Treatment of liver tumours with yttrium radioembolisation

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Received: 17 June 2013 / Accepted: 12 December 2013 / Published online: 16 January 2014
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Abstract The liver is a common site of malignant disease with hepatocellular carcinoma and liver metastases accounting for the majority of liver malignancies. Conventional treatment options are confined to chemotherapy, surgery and minimally invasive procedures such as radio-frequency ablation. External beam radiation therapy has a limited role in the treatment of liver malignancy, mainly due to the substantial risk of radiation-induced liver disease. Transarterial chemoembolisation is contraindicated in patients with portal vein thrombosis or advanced liver disease. Selective internal radiation therapy using yttrium-90 microspheres has emerged as a suitable treatment of liver tumours. In this review we discuss the principles behind this treatment, the process of patient selection, and the method of dose calculation and administration. We also highlight possible adverse effects and review the literature for data on response assessment and long-term outcome.

Keywords SIRT · Yttrium · Y-90 · Microspheres · Liver tumours · Liver metastasis

Introduction

The liver is a common site of malignant disease with hepatocellular carcinoma (HCC) and liver metastases accounting for the majority of liver malignancies.

As a site of metastatic disease, the liver is the exemplary organ of Paget's "seed and soil" hypothesis [1]. The liver's receptor-rich sinusoid system provides the necessary mechanism for lodging of the metastatic "seed" cells [2, 3] and its rich blood supply helps to create an environment conducive to clonal expansion of the metastatic "seeds". Metastatic disease to the liver outnumbers primary liver malignancy by ten to one [4] and approximately 50 % of liver metastases originate from a primary colorectal cancer [5]. The outcome of untreated colorectal liver metastases (CLM) is dismal with a 5-year survival rate of 8 % [6].

Cirrhosis, with the resultant destruction of normal liver architecture, is said to confer relative protection against liver metastases [7, 8]. However, factors leading to cirrhosis significantly increase the patients' risk of developing HCC, which is the sixth commonest cancer worldwide [9]. Recent years have seen an increase in HCC incidence particularly in North America and Europe [10, 11]. The prognosis of HCC is abysmal, with a 1-year survival rate of less than 50 % [10] and a 5-year survival rate of 15 % [12].

Treatment options

Conventional treatment options for both primary and secondary liver malignancies are confined to chemotherapy, surgery and minimally invasive procedures such as radio-frequency ablation which targets a few small lesions. External beam radiation therapy has a limited role in the treatment of liver malignancy, mainly due to the substantial risk of radiation-induced liver disease at radiation doses (30–40 Gy) [13–15] significantly below tumoricidal doses (70 Gy in radiation-only therapy, 50 Gy when combined with chemotherapy) [16, 17].

Colour figures online at <http://link.springer.com/article/10.1007/s40336-013-0046-7>

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In HCC, surgical resection and liver transplantation offer the best curative potential, with reported 5-year recurrence-free survival rates of up to 90 % [18], but these approaches only benefit patients with limited or early stage disease; indeed, only 20 % of patients with HCC are considered surgical candidates [19]. The remaining patients present with advanced disease and are not amenable to surgery. Systemic chemotherapy with sorafenib, an oral multi-tyrosine kinase inhibitor, has given disappointing results, with an 8 % response rate and 10.7 months of median overall survival compared to 7.9 months for patients receiving placebo [20].

Surgical resection offers the best chance of survival in CLM too [21, 22]. However, only 10–15 % of cases are resectable at diagnosis [23]. Neoadjuvant chemotherapy is effective in downstaging metastatic lesions, rendering one-third of unresectable cases amenable to surgery [24–27]. However, the response rate to chemotherapy is between 31 and 56 % [28, 29]. Furthermore, even in patients who are treated surgically the prognosis remains poor, with a 5-year survival rate of 38 % [30].

A variety of minimally invasive procedures have been put forward as potential alternative treatments of focal liver lesions, including percutaneous ethanol injection, cryoablation and microwave/radiofrequency ablation (RFA); RFA is currently the standard of care in ablative therapy [31]. The main limitation of this technique is that effective ablation of tumour beyond 3 cm can be difficult to achieve [32]. The location of the tumour may also dictate the feasibility of the technique. Lesions located near blood vessels can be difficult to ablate due to the “heat sink” effect [33], while ablation of lesions near the hilum, gallbladder, gastrointestinal (GI) tract and skin surface carries a risk of collateral damage to these structures [34]. In addition, since only lesions visible on imaging can be targeted with these techniques, there is a potential for recurrence from microscopic foci. Available data on this theoretical risk are equivocal. It has been shown that, compared to surgical resection, RFA has a higher recurrence rate and a lower survival rate [35]. Conversely, Chen et al. [36], Hong et al. [37] and Montorsi et al. [38] reported similar survival rates between RFA and surgical resection.

It is clear that there is a therapeutic gap between surgical resection, systemic therapy and targeted minimally invasive procedures such as RFA and cryoablation. The realisation that both primary and metastatic liver lesions derive 95 % of their blood supply from the hepatic artery (whereas normal liver parenchyma receives 25 % of its blood supply from the hepatic artery) [39] prompted the development of loco-regional transarterial embolisation treatment of selected liver lobes or segments, which may bridge this gap. This treatment can be performed using chemotherapeutic agents and is known as transarterial chemoembolisation (TACE).

There is strong evidence that TACE significantly improves survival in intermediate-stage HCC [40–42], and although a recent meta-analysis shows conflicting results [43], TACE is the current first-line treatment in intermediate-stage HCC [44]. Conventionally, portal vein thrombosis (PVT) is thought to be a contraindication to TACE [44] but there is increasing evidence that challenges this view [45]. Apart from chemotherapeutic agents, radioactive substances can also be used for transarterial loco-regional treatment of the liver, in an approach termed selective internal radiation therapy (SIRT).

Selective internal radiation therapy

The ideal SIRT agent would be one that preferentially targets the tumour tissue and has little effect on the normal liver parenchyma or other organ systems. Such a therapeutic agent should also have limited radiation range, therefore minimising radiation protection issues. The first SIRT agent was iodine-131 (^{131}I)-labelled lipiodol [46]. Evidence for the effectiveness of ^{131}I -lipiodol is limited; although a prospective randomised-controlled trial by Raoul et al. [47] comparing ^{131}I -lipiodol SIRT and cisplatin TACE suggested that ^{131}I -lipiodol may be as effective as TACE. An advantage of ^{131}I -lipiodol is that it can be safely used in patients with PVT [48, 49], in whom TACE is contraindicated. However, as well as emitting beta particles, ^{131}I is also a gamma emitter with a principal gamma photon energy of 364 keV, necessitating radioprotection constraints. In addition, ^{131}I -lipiodol production is currently produced only in France. These factors limit the widespread use of ^{131}I -lipiodol.

Compared to ^{131}I -lipiodol, the yttrium-90 (^{90}Y) microsphere is a near-perfect SIRT agent as ^{90}Y is a pure beta emitter with a half-life of 64.2 h, decaying into stable zirconium-90. The maximum beta-particle energy is 2.27 MeV (mean energy 0.93 MeV) and the maximum range in tissue is 11 mm (mean 2.5 mm), thus limiting radiation damage to a small region around the uptake site. In addition, although ^{90}Y emits no gamma radiation, Bremsstrahlung photons are emitted when the beta particles interact with tissues, thus allowing post-procedural imaging to evaluate distribution of the therapeutic dose.

In ^{90}Y -SIRT, ^{90}Y -labelled microscopic resin or glass beads are delivered through intra-arterial infusion of selected branches of the hepatic artery by selective angiocatheterisation. Once injected, the radiolabelled microspheres lodge within the tumour vascular bed permanently [50, 51] and are neither metabolised nor excreted. It has been shown that ^{90}Y -microspheres preferentially accumulated at the edge of the tumours and were able to deliver activity upward of 100 Gy to tumour tissues [50].

Table 1 Comparison of physical characteristics between TheraSpheres and SIR-Spheres

	TheraSpheres	SIR-Spheres
Carrier	Glass	Resin
Diameter (μm)	20–30	20–60
Specific gravity (g/dL)	3.6	1.6
Activity/microsphere (Bq)	2,500	50
Number of particles per standard dose	1.2 million	40–80 million

The activity per particle is higher in TheraSpheres than SIR-Spheres, therefore treatment using TheraSpheres requires fewer particles to achieve the same dose and is thought to be less embolic. Conversely, because of the increased number of particles, SIR-spheres is thought to provide more homogeneous radiation coverage and “cross-fire” than TheraSpheres

The tumoricidal effect of SIRT, and radiation therapy in general, occurs as a result of DNA double strand breaks and activation of other cellular pathways [52]. In contrast to TACE, SIRT with ^{90}Y -microspheres is not designed to induce ischaemia. In fact, effective radiation-induced cell death depends on the generation of free radicals, which is in turn dependent on the presence of oxygen [53, 54].

Selective internal radiation therapy with ^{90}Y -microspheres was first reported in 1961 [55] and the technique showed promising early results [56, 57]. However, leaching of ^{90}Y from the microspheres in the first-generation devices [58] led to a decline in its use in the 1970s and 1980s. Since then, there has been a resurgence of ^{90}Y -SIRT following the introduction, in the 1990s, of two new ^{90}Y -microsphere devices which overcome the leaching problem: TheraSpheres (MDS Nordion, Ottawa, Canada), which consists of ^{90}Y -embedded glass microspheres and is licensed by the FDA for the treatment of HCC; and SIR-Spheres (SIRTEX Medical, Lane Cove, Australia), which consists of ^{90}Y -bound resin microspheres and is licensed by the FDA for treatment of CLM. Both devices have regulatory approval in the European Union for the treatment of liver malignancies. Table 1 compares the physical characteristics of these two products.

Patient selection and contraindications

Patients who benefit most from ^{90}Y -microspheres are those with liver predominant primary or metastatic disease who are not eligible for curative surgery. The decision to opt for ^{90}Y -microsphere therapy should result from multidisciplinary discussion between experts from medical oncology, radiation oncology, surgery, interventional radiology and nuclear medicine, while also taking into account the patient's preference. As ^{90}Y -microsphere therapy has not been demonstrated to be curative, the patient's disease status and eligibility for curative surgery should be ascertained on triple-

phase CT or MRI with gadolinium contrast. The presence and extent of extrahepatic disease, which may ultimately determine the prognosis regardless of the treatment of the liver disease, should also be determined.

Contraindications, as listed by the Consensus Panel Report from the Radioembolization Brachytherapy Oncology Consortium (REBOC) [59] and by the EANM guideline [60] are the following:

1. Disseminated extrahepatic disease.
2. Severely abnormal excretory liver function tests or ascites suggestive of clinical liver failure.
3. Hepatopulmonary shunt >20 %.
4. Vascular variants and anomalies as demonstrated on pre-treatment angiography which cannot be corrected by embolisation and which may lead to reflux of hepatic arterial blood to the stomach, pancreas or bowel.

Although PVT is also listed as a contraindication by both the REBOC group and in the EANM guideline, there is mounting evidence that PVT, even when the main trunk is involved, is not an absolute contraindication to SIRT (please see below section on “[Special circumstances](#)”). Indeed, PVT is no longer listed as a contraindication in more up-to-date patient selection guidelines such as the one produced by Coldwell et al. [61].

Effects of cumulative radiation dose from SIRT and previous radiotherapy have not been documented and prior radiotherapy is thus a relative contraindication to SIRT. Patients whose life expectancy is less than 1 month are also considered unsuitable for SIRT for radiation protection reasons.

Patient work-up

In addition to multidisciplinary discussion, patients being considered for ^{90}Y -microspheres should undergo [59, 60]:

1. Staging scans, for determination of extrahepatic disease status and burden
2. Pre-treatment angiography, for mapping of visceral vessels and embolisation of collateral vessels
3. Hepatic arterial infusion of $^{99\text{m}}\text{Tc}$ -MAA and subsequent scintigraphy for
 - (a) evaluation of lung and gastrointestinal shunting and
 - (b) dose calculation of ^{90}Y -microsphere SIRT.

Visceral angiography

The purpose of pre-treatment visceral angiography is three-fold. First, the arterial blood supply of the liver needs to be mapped. The classic hepatic arterial pattern is found in only

Fig. 1 **a** Work-up angiogram for ^{90}Y -microsphere treatment. The right gastric artery and the gastroduodenal artery (arrows) were embolised during this examination. **b** Angiogram performed just prior to injection of ^{90}Y -microspheres, 1 week after **a**. A new collateral

vessel has formed around the gallbladder fossa (black arrowhead). This was not thought to be significant and the patient received 1.1 GBq ^{90}Y -microspheres to the whole liver. Note migrated coil in the right hepatic artery (white arrowhead)

57–61 % of the population [62] and there may be variant arterial supply to the liver from the aorta, celiac trunk and superior mesenteric artery, necessitating multiple vessel catheterisation and infusion to achieve the desired SIRT dose. In addition, stenosis of the hepatic artery may limit the flow rate of ^{90}Y -microspheres and is a contraindication to such therapy. This can be demonstrated on pre-treatment angiography.

Second, the arterial supply of the gastroduodenal territory may arise from the hepatic artery or the territory may receive collaterals from the hepatic arterial tree (Fig. 1a). Inadvertent delivery of ^{90}Y -microspheres into these vessels can cause GI ulceration and pancreatitis [63, 64]. Thus, routine pre-treatment embolisation of the gastroduodenal artery, right gastric artery and other collateral vessels is recommended [65]. As these vessels can revascularise and new collaterals can rapidly form [66] (Fig. 1b), it is also recommended that embolisation be performed close to the actual SIRT treatment date (e.g. within 1 week) and a check angiogram should be done just prior to infusion of ^{90}Y -microspheres to exclude revascularisation.

Finally, during pre-treatment angiography, 75–150 MBq of $^{99\text{m}}\text{Tc}$ -MAA is infused at the same rate planned for the ^{90}Y -microsphere treatment with the catheter also in the same position as for the planned SIRT procedure to facilitate calculation of hepatopulmonary shunt.

Hepatopulmonary shunt

The individual ^{90}Y -microspheres can be as small as 20 μm and can traverse the hepatic sinusoids into the right heart

and pulmonary circulation. In addition, arteriovenous malformations, either congenital or related to tumours, cause blood to bypass the capillary bed and be shunted from hepatic arterial tree to systemic venous circulation and subsequently the lungs. The amount of shunting, the lung shunt fraction (LSF), is defined as $\frac{\text{lung counts}}{\text{lung} + \text{liver counts}}$ on scintigraphy after intra-arterial infusion of $^{99\text{m}}\text{Tc}$ -MAA as described above. Before injection of $^{99\text{m}}\text{Tc}$ -MAA, attenuation correction with $^{99\text{m}}\text{Tc}$ or cobalt-57 flood source should be performed to avoid overestimation of the LSF [67]. Administration of ^{90}Y -microspheres in the presence of a significant shunt carries a risk of inducing radiation pneumonitis. Radioembolisation is therefore not recommended in the presence of a LSF above 20 % (Fig. 2). It is estimated that 20 % of patients with HCC and 5 % of patients with CLM have a LSF >20 % [68]. Tumour thrombosis of the hepatic vein increases the likelihood of significant lung shunt [69].

Dosimetry

For glass microspheres, the prescribed dose is calculated as follows:

$$A = \frac{D \times M}{50}$$

where A is the prescribed dose in Gy, D the nominal target dose, typically 100–120 Gy for the liver; and M is the mass of the planning target volume (i.e. the whole liver or the

Fig. 2 ^{99m}Tc MAA lung shunt study in a patient with colorectal liver metastases. There is intense and heterogeneous uptake within the enlarged liver due to extensive tumour replacement (*green dotted line*). Markedly increased activity is also seen in both lungs (*purple dotted lines*). The LSF was 32 %. Therefore, this patient did not receive ^{90}Y -microspheres due to the high risk of radiation pneumonitis (colour figure online)

Fig. 3 ^{99m}Tc -MAA study in a patient with HCC demonstrated markedly increased gallbladder uptake, with 18.4 % of injected activity distributed to the gallbladder. The LSF was only 7 %. The patient had subsequently undergone ^{90}Y -microspheres SIRT with the catheter tip placed beyond the origin of the cystic artery to avoid inadvertent microsphere delivery to the gallbladder and associated radiation injury. The patient recovered uneventfully with no significant complication (colour figure online)

Table 2 ^{90}Y SIR-Spheres dose adjustment in the presence of lung shunt

% Lung shunt	Dose reduction of ^{90}Y SIR-Spheres
<10	No dose reduction
10–15	20 % reduction of prescribed activity
16–20	40 % reduction of prescribed activity
>20	^{90}Y SIR-Sphere treatment not recommended unless potential cumulative lung dose is <30 Gy

The percentage of lung shunt is calculated from scintigraphy obtained after intra-arterial infusion of ^{99m}Tc -MAA

selected lobe or segments) in kg. The cumulative lung dose should be kept below 30 Gy.

Several methods of calculating the prescribed dose for resin microspheres have been proposed, including the empirical method which is no longer recommended due to the emergence of an adverse toxicity profile [59]. The manufacturers' User's Manual and Package Insert of SIR-Spheres details two methods of dose calculation based on the body surface area (BSA) or the partition model. The partition model aims to prescribe the maximum dose tolerated by normal liver and lung parenchyma and requires clear delineation of tumour from normal liver parenchyma on ^{99m}Tc -MAA scintigraphy. As most patients being considered for ^{90}Y -microsphere therapy have multiple liver lesions, this method is often not practicable. The BSA method, which takes into account the patient's size, is the recommended method for calculating prescribed dose:

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

where A is the activity in GBq, BSA, the body surface area, m^2 , defined as $0.20247 \times \text{height (m)}^{0.725} \times \text{weight (kg)}^{0.425}$; and tumour volume and liver volume are derived from CT or MRI scans.

The final prescribed dose is adjusted according to the amount of lung shunt via two methods. First, the final prescribed dose can be adjusted so that the cumulative lung dose remains below 30 Gy, which is the upper limit recommended by REBOC [59]. Cumulative lung dose can be calculated according to the following equation:

$$D_{\text{lung}} = \frac{49,670 \times (A_{\text{total}} \times \frac{\text{LSF}}{100})}{M_{\text{lung}}}$$

where D_{lung} is the cumulative lung dose in Gy, A_{total} is the total prescribed activity in GBq, LSF is the lung shunt fraction, and M_{lung} is the mass of the lungs, assumed to be 1,000 g.

Alternatively, the final prescribed dose can be empirically adjusted according to Table 2.

During the delivery of ^{90}Y -microspheres, it is recommended that flow of the catheterised hepatic arterial branch be regularly checked by injection of contrast media. If the antegrade arterial flow has slowed down then the infusion of ^{90}Y -microspheres should be terminated, even if the prescribed dose has not been fully delivered [59].

Adverse reactions and complications

Intra-arterial administration of ^{90}Y -microspheres is generally well tolerated by patients [70]. Fatigue, nausea, vomiting, low-grade pyrexia, and abdominal discomfort are by far the commonest adverse reactions, reported in 20–50 % of patients, and they tend to be self-limiting, usually resolving within a few hours [70–73]. At our institution, we have sometimes used a tapering dose of steroids to alleviate these symptoms.

Inadvertent delivery of microspheres to non-target organs can cause complications due to radiation (Fig. 3). Excessive radiation dose to the lungs can cause radiation pneumonitis [74] which is a rare event when the proper dosimetric procedure is followed [70], although a recent study questioned the validity of the conventional lung dosimetry method in predicting radiation pneumonitis [75]. The literature on ^{90}Y -microsphere SIRT-related GI ulceration is limited but this condition has been reported to occur in 0–11 % of patients [70, 76]. Pre-treatment embolisation of collateral vessels serves to reduce the likelihood of GI ulceration due to reflux of ^{90}Y -microspheres into extrahepatic arteries. However, new collateral formation is common and Abdelmaksoud et al. [66] showed that despite re-embolisation immediately before delivery of ^{90}Y -microspheres, 7 % of patients still developed gastroduodenal ulceration. Reversible gastritis and duodenitis have also been reported in the absence of extrahepatic microsphere deposition [77]. Although most safety and toxicity studies demonstrate only mild-to-moderate GI ulceration after ^{90}Y -microsphere SIRT, this entity can be difficult to treat. In isolated cases, GI ulcerations persist up to 12 months post-SIRT [78]. Post-treatment Bremsstrahlung SPECT/CT may help to predict the likelihood of GI ulceration [79]. At our institution, we tend to commence patients on a proton pump inhibitor 1 week prior to ^{90}Y -microsphere treatment and continue this drug for 4 weeks after treatment to prevent this complication.

As a large volume of blood is circulated through the liver, radiation effects on the various components of blood is unavoidable. Pancytopenia was observed in one of the earliest studies of ^{90}Y -microspheres [58] but has not been reported since. Isolated cases of transient thrombocytopenia

following ^{90}Y -microsphere SIRT have also been reported [80, 81]. Lymphopenia is a common complication observed by Carr et al. [82, 83] in a large proportion of patients who underwent ^{90}Y -microsphere SIRT; the absence of lymphocyte count recovery was associated with poor survival [83].

One of the most serious complications after ^{90}Y -microsphere therapy is radioembolisation-induced liver disease (REILD), i.e. post-treatment liver failure that is not attributable to disease progression. Veno-occlusive disease has been shown to be the histological manifestation [84]. In the largest cohort to date, consisting of 515 patients with primary and metastatic liver malignancies, Kennedy et al. [85] reported a 4 % incidence of REILD after resin ^{90}Y -microsphere SIRT in patients with unresectable liver tumours. The same paper also reported a strong correlation between the rate of REILD and the empirical dosimetry method. Although it has been suggested that REILD does not develop below the dose of 1.5 GBq with glass ^{90}Y -microspheres [86], in a cohort consisting of 291 patients with HCC, Salem et al. [73] reported grade 3/4 bilirubin/aspartate transaminase toxicity in 19 % of patients. This toxicity is associated with previous treatment with chemotherapy and whole-liver ^{90}Y -microsphere treatment [84], and treating the two lobes of liver sequentially a few weeks apart, rather than treating the whole liver in one procedure, may help to mitigate it [87]. Paradoxically, a more recent study examining the role of a modified dosimetry regime in preventing REILD [88] found that in patients with cirrhosis, selective liver radioembolisation (instead of whole-liver treatment) was associated with increased incidence of REILD. Most cases that developed REILD in this study received radiation upwards of 0.8 GBq. The authors suggested that one explanation for finding might be a relative increase in radiation per treated volume in selective treatment. The same study also found cirrhosis, previous liver insult (including systemic chemotherapy), small liver and abnormal pre-treatment bilirubin to be associated with increased risk of REILD.

At our institution, we have shown a low rate of adverse effects in patients who were carefully selected for SIRT. Out of a small cohort of 21 patients, four developed reversible adverse effects (two cases of radiation hepatitis, and one case each of cholecystitis and peptic ulceration) [89]. The rate of adverse effects in our current cohort of more than 200 cases is being analysed for publication.

Response assessment and prediction

Although, conventionally, tumour response assessment is most commonly performed using size-based criteria (WHO [90], RECIST [91] and RECIST 1.1 [92]), malignant

Fig. 4 **a** Pre- ^{90}Y -microspheres contrast-enhanced CT shows two lesions in the right lobe of the liver. **b** Post-treatment CT 3 months after SIRT demonstrated reduced density in the posterior lesion (*red dotted line*) but only a minimal decrease in size. Follow-up CT after 6 months showed further shrinkage of the posterior lesion. The other lesion was unchanged on follow-up CT (colour figure online)

Fig. 5 **a, b** Pre-treatment CT and FDG demonstrated three metastatic deposits within the liver. **c** Post-treatment CT showed slight enlargement of the middle lesion (albeit with reduced attenuation) (*white arrowheads*) and was reported as progressive disease. **d** FDG PET confirmed reduction in metabolic activity in all three lesions, indicating that there was, in fact, a good response (colour figure online)

lesions often do not demonstrate a size change even when there is a histological response [93].

Alternative methods of assessing treatment response include FDG (^{18}F -fluorodeoxyglucose) PET, CT attenuation and diffusion-weighted MRI. A reduction of metabolic activity on FDG PET (Fig. 4) is more sensitive in

detecting responding lesions than size-based CT criteria in patients treated with ^{90}Y -microsphere SIRT [94–96]. As ^{90}Y -microsphere SIRT induces necrosis within treated tumours [51, 97], a decrease in CT attenuation and diminished enhancement of tumours have been used to assess response (Fig. 5). These changes have been shown

Table 3 List of publications which report on the response rate and/or survival of patients with hepatic metastases treated with ^{90}Y -microsphere therapy

References	Population	<i>n</i>	Response criteria	Response	Time-to-progression	Survival
Cianni et al. [137]	Breast mets	52	RECIST	PR 56 %; SD 35 %; PD 10 %		11.5 mo
Ezzidin et al. [138]	NET mets	23 (failed Lu-177 PRRT)	RECIST	30 % response		29 mo
			Biochem	54 % showed improvement		
			Symptom	80 % reported improvement		
Ulrich et al. [103]	CLM	66	RECIST 1.1	PR 10 %; SD 54 %; PD 35 %		
Haug et al. [139]	Breast mets	58	CT/MRI	PR 25.6 %; SD 62.8 %; PD 11.6 %		10.8 mo Responders 14.9 mo; non-responders 9.9 mo
Bester et al. [116]	Mets	390 (RE 229; standard care 51)				RE 12 mo; standard care 6.3 mo
Paprottka et al. [140]	NET mets	42	RECIST	PR 22.5 %; SD 75 %; PD 2.5 %		
Memon et al. [141]	NET mets		WHO	CR 1.2 %; PR 62.7 %		1, 2, 3 year survival rate = 72.5, 62.5, 45 %
			EASL	CR 10.5 %; PR 43.4 %		
Cao et al. [142]	NET mets	58		CR 11.8 %; PR 27.5 %; SD 27.5 %; PD 33.2 %		36 mo
Cosimelli et al. [143]	CLM	50	RECIST	CR 2 %; PR 22 %; SD 24 %; PD 44 %		12.6 mo
Hendlish et al. [144]	CLM	44 (RE + 5FU 21; 5FU-alone 23)			RE + 5FU 5.5 mo; 5FU-alone 2.1 mo	RE + 5FU 10 mo; 5FU-alone 7.3 mo
Cianni et al. [145]	CLM	41	RECIST	CR 4.9 %; PR 41.5 %; SD 34.1 %; PD 19.5 %	9.2 mo	11.6 mo
Mulcahy et al. [128]	CLM	72		40.3 % response	15.4 mo (hepatic progression)	34.6 mo Tumour burden <25 % 18.7 mo; >25 % 5.2 mo Extrahepatic disease 7.9 mo; liver only disease 21 mo
van Hazel et al. [146]	CLM	25 (RE + irinotecan)		PR 48 %; SD 39 %	6 mo	12.2 mo
Jakobs et al. [147]	CLM	41	RECIST	PR 7 %; SD 25 %; PD 4 %		10.5 m Responders 29.3 mo; non-responders 4.3 mo
Jakobs et al. [148]	Breast mets	30	RECIST	PR 61 %; SD 35 %; PD 4 %		11.7 m Responders 23.6 mo; non-responders 5.7 mo
Kennedy et al. [149]	NET mets	148		SD 22.7 %; PR 60.5 %; CR 2.7 %; PD 4.9 %		70 mo
King et al. [150]	NET mets	34 (RE + 5FU infusion)	Symptom	55 % reported improvement		29.4 mo
			Size	CR 18 %; PR 11 %		
Sato et al. [151]	Mets	137	WHO	CR 2.1 %; PR 40.7 %		9.9 mo

Table 3 continued

References	Population	<i>n</i>	Response criteria	Response	Time-to-progression	Survival
Stuart et al. [152]	Mets	30	RECIST	PR/SD 47 %	Mets from other primaries 7.3 mo; CLM 2.9 mo	Mets from other primaries 19.8 mo; CLM 8.2 mo
Bangash et al. [126]	Breast mets	27	CT	PR 39.1 %; SD 52.1 %; PD 2 %		ECOG PS0 6.8 mo; other ECOG PS 2.6 mo Tumour burden <25 % 9.4 mo; >25 % 2.1 mo
Coldwell et al. [153]	Breast mets	44	PET CT	63 % response PR 47 %		
Sharma et al. [113]	CLM	20 (RE + FOLFOX)	PET	95 % response PR 90 %; SD 2 %	9.3 mo	
Kennedy et al. [71]	CLM	208	CT	PR 35 %		Responders 10.5 mo; non-responders 4.5 mo
Mancini et al. [154]	CLM	35	PET RECIST	91 % response PR 12.5 %; SD 75 %; PD 12.5 %		
Stubbs et al. [155]	CLM	100		PD 6.25 %		
Lewandowski et al. [127]	CLM	27	CT	35–36 % response		Tumour burden <25 = 11.1 mo; >25 % = 5.3 mo
			PET	73–88 % response		

CLM colorectal liver metastases, *mets* metastases, *NET* neuroendocrine tumour, *RE* radioembolisation, *Lu-177 PRRT* ¹⁷⁷Lu peptide receptor therapy, *FOLFOX* 5-fluorouracil and oxaliplatin regime, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *mo* months

to correlate with FDG PET metabolic response better than size reduction [98–100]. Normalisation of diffusion on diffusion-weighted MRI has also been suggested as another method of detecting response when there is no change in size [100].

As the delivery of ⁹⁰Y-microspheres to the tumour depends on the vascularity of the tumour, it stands to reason that the degree of tumour perfusion may be correlated with treatment response. However, the utility of pre-treatment ^{99m}Tc-MAA study in predicting response and outcome is controversial. While some authors have shown that quantitative assessment of ^{99m}Tc-MAA tumoral uptake on SPECT/CT performed as part of dosimetry calculation can predict response, time-to-progression and overall survival [101, 102], others have found no correlation between tumoral MAA uptake and response rate [103]. More recently, textural features on pre-treatment triple-phase CT have been shown to predict response and survival in patients with hepatic malignancy [104]. These methods await confirmation and may allow for better patient selection in the future.

Clinical use

The last decade has seen an explosion of studies investigating the clinical efficacy of ⁹⁰Y-microspheres, with more than 70 papers published on this topic (Tables 3, 4, 5). Despite this wealth of literature, it is difficult to objectively assess the effectiveness of ⁹⁰Y-microspheres as a loco-regional treatment for hepatic malignancy for the following reasons. First, most of the published findings are derived from retrospective data, describing single-centre experiences. Patient cohorts in these studies tended to be heterogeneous, with vastly different performance status and liver function. Most would have also undergone multiple lines of treatment prior to being considered for ⁹⁰Y-microsphere SIRT as salvage therapy. This limits the inference that can be drawn when comparing the response rate and survival benefit of ⁹⁰Y-microspheres to other treatment options. Second, the methods for assessing response, reported in the literature, also vary widely, with some studies using size-based criteria such as WHO and RECIST and others using criteria that take into account CT

Table 4 List of publications which report on the response rate and/or survival of patients with primary liver malignancies treated with ^{90}Y -microsphere therapy

References	Population	<i>n</i>	Response criteria	Response	Time-to-progression	Survival
Mazzaferro et al. [156]	HCC	52	WHO	CR 8 %; PR 35 %; SD 38 %; PD 19 %	11 mo	15 mo
			EASL	CR 9 %; PR 31 %; SD 35 %; PD 25 %		
Mouli et al. [111]	ICC	46	WHO	PR 25 %; SD 73 %; PD 2 %		
			EASL	PR/CR 73 %; SD 27 %		
Hoffman et al. [157]	ICC	34	RECIST	PR 35 %; SD 50 %; PD 15 %	9.8 mo	22 mo post-treatment; 43.7 mo post-diagnosis OS in patients categorised as PR, SD, PD = 35.5, 17.7 and 5.7 mo
Iñarrairaegui et al. [112]	HCC	21				27 mo
Haug et al. [158]	ICC	26	RECIST	PR 22 %; SD 65 %; PD 13 %		
Lambert et al. [159]	HCC	29	mRECIST	CR 15 %; PR 35 %; SD 30 %; PD 20 %		12.3 mo
Sangro et al. [125]	HCC	325				12.8 mo BCLC A 24.4 mo; BCLC B 16.9 mo; BCLC C 10.0 mo
Salem et al. [160]	HCC	245 (123 RE; 122 chemo)		Response rate in RE 49 %; in chemo 36 %	RE 13.3 mo; chemo 8.4 mo	RE 20.5 mo; chemo 17.4 mo
Hilgard et al. [161]	HCC	108	EASL	PR 37 %; SD 53 %; PD 6 %	10 mo	16.4 mo
Holt et al. [162]	HCC	20	RECIST	PR 15 %; SD 75 %; PD 10 %		
Carr et al. [118]	HCC	932 (99 RE; 592 TACE; 142 no Rx)				RE 11.5 mo; TACE 8.5 mo (*no significant difference when adjusted for bilirubin and PVT)
Iñarrairaegui et al. [124]	HCC	72				13 mo
Salem et al. [73]	HCC	291	WHO	42 % response		7.9 mo Child-Pugh A 17.2 mo; Child-pugh B 7.7 mo; Child-Pugh B with PVT 5.6 mo
			EASL	57 % response (CR 23 %; PR 34 %)		
Saxena et al. [163]	ICC	25	RECIST	PR 24 %; SD 11 %; PD 20 %		9.3 mo
Tsai et al. [164]	HCC	22 (patients with PVT)	RECIST	PR 8 %; SD 50 %; PD 42 %		7 mo
D'Avola et al. [115]	HCC	78 (35 RE; 43 no Rx)				RE 16 mo; No Rx 8 mo
Kooby et al. [117]	HCC	71 (27 RE; 44 TACE)		RE PD 33 %; TACE PD 36 %		RE 6 mo; TACE 6 mo
Reardon et al. [165]	Primary liver	21				3.9 mo
Goin et al. [123]	HCC	121				Low risk 15.3 mo; high risk 3.5 mo
Kulik et al. [135]	HCC	108	WHO	42.2 % response		

Table 4 continued

References	Population	<i>n</i>	Response criteria	Response	Time-to-progression	Survival
Ibrahim et al. [122]	ICC	24	EASL WHO	70 % response PR 27 %; SD 68 %; PD 5 %		14.9 mo ECOG PS0 31.8 mo; ECOG PS1 6.1 mo; ECOG PS2 1 mo; No PVT 31.8 mo; PVT 5 mo
Carr et al. [82]	HCC	65		PR 25 %		Okuda stage I 21.3 mo; Okuda stage II 9.9 mo

ICC intrahepatic cholangiocarcinoma, HCC hepatocellular carcinoma, RE radioembolisation, TACE transarterial chemoembolisation, FOLFOX 5-fluorouracil and oxaliplatin regime, CR complete response, PR partial response, SD stable disease, PD progressive disease, mo months, PVT portal vein thrombosis

Table 5 List of publications which report on the response rate and/or survival mixed groups of liver malignancies treated with ^{90}Y -microsphere therapy

References	Population	<i>n</i>	Response criteria	Response	Time-to-progression	Survival
Gil-Alzugaray et al. [88]	Mixed	260		66.7–67.2 % disease control at 3 months		
Kucuk et al. [166]	Mixed	78	FDG or Ga-68	55 % responders; 45 % non-responders		Responders 25.6 months; non-responders 20.5 months
Kennedy et al. [85]	Mixed	515	RECIST	CR 4.5 %; PR 9.5 %; SD 76.8 %; PD 9 %		
Jiao et al. [167]	Mixed	21	CT	13 % response		
		21	PET	86 % response		
Popperl et al. [168]	Mixed	23	PET	76.9 % response; 15.4 % stable; 7.7 % progression		
Lim et al. [169]	Mixed	46		PR 26.1 %	8.6 mo	

CR complete response, PR partial response, SD stable disease, PD progressive disease, mo months

attenuation (modified RECIST [105] and EASL [106]) or criteria based on metabolic response on PET. As reported by Salem's group [107–109] and Shim et al. [110], the response rates derived from these methods differ significantly, again limiting the way the existing literature can be interpreted.

Nevertheless, ^{90}Y -microsphere treatment has been shown to have an emerging role in the management of a group of patients who have exhausted other treatment options.

Response rate

Regardless of the response assessment method employed, ^{90}Y -microspheres appear to have a good response rate, in

the region of 30 % in HCC and 40 % in CLM (but as high as 90 % when assessed with metabolic activity on FDG PET [71]; see Tables 3, 4, 5).

In a small proportion of patients, ^{90}Y -microsphere SIRT has led to sufficient downstaging of tumour to allow resection [111–113] or RFA [114].

Long-term outcome

Comparative studies suggest that ^{90}Y -microspheres can significantly prolong survival. D'Avola et al. [115] showed that the median survival in HCC patients who have undergone ^{90}Y -SIRT is double that of those receiving conservative management (16 vs 8 months); similarly, in metastatic liver disease from other primary cancers,

median survival with ^{90}Y -microspheres was 12 months compared to 6.3 months on standard care [116]. When compared to other intra-arterial treatments for HCC, ^{90}Y -microsphere SIRT demonstrates equivalent efficacy to TACE [117, 118] but is associated with a slightly better quality of life [119].

More uncommonly, radiation lobectomy may develop after ^{90}Y -microsphere SIRT treatment. In this condition, first described by Jakobs et al. [120] in 2008, patients show a reduction of ipsilateral hepatic lobar volume, contralateral lobar hypertrophy, liver fibrosis and in some cases portal hypertension. It has subsequently been shown to be associated with higher response rate and survival advantage in patients with primary liver cancers [121], with a 46 % 5-year survival rate being reported in HCC patients.

A significant difference in outcome has been reported between patients having different clinical statuses. Patients who have a good performance status, low tumour burden and relatively preserved liver functions benefited the most from ^{90}Y -microspheres [73, 82, 122–128]. Furthermore, in a meta-analysis that included many of the studies included in Tables 3, 4, 5, Vente et al. [129] found that in patients with CLM, use of ^{90}Y -microspheres as first-line therapy provided significantly better disease control (i.e. “partial response” and “stable disease”) than in the salvage setting. Thus, there is an argument for treating with ^{90}Y -microspheres much earlier in the disease process rather than using ^{90}Y -microspheres as a salvage therapy, as is done in current practice. To this end, several prospective trials [130–132] are under way which aim to establish the efficacy of ^{90}Y -microspheres as a first-line therapy.

Special circumstances

Some comorbidities can increase the treatment risk of patients undergoing ^{90}Y -microsphere SIRT.

Portal vein thrombosis is a common complication in patients with primary liver malignancy. While the liver has a dual blood supply via the portal vein and hepatic artery, thrombosis of the portal vein would leave the area of liver it supplies relying more heavily on arterial circulation. Arterial radioembolisation with ^{90}Y -microspheres is therefore conventionally thought to be contraindicated [59, 60]. However, several authors have demonstrated the feasibility and relative safety of ^{90}Y -microsphere treatment in the presence of PVT [133–135].

Another common complication in patients with hepatic malignancy is biliary obstruction. Few reports exist on the safety and efficacy of ^{90}Y -microsphere SIRT in this setting but in a cohort of 12 patients with malignant biliary obstruction at a lobar or segmental level (but normal serum

bilirubin) Gaba et al. [136] found ^{90}Y -microsphere SIRT to be safe with no biliary complication after treatment.

Conclusion

^{90}Y -microsphere SIRT is a promising technique in the treatment of hepatic malignancy. Both the devices and the technique have been refined over the last four decades to the point where ^{90}Y -microsphere SIRT is not only feasible and safe, but also has a better toxicity profile, response rate and outcome than systemic therapy. While a wealth of literature has already been published on ^{90}Y -microsphere SIRT, there is a need to establish its efficacy against other therapeutic options, especially in early stage disease. The prospective, randomised-controlled trials that are currently being conducted will hopefully be able to provide guidance in this regard.

Conflict of interest Both authors (Henry H. Tam and Adil Al-Nahhas) confirm that there is no conflict of interest in publishing this manuscript.

Human and Animal Studies This article does not contain any studies with human or animal subjects performed by any of the authors listed above.

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