Radioembolization Treatment for Hepatic Malignancies

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1. Introduction

Yttrium-90 (^{90}Y) radioembolization (RE) is an established treatment modality for chemotherapy resistant, irresedable hepatic malignancies. After injection into the hepatic artery, these microspheres distribute according to vascularity and ideally lodge in the arterioles in and around the tumours, delivering high local radiation absorbed doses, while sparing the normal liver parenchyma.

2. Methodology

This guideline is based on available scientific literature on the subject, the previous guideline (Aanbevelingen Nucleaire Geneeskunde 2007), international guidelines from EANM and/or SNMMI if available and applicable to the Dutch situation.

3. Indications

Most important *indications* are:

a. unequivocal malignancy of the liver
b. not amenable to liver transplant, surgical resection or curative ablation (such as RFA)
c. not amenable to, not willing to receive, or refractory to (local) chemotherapy according to national guidelines
d. compensated or at most early decompensated (Child-Pugh ≤ B7) liver cirrhosis
e. performance state (ECOG) ≤2
f. life expectancy >6 months
g. liver-dominant disease (note: limited extra-hepatic disease is acceptable)

Absolute contra-indications are:

a. serum bilirubin >34,2 micromol/l (2 mg/dl)
b. glomerular filtration rate <35 ml/min
c. INR >1,5
d. leukocytes <2 10^9/l and/or platelet count <60 10^9/l
e. portal vein thrombosis (main branch)
f. extra-hepatic deposition of the scout dose ^{99m}Tc-MAA (see below)
g. unacceptable lung shunt (see below)

Relative contra-indications are:

a. abnormalities of the bile ducts (such as stents) with an increased chance of

infections of the bile ducts (papillotomy and cholecystectomy are allowed)
b. extensive and untreated portal hypertension (large varices at oesophago-gastro-duodenoscopy)
c. chemotherapy, surgery and/or external beam radiation therapy within 4 weeks of treatment
d. pregnancy
e. active hepatitis

4. Relation to other therapies

At present, ^{90}Y-RE is indicated in a salvage setting only and when all other treatments (according to national guidelines) have failed. Alternatively, it may act as a bridge to liver transplant or as a bridge / adjunct to curative resection (i.e. radiation segmentectomy). Treatment in a first-line setting in patients with liver metastasis of a colorectal carcinoma is currently under investigation.

Holmium microspheres for radioembolization are currently under investigation. The poly(L-lactic acid) (PLLA) microspheres are preloaded with ^{165}Ho acetylacetonate and prepared by a straightforward solvent evaporation method. ^{166}Ho has several advantageous properties when compared to ^{90}Y. Its beta energy may be marginally lower than ^{90}Y's (1,8 MeV compared to 2,2 MeV), but ^{166}Ho is also a gamma emitter (81 keV), making nuclear imaging possible. Also, holmium is a highly paramagnetic metal, and as such may be visualised by MRI as well as CT. Quantitative imaging of holmium microspheres allows for dosimetry and individualized treatment planning. Because the beta energy of ^{166}Ho is slightly lower than ^{90}Y's and the physical half-life is significantly shorter (27 h), the absorbed radiation dose of ^{166}Ho is notably lower than that of ^{90}Y (^{166}Ho: 8,7 mGy MBq-1; ^{90}Y: 28 mGy MBq-1). Therefore, to deliver a radiation dose equivalent to ^{90}Y, roughly three times the amount of radioactivity has to be administered. Clinical trials are ongoing.

5. Medical information necessary for planning

This includes:
a. medical history and demographic data
b. physical exam
c. blood tests
d. FDG-PET to evaluate extra-hepatic disease in FDG avid malignancies
e. multiphase CT to evaluate liver vasculature (earlier phase arterial CT is preferred over standard arterial CT, plus portovenous phase)

6. Radiopharmaceutical

Medical device:	resin microspheres (SIR-Spheres®, Sirtex Medical Limited, Australia) or glass microspheres (TheraSphere®, BTG International Ltd., UK)
Nuclide:	Yttrium-90
Half-life:	2,67 days
Activity:	Patient specific
Administration:	Intra-arterial

The following methods may be used for activity calculation:

The resin microspheres (BSA) method

The standard body surface area (BSA) formula for resin microspheres is based on BSA, and the fraction of the total liver volume invaded by tumour:

$$Prescribed\ activity\ (GBq) = (BSA\ (m^2) - 0.2) + \frac{tumor\ involvement\ (\%)}{100}$$

In the case of a significant shunt to the lungs the prescribed activity is empirically reduced (10-15% shunt fraction; 20% activity reduction; 15-20% shunt fraction: 40% activity reduction; > 20% shunt fraction: no treatment).

The glass microspheres method

Activity calculation for glass microspheres (MIRD method) is based on an estimation of the mean absorbed dose in the target liver volume. It uses a simplified calculation method derived from the MIRD equations for dose calculation. An absorbed dose of 50 Gy per GBq per kilogram tissue is used with assumptions of homogeneous intrahepatic microsphere distribution and absorption of all the administered activity and energy in the liver, using the following formula:

$$Prescribed\ activity\ (GBq) = \frac{Desired\ dose\ (Gy) \times M_{Target}\ (kg)}{50\ (J/GBq)}$$

where M_{Target} is the mass of the target volume in kg. The desired dose may range from 80-120 Gy depending on the clinical judgment of the treating physician. The lung dose should not exceed 30 Gy (or 50 Gy for repeated treatment), which, with the above-mentioned assumptions and an assumed lung mass of 1 kg, is equivalent to an absolute lung shunt of approximately 600 MBq of ^{90}Y-microspheres.

The partition method

This method involves selecting safe absorbed doses to the normal liver and lung and implanting the maximum activity that does not exceed these limits. The tumour and normal liver compartments are in general delineated on anatomical imaging modalities, and the anticipated activity in these compartments is calculated on scout dose SPECT imaging using ^{99m}Tc-MAA. The ratio between the activity concentrations in the tumour and normal liver compartments ($R_{T/N}$) is calculated as:

$$R_{T/N} = \frac{A_{Tumor}\ (GBq)/M_{Tumor}\ (kg)}{A_{Normal\ liver}\ (GBq)/M_{Normal\ liver}\ (kg)}$$

where A is the activity in GBq and M is the mass of the compartment in kg. Subsequently the prescribed activity may be calculated as:

$$= D_{Normal\ liver}\ (Gy) \times \frac{R_{T/N} \times M_{Tumor}\ (kg) + M_{Normal\ liver}\ (kg)}{50\ (J/GBq) \times (1 - LSF)}$$

where $D_{Normal\ liver}$ is the maximum desired absorbed dose to the normal liver in Gy, $R_{T/N}$ follows from the first equation, and LSF is the lung shunt fraction. Importantly, it adjusts for the difference between absorbed dose to the tumour and the normal liver (T/N). However, the partition model is still not routinely used.

7. Radiation safety

Most patients may be discharged on the day of treatment without written instructions according to the National Regulatory Committee (NRC) contact regulations in the US. The threshold of 1 mSv will not be reached if a maximum of 5 GBq of activity is administerd. Patients who have prolonged contact with children, pregnant women, a significant caregiver or bed partner may be discharged on the day of treatment if less than 3 GBq is administered. Most institutions use the NRC contact scenario only, and this is considered acceptable practice in the US.

The common adverse events after administration of radioactive microspheres to the liver are fever, abdominal pain, nausea, vomiting and fatigue. These adverse events are all part of the so-called post-RE syndrome. An abnormality of liver function tests is also likely to occur. This may be up to grade 3 or 4 (CTCAE version 4.03) in the case of AST/SGOT and ALT/SGPT, without direct clinical relevance. In general these effects are transient. The frequency of radiation hepatitis or RE-induced liver disease (REILD) is low (<5%) due to the inhomogeneous distribution of activity that may be anticipated. Veno-occlusive disease may occur following radiation damage to the central veins. This is caused by activation of the coagulation system probably by radiation-induced endothelial damage.

General prophylactic medication consist of pre- and post-hydration, corticosteroids (dexamethasone 10 mg IV 1 h before angiography), anti-emetics (ondansetron 8 mg IV 1 h before angiography).

The following effects are directly related to inadvertent deposition of the microspheres in organs other than the liver, and should therefore be classified as technique related. The development of acute peptic ulceration (<5%) is suggested by the symptoms of ulceration and diagnosed by endoscopy. The post treatment SPECT/CT will determine if there are microspheres lodged in the pancreas or other organs, but additional tests such as serum amylase are also indicated if pancreatitis is suspected (<1%). High levels of implanted radiation and/or excessive shunting to the lungs may lead to radiation pneumonitis (<1%). This may be suspected if patients develop a non-productive cough several days or weeks after the implantation of the microspheres and is diagnosed by function tests and imaging. A rare complication is a radiation-induced cholecystitis (<1%). This side effect may be expected a few weeks after the intervention.

8. Patient preparation/essentials for procedure

The treatment includes preparatory angiography followed by treatment, 1-2 weeks later. For both procedures patients may be hospitalized on the day before angiography with adequate pre- and post-hydration, considering the tendency for renal insufficiency in the cirrhotic patient with hyperdynamic circulation and the considerable amounts of contrast that may be administered. Patients are discharged approximately 24 h after the intervention unless complications occur.

During the preparatory procedure the patient is subjected to an angiography of the upper abdominal vessels. The coeliac trunk and upper mesenteric artery must be visualised, followed by coiling of relevant (aberrant) vessels, especially branches of the

coeliac axis supplying extra-hepatic tissue. After successful angiography and coiling of the relevant vasculature the position of the catheter is documented and a test dose of 150 MBq technetium-99m (^{99m}Tc) macro aggregated albumin (MAA) is injected into the hepatic arteries (note: for a selective approach the activity may be split). Directly after the procedure (within 60 min of administration), a SPECT/CT is acquired to determine the distribution to the lungs or other non-target organs (extra-hepatic deposition). Planar imaging of the thorax and abdomen is performed, as well as SPECT/CT of the abdomen (approximately 45 min acquisition time).

1-2 weeks following the preparatory angiography patients will receive the prescribed activity of ^{90}Y microspheres. The catheter is positioned at exactly the same location as during the preparatory angiography to avoid technique-induced differences in biodistribution between the test dose and the therapeutic dose.

Profylactic proton pump inhibition (e.g. pantoprazol 40 mg) is recommended, starting on the day of the preparatory procedure for a period of 6 weeks.

9. Acquisition

Pre- and post-treatment imaging may be performed on a dual-headed gamma-camera / SPECT/CT system. Pre-treatment ^{99m}Tc-MAA planar and SPECT images can be acquired on a 128x128 matrix using a 129,5-150,5 keV energy window and a low energy general purpose collimator. For post-treatment ^{90}Y Bremsstrahlung, SPECT imaging with the combination of a high energy general purpose collimator and a wide 50-250 keV energy window can be used, which yields images with a favourable combination of sensitivity and contrast. SPECT imaging can be performed with 120 projections over a non-circular orbit of 180˚.

As an alternative to post-treatment SPECT/CT imaging, PET/CT images may be acquired. ^{90}Y PET was shown to be feasible in phantoms and patients. Per MBq, ^{90}Y emits 32 positrons per sec with a maximum energy of 758 keV. Consequently, annihilation photon pairs are produced approximately 700 times less often than Bremsstrahlung photons (E >50 keV). Nevertheless, ^{90}Y PET may allow for the detection of extra-hepatic activity and accurate tumour and liver dose estimation, since the spatial resolution is expected to be comparable to that of ^{18}F PET, which has a maximum positron energy of 633 keV. Additionally, advanced correction techniques for scatter, random, and attenuation effects that are clinically available for ^{18}F PET, can be directly applied to ^{90}Y PET.

For lung shunt calculation, abdominal and thoracic geometric mean images can be obtained from the respective anterior and posterior projections. An anterior thorax projection of a cobalt-57 (^{57}Co) flood-source placed behind the patient can be acquired to aid delineation of the lung regions.

10. Interpretation

Pre-treatment ^{99m}Tc-MAA SPECT/CT

Acquisition should take place directly after preparatory angiography, within 1 h of injection, because of the stability of ^{99m}Tc-MAA. Images should be evaluated qualitatively

and quantitatively. The lung dose resulting from lung shunting should not exceed 30 Gy. If the amount of lung shunting cannot be reduced using standard radiological interventional techniques, the patient will not be eligible for a therapeutic dose of ^{90}Y. The SPECT/CT scan after the test dose should be carefully checked for extra-hepatic depositions of ^{99m}Tc-MAA. Excessive extra-hepatic deposition in stomach, duodenum or pancreas are absolute contraindications for RE. Extra-hepatic depositions in gallbladder or hepatic falciform artery are not contraindications for RE. Note: free ^{99m}Tc-pertechnetate may lead to diffuse uptake in thyroid, stomach, kidneys and bladder. To avoid this, preparation with perchlorate (300 mg IV) may be considered.

Post-treatment ^{90}Y SPECT/CT or PET/CT

When extra-hepatic depositions are observed in stomach, duodenum or pancreas this should be monitored carefully during follow-up.

11. Report

The clinical report should contain the information from pre-treatment patient preparation, the treatment itself (including administered activity, target vessels and volumes), and complications and/or adverse events. Advice for follow-up should be given (i.e. clinical follow-up at 2 and 4 weeks after treatment, blood tests to be done at 4 weeks after treatment and response evaluation at 3 months after treatment).

12. Literature

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