Radioembolisation with Yttrium-90 Microspheres for Hepatocellular Carcinoma – Method and Results

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Abstract
Microsphere and particle technology with selective transport of tumouricidal substances or radiation represents a new generation of therapeutics in interventional oncology. With the intrahepatic application of radioactive microspheres via the hepatic artery (radioembolisation), local ablation can be performed on even diffuse and multifocal liver tumours, which hitherto could only be approached with systemic therapy. The current standard for radioembolisation is the use of yttrium-90 glass or resin microspheres. The indications, technique and results of radioembolisation with yttrium-90 microspheres for the treatment of hepatocellular carcinoma (HCC) are discussed in this article.

Keywords
Yttrium-90 microspheres, Y-90, radioembolisation, selective internal radiotherapy, hepatocellular carcinoma, portal vein thrombosis, survival, time to progression

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Compared with other malignant tumours, hepatocellular carcinoma (HCC) exhibits particular characteristics regarding its supply vessels and tumour biology. If a potentially curative surgical approach such as resection or liver transplantation is not an option due to technical or prognostic reasons, these characteristics are a fundamental prerequisite for effectively treating this tumour by local ablation methods. First, HCCs are frequently relatively well differentiated tumours showing slow growth kinetics and, unlike other more malignant tumours, lead to extrahepatic metastases relatively late in the course of the disease. Second, tumours growing in the liver draw their supply of nutrients and oxygen almost exclusively from the hepatic artery, whereas the surrounding healthy (or cirrhotic) liver tissue is predominantly supplied from the portal vein. This differential blood supply facilitates selective therapeutic access to liver tumours via the hepatic artery, without significant damage to the surrounding tissue. Today, transarterial procedures are the most important techniques for local tumour ablation in the liver, and the most frequently used transarterial method is chemoembolisation, in which the tumour is destroyed by a combination of interruption of the arterial blood supply (embolisation) with concomitant application of a chemotherapeutic agent. However, radioembolisation or selective internal radiotherapy (SIRT) is also gaining in importance. With this method, various radionuclides bound to different particle carriers are introduced into the tumour via the hepatic arteries. Besides the radionuclide yttrium-90, which is highly suitable due to its physical properties, iodine-131 and, more recently, rhenium-188 have been utilised for radioembolisation. However, since Y-90 microspheres are used more widely and are commercially available, they will be the major subject of this article.

Overview and History
Although the clinical application of Y-90 microsphere radioembolisation in patients with primary and secondary liver tumours has increased only in the last five to seven years, it is the oldest method of transarterial therapy for liver tumours described. Y-90 is a pure β-emitter with energy of 2.24MeV. The half-life is approximately 64 hours. Within tissue, the radiation emitted by Y-90 has a mean range of 2.5–3.5mm. Despite numerous reports over the last few decades, radioembolisation with Y-90 microspheres has only recently gained considerable importance in the treatment of primary and secondary liver tumours because of the appreciation that these patients may greatly profit from the sole or supportive local ablation of tumour nodules in the liver. In addition, due to numerous technical improvements in both the production of microspheres and in pre-treatment imaging, it has become clear that the toxicity of local radioembolisation is actually much lower than that of most systemic oncological therapies.

After a short comparison of the products available for Y-90 radioembolisation today, the indications for patients with HCC will be discussed in this article. The clinical and vascular anatomy pre-conditions for microsphere treatment as well as the preparation of
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the patient for this therapy will be further subjects, followed by a description of the dosimetric consideration and the therapeutic procedure. Finally, the results of recent studies on HCC will be reported.

Products

Currently, two products with different physical properties are commercially available for treatment with Y-90 microspheres. The details are shown in Table 1. Therasphere consists of non-degradable glass microspheres incorporating Y-89, which, after production of the spheres, is converted to radioactive Y-90 by a neutron beam in a reactor. By contrast, SIR-Spheres® are resin particles, to the surface of which the radionuclide is bound after production. It appears that Therasphere contains a substantially higher amount of radioactivity per particle than SIR-Spheres.

Indications for Selective Internal Radiotherapy with Y-90 Microspheres in Patients with Hepatocellular Carcinoma as Part of a Multimodal Therapy Strategy

Therapy of HCC is performed in a multidisciplinary approach, with surgical, locoregional and systemic treatments following one another in succession or even undertaken simultaneously. To illustrate this, our institutional treatment algorithm (see Figure 1), based on the recommendations of the European Association for the Study of the Liver (EASL) and the Barcelona Clinic Liver Cancer Group (BCLC), shows the current position of SIRT with Y-90 micropheres embedded in a multimodal therapeutic strategy for HCC. Although surgery, and in particular liver transplantation, is still the only real curative treatment option for patients with HCC, 70–80% of patients with HCC at the time of initial diagnosis are already at a tumour stage that is ineligible for a surgical approach. While patients with intermediate tumour stages can be effectively treated by the conventional locoregional ablation methods, such as radiofrequency ablation (RFA) and transarterial chemoembolisation (TACE), patients in more advanced tumour stages, for instance with macrovascular invasion of vessels (portal vein thrombosis) is impossible or ineffective, systemic therapy with sorafenib is the only options.

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Table 1: Differences in the Commercial Y-90 Microsphere Products

<table>
<thead>
<tr>
<th></th>
<th>Y-90 Glass Microspheres (Therasphere, MDS Nordion)</th>
<th>Y-90 Resin Microspheres (SIR-Spheres, Sirtex)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of microspheres per dose</td>
<td>Can be modified (3, 5, 7, 10, 15 and 20GBq, corresponding to 1.2; 2; 2.8; 4; 6; 8 x 10⁶ particles)</td>
<td>Cannot be modified (~50 x 10⁶ particles)</td>
</tr>
<tr>
<td>Particle size</td>
<td>20–30µm</td>
<td>20–60µm</td>
</tr>
<tr>
<td>Specific activity</td>
<td>2,500</td>
<td>50</td>
</tr>
<tr>
<td>Licensed in Europe</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Embolising effect</td>
<td>No</td>
<td>Yes, therefore contraindicated in PVT</td>
</tr>
<tr>
<td>Angiographic control during administration</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Activity applied</td>
<td>Dependent on target volume of the vascular territory treated</td>
<td>Dependent on body surface area and size of tumour</td>
</tr>
</tbody>
</table>

- verified tumour (histology or non-invasive criteria according to American Association for the Study of Liver Diseases (AASLD));
- adequate liver function;
- no extrahepatic metastases;
- arterial hypervascularisation of the tumour;
- no or correctable visceral shunt;
To ensure a high level of safety for the therapy, a number of pre-treatment procedures and evaluations must be completed.

Clinical and Biochemical Evaluation
The purpose of clinical and biochemical examination of the patient is to ensure adequate liver function, which is an important prerequisite for the therapy. Based on the Child-Turcotte-Pugh classification of liver dysfunction in cirrhosis, a score of six to seven should not be exceeded. Other absolute and relative contraindications for the treatment are shown in Table 2.

Imaging
Cross-sectional imaging with contrast-enhanced ultrasound (CEUS), computed tomography (CT) and/or magnetic resonance tomography (MRT) is of decisive significance for establishing the indication for radioembolisation, as well as for planning the procedure. Cross-sectional imaging is used to:

- evaluate the intrahepatic distribution of the tumour;
- exclude extrahepatic metastasis;
- exclude possible other contraindications; and
- measure target volume and/or tumour burden.

Therasphere
The target volume is defined as the proportion of the liver that is supplied by the artery to be injected. For example, the target volume for a treatment via the right lobar branch of the hepatic artery (assuming normal anatomy) is the right liver lobe. Besides the target volume, tumour burden within the target volume is estimated by CT or MRI volumetry, as a tumour burden of $>70\%$ of the entire liver is a risk factor for complications and limited efficacy. Dosimetry for Therasphere uses the target volume and then follows the considerations indicated below in detail (see paragraph on dosimetry).

SIR-Spheres
Dosimetry when using SIR-Spheres is based on body surface area and tumour burden (Radioembolisation Brachytherapy Oncology Consortium [REBOC], see below). To quantify tumour burden, both tumour volume and total liver volume must be determined by CT volumetry.

Pre-treatment Angiography
Prior to the therapy with Y-90 microspheres, a pre-treatment or preparation angiography is necessary. In addition to evaluation of the vascularity of the tumour (see Figure 2), a major objective of pre-treatment angiography is to detect possible normal arterial variants and to establish the precise positions for the catheters during the treatment session so that the microspheres cover all the areas affected by the tumour and potential complications are avoided. The spread of particles into an extrahepatic blood vessel inducing radiation necrosis in other gastrointestinal organs such as small bowels or pancreas is a serious complication of radioembolisation. To prevent this potential complication, all collaterals arising from the hepatic arterial bed of the target area supplying extrahepatic tissues must be occluded by coil embolisation prior to treatment. Depending on the main target area, this often applies to the right gastric artery and the gastroduodenal artery (see Figure 3). The risk of inducing ischaemia in the supplied gastrointestinal organs by occlusion of a single vessel is extremely low with respect to the marked collateralisation of the gastrointestinal arterial network. However, the gallbladder needs special attention, since collateralisation here is only marginal. In addition to the large and regularly present gastrointestinal vessels originating from the hepatic artery, there is a great variety of (generally small) accessory vessels to the gastrointestinal region arising from arterial bed of the liver. These vessels must be attempted to be identified and occluded by the preparation angiography. If this is unsuccessful, an attempt should be made to position the microcatheter distal to the origin of the collateral gastrointestinal vessels.

Shunt Diagnosis Using 99mTc-labelled Macroaggregated Albumin Scan
Following coil embolisation of gastrointestinal vessels, the microcatheter is inserted into the proper hepatic artery (for therapy of the whole liver) or selectively in the right or left hepatic artery (for selective therapy of only one lobe). Then, as a surrogate for Y-90 microspheres, 150MBq of technetium 99-labelled macroaggregated
albumin (MAA) is injected via the microcatheter. With a particle size of between 10 and 90μm. MAA is very similar in particle size to Therasphere (20–30μm) and SIR-Spheres (20–60μm). Scintigraphic images (as a planar whole-body scan or SPECT/CT) thus provide information about the expected distribution of Y-90 microspheres during therapy.

The fraction of particles that dislocate into the lungs (usually through tumour-associated shunt vessels), and therefore the radiation dose to the lung is quantified using a region-of-interest (ROI) technique from:

\[
\text{Shunt}_{\text{LUNG}} = \sqrt{\text{ROILung}_{\text{anterior}} \cdot \text{ROILung}_{\text{posterior}}} \div \sqrt{\text{ROILiver}_{\text{anterior}} \cdot \text{ROILiver}_{\text{posterior}} + \text{ROILiver}_{\text{anterior}} \cdot \text{ROILiver}_{\text{posterior}}}
\]

In addition, a potential gastrointestinal accumulation of spheres can be detected and, in particular by single photon emission computed tomography (SPECT/CT), precisely located. Should there be such an extrahepatic abdominal MAA accumulation, i.e. a gastrointestinal shunt of microspheres, the pre-treatment angiography must be repeated to identify the collateral vessel responsible and occlude it. If no relevant vessel can be identified or occluded in a repeat angiography and an additional MAA scan confirms the existence of the extrahepatic accumulation, this has to be considered as a non-correctable gastrointestinal shunt, representing a relative contraindication for radioembolisation.

**Dosimetry and Calculation of Therapeutic Activity with Y-90 Microspheres**

The aim of dosimetry for radioembolisation of malignant hepatic tumours with Y-90 microspheres is to optimise the radiation dose in the tumour while at the same time complying with the dose restrictions for the surrounding tissues at risk. These are the parts of the liver not affected by the tumour, the lungs and the abdominal organs in the region supplied by the hepatic artery into which the microspheres are administered.

After correcting any gastrointestinal shunt that may be present by vascular occlusion, further distribution of the microspheres into the region supplied by the vessel in which the spheres are injected and into shunts originating from it is proportional to the blood flow in the tissue. Dosimetry has to assess whether by using the maximum tolerable activity, the prospect of an adequate radiation effect in the tumour can be realised. This requires an understanding not only of the physical basics of dose calculation but also of the dose/efficacy relationship and the dose limits for the organs at risk, as well as of prognostic risk factors from the primary disease and previous treatments or co-morbidities.

**Tolerance Doses for Therapy with Y-90 Microspheres**

Considering tolerance doses for normal and tumour tissues, there is a fundamental difference between percutaneous radiotherapy, which has a high dose rate (in the order of 10–100Gy/h), and radionuclide therapy, with its low dose rate (in the order of 0.1Gy/h). The biological efficacy of a given dose is less for a low dose rate, but the scale of the decrease (in efficacy) depends on the radiobiological properties of the tissues irradiated and is typically more marked in normal tissue than in many tumours. As a result, toxicity in normal tissue may be less with a low dose rate than with a high dose rate while producing the same therapeutic effect in the tumour. Considering also that the dose distribution of Y-90 is inhomogeneous and that the tolerance of normal organs depends on the percentage volume irradiated of the whole organ, it is not surprising that the tolerance doses for the lungs and liver known from percutaneous radiotherapy can be exceeded for radioembolisation with Y-90 microspheres without increasing toxicity. The tolerance dose for the lungs was originally suggested by Ho et al. to be 30Gy for a single treatment and 50Gy for cumulative treatments. The REBOC consensus panel adopted this recommendation recently after a systematic review of the literature, and also restricted the cumulative dose for the lungs to 30Gy.
Liver

In addition, the panel recommended a liver dose of 100–120Gy for Therasphere as the best compromise at the time between response rates and delayed radiotoxic reactions in the healthy liver, and an activity of approximately 1.5–2.0GBq for SIR-Spheres. However, some individual studies demonstrated that, without risk factors, a single administration with a dose of 150Gy shows no enhanced toxicity.10,11 In the presence of a pre-existing impairment of liver function, these limits must be reduced. Since radiation tolerance of the liver depends on the volume irradiated, dose escalation may be indicated if administration of the microspheres is restricted to a single lobe, or even to just one or several liver segments affected by the malignant disease.

The Y-90 doses for gastrointestinal organs cannot be determined in practice, so their tolerance doses are not known. Therefore, preventing gastrointestinal toxicity requires the scrupulous occlusion of the afferent vessels to the intestines, stomach or pancreas.

Calculating Therapeutic Activity for Yttrium-90 Glass Microspheres (Therasphere)

The planned target volume (PTV) is the portion of the liver tissue surrounding the target tumour that is perfused by the vessels distal from the injection site defined in the pre-treatment angiography. With good liver function, typical mean target volume doses of 100–120Gy are indicated; dose escalation up to 150Gy is considered to be ‘low-risk’ in the literature.10 In reduced liver function (liver cirrhosis) and/or pre-existing toxic damage (e.g. from chemotherapy), dose reduction to 80–100Gy may be considered. When a lung dose below 30Gy is maintained, no radiation-induced pulmonary toxicity need be envisaged.1 In practice, so their tolerance doses are not known. Therefore, the therapeutic activity must be adjusted by aliquoting and calibration by the user. This presents a higher risk of contamination and higher exposure to radiation for the staff, but, on the other hand, compared with Therasphere there is more flexibility with the timing of therapy. The high particle count can cause an embolism in the bloodstream being treated and, as a result, reflux of particles into structures not belonging to the region being treated may be possible. Therefore, SIR-Spheres must be administered with interruptions for angiographic evaluation of blood flow. If reflux starts to appear, administration must be discontinued even if the chosen therapeutic activity has not yet been attained.

THERAPY PROCEDURE OF RADIOEMBOLISATION WITH Y-90 MICROSPHERES

The first step in the therapeutic session is, once more, the angiographic visualisation of the hepatic arterial vessels after introduction of a macrocatheter into the coeliac trunk. Attention must be paid to any changes in the anatomy and flow rates compared with the situation in the preparation angiography. In rare cases, coil embolisation of the gastroduodenal artery may have produced collateralisation of previously invisible gastrointestinal vessels originating in the hepatic vascular system. Additional coil embolisation of such vessels is mandatory in this situation in order to prevent spread of particles to the gastrointestinal region, and must be performed directly before injecting the microspheres. Once no further gastrointestinal flow of the contrast agent can be detected, the coil embolisation device is removed and the microspheres are injected.
be detected (with or without new embolisation), a coaxial microcatheter is introduced via the macrocatheter and positioned at the previously defined treatment location (usually the right or left hepatic artery). The correct position of the tip of the catheter is once again confirmed by administering contrast agent via the microcatheter. The Y-90 microspheres are then injected using a special injector on which the pressure created during injection is displayed at any time. This can be performed under intermittent fluoroscopy to exclude displacement of the microcatheter during therapy. When using SIR-Spheres, contrast agent must also be given intermittently in order to identify any embolisation of the arterial transport vessels in good time, and to be able to react to any potential microsphere reflux. Following injection of the Y-90 microspheres, the patient must be monitored according to national guidelines for patients after radionuclide treatment.

**Radiation Protection Before and During Selective Internal Radiotherapy with Y-90 Microspheres**

Y-90 microsphere handling and treatment must be performed under the responsibility of an authorised user, who in most countries is a nuclear medicine physician. Administration has to take place in a radio safety controlled area in conjunction with a qualified medical physicist. Particular caution is required regarding radiation protection when handling Y-90. Compared with the pure gamma emitter technetium-99m, the dose for an unshielded source of Y-90 at a distance of 30cm is higher by a factor of 450. Therefore, attention must be paid to providing an adequate shield, and every risk of contamination has to be minimised. In addition to the official film badges and dosimeters, personal dosimetry requires special β-sensitive finger-ring dosimeters. In the case of room contamination, it is usually difficult to remove microspheres from uneven floor surfaces. Therefore, decontamination of the angiography room can be a problem and may require long-term closure. Therefore, extra barriers to contamination in the form of several covers are urgently recommended. All potentially radioactive waste must be collected in adequately shielded containers and disposed of in compliance with the law. The exposure to radiation anticipated from treated patients for individual members of the population is below the recommended. All potentially radioactive waste must be collected and is thus clearly better than the historical controls18 of 244 and 64 days, respectively.

A major side effect after chemoembolisation is represented by the post-embolisation syndrome (PES) with fever, nausea and abdominal pain. The occurrence of PES following therapy with Y-90 microspheres or chemoembolisation has been compared in a small number of patients.15 It was shown that, notwithstanding a better radiological tumour response, PES following therapy with Y-90 microspheres appeared approximately four times less often than after chemoembolisation, which is indicative of the different mechanisms of action of the two methods in destroying tumour tissue.

However, a common laboratory adverse event with no described clinical consequences to date is the transient lymphopenia first described by Carr in 2004,20 which occurs in 60–75% of cases. Median survival was given in this study for Okuda I patients as 628–649 days and for Okuda II patients as 302–324 days, and is thus clearly better than the historical control18 of 244 and 64 days, respectively.

Similar median survival times (Okuda I patients: 628 days; Okuda II patients: 324 days) were also reported in what was, until recently, the largest analysis, by Geschwind et al., in which 80 patients from a multicentre databank were studied retrospectively.19 At the same time the various scoring systems for HCC were compared with regard to risk stratification, with the conclusion that the Cancer of the Liver Italian Program (CLIP) score gave the most reliable results. However, the proposed randomised study using the CLIP score as a selection criterion and comparing Y-90 microsphere radioembolisation with chemoembolisation has not yet been carried out.

An important amendment with respect to the indication profile of radioembolisation was the treatment in patients with portal vein thrombosis (PVT), since for these patients there was hitherto no reasonable locoregional treatment option. In a recently published, two-centre phase II study of 108 patients who were treated with
Y-90 radioembolisation, an advantageous toxicity profile was confirmed for patients with PVT, which was present in 34% of those with advanced HCC. The most frequent adverse events in the PVT group were increased bilirubin and the development of ascites, but these symptoms were interpreted first and foremost as related to progressive liver cirrhosis, and were only in particular cases associated with the intervention. No cases of gastrointestinal ulcers or radiogenic interstitial pneumonia among PVT patients have been reported, although the cumulative hepatic doses of 130–140Gy administered in this study were a little higher than in previous studies. The relationship between PVT and survival could be clearly shown. Median survival, in particular in patients with main-branch PVT, was markedly reduced to 193 days compared with 511 days for patients without PVT and 347 days for patients with thrombosis of a lobar or segmental branch of the portal vein. These results are corroborated by another study of the same group, which contains the largest cohort of HCC patients treated with radioembolisation so far. In this study, the radiological overall response rates of HCC tumours to Y-90 microspheres were 42 and 57% based on World Health Organization (WHO) and European Association for the Study of the Liver (EASL) criteria. The time to progression was calculated to be 7.9 months. Survival strongly differed between patients with Child–Pugh A (17.2 months) and B (7.7 months).

Radioembolisation for Hepatocellular Carcinoma – Conclusions for Clinical Practice

The treatment of locally advanced HCC with selective internal radiotherapy using Y-90 microspheres can today be considered as an established alternative option in the context of a multimodal treatment strategy. The good local tumour response rates even after a single treatment make it unnecessary to frequently repeat the therapeutic sessions. The available data suggest an extension of survival. In future trials, this method should demonstrate its equivalence or superiority compared with established locoregional therapy methods. In the case of advanced HCC, a comparison or combination with systemic sorafenib therapy is mandatory.

Philip Hilgard is an Associate Professor of Medicine and Head of the Department for Gastroenterology at the Academic Teaching Hospital EKV in Mühlheim/Ruhr. His main interests are hepatology, gastrointestinal oncology and interventional endoscopy. He has worked to establish new locoregional and systemic treatment options for the palliative treatment of hepatocellular carcinoma and is a well-known specialist in this field. Dr Hilgard has published numerous original papers and reviews in peer-reviewed journals. He worked at university hospitals in Essen and Mainz and received his scientific training at the Marion Bessin Liver Research Center of the Albert Einstein College of Medicine in New York.