Clinical, dosimetric, and reporting considerations for Y-90 glass microspheres in hepatocellular carcinoma

Updated 2022 recommendations from an international multidisciplinary working group

Salem, R., Padia, S.A., Lam, M. et al. Clinical, dosimetric, and reporting considerations for Y-90 glass microspheres in hepatocellular carcinoma: updated 2022 recommendations from an international multidisciplinary working group. Eur J Nucl Med Mol Imaging 50, 328–343 (2023). https://doi.org/10.1007/s00259-022-05956-w

Introduction and background

The TheraSphere Global Dosimetry Steering Committee (DSC) is comprised of interventional radiologists, radiation oncologists, nuclear medicine physicians, clinical scientists, medical oncologists, and physicists involved in the treatment of hepatocellular carcinoma (HCC) with yttrium-90 (Y-90) glass microsphere–based transarterial radioembolization (TARE).

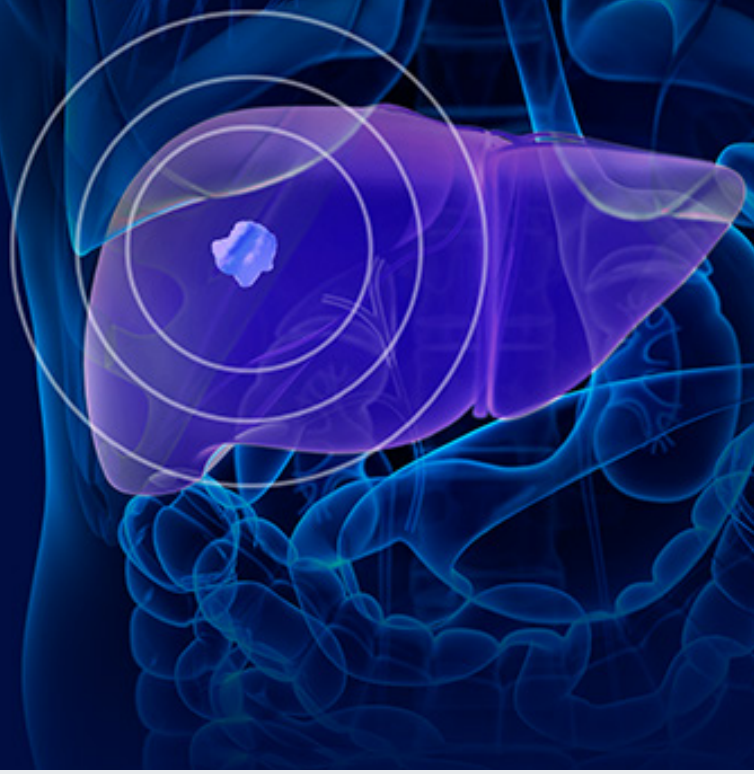
Literature published between January 2019 and September 2021 was reviewed, discussed, and adjudicated by the Delphi method.

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, 2, 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].

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.

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 recommendations included in this updated document incorporate both the critical literature review and the expert opinion and experience of members of the committee.



Introduction and background

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.

SCENARIO 1:

Radiation segmentectomy recommendations using Y-90 glass microspheres

SCENARIO 2:

Radiation lobectomy recommendations using Y-90 glass microspheres

SCENARIO 3:

Multifocal unilobar HCC without macrovascular invasion recommendations using Y-90 glass microspheres

SCENARIO 4:

Multifocal bilobar HCC without macrovascular invasion recommendations using Y-90 glass microspheres

SCENARIO 5:

HCC with macrovascular invasion recommendations using Y-90 glass microspheres

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.

Key definitions

CURATIVE INTENT:

Radiation segmentectomy: Localized disease (one or multiple tumors located in ≤ 2 segments), with contemporary and modern treatment approaches delivering superselectively 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 ≤ 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.

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 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 90Y 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.

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

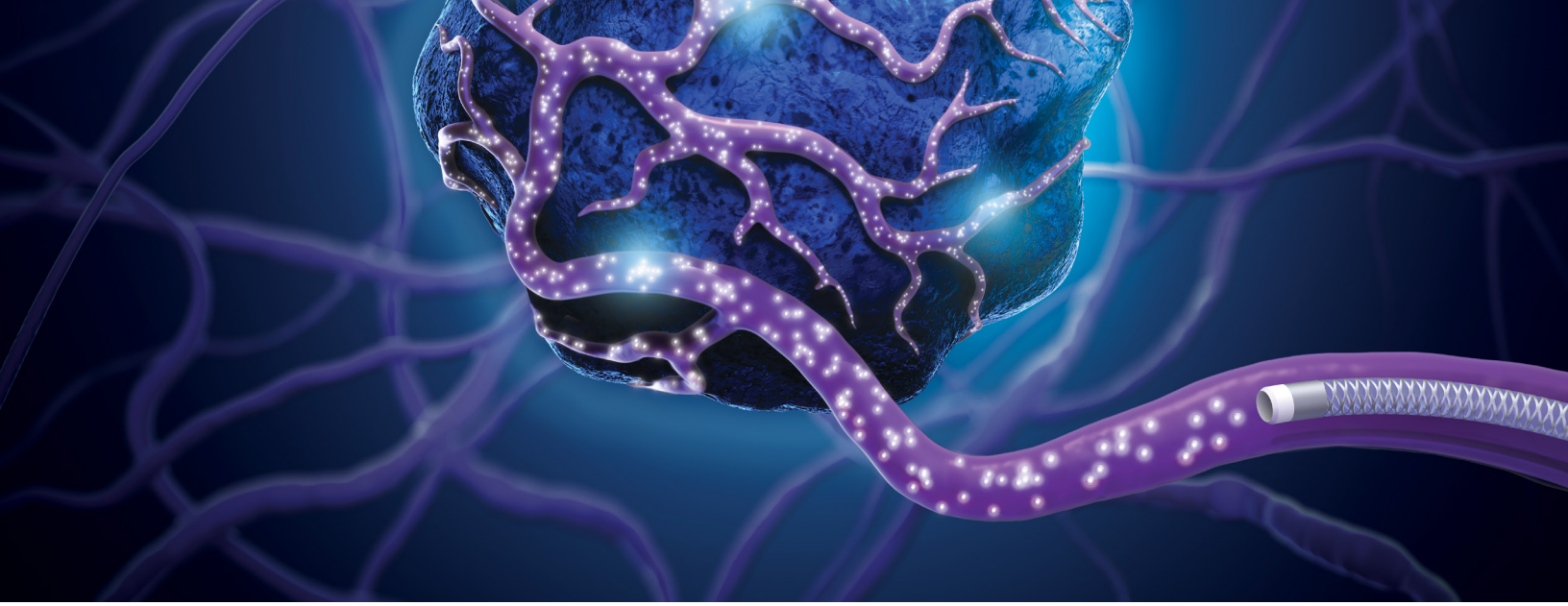
Key definitions

SINGLE-COMPARTMENT MODEL:

A MIRD dosimetry model that assumes the 90Y 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, 13, 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].



Degree and strength of recommendation

DEGREE OF RECOMMENDATION

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

STRENGTH OF CONSENSUS

STRONG

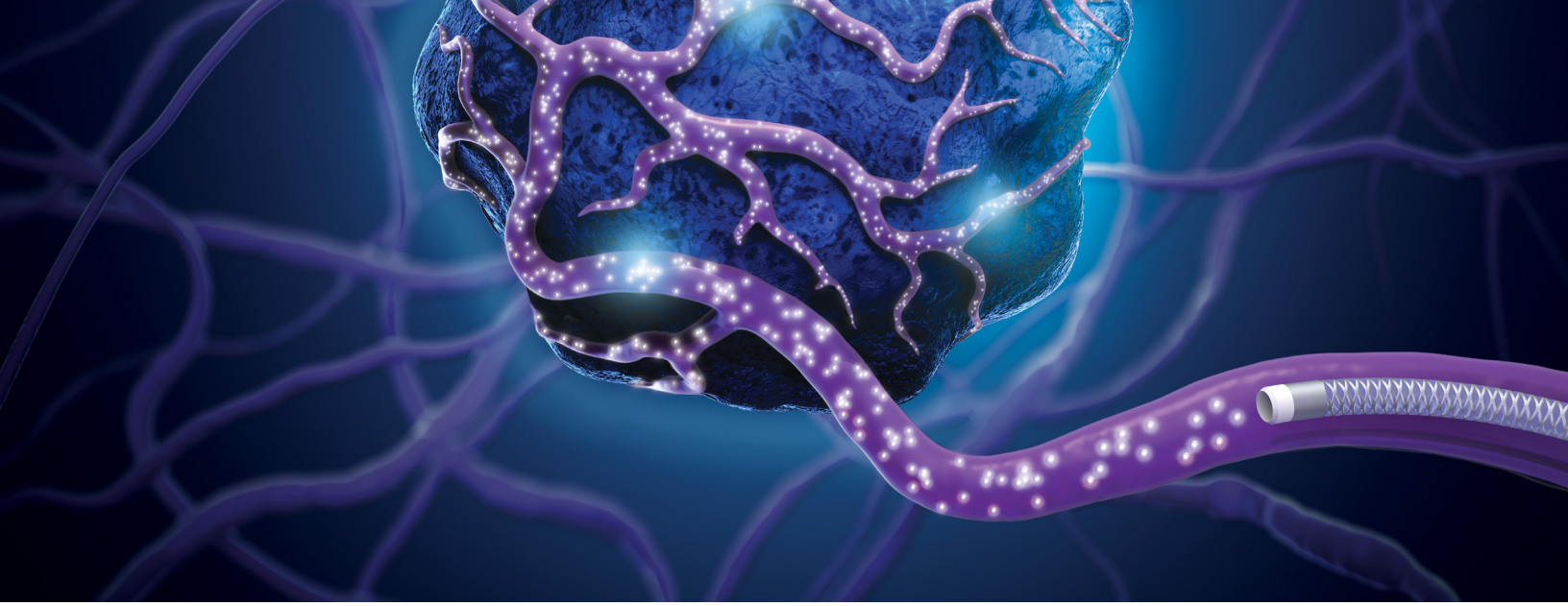
≥80% CONSENSUS

MODERATE

50–79% CONSENSUS

WEAK

≤49% CONSENSUS



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.

CURATIVE INTENT

Scenario 1
Radiation segmentectomy: Localized disease (one or multiple tumors located in ≤ 2 segments), with contemporary and modern treatment approaches delivering superselectively 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 ≤ 2 segments but rather inclusive of smaller hepatic segmentectomy

Page 8

Scenario 2
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)

Page 10

PALLIATIVE INTENT

Scenario 3
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

Page 12

Scenario 4
Multifocal bilobar disease without MVI/PVT, with the goal of palliating and delaying progression, usually in combination or in sequence with systemic treatment

Page 13

Scenario 5
HCC with MVI/PVT, with the goal of palliating and delaying progression; in select patients, intent may be conversion to curative options

Page 14

Scenario 1

Radiation segmentectomy recommendations using Y-90 glass microspheres

A **STRONGLY RECOMMENDED**

STRONG **≥80% CONSENSUS**

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

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, 55, 56, 57, 58]

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

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]

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 ≤2 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]

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

Scenario 1

Radiation segmentectomy recommendations using Y-90 glass microspheres

TREATMENT PLANNING

DIAGNOSTIC STUDIES AND TARGET VOLUME DEFINITION

1. 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
2. Determine angiosome volume by cone-beam CT; this is the gold standard for perfused volume determination and preferred method when available [3, 18, 19]
3. If there is associated segmental portal venous invasion, treat the territory that encompasses the MVI/PVT confirmed by cone-beam CT [15]
4. 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 ≥1 cm is recommended [62]

MAPPING AND 99MTC-MAA

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]
2. Perform lobar technetium-99 m macroaggregated albumin (99mTc-MAA) and segmental Y-90 infusion to limit the number of catheterizations of the small segmental branch perfusing tumor [16]
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 99mTc-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 99mTc-MAA can be made at this time

DOSE CALCULATION AND DOSIMETRY CONSIDERATIONS

1. Single-compartment model dosimetry is adequate and preferred [3]
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 >500 Gy to the perfused volume were reported [29]. Prospective validation demonstrates an adverse event profile that is minimal using this approach [20]
3. Recent publications have demonstrated that higher doses to the segment ≥400 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)
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 ≥297 Bq) may be associated with increased pathologic necrosis in small tumors treated with radiation segmentectomy [1, 42]

TREATMENT DELIVERY

1. Ensure no contrast refluxes into an adjacent angiosome prior to treatment
2. The entire tumor (and microsatellites) should lie within the perfused angiosome
3. Prime the TheraSphere® injection system slowly
   a) There is a low margin of error in radiation segmentectomy given the small territory
   b) Prime the system slowly to minimize the risk of bubble formation
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]
5. Same-day planning 99mTc-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]

OUTCOME ASSESSMENT/ FOLLOW-UP

1. Ideally, use the same imaging modality that was used for initial assessment of disease burden (contrast-enhanced CT or multiphase contrast-enhanced MR)
2. If complete mRECIST response at 3–6 months is not achieved, consider retreatment [3, 15, 66, 67]

Scenario 2

Radiation lobectomy recommendations using Y-90 glass microspheres

B **RECOMMENDED** **STRONG** **≥80% CONSENSUS**

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, 22, 23, 24]

PATIENT SELECTION

1. Radiation lobectomy applies to unresectable Child–Pugh A patients in the following scenarios:
   a) Inadequate FLR and/or
   b) Test of time is desired for tumor biology and response prior to surgery and/or
   c) Need for the treated tumor to be retracted away from hepatic vein and/or IVC
   d) Potential delay of surgery or definitive treatment instead of surgery

2. Borderline resectable patients are considered, and therefore should not have comorbidities that would preclude surgery

Scenario 2

Radiation lobectomy recommendations using Y-90 glass microspheres

TREATMENT PLANNING

DIAGNOSTIC STUDIES AND TARGET VOLUME DEFINITION

Contrast-enhanced cone-beam CT in the angiography suite should be performed to assess/ensure tumor coverage within the treated lobe

MAPPING AND 99MTC-MAA

1. Perform lobar 99mTc-MAA and lobar Y-90 infusion. Catheter placements should be to facilitate similar distribution pattern
2. Elevated lung dose may be an issue if the lung shunt fraction is high in the context of large perfused volume

DOSE CALCULATION AND DOSIMETRY CONSIDERATIONS

1. Using a multicompartment model with 99mTc-MAA, a recent randomized study demonstrated that tumor response in patients with ≥30% hepatic reserve is optimized and overall survival extended when the minimum planned tumor-absorbed dose is ≥205 Gy (with a mean of 331 Gy) and normal tissue–absorbed dose (NTAD) is ≤120 Gy attained by treating on week 1 (Wednesday) [1]. A minimum threshold absorbed dose of normal injected liver >88 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 ≥1.1 mg/dL or <1.1 mg/dL, respectively, using 4-day decay, to minimize hepatic dysfunction [41]
2. 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 >30%), targeting a lobar absorbed dose >150 Gy (with a mean of 178 Gy) with a whole liver dose <150 Gy, by treating on week 1 (Wednesday), for well-selected patients (Child–Pugh A and hepatic reserve >30%) was safe and can be used [1]. Retreatment should be considered if minimal hypertrophy is noted at months 1–3
3. Existing literature supports treatment on week 1 (Wednesday) to week 2 (Tuesday). No optimal day has been identified [21, 22, 68]
4. Repeated treatment of the same volume has been performed and is safe when carefully considering dosimetry and liver function

TREATMENT DELIVERY

1. 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]
2. 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 ≥400 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]
   a) Modified radiation lobectomy is favored over single lobar infusion when technically feasible
   b) In the setting of a), if patient does not undergo surgery, tumor control has been maximized by performing curative high absorbed dose segmentectomy treatment

OUTCOME ASSESSMENT/ FOLLOW-UP

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
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]
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]
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, 28, 29]
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]

Scenario 3

Multifocal unilobar* HCC without macrovascular invasion recommendations using Y-90 glass microspheres

B RECOMMENDED **STRONG** ≥80% CONSENSUS

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

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, 31, 32, 45, 46]

TREATMENT PLANNING

MAPPING AND 99MTC-MAA

Injection of 99mTc-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

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

*The use of TheraSphere outside the labelled indication has not been established.

Scenario 4

Multifocal bilobar* HCC without macrovascular invasion recommendations using Y-90 glass microspheres

B RECOMMENDED **STRONG** ≥80% CONSENSUS

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

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 99MTC-MAA

Multiple variations of 99mTc-MAA administration exist. Options include:
a) Injection of 99mTc-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 99mTc-MAA into RHA and LHA, respectively
d) Sequential lobar infusion of 99mTc-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, 75, 76, 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 ≥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

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 99mTc-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

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

*The use of TheraSphere outside the labelled indication has not been established.

Scenario 5

HCC with macrovascular invasion* recommendations using Y-90 glass microspheres

A STRONGLY RECOMMENDED

MODERATE

50–79% CONSENSUS

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

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, 35, 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
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, ≥30% 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, 38, 39]
3. Larger tumors (e.g., >10 cm) with MVI/PVT have been effectively treated with glass microsphere TARE using multicompartment dosimetry [1, 37, 39]

TREATMENT PLANNING

DIAGNOSTIC STUDIES AND TARGET VOLUME DEFINITION

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 99MTC-MAA

99mTc-MAA MVI/PVT targeting evaluation should be performed [1, 39, 79]

DOSE CALCULATION AND DOSIMETRY CONSIDERATIONS

1. Multicompartment 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
2. For the multicompartment model, 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]. The ideal candidate has good MVI/PVT 99mTc-MAA targeting (treatment intensification), as a suboptimal response is likely if there is no 99mTc-MAA MVI/PVT targeting or tumor-absorbed dose is <205 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]. Multicompartment 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]

TREATMENT DELIVERY

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
2. A more conservative approach, including treatment planning using multicompartment 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]

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

*The use of TheraSphere outside the labelled indication has not been established.

Author information

Riad Salem
Department of Radiology
Northwestern Feinberg School of Medicine
676 N. St. Clair, Suite 800, Chicago, IL, USA

Siddharth A. Padia
Department of Radiology
University of California-Los Angeles
Los Angeles, CA, USA

Marnix Lam
Department of Radiology and Nuclear Medicine
University Medical Center Utrecht
Utrecht, The Netherlands

Carlo Chiesa
Department of Nuclear Medicine
Fondazione IRCCS Istituto Nazionale Tumori
Milan, Italy

Paul Haste
Department of Interventional Radiology
Indiana University School of Medicine
Indianapolis, IN, USA

Bruno Sangro
Liver Unit
Clinica Universidad de Navarra and CIBEREHD
Pamplona, Spain

Beau Toskich
Department of Radiation Oncology
Mayo Clinic
Jacksonville, FL, USA

Kirk Fowers
Boston Scientific Corporation
Marlborough, MA, USA

Joseph M. Herman
Department of Radiation Medicine
Northwell Health
New Hyde Park, NY, USA

S. Cheenu Kappadath
Department of Imaging Physics
University of Texas MD Anderson Cancer Center
Houston, TX, USA

Thomas Leung
Comprehensive Oncology Centre
Hong Kong Sanatorium and Hospital
Hong Kong, China

Daniel Y. Sze
Department of Radiology
Stanford University School of Medicine
Palo Alto, CA, USA

Edward Kim
Department of Interventional Radiology
Mount Sinai
New York City, NY, USA

Etienne Garin
INSERM, INRA
Centre de Lutte Contre Le Cancer Eugène Marquis, Institut
NUMECAN (Nutrition Metabolisms and Cancer)
Univ Rennes, 35000, Rennes, France

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

References*

1. Garin E, Tselikas L, Guiu 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.
2. 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.
3. 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.
4. 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.
5. 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.
6. Reig M, Forner A, Rimola J, Ferrer-Fábrega 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.
7. 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.
8. 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.
9. Report 85: fundamental quantities and units for ionizing radiation. J ICRU. 2011;11:1–31. https://doi.org/10.1093/jicru/ndr011.
10. 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.
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.
12. 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.
13. 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.
14. 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.
15. 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.
16. 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.
17. 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.
18. 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
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, Toshima T, Lewis S, Kamath A, Argiriadi P, et al. A comparative study of portal vein embolization versus radiation lobectomy with yttrium-90 micropheres 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, Schernthaner 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.

*References align with full publication.

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.

TheraSphere™ Yttrium-90 Glass Microspheres

INDICATION FOR USE: TheraSphere is indicated for use as selective internal radiation therapy (SIRT) for local tumor control of solitary tumors (1-8 cm in diameter), in patients with unresectable hepatocellular carcinoma (HCC), Child- Pugh Score A cirrhosis, well-compensated liver function, no macrovascular invasion, and good performance status. CONTRAINDICATIONS: TheraSphere is contraindicated in patients: whose Tc-99m macroaggregated albumin (MAA) hepatic arterial perfusion scintigraphy shows any deposition to the gastrointestinal tract that may not be corrected by angiographic techniques • who show shunting of blood to the lungs that could result in delivery of greater than 16.5 mCi (0.61 GBq) of Y-90 to the lungs. Radiation pneumonitis has been seen rarely in patients receiving doses to the lungs greater than 30 Gy in a single treatment. • in whom hepatic artery catheterization is contraindicated, such as patients with vascular abnormalities or bleeding diathesis • who have pulmonary insufficiency (conventionally defined by an arterial oxygen pressure (Pa,O2) of < 60 mmHg, or oxygen saturation (Sa,O2) of < 90%) or severe liver dysfunction, including hepatic encephalopathy, clinically evident ascites or treatment with diuretics for ascites • with portal vein thrombosis (PVT) Type 4 involvement and lack of Tc-99m MAA deposition on the PVT seen on the Tc-99m MAA imaging with >70% tumor replacement in the liver • with comorbidities or poor overall health (e.g., ECOG performance status rating > 2) which may make the patient a poor candidate for locoregional radiation treatment. • who are pregnant. WARNINGS: The following pre-treatment, high-risk factors (disease characteristics) have been associated with serious adverse events deemed possibly related to use of the device: infiltrative tumor type • tumor nodules too numerous to count • AST or ALT > 5 times ULN • bilirubin > 2 mg/dL • tumor volume > 50% combined with albumin < 3 g/dL. Keep the TheraSphere dose vial upright and stored in its lead pot before and during patient treatment, except as required for radiation measurement. Do not open the dose vial acrylic shield prior to patient treatment. Post-treatment, waste materials require caution to prevent contamination and beta shielding due to residual glass microspheres. PRECAUTIONS: GENERAL PRECAUTIONS: As in any intra-arterial procedure, aseptic technique should be practiced, and care should be taken to ensure minimum patient anesthesia exposure extraneous to therapeutic objective. • Consideration of patient comorbidities should be used when determining the type and volume of fluid to infuse via catheter to avoid electrolyte imbalance, fluid shift, and hyperglycemia. • It is important to avoid any aggressive arterial procedure that may lead to arterial spasm that impairs TheraSphere distribution into the perfused liver target volume which may lead to underdosing or non- target deposition of TheraSphere. PRECAUTION IN PATIENTS WITH IMPAIRED LIVER FUNCTION: No efficacy or safety data from the LEGACY study are available to support the use of the device in patients with Child-Pugh score B or C cirrhosis. PRECAUTION IN VULNERABLE PATIENTS: No effectiveness or safety data are available to support the use of the device in children or breast- feeding women. ENDOCRINE DISRUPTION, CARCINOGENICITY, MUTAGENICITY, TOXICITY TO REPRODUCTION: Ideally the use of this radioactive device in women of childbearing capability should be performed during the first few (approximately 10) days following the onset of menses. RADIATION SAFETY: Radioactive products should be used only by healthcare professionals who are qualified by specific training in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides. • As in the use of any radioactive material, ensure minimum radiation exposure to the patient extraneous to the therapeutic objective, and to minimize radiation exposure to workers and others in contact with the patient. RELEASE AND POST-TREATMENT PRECAUTIONS: Post treatment patient care: use universal precautions for body fluid contact. Trace Y-90 may be detectible in blood and urine; handle with gloves and dispose as normal body fluids. The radiation field is expected to be less than 1 mrem/h (10 µSv/h) at 3 ft (1 m) from the patient's abdomen. Supplemental shielding and segregation of the patient are not required to maintain exposure to others below regulated limits. • Release instructions: The patient should follow good hygiene (e.g., proper hand washing). Caregivers, family, and others do not require restrictions on patient contact; however, they can minimize their radiation exposure by avoiding prolonged time (>12 hours per day) within 1 ft (0.3 m) of the patient's abdomen for the first week post therapy. Patients should be advised that radiation emitted from the patient may be detectible at security screening (e.g., international travel). • Special precautions post-administration: If the patient requires hospitalization, surgery, medical assessment or treatment regarding any part of their thorax or abdomen within first 2 weeks of treatment, the patient should advise the hospital and treating physician of the Y-90 TheraSphere implant. The physician should consult their radiation safety staff for handling and disposal of liver tissue. • Special liver tissue handling: Special liver tissue handling may be required for post-treatment surgery, explant, or transplant since the glass microspheres remain permanently implanted in the liver tissue. Disclosure of the treatment will be required if cremation is considered. POTENTIAL ADVERSE EVENTS: The use of this product leads to irradiation of both tumorous and normal liver tissue. As a result, patients with compromised liver function may be at greater risk of liver function impairment and hence could experience complications. Clinical side effects usually occur within the first 4 to 6 weeks after treatment. Based on clinical trial data, literature reviews and post market surveillance, adverse events potentially associated with treatment using Y-90 microspheres, including TheraSphere, may include the following: Allergic reaction • Altered liver function, acute or chronic • Anorexia • Anxiety • Ascites • Bile Duct injury • Bleeding/hemorrhage • Chills / rigors • Cholecystitis (inflammatory or infectious) • Colitis • Death • Dehydration • Diarrhea • Dizziness • Dyspnea • Edema (any location) • Electrolyte abnormalities • Elevated BUN/creatinine • Fall • Fatigue • Fever • Gastrointestinal bleeding / hemorrhage • Gastrointestinal ulcer or ulceration • Hepatic encephalopathy • Hepatorenal failure • Hiccups • Hypertension • Hypotension • Infection (any location) • Liver failure, acute or chronic • Lymphopenia • Malaise • Mood alteration • Muscle weakness • Nausea • Neutropenia • Pain (any location) • Pancreatitis • Platelet count abnormalities • Pleural effusion • Portal hypertension • Pre-existing chronic liver disease decompensation • Pulmonary edema • Pulmonary fibrosis • Radiation hepatitis • Radiation induced disease, acute • Radio Embolization Induced Liver Disease (REILD) • Sepsis • Supraventricular arrhythmia • Thrombosis (arterial or venous) • Tumor inflammation (including tumor edema) • Tumor-lysis syndrome • Vomiting • Weight loss. Complications related to the administration procedure itself may include: Allergic reaction: Arterial injury including vessel dissection • Aspiration pneumonia • Bruising/bleeding/hematoma at site • Constipation/abdominal distension • Fatigue • Flushing • Infection • Nausea • Nerve damage. CAUTION: Federal (USA) law restricts this device to sale by or on order of a physician. PI-992004-AA. Note: Dose to the liver does not exceed 150 Gy.

Boston Scientific

Advancing science for life™

Peripheral Interventions
300 Boston Scientific Way
Marlborough, MA 01752-1234
www.bostonscientific.com

To order product or for more information contact customer service at 1.888.272.1001.

PI-1555904-AA