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REVIEW ARTICLE

Yttrium-90 hepatic radioembolization: clinical review and current techniques in interventional radiology and personalized dosimetry

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ABSTRACT

In recent years, yttrium-90 (⁹⁰Y) microsphere radioembolization has been establishing itself as a safe and efficacious treatment for both primary and metastatic liver cancers. This extends to both first-line therapies as well as in the salvage setting. In addition, radioembolization appears efficacious for patients with portal vein thrombosis, which is currently a contraindication for surgery, transplantation and transarterial chemoembolization. This article reviews the efficacy and expanding use of ⁹⁰Y microsphere radioembolization with an added emphasis on recent advances in personalized dosimetry and interventional radiology techniques. Directions for future research into combination therapies with radioembolization and expansion into sites other than the liver are also explored.

INTRODUCTION

Yttrium-90 (⁹⁰Y) microsphere radioembolization is a promising treatment modality that has emerged for the management of patients with liver cancer. Liver tumours, both primary and metastatic, form a large proportion of solid tumours with a variety of therapeutic options. Radioembolization with the radioisotope ⁹⁰Y is a procedure in which resin or glass microspheres containing ⁹⁰Y are administered directly into the hepatic arteries which supply the hepatic tumour.¹

Historical background

One of the first pioneers in performing radioembolization with ⁹⁰Y microspheres for colorectal cancer (CRC) hepatic metastases was Ariel,² a surgeon from New York, in animal experiments and subsequently in two human volunteers. Nolan and Grady³ then described the use of ⁹⁰Y oxide to treat hepatocellular carcinoma (HCC) in humans. Subsequent clinical trials involved several successful treatments of metastatic CRC to the liver.^{4,5} This therapeutic modality has since been incorporated into early nuclear medicine literature following its initial clinical applications.^{6–8} ⁹⁰Y

microsphere radioembolization is presently used for local control of both primary as well as metastatic liver tumours which are unresectable.

Radioembolization concepts

Unlike the majority of organs, there exists a dual hepatic blood supply for the liver: the portal vein and hepatic artery. Primary HCC nodules demonstrate reduction in portal vein and normal hepatic artery supply, whereas abnormal artery supply (intranodular arterial supply through newly formed abnormal arteries) gradually increases.⁹ Metastatic liver tumours >3 mm derive 80–100% of their blood supply from arterial rather than portal hepatic circulation.¹⁰ These concepts are the basis for intra-arterial administration of ⁹⁰Y microspheres. Two parts are present in this radioembolization procedure: embolization and brachytherapy. The angiographic end points of embolization and sometimes stasis as well as the requirement to adjust the delivery according to angiographic findings under fluoroscopy define this therapy as an embolization procedure. The administration of radiation with dosimetry based on tumour and target volumes

define this therapy as a brachytherapy procedure.¹¹ Radioembolization is thus a combination of both radiation with embolization although the tissue effects are primarily mediated by radiation injury. Although the terms “selective internal radiation therapy” and “radioembolization” have been used synonymously, the Society of Interventional Radiology (Fairfax, VA) prefers the term “radioembolization”.¹²

Yttrium-90 properties and microspheres

⁹⁰Y is a beta emitter with a 64.2-h physical half-life, in which up to 94% of the ⁹⁰Y microspheres radiation dose can be delivered during the first 11 days following treatment, after which it decays into stable zirconium. ⁹⁰Y microspheres entrapped in the microvasculature of the liver emit β -radiation with a mean energy of 0.94 MeV, maximum energy of 2.26 MeV, mean tissue penetration of 2.5 mm and maximum penetration of 11 mm. By Medical Internal Radiation Dose (MIRD) principle, one gigabecquerel (GBq) of ⁹⁰Y uniformly distributed throughout 1 kg of tissue provides an absorbed dose of approximately 50 Gy.¹¹

There are currently two types of ⁹⁰Y microspheres available commercially. TheraSphere™ (glass microspheres; BTG, London, UK) was approved by the US Food and Drug Administration in 1999 for the therapy of unresectable HCC in patients.¹ SIR-Spheres™ (resin microspheres; Sirtex Medical Limited, NSW, Australia) were approved by the Food and Drug Administration in 2002 for the therapy of colorectal metastases in conjunction with intrahepatic floxuridine.¹

The average size of resin microspheres is up to 30% larger than glass microspheres, whereas specific activity is higher for the glass microspheres. This translates to lesser particles infused per GBq of ⁹⁰Y activity of TheraSphere than SIR-Spheres. Glass microspheres contain 2500 Bq per microsphere and approximately 1–2 million microspheres are infused for a typical patient. Resin microspheres contain approximately 50 Bq per microsphere, and a typical treatment contains 40–60 million microspheres. This may have an embolic effect resulting in slowed antegrade hepatic arterial flow. Table 1 shows a comparison of the properties of the glass and resin microspheres.

Resin microspheres are received as 3-GBq vials that can be dispensed according to the prescribed activity for each patient. Glass microspheres are generally planned for arrival a few days

before the treatment, and based on the decay rate, the entire vial is delivered to the tumour.

YTTRIUM-90 DOSE ACTIVITY PRESCRIPTION

For the resin microspheres, there are generally two accepted methods for calculating the prescribed activity: body surface area (BSA) method and the partition model. The BSA method is the most commonly used but is semi-empirical. The second method is the “partition model”, which enables personalized radiation planning based on absorbed doses (Gy). A third method which is the earliest and empirical method is no longer recommended.

Limitations of semi-empirical methods

Experts in radionuclide internal dosimetry have long criticised the common practice of empiric activity prescription for therapeutic purposes. Even the common practice of modifying prescribed activities based on body weight or BSA is semi-empirical and stems historically from the experiences of systemic chemotherapy. However, therapeutic radiopharmaceuticals exert their biological response primarily by the deterministic effects of radiation and are therefore not a “drug” and should not be regarded as such. Implicit within empirical or semi-empirical methods are biophysical assumptions which the user has knowingly or unknowingly accepted to be applicable to their patient. Any studies demonstrating apparent safety in spite of empirical or semi-empirical methods only lead to the logical conclusion that these methods have a conservative tendency to underdose, sacrificing efficacy for safety.

In the context of resin microsphere activity prescription, the BSA method¹³ is the most commonly used method owing to its simplicity, attributable to its many assumptions.¹⁴ The BSA method was devised more than a decade ago¹⁵ when there was little emphasis on the importance of microsphere radiobiology and before the advent of hybrid scintigraphy. The BSA method was therefore clinically appropriate within the context of its initial design. However, its semi-empirical nature inherently limits its ability to scientifically evolve with new and better technology. In the face of widespread availability of hybrid tomographic scintigraphy today, the ethics of subjecting patients to a decade-old treatment paradigm is questionable.

Recently, Bernardini *et al* compared dosimetric parameters between BSA methodology *vs* partition model on 28 patients of various tumour types. From their heterogeneous patient cohort,

Table 1. Properties of glass and resin yttrium-90 microspheres

Characteristics	Glass microspheres	Resin microspheres
Trade name	TheraSphere™	SIR-Spheres™
Diameter of microsphere (μm)	20–30	20–60
Specific gravity (g dl^{-1})	3.6	1.6
Specific activity (Bq per sphere)	2500	50
Number of microspheres per 3-GBq vial	1.2×10^6	$40\text{--}80 \times 10^6$
Material	Glass with yttrium in matrix	Resin with bound yttrium

TheraSphere™ obtained from BTG, London, UK and SIR-Spheres™ from Sirtex Medical Limited, NSW, Australia.

they found no correlation between the activities prescribed by BSA methodology and tumour-to-normal liver (T/N) ratios or percentage tumour involvement. On the other hand, activities prescribed by the partition model were shown to correlate with T/N ratios and percentage tumour involvement.¹⁶ Another recent study by Lam et al¹⁷ involving 45 patients with colorectal liver metastasis did not show correlation between activities prescribed by the BSA method and absorbed doses averaged across the whole liver. All of these observations are not surprising given the semi-empirical nature of the BSA method because its formularism sacrifices personalization in favour of simplicity.¹⁴

Personalized predictive dosimetry

The modern era of personalized medicine demands the measurement of patient-specific biophysical parameters to individualize treatment so as to maximize the desired effect while minimizing toxicity. This is especially important in oncology because patients may be frail or have limited prognosis. Hybrid tomographic scintigraphy with integrated CT represents a technological leap from planar scintigraphy and has the potential to modernize radionuclide therapy from an art into a science to achieve predictable and reproducible results. Single-photon emission tomography with integrated CT (SPECT/CT) and positron emission tomography with integrated CT (PET/CT) overcomes many of the technological limitations which have traditionally plagued planar and single-photon emission tomography (SPECT)-only scintigraphy to allow more accurate measurements of dosimetric parameters.

⁹⁰Y microsphere radioembolization is well placed to lead the science in personalized radionuclide therapy because the permanently implanted microspheres negate tedious time-activity measurements. Provided the angiographic conditions, especially catheter position, between exploratory angiography and radioembolization are identical, the technetium-99m macroaggregated albumin (^{99m}Tc MAA) SPECT/CT may be regarded as a “radiation simulation” study^{18,19}—a concept demonstrated for both resin¹⁹ and glass²⁰ microspheres. Today, the simplest method of personalized predictive dosimetry for radioembolization is by MIRD macrodosimetry.

MIRD macrodosimetry has been applied to resin microspheres as early as the 1990s, also known as the “partition model”.²¹ The MIRD equations are widely available from the literature.^{18,21,22} The partition model mathematically describes the bio-distribution of microspheres in a typical patient into three dosimetric compartments—tumour, non-tumorous liver and the lung. The use of count ratios from the ^{99m}Tc MAA mapping study and derivative parameters such as the hepatopulmonary shunt fraction and the T/N ratio allow the desired absorbed doses and activities to be estimated in each of the three compartments. This allows predictive dosimetry to be performed for the tumour, non-tumorous liver and the lung prior to radioembolization. With improvements in angiographic methods over the years, the original partition model has now evolved to take into account selective or superselective radioembolization depending on the case-specific clinical, angiographic and dosimetric circumstances.¹⁹ This has developed into a “multipartition”

model where vascular territories are mapped by catheter-directed CT [also known as intra-arterial CT (IACT) or CT hepatic angiography] and the ^{99m}Tc MAA biodistribution is tomographically mapped by SPECT/CT.¹⁹ In addition, the multipartition model improves radiation planning for large tumours that are supplied by multiple arteries by measuring the different T/N ratios for each arterial territory, allowing treatment personalization and absorbed dose optimization.¹⁹ For glass microspheres, its manufacturer advocates a MIRD-based dosimetry where the intended absorbed dose is averaged across the entire target arterial territory, and consequently, the absorbed doses to tumour and non-tumorous liver are not separately determined.¹⁸ However, the same general principles of MIRD macrodosimetry for tumour, non-tumorous liver and the lung also apply to glass microspheres.²⁰ Our recommendations for safe, effective and personalized predictive dosimetry by MIRD

Table 2. Recommendations for radioembolization personalized predictive dosimetry

Understand	1. Clinical history and baseline clinical status
	2. Angiographic findings and technical challenges
	3. Catheter positions for ^{99m} Tc MAA injections
Measure	1. Hepatopulmonary shunt fraction by ^{99m} Tc MAA SPECT/CT ²³
	2. Patient-specific lung mass by CT densitovolumetry ²³
	3. Tumour and normal tissue volumes by catheter-directed CT angiography ¹⁹
	4. T/N ratios for each target arterial territory by ^{99m} Tc MAA SPECT/CT ¹⁹
Decide	1. The dose limiting organ
	2. Whether the MIRD assumption of uniform activity distribution is reasonable
	3. Extent of dosimetric uncertainty and size of safety margin
Formulate	1. Apply MIRD macrodosimetry based on dose limiting organ
	2. Derive the safest achievable tumour absorbed dose
	3. Adjust radiation plan based on extent of dosimetric uncertainty
	4. Prescribe ⁹⁰ Y activity in accordance to radiation plan
Communicate	1. Discuss radiation plan with patient and multidisciplinary team
	2. Agree on treatment intent based on safest achievable tumour absorbed dose
	3. Ensure catheter positions for radioembolization are identical to ^{99m} Tc MAA injections

^{99m}Tc, technetium-99m; MAA, macroaggregated albumin; MIRD, medical internal radiation dose; SPECT, single-photon emission tomography; T/N, tumour-to-normal liver; ⁹⁰Y, yttrium-90.

macrodosimetry for radioembolization are summarized in Table 2.

Dosimetric uncertainty

Critics of predictive dosimetry based on ^{99m}Tc MAA SPECT/CT often cite studies which apparently do not show correlation between ^{99m}Tc MAA biodistribution and clinical outcomes. However, such studies were often confounded by a lack of radiobiological perspective and mislead less experienced readers.^{24–26} Others challenge ^{99m}Tc MAA predictive dosimetry based on the physical differences between MAA vs resin or glass microspheres and differences in injected microparticle load. Although these physical differences are undeniably true, the concept often overlooked is that ^{99m}Tc MAA SPECT/CT is meant to depict what the microsphere biodistribution is likely to be and was never intended to exactly replicate the actual microsphere biodistribution. When formulating the radiation plan, the nuclear medicine physician also considers information from angiography and relevant diagnostic imaging and clinical data to account for real-life dosimetric uncertainties. The extent of uncertainty is reflected in the radiation plan by how large or small the absorbed dose safety margin should be. This is then balanced with the safest achievable tumour absorbed dose and achievable treatment intent. It follows that some radioembolization candidates may be disqualified on the basis of unfavourable dosimetric parameters which risk unsafe or futile therapy. Preliminary data now exist to describe the general statistical limits of dosimetric uncertainty across a population of patients undergoing radioembolization using resin microspheres.²⁶

The key requirement for reliable predictive dosimetry is to obtain accurate input dosimetric parameters, of which tissue masses and count ratios are the most important. The increasingly common practice of lobar or segmental radioembolization demands more accuracy in tissue mass measurements within targeted arterial territories. This may be achieved by catheter-directed CT angiography, either by transferring the patient between the angiography suite and CT scanner or by hybrid angio-CT systems where available.¹⁹ Today, SPECT/CT is widely available for measurement of volumetric count ratios. The clinical use of ^{99m}Tc MAA SPECT/CT of the abdomen for calculating artery-specific T/N ratios, guided by catheter-directed CT, has been described.¹⁹ By including the lungs into the ^{99m}Tc MAA SPECT/CT acquisition, attenuation-corrected hepatopulmonary shunt fractions and patient-specific lung mass estimates by CT densitovolumetry can also be obtained.²³

Although MIRD macrodosimetry is conceptually simple to apply, its main weakness is its assumption of uniform activity distribution. Microspheres are always heterogeneously distributed, hence MIRD macrodosimetry should be used cautiously in cases where the activity biodistribution is highly heterogeneous. Such situations may be encountered in very large tumours or tumours that have been partially treated. Activity heterogeneity may be visualized directly by reviewing the ^{99m}Tc MAA SPECT/CT images or graphically expressed as dose–volume histograms. This is analogous to the external beam radiation therapy concept

of tomographic radiation planning using isodose maps and dose–volume histograms. Predictive dosimetry based on ^{99m}Tc MAA SPECT/CT dose–volume histograms is still the subject of research but promises to optimize radiation planning by overcoming the MIRD assumption of uniform activity distribution.²⁷

Absorbed dose thresholds

Although the principles of MIRD macrodosimetry may be applied to resin and glass microspheres, the biophysical characteristics of each device is different and therefore exert different tissue radiobiology. In other words, dose–response data for resin vs glass microspheres are not directly interchangeable unless additional calculations, such as the biologically effective dose (BED), have been performed.¹⁸ It follows that institutions where resin and glass microspheres are both available should separate these two devices when analysing their data.

Based on an expert panel, HCC mean absorbed dose thresholds for resin microspheres are >120 Gy for tumour response, <50 Gy to non-tumorous whole liver and <20 Gy to the lung.²⁸ Extrapolating from external beam radiation therapy data, resin microsphere normal tissue complication probability for non-tumorous whole liver was estimated by Cremonesi *et al*¹⁸ to be $\text{TD}_{5/5}$ 35 Gy and $\text{TD}_{50/5}$ 44 Gy, and for the lung to be $\text{TD}_{5/5}$ 23 Gy and $\text{TD}_{50/5}$ 30 Gy, where $\text{TD}_{5/5}$ and $\text{TD}_{50/5}$ represent the tolerance doses (TDs) that would result in 5% and 50% risk of severe complications within 5 years, respectively. Dose–volume histogram analysis of ^{90}Y PET/CT by Kao *et al*²⁹ identified the threshold for HCC complete response to be D_{70} >100 Gy using resin microspheres, where D_{70} is the minimum absorbed dose delivered to 70% tumour volume.

For colorectal liver metastasis treated with resin microspheres, Lam *et al*³⁰ evaluated a heterogeneous cohort of 25 patients and found responders to have a mean tumour absorbed dose of 82.7 ± 23.9 Gy, whereas non-responders had 31.0 ± 10.9 Gy. Flamen *et al*³¹ assessed the change in total lesion glycolysis of 39 lesions of colorectal liver metastasis and found responding lesions to have a median tumour absorbed dose of 66 Gy (95% CI 32–159 Gy), whereas lesions with poor response had 29 Gy (95% CI 1–98 Gy). An expert panel recommended the mean absorbed dose threshold for non-tumorous whole liver to be 50–70 Gy for colorectal liver metastasis, depending on liver reserve and prior systemic therapy.²⁸

For glass microspheres using Day 3 post-calibration specific activity of 1250 Bq/sphere delivered in sequential lobar radioembolization, Garin *et al*²⁰ found HCC thresholds to be >205 Gy for tumour response, <120 Gy to healthy liver and <30 Gy to the lung. Chiesa *et al*³² used glass microspheres 3.75 days post-calibration for unilobar radioembolization of HCC and found TCP_{50} to be approximately 500 Gy depending on the analysis method, where TCP_{50} is the tumour control probability representing 50% probability of lesion response. TCP_{50} was highly dependent on the lesion size: 250 Gy for lesions <10 cm³ and >1000 Gy for larger lesions. Normal tissue complication probability for non-tumorous whole liver was found to be $\text{TD}_{15/0.5}$ 75 Gy, where $\text{TD}_{15/0.5}$ is the TD that would result in 15% risk of severe complications within 0.5 years (*i.e.*

6 months) for Child-Pugh A patients without complete portal vein obstruction.³² There is currently no data on glass microspheres tumour absorbed dose thresholds for colorectal liver metastasis. It should be cautioned that “extended shelf-life” glass microspheres are likely to have different radiobiological characteristics due to lower specific activity and therefore the above-mentioned thresholds may not be wholly applicable.

For repeated radioembolization to the same arterial territory, the cumulative absorbed dose to healthy tissue and time interval between radioembolizations are important safety considerations. However, radiobiological guidance on this issue is scarce in the literature for both resin and glass microspheres and further research is warranted. All of the above data are summarized in [Table 3](#).

RADIOEMBOLIZATION: CLINICAL INDICATIONS, EFFICACY AND CONSIDERATIONS

The role for radioembolization in the management of primary and secondary liver malignancies

The liver is a common organ involved in malignancies which may be primary to the liver or metastatic from elsewhere. The most common form of primary liver tumour is HCC. HCC is a complex disease and management is influenced by various clinical parameters such as tumour burden and liver function. Conceptually a systematic, protocolized approach would ensure optimal therapy and improve patient outcomes.³³

HCC continues to be the sixth most common cancer, contributing the third highest cancer mortality worldwide.³⁴ Surgical resection, transplantation or radiofrequency ablation (RFA) in selected cases, is potentially curative in early HCC. Unfortunately, the large majority of HCCs present in locally advanced or metastatic stages or are poor surgical candidates for resection.³⁵ The median survival of untreated inoperable HCC is approximately 3–8 months. Hence, there is a great impetus for the efficacious employment of locoregional therapy.

The liver is also the dominant metastatic site for patients with CRC. Pre-existing data from the 1960s and 1970s have shown

that the median survival of patients who receive no treatment ranges between 3 to 12 months, with an overall median survival of 7 months.³⁶ Although surgery offers the most favourable outcomes, liver metastases resectability rates at the time of diagnosis are generally low and hence only a small proportion of patients may benefit from surgical approach. When surgery is not feasible, cytoreduction improves functionality and may prolong survival. As compared with cryoablation, RFA or microwave ablation techniques, radioembolization is a promising cytoreductive modality that encompasses the entire liver or a lobar volume. Even in a salvage setting, radioembolization appears to be a reasonable technique with a relative wide safety margin. The use of radioembolization against liver metastases from different primary cancers is also expanding. Such examples would include metastases from breast, uveal melanoma, neuroendocrine tumours, sarcoma, oesophageal, endometrial, lung, ovarian and squamous cell carcinoma of the anus.^{37,38}

In spite of its relatively recent development, radioembolization has yielded great promise and potential as a safe and efficacious treatment for locally advanced liver cancer.^{39,40} In both salvage and first-line therapy, radioembolization has demonstrated high response rates. A number of Phase III trials have pitted radioembolization against various treatment modalities such as systemic chemotherapy and transarterial chemoembolization. Currently, the Phase III trials are still ongoing and only with their completion would the true efficacy of radioembolization be known.⁴¹

Evidence for radioembolization in primary and secondary liver malignancies

Several studies have shown the efficacy of radioembolization in liver malignancies although indications and patient selection are varied. Summarized in [Table 4](#) are studies looking at the median survival of various liver tumours post radioembolization.⁴² From the summary, it is reasonable to conclude that radioembolization is efficacious in both primary and secondary liver tumours. Specifically, there is very high interest in the clinical use of radioembolization in locally advanced HCC because of the paucity of efficacious therapy in this group of patients.

Table 3. Absorbed dose thresholds (Gy) for yttrium-90 radioembolization

Tumour/normal organ	SIR-Spheres™ (Gy)	TheraSphere™ (Gy)
HCC ^{19,20,28,29,32}	Mean 91–120 (PR) $D_{70} > 100$ (CR)	Mean 205 (PR) TCP ₅₀ 500 (PR)
Colorectal ^{30,31}	Mean 66–83 (PR)	No data
Non-tumorous whole liver ^{18,20,28,32}	Mean 50–70	Mean 120
	TD _{5/5} 35	TD _{15/0.5} 75
	TD _{50/5} 44	
Lung ^{18,20,28}	Mean 20	Mean 30
	TD _{5/5} 23	
	TD _{50/5} 30	

CR, complete lesion response; D_{70} , minimum absorbed dose delivered to 70% tumour volume; HCC, hepatocellular carcinoma; PR, at least partial lesion response; TCP₅₀, tumour control probability representing 50% probability of lesion response; TD_{5/5} and TD_{50/5}, tolerance doses that would result in 5% and 50% risk of severe complications within 5 years.

TheraSphere™ obtained from BTG, London, UK and SIR-Spheres™ from Sirtex Medical Limited, NSW, Australia.

Table 4. Summary of outcomes of yttrium-90 microsphere radioembolization in liver malignancies

Study	Study design	Subjects, <i>n</i>	Median survival (months)
Primary liver tumours			
Hepatocellular CA			
Kulik <i>et al</i> 2008 ⁴³	Prospective	108	15.6
Sangro <i>et al</i> 2012 ⁴⁴	Prospective	325	13.1
Cholangiocarcinoma			
Saxena <i>et al</i> 2010 ⁴⁵	Prospective	25	9.3
Ibrahim <i>et al</i> 2008 ⁴⁶	Prospective	24	14.9
Rafi <i>et al</i> 2013 ⁴⁷	Retrospective	19	11.5
Hoffman <i>et al</i> 2012 ⁴⁸	Retrospective	33	22.0
Haug <i>et al</i> 2011 ⁴⁹	Retrospective	26	12.8
Sarcoma			
Oh <i>et al</i> 2013 ⁵⁰	Prospective	11	8.7
Secondary liver tumours			
Metastases from colorectal CA			
SIRFLOX trial ⁵¹	Randomized controlled trial	518	10.7
FOXFIRE ⁵²	Randomized controlled trial	364	Ongoing
Lewandowski <i>et al</i> 2014 ⁵³	Prospective	214	10.6
Benson <i>et al</i> 2013 ⁵⁴	Prospective	151	8.8
Metastases from breast CA			
Saxena <i>et al</i> 2014 ⁵⁵	Prospective	77	11.5
Jakobs <i>et al</i> 2008 ⁵⁶	Prospective	30	14.2
Coldwell <i>et al</i> 2012 ⁵⁷	Prospective	44	14.0
Cianni <i>et al</i> 2013 ⁵⁸	Retrospective	77	11.5
Metastases from pancreatic CA			
Michl <i>et al</i> 2014 ⁵⁹	Retrospective	19	9
Metastases from lung CA			
Murthy <i>et al</i> 2008 ⁶⁰	Prospective	6	2.7

CA, carcinoma.

Adapted from Khajornjiraphan *et al*⁴² with permission from Karger Publishers.

Reports of the efficacy of radioembolization in patients with vascular involvement in HCC have been particularly important because no other therapy has been shown to be efficacious. Portal vein tumour thrombosis (PVTT) occurs in 10–40% of HCC cases and is shown to be associated with an extremely poor prognosis.^{61–63} The median survival of patients with PVTT in HCC is estimated to be 2–4 months and is a stark contrast to patients with HCC without PVTT (10–24 months).^{63,64} This is not only attributed to the local and systemic effects of PVTT but also the limitation of treatment modalities. PVTT is currently contraindicated for curative surgery, transplantation and trans-arterial chemoembolization.^{65,66} By contrast, radioembolization is safe in the setting of PVTT due to its low embolic effect and may even lead to portal vein revascularization. Table 5 lists the studies in which patients with PVTT demonstrate good response

to radioembolization. Studies of ⁹⁰Y microsphere radioembolization in cases with portal vein thrombosis have demonstrated superiority of radioembolization in such cases.

The precise role of radioembolization in HCC can only be determined by prospective studies of which a number of them are ongoing. Table 6 summarizes some of the ongoing Phase II and III trials comparing radioembolization against other treatment modalities. Owing to differences in microsphere radiobiology, prospective studies comparing the clinical efficacy of SIR-Spheres *vs* TheraSphere are also warranted.

Clinical indications for radioembolization

Currently, radioembolization is indicated for the treatment of both locally advanced primary and metastatic cancers with the

Table 5. Response and median survival post yttrium-90 microsphere radioembolization in patients with hepatocellular carcinoma with and without portal vein tumour thrombosis (PVTT)

Study	PVTT status	Number of patients	Overall survival (months)
Salem et al 2010 ⁶⁷	Child-Pugh A	116	17.2
	No PVTT	81	22.1
	PVTT	35	10.4
	Child-Pugh B	122	7.7
	No PVTT	65	14.9
	PVTT	57	5.6
Hilgard et al 2010 ⁶⁸	All patients	108	16.4
	No PVTT	75	16.4
	PVTT	33	10
Sangro et al 2011 ⁶⁹	All patients	325	12.8
	No PVTT	249	15.3

Adapted from Lau et al⁷⁰ with permission from Karcher Publishers.

aim of maintaining quality of life and improving survival. There are also reports of HCC being downstaged to receive potentially curative therapies.^{43,44,70,71} Current indications for radioembolization in HCC are found in the following guidelines seen in Table 7: European Society of Medical Oncology,⁷² National Comprehensive Cancer Network,⁷³ National Institute for Health and Clinical Excellence^{74–76} and National Cancer Centre Singapore's Comprehensive Liver Cancer Clinic.⁷⁷ The current guidelines on radioembolization tend to be very similar, all suggesting the prerequisite of good liver function, proper vascular access as well as low hepatopulmonary shunting in order to prevent complications.

Contraindications and complications of radioembolization

Safety during treatment is of utmost priority and hence it is important to select patients carefully. Therefore, it is important to note the limitations and conditions from which patients must be excluded from radioembolization (Table 8).

About one-third of patients may experience immediate short-term abdominal pain following administration of radioembolization. An increase in number of ⁹⁰Y microspheres injected is associated with this particular adverse effect. Other mild adverse effects include a slight fever for several days or lethargy and mild nausea for up to 10 days after radioembolization. These side effects are collectively known as the post-radioembolization syndrome. More serious complications will include stomach or duodenal ulcers from the reflux of ⁹⁰Y microspheres into the gastrointestinal vascular bed or radiomicrosphere hepatitis if the non-tumorous liver absorbed dose threshold is exceeded. Radiomicrosphere hepatitis can be minimized by personalized predictive dosimetry to limit the non-tumorous absorbed dose, especially for patients with pre-existing liver disease. Radiomicrosphere pneumonitis is a complication associated with significant hepatopulmonary shunting. If the ^{99m}Tc MAA scan demonstrates significant hepatopulmonary shunting which may potentially exceed normal lung radiation

tolerance, then ⁹⁰Y radioembolization either should not proceed or a lung-limiting ⁹⁰Y activity should be prescribed based on predictive dosimetry.^{19,23,79}

YTTRIUM-90 MICROSPHERE RADIOEMBOLIZATION: INTERVENTIONAL RADIOLOGY

Typical approach

The interventional radiologist plays a crucial role in ⁹⁰Y microsphere radioembolization and is responsible for planning the vascular approach and safe delivery of the ⁹⁰Y microspheres. In the first procedure of exploratory hepatic angiography with ^{99m}Tc MAA simulation, it is important to delineate hepatic vascular anatomy, interrogate tumoural blood supply and seek out possible extrahepatic parasitization. The pre-procedural multidetector CT (MDCT) scan should be carefully studied. The arterial phase MDCT provides a road map of the hepatic arterial tree. Arteries likely to supply tumours should be identified along with any arterial anatomical variants.⁸⁰ The procedure typically starts with a right common femoral artery puncture to insert a vascular sheath. After which, the superior mesenteric artery is cannulated and a digital subtraction angiogram (DSA) performed to look for aberrant hepatic supply and main portal vein patency, although portal vein thrombosis is not an absolute contraindication to radioembolization.

In conventional hepatic anatomy, the celiac artery is then cannulated and a DSA performed, after which the appropriate hepatic artery is selected (usually with microcatheters and wires) and DSA performed to look for tumoural enhancement and to exclude extrahepatic supply.

Our centre's routine practice is to perform catheter-directed IACT, either with a hybrid angio-MDCT unit or a cone beam CT, from the final microcatheter position. This is to ensure adequate tumoural coverage as well as to exclude extrahepatic supply, both of which may not be readily evident on DSA. Once the interventional radiologist is satisfied with the hepatic

Table 6. Phase II and III yttrium-90 (⁹⁰Y) microsphere radioembolization clinical trials in hepatocellular carcinoma

Trial number	Sponsor	Size	Centres	Therapy 1	Therapy 2	PO	Start	End	Status
NCT01135056	Singapore General Hospital, Singapore	360	26 (Asia-Pacific)	SirSpheres™	Sorafenib	OS	July 2010	July 2015	R
NCT01482442	Hôpitaux de Paris, Paris, France	400	1 (France)	SirSpheres	Sorafenib	OS	November 2011	March 2015	C
NCT01556490	Nordion, Ottawa, Canada	400	2 (USA)	TheraSphere™	Sorafenib	OS	March 2012	October 2016	R
Phase II NCT01686880	Jules Bordet Institute, Brussels, Belgium	50	1 (Belgium)	SirSpheres	–	Perioperative morbidity	September 2012	October 2015	R
Phase II NCT00712790	Singapore General Hospital, Singapore	35	4 (Asia-Pacific)	SirSpheres, sorafenib	–	TTR	June 2008	June 2009	C
Phase II NCT01126645	University of Magdeburg, Magdeburg, Germany	665	34 (Europe)	SirSpheres, sorafenib	RFA, sorafenib	TTR, OS	December 2010	September 2014	R
Phase II NCT00956930	Northwestern University, Evanston, IL	124	1 (USA)	TheraSphere	TACE	TTP	August 2009	August 2018	R
Phase II NCT01381211	Ghent University, Ghent, Belgium	140	2 (Europe)	TheraSphere	DC-BEADS	TTP	September 2011	December 2016	R
NCT00109954	University of Pittsburgh, Pittsburgh, PA	120	1 (USA)	TheraSphere	Cisplatin, TACE	PFS	February 2005	–	A
Phase II NCT01900002	MD Anderson Cancer Center, Houston, TX	20	1 (USA)	TheraSphere, sorafenib	Sorafenib	Sorafenib and ⁹⁰ Y toxicity	September 2013	September 2017	R

A, active not recruiting; C, completed; DC BEADS, drug-eluting bead; OS, overall survival; PO, primary outcome; PPS, progression-free survival; RFA, radiofrequency ablation; TAFE, transarterial chemoembolization; R, recruiting; TTP, time to progression; TTR, time to response.

TheraSphere™ obtained from BTG, London, UK and SIR-Spheres™ from Sirtex Medical Limited, NSW, Australia.

Table 7. Comparison of guidelines on the use of radioembolization

Guideline	Description
ESMO	Indicated for use in patients with prior TACE failure, excellent liver function, macrovascular invasion and the absence of extrahepatic disease. ⁷² (Evidence: III)
NCCN	Radioembolization to be used in unresectable HCC which is not suitable for transplantation based on UNOS criteria (tumour ≤ 5 cm in diameter or 2–3 tumours ≤ 3 cm each, no macrovascular involvement, no extrahepatic disease), Child-Pugh A/B, no portal hypertension, suitable tumour location, adequate liver reserve. ⁷³ (Evidence: II A)
NICE	Indicated for patients with liver predominant disease with adequate liver function (bilirubin $< 34 \mu\text{mol l}^{-1}$ and synthesis function of liver normal) who are poor surgical candidates, not suitable for other locoregional ablative therapies. ^{74–76}
CLCC	Radioembolization to be used in locally advanced HCC $\pm$ vascular invasion in Child-Pugh A/B patients. ⁷⁷ (Evidence: II B)

CLCC, National Cancer Centre Singapore's Comprehensive Liver Cancer Clinic; ESMO, European Society of Medical Oncology; HCC, hepatocellular carcinoma; NCCN, National Comprehensive Cancer Network; NICE, National Institute for Health and Clinical Excellence; TACE, transarterial chemoembolization; UNOS, United Network for Organ Sharing.

All levels of evidence given are according to the Oxford Centre of Evidence Based Medicine.

angiography, a discussion with the attending nuclear medicine physician then takes place before the injection of the $^{99\text{m}}\text{Tc}$ MAA to clarify the final approach. After the injection, all catheters, wires and the sheath are removed and appropriately disposed of in nuclear waste bags and haemostasis of the common femoral artery is secured. The patient will then be sent for a $^{99\text{m}}\text{Tc}$ MAA SPECT/CT.

If the patient is suitable for treatment, radioembolization is typically performed 2 weeks later. A careful review of the $^{99\text{m}}\text{Tc}$ MAA SPECT/CT and a discussion with the attending nuclear medicine physician is important, particularly if there is extrahepatic deposition of $^{99\text{m}}\text{Tc}$ MAA. Our institutional preference at the Singapore General Hospital is to perform prophylactic embolization at the time of radioembolization, rather than at the time of exploratory angiography. This is to minimize unnecessary prophylactic coiling in patients who may be later disqualified on the basis of unfavourable dosimetry. Also, prophylactic coiling may induce hepatic-intestinal collaterals which may be even more unpredictable over time. On the day of radioembolization, once the necessary prophylactic coil embolizations have been completed, we will routinely perform IACT to ensure its effectiveness, *i.e.* to ensure no extrahepatic enhancement from the final microcatheter position. The ^{90}Y microspheres are then administered. Flow stasis may occur when using resin ^{90}Y microspheres due to a higher number of infused microspheres, which may sometimes result in incomplete

delivery of the prescribed activity.^{18,81} ^{90}Y microspheres should therefore be infused slowly. There may be a need to occasionally check for antegrade flow with a gentle contrast injection, taking care not to reflux the contrast column. At the end of the procedure, all wires, catheters and sheath are carefully removed and disposed of in nuclear waste bags. We prefer to secure haemostasis of the groin by closure device to avoid prolong contact with the puncture site in case of contamination.

Multiple injections vs vascular manipulation with coiling

The various options for radioembolization of tumours with multiple arterial supply have been well summarized by Ray et al.⁸² The strategies include splitting the prescribed activity into more than one administrative setup and using new microcatheters for each injection, flow-directed microcatheter repositioning with contrast injection and coil embolization of other hepatic arteries allowing flow redistribution to permit ^{90}Y microspheres injection from a single artery.⁸³ Our preference is

Table 8. Exclusion criteria to yttrium-90 (^{90}Y) microsphere radioembolization

Exclusion criteria to ^{90}Y radioembolization
Absolute contraindications
Intractable clinical ascites (in spite of optimal diuretic treatment) or any other clinical signs of liver failure on physical examination
Bleeding diathesis, not correctable by the standard forms of therapy
Severe peripheral vascular disease that would preclude arterial catheterization
Severe portal hypertension with hepatofugal flow
Relative contraindications
Complete main portal vein thrombosis
Adequate haematological, renal and hepatic function as follows:
Haematological
Leukocytes $< 2500 \mu\text{l}^{-1}$
Platelets $< 80,000 \mu\text{l}^{-1}$
Haemoglobin $< 9.5 \text{ g dl}^{-1}$
Total bilirubin $> 2.0 \text{ mg dl}^{-1}$
INR > 2.0
Hepatic function
ALP $> 5 \times$ institutional ULN
AST and ALT $> 5 \times$ institutional ULN
Albumin $< 2.5 \text{ g dl}^{-1}$
Renal function
Creatinine $> 2.0 \text{ mg dl}^{-1}$
Prior hepatic external beam radiation therapy

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; ULN, upper limit of normal.

SIRveNIB Trial Protocol Exclusion Criteria.⁷⁸

Figure 1. Digital subtraction angiograms (DSAs) and corresponding intra-arterial CT (IACT) showing multiple arterial supplies to a single tumour. Without IACT, it may be difficult to ensure complete lesional coverage. (a, b) DSA and IACT, respectively, with the microcatheter in the right hepatic artery. (c, d) DSA and IACT, respectively, with the microcatheter in the left hepatic artery. (e, f) DSA and IACT, respectively, with the microcatheter in the right gastroepiploic artery.

to perform the first option: splitting the prescribed activity to different administrative setups. This allows for more predictable absorbed dose delivery as calculated by the multipartition model, as well as reduces the chance of contamination. Flow redistribution is unpredictable and introduces additional dosimetric uncertainty and is therefore the least preferred interventional technique from the perspective of radiation planning.

Intra-arterial CT

The ability to perform catheter-directed IACT, either with a hybrid angio-MDCT system or a cone beam CT has been a boon to interventional radiologists performing radio-embolization. It allows us to fully appreciate tumoural and extrahepatic enhancement, thus improving patient safety. [Figures 1](#) and [2](#) both show good examples of cases using IACT.

Figure 2. (a) Digital subtraction angiogram (DSA) and (b, c) intra-arterial CT (IACT) showing usefulness of IACT for detection of extrahepatic enhancement for treatment of a large hepatocellular carcinoma. IACT acquired taken with the microcatheter at the proper hepatic artery. From this position, there is a small area of gastric enhancement (c) which would otherwise be missed on DSA alone. Eventually, the activity was split and delivered into the right and left hepatic arteries without incident.

Unanticipated ^{99m}Tc MAA deposition detected by SPECT/CT may occasionally require a second exploratory hepatic angiography with reinjection of MAA, depending on case complexity.⁸⁴ IACT can detect small areas of extrahepatic contrast enhancement which may help to reduce the need for the additional procedures. IACT also allows ^{90}Y microspheres to be injected into parasitic extrahepatic supply more confidently, e.g. the inferior phrenic artery.⁸⁵ From a radiation-planning perspective, IACT allows accurate assessment of target volumes to guide SPECT/CT-based personalized predictive dosimetry.^{19,86}

Prophylactic vessel coiling

All intrahepatic arteries that supply extrahepatic organs originating distal to the point of ^{90}Y microspheres release should be prophylactically embolized. At our centre, we perform the prophylactic coiling during the same session as radioembolization, following which we perform IACT to ensure no extrahepatic enhancement before injection of ^{90}Y microspheres.

However, it is now becoming less clear if routine prophylactic embolization of the gastroduodenal artery (GDA), cystic artery and the falciform artery are truly essential, particular with the advent of IACT.

Gastroduodenal artery

Traditionally, coiling of the GDA has been performed prior to ^{90}Y microspheres injection to minimize the risk of extrahepatic ^{90}Y microspheres deposition.¹¹ Schelhorn et al⁸⁷ demonstrated that coiling of the GDA may induce hepatic-intestinal collaterals which may in some circumstances render radioembolization unfeasible. In our practice with routine use of IACT, we have stopped routine prophylactic coiling of the GDA. If whole-liver radioembolization is required, a bilobar approach to ^{90}Y microsphere administration is performed.

Cystic artery

Routine prophylactic embolization of the cystic artery is not indicated. As described by Theysohn et al,⁸⁸ the majority of patients do not require cystic artery embolization. If there is significant ^{99m}Tc MAA activity in the gallbladder wall, the final microcatheter position may either be changed to one which is distal to the origin of the cystic artery or the cystic artery may be temporarily occluded with Gelfoam® (Pfizer Inc., New York, NY).⁸⁸

Falciform artery

A patent hepatic falciform artery (HFA) is an uncommon finding on DSA, although they are far more readily detected on IACT.⁸⁹ Burgmans et al⁸⁹ also demonstrated that the risk of symptomatic extrahepatic deposition of ^{90}Y microspheres into the HFA territory is rare even with a patent HFA, and thus routine embolization of the HFA is also not indicated. If there is indeed deposition of ^{99m}Tc MAA in the HFA vascular territory, this vessel can be embolized with gelfoam or coils, and additionally, ice packs may be placed on the anterior abdomen during radioembolization.⁹⁰

CONFIRMATION OF TECHNICAL SUCCESS

Owing to biophysical differences between soluble contrast molecules vs ^{90}Y microspheres, technical success should not be

inferred on the basis of angiographic findings alone. To confirm technical success, the biodistribution of ^{90}Y microspheres should be imaged by either bremsstrahlung SPECT/CT or ^{90}Y PET/CT. Although bremsstrahlung SPECT/CT is a significant technological improvement from planar scintigraphy, the inherent problem of poor spatial resolution still remains. It was recently shown that minuscule positron emission from ^{90}Y decay may be imaged by conventional PET scanners without hardware modification.⁹¹ ^{90}Y PET obtains high-resolution images for improved assessment of target⁹² and non-target activity,⁹³ superior to ^{90}Y bremsstrahlung SPECT/CT. The higher resolution of ^{90}Y PET improves diagnostic confidence for technical success confirmation, radiation plan verification and non-target activity detection.^{92,93} Diagnostic reporting guidelines for ^{90}Y PET/CT have recently been proposed.⁹² ^{90}Y PET voxel dosimetry may also be performed if clinically indicated to obtain absorbed doses and dose-volume histograms.²⁹ There is ongoing research to address the problem of high background noise in the reconstructed images due to the unfavourable combination of low ^{90}Y positron emission, intrinsic radioactivity from lutetium-based PET crystals and random events.

Post-procedure imaging

As with other forms of embolotherapy, size criteria [Response Evaluation Criteria in Solid Tumours (RECIST) or World Health Organization] alone has shown to be less accurate in gauging response.⁹⁴ Indeed, tumours that responded to radioembolization may show an initial transient increase in size. In their radiologic-pathological correlation study of HCCs in explanted liver, Riaz et al⁹⁵ showed that the European Association for the Study of the Liver disease necrosis criteria most accurately predicts complete pathological necrosis. Necrosis on imaging also appears to correlate with survival in a study of 21 patients with intrahepatic cholangiocarcinoma who undergo radioembolization, both modified RECIST and European Association for the Study of the Liver criteria, when applied to the delayed phase predicted overall survival but RECIST did not.⁹⁶ For hepatic colorectal metastases, fluorine-18 fludeoxyglucose PET/CT within 6–8 weeks may predict progression-free survival (PFS).⁹⁷

FUTURE DIRECTIONS AND RESEARCH

Radioembolization to sites other than the liver

As radioembolization is essentially a form of brachytherapy, there is no logical reason why radioactive microspheres cannot be used to treat tumours located elsewhere other than the liver. In principle, radioembolization may be performed to any site in the body, provided there is accessible vasculature, favourable tumour-vs-normal tissue targeting and adequate treatment simulation to ensure safety. A general theory of predictive dosimetry based on MIRD macrodosimetry to guide radioembolization to sites other than the liver has recently been proposed.⁹⁸ Since 2013, there have been reports of radioembolization to the kidney, spleen, lung and adrenal gland.⁹⁸ A clinical trial investigating kidney radioembolization for renal cell carcinoma is currently ongoing in Australia.⁹⁹ With the increasing sophistication of interventional radiology and nuclear medicine techniques, there is no doubt that radioembolization to sites other than the liver will continue to expand in the years to come.

Combination therapies with radioembolization

^{90}Y microsphere radioembolization is an effective treatment modality for locoregional control of HCC, but the abscopal effect, if any, may not address systemic disease adequately. Various studies have utilized concomitant radioembolization with conventional systemic chemotherapy in order to address this issue.^{100–102} An example would be the SIFLOX study; a randomized controlled trial in which a combination of ^{90}Y resin microsphere radioembolization + FOLFOX (oxaliplatin, leucovorin and 5-fluorouracil) chemotherapy regimen was compared against FOLFOX chemotherapy in unresectable liver metastases from metastatic colon cancer. Results from the trial showed mixed results; the trial did not meet the primary end point, as the addition of radioembolization to standard chemotherapy failed to improve overall PFS. However, its secondary end point was met, as it demonstrated that treatment with radioembolization extended the median liver PFS although it has minimal effect on extrahepatic disease. In view of this, more studies with different chemotherapy drugs are needed, as there is still a great potential for combinatorial therapy to be highly efficacious.¹⁰³ With advances in molecular targeted therapy, there are now even more possibilities for systemic therapy in combination with radioembolization. A case study was reported using radioembolization in combination with aflibercept (vascular endothelial growth factor inhibitor), with a folinic acid, fluorouracil, irinotecan (FOLFIRI) regimen for the treatment of a metastatic CRC.¹⁰⁴ Another example is a recent multicentre

Phase II trial examining the safety and efficacy of radioembolization followed by the multikinase inhibitor sorafenib.⁷¹

CONCLUSION

Radioembolization using ^{90}Y microspheres has seen incremental use in the treatment of both primary and secondary hepatic tumours as well as extrahepatic sites. In particular, there is emerging evidence regarding the efficacy of radioembolization for patients with locally advanced HCC and/or PVTT in which a paucity of efficacious treatment modalities currently exist. There have also been continuous advancements in personalized nuclear medicine and interventional radiology techniques for the improvement of radioembolization outcomes. Further Phase II and III clinical trials involving radioembolization either as monotherapy or as combination therapy are ongoing. Given the great potential of radioembolization, there is an impetus to explore additional avenues to enhance its safety and efficacy. This will expand the spectrum of use for radioembolization, opening more doors for those with few treatment options.

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REFERENCES

- Lewandowski RJ, Geschwind JF, Liapi E, Salem R. Transcatheter intraarterial therapies: rationale and overview. *Radiology* 2011; **259**: 641–57.
- Ariel IM. Radioactive isotopes for adjuvant cancer therapy; animal experimentation and preliminary results in human application. *Arch Surg* 1964; **89**: 244–9. doi: <http://dx.doi.org/10.1001/archsurg.1964.01320020008002>
- Nolan TR, Grady ED. Intravascular particulate radioisotope therapy: clinical observations of 76 patients with advanced cancer treated with $^{90}\text{-yttrium}$ particles. *Am Surg* 1969; **35**: 181–8.
- Ariel IM, Padula G. Treatment of symptomatic metastatic cancer to the liver from primary colon and rectal cancer by the intraarterial administration of chemotherapy and radioactive isotopes. *J Surg Oncol* 1978; **10**: 327–36. doi: <http://dx.doi.org/10.1002/jso.2930100407>
- Ariel IM, Padula G. Treatment of asymptomatic metastatic cancer to the liver from primary colon and rectal cancer by the intraarterial administration of chemotherapy and radioactive isotopes. *J Surg Oncol* 1982; **20**: 151–6. doi: <http://dx.doi.org/10.1002/jso.2930200304>
- Grady ED, Nolan TR, Crumley AJ, Larose JH, Cheek WV. Internal hepatic radiotherapy: II. intra-arterial radiocolloid therapy for hepatic tumors. *Am J Roentgenol Radium Ther Nucl Med* 1975; **124**: 596–9. doi: <http://dx.doi.org/10.2214/ajr.124.4.596>
- Harbert JC, Robertson JS, Held KD. *Nuclear medicine therapy*. New York, NY: Thieme Medical Publishers Inc.; 1987.
- Harbert JC, Ziesmann HA. Therapy with intraarterial microspheres. In: Freeman LM, Weissmann HS, eds. *Nuclear Medicine Annual*. New York, NY: Raven Press; 1987. pp. 295–319.
- Matsui O. Imaging of multistep human hepatocarcinogenesis by CT during intra-arterial contrast injection. *Intervirology* 2004; **47**: 271–6. doi: <http://dx.doi.org/10.1159/000078478>
- Lien WM, Ackerman NB. The blood supply of experimental liver metastases. II. A microcirculatory study of the normal and tumor vessels of the liver with the use of perfused silicone rubber. *Surgery*. 1970; **68**: 334–40.
- Kennedy A, Nag S, Salem R, Murthy R, McEwan AJ, Nutting CW, et al. Recommendations for radioembolization of hepatic malignancies using yttrium-90 microsphere brachytherapy: a consensus panel report from the radioembolization brachytherapy oncology consortium. *Int J Radiat Oncol Biol Phys* 2007; **68**: 13–23. doi: <http://dx.doi.org/10.1016/j.ijrobp.2006.11.060>
- Salem R, Lewandowski RJ, Gates VL, Nutting CW, Murthy R, Rose SC, et al. Research reporting standards for radioembolization of hepatic malignancies. *J Vasc Interv Radiol*. 2011; **22**: 265–78. doi: <http://dx.doi.org/10.1016/j.jvir.2010.10.029>
- Sirtex package insert for SIR-Spheres® microspheres. NSW, Australia: Sirtex Medical Limited [cited 26 February 2016]. Available from: <http://www.sirtex.com/media/8163/pi-ec-11.pdf>.
- Kao YH, Tan EH, Ng CE, Goh SW. Clinical implications of the body surface area method versus partition model dosimetry for yttrium-90 radioembolization using resin microspheres: a technical review. *Ann Nucl Med*. 2011; **25**: 455–61. doi: <http://dx.doi.org/10.1007/s12149-011-0499-6>

15. Van Hazel G, Blackwell A, Anderson J, Price D, Moroz P, Bower G, et al. Randomised phase 2 trial of SIR-Spheres plus fluorouracil/leucovorin chemotherapy versus fluorouracil/leucovorin chemotherapy alone in advanced colorectal cancer. *J Surg Oncol.* 2004; **88**: 78–85. doi: <http://dx.doi.org/10.1002/jso.20141>
16. Bernardini M, Smadja C, Faraggi M, Orio S, Petitguillaume A, Desbrée A, et al. Liver Selective Internal Radiation Therapy with (90)Y resin microspheres: comparison between pre-treatment activity calculation methods. *Phys Med.* 2014; **30**: 752–64. doi: <http://dx.doi.org/10.1016/j.ejmp.2014.05.004>
17. Lam MG, Louie JD, Abdelmaksoud MH, Fisher GA, Cho-Phan CD, Sze DY. Limitations of body surface area-based activity calculation for radioembolization of hepatic metastases in colorectal cancer. *J Vasc Interv Radiol.* 2014; **25**: 1085–93. doi: <http://dx.doi.org/10.1016/j.jvir.2013.11.018>
18. Cremonesi M, Chiesa C, Strigari L, Ferrari M, Botta F, Guerriero F, et al. Radioembolization of hepatic lesions from a radiobiology and dosimetric perspective. *Front Oncol.* 2014; **4**: 210. doi: <http://dx.doi.org/10.3389/fonc.2014.00210>
19. Kao YH, Hock Tan AE, Burgmans MC, Irani FG, Khoo LS, Gong LO RH, et al. Image-guided personalized predictive dosimetry by artery-specific SPECT/CT partition modeling for safe and effective 90Y radioembolization. *J Nucl Med.* 2012; **53**: 559–66. doi: <http://dx.doi.org/10.2967/jnumed.111.097469>
20. Garin E, Lenoir L, Edeline J, Laffont S, Mesbah H, Porée P, et al. Boosted selective internal radiation therapy with 90Y-loaded glass microspheres (B-SIRT) for hepatocellular carcinoma patients: a new personalized promising concept. *Eur J Nucl Med Mol Imaging.* 2013; **40**: 1057–68. doi: <http://dx.doi.org/10.1007/s00259-013-2395-x>
21. Ho S, Lau WY, Leung TW, Chan M, Ngar YK, Johnson PJ, et al. Partition model for estimating radiation doses from yttrium-90 microspheres in treating hepatic tumours. *Eur J Nucl Med.* 1996; **23**: 947–52. doi: <http://dx.doi.org/10.1007/BF01084369>
22. Smits ML, Elschot M, Sze DY, Kao YH, Nijssen JF, Iagaru AH, et al. Radioembolization dosimetry: the road ahead. *Cardiovasc Intervent Radiol.* 2015; **38**: 261–9. doi: <http://dx.doi.org/10.1007/s00270-014-1042-7>
23. Kao YH, Magsombol BM, Toh Y, Tay KH, Chow PKH, Goh AS, et al. Personalized predictive lung dosimetry by technetium-99m macroaggregated albumin SPECT/CT for yttrium-90 radioembolization. *EJNMMI Res* 2014; **4**: 33. doi: <http://dx.doi.org/10.1186/s13550-014-0033-7>
24. Kao YH. Disregard for basic dosimetric principles will lead to questionable results. *Clin Nucl Med.* 2013; **38**: 759. doi: <http://dx.doi.org/10.1097/RLU.0b013e31829f59aa>
25. Kao YH. Results confounded by a disregard for basic dose-response radiobiology. *J Nucl Med.* 2013; **54**: 1682–3. doi: <http://dx.doi.org/10.2967/jnumed.113.122846>
26. Kao YH. A clinical dosimetric perspective uncovers new evidence and offers new insight in favor of 99mTc-macroaggregated albumin for predictive dosimetry in 90Y resin microsphere radioembolization. *J Nucl Med.* 2013; **54**: 2191–2. doi: <http://dx.doi.org/10.2967/jnumed.113.128553>
27. Petitguillaume A, Bernardini M, Hadid L, de Labriolle-Vaylet C, Franck D, Desbrée A. Three-dimensional personalized Monte Carlo dosimetry in 90Y resin microspheres therapy of hepatic metastases: nontumoral liver and lungs radiation protection considerations and treatment planning optimization. *J Nucl Med.* 2014; **55**: 405–13. doi: <http://dx.doi.org/10.2967/jnumed.113.120444>
28. Lau WY, Kennedy AS, Kim YH, Lai HK, Lee RC, Leung TW, et al. Patient selection and activity planning guide for selective internal radiotherapy with yttrium-90 resin microspheres. *Int J Radiat Oncol Biol Phys* 2012; **82**: 401–7. doi: <http://dx.doi.org/10.1016/j.ijrobp.2010.08.015>
29. Kao YH, Steinberg JD, Tay YS, Lim GK, Yan J, Townsend DW, et al. Post-radioembolization yttrium-90 PET/CT—part 2: dose-response and tumor predictive dosimetry for resin microspheres. *EJNMMI Res* 2013; **3**: 57. doi: <http://dx.doi.org/10.1186/2191-219X-3-57>
30. Lam MG, Goris ML, Iagaru AH, Mittra ES, Louie JD, Sze DY. Prognostic utility of 90Y radioembolization dosimetry based on fusion 99mTc-macroaggregated albumin-99mTc-sulfur colloid SPECT. *J Nucl Med* 2013; **54**: 2055–61. doi: <http://dx.doi.org/10.2967/jnumed.113.123257>
31. Flamen P, Vanderlinden B, Delatte P, Ghanem G, Ameye L, Van Den Eynde M, et al. Corrigendum: multimodality imaging can predict the metabolic response of unresectable colorectal liver metastases to radioembolization therapy with Yttrium-90 labeled resin microspheres. *Phys Med Biol* 2014; **59**: 2549–51. doi: <http://dx.doi.org/10.1088/0031-9155/59/10/2549>
32. Chiesa C, Mira M, Maccauro M, Spreafico C, Romito R, Morosi C, et al. Radioembolization of hepatocarcinoma with (90)Y glass microspheres: development of an individualized treatment planning strategy based on dosimetry and radiobiology. *Eur J Nucl Med Mol Imaging.* 2015; **42**: 1718–38. doi: <http://dx.doi.org/10.1007/s00259-015-3068-8>
33. Saraswat VA, Pandey G, Shetty S. Treatment algorithms for managing hepatocellular carcinoma. *J Clin Exp Hepatol.* 2014; **4** (Suppl. 3): S80–9. doi: <http://dx.doi.org/10.1016/j.jceh.2014.05.004>
34. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin.* 2015; **65**: 87–108.
35. Forner A, Gilibert M, Bruix J, Raoul JL. Treatment of intermediate-stage hepatocellular carcinoma. *Nat Rev Clin Oncol.* 2014; **11**: 525–35. doi: <http://dx.doi.org/10.1038/nrclinonc.2014.122>
36. Gray BN. Colorectal cancer: the natural history of disseminated disease—a review. *Aust N Z J Surg.* 1980; **50**: 643–6.
37. Zurkiya O, Ganguli S. Beyond hepatocellular carcinoma and colorectal metastasis: the expanding applications of radioembolization. *Front Oncol.* 2014; **4**: 150. doi: <http://dx.doi.org/10.3389/fonc.2014.00150>
38. Sato KT, Lewandowski RJ, Mulcahy MF, Atassi B, Ryu RK, Gates VL, et al. Unresectable chemorefractory liver metastases: radioembolization with 90Y microspheres—safety, efficacy, and survival. *Radiology.* 2008; **247**: 507–15. doi: <http://dx.doi.org/10.1148/radiol.2472062029>
39. Padia SA, Kwan SW, Roudsari B, Monsky WL, Covelev A, Harris WP. Superselective yttrium-90 radioembolization for hepatocellular carcinoma yields high response rates with minimal toxicity. *J Vasc Interv Radiol.* 2014; **25**: 1067–73. doi: <http://dx.doi.org/10.1016/j.jvir.2014.03.030>
40. Kennedy AS, Ball D, Cohen SJ, Cohn M, Coldwell DM, Drooz A, et al. Multicenter evaluation of the safety and efficacy of radioembolization in patients with unresectable colorectal liver metastases selected as candidates for (90)Y resin microspheres. *J Gastrointest Oncol* 2015; **6**: 134–42.
41. Vente MA, Wondergem M, van der Tweel I, van den Bosch MA, Zonnenberg BA, Lam MG, et al. Yttrium-90 microsphere radioembolization for the treatment of liver malignancies: a structured meta-analysis. *Eur Radiol.* 2009; **19**: 951–9. doi: <http://dx.doi.org/10.1007/s00330-008-1211-7>
42. Khajornjiraphan N, Thu NA, Chow PK. Yttrium-90 microspheres: a review of its emerging clinical indications. *Liver Cancer*

- 2015; **4**: 6–15. doi: <http://dx.doi.org/10.1159/000343876>
43. Kulik LM, Carr BI, Mulcahy MF, Lewandowski RJ, Atassi B, Ryu RK, et al. Safety and efficacy of 90Y radiotherapy for hepatocellular carcinoma with and without portal vein thrombosis. *Hepatology* 2008; **47**: 71–81. doi: <http://dx.doi.org/10.1002/hep.21980>
 44. Sangro B. The ENRY analysis: a 325-patient European multicentre analysis. *EJC Suppl* 2012; **10**: 23–6. doi: [http://dx.doi.org/10.1016/S1359-6349\(12\)70036-8](http://dx.doi.org/10.1016/S1359-6349(12)70036-8)
 45. Saxena A, Bester L, Chua TC, Chu FC, Morris DL. Yttrium-90 radiotherapy for unresectable intrahepatic cholangiocarcinoma: a preliminary assessment of this novel treatment option. *Ann Surg Oncol*. 2010; **17**: 484–91. doi: <http://dx.doi.org/10.1245/s10434-009-0777-x>
 46. Ibrahim SM, Mulcahy MF, Lewandowski RJ, Sato KT, Ryu RK, Masterson EJ, et al. Treatment of unresectable cholangiocarcinoma using yttrium-90 microspheres: results from a pilot study. *Cancer*. 2008; **113**: 2119–28. doi: <http://dx.doi.org/10.1002/cncr.23818>
 47. Rafi S, Piduru SM, El-Rayes B, Kauh JS, Kooby DA, Sarmiento JM, et al. Yttrium-90 radioembolization for unresectable standard-chemorefractory intrahepatic cholangiocarcinoma: survival, efficacy, and safety study. *Cardiovasc Intervent Radiol*. 2013; **36**: 440–8. doi: <http://dx.doi.org/10.1007/s00270-012-0463-4>
 48. Hoffmann RT, Paprottka PM, Schön A, Bamberg F, Haug A, Dürr EM, et al. Transarterial hepatic yttrium-90 radioembolization in patients with unresectable intrahepatic cholangiocarcinoma: factors associated with prolonged survival. *Cardiovasc Intervent Radiol*. 2012; **35**: 105–16. doi: <http://dx.doi.org/10.1007/s00270-011-0142-x>
 49. Haug AR, Heinemann V, Bruns CJ, Hoffmann R, Jakobs T, Bartenstein P, et al. 18F-FDG PET independently predicts survival in patients with cholangiocellular carcinoma treated with 90Y microspheres. *Eur J Nucl Med Mol Imaging* 2011; **38**: 1037–45. doi: <http://dx.doi.org/10.1007/s00259-011-1736-x>
 50. Oh JC, Lam MG, Ganjoo KN, Louie JD, Sze DY. Y-90 radioembolization of primary and metastatic soft tissue sarcomas of the liver. *J Vasc Interv Radiol* **24**: S148. doi: <http://dx.doi.org/10.1016/j.jvir.2013.01.370>
 51. Gibbs P, GebSKI V, Van Buskirk M, Thurston K, Cade DN, Van Hazel GA, et al. Selective Internal Radiation Therapy (SIRT) with yttrium-90 resin microspheres plus standard systemic chemotherapy regimen of FOLFOX versus FOLFOX alone as first-line treatment of non-resectable liver metastases from colorectal cancer: the SIR-FLOX study. *BMC Cancer* 2014; **14**: 897. doi: <http://dx.doi.org/10.1186/1471-2407-14-897>
 52. Dutton SJ, Kenealy N, Love SB, Wasan HS, Sharma RA; FOXFIRE Protocol Development Group and the NCRI Colorectal Clinical Study Group. FOXFIRE protocol: an open-label, randomised, Phase III trial of 5-fluorouracil, oxaliplatin and folinic acid (OxMdG) with or without interventional Selective Internal Radiation Therapy (SIRT) as first-line treatment for patients with unresectable liver-only or liver-dominant metastatic colorectal cancer. *BMC Cancer* 2014; **14**: 497. doi: <http://dx.doi.org/10.1186/1471-2407-14-497>
 53. Lewandowski RJ, Memon K, Mulcahy MF, Hickey R, Marshall K, Williams M, et al. Twelve-year experience of radioembolization for colorectal hepatic metastases in 214 patients: survival by era and chemotherapy. *Eur J Nucl Med Mol Imaging* 2014; **41**: 1861–9. doi: <http://dx.doi.org/10.1007/s00259-014-2799-2>
 54. Benson AB, 3rd, Geschwind JF, Mulcahy MF, Rilling W, Siskin G, Wiseman G, et al. Radioembolisation for liver metastases: results from a prospective 151 patient multi-institutional Phase II study. *Eur J Cancer* 2013; **49**: 3122–30. doi: <http://dx.doi.org/10.1016/j.ejca.2013.05.012>
 55. Saxena A, Kapoor J, Meteling B, Morris DL, Bester L. Yttrium-90 radioembolization for unresectable, chemoresistant breast cancer liver metastases: a large single-center experience of 40 patients. *Ann Surg Oncol* 2014; **21**: 1296–303. doi: <http://dx.doi.org/10.1245/s10434-013-3436-1>
 56. Jakobs TF, Hoffmann RT, Fischer T, Stemmler HJ, Tatsch K, La Fougere C, et al. Radioembolization in patients with hepatic metastases from breast cancer. *J Vasc Interv Radiol* 2008; **19**: 683–90. doi: <http://dx.doi.org/10.1016/j.jvir.2008.01.009>
 57. Coldwell D, Sangro B, Salem R, Wasan H, Kennedy A. Radioembolization in the treatment of unresectable liver tumors: experience across a range of primary cancers. *Am J Clin Oncol* 2012; **35**: 167–77. doi: <http://dx.doi.org/10.1097/COC.0b013e3181f47923>
 58. Cianni R, Pelle G, Notarianni E, Saltarelli A, Rabuffi P, Bagni O, et al. Radioembolisation with (90)Y-labelled resin microspheres in the treatment of liver metastasis from breast cancer. *Eur Radiol* 2013; **23**: 182–9. doi: <http://dx.doi.org/10.1007/s00330-012-2556-5>
 59. Michl M, Haug AR, Jakobs TF, Paprottka P, Hoffmann RT, Bartenstein P, et al. Radioembolization with Yttrium-90 microspheres (SIRT) in pancreatic cancer patients with liver metastases: efficacy, safety and prognostic factors. *Oncology* 2014; **86**: 24–32. doi: <http://dx.doi.org/10.1159/000355821>
 60. Murthy R, Mutha P, Lee JH, Oh Y. Yttrium-90-labeled microsphere radioembolotherapy of liver-dominant metastases from thoracic malignancies. *J Vasc Interv Radiol* 2008; **19**: 299–300. doi: <http://dx.doi.org/10.1016/j.jvir.2007.11.002>
 61. Minagawa M, Makuuchi M. Treatment of hepatocellular carcinoma accompanied by portal vein tumor thrombus. *World J Gastroenterol* 2006; **12**: 7561–7.
 62. Cheung TK, Lai CL, Wong BC, Fung J, Yuen MF. Clinical features, biochemical parameters, and virological profiles of patients with hepatocellular carcinoma in Hong Kong. *Aliment Pharmacol Ther* 2006; **24**: 573–83. doi: <http://dx.doi.org/10.1111/j.1365-2036.2006.03029.x>
 63. Llovet JM, Bustamante J, Castells A, Vilana R, Ayuso Mdel C, Sala M, et al. Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. *Hepatology* 1999; **29**: 62–7. doi: <http://dx.doi.org/10.1002/hep.510290145>
 64. Schöninger-Hecke M, Müller C, Kutilek M, Oesterreicher C, Ferenci P, Gangl A. Hepatocellular carcinoma in Central Europe: prognostic features and survival. *Gut* 2001; **48**: 103–9. doi: <http://dx.doi.org/10.1136/gut.48.1.103>
 65. Jelic S, Sotiropoulos GC; ESMO Guidelines Working Group. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; **21**(Suppl. 5): v59–64. doi: <http://dx.doi.org/10.1093/annonc/mdq166>
 66. Omata M, Lesmana LA, Tateishi R, Chen PJ, Lin SM, Yoshida H, et al. Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma. *Hepatol Int* 2010; **4**: 439–74. doi: <http://dx.doi.org/10.1007/s12072-010-9165-7>
 67. Salem R, Lewandowski RJ, Mulcahy MF, Riaz A, Ryu RK, Ibrahim S, et al. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. *Gastroenterology* 2010; **138**: 52–64. doi: <http://dx.doi.org/10.1007/s00330-012-2556-5>

- <http://dx.doi.org/10.1053/j.gastro.2009.09.006>
68. Hilgard P, Hamami M, Fouly AE, Scherag A, Müller S, Ertle J, et al. Radioembolization with yttrium-90 glass microspheres in hepatocellular carcinoma: European experience on safety and long-term survival. *Hepatology* 2010; **52**: 1741–9. doi: <http://dx.doi.org/10.1002/hep.23944>
 69. Sangro B, Carpanese L, Cianni R, Golfieri R, Gasparini D, Ezziddin S, et al. Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. *Hepatology* 2011; **54**: 868–78. doi: <http://dx.doi.org/10.1002/hep.24451>
 70. Lau WY, Sangro B, Chen PJ, Cheng SQ, Chow P, Lee RC, et al. Treatment for hepatocellular carcinoma with portal vein tumor thrombosis: the emerging role for radioembolization using yttrium-90. *Oncology* 2013; **84**: 311–18. doi: <http://dx.doi.org/10.1159/000348325>
 71. Chow PK, Poon DY, Khin MW, Singh H, Han HS, Goh AS, et al. Multicenter phase II study of sequential radioembolization—sorafenib therapy for inoperable hepatocellular carcinoma. *PLoS One* 2014; **9**: e90909.
 72. Verslype C, Rosmorduc O, Rougier P; ESMO Guidelines Working Group. Hepatocellular carcinoma: ESMO-ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2012; **23**(Suppl. 7): vii41–8.
 73. NCCN. Guidelines version 2.2016 on Hepatobiliary Cancers. In: *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines)*. Fort Washington, PA: National Comprehensive Cancer Network [cited 26 February 2016]. Available from: http://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf2015.
 74. National Institute for Health and Clinical Excellence. *Selective internal radiation therapy for primary hepatocellular carcinoma. NICE guideline (IPG460)*. 2013.
 75. National Institute for Health and Clinical Excellence. *Selective internal radiation therapy for nonresectable colorectal metastases in the liver. NICE guideline (IPG401)*. 2013.
 76. NHS England. *Interim clinical commissioning policy statement: selective internal radiotherapy (SIRT)*. Reference: B01/PS/a. 2013
 77. NCCS. *Comprehensive Liver Cancer Clinic (CLCC) Guidelines*. National Cancer Centre Singapore (NCCS); 2014 [cited 2015 July 27] Available from: <http://www.nccs.com.sg/PatientCare/ComprehensiveLiverCancer-Clinic/Documents/CLCC%20guideline%20Final%20Ver%20to%20upload%20PDF%2026092014.pdf>
 78. Clinicaltrials.gov. Study to compare selective internal radiation therapy (SIRT) versus sorafenib in locally advanced hepatocellular carcinoma (HCC) (SIRveNIB); 2010 [cited 26 February 2016] Available from: <https://clinicaltrials.gov/ct2/show/NCT01135056?term=pierce+chow&rank=5>.
 79. Giammarile F, Bodei L, Chiesa C, Flux G, Forrer F, Kraeber-Bodere F, et al. EANM procedure guideline for the treatment of liver cancer and liver metastases with intra-arterial radioactive compounds. *Eur J Nucl Med Mol Imaging* 2011; **38**: 1393–406. doi: <http://dx.doi.org/10.1007/s00259-011-1812-2>
 80. Paprottka PM, Jakobs TF, Reiser MF, Hoffmann RT. Practical vascular anatomy in the preparation of radioembolization. *Cardiovasc Intervent Radiol* 2012; **35**: 454–62. doi: <http://dx.doi.org/10.1007/s00270-011-0169-z>
 81. Murthy R, Xiong H, Nunez R, Cohen AC, Barron B, Szklaruk J, et al. Yttrium 90 resin microspheres for the treatment of unresectable colorectal hepatic metastases after failure of multiple chemotherapy regimens: preliminary results. *J Vasc Interv Radiol* 2005; **16**: 937–45. doi: <http://dx.doi.org/10.1097/01.RVI.0000161142.12822.66>
 82. Ray CE, Jr, Gaba RC, Knuttinen MG, Minocha J, Bui JT. Multiple arteries supplying a single tumor vascular distribution: microsphere administration options for the interventional radiologist performing radioembolization. *Semin Intervent Radiol* 2014; **31**: 203–6.
 83. Karunanithy N, Gordon F, Hodolic M, Al-Nahhas A, Wasan HS, Habib N, et al. Embolization of hepatic arterial branches to simplify hepatic blood flow before yttrium 90 radioembolization: a useful technique in the presence of challenging anatomy. *Cardiovasc Intervent Radiol* 2011; **34**: 287–94. doi: <http://dx.doi.org/10.1007/s00270-010-9951-6>
 84. Barentsz MW, Vente MA, Lam MG, Smits ML, Nijssen JF, Seinsträ BA, et al. Technical solutions to ensure safe yttrium-90 radioembolization in patients with initial extra-hepatic deposition of (99m)technetium-albumin macroaggregates. *Cardiovasc Intervent Radiol* 2011; **34**: 1074–9. doi: <http://dx.doi.org/10.1007/s00270-010-0088-4>
 85. Burgmans MC, Kao YH, Irani FG, Dames EL, Teo TK, Goh AS, et al. Radioembolization with infusion of yttrium-90 microspheres into a right inferior phrenic artery with hepatic tumor supply is feasible and safe. *J Vasc Interv Radiol* 2012; **23**: 1294–301. doi: <http://dx.doi.org/10.1016/j.jvir.2012.07.009>
 86. Rhee TK, Omary RA, Gates V, Mounajjed T, Larson AC, Barakat O, et al. The effect of catheter-directed CT angiography on yttrium-90 radioembolization treatment of hepatocellular carcinoma. *J Vasc Interv Radiol* 2005; **16**: 1085–91. doi: <http://dx.doi.org/10.1097/01.RVI.0000177063.92678.21>
 87. Schelhorn J, Theysohn J, Ertle J, Schlaak JF, Mueller S, Bockisch A, et al. Selective internal radiation therapy of hepatic tumours: is coiling of the gastroduodenal artery always beneficial? *Clin Radiol* 2014; **69**: e216–22. doi: <http://dx.doi.org/10.1016/j.crad.2013.12.015>
 88. Theysohn JM, Müller S, Schlaak JF, Ertle J, Schlosser TW, Bockisch A, et al. Selective internal radiotherapy (SIRT) of hepatic tumors: how to deal with the cystic artery. *Cardiovasc Intervent Radiol* 2013; **36**: 1015–22. doi: <http://dx.doi.org/10.1007/s00270-012-0474-1>
 89. Burgmans MC, Too CW, Kao YH, Goh AS, Chow PK, Tan BS, et al. Computed tomography hepatic arteriography has a hepatic falciform artery detection rate that is much higher than that of digital subtraction angiography and 99mTc-MAA SPECT/CT: implications for planning 90Y radioembolization? *Eur J Radiol* 2012; **81**: 3979–84. doi: <http://dx.doi.org/10.1016/j.ejrad.2012.08.007>
 90. Schelhorn J, Ertle J, Schlaak JF, Mueller S, Bockisch A, Schlosser T, et al. Selective internal radiation therapy of hepatic tumors: procedural implications of a patent hepatic falciform artery. *SpringerPlus* 2014; **3**: 595. doi: <http://dx.doi.org/10.1186/2193-1801-3-595>
 91. Lhommel R, Goffette P, Van den Eynde M, Jamar F, Pauwels S, Bilbao JJ, et al. Yttrium-90 TOF PET scan demonstrates high-resolution biodistribution after liver SIRT. *Eur J Nucl Med Mol Imaging* 2009; **36**: 1696. doi: <http://dx.doi.org/10.1007/s00259-009-1210-1>
 92. Kao YH, Steinberg JD, Tay YS, Lim GK, Yan J, Townsend DW, et al. Post-radioembolization yttrium-90 PET/CT—part 1: diagnostic reporting. *EJNMMI Res* 2013; **3**: 56. doi: <http://dx.doi.org/10.1186/2191-219X-3-56>
 93. Kao YH, Tan AE, Lo RH, Tay KH, Tan BS, Chow PK, et al. Non-target activity detection by post-radioembolization yttrium-90 PET/CT: image assessment technique and case examples. *Front Oncol* 2014; **4**: 11. doi: <http://dx.doi.org/10.3389/fonc.2014.00011>

94. Keppke AL, Salem R, Reddy D, Huang J, Jin J, Larson AC, et al. Imaging of hepatocellular carcinoma after treatment with yttrium-90 microspheres. *AJR Am J Roentgenol* 2007; **188**: 768–75. doi: <http://dx.doi.org/10.2214/AJR.06.0706>
95. Riaz A, Kulik L, Lewandowski RJ, Ryu RK, Giakoumis Spear G, Mulcahy ME, et al. Radiologic-pathologic correlation of hepatocellular carcinoma treated with internal radiation using yttrium-90 microspheres. *Hepatology* 2009; **49**: 1185–93. doi: <http://dx.doi.org/10.1002/hep.22747>
96. Camacho JC, Kokabi N, Xing M, Prajapati HJ, El-Rayes B, Kim HS. Modified response evaluation criteria in solid tumors and European Association for The Study of the Liver criteria using delayed-phase imaging at an early time point predict survival in patients with unresectable intrahepatic cholangiocarcinoma following yttrium-90 radioembolization. *J Vasc Interv Radiol* 2014; **25**: 256–65. doi: <http://dx.doi.org/10.1016/j.jvir.2013.10.056>
97. Zerizer I, Al-Nahhas A, Towey D, Tait P, Ariff B, Wasan H, et al. The role of early ¹⁸F-FDG PET/CT in prediction of progression-free survival after ⁹⁰Y radioembolization: comparison with RECIST and tumour density criteria. *Eur J Nucl Med Mol Imaging* 2012; **39**: 1391–9. doi: <http://dx.doi.org/10.1007/s00259-012-2149-1>
98. Kao YH. General theory of predictive dosimetry for yttrium-90 radioembolization to sites other than the liver. *Cardiovasc Intervent Radiol* 2014; **37**: 1114–7. doi: <http://dx.doi.org/10.1007/s00270-013-0783-z>
99. *Pilot study of Selective Internal Radiation Therapy (SIRT) with yttrium-90 resin microspheres (SIR-Spheres microspheres) in patients with renal cell carcinoma (STX0110, "RESIRT")*. NSW, Australia: Sirtex Technology Pty Ltd. [cited 6 March 2015]. Available from: <http://www.australiancancertrials.gov.au/>.
100. Sharma RA, Van Hazel GA, Morgan B, Berry DP, Blanshard K, Price D, et al. Radioembolization of liver metastases from colorectal cancer using yttrium-90 microspheres with concomitant systemic oxaliplatin, fluorouracil, and leucovorin chemotherapy. *J Clin Oncol* 2007; **25**: 1099–106. doi: <http://dx.doi.org/10.1200/JCO.2006.08.7916>
101. Kosmider S, Tan TH, Yip D, Dowling R, Lichtenstein M, Gibbs P. Radioembolization in combination with systemic chemotherapy as first-line therapy for liver metastases from colorectal cancer. *J Vasc Interv Radiol* 2011; **22**: 780–6. doi: <http://dx.doi.org/10.1016/j.jvir.2011.02.023>
102. Cohen SJ, Konski AA, Putnam S, Ball DS, Meyer JE, Yu JQ, et al. Phase I study of capecitabine combined with radioembolization using yttrium-90 resin microspheres (SIR-Spheres) in patients with advanced cancer. *Br J Cancer* 2014; **111**: 265–71. doi: <http://dx.doi.org/10.1038/bjc.2014.344>
103. van Hazel GA, Heinemann V, Sharma NK, Findlay MPN, Ricke J, Peeters M, et al. SIRFLOX: randomized Phase III trial comparing first-line mFOLFOX6 (plus or minus bevacizumab) versus mFOLFOX6 (plus or minus bevacizumab) plus selective internal radiation therapy in patients with metastatic colorectal cancer. *J Clin Oncol* Feb 2016. Epub ahead of print. doi: <http://dx.doi.org/10.1200/JCO.2015.66.1181>
104. De Souza A, Daly KP, Yoo J, Saif MW. Safety and efficacy of combined yttrium 90 resin radioembolization with aflibercept and FOLFIRI in a patient with metastatic colorectal cancer. *Case Rep Oncol Med* 2015; **2015**: 461823. doi: <http://dx.doi.org/10.1155/2015/461823>