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GUIDELINES

EANM procedure guideline for the treatment of liver cancer and liver metastases with intra-arterial radioactive compounds

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Abstract Primary liver cancers (i.e. hepatocellular carcinoma or cholangiocarcinoma) are worldwide some of the most frequent cancers, with rapidly fatal liver failure in a large majority of patients. Curative therapy consists of surgery (i.e. resection or liver transplantation), but only 10–20% of patients are candidates for this. In other patients, a variety of palliative treatments can be given, such as chemoembolization, radiofrequency ablation or recently

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introduced tyrosine kinase inhibitors, e.g. sorafenib. Colorectal cancer is the second most lethal cancer in Europe and liver metastases are prevalent either at diagnosis or in follow-up. These patients are usually treated by a sequence of surgery, chemotherapy and antibody therapy [Okuda et al. (Cancer 56:918–928, 1985); Schafer and Sorrell (Lancet 353:1253–1257, 1999); Leong et al. (Arnold, London, 1999)]. Radioembolization is an innovative therapeutic approach defined as the injection of micron-sized embolic particles loaded with a radioisotope by use of percutaneous intra-arterial techniques. Advantages of the use of these intra-arterial radioactive compounds are the ability to deliver high doses of radiation to small target volumes, the relatively low toxicity profile, the possibility to treat the whole liver including microscopic disease and the feasibility of combination with other therapy modalities. Disadvantages are mainly due to radioprotection constraints mainly for ^{131}I-labelled agents, logistics and the possibility of inadvertent delivery or shunting [Novell et al. (Br J Surg 78:901–906, 1991)]. The Therapy, Oncology and Dosimetry Committees have worked together in order to revise the European Association of Nuclear Medicine (EANM) guidelines on the use of the radiopharmaceutical ^{131}I-Lipiodol (Lipiocis®, IBA, Brussels, Belgium) and include the newer medical devices with ^{90}Y-microspheres. ^{90}Y is either bound to resin (SIR-Spheres®, Sirtex Medical, Lane Cove, Australia) or embedded in a glass matrix (TheraSphere®, MDS Nordion, Kanata, ON, Canada). Since ^{90}Y-microspheres are not metabolized, they are not registered as unsealed sources. However, the microspheres are delivered in aqueous solution: radioactive contamination is a concern and microspheres should be handled, like other radiopharmaceuticals, as open sources. The purpose of this guideline is to assist the nuclear medicine physician in treating and managing patients undergoing such treatment.

Keywords Guidelines · Nuclear medicine · Liver cancer · ^{131}I-Ethiodized oil · ^{131}I-Lipiodol · Lipiocis® · ^{90}Y-Microspheres · SIR-Spheres® · TheraSphere® · Resin-based spheres · Glass spheres · Radiomicrospheres

Purpose

The purpose of this guideline is to assist nuclear medicine specialists in:

1. Evaluating patients who might be candidates for treatment using intra-arterial radioactive compounds for primary or secondary liver cancer
2. Providing information for performing this treatment
3. Understanding and evaluating the consequences of this therapy

^{131}I-Lipiodol is a consolidated treatment option and the previous European Association of Nuclear Medicine (EANM) guidelines have been revised for its use. The newer ^{90}Y-microsphere therapy is rapidly expanding throughout the nuclear medicine community. To date, published data on microspheres, particularly on dosimetry features and the characterization of the objective response, are still preliminary. Therefore, the aim of this part of the document is to set up a first basic procedure to guide nuclear medicine physicians in treatment with radiolabelled microspheres.

Background information and definitions

Definitions

1. Radionuclides
   - ^{131}I is a beta-emitting radionuclide with a physical half-life of 8.04 days. The maximum and mean beta particle energies are 0.61 and 0.192 MeV, respectively. The maximum and mean ranges in soft tissue are 2.4 and 0.9 mm, respectively. ^{131}I emits a principal gamma photon of 364 keV (81% abundance).
   - ^{90}Y is a beta-emitting radionuclide with a physical half-life of 2.67 days (64.2 h), without emission of gamma photons, but with the emission of secondary "bremsstrahlung" X photons.[1] The maximum and mean beta particle energies are 2.26 and 0.94 MeV, respectively. The maximum and mean ranges in soft tissue are 11 and 4 mm, respectively.
2. Radioactive compounds
   - Ethiodized oil is a 38% iodine-rich fatty acid ethyl ester from naturally occurring poppy seed oil. Its content of stable ^{127}I is substituted with ^{131}I by simple exchange reaction.
   - ^{90}Y-microspheres (Table 1):

     Resin-based microspheres are microspheres of acrylic polymer with a size between 20 and 60 μm in diameter, in which ^{90}Y is bound to the carboxylic group of the polymer after production of microspheres.

     Glass microspheres are microspheres of glass with 20–30 μm of medium size, in which ^{89}Y, embedded in the glass matrix, is activated to ^{90}Y in a nuclear reactor.

[1] Additionally, it is important to notice a very small abundance of emitted positrons, since ^{90}Y-microsphere imaging is possible on positron emission tomography (PET) devices.

Table 1 Comparison of ^{90}Y-microspheres

Characteristics	SIR-Spheres®	TheraSphere®
Material	Resin	Glass
Particle size (μm)	20–60	20–30
Number of spheres per vial (range in million)	40–80	1.2–8
Specific gravity	Low	High
Embolic effect	Moderate	Mild
Activity per sphere (Bq)	40–70	2,500
Activity available (GBq)	3	3, 5, 7, 10, 15, 20
Handling for dispensing	Required	Not required
Splitting one vial for two or more patients	Possible	Not possible
Delivery route	Transcatheter, intra-arterial (hepatic) Hepatic ports (rare)	Transcatheter, intra-arterial (hepatic)

Modified from Salem and Thurston [28]

3. Therapy
   - In this context, therapy means the intrahepatic, intra-arterial administration of ^{131}I-Lipiodol (Lipiocis®) or ^{90}Y-microspheres, i.e. SIR-Spheres® (resin spheres) or TheraSphere® (glass spheres).

Background

The treatment of hepatocellular carcinoma (HCC) via the hepatic arterial route is based on the existence of arterial tumoural hypervascularization. Tumours bigger than 2 cm in diameter draw more than 80% of their blood supply from the hepatic artery. Normal liver parenchyma draws more than 80% of blood from the portal vein. Highly selective tumour uptake can thus be achieved by delivery of radioactive compounds into the hepatic artery, which represents almost exclusively the arterial supply to liver tumours [1–4].

Conversely, liver metastases may have variable vascularity, from avascular hepatic cysts, to normal hepatic parenchyma, less vascularized metastatic lesions (i.e. colon, pancreas, breast), and finally hypervascular metastases (i.e. renal, neuroendocrine, thyroid). With radioactive compounds, the small size of the particles offsets the relative "hypovascularity" of metastatic tumours, provided the treatment is selective, resulting in a high absorbed dose delivered to the lesions and relatively low absorbed dose to the normal parenchyma.

With ^{131}I-Lipiodol, a proportion of compounds migrates towards tumour microenvironment through an increased vessel permeability. These radioactive compounds are slowly cleared because of the lack of lymphatic vessels and Kupffer cells, and endocytosis. Twenty-four hours post administration, 75–90% of the administered activity is trapped in the liver. A fraction of the administered activity distributes into normal liver tissue [5–7].

In ^{90}Y-microsphere therapy, pre-therapy intra-arterial ^{99m}Tc-labelled albumin macroaggregate[2] (MAA) scintigraphy[3] (see below) is mandatory to quantify potential liver-lung shunting and to exclude blood reflux to bowel, stomach or pancreas [8, 9].

The therapeutic efficacy of the method derives essentially from radiation as opposed to the ischaemia associated with chemoembolization or pure embolization. The radiobiological effect results from beta irradiation which favours destruction of tumour cells surrounding microvessels containing a high radioactive ligand concentration [10–17].

The main difference between glass spheres and resin spheres is the activity in each sphere, being much higher in a glass sphere (about 2,500 Bq) at production time, with respect to about 50 Bq in one resin sphere. Commercially available vials of glass spheres contain up to 20 GBq, while resin sphere ones up to 3 GBq. For the same desired activity, glass spheres probably have less embolic effect on microvessels, being injected in much limited number. Potentially, for the same chosen activity, the higher number of resin spheres could provide more uniform dose distribution, with a higher biological effect (toxicity and efficacy). Finally, a potential disadvantage of glass spheres is the often quoted but never demonstrated influence of gravity on their biodistribution [18–22].

[2] ^{99m}Tc-labelled albumin microspheres are not widely available but could also be used.

[3] Planar and, possibly, single photon emission computed tomography (SPECT).

Indications and contraindications

Indications

^{131}I-Lipiodol

Clinical:
Palliative treatment of histologically confirmed, inoperable primary HCC.
Experimental:
Liver metastases.
Adjuvant after liver tumour resection and neoadjuvant before resection or liver transplantation.
Rejected:
Cholangiocarcinoma, the other primary liver cancer in adults, is generally not considered for treatment following unfavourable early trial results. Primary liver cancer in children, hepatoblastoma, has never been considered for treatment because of radiation protection issues and the presence of other treatment options.

^{90}Y-microspheres

Clinical:
Unresectable liver cancers, both primary and metastatic.
Experimental:
Neoadjuvant before resection or liver transplantation.

Contraindications

1. General

Absolute

- Pregnancy; breastfeeding
- Life expectancy less than 1 month[4]

Relative

- Child-Pugh score higher than B7
- High intrahepatic tumour burden[5]
- High extrahepatic tumour burden
- Acute or severe chronic renal failure (i.e. creatinine clearance<30 ml/min)
- Acute or severe chronic pulmonary disease
- Contraindications to hepatic artery catheterization (i.e. unmanageable coagulation disturbance, renal failure, allergy to contrast media, vascular abnormalities …)

2. Specific for the radioactive compounds

Lipiocis®

- Clinically evident liver failure, such as hepatic encephalopathy or ascites
- Child-Pugh exceeding B7 in cases of whole liver or lobar treatment

Special warnings

- Although the treatment results are less favourable, ^{131}I-Lipiodol **is not** contraindicated in cases of partial or total thrombosis of the portal vein.
- Low uptake in lungs (resulting from shunts), thyroid and gastrointestinal tract (resulting from free iodine) are commonly seen and do not raise particular clinical problems.
- A relative contraindication concerns medical risk for isolation, due to the associated gamma emission.

SIR-Spheres®

- Markedly abnormal excretory liver function tests
- Ascites or clinical liver failure
- Abnormal vascular anatomy that would result in significant reflux of hepatic arterial blood to the stomach, pancreas or bowel (determined by pre-treatment angiogram)
- Lung shunting of the hepatic artery blood flow greater than 20% (determined by pre treatment intra-arterial ^{99m}Tc-MAA scintigraphy)
- Disseminated extrahepatic malignant disease
- A relative contraindication concerns previous external beam radiation therapy (EBRT) to the major volume of the liver
- Patients treated with capecitabine within 2 months prior to injection or who will be treated with capecitabine at any time following treatment with SIR-Spheres®
- Main portal vein thrombosis

Special warnings

- Inadvertent delivery of SIR-Spheres® to the gastrointestinal tract or pancreas will cause acute abdominal pain, acute pancreatitis or peptic ulceration.
- High levels of implanted radiation and/or excessive shunting to the lung may lead to radiation pneumonitis.
- Excessive radiation to the normal liver parenchyma may result in radiation hepatitis.
- Inadvertent delivery of SIR-Spheres® to the gall bladder may result in cholecystitis.
- Patients treated with angiogenesis inhibitors that could affect the quality of the blood vessels and induce complications during angiography.

[4] Even in cases of palliative treatments, this criterion was defined essentially for radioprotection reasons.
[5] In this case, multiple steps proceeding with partial hepatic administration are possible.

TheraSphere®

- When pretreatment intra-arterial ^{99m}Tc-MAA scintigraphy shows any deposition to the gastrointestinal tract that may not be corrected by angiographic techniques
- In the case of shunting of blood to the lungs that could result in delivery of greater than 610 MBq of ^{90}Y to the lungs (for determination of the activity see below): radiation pneumonitis has been seen in patients receiving doses to the lungs greater than 30 Gy (evaluated without attenuation correction) in a single treatment
- In the case of severe liver dysfunction or pulmonary insufficiency

Special warnings

- Infiltrative tumour type
- "Bulk disease" (tumour volume>70% of the target liver volume or multiple tumour nodules)
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT)>5 times upper limit of normal (ULN)
- Bilirubin>1 time ULN
- Tumour volume>50% combined with an albumin <3 g/dl
- Patients treated with angiogenesis inhibitors that could affect the quality of the blood vessels and induce complications during angiography

Procedure

Facility and personnel

The facilities required will depend on national legislation for the emission of beta- (^{90}Y-microspheres) and beta- and gamma-emitting (^{131}I-Lipiodol) therapy agents. If required by law, the patient should be admitted to an approved isolation facility comprising an appropriately shielded room and en suite bathroom facilities. Radioprotection issues are more critical when using ^{131}I-Lipiodol, due to the gamma emission, the half-life and the higher possibility of contamination [23].

The facility in which treatment is administered must have appropriate personnel, radiation safety equipment, procedures available for waste handling and disposal, handling of contamination, monitoring personnel for accidental contamination and controlling contamination spread.

The administration of ^{131}I-Lipiodol and ^{90}Y-microspheres should be undertaken by trained medical staff with supporting physics and nursing staff.

Physicians responsible for treating patients should have an understanding of the clinical pathophysiology and natural history of the disease processes, should be familiar with other forms of therapy and should be able to liaise closely with other physicians involved in managing the patient.

Clinicians involved in unsealed source therapy must be knowledgeable about and compliant with all applicable national and local legislation and regulations.

To summarize, the development and establishment of an interdisciplinary team (interventional radiology; medical, radiation and surgical oncology; transplant surgery; nuclear medicine; hepatology; medical physics; and radiation safety) is crucial to the success of the treatment.

Patient preparation and data required

Patients considered for Lipiocis®, SIR-Spheres® or TheraSphere® therapy should be accurately staged according to international standards. Clinical history, physical examination, laboratory values and performance status are evaluated.

Parameters to assess the result of ^{131}I-Lipiodol, SIR-Spheres® and TheraSphere® therapy include determination of tumour load, volume and serum tumour markers such as alpha-fetoprotein (AFP) or carcinoembryonic antigen (CEA).

Pre-therapy evaluation of serum liver enzymes, cholinesterase, blood cell count, coagulation and creatinine should be monitored and known before the procedure.

Angiography performed by high-speed multislice CT (angio-CT) may be valuable as a noninvasive tool for procedure planning, in order (1) to visualize the hepatic vascular organization for access, i.e. anatomical variations such as a right hepatic artery arising from the superior mesenteric artery, (2) to verify the presence or absence of portal venous thrombosis in the portal venous phase, and the possible presence of major arteriovenous malformations or aberrant vasculature causing a significant systemic spillover of radioactive compounds into the general circulation, and (3) to place coils.

Radioactive compounds are generally not indicated in the presence of extensive extrahepatic metastases such as bone, especially if this may negatively influence optimal palliation and symptom-free quality of life. However, in some debatable cases deviant approaches may be considered.

In the case of hepatic metastases, staging with ^{18}F-fluorodeoxyglucose (FDG) PET should be considered for the exclusion of extrahepatic manifestations and evaluation of hepatic disease. Since the aim is often palliative, a small extrahepatic tumour burden is not a contraindication for this modality. ^{18}F-FDG PET has also been successfully used to assess the outcome of therapy.

To summarize, selection of patients with adequate hepatic reserve and good functional status will maximize the beneficial therapeutic effect with minimal risk to normal liver parenchyma.

Patient information and instruction

Patients should receive both written and verbal information about the procedure prior to therapy. Informed written consent must be obtained from the patient.

Patients should be told that this therapy is not likely to cure their disease and is a palliative treatment directed to their liver lesion(s).

Patients must be informed of the potential side effects of therapy.

Patients must be advised to reduce unnecessary radiation exposure and contamination to family members and the public. Particular caution should be used for ^{131}I-Lipiodol. Written instructions should be provided where required.

Administration

^{131}I-Lipiodol

^{131}I-Lipiodol is supplied in solution for use at room temperature. Lipiodol is a viscous oil which offers high resistance to syringe dispensing and catheter injection. The radiopharmaceutical may be diluted with 2–10 ml unlabelled Lipiodol to increase the total volume of injection.

^{131}I-Lipiodol should be prepared in an appropriately ventilated cabinet to avoid radioiodine aerosol inhalation. Care should be taken to use Luer-Lok syringes and taps of a material which does not dissolve in Lipiodol.

The treatment can be implanted via the hepatic artery using an implanted catheter with port or transfemorally (preferred method). In cases of transfemoral administration, the hepatic artery catheterization should be undertaken under X-ray guidance by an appropriately trained interventional radiologist.

A fixed activity of 2.22 GBq (60 mCi) ^{131}I-Lipiodol is injected slowly through a hepatic artery catheter, leading to a mean dose in the liver of approximately 50 Gy. The administered activity may be modified for medical reasons such as tumour load, on the basis of dosimetric calculation or according to local legislation.

In the case of normal anatomy, ^{131}I-Lipiodol is usually administered using a catheter placed in the proper hepatic artery distally from the origin of the gastroduodenal artery. In the case of anatomical variations, separate administration procedures of the right and left hepatic system may be necessary. Super- or hyperselective administration of more distally located hepatic branches may be considered in selected cases.

In any case, the radiopharmaceutical is administered by slow intra-arterial injection under fluoroscopic control of the steady flow of Lipiodol bubbles in the right direction. Tumoural liver to non-tumoural liver binding ratios of 2.3:12 after 24 h have been calculated on the basis of post-therapeutic scintigraphy (reference).

Major arteriovenous spillover is uncommon and should be a reason to abort the procedure and consider other treatments. In minor spillover, the procedure may be continued on the basis of expert assessment and procedure technique.

Slight pulmonary uptake is possible as a result of arteriovenous shunting in the liver after release of ^{131}I-Lipiodol bound to non-tumoural liver. Major pulmonary uptake indicates significant arteriovenous shunting in the liver. Variable thyroid activity may be seen as a result of free ^{131}I uptake from the general circulation and does not represent a problem. In particular, the use of stable iodine (or potassium perchlorate) to prevent thyroid uptake is generally not recommended. Other organs do not normally show an appreciable uptake. High gastrointestinal uptake is only seen when activity is spilled to supplying arteries other than hepatic in relation to catheter placement and coiling procedure [24].

Depending on the patient conditions, side effects after the previous treatment (in particular respiratory symptoms), tumour response and dosimetry, ^{131}I-Lipiodol can be repeated 2, 5, 8 and 12 months after the first injection, according to the manufacturer's indications.

^{90}Y-microspheres

The essential steps of ^{90}Y-microsphere therapy include (1) visceral angiography to map tumour-perfusing vessels, embolize collateral vessels and assess portal vein patency, (2) assessment of pulmonary and gastrointestinal shunts by intra-arterial administration of ^{99m}Tc-MAA and scintigraphy,[6] and (3) determination of the optimal therapeutic activity (treatment planning), possibly by dosimetric evaluation on ^{99m}Tc-MAA images [8, 9].

Every attempt should be made to deliver the ^{90}Y-microspheres most selectively into the tumour. Nonetheless, any treatment will invariably result in some degree of irradiation of the normal liver parenchyma. ^{90}Y-microspheres are delivered according to the tumour burden. In general the radiopharmaceutical is delivered at the lobar artery level to be distributed to numerous tumours in that lobe. Sometimes, in cases of lower tumour load, a more selective delivery at the segmental artery level is possible (see below).

[6] Preferably SPECT scintigraphy, as well as SPECT/CT hybrid imaging (or offline coregistration of available CT with SPECT).

To ensure safe and accurate delivery of treatment, vascular mapping, performed with adequate arterial phase CT scan, will allow an accurate calculation of the target volumes [the volume used for activity calculation could be considered as the volume of the liver segment(s) being supplied by the artery to be infused].

Hepatic arterial anatomy includes frequent variants and anomalies in the blood supply to the liver and from the liver to the gut. Possible reflux of ^{90}Y-microspheres into gastroduodenal or gastric circulation may result in grave clinical consequences, including severe ulceration, gastrointestinal bleeding or pancreatitis. Thus, to ensure safe and accurate delivery of ^{90}Y-microspheres, all patients should undergo mesenteric angiography to assess arterial variants. Hepatic arterial catheterization should be performed. Prophylactic coil embolization of the gastroduodenal artery (and optionally the right gastric artery and its pancreaticoduodenal branches) is of no clinical consequence and is to be considered, depending on patient's anatomy and radiological expertise, since it may minimize the risk of reflux (i.e. gastric or small bowel flow) during ^{90}Y-microspheres infusion [25].

HCC is characterized by arteriovenous shunting bypassing the capillary bed. In the case of arteriovenous shunt, both lungs are uniformly perfused through the vena cava, heart and lung arteries.

This shunting to the lungs will result in possible radiation pneumonitis after the administration of ^{90}Y-microspheres.[7] Therefore, when treatment planning is undertaken, lung shunting should be detected and quantified. This is performed with ^{99m}Tc-MAA scintigraphy during the angiography procedure; 75–150 MBq of ^{99m}Tc-MAA are administered in the proper hepatic artery (or in any branch of the hepatic artery when super- or hyperselective treatment is planned) through the hepatic catheter. Since the size of ^{99m}Tc-MAA particles closely mimics that of ^{90}Y-microspheres, liver-lung shunting is assessed with planar and/or tomographic (SPECT) images. Planar imaging is used for liver-lung shunting calculation and SPECT (or SPECT/CT) for gastrointestinal shunting and appreciation of tumour uptake within the liver. Images can also confirm the absence of gastric or duodenal flow.[8]

In the case of multifocal HCC, liver-lung shunting should be assessed before each treatment at the lobar level, because tumours located in different lobes may shunt to varying degrees.

The lung shunt fraction (LSF) is determined by the following equation:

$$Lung\ shunt\ fraction = \frac{lung\ counts}{lung + liver\ counts}$$

The estimate of LSF without attenuation correction gives a large overestimation with respect to attenuation-corrected evaluations, as an obvious consequence of reduced photon attenuation in lungs with respect to abdominal attenuation. Simple pre-injection ^{99m}Tc or ^{57}Co flood-based attenuation correction scan is then advised. Scatter correction could be also important especially for the right lung strongly influenced by liver photon emission.

Labelling should be performed just before the administration, and scintigraphy should be performed as soon as possible after angiography. Visibility of thyroid, stomach, body contour and urinary bladder in the ^{99m}Tc-MAA image gives qualitatively the degree of circulating free pertechnetate.[9]

Only when the possibility of extrahepatic shunting has been evaluated and the patient deemed acceptable for treatment may ^{90}Y-microspheres be administered in the interventional radiology department. Individually determined patient-specific activities are used. In the case of main hepatic artery injection, radiation is distributed to both lobes of the liver (although with TheraSphere® whole liver treatment is not recommended). If the lesions are limited to one lobe, the catheter can be selectively inserted either into the left or right lobar artery supplying the affected lobe, thus sparing the contralateral. In selected cases, hyperselective (i.e. single segment) treatments can be considered.

Gentle infusion (no excessive pressure) should be used to strictly avoid backflow, using the specially designed manufacturer's device.

Differences in administering the two kinds of ^{90}Y-microspheres are related to the different product characteristics (Table 1). Since resin-based microspheres (SIR-Spheres®) incorporate a smaller amount of ^{90}Y than glass microspheres (TheraSphere®), the specific activity is much lower (1/50). Thus, for a fixed injected activity, the two types of ^{90}Y-microspheres produce significantly different embolic loads. The mechanisms of action of the two available ^{90}Y-microspheres are different as well, and a full understanding of these differences should help to decide which device might best be applied to patients (see below).

[7] According to Semenenko and Li [26], the threshold for induction of radiation pneumonitis with external beam therapy is 17.5 Gy when the whole lung is uniformly irradiated with 2 Gy per daily fraction. These limits however cannot be applied as such to radionuclide treatments since (a) they refer to different dose rate and fractionation and above all (b) microsphere irradiation is microscopically nonuniform. No rigorous normal tissue complication probability curve is available for lung irradiated with microspheres. The empirical absorbed dose limit of 30 Gy (evaluated without attenuation correction) is generally adopted.

[8] Perchlorate administration prior to MAA scan could be necessary to exclude gastric uptake of free ^{99m}Tc.

[9] The shortest interval between labelling of MAA and scintigraphy should interleave, since the well-known MAA spontaneous unlabelling can simulate false gastrointestinal shunt, due to circulating ^{99m}Tc.

Depending on the patient's condition, life expectancy and tumour response, treatment can be repeated or fractionated. In this regard, the risk related to the invasive and cumbersome intra-arterial administration should be considered. It is important to notice, however, that more hypervascular lesions retain a higher number of spheres. This may ultimately result in a higher tumour to normal liver ratio. Nevertheless, the actual absorbed dose to the normal hepatic parenchyma must be estimated and the activity adjusted accordingly. Therefore, during subsequent treatments, if tumour hypervascularity is decreased, fewer microspheres are absorbed by tumour, and the corresponding normal parenchymal dose may be increased, if the same activity is administered. Moreover, previously treated lesions may have altered microvascularity flow dynamics. Then, in repeated treatments, repeated ^{99m}Tc-MAA scans are advised.

Treatment planning

Lipiodol treatment planning

There is no treatment planning method proposed for Lipiodol. Dosimetric data obtained with peri-treatment dosimetry are reported in Table 2.

Microsphere treatment planning

To date, different methods for the calculation of the amount of radioactivity to be administered have been applied, namely empirical and dosimetric ones. Empirical methods have been tested for resin spheres and are based on a broad estimate of tumour involvement (T) in the liver [tumour volume/(tumour+liver volumes)].

The first empirical method proposed for SIR-Spheres® is based only on T: the larger the tumour burden, the higher the recommended activity in increments of 0.5 GBq per 25% tumour burden. Thus, the recommended activity is 2 GBq if T< 0.25; 2.5 GBq if 0.25<T<0.5; and 3 GBq if T>0.5.

The second empirical method proposed for SIR-Spheres® incorporates body surface area (BSA, measured in square metres).[10] Therefore, the activity to be administered is:

$$A(GBq) = (BSA - 0.2) + \frac{tumor\ volume}{total\ liver\ volume}$$

Empirical methods are in use with reported objective responses and low incidence of toxicity. Nevertheless, this approach may intrinsically expose patients to the risk of unnecessary toxicity or tumour underdosage. It must be noted that these methods do not take into account the degree of tumour uptake. Therefore, dosimetric methods should be generally recommended.

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

Dosimetric methods include the so-called non-compartmental MIRD macrodosimetry proposed for TheraSphere® by Salem et al. [27–30] and the compartmental MIRD macrodosimetry which can be applied to both kinds of spheres proposed by Gulec et al. [31]. The latter one includes a dosimetric calculation, with variable accuracy, by measuring the liver and tumour volumes, tumour to normal tissue ratio in the liver, and percentage of activity shunted to the lung. These dosimetric models are based on whole liver infusion. Therefore, if a lobar treatment is intended, the activity should be calculated assuming whole liver volume "corrected" to the proportional volume of the target lobe to be treated.

Please consider that only the compartmental MIRD macrodosimetry takes into account the tumour uptake. Consider also that this convenient treatment planning requires only one ^{99m}Tc-MAA SPECT scan since microspheres are trapped permanently in capillaries and no biological clearance occurs.

Whatever method used, activity should be supplementarily adjusted, i.e. decreased, depending on the presence and extent of LSF, estimated with MAA scintigraphy. Indications for SIR-Spheres® are: less than 10% LSF, no reduction; 10–15% LSF, 20% reduction; 15–20% LSF, 40% reduction; above 20% LSF, the technique is contraindicated. For TheraSphere®, an empirical absorbed dose limit of 25–30 Gy (evaluated without attenuation correction) is generally assumed.

Assuming homogeneous activity distribution in the liver, tumour and lung (if any shunting occurs) slightly simplified MIRD-based dose equations can be used as a compartmental MIRD macrodosimetry:

$$D_{liver}[Gy] = \frac{Injected\ Activity[GBq] \times 50 \times fractional\ uptake_{liver}}{m_{liver}[kg]},$$

with the fractional uptake (FU) of radioactivity in the liver defined as:

$$FU_{liver} = (1 - LSF)\left[\frac{m_{liver}}{TLR \times m_{tumour} + m_{liver}}\right]$$

Table 2 Absorbed dose estimates for intra-arterial hepatic ^{131}I-Lipiodol administration

Organ	Gy/GBq[a]	Gy/GBq[b]
Liver tumour	43 ± 22	Mean 68, range 36–130
Liver parenchyma	5 ± 4	Mean 4.1, range 2.1–6.2
Lung	3 ± 1	Mean 3.6, range 1.2–6.0
Gonads	0.5	NA
Whole body	0.5	Mean 0.5, range 0.3–0.6

[a] Source: "Lipiocis et hepatocarcinome" monograph by CIS Biomedical; note that data from this source have been obtained in a particular patient group with HCC and may vary with age and comorbidity

[b] Values adapted from Monsieurs et al. [42]

The injected activity should be corrected for the residual activity in the vial (approximately up to 5% with TheraSphere®, while it is dependent upon user choice with SIR-Spheres®). A more accurate evaluation of the net injected activity can be performed by measuring in a fixed geometry the exposure dose rate of the initial vial and of the residue in the catheter and the entire disposal thrown in the waste box. The tumour to liver ratio (TLR) and LSF can be determined using ^{99m}Tc-MAA scan. As a matter of fact, TLR cannot be accurately determined unless using an attenuation-corrected SPECT scan. If this is not available, a toxicity-oriented dosimetry for evaluating mean liver absorbed dose can be performed using the equation above, assuming $m_{tumour}=0$ (non-compartmental MIRD model). If a selective administration to a lobe or to a hepatic segment is planned, the two above equations should be applied replacing m_{liver} with m_{lobe} or $m_{segment}$.

The fraction of the administered activity in the tumour is:

$$FU_{tumour} = (1 - LSF)\left[\frac{TLR \times m_{tumour}}{TLR \times m_{tumour} + m_{liver}}\right]$$

The dose to the tumour can then be determined with:

$$D_{tumour}[Gy] = \frac{Injected\ Activity[GBq] \times 50 \times FU_{tumour}}{m_{tumour}[kg]},$$

The tumour mass (and liver mass) should be derived from the measured volumes on CT images of tumour and liver. The densities of both tissues are slightly higher than 1 g/cm^3, but their mass can be equalled to their volume within the accuracy of this dosimetry. For both doses complete decay of ^{90}Y within the uptake compartment is assumed.

Reference values

There are few established threshold values for liver toxicity and tumour response in microsphere treatment. In EBRT Emami et al. [32] showed that the threshold for 5% risk in 5 years for radiation-induced liver disease (RILD) in the hypothetical modellistic case of a whole liver uniform irradiation is at a mean liver dose of 30 Gy; 50% of the patients are at risk at 43 Gy. That uniform irradiation of the whole liver tissue is never the case with microsphere radioembolization. Moreover, recent publications (MIRD 20) on radiopeptide therapy suggest that EBRT absorbed dose thresholds should be converted into biological effective dose (BED) thresholds, thus taking into account the dose-rate effect, in order to be applied to nuclear medicine treatments. When transposed in BED, the aforementioned liver EBRT values correspond to 54 Gy_{BED} and 77 Gy_{BED} respectively, assumed for liver $\alpha/\beta=2.5$ Gy and $T_{1/2rep}=2.5$ h, as showed by Cremonesi et al. [33]. In order to reach such limits with ^{90}Y-microspheres in a whole liver treatment, absorbed doses of 36 and 46 Gy are necessary, respectively. RILD was indeed observed, by Yorke et al. [34], in a small fraction of patients who had undergone ^{90}Y-microsphere therapy, after much higher mean doses to a single liver lobe. Evidence of the strong impact of nonuniform dose distribution seems to explain the lack of liver complications, even at very high absorbed doses (up to 150 Gy).

Moreover, considering the microanatomy of the liver lobules and the markedly different number of resin versus glass spheres, the doses to each structure can be significantly different for the same mean absorbed dose.

Considering as toxicity a failure in global liver function (bilirubin, albumin, prothrombin time), the maximum tolerated absorbed dose (MTD) by the healthy parenchyma should differ according to the kind of treatment and the organ functional reserve: a lobar or segment treatment supports higher absorbed dose with respect to whole liver treatment, since the remainder of the tissue can supply the liver function.

In this sense, the review paper by Chiesa et al. [35] lists many published evidences of the fact that tolerability of radioembolization depends on the initial cirrhotic status (Child-Pugh score, or basal bilirubin level).

Strigari et al. [36] treated 73 HCC patients with SIR-Spheres®, with a lobar approach in 38 cases. An empirical BSA treatment planning method was adopted. Hepatic failures according to Common Terminology Criteria for Adverse Events (CTCAE) v4 of degree G2, G3 and G4 (death related to adverse event) were observed in 31, 21 and 11% of cases, clearly showing the limits of the BSA methodology. Post-therapy retrospective ^{90}Y bremsstrahlung imaging compartmental dosimetry was performed. The resulting normal tissue complication probability has 50% probability of G2 or higher degree complication at BED= 93 Gy_{BED}, averaged on the entire liver volume, which corresponds to a mean liver dose of 52 Gy. Such a value is definitely higher than the Emami et al.'s 43 Gy, showing that absorbed doses with microspheres must be interpreted in different ways with respect to external beam doses. Tumour response according to density variation (European Association for the Study of the Liver criteria) rather than to dimensional criteria was obtained in 26% (complete response, CR) and 51% (partial response, PR) of cases, with an excellent global response rate of 77%. The median dose averaged on the tumour volume of the CR group was 111 Gy, while if CR and PR are considered, the median value was 97 Gy. The tumour control probability curve has a plateau of sure efficacy above 200 Gy. Again we see that these values are higher than those currently employed in EBRT.

SIR-Spheres® A typical treatment consists of injecting about 40–80 million of ^{90}Y-SIR-Spheres® (with specific

activity of 50 Bq per sphere). SIR-Spheres® are provided in a vial with water for injection. Standard 10- or 20-ml injection syringes preloaded with sterile water are required to infuse the microspheres into the delivery catheter.

Given the higher embolic load with SIR-Spheres®, no blind infusions should be performed. Virtually all complications from SIR-Spheres® arise from the inadvertent delivery of SIR-Spheres® into small blood vessels that go to the pancreas, stomach or duodenum. The catheter must be placed well distal to the gastroduodenal artery and any other artery that is supplying blood to the gut. If there is any possibility of SIR-Spheres® passing down the gastroduodenal artery then the implantation must not proceed.

SIR-Spheres® must be delivered slowly at a rate of no more than 5 ml/min as rapid delivery may cause reflux back down the hepatic artery and into other organs. The radiologist must repeatedly check the position of the catheter during the procedure to ensure it remains correctly placed and that reflux does not occur. This is performed by injecting contrast medium through the left-hand port of the delivery set. At the conclusion of the procedure, the catheter is removed.

Following radiobiological principles and personalized dosimetry, based on absorbed dose and bioeffective dose calculation, a multi-cycle setting, in order to increase the cumulative dose to the tumour, while preserving the radiation effect to the normal liver tissue, has recently been proposed by Cremonesi et al. [33].

Advantages of the SIR-Spheres® treatment: The activity vial may be tailored for the patient in the nuclear medicine radiopharmacy. The infusion is performed with alternating injections of sterile water and contrast medium, allowing direct monitoring of the treatment. The lower specific gravity theoretically is in favour of a better suspension.

Limitations to the SIR-Spheres® treatment: The shelf life of the device is 24 h, restricting clinical flexibility and patient scheduling. The need for human technical manipulation may imply radiation containment or, more critically, may result in methodological errors. Finally, since SIR-Spheres® are moderately embolic, it may happen that the whole dose cannot be delivered, and a microembolic effect may cause transient hypoxia, potentially limiting the effect of the radiation.

TheraSphere® A typical treatment consists in injecting 1.2–8 million of ^{90}Y-TheraSphere® (with specific activity of 2,500 Bq per sphere). The volume of saline solution required to infuse a vial of TheraSphere® is low (typically 27–180 ml). Furthermore, given the low number of microspheres infused with TheraSphere®, the entire vascular bed is never completely saturated and continuous fluoroscopic guidance during the infusion is not necessary. A complete infusion usually requires 20–60 ml and 5 min.

The mean absorbed dose recommended by the producer that should be delivered to a lobe of the liver is between 80 and 150 Gy. Patients with significant cirrhosis should be treated with a lower absorbed dose (80–100 Gy). The recommended target absorbed dose for HCC is 120 Gy (due to the underlying cirrhosis) and 150 Gy for metastases.

The lung dose must be calculated and not exceed 30 Gy (evaluated without attenuation correction). However, in patients with compromised pulmonary function (i.e. chronic obstructive pulmonary disease or previous lung resection), caution must be taken as the organ reserve is limited.

TheraSphere® is supplied in six sizes of activities: 3, 5, 7, 10, 15 and 20 GBq. Thus, the appropriate vial must be ordered and the activity decayed to the required treatment activity. The shelf life of a TheraSphere® dose is 15 days from the dose calibration date.

Advantages of the TheraSphere® treatment: This configuration requires no physical manipulation. Given the relatively low number of microspheres, embolic effects are limited. Therefore, (1) TheraSpheres® can be used also in patients with compromised portal venous flow or portal vein thrombosis; (2) oxygenation is maintained in tumours and objective responses induced by the irradiation are theoretically improved; and (3) in nearly all cases the target tissues receive more than 95% of the planned absorbed dose without reaching flow stasis. Moreover, to improve the uniformity of dose distribution within a lesion, the same activity can be injected choosing among different numbers of spheres (i.e. different initial activity) administered after different decay intervals.

Limitations to the TheraSphere® treatment: The low number of spheres may result in inadequate tumour coverage for very large tumours, although the number of spheres can be tailored to the needs by selecting a higher activity vial and by using it later after some degree of decay. The specific gravity of glass microspheres is high compared to resin microspheres and may theoretically limit microsphere distribution.

Precautions, follow-up and side effects

Usual arteriography precautions should be observed before and after the procedure, including correction of clotting disorders and use of an arterial plug or compression bandage after catheter removal.

Treatment should be administered under safe aseptic conditions appropriate to intra-arterial injection in premises approved for unsealed source therapy.

Nursing personnel must be trained in radiation safety. Any significant medical conditions should be noted and contingency plans made in case radiation precautions must be breached for a medical emergency. Concern about radiation exposure should not interfere with the prompt appropriate medical treatment of the patient.

With ^{131}I-Lipiodol, care should be taken to ensure minimum radiation exposure to the patient extraneous to the therapeutic objective, to the workers in contact with the patient, to family members and the public. Dose rate to the workers should be monitored during the treatment. Written instructions should be provided where required. With ^{90}Y-microspheres the required radiation protection attention is minimal since the external dose rate is low. However, a particular caution should be used for bremsstrahlung radiation.

Current medication used by the patient does not have to be discontinued. No drug interactions with other medications have been reported to date. However, it is essential to discontinue the treatments with chemotherapy agents having a radiation sensitizer potential in order to avoid possible radiation hepatitis. In patients who have been treated with capecitabine within 2 previous months resin microsphere therapy is considered contraindicated, although there is still debate on this issue. Therefore, capecitabine therapy should be discontinued at least for 2 months before ^{90}Y-microsphere therapy and must not be prescribed at any time after treatment.

Prophylactic administration of antiulcer medication (for 2 weeks) and steroids (for 5–7 days) after treatment will mitigate the risk of pain from non-target radiation into the gastrointestinal tract and provide relief from fatigue. In the case of ^{131}I-Lipiodol, although some thyroid uptake of free ^{131}I has been reported, the use of thyroid protection such as with potassium iodide (100 mg/day) may be debated by the arguments of the low degree of uptake, grave prognosis of the patients, long duration of the treatment, and remote but possible side effects of stable iodide overload. Bacher et al. recommended thyroid protection especially in repeated treatments in patients with good prognosis, since a significantly different thyroid dose is noted in unprotected patients (13.8±5.0 Gy vs 7.2±2.2 Gy).

Following the therapeutic injection, patients should be hospitalized for clinical reasons. The hospitalization in an approved isolation facility with appropriate shielding should be carried out according to national legislation, considering that external exposure rates are particularly higher for ^{131}I than for ^{90}Y.

After the treatment, patients should avoid pregnancy for at least 4 months. In reality, it is unlikely that women of childbearing age will be eligible for this therapy. Anyway, Gulec et al. [31] calculated that pregnancy shortly after a simulated treatment with ^{90}Y-microspheres does not induce a relevant irradiation to the embryo.

In the case of Lipiocis® (and to a lesser degree, ^{90}Y-microspheres[11]), urinary radioactive excretion is of particular concern during the first 2 days post administration. Patients should be advised to observe rigorous hygiene to avoid urine contamination during this time. In cases of incontinence, bladder catheterization or, alternatively, the use of condom catheters or incontinence napkins should be performed for radioprotection of relatives and caregivers.

Quantitative whole-body scintigraphic imaging 1 week post therapy is recommended to confirm the distribution of ^{131}I-Lipiodol. Lipiodol is also, by virtue of its high iodine content, a contrast agent visible on CT without supplementary contrast administration. This can be combined with SPECT images for dosimetry calculations.

For ^{90}Y-microspheres, bremsstrahlung images, or one or two frames of 30-min PET acquisition, performed a few hours after the administration are useful to locate the activity [37].

Post-procedural follow-up of the patient to assess any treatment-emergent side effects and tumour response is conducted at 30 days and then at 2- to 3-month intervals thereafter.

Side effects

^{131}I-Lipiodol

Early:

- Moderate and temporary pyrexia (29%)
- Hepatic pain on injection (12.5%)
- Moderate and temporary alterations of liver enzymes (20%)
- Thrombocytopenia and bone marrow suppression

Delayed:

- Interstitial pneumonitis (0.5%)
- Moderate, reversible leucopenia (7%)
- Hepatic insufficiency (limited hepatic reserve: post resection, cirrhosis, irradiation)

^{90}Y-microspheres

Common side effects:

- Fatigue
- Abdominal pain
- Nausea
- Fever
- Transitory elevation of transaminases

Possible severe adverse events (2–8%):

- Chronic abdominal pain
- Non-target irradiation and/or attenuated radiation in adjacent structures:

Radiation gastritis, gastrointestinal ulceration, upper gastrointestinal bleeding, pancreatitis

[11] Urinary excretion over the first 8 days is about 40% for Lipiocis®, whereas for SIR-Spheres® it is less than 0.1% and for TheraSpheres® less than 0.01%.

Radiation pneumonitis, right pleural effusion
Radiation-induced liver disease (hepatitis, hepatic fibrosis and portal hypertension, cholecystitis, radionecrosis of a segment, liver failure)

Radiopharmaceutical

1. Approved name: ^{131}I-Lipiodol

The radionuclide is supplied in ready to use 2-ml solution for injection, stored in a 4-ml cone-shaped glass vial. The specific activity is 1.1 GBq/ml at calibration.

Quality control:

Stability data demonstrate<5% free radioiodine within 1 week of manufacturing at ambient temperature. Quality control checks are not usually required prior to therapy. Radiochemical purity may be checked with thin-layer chromatography with radioactivity of the spot to equal or exceed 95% of the total activity.

The activity to be administered must be checked using an isotope calibrator.

The shelf life is 3 days after the date of calibration indicated on the label, i.e. 7 days after the date of manufacturing.

2. Approved name: SIR-Spheres® ^{90}Y-microspheres

SIR-Spheres® consist of biocompatible resin-based microspheres containing ^{90}Y.

The SIR-Spheres® administration set consists of a Perspex shield, the dose vial, and inlet and outlet tubing with needles. Each vial contains 40–80 million microspheres and 3 GBq of ^{90}Y (at the time of calibration) in a total of 5 ml water for injection.

3. Approved name: TheraSphere® ^{90}Y glass microspheres

TheraSphere® consists of insoluble glass microspheres in which ^{90}Y is an integral constituent of the glass.

TheraSphere® is supplied in 0.6 ml of sterile, pyrogen-free water contained in a 1.0-ml V-bottom vial secured within a 12-mm clear acrylic vial shield. It is available in the following six activity sizes: 3, 5, 7, 10, 15 and 20 GBq. The number of microspheres per vial is 1.2, 2, 2.8, 4, 6 and 8 million, respectively.

General considerations for ^{90}Y

β^- emissions from ^{90}Y can travel more than 10 m in air but are significantly reduced by less than 1 cm of acrylic; therefore, the primary concern is exposure to the eyes, skin and hands.

Although clinically inconsequential, ^{90}Y-microspheres (resin and glass) contain trace amounts of long-lived radioactive contaminants such as europium isotopes ^{152}Eu and ^{154}Eu.[12]

Issues requiring further clarification

1. Minimum/optimal time interval between repeated treatments, when indicated
2. Role of intra-arterial radioactive compounds in terms of survival gain, progression-free survival and quality of life
3. Comparison among different radioactive compounds
4. Therapeutic potential of ^{188}Re-Lipiodol and ^{166}Ho poly-lactic acid microspheres [38]
5. Options for combined therapy/sequence with chemotherapy and other anti-cancer drugs [39–41]
6. Validation of treatment planning techniques in predicting therapeutic efficacy and preventing toxicity

Disclaimer

The EANM has written and approved guidelines to promote the cost-effective use of high-quality nuclear medicine therapeutic procedures. These generic recommendations cannot be rigidly applied to all patients in all practice settings. The guidelines should not be deemed inclusive of all proper procedures or exclusive of other procedures reasonably directed to obtaining the same results. Advances in medicine occur at a rapid rate. The date of a guideline should always be considered in determining its current applicability.

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[12] The glass microspheres are placed directly in the reactor to activate the ^{90}Y: the manufacturing process may result in increasing the amount of contaminants.

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