the dose adjustment of lung shunt (table 3) if the percentage lung shunting is greater than 10%[39].

3. Radioembolization

3.2. Complications and side effects

3.2.2. Intrahepatic complications

Before performing the RE some pre medications should be administered.

1. Gastrointestinal (GI) prophylaxis to prevent GI inflammation and ulceration:

Due to the possibility of small unrecognized arterial vessels coursing to the GI system the routine use of prophylactic antiulcer medications in all patients is recommended. A proton pump inhibitor (e.g. omeprazole or pantoprazole) or H2-blocker (e.g. ranitidine) commencing 1 week prior to RE and continuing for at least 4 weeks post treatment is to be administered.

2. Anti-nausea prophylaxis

Anti-emetics (e.g. ondansetron or granisetron) are recommended prior to and after RE to reduce post-treatment nausea.

2. Post embolization syndrome prophylaxis

Fever, malaise and lethargy can occur due to the radiation injury and embolic effect of the RE on the tumour neo-vasculature. Provided the patient is not diabetic – and oral steroids are not otherwise contra-indicated – a tapering 5-day steroid dose pack of oral corticosteroids is recommended. However, this is not a routine practice at all centres.

2. Pain control

Oral analgesia may be required for 1 week following treatment to relieve pain from radiation injury and the embolic effect of microspheres, as well as liver capsular pain from tumour edema[22]. Using slow infusion of an i.v. analgesia (e.g. pethidin) and a corticosteroid during therapy with resin microspheres could be helpful against embolization symptoms.

3.1. Application of the calculated dose

On the treatment day, the calculated activity is injected after confirming the absence of collateral vessels connecting to the gastrointestinal tract. Administration is performed in an

angiography suite, primarily by an interventional radiologist. The catheter is usually positioned in essentially the same location as that used at arteriography for therapy planning. There are two different administration sets for application of resin and glass microspheres. The preparation of these sets and the method of injection have been described in detail in the respective instructions manuals [22, 32].

During the application direct tracking of microspheres distribution is not feasible and not required when using glass microspheres. But, it should be performed if resin microspheres are administered because the resin microspheres have an embolic tendency. In this case the radiologist must repeatedly check with fluoroscopy to make sure that resin microspheres are being delivered to the liver and no reflux is occurring back down the artery as this will result in spillage into other organs such as the stomach and duodenum.

It is highly recommended to perform Bremsstrahlung (BS) scintigraphy up to 24 hours after application of the microspheres to document the distribution of microspheres within the liver. Accidental extrahepatic spread of microspheres can also be visualized on post-therapeutic BS images. In case of adverse events this may allow for a faster diagnosis and early initiation of treatment. Although whole body and planar BS scans can detect diffuse extrahepatic ^{90}Y microspheres accumulations in the lungs, intestinal tract or along HFA, their analysis may be difficult and even misleading due to the low spatial resolution and organ superposition. Distinguishing between the accumulation of 90Y in the liver and in some adjacent organ demands the analysis of tomographic images. In a study obtained by our group the sensitivity, specificity, positive predictive value, negative predicative value and accuracy of SPECT and SPECT/CT in prediction of GI ulcer were 13 %,88%,8%,92%, 82 % and 87%,100%,100%,99 %, 99% respectively[40].

Overall, the incidence of complications after RE, if patients are selected appropriately and target delivery is performed meticulously, is low[5]. The complications can be divided into extrahepatic and intrahepatic.

There is also frequent observation of post embolization symptoms that are not addressed as complications. It is quite common for patients undergoing RE with resin microspheres to experience mild post embolization syndrome during the therapy, on the day of treatment and for up to 1-2 weeks after treatment. These symptoms include fatigue, nausea, and abdominal pain[19]. The most prominent aspect of post embolization syndrome is fatigue, occurring in over 50% of the patients[13].

3.2.1. Extrahepatic complications

Serious complications have been reported when microspheres were inadvertently deposited in excessive amounts in organs other than liver. Reported conditions include gastrointestinal ulceration/bleeding, gastritis/duodenitis, cholecystitis, pancreatitis, and radiation pneumonitis [5, 7, 27, 41-43].

Delayed cases of gastroduodenal ulceration were observed despite a standard pre-treatment evaluation and the contribution of experienced interventional radiologists [31]. These cases that would be associated with small amounts of Tc-MAA misplaced into the stomach and

undetected by conventional scintigraphic planar images could have been avoided by the use of SPECT/CT [34, 44].

One important complication is affection of the non tumorous hepatic parenchyma by radiation. Cases of veno-occlusive disease, radiation hepatitis and hepatic fibrosis have been described. To avoid liver complication the therapeutic doses should be adjusted as accurately as possible and careful dosimetric studies should be carried out. Transient elevation in liver function tests may occur in patients following RE, specifically a mild increase in alanine transaminase, alkaline phosphatise and bilirubin[22]. As expected, the likelihood of toxicity is often related to the patient's pretreatment liver condition and bilirubin level [5, 21, 45, 46].

3.2.2.1. Radioembolization Induced Liver Disease (REILD)

This mechanism involves the irradiation of normal parenchyma beyond its tolerance (30 Gy) [47]. REILD is a rare complication of RE,occurring in about 0%-4% of the patients, since this technique allows the safe delivery of radioactive particles to liver tumours sparing healthy liver tissue and induce 4-6 times higher tumour absorbed doses from 90Y-microsphere comparing those to the normal liver tissue[48, 51]. REILD may result in various degrees of hepatic decompensation and is hard to distinguish from hepatic veno-occlusive disease. In contrast to radiation induced liver disease from external radiation characterized by symptomatic ascites and elevated liver enzymes but usually not bilirubin, radioembolization-induced liver disease presents with ascites, usually with non-elevated transaminases (except for ALP and GGPT), and significant bilirubin increase.

Kennedy et al studied the incidence of REILD after 680 RE with resin microspheres. REILD was observed after 28 treatments (4%). Their data suggest an association between the amount of activity delivered to the patient and REILD [52]. There may also be an association between the use of the empiric method for the calculation of the dose (for resin microspheres) and toxicity [39].

In another study, age, bilirubin at baseline, treatment approach (whole-liver vs. unilobar), and the amount of activity administered relative to the total volume treated were found to be independent risk factors for the development of REILD[53, 54].

To reduce the possibility of REILD, prophylactic administration of corticosteroid, ursodeoxycholic acid, low-molecular weight heparin, glutamine infusion, prostaglandin-E1, pentoxyfilline and defibrotide may be of benefit [55-57].

High doses of corticosteroids traditionally are administered in an attempt to decrease intrahepatic inflammation. Treatment results are variable and mostly not gratifying, as the condition progresses in some patients to hepatic insufficiency of various degrees[5]. In most patients the only treatment needed is the use of diuretics and sodium restriction to maintain water and sodium balance. Hepatotoxic drugs should be avoided and infections should be identified and treated promptly.

4. Follow up

The most appropriate length of follow-up and the time points to technical success are not yet well defined and follow up schedules vary depending on the treatment plan of each patient.

Continual monitoring of liver function tests is recommended to determine the outcome of treatment. This includes monitoring for stabilization in liver function tests implying the control of disease[22]. A biweekly assessment in order to rule out REILD is recommendable in the first two months after RE.

Abdominal and whole body imaging should be performed for response evaluation as well as for evaluation of extra hepatic metastases. The frequency and the interval of post-RE imaging tests should be planned according to the tumour type and individual treatment plan. In our department patients receive the first post-RE imaging consisted of abdomen MRI and a metabolic imaging, normally FDG-PET/CT if the HCC was FDG avid, 4 weeks after the therapy. The next series of imaging are performed 3, 6, 9 and 12 months after therapy unless there are some other reasons for further imaging studies such as disease progression or performing other therapies such as chemotherapy.

5. Clinical results of the radioembolization in HCC

All the evidence that supports the use of RE in HCC is based on retrospective series or non-controlled prospective studies (levels of evidence II-2 and II-3) and no randomized controlled trials have been published comparing RE with other loco-regional, systemic therapies or best supportive care[58]. Most series of RE for HCC have reported on the outcome of patients at different stages that had progressed or relapsed after TACE or were considered poor candidates for TACE due to the presence of portal vein invasion or bulky tumors.

Geschwind et. al. [59, 60] published a comprehensive analysis on using glass microspheres for HCC which showed improved survival in Okuda I when compared to Okuda II. In this study patients classified as Okuda stage I (n= 54) and II (n= 26) had median survival durations and 1-year survival rates of 628 days and 63%, and 384 days and 51%, respectively (P=.02)[60].

In a prospective study on 291 patients, 526 treatments with glass microspheres were performed and response rates were 42% and 57% based on WHO and EASL criteria, respectively. The overall time to progression was 7.9 months and survival times differed between Child-Pugh A and B patients (A:17.2 months, B:7.7 months, P=0.002). Child-Pugh A patients, with or without PVT, benefited most from treatment and Child-Pugh B patients with PVT had the worst outcomes[61]. They survived for only 5.6 months (95% CI:4.5–6.7).

In a multicenter analysis 325 patients were treated with a median activity of 1.6 GBq resin microspheres[62]. Typically, patients were Child-Pugh class A (82.5%) had underlying cirrhosis (78.5%) and good (ECOG) performance status (ECOG 0-1; 87.7%). Over half of the patients had advanced BCLC staging (BCLC C,56.3%) and one-quarter had intermediate

staging (BCLC B, 26.8%). The median overall survival was 12.8 months but varied significantly between the patients with different disease stages (BCLC A, 24.4 months; BCLC B, 16.9 months; BCLC C, 10.0 months). Consistent with this finding, survival varied significantly by ECOG status, hepatic function (Child-Pugh class, ascites, and baseline total bilirubin), tumor burden (number of nodules, alpha-fetoprotein), and presence of extrahepatic disease. In this study the most significant independent prognostic factors for survival upon multivariate analysis were ECOG status, tumor burden (nodules >5), INR >1.2 and extrahepatic disease. Common adverse events were: fatigue, nausea/vomiting, and abdominal pain. Grade 3 or higher increases in bilirubin were reported in 5.8% of patients. All-cause mortality was 0.6% and 6.8% at 30 and 90 days, respectively[62].

In a retrospective analysis, Salem et al. [63]compared RE with TACE regarding time to progression and toxicity. RE resulted in longer time-to-progression and less toxicity in this study. The survival times of the patients were similar for both treatment modalities, however; post-hoc analyses of sample size indicated that a randomized study with more than1000 patients would be required to establish equivalence of survival times between patients given the different therapies.

In a recently published meta analysis of 14 papers, Venti et. al[64] showed almost 80 % any response (AR =(CR+PR+SD)) for a total of 325 patients with HCC. In this meta analysis treatment with resin microspheres was associated with a significantly higher proportion of AR compared to that of glass microsphere treatment (0.89 vs. 0.78 (p=0.02)). Median survival from RE varied between 7.1 and 21.0 months, and median survival from diagnosis or recurrence was 9.4– 24.0 months.

In a study of 108 patients with advanced HCC and liver cirrhosis[65] complete responses were determined in 3% of patients, partial responses in 37%, stable disease 53%, and primary progression in 6% of patients. Time to progression was 10.0 months and the median overall survival was 16.4 months.

5.1. Radioembolization of patients with portal vein thrombosis

A compromised portal vein blood flow is usually considered a contraindication for TACE[66].

Due to the lack of significant macroembolic effect causing liver decompensation, portal vein thrombosis is not an absolute contraindication to RE. However, patients with main portal vein thrombosis have a poor prognosis after RE with a median overall survival ranging from 3 to 6 months[67, 68]. On the Contrary, patients with branch (segmentary or lobar) portal vein thrombosis may achieve an unforeseeable median survival post-RE of 10 to 14 months[67, 69].

5.2. Treating and Downsizing of HCC as a bridging to transplantation or resection

Patients with HCC are only conferred the United Network for Organ Sharing (UNOS) priority status upgrade if they meet the Milan (T2) criteria [70]. Therefore, if a patient can be down-staged from T3 to T2, the immediate advantage is a significant gain in status and therefore

much quicker access to a potentially life-saving organ. Lewandowski et al.[71] treated 86 patients with either TACE (n = 43) or RE (n = 43). The patients treated with RE achieved a median dose of 110 Gy. Median tumor size was similar in both groups. Partial response rates favored RE versus TACE (61% vs. 37%). Downstaging to UNOS T2 was achieved in 31% of TACE and 58% of RE patients. Time to progression according to UNOS criteria was similar for both groups. Event-free survival was significantly greater for RE than TACE (17.7 vs. 7.1 months, p =0.0017). Overall survival favored RE compared to TACE (censored 35.7/18.7 months; p = 0.18; uncensored 41.6/19.2 months; p = 0.008). The authors concluded that RE may outperform TACE for downstaging HCC from UNOS T3 to T2. There was also a significant difference between these two groups considering the median number of hospitalization days, being two days for TACE and 0 for RE (p < 0.001)[71].

Author, year	n	Response rate	Median survival
Lau[31], 1998	71	PR:27%, SD:65%	9.4 months
Goin[77], 2005	121		Low risk: 15.5 months
			High risk: 3.6 months
Salem[21], 2005	43	PR: 47 %	Okuda I: 24 months
			Okuda II: 13 months
Young[51], 2007	41		Okuda I: 21.7 months
			Okuda II: 14.2 months
Kulik[67], 2008	108	PR: 42%	No PVT: 15.4 months
		SD: 35 %	Branch PVT: 10.0 months
			Mail PVT: 4.4 months
Inarrairaegui[78], 2010	62		13 months
			< 5 nodules: 19 months
			> 5 nodules: 8 months
Hilgard[65], 2010	108	CR: 3%	16.4 months
		PR: 37 %	
		SD: 53%	
Salem, 2010	291	CR: 23 %	BCLC A: 26.9 months
		PR: 34 %	BCLC B: 17.2 months
			BCLC C: 7.3 months
			BCLC D: 2.5 months
Sangro[62], 2011	325		12.8 months
			BCLC A:24.4 months
			BCLC B: 16.9 months
			BCLC C: 10.0 months

PR: partial response; CR: complete response; SD: stable disease; PVT: portal vein thrombosis;

Table 4. Response rate and median survival of patients with HCC underwent RE

HCC arising from the caudate lobe is rare and has a poorer prognosis than HCC arising from the other hepatic lobes[72, 73]. In a retrospective study by Ibrahim et al[74] the effect of RE of unresectable HCC in caudate lobe was investigated in 8 patients who received a median radiation dose of 117 Gy. All patients presented with both cirrhosis and portal hypertension. Four patients were UNOS stage T3. One patient (13%) showed complete tumor response by WHO criteria, and three patients (38%) showed complete response using EASL guidelines. Serum AFP decreased by more than 50% in most patients (n = 6, 75%). Four patients (50%) were UNOS downstaged from T3 to T2, three of who underwent transplantation. One specimen showed histopathologic evidence of 100% complete necrosis, and two specimens demonstrated greater than 50% necrosis. Thus, RE seems to be a feasible, safe, and effective treatment option for patients with unresectable caudate lobe HCC.

Kulik et al.[75] reported a study of 35 patients with T3 unresectable HCC with RE with the intention of downstaging to resection or RFA. The study showed that RE can be used as a bridge to transplantation, surgical resection, or RFA. This allows the patients more time to wait for donor organs and thus increase their chance to undergoing liver transplantation[59]. Post RE downstaging followed by tumor resection or transplantation provides the possibility of long-term survival in a select subgroup (UNOS T3 stage) with otherwise limited options[76].

In Table 4 a summary of literatures on RE of HCC with more than 40 patients is demonstrated.

6. Conclusion

RE is a promising treatment modality to achieve regional tumour response and disease control in HCC. It offers survival benefit with a low toxicity profile. Recent investigations showed favorable survival outcomes even in patients with limited hepatic reserve and portal vein thrombosis that were excluded from most therapeutic options. However, Caution regarding patient selection, treatment preparation and performance is particularly important to prevent serious toxicity. Improvements in predicting dosimetry will lead to optimization of treatment outcome even in borderline treatment candidates.

RE has also been successfully used to bridge and downstage patients to resection, ablation or transplantation. With the sustained accumulation of promising clinical results, RE is moving forward from the salvage setting indication to the use in earlier stages of metastatic disease. Clinical trials should further define the precise role of RE in the treatment paradigm.

Author details

Hojjat Ahmadzadehfar[*], Amir Sabet and Hans Jürgen Biersack

*Address all correspondence to: hojjat.ahmadzadehfar@ukb.uni-bonn.de or nuclearmedicine@gmail.com

Department of Nuclear Medicine, University Hospital Bonn, Germany

References

[1] Eary, J. Principles of Therapy with Unsealed Sources. In: Eary J, Brenner W, eds. NU-CLEAR MEDICINE THERAPY (2007).

[2] Jarnagin, W. R, Gonen, M, Fong, Y, Dematteo, R. P, Ben-porat, L, et al. Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. Ann Surg (2002). discussion-7., 236, 397-406.

[3] Mulcahy, M. F, Lewandowski, R. J, Ibrahim, S. M, Sato, K. T, Ryu, R. K, et al. Radio-embolization of colorectal hepatic metastases using yttrium-90 microspheres. Cancer (2009). , 115, 1849-58.

[4] Greco, C, & Catalano, G. Di Grazia A, Orecchia R. Radiotherapy of liver malignan-cies. From whole liver irradiation to stereotactic hypofractionated radiotherapy. Tu-mori (2004). , 90, 73-9.

[5] Murthy, R, Nunez, R, Szklaruk, J, Erwin, W, Madoff, D. C, et al. Yttrium-90 micro-sphere therapy for hepatic malignancy: devices, indications, technical considerations, and potential complications. Radiographics (2005). Suppl 1: S, 41-55.

[6] Campbell, A. M, Bailey, I. H, & Burton, M. A. Analysis of the distribution of intra-arterial microspheres in human liver following hepatic yttrium-90 microsphere ther-apy. Phys Med Biol (2000). , 45, 1023-33.

[7] Salem, R, & Thurston, K. G. Radioembolization with 90Yttrium microspheres: a state-of-the-art brachytherapy treatment for primary and secondary liver malignancies. Part 1: Technical and methodologic considerations. J Vasc Interv Radiol (2006). , 17, 1251-78.

[8] Lien, W. M, & Ackerman, N. B. The blood supply of experimental liver metastases. II. A microcirculatory study of the normal and tumor vessels of the liver with the use of perfused silicone rubber. Surgery (1970). , 68, 334-40.

[9] Vente, M. A, Nijsen, J. F, De Wit, T. C, Seppenwoolde, J. H, Krijger, G. C, et al. Clini-cal effects of transcatheter hepatic arterial embolization with holmium-166 poly(L-lactic acid) microspheres in healthy pigs. Eur J Nucl Med Mol Imaging (2008). , 35, 1259-71.

[10] Lin, Y. C, Tsai, S. C, Hung, G. U, Lee, J. C, Huang, Y. S, et al. Direct injection of (188)Re-microspheres in the treatment of hepatocellular carcinoma: compared with traditional percutaneous ethanol injection: an animal study. Nuklearmedizin (2005). , 44, 76-80.

[11] Liu, L, Jiang, Z, Teng, G. J, Song, J. Z, Zhang, D. S, et al. Clinical and experimental study on regional administration of phosphorus 32 glass microspheres in treating hepatic carcinoma. World J Gastroenterol (1999). , 5, 492-505.

[12] Amoui, M, Pirayesh, E, Akhlaghpoor, S, Tolooee, B, Poorbeigi, H, et al. Correlation Between CT/MRI and Bremsstrahlung SPECT of 32P After Radioembolization of Hepatic Tumors. Iran J Radiol (2010). , 7, 1-5.

[13] Ahmadzadehfar, H, Biersack, H. J, & Ezziddin, S. Radioembolization of liver tumors with yttrium-90 microspheres. Semin Nucl Med (2010). , 40, 105-21.

[14] Sarfaraz, M, Kennedy, A. S, Lodge, M. A, Li, X. A, Wu, X, et al. Radiation absorbed dose distribution in a patient treated with yttrium-90 microspheres for hepatocellular carcinoma. Med Phys (2004). , 31, 2449-53.

[15] Sarfaraz, M, Kennedy, A. S, Cao, Z. J, Sackett, G. D, Yu, C. X, et al. Physical aspects of yttrium-90 microsphere therapy for nonresectable hepatic tumors. Med Phys (2003). , 30, 199-203.

[16] Dancey, J. E, Shepherd, F. A, Paul, K, Sniderman, K. W, Houle, S, et al. Treatment of nonresectable hepatocellular carcinoma with intrahepatic 90Y-microspheres. J Nucl Med (2000). , 41, 1673-81.

[17] Stubbs, R. S, Cannan, R. J, & Mitchell, A. W. Selective internal radiation therapy (SIRT) with 90Yttrium microspheres for extensive colorectal liver metastases. Hepatogastroenterology (2001). , 48, 333-7.

[18] Lawrence, T. S, Robertson, J. M, Anscher, M. S, Jirtle, R. L, Ensminger, W. D, et al. Hepatic toxicity resulting from cancer treatment. Int J Radiat Oncol Biol Phys (1995). , 31, 1237-48.

[19] Kennedy, A, Nag, S, Salem, R, Murthy, R, Mcewan, A. J, et al. Recommendations for radioembolization of hepatic malignancies using yttrium-90 microsphere brachytherapy: a consensus panel report from the radioembolization brachytherapy oncology consortium. Int J Radiat Oncol Biol Phys (2007). , 68, 13-23.

[20] Lewandowski, R. J, Thurston, K. G, Goin, J. E, Wong, C. Y, Gates, V. L, et al. Y microsphere (TheraSphere) treatment for unresectable colorectal cancer metastases of the liver: response to treatment at targeted doses of 135-150 Gy as measured by [18F]fluorodeoxyglucose positron emission tomography and computed tomographic imaging. J Vasc Interv Radiol (2005). , 16, 1641-51.

[21] Salem, R, Lewandowski, R. J, Atassi, B, Gordon, S. C, Gates, V. L, et al. Treatment of unresectable hepatocellular carcinoma with use of 90Y microspheres (TheraSphere): safety, tumor response, and survival. J Vasc Interv Radiol (2005). , 16, 1627-39.

[22] Eiber, H. B, Goldbloom, A. A, Boyd, L. J, Chapman, I, & Deutschberger, O. Newer clinical and laboratory studies in the aged. II. Correlated serum lipid partitions and

lipoprotein molecules (Sf 0-400) in patients 80-100 years of age: preliminary report. Bull N Y Acad Med (1954). , 30, 719-20.

[23] Ramirez de Molina ARodriguez-Gonzalez A, Gutierrez R, Martinez-Pineiro L, Sanchez J et al. Overexpression of choline kinase is a frequent feature in human tumor-derived cell lines and in lung, prostate, and colorectal human cancers. Biochem Biophys Res Commun (2002). , 296, 580-3.

[24] Hara, T, Kosaka, N, & Kishi, H. PET imaging of prostate cancer using carbon-11-choline. J Nucl Med (1998). , 39, 990-5.

[25] Roedl, J. B, Halpern, E. F, Colen, R. R, Sahani, D. V, Fischman, A. J, et al. Metabolic tumor width parameters as determined on PET/CT predict disease-free survival and treatment response in squamous cell carcinoma of the esophagus. Mol Imaging Biol (2009). , 11, 54-60.

[26] Covey, A. M, Brody, L. A, Maluccio, M. A, Getrajdman, G. I, & Brown, K. T. Variant hepatic arterial anatomy revisited: digital subtraction angiography performed in 600 patients. Radiology (2002). , 224, 542-7.

[27] Leung, T. W, Lau, W. Y, Ho, S. K, Ward, S. C, Chow, J. H, et al. Radiation pneumonitis after selective internal radiation treatment with intraarterial 90yttrium-microspheres for inoperable hepatic tumors. Int J Radiat Oncol Biol Phys (1995). , 33, 919-24.

[28] Liu, D. M, Salem, R, Bui, J. T, Courtney, A, Barakat, O, et al. Angiographic considerations in patients undergoing liver-directed therapy. J Vasc Interv Radiol (2005). , 16, 911-35.

[29] Sabet, A, Ahmadzadehfar, H, Muckle, M, Haslerud, T, Biermann, K, et al. Significance of Oral Administration of Natrium Perchlorate in Planning of Liver Directed Radioembolisation. 23rd Annual EANM Congress. Vienna, Austria (2010).

[30] Ahmadzadehfar, H, Sabet, A, Biermann, K, Muckle, M, Brockmann, H, et al. The significance of 99mTc-MAA SPECT/CT liver perfusion imaging in treatment planning for 90Y-microsphere selective internal radiation treatment. J Nucl Med (2010). , 51, 1206-12.

[31] Lau, W. Y, Ho, S, Leung, T. W, Chan, M, Ho, R, et al. Selective internal radiation therapy for nonresectable hepatocellular carcinoma with intraarterial infusion of 90yttrium microspheres. Int J Radiat Oncol Biol Phys (1998). , 40, 583-92.

[32] Eiber, I. S. Biologic reaction for pregnancy with male frogs Rana ridibunda.]. Akush Ginekol (Mosk) (1951). , 4, 40-2.

[33] Salem, R, & Hunter, R. D. Yttrium-90 microspheres for the treatment of hepatocellular carcinoma: a review. Int J Radiat Oncol Biol Phys (2006). S, 83-8.

[34] Hamami, M. E, Poeppel, T. D, Muller, S, Heusner, T, Bockisch, A, et al. SPECT/CT with 99mTc-MAA in Radioembolization with 90Y Microspheres in Patients with Hepatocellular Cancer. J Nucl Med (2009). , 50, 688-92.

[35] Denecke, T, Ruhl, R, Hildebrandt, B, Stelter, L, Grieser, C, et al. Planning transarterial radioembolization of colorectal liver metastases with Yttrium 90 microspheres: eval‐uation of a sequential diagnostic approach using radiologic and nuclear medicine imaging techniques. Eur Radiol (2008). , 18, 892-902.

[36] Moroz, P, Anderson, J. E, Van Hazel, G, & Gray, B. N. Effect of selective internal radi‐ation therapy and hepatic arterial chemotherapy on normal liver volume and spleen volume. J Surg Oncol (2001). , 78, 248-52.

[37] Lewandowski, A, & Salem, R. Yttrium-90 Radioembolization of Hepatocellular Car‐cinoma and Metastatic Disease to the Liver. SEMINARS IN INTERVENTIONAL RA‐DIOLOGY (2006). , 23, 64-72.

[38] Murthy, R, Habbu, A, & Salem, R. Trans-arterial hepatic radioembolisation of yttri‐um-90 microspheres. Biomedical Imaging and Intervention Journal (2006).

[39] Riaz, A, Lewandowski, R. J, Kulik, L. M, Mulcahy, M. F, Sato, K. T, et al. Complica‐tions Following Radioembolization with Yttrium-90 Microspheres: A Comprehensive Literature Review. J Vasc Interv Radiol (2009).

[40] Ahmadzadehfar, H, Muckle, M, Sabet, A, Wilhelm, K, Kuhl, C, et al. The significance of bremsstrahlung SPECT/CT after yttrium-90 radioembolization treatment in the prediction of extrahepatic side effects. Eur J Nucl Med Mol Imaging (2011).

[41] Murthy, R, Brown, D. B, Salem, R, Meranze, S. G, Coldwell, D. M, et al. Gastrointesti‐nal complications associated with hepatic arterial yttrium-90 microsphere therapy. Journal of Vascular and Interventional Radiology (2007). , 18, 553-62.

[42] Carretero, C, Munoz-navas, M, Betes, M, Angos, R, Subtil, J. C, et al. Gastroduodenal injury after radioembolization of hepatic tumors. Am J Gastroenterol (2007). , 102, 1216-20.

[43] Salem, R, Parikh, P, Atassi, B, Lewandowski, R. J, Ryu, R. K, et al. Incidence of radia‐tion pneumonitis after hepatic intra-arterial radiotherapy with yttrium-90 micro‐spheres assuming uniform lung distribution. Am J Clin Oncol (2008). , 31, 431-8.

[44] Ahmadzadehfar, H, Sabet, A, Biermann, K, Brockmann, H, Kuhl, C, et al. The signifi‐cance of Tc-99m-MAA SPECT-CT liver perfusion imaging in treatment planning for yttrium 90 microsphere selective internal radiation treatment. J NUCL MED MEET‐ING ABSTRACTS (2009). , 50, 1662.

[45] Kennedy, A. S, Coldwell, D, Nutting, C, Murthy, R, Wertman, D. E, et al. Resin 90Y-microsphere brachytherapy for unresectable colorectal liver metastases: modern USA experience. Int J Radiat Oncol Biol Phys (2006). , 65, 412-25.

[46] Goin, J. E, Salem, R, Carr, B. I, Dancey, J. E, Soulen, M. C, et al. Treatment of unresect-able hepatocellular carcinoma with intrahepatic yttrium 90 microspheres: factors associated with liver toxicities. J Vasc Interv Radiol (2005). , 16, 205-13.

[47] Ingold, J. A, Reed, G. B, Kaplan, H. S, & Bagshaw, M. A. Radiation Hepatitis. Am J Roentgenol Radium Ther Nucl Med (1965). , 93, 200-8.

[48] Fox, R. A, Klemp, P. F, Egan, G, Mina, L. L, Burton, M. A, et al. Dose distribution following selective internal radiation therapy. Int J Radiat Oncol Biol Phys (1991). , 21, 463-7.

[49] Sangro, B, Bilbao, J. I, Boan, J, Martinez-cuesta, A, Benito, A, et al. Radioembolization using 90Y-resin microspheres for patients with advanced hepatocellular carcinoma. Int J Radiat Oncol Biol Phys (2006). , 66, 792-800.

[50] Kennedy, A. S, Nutting, C, Jakobs, T, Cianni, R, Notarianni, E, et al. A First Report of Radioembolization for Hepatic Metastases From Ocular Melanoma. Cancer Invest (2009).

[51] Young, J. Y, Rhee, T. K, Atassi, B, Gates, V. L, Kulik, L, et al. Radiation dose limits and liver toxicities resulting from multiple yttrium-90 radioembolization treatments for hepatocellular carcinoma. J Vasc Interv Radiol (2007). , 18, 1375-82.

[52] Kennedy, A. S, Mcneillie, P, Dezarn, W. A, Nutting, C, Sangro, B, et al. Treatment parameters and outcome in 680 treatments of internal radiation with resin 90Y-microspheres for unresectable hepatic tumors. Int J Radiat Oncol Biol Phys (2009). , 74, 1494-500.

[53] Seidensticker, R, Seidensticker, M, Damm, R, Mohnike, K, Schutte, K, et al. Hepatic toxicity after radioembolization of the liver using (90)y-microspheres: sequential lobar versus whole liver approach. Cardiovasc Intervent Radiol (2012). , 35, 1109-18.

[54] Sangro, B, Gil-alzugaray, B, Rodriguez, J, Sola, I, Martinez-cuesta, A, et al. Liver disease induced by radioembolization of liver tumors: description and possible risk factors. Cancer (2008). , 112, 1538-46.

[55] Senzolo, M, Germani, G, Cholongitas, E, Burra, P, & Burroughs, A. K. Veno occlusive disease: update on clinical management. World J Gastroenterol (2007). , 13, 3918-24.

[56] Bayraktar, U. D, Seren, S, & Bayraktar, Y. Hepatic venous outflow obstruction: three similar syndromes. World J Gastroenterol (2007). , 13, 1912-27.

[57] Chopra, R, Eaton, J. D, Grassi, A, Potter, M, Shaw, B, et al. Defibrotide for the treatment of hepatic veno-occlusive disease: results of the European compassionate-use study. Br J Haematol (2000). , 111, 1122-9.

[58] Sangro, B, Inarrairaegui, M, & Bilbao, J. I. Radioembolization for hepatocellular carcinoma. J Hepatol (2012). , 56, 464-73.

[59] Riaz, A, Lewandowski, R. J, Kulik, L, & Salem, R. Yttrium-90 radioembolization us-
ing Thera- Sphere(R) in the management of primary and secondary liver tumors. Q J
Nucl Med Mol Imaging (2009). , 53, 311-6.

[60] Geschwind, J. F, Salem, R, Carr, B. I, Soulen, M. C, Thurston, K. G, et al. Yttrium-90
microspheres for the treatment of hepatocellular carcinoma. Gastroenterology (2004).
S, 194-205.

[61] Salem, R, Lewandowski, R. J, Mulcahy, M. F, Riaz, A, Ryu, R. K, et al. Radioemboli-
zation for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive
report of long-term outcomes. Gastroenterology (2009).

[62] Sangro, B, Carpanese, L, Cianni, R, Golfieri, R, Gasparini, D, et al. Survival after yttri-
um-90 resin microsphere radioembolization of hepatocellular carcinoma across Bar-
celona clinic liver cancer stages: a European evaluation. Hepatology (2011). , 54,
868-78.

[63] Salem, R, Lewandowski, R. J, Kulik, L, Wang, E, Riaz, A, et al. Radioembolization re-
sults in longer time-to-progression and reduced toxicity compared with chemoembo-
lization in patients with hepatocellular carcinoma. Gastroenterology (2011). e2., 140,
497-507.

[64] Vente, M. A, Wondergem, M, & Van Der Tweel, I. van den Bosch MA, Zonnenberg
BA et al. Yttrium-90 microsphere radioembolization for the treatment of liver malig-
nancies: a structured meta-analysis. Eur Radiol (2009). , 19, 951-9.

[65] Hilgard, P, Hamami, M, Fouly, A. E, Scherag, A, Muller, S, et al. Radioembolization
with yttrium-90 glass microspheres in hepatocellular carcinoma: European experi-
ence on safety and long-term survival. Hepatology (2010). , 52, 1741-9.

[66] Bruix, J, & Sherman, M. Management of hepatocellular carcinoma: an update. Hepa-
tology (2011). , 53, 1020-2.

[67] Kulik, L. M, Carr, B. I, Mulcahy, M. F, Lewandowski, R. J, Atassi, B, et al. Safety and
efficacy of 90Y radiotherapy for hepatocellular carcinoma with and without portal
vein thrombosis. Hepatology (2008). , 47, 71-81.

[68] Woodall, C. E, Scoggins, C. R, Ellis, S. F, Tatum, C. M, Hahl, M. J, et al. Is selective
internal radioembolization safe and effective for patients with inoperable hepatocel-
lular carcinoma and venous thrombosis? J Am Coll Surg (2009). , 208, 375-82.

[69] Inarrairaegui, M, Thurston, K. G, Bilbao, J. I, Avola, D, & Rodriguez, D. M et al. Radi-
oembolization with use of yttrium-90 resin microspheres in patients with hepatocel-
lular carcinoma and portal vein thrombosis. J Vasc Interv Radiol (2010). , 21, 1205-12.

[70] Mazzaferro, V, Regalia, E, Doci, R, Andreola, S, Pulvirenti, A, et al. Liver transplanta-
tion for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N
Engl J Med (1996). , 334, 693-9.

[71] Lewandowski, R. J, Kulik, L. M, Riaz, A, Senthilnathan, S, Mulcahy, M. F, et al. A Comparative Analysis of Transarterial Downstaging for Hepatocellular Carcinoma: Chemoembolization Versus Radioembolization. Am J Transplant (2009).

[72] Takayama, T, & Makuuchi, M. Segmental liver resections, present and future-caudate lobe resection for liver tumors. Hepatogastroenterology (1998). , 45, 20-3.

[73] Takayasu, K, Muramatsu, Y, Shima, Y, Goto, H, Moriyama, N, et al. Clinical and radiologic features of hepatocellular carcinoma originating in the caudate lobe. Cancer (1986). , 58, 1557-62.

[74] Ibrahim, S. M, Kulik, L, Baker, T, Ryu, R. K, Mulcahy, M. F, et al. Treating and downstaging hepatocellular carcinoma in the caudate lobe with yttrium-90 radioembolization. Cardiovasc Intervent Radiol (2012). , 35, 1094-101.

[75] Kulik, L. M, Atassi, B, Van Holsbeeck, L, Souman, T, Lewandowski, R. J, et al. Yttrium-90 microspheres (TheraSphere) treatment of unresectable hepatocellular carcinoma: downstaging to resection, RFA and bridge to transplantation. J Surg Oncol (2006). , 94, 572-86.

[76] Inarrairaegui, M, Pardo, F, Bilbao, J. I, Rotellar, F, Benito, A, et al. Response to radioembolization with yttrium-90 resin microspheres may allow surgical treatment with curative intent and prolonged survival in previously unresectable hepatocellular carcinoma. Eur J Surg Oncol (2012). , 38, 594-601.

[77] Goin, J. E, Salem, R, Carr, B. I, Dancey, J. E, Soulen, M. C, et al. Treatment of unresectable hepatocellular carcinoma with intrahepatic yttrium 90 microspheres: a risk-stratification analysis. J Vasc Interv Radiol (2005). , 16, 195-203.

[78] Inarrairaegui, M, Martinez-cuesta, A, Rodriguez, M, Bilbao, J. I, Arbizu, J, et al. Analysis of prognostic factors after yttrium-90 radioembolization of advanced hepatocellular carcinoma. Int J Radiat Oncol Biol Phys (2010). , 77, 1441-8.