



# Clinical, dosimetric, and reporting considerations for Y-90 glass microspheres in hepatocellular carcinoma: updated 2022 recommendations from an international multidisciplinary working group

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Received: 21 April 2022 / Accepted: 23 August 2022 / Published online: 17 September 2022  
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## Abstract

**Purpose** In light of recently published clinical reports and trials, the TheraSphere Global Dosimetry Steering Committee (DSC) reconvened to review new data and to update previously published clinical and dosimetric recommendations for the treatment of hepatocellular carcinoma (HCC).

**Methods** The TheraSphere Global DSC is comprised of health care providers across multiple disciplines involved in the treatment of HCC with yttrium-90 (Y-90) glass microsphere–based transarterial radioembolization (TARE). Literature published between January 2019 and September 2021 was reviewed, discussed, and adjudicated by the Delphi method. Recommendations included in this updated document incorporate both the results of the literature review and the expert opinion and experience of members of the committee.

**Results** Committee discussion and consensus led to the expansion of recommendations to apply to five common clinical scenarios in patients with HCC to support more individualized efficacious treatment with Y-90 glass microspheres. Existing clinical scenarios were updated to reflect recent developments in dosimetry approaches and broader treatment paradigms evolving for patients presenting with HCC.

**Conclusion** Updated consensus recommendations are provided to guide clinical and dosimetric approaches for the use of Y-90 glass microsphere TARE in HCC, accounting for disease presentation, tumor biology, and treatment intent.

**Keywords** Radioembolization · Yttrium-90 · Dosimetry · Hepatocellular carcinoma

## Abbreviations

ALBI	Albumin-bilirubin
BCLC	Barcelona Clinic Liver Cancer
CT	Computed tomography
FLR	Future liver remnant
HBS	Hepatobiliary scintigraphy
HCC	Hepatocellular carcinoma
HIDA	Hepatobiliary iminodiacetic acid
MR	Magnetic resonance
MVI/PVT	Macrovascular invasion/portal vein thrombosis

NTAD	Normal tissue–absorbed dose
TAD	Tumor-absorbed dose
TARE	Transarterial radioembolization
Y-90	Yttrium-90

## Introduction

Over the past decade, there has been an increasing use of transarterial radioembolization (TARE) using yttrium-90 (Y-90) glass microspheres in patients with hepatocellular carcinoma (HCC) across the Barcelona Clinic Liver Cancer (BCLC) classification spectrum. Since the previous publication of clinical and dosimetric considerations for TARE with Y-90 glass microspheres, additional published work has demonstrated the critical role of personalized dosimetry, optimizing dosing and patient selection in achieving

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This article is part of the Topical Collection on Dosimetry

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improved clinical outcomes [1–3]. Additionally, several investigations demonstrated that increasing tumor-absorbed dose increases the likelihood of achieving complete pathologic necrosis, without compromising safety, while limiting toxicity by minimizing normal liver tissue exposure [4, 5]. These investigations have led to the inclusion of TARE in the updated BCLC staging system for treatment of single-HCC lesions  $\leq 8$  cm [6]. The decision to use single-compartment or multicompartiment dosimetry in these studies underscores the importance of matching the appropriate TARE treatment approach with specific patient characteristics and treatment goals [1–3]. Given the number of new trials, recent publications, and their rapid impact on clinical practice, the TheraSphere Global DSC was reconvened to evaluate these new data and to update the recommendations [7].

## Methods

The committee, comprised of interventional radiologists, radiation oncologists, nuclear medicine physicians, clinical scientists, medical oncologists, and physicists, reconvened for four 2-h virtual meetings, with an additional offline review in preparation for the process of updating the recommendations. During the first meeting, the committee reviewed the prior recommendations, recently published literature, and discussed updates. To identify literature since the prior recommendations, a PubMed search using a combination of the following search terms was conducted: transarterial radioembolization, TARE, brachytherapy, internal radiation therapy, SIRT, Y90, yttrium-90, TheraSphere, hepatocellular carcinoma, and HCC. The committee also considered whether new data warranted changing the degree of recommendation and/or the strength of consensus from the previous recommendations (Tables 1 and 2). Briefly, per the Delphi method, consensus was defined during virtual meetings as outlined in Table 2; strong disagreements by members were recorded and highlighted within the recommendation as caveats, where applicable. During the second and third meetings, committee members reviewed the revised recommendations and discussed each

**Table 2** Strength of consensus

Strength of consensus	Definition
Strong	$\geq 80\%$ consensus
Moderate	50–79% consensus
Weak	$\leq 49\%$ consensus

change collectively. Between the meetings, the lead author (RS) revised the recommendations based upon committee discussion and comments. The fourth and final meeting was a comprehensive review of the recommendations and a review of the draft manuscript. Steering committee members then had the opportunity to review and refine the manuscript independently, and final comments were incorporated into the manuscript by the lead author. All authors formally endorsed the manuscript and its recommendations prior to submission.

The reviewed literature included all published studies of TARE with glass microspheres for HCC since January 1, 2019; additional studies outside of this timeframe were reviewed if suggested by steering committee members. Publications addressing technical challenges rather than clinically oriented approaches were not included in the review. The recommendations included in this updated document incorporate both the critical literature review and the expert opinion and experience of members of the committee. All recommendations made in Tables 3, 4, 5, 6, and 7 are subject to regulatory and clinical standards within each country.

In light of the changing paradigms and treatment goals associated with Y-90 glass microsphere TARE, the committee agreed to expand the clinical scenarios from four to five, separating multifocal unilobar and bilobar disease recommendations, and to revise the definition of each. The scenarios subsequently addressed in the updated recommendations are as follows:

Curative intent:

- *Radiation segmentectomy*: Localized disease (one or multiple tumors located in  $\leq 2$  segments), with contemporary and modern treatment approaches delivering

**Table 1** Degree of recommendation

Degree	Meaning
A	Strongly recommended (good evidence that the measure is effective, and benefits outweigh the harms)
B	Recommended (at least moderate evidence that the measure is effective and that benefits exceed harms)
C	No recommendation for or against (at least moderate evidence that the measure is effective, but benefits are similar to harms and a general recommendation cannot be justified)
D	Recommended against (at least moderate evidence that the measure is ineffective or that harms exceed the benefits)
E	Insufficient, low quality, or contradictory evidence (the balance between benefit and harms cannot be determined)

**Table 3** Scenario 1: radiation segmentectomy recommendations using Y-90 glass microspheres

Treatment intent	Definitive therapy if non-transplant candidate (ex: solitary T1, solitary/multifocal UNOS T2–T3). Tumor control with potential for additional curative treatment in appropriately selected patients (ex: solitary/multifocal UNOS T1–T2–T3) for bridging/downstaging to transplantation
Patient selection	<ol style="list-style-type: none"> <li>1. Child–Pugh A and select B7, tumor stage UNOS T1–T3 (may consider Child–Pugh B7–C [rare scenario] if bridging or downstaging to transplant and segmental infusion possible) [5, 15, 29, 54–58]</li> <li>2. Treatment may be performed in patients with prior liver therapy (i.e., surgical resection, ablation, external beam radiation therapy, or stereotactic body radiation therapy) [5, 15, 56, 59]. In patients with prior chemoembolization, angiographic assessment of vascular supply and patency during mapping angiography will determine TARE eligibility. While patients can receive Y-90 glass microsphere TARE after external beam radiation therapy or stereotactic body radiation therapy, more data is needed to determine efficacy and safety. Early data suggests it is safe in patients with preserved liver function</li> <li>3. Tumors abutting the colon, gallbladder, and stomach can be safely treated; radiation toxicity in this specific setting of adjacent structures has been reported but is extremely rare [60]</li> <li>4. Multiple radiation segmentectomy infusions in two separate Couinaud segments may be performed for multifocal disease during the same session, including two segments that would define a bilobar disease in patients with normal underlying liver or well-compensated cirrhosis (ex: 1 lesion in segment 6, 1 lesion in segment 2) [15, 16]. Historically, radiation segmentectomy was defined as <math>\leq 2</math> segments; however, current definitions include infusion of Y-90 glass microspheres to much smaller segments of liver, referred to as angiosomes, with the intent of delivering ablative dose to tissue. Recent investigations have reported Y-90 glass microsphere TARE infusion in up to 25% in ALBI-1 with excellent tolerability and noted additional liver toxicities above 14% in ALBI-2 and Child–Pugh B patients [17]</li> <li>5. In patients with previous hepatectomy, the choice to use radiation segmentectomy should be approached with caution considering remaining FLR and potential toxicity. Pretreatment considerations would include the magnitude of post-hepatectomy hypertrophy, time from resection to recurrence, and the total volume of liver parenchyma. Therefore, the use of radiation segmentectomy in this setting requires further investigation</li> </ol>
Treatment planning	
Diagnostic studies and target volume definition	<p>Diagnostic imaging should ideally be multiphase contrast-enhanced magnetic resonance (MR) [61]; contrast-enhanced computed tomography (CT) can also be used. Both imaging modalities are considered acceptable</p> <ol style="list-style-type: none"> <li>1. Determine angiosome volume by cone-beam CT; this is the gold standard for perfused volume determination and preferred method when available [3, 18, 19]</li> <li>2. If there is associated segmental portal venous invasion, treat the territory that encompasses the MVI/PVT confirmed by cone-beam CT [15]</li> <li>3. If there is a suspicion of microsatellite lesions, treat a wider territory (i.e., the larger the lesion, the wider the safety margin necessary) confirmed by cone-beam CT; an angiographic/cone-beam CT margin of <math>\geq 1</math> cm is recommended [62]</li> </ol>
Mapping and $^{99m}\text{Tc}$ -MAA	<ol style="list-style-type: none"> <li>1. The need for prophylactic embolization is very low (unless distal branch from infusion site leads to the gastrointestinal tract) (e.g., left hepatic artery injection with accessory left gastric artery arising distally, left hepatic artery injection with esophageal branch arising distally) [63]</li> <li>2. Perform lobar technetium-99 m macroaggregated albumin (<math>^{99m}\text{Tc}</math>-MAA) and segmental Y-90 infusion to limit the number of catheterizations of the small segmental branch perfusing tumor [16]</li> <li>3. Elevated lung shunt fraction limiting the intended dose is rarely an issue because of minimal tumor load (low shunting) and limited prescribed activities (small, perfused volumes) [16]. In the case of small tumors (i.e., those less than 5 cm) and in the absence of MVI/PVT, the risk of high lung shunt is low. In such cases, it may be possible to eliminate the <math>^{99m}\text{Tc}</math>-MAA mapping step from the treatment planning process [16, 64]; however, more studies evaluating this concept are needed. In such cases, dosimetry is still required for dose determination. No formal recommendation on eliminating the <math>^{99m}\text{Tc}</math>-MAA can be made at this time</li> </ol>

**Table 3** (continued)

Treatment intent	Definitive therapy if non-transplant candidate (ex: solitary T1, solitary/multifocal UNOS T2–T3). Tumor control with potential for additional curative treatment in appropriately selected patients (ex: solitary/multifocal UNOS T1–T2–T3) for bridging/downstaging to transplantation
Dose calculation and dosimetry considerations	<ol style="list-style-type: none"> <li>1. Single-compartment model dosimetry is adequate and preferred [3]</li> <li>2. Target-absorbed dose to the perfused treatment volume of at least 400 Gy to the angiosome with no established upper limit. A median of 400 Gy resulted in 100% of patients achieving complete pathologic necrosis in tumor explants [3, 4]. Similar results using &gt; 500 Gy to the perfused volume were reported [29]. Prospective validation demonstrates an adverse event profile that is minimal using this approach [20]</li> <li>3. Recent publications have demonstrated that higher doses to the segment <math>\geq 400</math> Gy yield better pathologic and clinical outcomes [3, 16, 42]. An upper threshold dose limit may exist, but it is currently unknown based on the available literature. In case of a small, treated volume, the dose is oftentimes determined by the lowest available vial (i.e., 3 GBq at calibration)</li> <li>4. Recommend week 1 (Wednesday/Thursday/Friday) or early week 2 dosing (Monday/Tuesday) to replicate published outcomes [3, 11]. With glass microspheres, there is preliminary data to suggest that late first-week and early second-week microsphere-specific activity (estimated <math>\geq 297</math> Bq) may be associated with increased pathologic necrosis in small tumors treated with radiation segmentectomy [1, 42]</li> </ol>
Treatment delivery	<ol style="list-style-type: none"> <li>1. Ensure no contrast refluxes into an adjacent angiosome prior to treatment</li> <li>2. The entire tumor (and microspheres) should lie within the perfused angiosome</li> <li>3. Prime the TheraSphere® injection system slowly <ol style="list-style-type: none"> <li>a). There is a low margin of error in radiation segmentectomy given the small territory</li> <li>b). Prime the system slowly to minimize the risk of bubble formation</li> </ol> </li> <li>4. Consider a 2.1/2.4 French (or smaller) microcatheter in a segmental branch. Exercise caution if using smaller than 2 French due to a risk of incomplete administration [12, 65]</li> <li>5. Same-day planning <math>^{99m}\text{Tc}</math>-MAA and treatment approaches may be considered (i.e., low activity administration needed for high absorbed dose, with a very low chance of high lung-absorbed dose) [16, 64]</li> </ol>
Outcome assessment/follow-up	<ol style="list-style-type: none"> <li>1. Ideally, use the same imaging modality that was used for initial assessment of disease burden (contrast-enhanced CT or multiphase contrast-enhanced MR)</li> <li>2. If complete mRECIST response at 3–6 months is not achieved, consider retreatment [3, 15, 66, 67]</li> </ol>
Strength of recommendation	A
Degree of consensus	Strong

superselctively to subsegments of liver, referred to as angiosomes (i.e., hepatic territory perfused by a specific branch of the hepatic artery), with the intent of delivering an ablative dose to tumor and normal tissue. Radiation segmentectomy no longer narrowly defined as  $\leq 2$  segments but rather inclusive of smaller hepatic segmentectomy

- *Radiation lobectomy*: Unilobar disease, with the ultimate goal of disease control and contralateral lobar hypertrophy in the context of small future liver remnant (FLR), as a bridge to surgery (resection)

#### Palliative intent:

- Multifocal unilobar disease without macrovascular invasion or portal vein thrombosis (MVI/PVT), with the goal of palliation and delay in progression; in select patients, intent may be conversion to curative options
- Multifocal bilobar disease without MVI/PVT, with the goal of palliating and delaying progression, usually in combination or in sequence with systemic treatment

- HCC with MVI/PVT, with the goal of palliating and delaying progression; in select patients, intent may be conversion to curative options

Key definitions used throughout this document were defined in the original publication and are reprinted below for ease of reference [7]:

- *Mean absorbed dose*: Quantity is expressed in gray (Gy) in order to describe the average energy (J) deposited within a volume of interest (VOI) within a specific given mass (kg). The mean absorbed dose is referred to as “Dose” and is distinctly different than “Activity” or “Dosage” (GBq) [8, 9].
- *MIRD schema*: The Medical Internal Radiation Dose (MIRD) schema is applicable to both the single-compartment and multicompartment dosimetry models. The mean absorbed dose ( $D$ ) in any specific VOI (i.e., perfused volume, lobe, tumor or normal tissue) with mass of any VOI, denoted as  $M$ , with the assumption that  $D$  is distributed uniformly in each volume with

**Table 4** Scenario 2: radiation lobectomy recommendations using Y-90 glass microspheres

Treatment intent	To increase the number of patients who can undergo curative surgical resection given limited organ availability for liver transplantation (ex: UNOS T2-T3, unilobar T4a) [21–24]
Patient selection	<ol style="list-style-type: none"> <li>Radiation lobectomy applies to unresectable Child–Pugh A patients in the following scenarios: <ol style="list-style-type: none"> <li>Inadequate FLR and/or</li> <li>Test of time is desired for tumor biology and response prior to surgery and/or</li> <li>Need for the treated tumor to be retracted away from hepatic vein and/or IVC</li> <li>Potential delay of surgery or definitive treatment instead of surgery</li> </ol> </li> <li>Borderline resectable patients are considered, and therefore should not have comorbidities that would preclude surgery</li> </ol>
Treatment planning	
Diagnostic studies and target volume definition	1. Contrast-enhanced cone-beam CT in the angiography suite should be performed to assess/ensure tumor coverage within the treated lobe
Mapping and <sup>99m</sup> Tc-MAA	<ol style="list-style-type: none"> <li>Perform lobar <sup>99m</sup>Tc-MAA and lobar Y-90 infusion. Catheter placements should be to facilitate similar distribution pattern</li> <li>Elevated lung dose may be an issue if the lung shunt fraction is high in the context of large perfused volume</li> </ol>
Dose calculation and dosimetry considerations	<ol style="list-style-type: none"> <li>Using a multicompartiment model with <sup>99m</sup>Tc-MAA, a recent randomized study demonstrated that tumor response in patients with <math>\geq 30\%</math> hepatic reserve is optimized and overall survival extended when the minimum planned tumor-absorbed dose is <math>\geq 205</math> Gy (with a mean of 331 Gy) and normal tissue-absorbed dose (NTAD) is <math>\leq 120</math> Gy attained by treating on week 1 (Wednesday) [1]. A minimum threshold absorbed dose of normal injected liver <math>&gt; 88</math> Gy with week 1 (Wednesday) dosing in Child–Pugh A patients ensures a minimum 10% hypertrophy [25]. As an alternative planning criterion, a retrospective study of normal tissue complication probability determined the maximum tolerable dose for Child A patients at 50 Gy or 90 Gy whole non-tumoral liver (including perfused and non-perfused normal liver) with a bilirubin level <math>\geq 1.1</math> mg/dL or <math>&lt; 1.1</math> mg/dL, respectively, using 4-day decay, to minimize hepatic dysfunction [41]</li> <li>If using a single-compartment model, a 140–150 Gy lobar absorbed dose limit is recommended given implied Child–Pugh A status for radiation lobectomy patients [21, 25]. A recent randomized study demonstrated that for well-selected patients (Child–Pugh A and hepatic reserve <math>&gt; 30\%</math>), targeting a lobar absorbed dose <math>&gt; 150</math> Gy (with a mean of 178 Gy) with a whole liver dose <math>&lt; 150</math> Gy, by treating on week 1 (Wednesday), for well-selected patients (Child–Pugh A and hepatic reserve <math>&gt; 30\%</math>) was safe and can be used [1]. Retreatment should be considered if minimal hypertrophy is noted at months 1–3</li> <li>Existing literature supports treatment on week 1 (Wednesday) to week 2 (Tuesday). No optimal day has been identified [21, 22, 68]</li> <li>Repeated treatment of the same volume has been performed and is safe when carefully considering dosimetry and liver function</li> </ol>
Treatment delivery	<ol style="list-style-type: none"> <li>Radiation lobectomy is most commonly encountered with right lobe HCC. Treat the right lobe tumor and induce left lobe hypertrophy in anticipation of surgery [21, 22, 24, 69, 70]</li> <li>Treatment should be administered in a lobar manner (i.e., such that the entire lobe is treated). If segmental treatment might otherwise be technically feasible but the goal is for contralateral lobar hypertrophy to bridge to resection, one can consider “modified” radiation lobectomy, where a single-session segmental tumor infusion (single-compartment dose to segment <math>\geq 400</math> Gy; radiation segmentectomy, see previous section) is followed by lobar infusion, with the second vial delivering single-compartment 100 Gy to the lobe for hypertrophy [3, 21, 71] <ol style="list-style-type: none"> <li>Modified radiation lobectomy is favored over single lobar infusion when technically feasible</li> <li>In the setting of a), if patient does not undergo surgery, tumor control has been maximized by performing curative high absorbed dose segmentectomy treatment</li> </ol> </li> </ol>

**Table 4** (continued)

Treatment intent	To increase the number of patients who can undergo curative surgical resection given limited organ availability for liver transplantation (ex: UNOS T2-T3, unilobar T4a) [21–24]
Outcome assessment/follow-up	<ol style="list-style-type: none"> <li>1. Imaging with dynamic assessment of FLR is recommended at 1 month, 3 months, 6 months, and 9 months after treatment. Tumor volume should be subtracted from total right lobe volume when calculating FLR</li> <li>2. Allow at least 3–6 months for hypertrophy; a longer wait time is acceptable as long as the tumor is well controlled [25, 27, 69]</li> <li>3. Portal vein embolization after lack of hypertrophy from Y-90 radioembolization is currently investigational [22, 24]. Radioembolization after portal vein embolization is also investigational [22]</li> <li>4. Pre- and post-TARE hepatobiliary scintigraphy or Eovist® (USA) or Primovist® (EU) (gadolinium-EOB-DTPA) using MRI to further determine if adequate FLR was attained, if additional treatment is required, or if the patient is ultimately suitable for subsequent surgical resection is investigational [27–29]</li> <li>5. The decision to proceed with resection post TARE is jointly decided upon with surgeons. In some cases, resection may be deemed unnecessary given complete tumor response and radiation lobectomy becomes definitive treatment [21, 24]</li> </ol>
Strength of recommendation	B
Degree of consensus	Strong

permanent microsphere implantation and no biological clearance [10, 11]. Using this schema,  $D$  in a VOI is computed as:

where  $A$  is the net activity of  $^{90}\text{Y}$  implanted in the VOI, and  $F$  is the lung shunt fraction. As an example, if 2.2 GBq of glass microspheres was infused with a residual of 1% and a lung shunt of 5%, the net implanted activity in the liver tissue would be  $2.2 \times (0.99) \times (0.95) = 2.07$  GBq, and 2.07 GBq would represent the final activity within a MIRD formula for determining final tissue dose.

$$D_{(\text{Gy})} = \frac{A_{(\text{GBq})} \times (50_{(\text{Gy/kg/GBq})}(1 - F))}{M_{(\text{kg})}}$$

- **Single-compartment model:** A MIRD dosimetry model that assumes the  $^{90}\text{Y}$  microspheres (and therefore absorbed dose) are distributed uniformly within the VOI. In this model, only a uniform averaged  $D$  value over the VOI is calculated, without consideration of Y-90 activity distribution within the tumor and normal parenchyma. In reality, hypervascular tumors will absorb more microspheres and receive a higher dose, while the normal hepatic tissue will absorb fewer spheres and receive a lower dose [12–14].
- **Multicompartment model:** A MIRD-based dosimetry approach where  $D$  is determined in more than one VOI, such as the tumor VOI and the normal parenchyma VOI. The lung also represents another compartment to which  $D$  can be estimated (based on a single-compartment model). Partition modeling refers to the multicompartment dosimetry approach reporting the tumoral

and non-tumoral doses separately with a single averaged tumor to averaged non-tumoral uptake ratio (T:N ratio) [10].

## Results

Relevant publications from the literature review, including additional suggestions by the committee, resulted in the inclusion of 31 new publications [1–6, 16, 17, 19, 20, 24–26, 28–31, 35, 36, 41, 47, 48, 50–58] and formed the basis for updates to the recommendations.

## Clinical scenarios

### Scenario 1: radiation segmentectomy for HCC

Radiation segmentectomy has been previously defined as the administration of Y-90 to  $\leq 2$  Couinaud segments with curative intent. In practical terms, this translates to subselective or superselective radioembolization. In most scenarios, a superselective, subsegmental infusion covering significantly  $\leq 1$  is achieved [15, 16]. For radiation segmentectomy, the percentage total liver volume that is treated should be considered. As long as a minimal amount of tissue is exposed, radiation segmentectomy may be considered in the setting of prior surgical resection (particularly if robust post-surgical hypertrophy has been observed). In the presence of stable but reduced hepatic function, radiation segmentectomy should be undertaken using caution and consideration of alternate options [3, 17–19]. Details are included in Table 3.

**Table 5** Scenario 3: multifocal unilobar HCC without macrovascular invasion recommendations using Y-90 glass microspheres

Treatment intent	Palliation and delaying disease progression ahead of initiation of systemic therapy or downstaging to resection. The goal should be to provide optimal tumor-absorbed dose and keep NTAD below a safe ceiling for the following reasons: a) Many patients are treated with palliative intent due to a multifocal disease within a single lobe b) Liver function should be preserved in order that subsequent treatment is potentially possible (e.g., surgery after downstaging, repeat radioembolization, chemoembolization, local ablative therapies, systemic therapy) [21, 22, 72]
Patient selection	1. Patients should have Child–Pugh A or B7 cirrhosis. The committee recommends that multidisciplinary discussions and individualized patient characteristics be considered prior to considering treatment with Y-90 glass microspheres, especially in patients more severe hepatic dysfunction [1, 23, 30–32, 45, 46]
Treatment planning	
Mapping and <sup>99m</sup> Tc-MAA	Injection of <sup>99m</sup> Tc-MAA in the lobar hepatic artery in order to perfuse the entire lobe
Dose calculation and dosimetry considerations	1. If possible, multicompartment dosimetry model is preferred over a single-compartment model to maximize tumor-absorbed dose and evaluate normal parenchyma absorbed dose [1, 41] 2. In a multicompartment model, prediction of the normal liver absorbed dose is typically more accurate than the tumor-absorbed dose, especially for small tumors. A recent randomized study demonstrated that tumor response in patients with ≥ 30% hepatic reserve is optimized and overall survival extended when the minimum tumor-absorbed dose is ≥ 205 Gy, with > 250 Gy where possible (with a mean of 331 Gy), and NTAD is ≤ 120 Gy attained by treating on week 1 (Wednesday) [1]. Although there are several investigations looking into the upper limit of dose to normal parenchyma averaged over the whole liver (examples, 50 Gy or 90 Gy whole liver with a bilirubin level ≥ 1.1 mg/dL or < 1.1 mg/dL, respectively, using 4-day decay), this continues to be investigational [41] 3. Optimal tumor-absorbed dose (i.e., dose associated with response) is ≥ 205 Gy, with > 250 Gy where possible (with a mean of 331 Gy) [1, 32, 39, 55, 73]. This is only feasible if the multicompartment model can be applied. Recent publications demonstrated that tumor response and median overall survival improved with increasing tumor-absorbed dose [1, 2]
Treatment delivery	1. Single-compartment dosimetry supports 120–150 Gy to the perfused lobe [1, 13] 2. Multicompartment dosimetry supports a minimum tumor-absorbed dose of ≥ 205 Gy, with > 250 Gy where possible (with a mean of 331 Gy) treating on week 1 (Wednesday) [1]. Treatment between week 1 (Wednesday) and week 2 (Tuesday) is acceptable 3. The decision on perfused volume or tumor and NTAD should be based on treatment intent relative to clinical status, liver function, tumor load, targeting, vascularity, and previous treatments [39]
Outcome assessment/follow-up	1. Multiphase CT or MR should be performed every 3 months following treatment with consideration for FLR, hypertrophy, candidacy for surgical resection, and/or systemic therapy. In the palliative intent setting, caution is warranted with an overly aggressive approach to retreatment in patients with stable disease or partial response. Retreatment in the form of radioembolization, chemoembolization, or systemic therapy should typically be considered only in the setting of progressive disease. Empirically initiating systemic therapy following partial or complete response, or stable disease, remains investigational and should be individualized
Strength of recommendation	B
Degree of consensus	Strong

The objective is ablative dosing for both tumoral and non-tumoral compartments as both are expendable in this scenario [3]. The strength of these recommendations was an A in the previous version and remains an A with a strong degree of consensus from the committee; this recommendation was further reinforced by the findings of the prospective RASER study [20]. Partition dosimetry was not recommended by the panel in this scenario.

### Scenario 2: radiation lobectomy for HCC

In unilobar HCC patients, resection is often not possible due to small FLR. For these patients, radiation lobectomy may be an option, as delivery of a high dose of radiation to one lobe may trigger the hypertrophy-atrophy complex, inducing

hypertrophy in the contralateral lobe and thereby increasing the functional liver volume while controlling tumor growth in the treated lobe (Table 4) [21–24]. The increased FLR may allow for subsequent curative resection.

Depending on patient biology and mapping results, either single-compartment or multicompartment dosimetry approaches may be used [1, 21, 25, 26]. Hepatobiliary scintigraphy (HBS), including <sup>99m</sup>Tc-iminodiacetic acid (HIDA) or <sup>99m</sup>Tc-mebrofenin, and the use of Eovist/Primovist contrast media in magnetic resonance imaging are emerging investigational techniques that are being implemented for regional functional assessment of the FLR before and after Y-90 treatment. Additional data are needed to support a strong recommendation of their use as a standard of care in radiation lobectomy and resection planning [27–29]. The strength of these recommendations was previously

**Table 6** Scenario 4: multifocal bilobar HCC without macrovascular invasion recommendations using Y-90 glass microspheres

Treatment intent	Palliation and delaying disease progression. The goal should be to provide sufficient tumor-absorbed dose and keep NTAD dose below a safe ceiling for the following reasons: a) Most patients are treated with palliative intent due to late-stage disease with diffuse multifocal lesions with or without large tumor load in both lobes requiring higher exposure to normal tissue to effectively treat [35] b) Liver function should be preserved to permit subsequent treatment using repeat radioembolization, chemoembolization, or systemic therapy [24, 35, 36]
Patient selection	1. Bilobar HCC patients for Y-90 should have Child–Pugh A cirrhosis and appropriate performance status. At least 30% hepatic reserve is ideal [45, 46]
Treatment planning	
Mapping and <sup>99m</sup> Tc-MAA	1. Multiple variations of <sup>99m</sup> Tc-MAA administration exist. Options include: a) Injection of <sup>99m</sup> Tc-MAA in the proper hepatic artery in order to perfuse the entire liver b) Injection in the lobe with higher tumor burden (yields most conservative estimate) c) Injection in both lobes with a split vial of <sup>99m</sup> Tc-MAA into RHA and LHA, respectively d) Sequential lobar infusion of <sup>99m</sup> Tc-MAA requiring 2 separate mapping angiogram procedures on separate days (most accurate for multicompartment dosimetry)
Dose calculation and dosimetry considerations	1. A multicompartment dosimetry model is preferred over single compartment to evaluate normal parenchyma-absorbed dose relative to treatment intent [1, 35, 41] 2. In a multicompartment model, prediction of the normal liver absorbed dose is typically more accurate than the tumor-absorbed dose, especially for small tumors [41, 43]. Targeting from 40 to 70 Gy absorbed dose to the entire normal liver tissue may be performed safely in a Child–Pugh A patient [35, 74–77]. Additional data is needed to identify the appropriate post-calibration day of treatment 3. Contemporary techniques use multicompartment dosimetry in this population to achieve optimal results [35, 47]. Optimal tumor-absorbed dose (i.e., dose associated with response) is $\geq 205$ Gy, with $> 250$ Gy where possible (with a mean of 331 Gy) [1, 32, 39, 55, 73]. This is only feasible if the multicompartment model can be applied 4. Single-compartment dosimetry supports 120 Gy (range 80–150 Gy) to the perfused tissue [13]. The decision on absorbed dose should be based on clinical status, liver function, tumor load, targeting, vascularity, and previous treatments
Treatment delivery	1. To treat bilobar disease, the treating physician has the discretion to choose single-session bilobar or staged sequential lobar treatment [35]. In general, staged sequential lobar treatment is preferred and the lobe with more extensive disease should be treated first. Second treatment, if stage approach is adopted, is recommended at 4–8 weeks once liver function tests are assessed [31, 41, 47, 78]. For highly aggressive bilobar disease in a patient with Child–Pugh A cirrhosis and with good tumor targeting on <sup>99m</sup> Tc-MAA (i.e., high tumor-absorbed dose; low normal liver absorbed dose), single-session bilobar treatment (2 unilobar injections) based on multicompartment dosimetry can be considered [35, 47]. Multidisciplinary discussions are recommended to include the use of systemic therapy in aggressive biology disease.
Outcome assessment/follow-up	1. Multiphase CT or MR should be performed every 3 months following treatment. Given the palliative intent in this setting, caution is warranted with an overly aggressive approach to retreatment in patients with stable disease or partial response. Retreatment in the form of radioembolization, chemoembolization, or systemic therapy should typically be considered only in the setting of progressive disease. Empirically initiating systemic therapy following partial or complete response, or stable disease, remains investigational and should be individualized
Strength of recommendation	B
Degree of consensus	Strong

a B with strong consensus from the committee; despite these additional studies and data, the committee deemed the data to be insufficient to raise the grade to A and maintained the grade of B with strong consensus.

### Scenario 3: multifocal unilobar HCC without macrovascular invasion (MVI/PVT)

For patients with multifocal unilobar disease without MVI/PVT, radioembolization can be used for palliation and prevention of disease progression (Table 5). In this population, the goal should be to maximize tumor dose

while preserving liver function. The committee recommends that radioembolization be used for Child–Pugh A patients and that a multidisciplinary tumor board review be conducted, especially for Child–Pugh B patients who have more severe hepatic dysfunction [1, 23, 30–32]. In select cases, this group of patients may be considered for resection if they exhibit responses and hypertrophy features of radiation lobectomy.

Previously, multifocal unilobar and bilobar diseases were grouped together and granted a B grade with a strong committee consensus; this newly created unilobar disease



**Table 7** Scenario 5: HCC with macrovascular invasion recommendations using Y-90 glass microspheres

Treatment intent	Palliation and enabling disease control, combining and/or bridging to systemic treatment. Surgical conversion or downstaging may be possible [1, 34, 35]
Patient selection	<ol style="list-style-type: none"> <li>1. Child–Pugh A patients with good tumor and MVI/PVT targeting and low NTAD can be considered when locoregional therapy is selected prior to the initiation of systemic therapy [1, 34–36, 45, 46]. Those with unilobar MVI/PVT should be considered for TARE, with early consideration for systemic therapy. Patients with bilobar MVI/PVT should be considered for upfront systemic therapy, especially if associated with CP B disease; these patients are unlikely to benefit from initial treatment with TARE</li> <li>2. Treatment can be considered for segmental, lobar, or branch MVI/PVT, with follow-up imaging dictating when to consider adding systemic therapy. For main MVI/PVT with good targeting, <math>\geq 30\%</math> hepatic reserve, and unilobar treatment, some patients may benefit from TARE; however, early (1 month) post-Y-90 combination with systemic agents may be an option for this population [1, 34, 35, 37–39]</li> <li>3. Larger tumors (e.g., <math>&gt; 10</math> cm) with MVI/PVT have been effectively treated with glass microsphere TARE using multicompartiment dosimetry [1, 37, 39]</li> </ol>
Treatment planning	
Diagnostic studies and target volume definition	1. Treatment should be performed in a location that is proximal enough to perfuse all feeding vessels both into the tumor and to the tumor thrombus. The use of contrast-enhanced cone-beam CT during angiographic mapping can aid in detection of MVI/PVT perfusion
Mapping and $^{99m}\text{Tc}$ -MAA	1. $^{99m}\text{Tc}$ -MAA MVI/PVT targeting evaluation should be performed [1, 39, 79]
Dose calculation and dosimetry considerations	<ol style="list-style-type: none"> <li>1. Multicompartiment dosimetry is preferred to maximize sparing of normal parenchyma [1, 35, 40]. This approach may be challenging in the setting of infiltrative disease, where tumor and normal parenchyma cannot be differentiated</li> <li>2. For the multicompartiment model, a recent randomized study demonstrated that tumor response in patients with <math>\geq 30\%</math> hepatic reserve is optimized and overall survival extended when the minimum tumor-absorbed dose is <math>\geq 205</math> Gy, with <math>&gt; 250</math> Gy where possible (with a mean of 331 Gy), and NTAD is <math>\leq 120</math> Gy, attained by treating on week 1 (Wednesday) [1]. The ideal candidate has good MVI/PVT <math>^{99m}\text{Tc}</math>-MAA targeting (treatment intensification), as a suboptimal response is likely if there is no <math>^{99m}\text{Tc}</math>-MAA MVI/PVT targeting or tumor-absorbed dose is <math>&lt; 205</math> Gy [39]. In such cases, advanced angiographic techniques may be attempted, e.g., boost dosing, if specific vessels can be identified. The use of systemic therapy in patients without significant uptake on MAA should also be strongly considered [1, 40]. Multicompartiment dosimetry with good MVI/PVT and tumor targeting may be considered to downstage patients to surgery. Preservation of FLR function is a key consideration [1, 39]</li> </ol>
Treatment delivery	<ol style="list-style-type: none"> <li>1. An aggressive dosing approach (similar to radiation lobectomy) can be used for unilobar disease and Child–Pugh A liver function if lung shunt fraction permits</li> <li>2. A more conservative approach, including treatment planning using multicompartiment dosimetry, or consideration of systemic therapy, should be used for bilobar disease (similar to patients with multifocal bilobar HCC), especially when portal perfusion of a large portion of the functional liver is compromised by tumor invasion [35]</li> </ol>
Outcome assessment/follow-up	Multiphase CT/MR should be performed every 3 months following treatment. Systemic therapy or enrollment into clinical trials should be considered for patients who not only demonstrate progression but should also be considered in the setting of stable disease in order to prolong time to progression and capitalize on the combination effect of locoregional and systemic therapies. Given the palliative intent in this setting, caution is warranted with an overly aggressive approach to retreatment in patients with stable disease or partial response
Strength of recommendation	A
Degree of consensus	Moderate

section has been given a grade of B with strong committee consensus.

#### Scenario 4: multifocal bilobar HCC without MVI/PVT

In multifocal bilobar HCC without MVI/PVT, the primary goals of treatment are frequently palliation, delaying disease progression, and sequencing with other liver-directed therapies and/or systemic treatment (Table 6). As with

other clinical scenarios, the goal should be to maximize the dose of radiation delivered to the tumor while minimizing the dose to remaining normal liver parenchyma. Previously, multifocal unilobar and bilobar diseases were grouped together and given a grade of B with a strong committee consensus; this newly created bilobar disease section has been given a grade of B with strong committee consensus.

### Scenario 5: HCC with MVI/PVT

Patients with portal vein thrombosis (MVI/PVT), indicative of advanced HCC, generally have a poor prognosis. Such patients are not usually considered transplantation or resection candidates and may not achieve optimal outcomes with chemoembolization [1, 33–35]. With careful patient selection and dosimetric planning, radioembolization may achieve a long-term durable response without compromise of hepatic function in this population (Table 7) [1, 34–39]. The committee recommended a shift in defining which patients with MVI/PVT should be selected for treatment with Y-90 glass microsphere TARE, narrowing from previous broader recommendations to those who are Child–Pugh A5 or A6 (except in the case of segmental MVI/PVT where radiation segmentectomy may be considered [1, 34–36]). Multicompartment dosimetry is preferred in these patients to ensure that the maximum tumor-absorbed dose (TAD) is achieved while minimizing the dose to the normal tissue-absorbed dose (NTAD) and allowing the assessment of MVI/PVT targeting evaluation during pretreatment planning [1, 35, 40]. As with the approaches discussed earlier, an adequately high specific activity (the amount of radioactivity per microsphere at the time of administration) is important to achieve a desired TAD in the MVI/PVT with potentially limited microsphere deposition [1]. Given data from this and other recent studies, the committee chose to increase the degree of recommendation from B to A, with a moderate degree of committee consensus.

### Discussion

Results from over 30 manuscripts and abstracts published since 2019 prompted an update to treatment recommendations for Y-90 glass microsphere-based TARE in HCC patients; these included the DOSISPHERE-01, LEGACY, and TARGET studies [1–3]. While previous studies highlighted the improved overall survival in patients achieving complete response upon imaging, data from the recent DOSISPHERE-01 and TARGET studies further established associations between TAD, tumor response, and overall survival [1, 2]. For patients with limited disease, ablative Y-90 TARE remains the most effective and well-tolerated treatment option in eligible patients. Important new updates to the recommendations based on recent publications include more specific dosimetric recommendations for radiation segmentectomy and lobectomy, separating multifocal unilobar and bilobar diseases into different sets of recommendations and providing context in which Y-90 glass microsphere TARE should be used for patients with portal vein thrombosis. Additional multicompartment dosimetry updates included proposed new thresholds for tumor and NTAD

and incorporated the impact of underlying liver function [3, 4, 41–43]. Multiple publications focused on the utility of  $^{99m}\text{Tc}$ -MAA imaging to estimate Y-90 glass microsphere distribution confirm the distribution of treatment and whether to select tumor or NTAD as the primary driver in choosing the appropriate Y-90 activity using multicompartment dosimetry [1, 41, 43].

### Ablative dosing approaches in radiation segmentectomy

Recent publications, including LEGACY and its companion publications, have reported on higher selective treatment-absorbed doses for radiation segmentectomy [3, 4, 42]. Higher absorbed dose in selective ablative Y-90 glass microsphere TARE led to increased rates of complete pathologic necrosis, e.g.,  $\geq 400$  Gy; complete and extensive pathologic necrosis have been shown to be associated with reduced recurrence in patients bridging to transplant [5, 42]. However, a maximum perfused volume-absorbed dose has not yet been identified. Recent publications also refined guidance for albumin-bilirubin (ALBI)-1/Child–Pugh A and ALBI-2/Child–Pugh B patients from up to 2 Couinaud segments to specific volume recommendations [17]. The use of cone-beam CT or angio-CT with selective intra-arterial contrast enhancement provides the best preprocedural volume definitions for accurate dosimetry calculations, provides the most accurate arterial flow assessing for non-target flow and coverage of microsatellites, and ensures dose target accuracy [19].

### Improving conversion to resection

Recent studies and published recommendations have demonstrated the utility of personalized dosimetry in converting unresectable patients to candidates for resection [1, 3, 4, 21, 23, 25, 44]. Some recent publications showed that such an approach not only increased overall tumor response, but approximately doubled response rates when the TAD exceeded 300 Gy [1, 3]. In one of these investigations, multicompartment dosimetry used in multifocal unilobar HCC with or without MVI/PVT offered superior conversion of unresectable HCC compared to standard lobar single-compartment dosimetry (36% versus 4%, respectively) [1]. Single-compartment dosimetry using radiation lobectomy or modified lobectomy imparts local tumor control and contralateral lobe hypertrophy as a bridging strategy prior to resection. Collectively, these data demonstrated that treatment efficacy outcomes exhibit a continuum of improvement as TAD is escalated [3, 4, 21, 23]. Select studies provide guidance on the NTAD maximum and support evaluation of liver function, i.e., baseline bilirubin, prior to selecting NTAD targets [41]. Treatment outcome data regarding the

use of NTAD to guide Y-90 glass microsphere activity selection are limited; further clinical data is needed to strengthen recommendations.

### **Differing treatment approaches for unilobar and bilobar HCC**

Based on approvals of new systemic treatment options, the committee decided to divide unilobar and bilobar diseases without MVI/PVT into two separate clinical scenarios [30]. Systemic therapy is the current standard of care for advanced disease; however, it is important to consider TARE early in treatment planning, as it plays an important role in providing a cytotoxic effect, while ensuring tumor control, preserving liver function, and keeping future treatment options available [45, 46]. In these patients, multicompartment dosimetry is preferred to adequately assess TAD and NTAD relative to the extent of disease and liver function. Select centers have published Y-90 glass microsphere TARE experience in patients undergoing bilobar treatment, demonstrating that a multicompartment dosimetry approach is appropriate and beneficial in bilobar HCC [35, 43, 47].

The NTAD values proposed for unilobar treatment, 50–90 Gy based on baseline bilirubin levels, are higher than those recommended for bilobar patients, 40–70 Gy. However, additional clinical data are needed to better define the appropriate range for bilobar patients [41, 43]. In the case that multicompartment dosimetry is not feasible and single-compartment dosimetry is used, a lower target (i.e., 120 Gy to the perfused volume) is recommended for bilobar HCC patients; planning for such treatment should include careful evaluation of clinical status and liver function when evaluating possible treatment options. A more conservative approach to TAD and NTAD is recommended in the palliative setting as compared to in patients where treatment intent includes downstaging or conversion to resection.

### **Treatment goals for HCC with MVI/PVT**

In HCC patients with MVI/PVT, treatment goals (i.e., potential downstaging or conversion to resection) and careful patient selection should drive the decision as to whether TARE should be used as monotherapy or in conjunction with systemic treatment. In both DOSISPHERE-01 and TARGET, Y-90 glass microsphere TARE was evaluated in patients with MVI/PVT as monotherapy [1, 2]. Patients in DOSISPHERE-01 were selected based on a dual targeting of tumor and MVI/PVT, crucial to tumor control and resolution of MVI/PVT [1]. Over 40% of patients with MVI/PVT in DOSISPHERE-01 who were treated with multicompartment dosimetry were converted to resection, compared to no patients in the single-compartment dosimetry arm. In the presence of ongoing cirrhotic liver function decline,

systemic agents may be considered early on in treatment and in combination with Y-90 following a multidisciplinary review; however, further investigation is needed to better determine specific timing and treatment algorithms [48, 49]. Multicompartment dosimetry is the preferred treatment option in this patient population.

### **Future directions**

As noted throughout the recommendations, there remain several areas which require additional investigations to better understand optimized patient selection and outcomes. The investigational research areas identified by the committee as high interest and requiring additional data and publications to inform clinical practice are detailed in Table 8. The committee encourages the collection and publication of clinical data to further provide evidence relating to the updated recommendations in these key areas of Y-90 glass microsphere TARE for HCC patients. Here, we briefly discuss two of these areas in which research is currently being or was recently conducted: the use of functional assessments in treatment planning and increasing reproducibility of dosimetric approaches.

#### **Functional assessments in treatment planning**

In a parallel advancement in treatment planning for Y-90 glass microsphere TARE patients with insufficient FLR, functional assessments have been proposed in addition to volume assessments. Traditionally, the timing to undergo resection has focused solely on hypertrophy of the contralateral lobe; however, mounting evidence suggests a role for hepatobiliary scintigraphy to assess regional adequate liver function in confirming treatment candidacy [27–29]. Though the time course of function and volume recovery are parallel, functional recovery lags behind volume. Functional assessment may better drive key clinical decisions regarding treatment success, such as follow-up duration, the need for additional Y-90 treatment, and surgical timing or additional observations. Additional investigation is necessary to confirm the utility of functional assessment in making such treatment decisions.

#### **Variability and reproducibility of dosimetry**

One oft-cited concern with using more complex dosimetry-based approaches is the prediction reproducibility in the treatment phase; however, there are now several tools available to help address these challenges. Several commercial dosimetry software options are available, streamlining calculation of multicompartment dosimetry. Advancements in catheter technique in addition to refinement of the use of

**Table 8** High-priority investigational research areas

	Priority area
1	Evaluation of regional liver function of the FLR using newer imaging modalities to assess pre- and post-Y-90 functional liver volume • Hepatobiliary scintigraphy ( $^{99m}\text{Tc}$ -iminodiacetic acid (HIDA) or $^{99m}\text{Tc}$ -mebrofenin) [27] • Eovist/Primovist gadolinium-based contrast agent and MRI imaging
2	Radiation segmentectomy: Evaluation of a streamlined workflow and of clinical outcomes in select populations (due to low lung shunt fraction) Same-day $^{99m}\text{Tc}$ -MAA imaging and Y-90 glass microsphere TARE • Elimination of $^{99m}\text{Tc}$ -MAA imaging • Use in patients post-hepatectomy • Specific activity impact on rates of complete histopathologic necrosis
3	Radiation lobectomy: • Comparing the outcomes of Y-90 glass microsphere TARE as an alternative to portal vein embolization • Evaluating multicompartment dosimetry
4	Establishing the NTAD limit by • Examining baseline bilirubin impact on a recommended NTAD maximum • Using multicompartment targets in dosimetry planning
5	Studying bilobar disease treatment algorithms addressing: • Sequence of Y-90 glass microsphere TARE, immune checkpoint inhibitors, and/or tyrosine kinase inhibitors • Optimal outcomes of sequential lobar treatment or Y-90 glass microsphere TARE limited to $\leq 70\%$ of the whole liver volume
6	Exploring the sequencing/combo of TARE with systemic therapy
7	Exploring the role of glass-based TARE as first-line treatment in locally advanced HCC (MVI/PVT, no metastases)

$^{99m}\text{Tc}$ -MAA imaging to estimate Y-90 glass microsphere distribution have led to improved clinical utility [50–53]. NTAD exhibits better reproducibility, which provides confidence in its use as a safety threshold. Although reproducibility in TAD may be suboptimal, it has been shown to be predictive of patient outcomes (such as tumor response and overall survival) in DOSISPHERE-01, TARGET, and other recent single-center publications [1, 2, 50, 51, 53]. To date, publications evaluated all patients to ascertain reproducibility. However, it may be appropriate to screen out patients in whom multicompartment tumor dosimetry predictions may be unreliable; in those cases, defaulting to MIRD is recommended. Recent publications note that variability may be driven by a limited sample size of published data, operator experience, and variability of tumor flow (and hence T:N) in the presence of multifocal disease, suggesting further optimization of patient selection is needed to improve accuracy and reproducibility of multicompartment dosimetry [52].

## Conclusions

While Y-90 glass microsphere TARE is a key tool in the HCC treatment arsenal, appropriate patient selection, multidisciplinary review, and consideration of alternative or combination treatment in the algorithm are critical to achieving optimal patient outcomes. A number of advancements have been incorporated into the updated HCC treatment recommendations for Y-90 glass microsphere TARE presented here in an effort to improve patient selection, toxicity profiles, and outcomes.

**Acknowledgements** We thank Evelyn Schnuerer, MSc. (Boston Scientific Corporation), Alexandra J. Greenberg-Worisek, PhD, MPH (Boston Scientific Corporation), and Paginae Incorporated, funded by Boston Scientific for medical writing assistance.

**Author contribution** All authors conceived and designed the recommendations, contributed relevant data, participated in drafting, and approved the final manuscript.

**Funding** Author consultants were paid by Boston Scientific and received remuneration for time spent on this work. The work is under the sole responsibility the authors and does not represent the views or opinions of Boston Scientific Corporation.

**Data availability** All data reviewed in the creation of these recommendations can be found in the published literature, per the manuscript's bibliography.

## Declarations

**Ethics approval and consent to participate** Not applicable.

**Consent for publication** Not applicable.

**Competing interests** Riad Salem is a consultant for Boston Scientific, AstraZeneca, Genentech, Sirtex, Cook, Eisai, Bard, and QED Therapeutics.

Siddharth Padia is a consultant for Boston Scientific Corporation, Teleflex Medical, Guerbet, Varian Medical Systems, and Johnson and Johnson.

Marnix Lam is a consultant for Boston Scientific, Terumo, and Quirem, and he receives research support from Boston Scientific, Terumo, Quirem, and Novartis.

Carlo Chiesa is a consultant for Terumo and Boston Scientific, and he received a research grant in 2017 from the latter company.

Paul Haste is a consultant for Boston Scientific.

Bruno Sangro received consulting fees from Adaptimmune, AstraZeneca, Bayer, BMS, Boston Scientific, Eisai, Exelixis, Eli-Lilly, IPSEN, Merck, Onxeo, Roche, Sirtex, and Terumo; lecture fees from Astra-Zeneca, Bayer, BMS, Eisai, Eli-Lilly, Incyte, IPSEN, Roche, and Sirtex; and institutional research grants from BMS and Sirtex.

Beau Toskich is a consultant for AstraZeneca, Genentech, Eisai, Boston Scientific, Sirtex Medical, Turnstone Biologics, Johnson and Johnson, HistoSonics, and VIVOS.

Kirk Fowers is an employee of Boston Scientific Corporation.

Joseph M. Herman is a consultant for Boston Scientific and HistoSonics and received institutional support for the Canopy Cancer Collective Learning Health Network.

S. Cheenu Kappadath has been a consultant for Boston Scientific, Sirtex Medical, ABK Biomedical, and Terumo Medical.

Thomas Leung is a consultant for Boston Scientific, SIRTEX, AstraZeneca, Eisai, and Ipsen.

Daniel Y. Sze was a consultant for Argon, Artio Medical, Astra-Zeneca, Bayer, BlackSwan Vascular, Boston Scientific, Bristol-Myers Squibb, Eisai, FluidX, W. L. Gore, Guerbet, Koli, RadiAction, Sirtex, Terumo, TriSalus Life Sciences, and Varian; received institutional research support from Boston Scientific, Merit Medical, and Sirtex; and serves on Independent Data Safety Monitoring Boards for W. L. Gore and Replimune.

Edward Kim is an advisory board member, speaker, and consultant for Boston Scientific; a consultant for Bristol-Myers Squibb; and an advisory board member for Genentech and Eisai.

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## References

- Garin E, Tselikas L, Guieu B, Chalaye J, Edeline J, de Baere T, et al. Personalised versus standard dosimetry approach of selective internal radiation therapy in patients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): a randomised, multicentre, open-label phase 2 trial. *The Lancet Gastroenterology & hepatology*. 2021;6:17–29. [https://doi.org/10.1016/s2468-1253\(20\)30290-9](https://doi.org/10.1016/s2468-1253(20)30290-9).
- Lam M, Garin E, Maccauro M, Kappadath SC, Sze D, Turkmen C, et al. A Global Evaluation of advanced dosimetry in transarterial radioembolization of hepatocellular carcinoma with yttrium-90: the TARGET Study. *European Journal of Nuclear Medicine and Molecular Imaging*. 2022;in press.
- Salem R, Johnson GE, Kim E, Riaz A, Bishay V, Boucher E, et al. Yttrium-90 radioembolization for the treatment of solitary, unresectable HCC: the LEGACY Study. *Hepatology* (Baltimore, Md). 2021. doi:<https://doi.org/10.1002/hep.31819>.
- Gabr A, Riaz A, Johnson GE, Kim E, Padia S, Lewandowski RJ, et al. Correlation of Y90-absorbed radiation dose to pathological necrosis in hepatocellular carcinoma: confirmatory multicenter analysis in 45 explants. *Eur J Nucl Med Mol Imaging*. 2021;48:580–3. <https://doi.org/10.1007/s00259-020-04976-8>.
- Gabr A, Kulik L, Mouli S, Riaz A, Ali R, Desai K, et al. Liver transplantation following yttrium-90 radioembolization: 15-year experience in 207-patient cohort. *Hepatology* (Baltimore, MD). 2021;73:998–1010. <https://doi.org/10.1002/hep.31318>.
- Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado A, et al. BCLC strategy for prognosis prediction and treatment recommendation Barcelona Clinic Liver Cancer (BCLC) staging system. The 2022 update. *J Hepatol*. 2021. <https://doi.org/10.1016/j.jhep.2021.11.018>.
- Salem R, Padia SA, Lam M, Bell J, Chiesa C, Fowers K, et al. Clinical and dosimetric considerations for Y90: recommendations from an international multidisciplinary working group. *Eur J Nucl Med Mol Imaging*. 2019;46:1695–704. <https://doi.org/10.1007/s00259-019-04340-5>.
- Bolch WE, Eckerman KF, Sgouros G, Thomas SR. MIRD pamphlet no. 21: a generalized schema for radiopharmaceutical dosimetry--standardization of nomenclature. *J Nucl Med*. 2009;50:477–84. <https://doi.org/10.2967/jnumed.108.056036>.
- Report 85: fundamental quantities and units for ionizing radiation. *J ICRU*. 2011;11:1–31. <https://doi.org/10.1093/jicru/ndr011>.
- Gulec SA, Mesoloras G, Stabin M. Dosimetric techniques in 90Y-microsphere therapy of liver cancer: the MIRD equations for dose calculations. *J Nucl Med*. 2006;47:1209–11.
- Dezarn WA, Cessna JT, DeWerd LA, Feng W, Gates VL, Halama J, et al. Recommendations of the American Association of Physicists in Medicine on dosimetry, imaging, and quality assurance procedures for 90Y microsphere brachytherapy in the treatment of hepatic malignancies. *Med Phys*. 2011;38:4824–45. <https://doi.org/10.1118/1.3608909>.
- Salem R, Thurston KG. Radioembolization with 90yttrium microspheres: a state-of-the-art brachytherapy treatment for primary and secondary liver malignancies. Part 2: special topics. *Journal of Vascular and Interventional Radiology: JVIR*. 2006;17:1425–39. <https://doi.org/10.1097/01.Rvi.0000235779.88652.53>.
- Salem R, Thurston KG. Radioembolization with 90Yttrium microspheres: a state-of-the-art brachytherapy treatment for primary and secondary liver malignancies. Part 1: technical and methodologic considerations. *Journal of Vascular and Interventional Radiology: JVIR*. 2006;17:1251–78. <https://doi.org/10.1097/01.Rvi.0000233785.75257.9a>.
- Salem R, Thurston KG, Carr BI, Goin JE, Geschwind JF. Yttrium-90 microspheres: radiation therapy for unresectable liver cancer. *Journal of Vascular and Interventional Radiology: JVIR*. 2002;13:S223–9. [https://doi.org/10.1016/s1051-0443\(07\)61790-4](https://doi.org/10.1016/s1051-0443(07)61790-4).
- Padia SA, Johnson GE, Horton KJ, Ingraham CR, Kogut MJ, Kwan S, et al. Segmental yttrium-90 radioembolization versus segmental chemoembolization for localized hepatocellular carcinoma: results of a single-center, retrospective, propensity score-matched study. *Journal of Vascular and Interventional Radiology: JVIR*. 2017;28:777–85.e1. <https://doi.org/10.1016/j.jvir.2017.02.018>.
- Gabr A, Ranganathan S, Mouli SK, Riaz A, Gates VL, Kulik L, et al. Streamlining radioembolization in UNOS T1/T2 hepatocellular carcinoma by eliminating lung shunt estimation. *J Hepatol*. 2020;72:1151–8. <https://doi.org/10.1016/j.jhep.2020.02.024>.
- De la Garza-Ramos C, Overfield CJ, Montazeri SA, Liou H, Paz-Fumagalli R, Frey GT, et al. Biochemical safety of ablative yttrium-90 radioembolization for hepatocellular carcinoma as a function of percent liver treated. *J Hepatocell Carcinoma*. 2021;8:861–70. <https://doi.org/10.2147/jhc.S319215>.
- Louie JD, Kothary N, Kuo WT, Hwang GL, Hofmann LV, Goris ML, et al. Incorporating cone-beam CT into the treatment planning for yttrium-90 radioembolization. *Journal of Vascular and*

- Interventional Radiology: JVIR. 2009;20:606–13. <https://doi.org/10.1016/j.jvir.2009.01.021>.
19. Stein SI, Soliman MM, Sparapani J, Doustaly R, Cobb BW, Malhotra A, et al. Conventional hepatic volumetry may lead to inaccurate segmental yttrium-90 radiation dosimetry. *Cardiovasc Intervent Radiol*. 2021. <https://doi.org/10.1007/s00270-021-02898-y>.
  20. Kim E, Sher A, Abboud G, Schwartz M, Facciuto M, Tabrizian P, et al. Radiation segmentectomy for curative intent of unresectable very early to early stage hepatocellular carcinoma (RASER): a single-centre, single-arm study. *Lancet Gastroenterol Hepatol*. 2022. [https://doi.org/10.1016/S2468-1253\(22\)00091-7](https://doi.org/10.1016/S2468-1253(22)00091-7)
  21. Gabr A, Riaz A, Mouli S, Desai K, Thornburg B, Salem R, et al. Modified radiation lobectomy: an evolving paradigm to convert patients to liver resection candidacy. *Semin Interv Radiol*. 2019;36:343–8. <https://doi.org/10.1055/s-0039-1696648>.
  22. Ahmed A, Stauffer JA, LeGout JD, Burns J, Croome K, Paz-Fumagalli R, et al. The use of neoadjuvant lobar radioembolization prior to major hepatic resection for malignancy results in a low rate of post hepatectomy liver failure. *Journal of Gastrointestinal Oncology*. 2021;12:751–61. <https://doi.org/10.21037/jgo-20-507>.
  23. Gabr A, Polineni P, Mouli SK, Riaz A, Lewandowski RJ, Salem R. Neoadjuvant Radiation Lobectomy As an Alternative to Portal Vein Embolization in Hepatocellular Carcinoma. *Semin Nucl Med*. 2019;49:197–203. <https://doi.org/10.1053/j.semnuclmed.2019.01.009>.
  24. Bekki Y, Marti J, Tushima T, Lewis S, Kamath A, Argiriadi P, et al. A comparative study of portal vein embolization versus radiation lobectomy with yttrium-90 microspheres in preparation for liver resection for initially unresectable hepatocellular carcinoma. *Surgery*. 2021;169:1044–51. <https://doi.org/10.1016/j.surg.2020.12.012>.
  25. Palard X, Edeline J, Rolland Y, Le Sourd S, Pracht M, Laffont S, et al. Dosimetric parameters predicting contralateral liver hypertrophy after unilobar radioembolization of hepatocellular carcinoma. *Eur J Nucl Med Mol Imaging*. 2018;45:392–401. <https://doi.org/10.1007/s00259-017-3845-7>.
  26. Chiesa C, Sjogreen-Gleisner K, Walrand S, Strigari L, Flux G, Gear J, et al. EANM dosimetry committee series on standard operational procedures: a unified methodology for (99m)Tc-MAA pre- and (90)Y peri-therapy dosimetry in liver radioembolization with (90)Y microspheres. *EJNMMI Physics*. 2021;8:77. <https://doi.org/10.1186/s40658-021-00394-3>.
  27. Allimant C, Deshayes E, Kafrouni M, Santoro L, de Verbizier D, Fourcade M, et al. Hepatobiliary scintigraphy and glass (90)Y radioembolization with personalized dosimetry: dynamic changes in treated and nontreated liver. *Diagnostics (Basel, Switzerland)*. 2021;11. <https://doi.org/10.3390/diagnostics11060931>.
  28. van der Velden S, Braat M, Labeur TA, Scholten MV, van Delden OM, Bennink RJ, et al. A pilot study on hepatobiliary scintigraphy to monitor regional liver function in (90)Y radioembolization. *J Nucl Med*. 2019;60:1430–6. <https://doi.org/10.2967/jnumed.118.224394>.
  29. Syed M, Shah J, Montazeri SA, Grajo JR, Geller B, Toskich B. Analysis of dynamic hepatobiliary contrast-enhanced MRI signal intensity after yttrium-90 radioembolization with glass microspheres for the treatment of hepatocellular carcinoma. *Abdominal Radiology (New York)*. 2021;46:2182–7. <https://doi.org/10.1007/s00261-020-02855-2>.
  30. Salem R, Gabr A, Riaz A, Mora R, Ali R, Abecassis M, et al. Institutional decision to adopt Y90 as primary treatment for hepatocellular carcinoma informed by a 1,000-patient 15-year experience. *Hepatology (Baltimore, MD)*. 2018;68:1429–40. <https://doi.org/10.1002/hep.29691>.
  31. 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. <https://doi.org/10.1053/j.gastro.2009.09.006>.
  32. Mazzaferro V, Sposito C, Bhoori S, Romito R, Chiesa C, Morosi C, et al. Yttrium-90 radioembolization for intermediate-advanced hepatocellular carcinoma: a phase 2 study. *Hepatology (Baltimore, MD)*. 2013;57:1826–37. <https://doi.org/10.1002/hep.26014>.
  33. Gorodetski B, Chapiro J, Scherthaner R, Duran R, Lin M, Lee H, et al. Advanced-stage hepatocellular carcinoma with portal vein thrombosis: conventional versus drug-eluting beads transcatheter arterial chemoembolization. *Eur Radiol*. 2017;27:526–35. <https://doi.org/10.1007/s00330-016-4445-9>.
  34. Abouchaleh N, Gabr A, Ali R, Al Asadi A, Mora RA, Kallini JR, et al. (90)Y radioembolization for locally advanced hepatocellular carcinoma with portal vein thrombosis: long-term outcomes in a 185-patient cohort. *J Nucl Med*. 2018;59:1042–8. <https://doi.org/10.2967/jnumed.117.199752>.
  35. Ho CL, Chen S, Cheung SK, Leung YL, Cheng KC, Wong KN, et al. Radioembolization with (90)Y glass microspheres for hepatocellular carcinoma: significance of pretreatment (11)C-acetate and (18)F-FDG PET/CT and posttreatment (90)Y PET/CT in individualized dose prescription. *Eur J Nucl Med Mol Imaging*. 2018;45:2110–21. <https://doi.org/10.1007/s00259-018-4064-6>.
  36. Memon K, Kulik L, Lewandowski RJ, Mulcahy MF, Benson AB, Ganger D, et al. Radioembolization for hepatocellular carcinoma with portal vein thrombosis: impact of liver function on systemic treatment options at disease progression. *J Hepatol*. 2013;58:73–80. <https://doi.org/10.1016/j.jhep.2012.09.003>.
  37. Ahn JC, Lauzon M, Luu M, Friedman ML, Kosari K, Nissen N, et al. Transarterial radioembolization versus systemic treatment for hepatocellular carcinoma with macrovascular invasion: analysis of the US National Cancer Database. *J Nucl Med*. 2021. <https://doi.org/10.2967/jnumed.121.261954>.
  38. Cardarelli-Leite L, Chung J, Klass D, Marquez V, Chou F, Ho S, et al. Ablative transarterial radioembolization improves survival in patients with HCC and portal vein tumor thrombus. *Cardiovasc Intervent Radiol*. 2020;43:411–22. <https://doi.org/10.1007/s00270-019-02404-5>.
  39. Garin E, Rolland Y, Pracht M, Le Sourd S, Laffont S, Mesbah H, et al. High impact of macroaggregated albumin-based tumour dose on response and overall survival in hepatocellular carcinoma patients treated with (90) Y-loaded glass microsphere radioembolization. *Liver International: official journal of the International Association for the Study of the Liver*. 2017;37:101–10. <https://doi.org/10.1111/liv.13220>.
  40. Garin E, Rolland Y, Edeline J, Icard N, Lenoir L, Laffont S, et al. Personalized dosimetry with intensification using 90Y-loaded glass microsphere radioembolization induces prolonged overall survival in hepatocellular carcinoma patients with portal vein thrombosis. *J Nucl Med*. 2015;56:339–46. <https://doi.org/10.2967/jnumed.114.145177>.
  41. Chiesa C, Mira M, Bhoori S, Bormolini G, Maccauro M, Spreafico C, et al. Radioembolization of hepatocarcinoma with (90)Y glass microspheres: treatment optimization using the dose-toxicity relationship. *Eur J Nucl Med Mol Imaging*. 2020;47:3018–32. <https://doi.org/10.1007/s00259-020-04845-4>.
  42. Toskich B, Vidal LL, Olson MT, Lewis JT, LeGout JD, Sella DM, et al. Pathologic response of hepatocellular carcinoma treated with yttrium-90 glass microsphere radiation segmentectomy prior to liver transplantation: a validation study. *Journal of Vascular and Interventional Radiology: JVIR*. 2021;32:518-26.e1. <https://doi.org/10.1016/j.jvir.2020.12.019>.
  43. Thomas MA, Mahvash A, Abdelsalam M, Kaseb AO, Kappadath SC. Planning dosimetry for (90) Y radioembolization with glass microspheres: evaluating the fidelity of (99m) Tc-MAA and

- partition model predictions. *Med Phys.* 2020;47:5333–42. <https://doi.org/10.1002/mp.14452>.
44. Baker T, Tabrizian P, Zendejas I, Gamblin TC, Kazimi M, Boudjema K, et al. Conversion to resection post radioembolization in patients with HCC: recommendations from a multidisciplinary working group. *HPB (Oxford)*. 2021. <https://doi.org/10.1016/j.hpb.2021.12.013>.
  45. Teyateeti A, Mahvash A, Long JP, Abdelsalam ME, Avritscher R, Chasen B, et al. Survival outcomes for yttrium-90 transarterial radioembolization with and without sorafenib for unresectable hepatocellular carcinoma patients. *J Hepatocell Carcinoma*. 2020;7:117–31. <https://doi.org/10.2147/jhc.S248314>.
  46. Kaseb AO, Kappadath SC, Lee SS, Raghav KP, Mohamed YI, Xiao L, et al. A prospective phase II study of safety and efficacy of sorafenib followed by (90)Y glass microspheres for patients with advanced or metastatic hepatocellular carcinoma. *J Hepatocell Carcinoma*. 2021;8:1129–45. <https://doi.org/10.2147/jhc.S318865>.
  47. Kappadath SC, Mikell J, Balagopal A, Baladandayuthapani V, Kaseb A, Mahvash A. Hepatocellular carcinoma tumor dose response after (90)Y-radioembolization with glass microspheres using (90)Y-SPECT/CT-based voxel dosimetry. *Int J Radiat Oncol Biol Phys.* 2018;102:451–61. <https://doi.org/10.1016/j.ijrobp.2018.05.062>.
  48. Zhan C, Ruohoniemi D, Shanbhogue KP, Wei J, Welling TH, Gu P, et al. Safety of combined yttrium-90 radioembolization and immune checkpoint inhibitor immunotherapy for hepatocellular carcinoma. *Journal of Vascular and Interventional Radiology: JVIR.* 2020;31:25–34. <https://doi.org/10.1016/j.jvir.2019.05.023>.
  49. Javan H, Dayyani F, Abi-Jaoudeh N. Therapy in advanced hepatocellular carcinoma. *Semin Interv Radiol.* 2020;37:466–74. <https://doi.org/10.1055/s-0040-1719187>.
  50. Jadoul A, Bernard C, Lovinfosse P, Gérard L, Lilet H, Cornet O, et al. Comparative dosimetry between (99m)Tc-MAA SPECT/CT and (90)Y PET/CT in primary and metastatic liver tumors. *Eur J Nucl Med Mol Imaging.* 2020;47:828–37. <https://doi.org/10.1007/s00259-019-04465-7>.
  51. Kafrouni M, Allimant C, Fourcade M, Vauclin S, Guiu B, Mariano-Goulart D, et al. Analysis of differences between (99m)Tc-MAA SPECT- and (90)Y-microsphere PET-based dosimetry for hepatocellular carcinoma selective internal radiation therapy. *EJNMMI Res.* 2019;9:62. <https://doi.org/10.1186/s13550-019-0533-6>.
  52. Meyers N, Jadoul A, Bernard C, Delwaide J, Lamproye A, Detry O, et al. Inter-observer variability of (90)Y PET/CT dosimetry in hepatocellular carcinoma after glass microspheres transarterial radioembolization. *EJNMMI Physics.* 2020;7:29. <https://doi.org/10.1186/s40658-020-00302-1>.
  53. d'Abadie P, Walrand S, Hesse M, Annet L, Borbath I, Van den Eynde M, et al. Prediction of tumor response and patient outcome after radioembolization of hepatocellular carcinoma using 90Y-PET-computed tomography dosimetry. *Nucl Med Commun.* 2021;42:747–54. <https://doi.org/10.1097/mnm.0000000000001395>.
  54. Riaz A, Gates VL, Atassi B, Lewandowski RJ, Mulcahy MF, Ryu RK, et al. Radiation segmentectomy: a novel approach to increase safety and efficacy of radioembolization. *Int J Radiat Oncol Biol Phys.* 2011;79:163–71. <https://doi.org/10.1016/j.ijrobp.2009.10.062>.
  55. Vouche M, Habib A, Ward TJ, Kim E, Kulik L, Ganger D, et al. Unresectable solitary hepatocellular carcinoma not amenable to radiofrequency ablation: multicenter radiology-pathology correlation and survival of radiation segmentectomy. *Hepatology (Baltimore, MD)*. 2014;60:192–201. <https://doi.org/10.1002/hep.27057>.
  56. Biederman DM, Titano JJ, Bishay VL, Durrani RJ, Dayan E, Tabori N, et al. Radiation segmentectomy versus TACE combined with microwave ablation for unresectable solitary hepatocellular carcinoma up to 3 cm: a propensity score matching study. *Radiology.* 2017;283:895–905. <https://doi.org/10.1148/radiol.2016160718>.
  57. Biederman DM, Titano JJ, Korff RA, Fischman AM, Patel RS, Nowakowski FS, et al. Radiation segmentectomy versus selective chemoembolization in the treatment of early-stage hepatocellular carcinoma. *Journal of Vascular and Interventional Radiology: JVIR.* 2018;29:30-7.e2. <https://doi.org/10.1016/j.jvir.2017.08.026>.
  58. Lewandowski RJ, Gabr A, Abouchaleh N, Ali R, Al Asadi A, Mora RA, et al. Radiation segmentectomy: potential curative therapy for early hepatocellular carcinoma. *Radiology.* 2018;287:1050–8. <https://doi.org/10.1148/radiol.2018171768>.
  59. Ali R, Riaz A, Gabr A, Abouchaleh N, Mora R, Al Asadi A, et al. Clinical outcomes of Y90 radioembolization for recurrent hepatocellular carcinoma following curative resection. *Eur J Nucl Med Mol Imaging.* 2017;44:2195–202. <https://doi.org/10.1007/s00259-017-3792-3>.
  60. Gates VL, Hickey R, Marshall K, Williams M, Salzig K, Lewandowski RJ, et al. Gastric injury from (90)Y to left hepatic lobe tumors adjacent to the stomach: fact or fiction? *Eur J Nucl Med Mol Imaging.* 2015;42:2038–44. <https://doi.org/10.1007/s00259-015-3122-6>.
  61. Atassi B, Bangash AK, Bahrani A, Pizzi G, Lewandowski RJ, Ryu RK, et al. Multimodality imaging following 90Y radioembolization: a comprehensive review and pictorial essay. *Radiographics: a review publication of the Radiological Society of North America, Inc.* 2008;28:81–99. <https://doi.org/10.1148/rg.281065721>.
  62. Molvar C, Lewandowski R. Yttrium-90 radioembolization of hepatocellular carcinoma-performance, technical advances, and future concepts. *Semin Interv Radiol.* 2015;32:388–97. <https://doi.org/10.1055/s-0035-1564704>.
  63. Hamoui N, Minocha J, Memon K, Sato K, Ryu R, Salem R, et al. Prophylactic embolization of the gastroduodenal and right gastric arteries is not routinely necessary before radioembolization with glass microspheres. *Journal of Vascular and Interventional Radiology: JVIR.* 2013;24:1743–5. <https://doi.org/10.1016/j.jvir.2013.07.011>.
  64. Gabr A, Kallini JR, Gates VL, Hickey R, Kulik L, Desai K, et al. Same-day (90)Y radioembolization: implementing a new treatment paradigm. *Eur J Nucl Med Mol Imaging.* 2016;43:2353–9. <https://doi.org/10.1007/s00259-016-3438-x>.
  65. Lewandowski RJ, Sato KT, Atassi B, Ryu RK, Nemcek AA Jr, Kulik L, et al. Radioembolization with 90Y microspheres: angiographic and technical considerations. *Cardiovasc Intervent Radiol.* 2007;30:571–92. <https://doi.org/10.1007/s00270-007-9064-z>.
  66. Memon K, Kulik L, Lewandowski RJ, Wang E, Riaz A, Ryu RK, et al. Radiographic response to locoregional therapy in hepatocellular carcinoma predicts patient survival times. *Gastroenterology.* 2011;141(526–35):35.e1-2. <https://doi.org/10.1053/j.gastro.2011.04.054>.
  67. Riaz A, Gabr A, Abouchaleh N, Ali R, Al Asadi A, Mora R, et al. Radioembolization for hepatocellular carcinoma: Statistical confirmation of improved survival in responders by landmark analyses. *Hepatology (Baltimore, MD)*. 2018;67:873–83. <https://doi.org/10.1002/hep.29480>.
  68. Spreafico C, Maccauro M, Mazzaferro V, Chiesa C. The dosimetric importance of the number of 90Y microspheres in liver transarterial radioembolization (TARE). *Eur J Nucl Med Mol Imaging.* 2014;41:634–8. <https://doi.org/10.1007/s00259-013-2674-6>.
  69. Vouche M, Lewandowski RJ, Atassi R, Memon K, Gates VL, Ryu RK, et al. Radiation lobectomy: time-dependent analysis of future liver remnant volume in unresectable liver cancer as a bridge to resection. *J Hepatol.* 2013;59:1029–36. <https://doi.org/10.1016/j.jhep.2013.06.015>.

70. Edeline J, Lenoir L, Boudjema K, Rolland Y, Boulic A, Le Du F, et al. Volumetric changes after (90)Y radioembolization for hepatocellular carcinoma in cirrhosis: an option to portal vein embolization in a preoperative setting? *Ann Surg Oncol*. 2013;20:2518–25. <https://doi.org/10.1245/s10434-013-2906-9>.
71. Vouche M, Degrez T, Bouazza F, Delatte P, Galdon MG, Hendlisz A, et al. Sequential tumor-directed and lobar radioembolization before major hepatectomy for hepatocellular carcinoma. *World J Hepatol*. 2017;9:1372–7. <https://doi.org/10.4254/wjh.v9.i36.1372>.
72. Matsumoto MM, Mouli S, Saxena P, Gabr A, Riaz A, Kulik L, et al. Comparing real world, personalized, multidisciplinary tumor board recommendations with BCLC algorithm: 321-patient analysis. *Cardiovasc Intervent Radiol*. 2021;44:1070–80. <https://doi.org/10.1007/s00270-021-02810-8>.
73. Chan KT, Alessio AM, Johnson GE, Vaidya S, Kwan SW, Monsky W, et al. Prospective trial using internal pair-production positron emission tomography to establish the yttrium-90 radioembolization dose required for response of hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys*. 2018;101:358–65. <https://doi.org/10.1016/j.ijrobp.2018.01.116>.
74. Chiesa C, Maccauro M, Romito R, Spreafico C, Pellizzari S, Negri A, et al. Need, feasibility and convenience of dosimetric treatment planning in liver selective internal radiation therapy with (90)Y microspheres: the experience of the National Tumor Institute of Milan. *The Quarterly Journal of Nuclear Medicine and Molecular Imaging: official publication of the Italian Association of Nuclear Medicine (AIMN) [and] the International Association of Radiopharmacology (IAR), [and] Section of the So*. 2011;55:168–97.
75. Haste P, Tann M, Persohn S, LaRoche T, Aaron V, Mauxion T, et al. Correlation of technetium-99m macroaggregated albumin and yttrium-90 glass microsphere biodistribution in hepatocellular carcinoma: a retrospective review of pretreatment single photon emission CT and posttreatment positron emission tomography/CT. *Journal of Vascular and Interventional Radiology: JVIR*. 2017;28:722–30.e1. <https://doi.org/10.1016/j.jvir.2016.12.1221>.
76. Balagopal A, Kappadath SC. Characterization of (90) Y-SPECT/CT self-calibration approaches on the quantification of voxel-level absorbed doses following (90) Y-microsphere selective internal radiation therapy. *Med Phys*. 2018;45:875–83. <https://doi.org/10.1002/mp.12695>.
77. 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. <https://doi.org/10.1007/s00259-015-3068-8>.
78. Seidensticker R, Seidensticker M, Damm R, Mohnike K, Schütte K, Malfertheiner P, et al. Hepatic toxicity after radioembolization of the liver using (90)Y-microspheres: sequential lobar versus whole liver approach. *Cardiovasc Intervent Radiol*. 2012;35:1109–18. <https://doi.org/10.1007/s00270-011-0295-7>.
79. Garin E, Rolland Y, Laffont S, Edeline J. Clinical impact of (99m) Tc-MAA SPECT/CT-based dosimetry in the radioembolization of liver malignancies with (90)Y-loaded microspheres. *Eur J Nucl Med Mol Imaging*. 2016;43:559–75. <https://doi.org/10.1007/s00259-015-3157-8>.

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