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GUIDELINES

Clinical and dosimetric considerations for Y90: recommendations from an international multidisciplinary working group

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Abstract

The TheraSphere Global Dosimetry Steering Committee was formed in 2017 by BTG International to review existing data and address gaps in knowledge related to dosimetry. This committee is comprised of health care providers with diverse areas of expertise and perspectives on radiation dosimetry. The goal of these recommendations is to optimize glass microspheres radiation therapy for hepatocellular carcinoma while accounting for variables including disease presentation, tumour vascularity, liver function, and curative/palliative intent. The recommendations aim to unify glass microsphere users behind standardized dosimetry methodology that is simple, reproducible and supported by clinical data, with the overarching goal of improving clinical outcomes and advancing the knowledge of dosimetry.

Keywords Hepatocellular carcinoma · Radioembolization · Yttrium-90 · Liver cancer

Introduction

The worldwide implementation of Yttrium-90 (^{90}Y) radioembolization for the treatment of liver cancer has dramatically increased over the past decade. ^{90}Y radioembolization is now a key component in the treatment algorithm for liver cancer [1]. It has been given positive recommendations and incorporated into the National Comprehensive Cancer Network (NCCN) guidelines for hepatocellular carcinoma (HCC) [2]. While ^{90}Y has traditionally been used in advanced stage, its recent application in earlier and intermediate stage HCC has also shown favourable results [3].

Despite the growing adoption of radioembolization, further refinements in planning and therapeutic technique are being pursued. One key target is the need to refine dosimetry planning. Currently, the two commercially available ^{90}Y devices use different dosimetric models. Resin microspheres (SIR-Spheres®, Sirtex, AU) are used with an activity-based empiric

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method calculation, largely on the patient's body surface area; some investigators have supplemented a partition model [4]. Glass ^{90}Y microspheres (TheraSphere®, BTG Biocompatibles, UK) are approved with a standardized dosimetric model largely based on uniform absorbed dose to volume of perfused tissue within a fixed dose range [5, 6]. According to the instructions for use, the dose to the liver should between 80 to 150 Gy [5, 6]. Usually, and especially in trials, it is recommended to use an absorbed dose of 80–150 Gy to the injected lobe. However, it has been demonstrated that providing, in carefully selected patients (Child A, unilobar disease, sufficient hepatic reserve), an absorbed dose >150 Gy to the treated lobe but with a mean dose to the whole liver (treated and not treated) <150 Gy, was well tolerated [7, 8]. Recent developments may allow for more precise individualized dosimetry [5, 6]. Radioembolization is most successful when tumoural dose is optimized and non-target deposition is minimized. The objective of radioembolization is to deliver an absorbed dose to the tumour(s) exceeding a tumouricidal threshold, while minimizing the absorbed dose to surrounding normal hepatic tissue and limiting lung parenchymal exposure.

Personalized precision dosimetry (e.g. absorbed dose distribution analysis by voxel dosimetry) has not been incorporated into the recently published and ongoing randomized clinical trials for ^{90}Y radioembolization; these studies were initiated when personalization was still under investigation [9]. Therefore, a consensus opinion is needed to summarize the current data and to recommend best practices for clinical practitioners and research investigators. As new prospective trials are designed, incorporation of a refined and personalized dosimetry model will be essential for improved outcomes.

Prior to treating a patient with radioembolization, several factors should be considered, including goals of therapy (curative/palliative), liver function and tumour vascularity. Therapy should be tailored according to these tenets, which are largely based on the overall extent of tumour in the liver. Potential treatment scenarios include macrovascular invasion, palliation to delay disease progression, bridging to surgical resection or transplant, or as definitive/curative intent in patients with localized, early tumours.

Based on intent, most patients can be categorized into four scenarios:

Curative:

a- Radiation Segmentectomy: Localized disease (single tumour or tumours confined to ≤2 segments), with application of ablative absorbed doses, as curative therapy or bridge to transplantation
b- Radiation Lobectomy: Unilobar disease, with intent of disease control, treatment-related contralateral lobar hypertrophy in patients with small future liver remnant, as bridge to resection

Palliative:

a- Multifocal unilobar or bilobar disease, with intent of palliation and delaying disease progression
b- Presence of vascular invasion regardless of size or distribution, with intent of palliation and delaying disease progression, combining with systemic treatment

Two to four members of the committee were initially assigned to each of these topics to propose dosimetry recommendations based on contemporary literature review. The committee reconvened every 4 months to formulate a consensus opinion amongst all members. The intent of this guideline document is to propose dosimetry methods to guide planning for radioembolization. As new data emerge in the future, this living document will continue to be updated.

Recommendations were graded according to the Degree of Recommendation (based on the clinical evidence) and the Strength of Consensus (based on expert panel experience/opinion), as outlined in Tables 1 and 2, respectively [10]. Many of the recommendations made in this document combine conclusions from the peer-reviewed literature and expert opinion. This evidence-ranking system was utilized for each recommendation. Strong consensus was determined based on >80% agreement of committee members during the in-person review panels. Strong disagreement by panel members (if present) were recorded and are highlighted in these recommendations.

Dosimetry planning for glass microspheres is based on a uniform distribution of microspheres in a perfused volume of tissue. While the standard method of using a single perfused volume to calculate absorbed dose has been traditionally used, hypervascular tumours, in reality, receive a higher absorbed dose compared to the normal hepatic parenchyma. For this reason, a multi-compartment model may lead to more precise dosimetry.

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 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 the harms exceed the benefits)
E	Insufficient, low quality or contradictory evidence (the balance between benefit and harms cannot be determined)

Table 2 Strength of consensus

Strength of consensus	Definition
Strong	≥80% consensus
Moderate	50–79% consensus
Weak	≤49% consensus

The package insert recommendation to determine relative absorbed dose in tumoural versus non-tumoural tissue is to quantitate planned dosimetry based on ^{99m}Tc-MAA SPECT/CT imaging [11]. ^{99m}Tc-MAA is administered during the mapping angiogram to assess lung shunting, potential extrahepatic non-target deposition through hepatico-enteric collateral vessels and intrahepatic distribution of activity. The scout dose ^{99m}Tc-MAA may be injected in the proper hepatic artery, selectively in both lobes, or selectively in one lobe (highest burden). However, it is important to recognize that in order to implement ^{99m}Tc-MAA for intrahepatic lobar dosimetry, injection of ^{99m}Tc-MAA and ^{90}Y microspheres should be in the same angiographic position, minimizing arterial spasm and the influence of vessel bifurcations, and injected slowly (20–30 s), in order to mimic microsphere infusion [12]. It is also important to note that scout doses of ^{99m}Tc-MAA may overestimate lung shunting, especially when planar imaging is used [13, 14]. Contemporary practice also supports the use of post-therapy imaging with ^{90}Y bremsstrahlung SPECT/CT or ^{90}Y PET/CT with the intent to (1) verify dose delivery and distribution, (2) gain information that facilitates calculation of normal liver and tumour dose, thereby assisting with expectation of clinical response or complication, and (3) have information that can be used to associate with tumour specific responses [15].

Definitions

Mean absorbed dose: quantity expressed in Gray (Gy) to describe the average amount of energy (J) deposited within a specific volume of interest (VOI) with a given mass (kg). The mean absorbed dose is often referred to as "Dose" and must not be mistaken for "Activity" or "Dosage" (GBq) [16, 17].

MIRD scheme: The Medical Internal Radiation Dose (MIRD) scheme is a dosimetry model used to calculate the mean absorbed dose "D" in any specific volume of interest, having a given mass "M" (e.g. whole liver, lobe, tumour, normal liver), assuming the absorbed dose is distributed uniformly in each volume and permanent implantation of the microspheres without biological clearance [18, 19]. Using the MIRD scheme, the dose in a specific volume of interest is computed using the equation: $D_{(Gy)} = A_{(GBq)} \times 50 / M_{(kg)}$ where "A" is the net activity of ^{90}Y ultimately implanted in the volume of interest. As an example, if 3 GBq of glass microspheres were infused with a residual of 1% and a lung shunt of 5%, the net implanted activity in the liver tissue would be 3 x (0.99) x (0.95) = 2.82 GBq. 2.82 GBq would be the final activity entered in the MIRD formula in order to determine final tissue dose.

Single-compartment model: A dosimetry model, based on the MIRD scheme, which assumes that the delivered ^{90}Y microspheres (and therefore absorbed dose) is distributed uniformly within the treated liver volume. In the single-compartment model, only the averaged absorbed dose value over the treated liver volume is calculated, neglecting the difference in distribution pattern of microspheres (especially between tumours and normal liver). In reality, this represents a simplification of the real distribution, as hypervascular tumours will receive a higher dose, and the normal hepatic parenchyma will receive a lower absorbed dose [20–22].

Multi-compartment model: A dosimetry approach, based on the MIRD scheme, in which the mean absorbed dose is calculated in more than one volume of interest (e.g. each individual tumour, perfused normal liver tissue, whole liver normal tissue). In the case of two compartments (entire tumour region and non-tumour liver tissue), this is also referred to as the "partition model" [18]. The goal of a multi-compartment modeling is to obtain a separate evaluation of the tumour and normal liver dose.

Clinical scenarios

Radiation segmentectomy for HCC

Radiation segmentectomy has recently emerged as a potentially curative therapy for patients with localized HCC [23]. Published data shows superiority to chemoembolization (TACE) with respect to tumour response and progression-free survival (PFS) [24]. Segmental radioembolization has also been shown to have similar outcomes compared to percutaneous thermal ablation, with lower rates of significant adverse events [25]. In cases where a tumour is isolated to ≤2 hepatic segments, it may be possible to deliver an ablative radiation absorbed dose by infusing only the affected segmental arteries [26, 27]. The risk of toxicity is mitigated by irradiation of a small volume of liver, albeit with higher doses for curative intent. Based on the local dose deposition from ^{90}Y (mean range is 2–4 mm), an aggressively high dose expected to ablate both tumour and treat normal functional liver can be delivered safely and effectively in the majority of patients.

RADIATION SEGMENTECTOMY

TREATMENT INTENT

Curative intent in appropriately selected patients (ex: solitary/multifocal UNOS T1-T2-T3 for bridging/downstaging to transplantation), definitive therapy if non-transplant candidate (ex: solitary T1, solitary/multifocal UNOS T2-T3).

PATIENT SELECTION

1. Child-Pugh A and B, tumour stage UNOS T1-T3 (may consider Child-Pugh C if bridging or downstaging to transplant and segmental infusion possible) [26, 28].
2. Treatment may be performed in patients with prior liver therapy (i.e. surgical resection, ablation, SBRT). In patients with prior chemoembolization, angiographic assessment of vascular supply and patency during mapping angiography will determine eligibility [29, 30]. While patients can receive ^{90}Y after external beam radiation, more data is needed to determine efficacy and safety.
3. Tumours abutting the colon, gallbladder and stomach can be safely treated; radiation toxicity in this specific setting of adjacent structures has not been demonstrated [31].
4. Treatment to two tumours in two separate segments may be performed during the same session in patients with normal underlying liver or well-compensated cirrhosis [24].

TREATMENT PLANNING

Diagnostic Studies and Target Volume Definition

Diagnostic imaging should ideally be multi-phase contrast enhanced MR; the role of Eovist® (USA) or Primovist® (EU) (gadolinium-EOB-DTPA) is evolving [32, 33]. Contrast-enhanced CT can also be used. Both imaging modalities are considered acceptable.

1. Determine angiosome volume by cone-beam CT; this is the gold standard and preferred method when available [34].
2. If there is associated segmental portal venous invasion, perfuse (and radioembolize) the territory that encompasses the PVT confirmed by cone-beam CT.
3. If there is a possibility of microsatellite lesions, perfuse a wider territory (i.e. the larger the lesion, the wider the safety margin necessary) confirmed by cone beam CT; a 1-cm angiographic margin is recommended.

Mapping and ^{99m}Tc-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 gastroduodenal arising distally, left hepatic artery injection with esophageal branch arising distally). [35].
2. Perform lobar technetium-99 m macroaggregated albumin (^{99m}Tc-MAA) and segmental ^{90}Y infusion to limit the number of catheterizations of the small segmental branch perfusing tumour [36].
3. Elevated lung shunt fraction limiting the intended dose is rarely an issue because of minimal tumour load (low shunting) and limited prescribed activities (small perfused volumes).

DOSE CALCULATION

1. Single-compartment model dosimetry is adequate and preferred.
2. Target absorbed dose to the treatment volume is at least 190 Gy to ≤2 segments. Contemporary data support the use of 250–300 Gy starting absorbed dose in this scenario [26–28].
3. The committee recognizes through clinical experience that higher doses to the segment (within recognized safety limits) yield better outcomes. An upper threshold dose limit may exist, but it is currently unknown based on the available literature.
4. Most committee members recommend late week 1 (Thurs/Fri) and early week 2 dosing (Mon/Tues) to replicate published outcomes [19]. This is relevant given differing number of microspheres and specific activity depending on the day of the week.

TREATMENT DELIVERY

1. Ensure no contrast refluxes into an adjacent angiosome.
2. The entire tumour (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 2.4 French (or smaller) microcatheter in a segmental branch. Exercise caution if using smaller than 2.1 French due to risk of catheter occlusion and unintentional large residual activity [21, 37].
5. Same-day planning 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 due to shunting) [38].

OUTCOME ASSESSMENT/FOLLOW-UP

1. Ideally use same imaging modality that was used for initial assessment of disease burden (contrast-enhanced CT or multi-phase contrast enhanced MR).
2. If complete mRECIST response at 3–6 months is not achieved, consider re-treatment [24, 39, 40].

STRENGTH OF RECOMMENDATION: A

DEGREE OF CONSENSUS: STRONG

Radiation lobectomy for HCC

Many cirrhotic patients with unilobar HCC are not candidates for surgical resection due to an insufficient volume of future liver remnant (FLR). If hypertrophy of the FLR is induced, these patients may eventually be candidates for surgical resection [41]. In those with significant portal hypertension where resection may never be a possibility, the ability to deliver higher doses to a single lobe may result in prolonged tumour response, while maintaining adequate hepatic function of the unaffected lobe that may hypertrophy [42].

RADIATION LOBECTOMY

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).

PATIENT SELECTION

1. Radiation lobectomy applies to Child-Pugh A patients who would otherwise be resected but:

a) have inadequate future liver remnant (FLR); and/or

b) embedded test-of-time is desired for tumour biology; and/or

c) need the treated tumour to be retracted away from hepatic vein and/or IVC

d) demonstrating tumour response prior to surgery is preferable.

2. Patients should be considered potentially operable candidates without comorbidities that would preclude surgery.

TREATMENT PLANNING

Diagnostic Studies and Target Volume Definition

1. Patients need complete cancer staging imaging prior to this approach being implemented.
2. Contrast-enhanced cone beam CT in the angiography suite should be performed to assess/ensure tumour coverage within the treated lobe.
3. Hepatobiliary scintigraphy is an emerging technique for functional assessment of FLR, but is still considered investigational [43].

Mapping and ^{99m}Tc-MAA

a) Perform lobar ^{99m}Tc-MAA and lobar ^{90}Y infusion.

b) Elevated lung shunt fraction limiting the intended dose may be an issue if tumour burden is high.

DOSE CALCULATION

1. Using a multi-compartment model ^{99m}Tc-MAA, the current threshold absorbed dose of healthy injected liver >88 Gy is based on data with first week dosimetry in a Child-Pugh A [44]. This will ensure at minimum a 10% hypertrophy.
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 patient [44].
3. Vials from Wednesday week 1 to Tuesday week 2 can be used. No optimal day has been identified [45].

TREATMENT DELIVERY

1. Radiation lobectomy is most commonly encountered with right lobe HCC. Treat the right lobe tumour and induce left lobe hypertrophy in anticipation of surgery [42, 46].
2. Treatment should be administered in a lobar manner. 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 tumour infusion (single-compartment dose to segment >190 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 [47].

a) Modified radiation lobectomy is favored over single lobar infusion when technically feasible.

b) If patient does not go to surgery, tumour control has been maximized by performing curative high absorbed-dose segmentectomy treatment.

OUTCOME ASSESSMENT/FOLLOW-UP

1. Imaging with dynamic measuring of FLR is recommended at 1, 3, 6 and 9 months after treatment. Early imaging is particularly recommended in order to assess disease biology as well as identify early hypertrophy and potentially expeditious resection.
2. Allow at least 3–6 months for hypertrophy; a longer wait time is acceptable as long as the tumour is well-controlled. The need for local tumour control is important due to potential long wait times [42, 44].
3. Portal vein embolization (PVE) after lack of hypertrophy from ^{90}Y radioembolization is currently investigational. Radioembolization after PVE is also investigational.

STRENGTH OF RECOMMENDATION: B

DEGREE OF CONSENSUS: STRONG

Several questions remain unanswered with regard to dosing considerations in this population. Direct comparison of several different lobar absorbed doses in a single study would aid in specifying optimal dosimetry to achieve hypertrophy. This approach would also need to be combined with comparison of first versus second week dosing.

Multifocal unilobar/bilobar HCC without macrovascular invasion (MVI)

For multifocal disease that is not amenable to radiation segmentectomy or radiation lobectomy, radioembolization may be considered for durable palliative treatment [3]. Due to the extent of the treated area in this setting, particularly in bilobar disease, an appropriate balance in dose must be reached in order to optimize tumour response without incurring intolerable hepatic toxicity. Studies have shown that higher tumour absorbed doses result in higher rates of objective response [7, 15, 48]. Inadequate radiation absorbed tumour dose may result in suboptimal tumour response, and excessive radiation absorbed dose to the functional parenchyma may lead to adverse outcomes such as hepatic failure due to radioembolization-induced liver disease (REILD) [49, 50].

MULTIFOCAL UNILOBAR/BILOBAR HCC WITHOUT MACROVASCULAR INVASION

TREATMENT INTENT

Palliation and delaying disease progression, combining and/or bridging to systemic treatment. The goal should be to provide optimal tumour absorbed dose and keep non-tumour exposure below a safe ceiling absorbed dose for the following reasons:

a) Most patients are treated with palliative intent due to late-stage disease with large tumour load.

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, or systemic therapy).

PATIENT SELECTION

1. Patients should have Child-Pugh A or early B (≤B7) cirrhosis. If more severe hepatic dysfunction, consider multidisciplinary discussion and individualized patient characteristics before considering ^{90}Y [51–53].

TREATMENT PLANNING

Mapping and ^{99m}Tc-MAA

1. Multiple variations of ^{99m}Tc-MAA administration exist. Options include [36]:

a) Injection of ^{99m}Tc-MAA in the common/proper hepatic artery in order to perfuse the entire liver.

b) Injection in the lobe with higher tumour burden (yields most conservative estimate).

c) Injection in both lobes with a split vial of ^{99m}Tc-MAA into RHA and LHA respectively (ideal for multi-compartment dosimetry).

d) Sequential lobar infusion of ^{99m}Tc-MAA requiring two separate mapping angiogram procedures on separate days (most accurate for multi-compartment dosimetry).

DOSE CALCULATION

1. A multi-compartment dosimetry model is preferred over a single-compartment model to maximize sparing of normal parenchyma.
2. In a multi-compartment model, prediction of the normal liver absorbed dose is typically more accurate than the tumour absorbed dose, especially for small tumours. Targeting up to 75 Gy absorbed dose to the entire healthy tissue (treated and untreated) may be performed safely in a Child-Pugh A cirrhotic patient [48, 54–56].
3. Optimal tumour absorbed dose (i.e., dose associated with response) is >200 Gy [15, 28, 53, 57]. This is only feasible if the multi-compartment model can be applied.
4. A single-compartment dosimetry supports 120 Gy (range 80–150 Gy) to the perfused tissue [21]. The decision on absorbed dose should be based on clinical status, liver function, tumour 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. In general, staged sequential lobar treatment is preferred and the lobe with more extensive disease should be treated first [52, 58]. For highly aggressive bilobar disease in a patient with Child-Pugh A cirrhosis and with good tumour targeting on ^{99m}Tc-MAA (i.e., high tumour absorbed dose; low healthy liver absorbed dose), single-session bilobar treatment can be considered.

OUTCOME ASSESSMENT/FOLLOW-UP

1. Multi-phase 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.

STRENGTH OF RECOMMENDATION: B

DEGREE OF CONSENSUS: STRONG

Due to the wide heterogeneity of patients in this treatment category, multiple potential areas of future improvement exist. Given that safety must be balanced with efficacy in this specific setting, evaluation of microsphere-specific activity (first versus second week shelf-life activity) is warranted. Several different methods exist to evaluate and calculate relative uptake of tumour to normal tissue, which require further refinement. This includes the potential heterogeneity of ^{90}Y uptake within a tumour itself or different amounts of uptake of different tumours within the same patient. These variables will affect the dosimetry calculations and the prescribed activity. Furthermore, the imaging modality (e.g., CT or MR, or MAA SPECT) used for identification and tumour segmentation also affects the estimation of the relative tumour to normal liver uptake.

HCC with macrovascular invasion

Portal vein tumour thrombus (PVT) is a manifestation of advanced HCC and portends a poor prognosis. These patients are not considered transplant candidates, surgical resection is generally not recommended, and chemoembolization has shown disappointing results with respect to toxicities and survival [59]. In contrast, radioembolization has shown promising efficacy in this setting [60]. Recent trials comparing radioembolization to sorafenib in the advanced stage did not show a survival advantage for locoregional therapy [61, 62]. However, radioembolization was delivered with a relatively low activity, which may have resulted in sub-optimal tumour response. The committee speculates that tailored dosimetry algorithms in patients with macrovascular invasion may yield better response rates and survival outcomes [8].

HCC WITH MACROVASCULAR INVASION

TREATMENT INTENT

Treatment intent is palliation and delaying disease progression, combining and/or bridging to systemic treatment. Surgical conversion or downstaging may be possible in rare cases [60].

PATIENT SELECTION

1. Child-Pugh A or early B (≤B7) cirrhotic patients [60, 63].
2. Treatment can be considered for segmental or lobar PVT, with follow-up imaging dictating when to consider adding systemic therapy. For main PVT, early (1 month) post-Y90 combination with systemic agents is advised as survival is limited in this population [60].

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 into both the tumour and to the tumour thrombus. Use of contrast-enhanced cone-beam CT during angiographic mapping can aid in detection of PVT perfusion.

Mapping and ^{99m}Tc-MAA

1. ^{99m}Tc-MAA PVT targeting evaluation should be performed [12].

DOSE CALCULATION

1. Multi-compartment dosimetry is preferred to maximize sparing of normal parenchyma [8].
2. For the multi-compartment model, the ideal candidate has good PVT ^{99m}Tc-MAA targeting and tumour absorbed dose >205 Gy (treatment intensification). A suboptimal response is likely if there is no ^{99m}Tc-MAA PVT targeting or tumour absorbed dose is <205 Gy; in this case, systemic therapy should be considered [8].

TREATMENT DELIVERY

1. An aggressive dosing approach (similar to radiation lobectomy) can be used for unilobar disease and Child-Pugh A liver function.
2. A more conservative approach 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 tumour invasion.

OUTCOME ASSESSMENT/FOLLOW-UP

Multi-phase 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: B

DEGREE OF CONSENSUS: MODERATE

Future directions

It is important to recognize that unlike bland or chemoembolization, radiation is the causal mechanism for cell death and tumour control with ^{90}Y glass microspheres. Therefore, practitioners are encouraged to become well-versed with dosimetry models and recommended dose prescriptions [64]. However, absorbed dose estimates may vary depending on the model applied even when identical clinical inputs (e.g. tumour/perfused liver volumes, hypervascularity) are used. Given this reality, caution is advised when performing cross-study comparisons of absorbed doses and clinical outcomes.

The role of cross-sectional imaging of MAA-SPECT/CT and ^{90}Y-SPECT/CT as a measure of tissue perfusion during planning continues to evolve. Post-treatment, spatial deposition assessed by PET/CT permits analyses of dose-response [65]. Since the goal of radiation treatment planning is to maximize tumour absorbed dose and spare normal parenchyma, future dosimetry strategies will need to incorporate extent of disease and quantify normal functional parenchymal volume to avoid hepatic decompensation, improve tumour response, and personalize treatments.

There are steady advances in our understanding of dosimetry and dose-response. Additional information on the response of normal liver tissue to radiation is needed. As stated in the introduction, this living document will continue to be updated as new data emerge. While the antitumoural efficacy of radioembolization has been clearly demonstrated over the last 20 years by hundreds of centers worldwide, this modality is undergoing a contemporary maturation with the recent advances in dosimetry, dose-response relationship and clinical applicability across all stages of HCC. Other unique applications highlight the versatility of this treatment, with curative intent using segmentectomy, bridge to resection using lobectomy, downstaging to transplantation, treatment-intensification in PVT, and palliative intent in bilobar disease. Despite these established clinical approaches, there remain many research opportunities for treatment optimization, combinations with other locoregional and systemic treatments, implementing more refined 3-D models, understanding retreatment and interaction with other radiotherapies (e.g. peptide-receptor, external beam), and individualization of patient dosimetry.

Disclosures

These recommendations reflect the committee's evaluation of the state of knowledge of clinical and dosimetric

considerations of radioembolization in hepatocellular carcinoma at the time of publication. Periodic review by the committee is anticipated in light of emerging data. Individualization of patient care is advocated as recommendations are not universal. Decisions to modify or disregard these recommendations are the responsibility of managing clinicians. Finally, this publication is not endorsed by any government entity or professional organization.

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Compliance with ethical standards

Conflict of interest All authors are advisors to BTG. Carlo Chiesa received a grant for research and sponsorship for participation to European congresses by BTG. Marnix Lam is an advisor to Terumo and receives research support from BTG, Terumo, Quirem and AAA.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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