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Overview

Current Status and Future Direction of Hepatic Radioembolisation

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Abstract

Radioembolisation is a locoregional treatment modality for hepatic malignancies. It consists of several stages that are vital to its success, which include a pre-treatment angiographic simulation followed by nuclear medicine imaging, treatment activity choice, treatment procedure and post-treatment imaging. All these stages have seen much advancement over the past decade. Here we aim to provide an overview of the practice of radioembolisation, discuss the limitations of currently applied methods and explore promising developments.

Key words: Hepatocellular carcinoma; metastatic colorectal cancer; personalised dosimetry; PET; radioembolisation

Introduction

Radioembolisation, also known as selective internal radiation therapy or transarterial radioembolisation, is a locoregional treatment modality for hepatic malignancies. It is an angio-guided treatment, where tumours are internally irradiated through injection of radioactive microspheres into the hepatic arterial vasculature. The microspheres lodge and cluster in distal arterioles inside tumours, where they emit high-energy beta-radiation [1]. This procedure relies on the principle that hepatic tumours are almost exclusively supplied by hepatic arteries, whereas healthy liver tissue is mainly supplied by the portal vein [2]. Thus, the radioactive microspheres will predominantly be distributed towards tumoral tissue, relatively sparing healthy liver tissue.

The treatment consists of several stages, starting with a work-up that includes a simulation procedure, in which surrogate particles are injected into a selected liver artery to predict microsphere distribution. Single photon emission computed tomography/computed tomography (SPECT/CT) imaging is then used to visualise these particles and rule out contraindications (e.g. gastrointestinal depositions). The same images can conveniently be used to predict absorbed dose to lesions and non-tumoral tissue, depending on the prescribed therapeutic activity, allowing treatment planning. This is conceptually similar to what is routinely carried out in the radiotherapy department. In a second session, the treatment angiography takes place, in which the beta-radiation-emitting therapeutic microspheres are administered. Post-treatment imaging is then carried out to visualise the microspheres, validating the prediction made with the simulation procedure and allowing the evaluation of the real imparted absorbed dose. Here we aim to provide an overview of the practice of radioembolisation, discuss the limitations of currently applied methods and explore promising developments.

Radioembolisation Microspheres

There are currently three types of commercially available microsphere (Table 1). These differ in the materials they are made of and the radioisotope they contain. Two products contain the isotope yttrium-90 (^{90}Y), a resin microsphere

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Table 1
Microsphere characteristics

	SIR-Spheres®	TheraSphere®	QuiremSpheres®
Radioisotope	Yttrium-90	Yttrium-90	Holmium-166
Half-life (h)	64.1	64.1	26.8 h
Main emitted radiation	Beta	Beta	Beta and gamma
Mean (maximum) tissue penetration (mm)	2.5 (11)	2.5 (11)	2.5 (8.4)
Visualisation method	Bremsstrahlung-SPECT Yttrium-90 PET	Bremsstrahlung-SPECT Yttrium-90 PET	MRI SPECT
Material	Resin	Glass	Poly-L-lactic acid
Microsphere size (µm; range)	32.5 (20–60)	25 (20–30)	30 (25–35)
Specific activity per sphere (Bq)	40–70	4354*, 1539†, 544‡	200–400
Millions of spheres in a typical administration	20–40	1.7† 4.8‡	12–24
Embolic effect	Moderate	Low	Moderate
Treatment planning method indicated in product leaflet.	BSA (two compartment)	Mono-compartment	Mono-compartment

BSA, body surface area; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single photon emission computed tomography.

* Measured, at the reference date [6].

† Four days after the reference time.

‡ Eight days after the reference time.

(SIR-Spheres®, Sirtex Medical Ltd, Woburn, MA, United States) and a glass microsphere (TheraSphere®, Boston Scientific, Marlborough, MA, United States) [3,4]. The third type are poly-L-lactic acid microspheres and contain holmium-166 (^{166}Ho) (QuiremSpheres®, Quirem Medical B.V., Deventer, the Netherlands) [5].

Both ^{166}Ho and ^{90}Y emit beta-radiation with a comparable energy level. Differences between the microspheres include a higher specific activity per sphere in glass microspheres compared with resin and holmium microspheres. This results in a lower number of injected glass particles (Table 1), which allows for the treatment of small volumes [7], as well as the treatment of main portal vein thrombosis (PVT) [8]. It also has radiobiological implications, for instance, a lower embolic effect compared with the moderate embolic effect of the other two microspheres [9].

Patient Selection

The most common indication for radioembolisation in Europe is hepatocellular carcinoma (HCC), followed by metastatic colorectal carcinoma (mCRC) [10]. In unilobar HCC, radioembolisation can be applied with curative intent in a limited number of cases, or as a bridge to hepatic resection (i.e. radiation lobectomy), when it is applied to induce hypertrophy of the future liver remnant while maintaining tumour control [11,12]. In bilobar or multifocal unilobar HCC, radioembolisation is mostly applied with palliative intent (Figure 1) [13]. For mCRC patients, the European Society for Medical Oncology consensus guideline states that radioembolisation should be considered for patients with liver-limited disease after exhausting the available systemic options, as a salvage treatment (Figure 2) [14].

There are several relative and absolute contraindications for radioembolisation (Table 2) [15,16]. A pre-treatment work-up includes evaluation of clinical performance status, haematological and biochemical status, assessment of the anatomy using CT-angiography/magnetic resonance angiography, and in specific situations molecular imaging with SPECT/CT (e.g. hepatobiliary scintigraphy to assess liver function) or positron emission tomography/computed tomography (PET/CT; e.g. ^{18}FDG-PET/CT to assess extrahepatic disease).

Whether the presence of extrahepatic disease should be permitted is a matter of debate, on the grounds that extrahepatic disease would go untreated in a locoregional treatment such as radioembolisation. In the current guidelines for HCC and mCRC, radioembolisation is recommended in cases with liver-dominant disease [14,17]. In randomised controlled trials (RCT) on HCC, the presence of extrahepatic disease was mostly excluded [18–20], whereas some RCTs in mCRC would include patients with limited extrahepatic disease (i.e. lymph node and lung metastases) [21].

Pre-treatment Work-up

The distribution of microspheres is mainly determined by catheter position, vascular anatomy and blood flow dynamics. Thus, prior to the actual treatment, a simulation angiography is carried out using a surrogate for ^{90}Y-microspheres in the form of gamma-radiation-emitting technetium-99m (^{99m}Tc) macroaggregated albumin (MAA) (multiple suppliers available; ±150 MBq) [22]. For the simulation of ^{166}Ho radioembolisation, a small amount of actual ^{166}Ho-microspheres (QuiremScout®; Terumo, Tokyo, Japan; ±250 MBq; ±2–3 million microspheres) can be used instead of ^{99m}Tc-MAA. The surrogate particles are injected into the position selected for the actual intra-arterial treatment. A SPECT/CT scan is carried out shortly afterwards to assess the predicted distribution of microspheres. Technical contraindications, such as extrahepatic deposition of activity or excessive lung shunting, can be ruled out using this procedure.

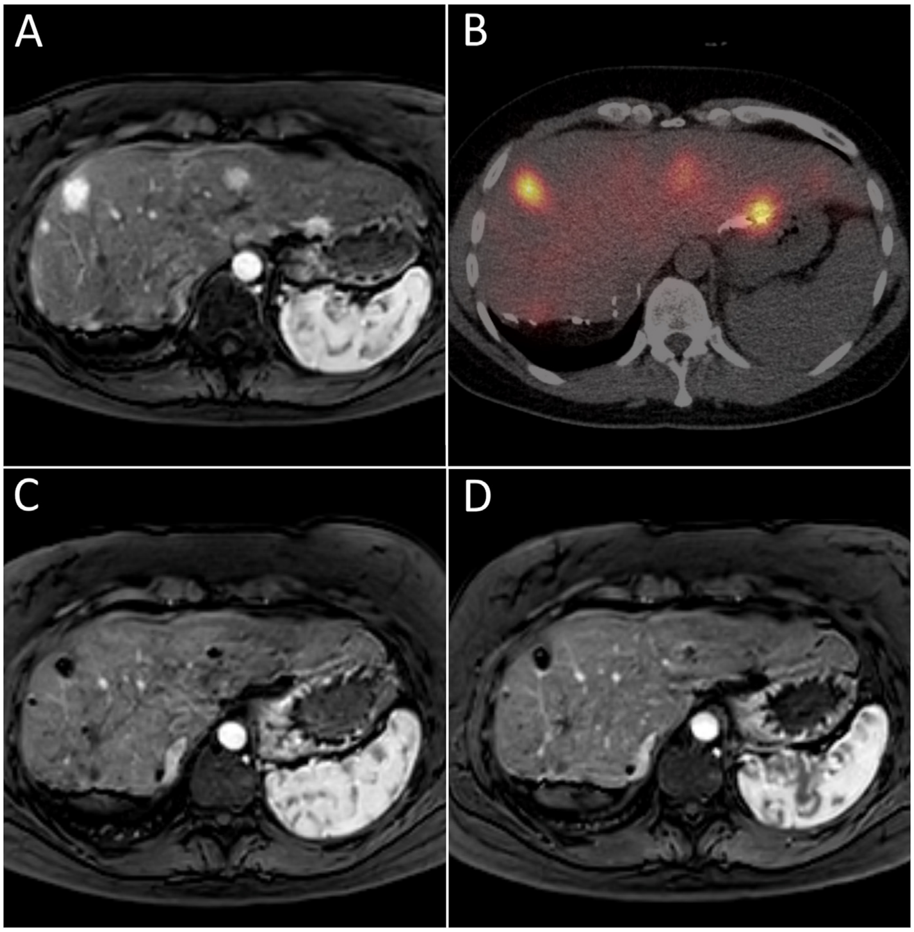

Fig 1. An example of a patient with a multifocal recurrent hepatocellular carcinoma (HCC), treated with ^{166}Ho-microspheres. (A) Magnetic resonance imaging (MRI) at baseline showing multiple hypervascular lesions in the remnant liver after right-sided hemi-hepatectomy, the largest in segment IV. (B) Post-treatment ^{166}Ho single photon emission computed tomography/computed tomography (SPECT/CT), showing good targeting of the HCC lesions. (C) MRI 1 day after treatment demonstrating depositions of microspheres inside the tumour in black. (D) MRI at 3 months post-treatment, showing avascular lesions.

Extrahepatic deposition occasionally occurs in organs with a close vascular relationship to the liver. Vessels such as the gastroduodenal artery, right gastric artery or cystic artery may arise from arteries that are targeted in radioembolisation [23]. Extrahepatic deposition of microspheres can potentially lead to gastrointestinal ulceration [15]. For this reason, such depositions are an absolute treatment contraindication [8], unless this situation is solved. When extrahepatic deposition is detected on the pre-treatment simulation SPECT/CT (or alternatively on cone beam CT during angiography), the culprit (non-target) vessel should be identified. The extrahepatic collateral flow can then be mitigated by embolisation of the culprit vessel using coils, or alternatively, the injection position can be moved to a distal location beyond the origin of the culprit vessel. In 96% of the cases, patients are deemed eligible for treatment after a second treatment simulation [24]. Another method, known as ‘skeletonisation’ (i.e. coil embolisation of all side branches of the hepatic artery), which used to be common practice, is no longer considered necessary, partly due to the use of injection positions that are located distally in the right and/or left hepatic arteries instead of a single proximal location in the proper hepatic artery [10].

Arteriovenous anastomoses, present in the hepatic tumours or parenchyma, allow microspheres to shunt towards the lungs through the venous circulation, which may lead to radiation pneumonitis [25]. Thus, excessive lung shunting is considered a contraindication. Lung shunting mostly occurs in HCC and is uncommon in other tumour types [26]. The currently applied safety threshold for lung shunting indicated by producers, based on planar imaging, is 30 Gy and up to 50 Gy cumulatively after multiple treatments for glass ^{90}Y- and ^{166}Ho-microspheres, and 20% lung shunt fraction for resin ^{90}Y-microspheres [3].

However, we do have strong indications that this method largely overestimates lung shunt fraction, both for the scan type used (planar instead of tomographic), and, above all, because MAA have different morphology and size compared with therapeutic microspheres [27].

Treatment Planning and Post-treatment Imaging

The dual vascularisation principle implies that most intra-arterially administered microspheres will accumulate

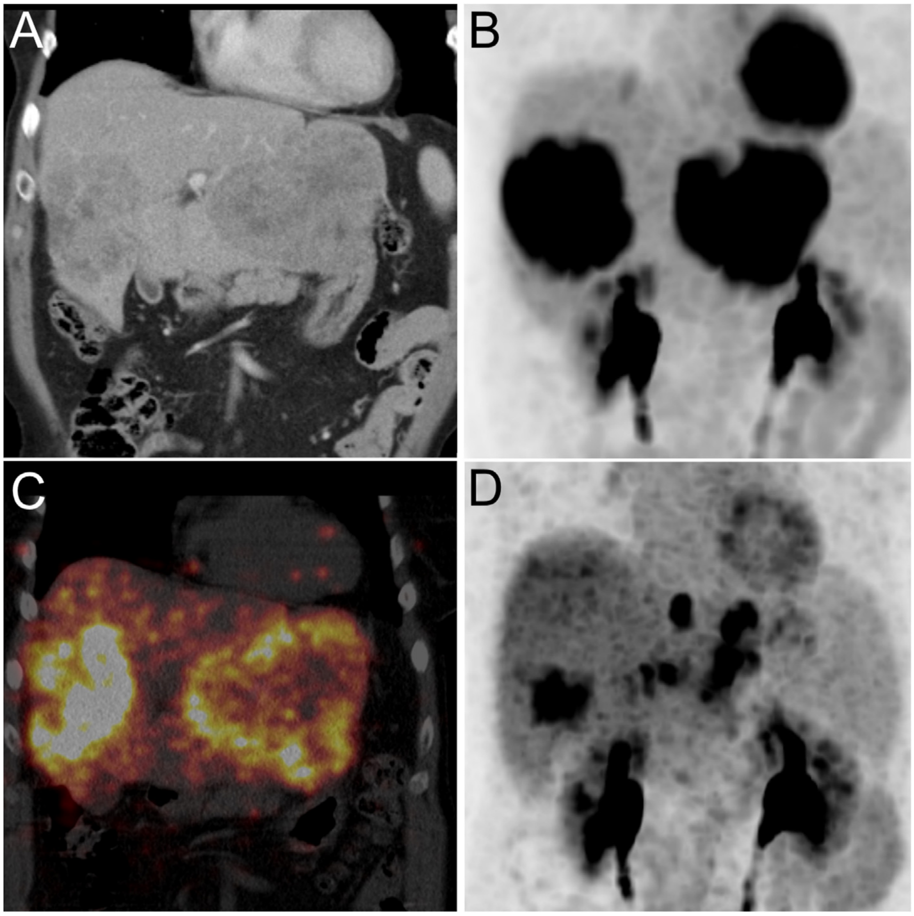

Fig 2. Example of a glass yttrium-90 (^{90}Y) radioembolisation of metastatic colorectal carcinoma in salvage setting. (A, B) Baseline portal-phase computed tomography scan and ^{18}FDG-positron emission tomography (^{18}FDG-PET) of a patient with two large metastases in the left and right liver lobes (10.3 and 9.2 cm). (C) Post-treatment ^{90}Y-PET showing favourable tumour targeting, post-treatment dosimetry revealed a tumour absorbed dose of 114 Gy to the lesion in the left lobe and 197 Gy to the lesion in the right lobe. (D) Three-month follow-up ^{18}FDG-PET showing partial response of the two treated lesions, as well as three small new hepatic lesions in the left lobe.

inside the tumour. However, this is not always the case, as the intrahepatic distribution difference, expressed by the tumour-to-non-tumour ratio (T/N), can vary greatly between patients. This ratio is dependent on many factors, e.g. tumour type, tumour vascularity, vascular invasion, selected injection position. A high T/N ratio allows for a relatively high tumour dose while maintaining a relatively low healthy liver absorbed dose.

Treatment activity planning methods differ depending on the type of microspheres used. Most commonly used are the body surface area (BSA)-based method for resin microspheres and the Medical Internal Radiation Dose

Table 2
Relative and absolute contraindications for radioembolisation

Criterion	Contraindications	
	Relative	Absolute
Clinical condition		ECOG performance score >2
Life expectancy		<3 months
Organ function	Mild to moderate laboratory abnormalities	Critical renal or bone marrow failure
Hepatic function	Cirrhosis (Child-Pugh score > B7), serum bilirubin >34.2 μmol/l (i.e. 2 mg/dl)	Uncompensated hepatic failure, active hepatitis
Biliary system	Biliary stents/bile duct abnormalities	Cholangitis
Macrovascular invasion		Main branch portal vein thrombosis, hepatic vein invasion
Technical aspects		Excessive lung shunt, uncorrectable gastrointestinal deposition of microspheres.

ECOG, Eastern Cooperative Oncology Group.

(MIRD) ‘mono-compartment’ method for glass and holmium microspheres. The BSA method was developed to curtail the high toxicity that was observed in early clinical studies [28]. The treatment activity is calculated using a formula that takes the fractional tumour involvement into account, and the BSA as a surrogate for liver size [3]. A large study in 680 patients that compared the BSA method with the previously used ‘empirical’ method found a lower rate of toxicity in the BSA cohort [29]. It also reported lower median prescribed activities in the BSA cohort compared with the ‘empirical’ cohort, 1.6 ± 0.5 GBq versus 2.0 ± 0.4 GBq, respectively. It is interesting to note that the actually administered activity was even lower (i.e. 1.1 ± 0.6 GBq), as in 98% of cases ($n = 491$) it was lowered even further based on physicians’ discretion (1.6 ± 0.5 GBq calculated with BSA method, 1.2 ± 0.6 GBq physician’s prescription).

The MIRD ‘mono-compartment’ activity calculation method is based on a desired average absorbed dose to the treated part of the liver [4,5]. An average absorbed dose ranging from 80 to 150 Gy is recommended for glass and a fixed 60 Gy absorbed dose for holmium microspheres. The treated ‘mono-compartment’ encompasses both tumour and non-tumorous tissue and does not differentiate between the two. However, these two recommended absorbed dose limits are markedly different. As for glass spheres, the recommended dose range is more broad. Furthermore, the target is more ambiguous, as the instruction for user reports ‘dto liver’, without specifying if the indication refers to the treated portion or to the whole liver.

For ^{166}Ho spheres, the limit was determined with an escalation study where 20, 40, 60, 80 Gy were imparted to whole liver [30]. Toxicity was observed at the last step; therefore 60 Gy was chosen as the safety limit. This value initially referred to the treated portion in case of lobar or segmental treatment, whereas in the new ^{166}Ho indications, it refers to the whole liver, no matter if the treatment is lobar. This means that a smaller treated region can tolerate a proportionally higher absorbed dose, in agreement with the basic radiobiology of parallel organs, the well-known volume effect in external beam, and with the most recent experimental findings in radioembolisation [31,32].

The main goal of these methods is to ensure treatment safety; however, the different microsphere concentration in tumour and non-tumoral tissue is not taken into consideration. The absorbed doses in these two compartments vary significantly among patients, mostly resulting in underdosing patients to sustain overall safety [33–35]. Furthermore, BSA was later shown to be a poor surrogate for liver volume, leading to underdosing in patients with large livers relative to their BSA and overdosing in relatively small livers (Figure 3) [36].

An alternative method for treatment planning is the ‘multi-compartment’ method. The first developed method in this direction is known as the partition model. This model takes three compartments into consideration: tumour, non-tumorous liver and lungs. Treatment planning aims at maximising the absorbed dose to the tumour while staying below the safety thresholds for healthy liver and the lungs [37]. The advantage of the partition model in comparison with the previously mentioned planning method is that it differentiates between absorbed dose to target and non-target tissue, as requested by the EU Directive 2013/59. One limitation is that the tumour absorbed dose is averaged over many lesions. More advanced methods evaluate absorbed dose for any single lesion. Furthermore, multi-compartment methods require threshold validations for both safety and efficacy. Clinical studies have shown large variations in these thresholds between tumour types and the used microspheres [16,38–40]. This subject, called dosimetry, will be discussed in the next section.

The weak point of treatment planning is the limited accuracy of absorbed dose prediction obtained with ^{99m}Tc MAA SPECT/CT, especially with regards to small lesions. The 95% confidence interval of the differences between predicted and actual lesion absorbed dose is as wide as some hundreds of Grays [41–45]. Such large uncertainties clearly pose limitations to the prognostic accuracy on lesion response. This mismatch depends, amongst others, on the different repositioning of catheter tip position between the

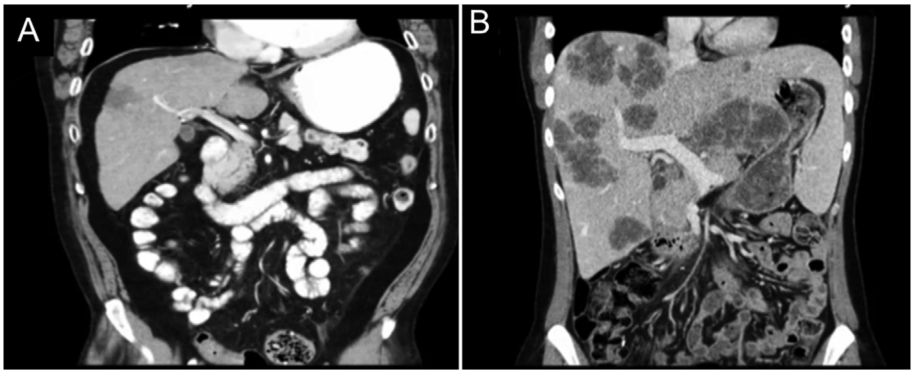

Fig 3. An example of two patients treated for metastatic colorectal carcinoma with resin yttrium-90 (^{90}Y)-microspheres using the body surface area (BSA) treatment planning method. Using the BSA method both patients received a similar amount of activity. For patient A, who has a small liver with a limited tumour volume, this resulted in an absorbed dose that was too high and resulted in radioembolisation-induced liver disease within 3 months post-treatment. In contrast, patient B, who has a large liver relative to their BSA with a large tumour volume, was underdosed and had disease progression within 3 months.

simulation and the therapy sessions, especially in the proximity of an arterial bifurcation [46,47]. However, the problem persists if repositioning is accurate [48]. Many other factors may be responsible for this mismatch too, including the use of two different kinds of particle in the two sessions, and a different number. The use of the same ^{166}Ho particle for the two sessions significantly reduced the prediction uncertainty on lesion absorbed dose [45,49]. As the prediction on non-tumoral liver tissue is less subject to uncertainty than lesions, another improvement in planning is using the dose–toxicity relationship in order to deliver the maximum tolerable absorbed dose [45].

The two isotopes used in radioembolisation can be imaged in several ways (Table 1). Post-treatment imaging has its rationale in the often-reported differences between the predicted and the actual therapeutic biodistribution. It can be used either to visually assess the intra- and extra-hepatic distribution of microspheres or for quantitative verification (dosimetry). The visual check allows prompt medical action in case of inadvertent deposition in the gastro-enteric tract, whereas post-treatment dosimetry is used to evaluate treatment success, validating the prediction made using the pre-treatment simulation. Suboptimal absorbed dose distribution can be corrected with a second administration, without waiting for disease recurrence [50].

Treatment Outcomes in Relation to Absorbed Dose

SPECT/CT images can be conveniently used to predict the absorbed dose to lesions and to the heathy tissue depending on the prescribed activity for therapy. This allows therapy to be optimised and personalised (treatment planning), as required by the EU Directive 2013/59 for nuclear medicine therapy, as well as external beam radiotherapy [51]. In the era of personalised medicine, we expect that such an option could significantly improve the clinical outcome of radioembolisation.

Radioembolisation is a generally well-tolerated treatment, which may be accompanied by mostly mild side-effects, including abdominal pain, nausea, vomiting, fatigue and fever, occurring within 4–6 weeks after treatment [15,52]. Side-effects almost always resolve without further treatment. Interestingly, in HCC patients with PVT (Barcelona Criteria for Liver Cancer [BCLC] C), the standard of care treatment with sorafenib produces more severe side-effects, with a more marked worsening of quality of life [53]. There are some more severe complications associated with radioembolisation, of which radioembolisation-induced liver disease (REILD) is the most severe and potentially fatal. In general, hyperbilirubinemia, hypoalbuminemia, jaundice and ascites as signs of liver failure are regarded as indicative of REILD, unless explained by biliary obstruction or disease progression [54]. The severity of the toxicity ranges from minor changes in biochemical markers, to REILD necessitating invasive medical treatment and fatal REILD. The exact incidence of toxicity after radioembolisation is controversial as different authors adopted different end point definitions. For instance, according to Kennedy *et al.* [29], REILD incidence was estimated to be 1–3% in most practices, whereas Strigari *et al.* reported CTCAE v4 toxicity of 32% $\geq$ grade 2, 21% $\geq$ grade 3, 11% $\geq$ grade 4 (death related to treatment) after resin ^{90}Y-microspheres for HCC planned with the BSA method [55]. They included any kind of liver toxicity, imputable both to treatment and to the natural history of disease itself (i.e. tumour and cirrhosis). REILD is associated with the baseline liver condition, indicated by the Child-Pugh score for cirrhosis. In total, 8/9 (89%) Child-Pugh B7 patients showed liver decompensation after standard administration of glass ^{90}Y-microspheres [56], whereas in a Child-Pugh A cohort planned with mixed criteria (standard indication and personalised dosimetry) it was 11%. Baseline bilirubin >1.1 mg/dl and absorbed dose to the whole non-tumoral liver were ascertained as risk factors for treatment-related liver decompensation, both with glass and resin ^{90}Y-microspheres [57,58]. Therefore, a proper patient selection and treatment planning are mandatory to limit the toxicity rate.

Hepatocellular Carcinoma

In HCC, according to the modified BCLC scheme, radioembolisation is mainly positioned for intermediate (BCLC B) and advanced (BCLC C) patients [52]. Several relationships between absorbed dose and tumour response were found in HCC patients treated with glass ^{90}Y-radioembolisation using post-treatment dosimetry [59]. One study found significantly higher tumour absorbed doses in responders (per mRECIST) compared with non-responders (225 Gy versus 83 Gy) [60]. Furthermore, all tumours that received a tumour absorbed dose >200 Gy had an objective response. Another study found a response rate of 89.7% in patients with tumour absorbed doses $\geq$205 Gy on ^{99m}Tc-MAA compared with 9.1% in tumour doses <205 Gy [51]. Moreover, a dose-toxicity relationship was shown in HCC treated with glass ^{90}Y-microspheres in two studies, proposing comparable safety thresholds of up to 90 Gy in the healthy liver tissue [51,58].

Initial results, confirming improved overall survival in HCC by dosimetric treatment planning, are available in a study on sequential cohorts and even in a prospective randomised trial. The first study reported that median overall survival of HCC Child A patients with PVT was 12 months versus 8 months for the cohort planned using dosimetry versus the standard indication of 80–150 Gy, albeit non-significant $P = 0.067$ [61]. Lesion volumes were not significantly different between the two PVT cohorts. On the other hand, for the two cohorts without PVT, lesions were significantly larger in the cohort treated using dosimetry. Despite that, median overall survival was preserved due to dosimetry, with a non-significant difference of 15 (dosimetry) versus 17 months (standard indication).

A RCT comparing resin ^{90}Y-radioembolisation with sorafenib in advanced HCC (SARAH trial), showed an improvement in tumour response and a decrease in adverse events [18]. However, they failed to show improvement in overall or progression-free survival. It is noteworthy that the BSA method was used, which is prone to underdosing [36].

A recently published post-hoc analysis of the SARAH trial showed improved overall survival and response in patients with tumour absorbed doses >100 Gy versus an absorbed dose <100 Gy (median overall survival 14.1 months versus 6.1 months; $P = 0.001$) [62]. Furthermore, pre-treatment ^{99m}Tc-MAA SPECT/CT dosimetry was an independent predictor of prolonged survival, suggesting that with improved treatment planning methods, a survival benefit might have been predicted and achieved [63]. The impact of pre-treatment dosimetry in HCC was studied in a recently completed RCT on glass ^{90}Y-microspheres (DOSISPHERE-01), which is a milestone in the progress of dosimetry in radioembolisation and in nuclear medicine therapy. Authors compared a prospective personalised dosimetry approach (multi-compartment, >205 Gy to index lesion) versus standard indication (mono-compartment dosimetry, 120 Gy average absorbed dose in the target volume). Prescribing the therapeutic activity according to pre-treatment dosimetry showed an improved response rate at 3 months after treatment (response rate: 79% versus 43%, $P = 0.0062$), as well as improved overall survival in the personalised dosimetry group (26.7 months versus 10.6 months, $P = 0.0096$) [64]. For treatment of HCC with glass ^{90}Y-microspheres, an international panel of experts now recommends >200 Gy as a threshold for tumour absorbed dose to achieve response using pre-treatment dosimetry on ^{99m}Tc-MAA SPECT/CT images [16].

It is interesting to note that such improved outcomes based on ^{99m}Tc-MAA SPECT/CT dosimetry were obtained despite the mentioned mismatch between pre- and post-treatment absorbed dose evaluation. This can be understood considering that such differences are zero on the average. Therefore, we have an average outcome improvement thanks to pre-treatment dosimetry if we consider average properties of a studied cohort (like median overall survival). On the contrary, we may have unexpected outcomes in individual patients when the actual lesion absorbed dose deviates from the prediction.

Metastatic Colorectal Cancer

In mCRC, dose-response relationships have also been established in mCRC treatment with resin ^{90}Y-microspheres, and more recently in ^{166}Ho- and glass ^{90}Y-microspheres. A conservative estimate for the minimum absorbed dose to reach metabolic response (50% reduction in total lesion glycolysis on ^{18}F-FDG-PET) was 40–60 Gy using resin ^{90}Y-microspheres, calculated on post-treatment ^{90}Y PET imaging [38]. In ^{166}Ho treatment of mCRC, the mean tumour absorbed dose was higher by 84% in responders versus patients with progressive disease. Furthermore, patients receiving tumour absorbed doses >90 Gy had a significantly higher overall survival versus patients with tumour absorbed doses <90 Gy [39]. In treatment with glass ^{90}Y-microspheres, a tumour absorbed dose ≥ 183 Gy on post-treatment dosimetry predicted a metabolic tumour response at 3 months with 97% specificity. Furthermore, the mean tumour absorbed dose was higher by 111% in responders versus patients with progressive disease ($P = 0.02$) [65].

Resin ^{90}Y-radioembolisation was investigated as a first-line treatment for mCRC in three large RCTs, the SIRFLOX, FOXFIRE and FOXFIRE Global [66]. These trials were designed to assess whether radioembolisation combined with first-line chemotherapy (FOLFOX) can improve overall survival compared with chemotherapy alone. Although an improved objective response rate (75.8% versus 63.7%, $P = 0.001$) and liver-specific progression-free survival (hazard ratio 0.90, 95% confidence interval 0.79–1.02, $P = 0.108$) were reported, an additional overall survival benefit was not shown. Treatment planning was carried out using the BSA method, modified to reduce the dose even further based on increasing lung shunt fractions and fractional liver involvement. Currently, there is one large RCT ongoing in glass ^{90}Y-radioembolisation of mCRC (EPOCH) as a second-line treatment versus chemotherapy [67]. However, the MIRD ‘mono-compartment’ is used for treatment planning. There are currently no RCTs in the treatment of mCRC using prospective dosimetry.

Future Perspectives

Currently used treatment planning methods (BSA and MIRD) in radioembolisation are the most significant limitations of this treatment and the currently published outcomes in literature. The lack of dosimetric treatment planning was advocated as one of the reasons of the failure of these large phase III trials on mCRC [68], as well as the SARAH study on HCC. Understanding dose-response relationships and the use of a more accurate simulator than MAA can lead to improved planning methods that permit a truly individualised approach. With this new device, the implementation of ‘multi-compartment’-based planning methods adds a new dimension to patient selection, allowing for exclusion of patients that are not expected to benefit from the treatment based on intrahepatic microsphere distribution on scout dose SPECT/CT. In contrast to the current practice, in which patients can receive radioembolisation if the ^{99m}Tc-MAA scan shows no extrahepatic deposition (about 90–95% of patients), pre-treatment dosimetry will be added to the selection process. A good probability of response requires that the predicted tumour dose reaches a pre-defined tumoricidal threshold, with an expected parenchyma dose staying below a pre-defined safety threshold. As discussed in the previous section, these thresholds vary between tumour types and dimension, and therapeutic particle used.

Once treatment planning has been matured, only then can the potential role of radioembolisation in earlier lines of disease treatment be properly studied. There are still several clinical trials underway that use BSA and ‘mono-compartment’ MIRD dosimetry (SIRCCA-trial: resin ^{90}Y-radioembolisation followed by cisplatin + gemcitabine (CIS-GEM) versus CIS-GEM as a first-line treatment for unresectable intrahepatic cholangiocarcinoma (ICC); EPOCH-trial: glass ^{90}Y-radioembolisation as a second-line treatment for mCRC followed by resumption of chemotherapy versus chemotherapy alone). Unfortunately, these studies suffer from the same limitations as previous phase III trials. These trials will need to be evaluated in the light of proper pre- and post-treatment dosimetry. Together with placement in earlier treatment lines, radioembolisation can also be studied as a combined treatment with other embolic therapies, such as trans-arterial chemoembolisation (DEBIR^{90}Y-trial) or locoregional ablative therapies (HORA EST-trial). The leading-edge research should combine immunotherapy and radioembolisation, the latter used either as a trigger of immune response (low tumour absorbed dose required) or as additional treatment (high tumour absorbed dose).

The next step in improving radioembolisation treatment planning may lie in voxel-based dosimetry. Simply put, a voxel is a three-dimensional pixel, i.e. the smallest measured spatial unit. Using voxel-based dosimetry one can extract information on the heterogeneity of the distribution of microspheres within each compartment, as ordinarily carried out in external beam radiotherapy planning. This may be a step forward with respect to ‘multi-compartment’ MIRD dosimetry, in which the absorbed dose is averaged over each compartment [28]. Metrics such as the D_{70} (i.e. lowest absorbed dose to 70% of the volume) and V_{100} (i.e. percentage of the volume with an absorbed dose above 100 Gy) are examples of spatially dependent parameters that may prove to be better at demonstrating dose-effect [56,69]. Unfortunately, such proof has not yet been obtained, and the mean absorbed dose in each compartment is still a good parameter [56,70].

A noteworthy advance in the field of radioembolisation comes in the development of specialised imaging systems. Traditional C-arm devices contain an X-ray tube and detector and can convey anatomical information in real-time but lack the ability to visualise radioactive particles. A novel device that integrates a gamma camera with the X-ray system may overcome this limitation and is currently in development [71,72]. In radioembolisation treatment this technology can visualise the distribution of microspheres as they are being injected, allowing physicians to adjust during treatment when necessary.

Conclusion

Radioembolisation is a safe and effective treatment for hepatic malignancies. RCTs failed to show survival benefit over current systemic treatments, partly due to imperfect treatment planning methods. Improved and personalised treatment planning methods, based on distinct prediction of absorbed dose to tumour and non-tumoral tissue, is under development and recently showed promising results in terms of improved clinical outcome.

Conflicts of interest

A.A. Alsultan reports personal fees from Boston Scientific, outside the submitted work. M.G.E.H. Lam reports grants, personal fees and non-financial support from Boston Scientific, personal fees and non-financial support from Terumo, personal fees, non-financial support and other from Quirem Medical, outside the submitted work. M. Maccauro reports personal fees from Boston Scientific, personal fees from Terumo, outside the submitted work. C. Chiesa reports grants and personal fees from Boston Scientific, personal fees from Terumo, personal fees from Alfasigma, outside the submitted work. M.L.J. Smits and A.J.A.T. Braat report personal fees from Boston Scientific, personal fees from Terumo, personal fees from SirTex, outside the submitted work.

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