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REVIEW INTERVENTIONAL ONCOLOGY

Trans-arterial Radioembolization Dosimetry in 2022

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Abstract Trans-arterial radioembolization is currently performed using ^{90}Y-loaded glass or resin microspheres and also using ^{166}Ho-loaded microspheres. The goal of this review is to present dosimetry and radiobiology concepts, the different dosimetry approaches available (simulation-based dosimetry and post-treatment dosimetry), main confounding factors as main clinical dosimetry results provided during the last decade for both hepatocellular carcinoma (HCC) and metastases of colorectal carcinoma (mCRC). Based on the different number of microspheres or different isotope used, radiobiology of the three devices is different, meaning that tumouricidal doses and maximal tolerated doses are different. Tumouricidal doses described for HCCs were 100–120 grays (Gy) with ^{90}Y resin microspheres and 205 Gy with ^{90}Y glass microspheres. For mCRC, it is 39–60 with ^{90}Y resin microspheres, 139 Gy with ^{90}Y glass microspheres and 90 Gy with ^{166}Ho microspheres. An impact of tumoural doses with overall survival has also been reported. Personalised dosimetry has been developed and is now recommended by several international expert groups. Level-one evidence of the major impact of personalised dosimetry on response and overall survival in HCC is now available, bringing a new standard approach for TARE in clinical practice as well as for trial design.

Keywords Radioembolization · Dosimetry · Hepatocellular carcinoma · mCRC

Introduction

In liver cancer, trans-arterial radioembolization (TARE) currently uses ^{90}Y-loaded microspheres, either glass microspheres (TheraSphere®, Boston Scientific Corporation, USA) or resin microspheres (SIR-Sphere®, Sirtex Medical Limited Australia), and more recently, ^{166}Ho-loaded microsphere (Quiremspheres®, Terumo Europe). The treatment itself (injection of ^{90}Y- or ^{166}Ho-loaded microspheres) is always preceded by a simulation (currently called work-up) including a diagnostic liver angiography with intra-arterial injection, at the treatment position, of ^{99m}Tc macro-aggregated albumin (MAA) to perform a liver perfusion scintigraphy (MAA scan) [1]. For ^{166}Ho-loaded microspheres, the simulation can also be performed with a scout dose of ^{166}Ho-loaded microspheres (Ho-scout) [2].

The goal of TARE is to deliver a tumouricidally absorbed dose to tumours, while sparing normal liver tissue and radiobiological rules apply [1]. For a deterministic radio-induced effect, a threshold-absorbed dose is mandatory to achieve to observe an effect, and the higher the absorbed dose is above this threshold, the more severe the effect is, up to the maximal effect achievable (complete pathological necrosis). Dosimetry is thus a key point for treatment planning, as with external beam radiotherapy.

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However, treatment planning is usually based either on an activity of ^{90}Y, expressed in giga-becquerels (GBq), to administer related to the body surface area (BSA) with SIR-Sphere® [3] or on an absorbed dose delivered to the liver: 80 to 150 grays (Gy) with TheraSphere® [4] or 60 Gy with Quiremspheres® [5]. But in reality, TARE planning should be based on the tumouricidal tumour dose necessary to reach to induce a tumour response, and on the maximal normal liver-tolerated dose to minimise liver damage.

Two dosimetry approaches are available with TARE. The first is simulation-based dosimetry (using the MAA quantification or Ho-scout quantification) prior to the treatment, allowing potential dosimetry personalisation. The second is direct ^{90}Y or ^{166}Ho quantification after the treatment, which is assumed to be more accurate but does not allow for personalised dosimetry. Many dosimetry studies have been performed, mainly during the last decade, and have contributed to a new refinement of TARE based on personalised dosimetry.

Dosimetry Concept

From a physical point of view, an absorbed dose is an energy, expressed in Joule (J) divided by a mass, expressed in kilogram (Kg). Absorbed dose is expressed in J/Kg or in Gy with 1 Gy = 1 J/Kg.

One difficulty is that the radiobiological effect depends not only on the absorbed dose, but also on the dose rate and the heterogeneity of the dose distribution, meaning that the same absorbed dose will not provide the same tissue damage if the dose rate or the heterogeneity of the dose distribution is different [1]. In this situation, tissue damage is higher if heterogeneity is lower [1].

With external beam radiation therapy (EBRT), the dose distribution is homogeneous, as radiation is provided by an external gantry that is fully physically calibrated. This differs with TARE, as the dose distribution depends on the biodistribution of the radio-labelled device injected, which is heterogeneous by nature [1].

Due to the difference in specific activity between ^{90}Y-loaded microspheres (50 Bq/ sphere for resin and 2500 Bq/sphere for glass, at calibration time) leading to a difference in the heterogeneity of the dose distribution (and due to a different physical half-life between ^{90}Y and ^{166}Ho), the radiobiological properties of each product are different, meaning that tumouricidal doses and maximal tolerated doses are different between each product and must be evaluated separately. This point has been evaluated in the simulation study of Walrand et al. [6], demonstrating that the dose leading to 50% of normal tissue damage was lower using ^{90}Y-loaded resin microspheres (40 Gy for a whole liver irradiation) than using ^{90}Y-loaded glass microspheres (60 Gy). This difference was explained by the higher number of ^{90}Y-loaded resin microspheres injected for the same activity (about 50-fold more resin spheres than glass spheres related on their difference of specific activity), which was responsible for a more homogeneous sphere distribution with resin microspheres and thus a higher radiobiological effect.

The difference in the number of microspheres injected for the same activity can also have a potential impact on the embolic effect, with a higher embolic effect with ^{90}Y-loaded resin microsphere, which might have a potential therapeutic effect, especially in the situation of poorly vascularised lesion such as metastases of colorectal carcinoma [1].

It has also been demonstrated that for the same device, specific activity has an impact on the dose distribution at the microscopic level for a same absorbed dose delivered at a macroscopic level. Indeed, a study conducted on pigs with ^{90}Y-loaded glass microspheres [7] found that for an absorbed dose of 50 Gy delivered to the normal liver, at a microscopic level, the volume of the treated liver receiving an absorbed dose higher than 30 Gy was only 28.7% for a high specific activity of 1532 Bq/microsphere (injection on day 4 after calibration) in comparison with 60.1% for a lower specific activity of 193 Bq/sphere (injection on day 12 after calibration).

These two studies underline the complexity of radiobiology of TARE, which depends not only on the absorbed dose, but also on the way it is delivered.

Dose Calculation, Medical Internal Radiation Dose (MIRD) Approach

Several dosimetric approaches are well-recognised: the simplest and most widely used is the MIRD approach; more complex approaches such as the biological effective dose evaluation (BED), uniform equivalent dose calculation (EUD), Monte Carlo simulation and kernel point evaluation [1, 8] are also used in some studies.

The MIRD approach assumes a homogeneous distribution of the doses. As microspheres are not biodegradable and remain trapped in the vessels after initial administration, the effective half-life is supposed to be the physical half-life of the radioactive isotope (^{90}Y or ^{166}Ho) thus simplifying the MIRD equation.

The energy deposition in a mass of 1 kg is 50 Gy for 1 GBq of ^{90}Y, and 15.87 Gy for 1 GBq of ^{166}Ho [6].

The absorbed dose “D” (Gy) delivered to a structure (also currently called Volume of Interest (VOI) or compartment), of a mass “M” (Kg), containing an activity “A” (GBq) of ^{90}Y is then calculated using the following

simplified MIRD formula (which is the same for resin or glass microspheres):

$$D_{(Gy)} = A_{(GBq)}.50/\ M_{(Kg)}$$

For ^{166}Ho-loaded microspheres, the simplified MIRD formula is:

$$D_{(Gy)} = A_{(GBq)}.15.87/\ M_{(Kg)}$$

Usually, the mass of the liver (in Kg) is assumed to be equal to its volume expressed in litres (L) multiplied by 1.03, and the mass of lungs is assumed to be equal to 1 kg.

Doses can be calculated for different VOIs: perfused liver, tumour, normal perfused liver, and lung tissues. Doses can also be extrapolated to the whole liver and the whole normal liver (then taking into account the non-treated liver volume).

In uni-compartment dosimetry, the dose is evaluated only for one VOI, usually for the perfused volume. This is the standard dosimetry approach used for ^{90}Y glass microspheres [4] and ^{166}Ho microspheres [5].

In the multi-compartment dosimetry, doses are evaluated for several VOI, including the tumour and the normal perfused liver.

Tumour control probability (TCP) curves (providing the probability of control for a tumour-absorbed dose) as well as non-tumour complication probability (NTCP) curves (probability of complication for a normal perfused liver dose) can be generated.

Doses can be evaluated for the whole VOI; this is the mean dose evaluation, which is the simplest approach. Doses can also be evaluated for each voxel of the VOI, which is called voxel dosimetry. Voxel dosimetry allows for the generation of dose-volume histogram (DVH), then mixed metrics based on doses and volumes can be generated as the "Dx" which is the minimum dose received by x% of the volume of the related structure (for example, for a tumour, D_{70} is the minimal dose received by a least 70% of the volume of the tumour), or the "Vy" with is the volume (%) receiving a dose $\geq$ y Gy (for example, for the normal liver, the V_{100} is the percentage of the volume of the normal liver receiving at least 100 Gy). These kinds of metrics, currently used with EBRT, are not widely used with TARE and have to be evaluated as they may contribute to new improvements in dosimetry.

Technical Issues and Confounding Factors for Dosimetry Evaluation

Many potential technical issues or confounding factors have to be highlighted in order to have a good understanding of dosimetry, and to be aware of the reasons why several dosimetry studies have brought sometimes poor or contradictory results.

Segmentation Approach

For the segmentation of the volume of interest (and therefore for the volumes evaluation), two approaches are available [1].

The first is diagnostic imaging using computed tomography (CT), magnetic resonance imaging (MRI), or cone beam computed tomography (CBCT). The imaging needs to be co-registered with single photon computed tomography/computed tomography (SPECT/CT) or positron emission tomography PET to evaluate the count number in the VOI. In this situation, only the counts within the anatomically delineated VOIs are taken into consideration for the dose calculation of this VOI. The advantage of this approach is that it achieves the most accurate and reproducible volume definition. However, in case of co-registration error, significant underestimation of the absorbed dose of this VOI can be observed due to an underestimation of the counts in the VOI.

The second approach available is based on a full SPECT/CT (or PET/CT) segmentation, semi-automated and threshold-based, previously validated by a phantom study where the mean error in the volume measurement was lower than 7%, with good reproducibility [9]. In this situation, the segmentation provides both the volume and the counts included in this volume (no co-registration required). However, in some complex cases, the thresholding may be difficult to perform, with potential error in volume assessment.

To overcome segmentation difficulties, a mixed approach can be used: first, an evaluation of volume based on anatomical tools, and a SPECT/CT or PET/CT segmentation with an optimisation of the thresholding to generate volumes closer to anatomical volume (no co-registration warranted, minimisation of volume error potentially generated by SPECT/CT or PET/CT segmentation alone).

The impact of this segmentation approach has been evaluated in a retrospective multicentric study on hepatocellular carcinoma (HCC) patients (TARGET study, Boston scientific); full results are pending.

Blood Flow Preservation and Reproducibility

Blood flow preservation is a major point being discussed more and more when evaluating dosimetry, especially for simulation-based dosimetry, regardless of the microsphere surrogate used (MAA or Ho-scout). Indeed, simulation-based dosimetry cannot be limited to an accurate quantification of the surrogate itself, but is a global approach

including angiographic considerations as blood flow and reproducibility between the work-up and the treatment. Several technical issues may impair the blood flow and reproducibility, such as spasm occurrence [1, 10, 11], proximity of arterial bifurcation [12], speed of surrogate injection [1], and catheter repositioning [13, 14]. Impairment of the blood flow must be researched in each procedure and can be suspected in cases of discrepancy between tumour targeting expected for hypervascularised lesions identified on anatomical imaging (CT/ MRI) and tumour targeting based on CBCT or MAA SPECT/CT.

A strong discrepancy between CT and MRI vascularity and CBCT or MAA tumoural targeting means that the simulation is not accurate due to blood flow impairment and that the simulation-based dosimetry will not be accurate (Fig. 1). In this situation, a new simulation has to be considered.

Several recommendations have been outlined to preserve the blood flow and improve the accuracy of the simulation-based dosimetry [1, 10, 15]:

- Limiting the risk of spasm whenever technically possible avoiding coil embolisation and favouring the use of a floppy catheter
- Limiting the risk of micro-thrombi occurrence (spending as little time as possible in arteries)
- Taking care of bifurcation proximity, (at more than 1 cm from catheter tip, whenever technically possible)
- Slow injection of the microsphere surrogate (over 20 to 30 s)
- Injecting the surrogate and ^{90}Y-microspheres at exactly the same position, including catheter tip orientation in the arterial tree

Tumour Type and Size

The clinical presentation and behaviour of HCC and mCRC are different.

Usually, TARE is used in HCC more frequently in first line, for a unifocal large lesion (or for several lesions), and HCC are typically highly hypervascularised. In fact, the mean reported percentage of MAA injected uptake by HCC is 32% and can reach more than 90% in large and highly vascularised tumours [16]. Tumour to non-tumour uptake ratios (T/NT) are usually high, with a mean T/NT of 7.2 [16].

Metastases treated by TARE, and especially metastasis from Mcrc, are more frequently multifocal disease, with small lesions, hardly previously treated, and with a variable vascularisation (more often less vascularised than HCC). In fact, in one study, the mean MAA incorporated by lesions was only 1.5% [17] and T/NT is usually lower, with a mean value of only 1.7 as reported in one study [18].

Tumour size has a direct impact on SPECT/CT or PET/CT quantification with a risk of partial volume effect. This is the reason why usually dosimetric evaluation of tumours smaller than 2 cm is not done [12, 19, 20]. Furthermore, the smaller the tumour is, the larger the effect of co-registration error on quantification will be. Tumour size also more than likely has an impact on the dose distribution with a more heterogeneous distribution for large lesions due to a more heterogeneous vascularisation and due to frequent necrosis areas. To overcome this issue, injecting more microspheres using a lower specific activity may be of interest (as it would increase the homogeneity of the dose distribution and radiobiological effect). However, more studies are required, as no data comparing the effect of particle number on tumour distribution and clinical outcome are available.

Prior Therapy

Prior therapy such as chemoembolisation [21] or antiangiogenic drugs [22] may induce arterial disorders and weakness, including spasm, occlusion, dissection, and coagulation disorders. In this situation, reproducibility of the two angiographic procedures may be not optimal. High discordance between MAA and microsphere distribution have already been described in this situation [28]. Prior therapy may also have an impact on safety.

The use of ^{99m}Tc Macro-Aggregated Albumin Lung Shunt Evaluation (LSF)

The use of MAA provides an overestimation of lung shunt quantification (and then an underestimation of liver and tumour doses). This is related to the fact that MAA particles are slightly lower in size in comparison with microspheres (90% of MAA particles between 10 and 40µ) and has been definitely demonstrated in a study evaluating LSF based on either MAA or ^{166}Ho microspheres [23].

Correlation between MAA-Based Dosimetry and ^{90}Y-Based Dosimetry

Many studies have compared the values of absorbed doses based on MAA-based dosimetry and ^{90}Y-based dosimetry with discrepant results, and it remains debated whether discrepancies between Y90-and MAA-based dosimetry relate to surrogacy issues of MAA or rather to the ability to deliver both products at the exact same position and under the exact same conditions.

Several of them found a poor correlation between MAA- and ^{90}Y-based dosimetry in tumours and normal liver tissue. They were mainly carried out in patients with metastatic disease using either resin microspheres [14, 24–26]

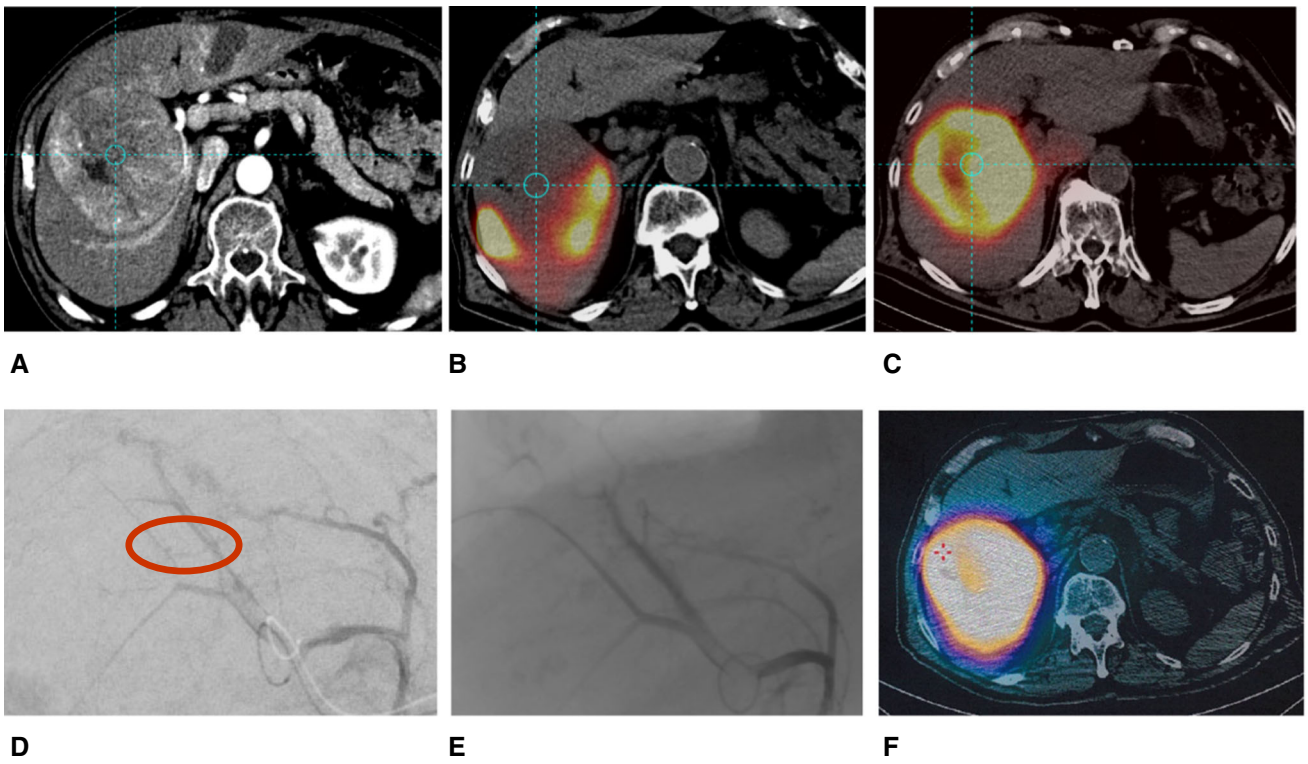

Fig. 1 Evaluation of the concordance between MAA targeting and tumour vascularity. **A** Large hypervascularised HCC on CT scan **B** First simulation with a MAA SPECT/CT showing a clear discordance between MAA targeting and tumour vascularity with about 40% of the tumour not targeted with MAA, suggesting the occurrence of a blood flow impairment and indicating that in this situation MAA-based dosimetry will not be accurate. For this case, blood flow impairment was in relation with a long and difficult procedure to try to optimise the catheter positioning (avoiding the cystic artery) with possibly a sub-optimal catheter position and potential diffuse spasm (± microthombi) **C** Second simulation performed 24 h later, using blood flow preservation recommendations, showing a good concordance between MAA targeting and tumour vascularity, validating the accuracy of the simulation and of MAA-based dosimetry. Comparison of the angiography of the first simulation (**D**) and the second simulation (**E**) showing a blood flow impairment in the first simulation **F** ^{90}Y SPECT/CT after microspheres injection using blood flow preservation recommendations, confirming the accurate targeting

or glass microspheres [13] and most often were biased by several technological issues such as catheter repositioning [24–26] or absence of spasm evaluation [14, 14, 24–26]. However, more and more recent studies, accurately designed, found a strong correlation between MAA-based dosimetry and ^{90}Y-based dosimetry for resin microspheres [28–33] as well as for glass microspheres [12, 20, 28, 29, 32] more frequently for HCCs [12 20–34]. For metastasis, a strong correlation between MAA- and ^{90}Y-based dosimetry was recently found for tumour as well as for normal liver dose evaluation [29], and a strong correlation for the Whole Normal Liver Dose (WNLD) but a weaker correlation for the Tumour Dose (TD) [33] was found in another study.

Usually, the correlation is higher for the Normal Perfused Liver Dose (NPLD) than for the TD [13, 19, 28, 32, 33]. In one study, the correlation was higher for HCC than for mCRC but equal between glass or resin spheres [29].

Correlation between MAA-Based Dosimetry and Clinical Outcome

Instead of focusing on MAA/^{90}Y correlation, many studies in HCC have evaluated and found a good predictive value of MAA dosimetry for response or overall survival for both glass and resin spheres [8, 16, 35–40].

This means, when accurately performed (i.e. avoiding technical issue) from a clinical point of view, MAA-based dosimetry is sufficiently accurate in predicting outcomes, even if some variability exists with regard to the prediction of actual ^{90}Y dosimetry.

Main Dosimetry Results

Hepatocellular Carcinoma (Table 1)

For HCC, the tumouricidally absorbed dose reported based on MAA quantification are between 205 and 257 Gy for

^{90}Y-loaded glass microspheres [8, 16, 35–38] and between 100 and 120 Gy for ^{90}Y-loaded resin microspheres [39, 40] (Table 1). Study type and level of evidence (LOE) are detailed in Table 1.

In the largest study with ^{90}Y resin microspheres evaluated for response (109 patients, RECIST 1.1), the mean TD for patients with disease control was 121.4 Gy vs only 85.1 Gy for patients with progression, $p = 0.0204$ [40]. This study [40] is the post hoc dosimetry analysis of the randomised SARAH trial [42].

In the largest study with glass microspheres (130 lesions, 85 patients) [37], the response rate based on European Association for the Study of the Liver (EASL) criteria was 91% for lesion with a TD $\geq$ 205 vs only 5.5% for a TD < 205, $p < 10^{-3}$. The false positive rate (corresponding to nonresponding lesions with a TD $\geq$ 205 Gy) was quite high, e.g. 33.3% for TDs $\geq$ 205 Gy, and $<$ 260 Gy, and very low, only 3.2%, for TD $\geq$ 260 Gy ($p = 0.0012$), in accordance with the fundamental radiobiology law: "the higher the dose above the threshold dose, the more severe the damage".

An impact on overall survival (OS) has also been demonstrated. With ^{90}Y resin microspheres, a median OS of 14.1 months (95% Confident Interval (CI): 9.6–18.6 months) has been reported for patients with a TD $>$ 100 Gy vs only 6.1 months (95% CI: 4.9–6.8 months) for those with a TD $<$ 100 Gy, $p < 0.0001$ [40]. For ^{90}Y glass microspheres, OS was 21 months (95% CI: 15–27 months) for a TD $>$ 205 Gy vs 6.5 months (95% CI: 3–24 months) for a TD $<$ 205 Gy,

Table 1 Multi-compartment dosimetry results for HCC: TD correlation with response rate (RR) RR and OS

Author/ Study type	Device	Patients/ Lesions	Lesion size *(cm)*	TTD *(Gy)*	RR for TD > TTD	OS for TD > TTD	Dosimetry Approach	LOE
Lau [39] RS	^{90}Y resin	18/na	na	120	87.5% vs 12.5%, $p = 0.005$	55.9w vs 26.5w p = 0.005	MAA	3
Hermann [40] RS	^{90}Y resin	121/na	na	100	na	14.1 vs 6 .1 $p = 0.0001$	MAA	3
Kao [41]	^{90}Y resin	10/na	na	< 91	100%	na	MAA	
Strigari [44] RS	^{90}Y resin	73/na	2.9	110	TCP 73%	na	^{90}Y SPECT	3
Alimant [43] RS	^{90}Y resin	37/na	5	61	TCP 76.5%	na	^{90}Y PET	3
Chiesa [8] PII	^{90}Y glass	48/65	5.6	257	85% vs na	na	MAA	2
Garin [16] RS	^{90}Y glass	36/58	7.1	205	na	18 m vs 9 m, $p = 0.032$	MAA	3
Garin [37] RS	^{90}Y glass	85/130	7.1	205	91% vs 5.5%, $p < 10^{-3}$	21 m vs 6.5 m, $p = 0.0052$	MAA	3
Ho [38] RS	^{90}Y glass	62/na	na	152/174/ 262	na	na	MAA	3
Garin RCT [62]	^{90}Y glass	56/48*		205	22% vs 77% $p = 0.0002$	7.1 m vs 26.6 m $p = 0.0029$	MAA	1
Chan [45] PII	^{90}Y glass	27/38	7.3	200	84% vs na	na	^{90}Y PET	2
Kappadath [46] RS	^{90}Y glass	34/53	4.1	160	50% TCP	na	^{90}Y SPECT	3
D'Abadie [19]	^{90}Y glass	26/73	na	113	na	14.6 m vs 5.6 m	^{90}Y PET	3
RS	^{90}Y resin	19/60	na	61	na	16 m vs 5.3 m $p < 0$ .001		

LOE = level of evidence, RCT = randomised and controlled study, PII = phase 2 study, RS = retrospective study, S = mean lesion size, TTD = tumour tumouricidal dose, TCP = tumour control probability, na = not available, TD available only for 48 patients

($p = 0.0052$), with a relative risk (RR) of death of 2.35 (95% CI:1.26–4.4) for a TD < 205 Gy ($p = 0.0053$) [37]. Impact of TD on OS was even higher for patients with portal vein thrombosis (PVT) with a RR of death of 6.99 (95% CI: 1.98–24.39) for a TD < 205 Gy ($p = 0.0025$) [37].

^{90}Y SPECT/CT or PET/CT dosimetry confirmed a strong dose response correlation with a quite similar range of tumouricidal absorbed dose for HCC than based on MAA quantification, also with a tendency to be a little bit lower between 61 and 110 Gy for resin [19, 43, 44] and between 160 and 200 Gy for glass [45, 46] with only one study [19] providing a significantly lower value of 188 Gy for glass (using anatomical segmentation and a dose point Kernel algorithm).

No dosimetry results are currently available for ^{166}Ho microspheres, but data should be available soon.

Metastases of Colorectal Carcinoma (Table 2)

For mCRC and ^{90}Y microspheres, most of the results have been provided using ^{90}Y resin microspheres and all using ^{90}Y PET dosimetry. Then, developing personalised dosimetry based on MAA dosimetry seems more challenging. It has to be underlined that for mCRC, FDG-PET/CT was used in all studies for tumour segmentation [27, 47–49]. Study type and LOE are detailed in Table 2.

The results of studies with ^{90}Y resin microspheres are quite homogeneous with the tumouricidal dose described between 39 and 60 Gy depending on the study [27, 47, 49].

In the study of Willowson et al. (22 patients, 63 lesions), the mean TD was 51 ± 19 Gy for responding lesions and 26 ± 19 Gy for nonresponding ones, $p < 0.0001$ [27]. The threshold TD of 50 Gy was predictive of response with a sensitivity of 91% [27]. In the study of Levillain et al. (24 patients, 57 lesion), the threshold TD of 39 Gy was predictive of response with a sensitivity of 80% and a specificity of 95% [47]. This value was also associated with an improvement in OS: the median OS was 5 months for a TD < 3 9 Gy versus 13 months for a TD > 39 Gy, $p = 0.0012$, [47].

With ^{90}Y glass microspheres, only one study was reported (85 lesions, 24 patients) [49]. Based again on ^{90}Y PET, the threshold tumour dose predicting a response with the greatest accuracy was 139 Gy (sensitivity 77%, specificity 89%), while a dose of 189 Gy predicted response with a specificity of 99% (but with a sensitivity of 45%) and was associated with better overall survival.

Two studies are available with ^{166}Ho microspheres [50, 51]; in the largest one (133 lesions, 40 patients) [50], the mean tumoural dose was 88% higher in patients with response than in patients with progressive disease (p = 0.011) and a mean tumour dose higher that 90 Gy was associated with a significant better overall survival (HR 0.16; 95%CI, 0.06–0.511; p = 0.0031).

Dosimetry and Liver Toxicity (Table 3)

The maximal liver-tolerated dose is more complex to define, as several confounding factors have to be taken into account, such as toxicity definition (including grade and reversibility), treatment line, underlying liver disease and severity, and hepatic reserve (non-irradiated liver) [1, 8]. NPLD and WNLD can be evaluated as proposed by Chiesa et al. [52] (then taking into account the hepatic reserve).

A specific syndrome has been described by Sangro et al. [53]; the Radioembolisation-induced liver disease (REILD) defined by the occurrence during the first 2 months after TARE of a rise in bilirubin over 51 µmol/L and/or ascites, in the absence of tumour progression or bile duct dilatation.

Studies evaluating liver dose and liver toxicities were mainly performed on HCC patients. Their type and LOE are detailed in Table 3.

Using ^{90}Y resin spheres in HCC patients, Strigari et al. [44] evaluated the NPLD (90Y SPECT/CT, Monte Carlo dose voxel kernel and BED). A NPLD of 52 Gy was predictive of a 50% probability of ≥ G2 liver toxicity in patient treated by a whole liver approach (absence of hepatic reserve). Allimant et al. [43] evaluated the area under the dose-volume histograms (AUDVHs) as dose parameter (^{90}Y PET/CT dosimetry, MIRD approach). Area under dose-volume histograms (AUDVHs) for the normal perfused liver was significantly higher for the patients with liver toxicity (REILD as defined by Sangro et al.) versus those without, respectively, 78.91 Gy versus 53.84 Gy, $p = 0.04$. In a mixed population of patients without underlying cirrhosis, including 71% of patients with mCRC, the mean NPLD was 36.7 Gy for patients with REILD versus only 25.7 Gy for those without REILD, $p = 0.02$ [53].

Using ^{90}Y glass spheres, Chiesa et al. [52] evaluated the WNLD (MAA-based dosimetry, MIRD approach). A WNLD of 75 Gy was predictive of a 15% probability of liver decompensation (any liver decompensation, irrespective of its severity and eventual reversibility). This limit has been updated based on the bilirubin level with a WNLD limit of < 50 Gy if bilirubin is > 1.1 mg/dL and < 90 Gy if bilirubin is < 1.1 mg/dL [54]. In another study [35], the NPLD was evaluated (MAA-based dosimetry, MIRD approach). Neither NPLD nor hepatic reserve alone were correlated with severe clinical permanent liver toxicity (Common Terminology Criteria for Adverse Event (CTCAE) V3, G ≥ 3). Only the association of a NPLD > 100 Gy with a hepatic reserve < 30% correlated with severe permanent liver toxicity ($p = 0.032$). NPLD has been directly evaluated with ^{90}Y PET/CT in one

Table 2 Multi-compartment dosimetry results for mCRC: TD correlation with RR and OS

Author/ study type	Device	Patients/ Lesion	TTD / se	TD (Gy) for R vs NR	OS for TD > TTD	Dosimetry Approach	LOE
van den Hoven [48] PII	^{90}Y resin	30/113	40–60 Gy/ na	na	na	^{90}Y PET	2
Willowson [27] RS	^{90}Y resin	22/63	50 Gy/ 91%	51.7 ± 19.6 vs 26.6 ± 19.6 $p = 1.8\ 10^{-5}$	na	^{90}Y PET	3
Levillain [47] RS	^{90}Y resin	57/na	39 Gy/ 80% 60 Gy/ 70%	na	13 m vs 5 m for TD > vs < 39 Gy, $p = 0.012$	^{90}Y PET	3
Alsultan [49] RS	^{90}Y glass	24/85	139 Gy/ 77%	196 Gy for CR, 177 Gy for PR vs 72 Gy for SD, 95 Gy for PD, $p < 0.01$	Prolonged OS for TD > 189 Gy, ns	^{90}Y PET	3
Bastiaannet* [51] RS	^{166}Ho	36/98	na	290 Gy for R vs 116 Gy for PD, $p = 0.01$	na	^{166}Ho SPECT/CT	3
Van Roekel [50] RS	^{166}Ho	40/133	90/100%	TD 77% higher for R vs PD, $p = 0.011$	HR = 0.15 for TD > 90 Gy, $p = 0.0031$	^{166}Ho SPECT/CT	3

LOE level of evidence; *PII* phase II study; *RS* retrospective study; *TTD* Tumour tumouricidal dose; se sensitivity for response prediction; *R* responders; *NR* non-responders; *CR* complete response; *PR* partial response; *SD* stable disease; *PD* progressive disease; *na* not available; *ns* not significant; *HR* hazard ratio

*Study with mixed population 22 patients with mCRC 15 patients with metastasis of other primary

study (Monte Carlo approach) in 27 patients with HCC and seven with liver metastasis [55]. An NPLD threshold of 54 Gy was predictive of more than 50% liver toxicity probability (toxicities of grade 2, laboratory test taken into account).

For PVT patients, another parameter beyond the normal liver dose had a major impact on safety: PVT targeting [35–37]. Indeed, in two studies, NPLD evaluated either alone or associated with a low hepatic reserve, was not associated with liver toxicity for PVT patients; in this situation, the only parameter strongly associated with liver toxicity was the absence of MAA-PVT targeting [34, 37].

For ^{166}Ho microspheres, the maximal tolerated dose has been defined in a phase one escalation dose study and is 60 Gy to the whole liver [56].

Cumulative liver dose has never been evaluated; this a limit of all those studies for patients with bilobar disease who received two sequential treatments (separated by 1–2 months), and liver-tolerated dose is still a challenge in this situation.

The use of hepatobiliary scintigraphy using ^{99m}Tc-mebrofenin has been proposed to evaluate liver function before TARE [57]. Indeed, hepatobiliary scintigraphy allows for an absolute evaluation of liver function as well as for regional evaluation of liver function (i.e. separate evaluation of the right liver and left liver function). Sufficient liver function is characterised by a ^{99m}Tc-mebrofenin clearance of at least 2.69 ml/min. Based on this evaluation, it should possible to define prior treatment if the function of the untreated liver will be sufficient (^{99m}Tc-mebrofenin clearance of the untreated liver has to be > 2.69 ml/min). However, the situation is not so simple. Indeed, liver function has been sequentially evaluated with ^{99m}Tc-mebrofenin before and after unilobar TARE [58]. A strong reduction in the function of the treated liver was observed but unexpected and transient decrease in the function of the untreated lever was observed until month 2 (minus 20%) before reaching a significant increase in month 3.

Nevertheless, evaluation of liver function could be helpful in difficult situations, i.e. when baseline liver function of the patient is limited, when the hepatic reserve is low, or in case of bilobar treatments.

Table 3 Multi-compartment dosimetry normal liver dose toxicity correlation

Author	Patients	Device/ histology	Toxicity definition	NLD metrics and value	Dosimetry Approach	LOE
Strigari [44] RS	77*	^{90}Y resin/ HCC	Any G ≥ 2	NTCP: 50% for NPLD > 52 Gy	^{90}Y SPECT	3
Allimant [43] RS	37	^{90}Y resin/ HCC	REILD	NPLD: 78.9 Gy vs 53.8 Gy, $p = 0.04$	^{90}Y PET	3
Sangro [53] RS	45**	^{90}Y resin/ HCC: 27% Other: 73%	REILD	NPLD: 36.7 Gy for L_{tox} vs 25.7, without L_{tox}, $p = 0.002$	MAA	3
Garin [35] RS	71	^{90}Y glass/ HCC	Permanent clinically relevant, G ≥ 3	NPLD: 100 Gy + HR < 30% increases risk of L_{tox} $p = 0.032$	MAA	3
Chiesa [52] PII	52	^{90}Y glass/ HCC	Any liver decompensation	NTCP = 15% for WNLD > 75 Gy	MAA	2
Garin [37] RS	85	^{90}Y glass/ HCC	Permanent clinically relevant, G ≥ 3	NPLD: 104.7 Gy for L_{tox} vs 79.5 Gy without L_{tox}, $p = 0.028$	MAA	3
Chiesa [54] PII	52	^{90}Y glass/ HCC	Any liver decompensation	NTCP = 15% for WNLD > 50 Gy and bilirubin level > 1.1 mg/dL NTCP = 15% for WNLD > 50 Gy and bilirubin level < 1.1 mg/dL	MAA	2
Chan [55] PII	35	^{90}Y glass/ HCC	Any G ≥ 2	NTCP: 50% for NPLD > 54 Gy	^{90}Y PET	2
Smith [56] PI	15	^{166}Ho	MTD	WLD: 60 Gy	PA /V	2

LOE level of evidence, RS retrospective study, PII phase 2 study, PI phase I study, NLD normal liver dose, NPLD normal perfused liver dose, WNLD whole normal liver dose, NTCP normal tissue complication probability, L_{tox} liver toxicity, *MTD* maximal tolerated dose, *WLD* Whole Liver Dose, PA/V dosimetry based on prescribed activity and whole liver volume

*Whole liver treatment for all patients,

**Whole liver treatment for 73% of the patients

Dosimetry and Contralateral Liver Hypertrophy

Few studies have evaluated dosimetry and contralateral liver hypertrophy.

It has to be considered that after TARE, contralateral liver hypertrophy could occur in relation with injuries of the normal perfused liver and/or with tumour response (related to a production of cytokine and growth factors) [59]. It is mandatory to keep in mind this concept of two different target tissues as threshold doses inducing tumour damage or normal perfused liver damage.

Only one retrospective study evaluated the potential impact of MAA-based dosimetry and future remnant liver (FLR) hypertrophy in HCC patients treated with ^{90}Y glass microspheres [59]. FLR hypertrophy ≥ 10% was significantly more frequent for patients with a high NPLD (≥ 88 Gy, i.e. in 92.2% for a NPLD ≥ 88 Gy versus 65.7% for a NPLD < 88 Gy, $p = 0.032$). FLR hypertrophy ≥ 10% was also significantly more frequent for patients with a TD ≥ 205 Gy and a tumour volume (TV) ≥ 100 cm^3 in patients with initial FRL < 50%. Finally, FLR hypertrophy ≥ 10% was seen in 83.9% of the patients with either a NPLD ≥ 88 Gy or a TD ≥ 205 Gy for tumours larger than 100cm^3 (85% of the cases), versus only 54.5% (p = 0.0265) for patients with none of those parameters.

Recently, a retrospective study evaluated post-procedural ^{90}Y PET/CT dosimetry in a population of 56 mixed patients (HCC, cholangiocarcinoma and metastases) treated with ^{90}Y resin microspheres [60]. NPLD and normal perfused liver V_{30} (fraction of perfused liver receiving at least 30 Gy) were correlated to FLR hypertrophy especially for patient with a low initial FRL (< 30%). A normal perfused liver V_{30} of 49% was predictive of an increase of the FLR to a value ≥ 40% with the best accuracy (sensitivity 80%, specificity 81.8%, accuracy 80.9%).

For the first time, those two studies supply dosimetry data that could be helpful to personalise treatment with the objective to stimulate FLR.

Personalised Dosimetry

Multi-Compartment Personalised Dosimetry

Multi-compartment personalised dosimetry is necessarily based on the evaluation of the simulation-based dosimetry.

The clinical impact of personalised dosimetry has been evaluated only with ^{90}Y-loaded glass microspheres and for HCC.

A first retrospective study compared 20 patients treated with a standard dosimetry approach (80–150 Gy to the liver) and 51 who received a personalised dosimetry approach targeting more than 205 Gy to the tumour [35]. The RR was significantly improved: 86% with personalised dosimetry versus 55% with standard dosimetry, $p = 0.001$, without impacting the safety profile.

In a second retrospective study focused on PVT patients, including PVT targeting evaluation, personalised dosimetry targeting > 205 Gy to the tumours provided good clinical results in a retrospective study (41 patients) with an OS of 20.2 months for patients with both a tumour dose > 205 Gy and a good PVT targeting on MAA (good candidates) versus only 3 months ($p < 0.001$) if one or both criteria were absent (poor candidate) [36].

In the study of Spreafico et al., the main dosimetry endpoint was to provide the supposed maximal tolerated dose for the whole normal liver, whatever the tumour dose [61]. In this study, 120 HCC patients with PVT were treated using this concept with ^{90}Y-loaded glass microspheres. The median OS reported was 14.1 months (CI 95%: 10.7–17.5) comparing favourably with a median OS of 10.4 (CI 95%: 7.2–16.6) and 10 months (CI 95%: 7.7–10.9) previously reported in studies without personalised dosimetry [53, 54], but comparing less favourably to with results achieved with personalised dosimetry based on targeting > 205 Gy to the tumour (median OS 18 months) [36].

Finally, level 1 evidence of the clinical impact of personalised dosimetry has been provided with the multicentre randomised phase II study DOSISPHERE-01 [62], still using glass microspheres. Sixty HCC patients with large lesions (mean size about 11 cm) and often with PVT (68%) were randomised to receive ^{90}Y glass microspheres either with personalised dosimetry (targeting a TD > 205 Gy and if possible > 250–300 Gy) or standard dosimetry (targeting 120 ± 20 Gy to the perfused liver). The response rate was strongly increased with personalised dosimetry (71% dosimetry vs 36% for standard dosimetry, $p = 0.0074$) as OS, with a median OS more than double with personalised dosimetry (26.6 months vs 10.7 months for standard dosimetry, p = 0.0096).

Uni-Compartment Personalised Dosimetry: Radiation Segmentectomy and Lobectomy

Personalised dosimetry based on uni-compartment dosimetry is also an option when the fraction of untreated liver is sufficient to preserve safety, with the concepts of radiation segmentectomy and radiation lobectomy. In this situation, the goal is to maximise the mean absorbed dose to the perfused volume (without evaluation of the TD and NLD) with the objective to maximise the TD. By definition, with ^{90}Y-loaded glass microspheres, providing more than 150 to the perfused volume is a treatment intensification [35].

Radiation segmentectomy was described first by Riaz et al. in 84 patients with lesions < 5 cm treated by ^{90}Y glass microspheres [63]. Using a high median segmental absorbed of 524 Gy, no clinically relevant liver toxicity was reported [63]. A segmental dose > 400 Gy has been identified to be predictive of complete pathological response in 100% of the cases in 45 HCC patients with a median tumour size of 2.5 cm (min: 1.3 cm–max: 8 cm) [64].

For radiation lobectomy, the DOSISPHERE trial supports the use of lobar dose > 150 Gy if the whole liver dose is < 150 Gy for a Child Pugh A patient and mainly unilobar treatment [62]. Indeed, based on central dosimetry evaluation, 52% of the treated patients received a PLD > 150 Gy, RR was 86.2% versus 33.3% for patients with a PLD, respectively > 150 Gy versus < 150 Gy ($p < 10^{-3}$), and median OS was 30.8 months (95% CI: 11.7-not reach) vs 10.3 months (95% CI: 5.6–17.6) for patients with a PLD respectively > 150 Gy versus < 150 Gy, $p = 0.0064$ (unpublished data from DOSISPHERE study).

International Dosimetry Recommendations

Based on published data, the use of personalised dosimetry is now recommended by four international recommendation papers for HCC and other tumours, regarding ^{90}Y resin microspheres [65–67], ^{90}Y glass microspheres [15, 67], and ^{166}Ho microsphere [67]. Main recommendations for ^{90}Y-loaded microspheres (where more data are available) are summarised in Table 4.

Conclusion

During the last decade, many studies have provided sustained data confirming the dose response relationship awaited with TARE. Tumouricidal doses have been identified for the different devices and for different tumour types. Liver-tolerated doses have also been described also

Table 4 Main international personalised dosimetry recommendations for 90Y microspheres

		Multi-Compartment		Uni-Compartment	
		Tumour Dose	Normal Liver Dose	Rad Seg PLD (1–2 segments)	Rad Lob PLD (lobe)
^{90}Y glass	HCC	> 205 Gy	WNLD < 75 Gy (range 50–90 Gy**)	250–300 Gy	140–150 Gy
		> 250–300 Gy*	NPLD < 100 if HR < 30%	> 400 Gy for HCC CPN	> 150 Gy if WLD < 150 Gy for
	mCRC	> 189 Gy	WNLD < 75 Gy (range 50–90 Gy**)		Child A and HR > 30%
					***
^{90}Y resin	HCC	> 100–120 Gy	PLD < 40 Gy	> 150 Gy	****
	mCRC	> 100 Gy	PLD < 40 Gy		

Values proposed have been provided in the three dosimetry recommendations paper: Salem et al. [13], Levillain et al. [59] and Weber et al. [60]

Rad Seg = Radiation Segmentectomy; Rad Lob = Radiation Lobectomy; WNLD = Whole Normal Liver Dose; NPLD = Normal Perfused Liver Dose; WLD = Whole Liver Dose; PLD = Perfused Liver Dose; HR = Hepatic Reserve (% of liver spared from radiation); CPN = complete pathological necrosis

*For large lesion,

**< 50 Gy if bilirubin level > 1.1 mg/dL and < 90 Gy if bilirubin level < 1.1 mg/dL

***A multi-compartment approach can be used targeting a NPLD > 88 Gy

****A multi-compartment approach can be used targeting a NPLD > 70 Gy

more complex to identify. Personalised dosimetry has been developed and is now recommended by several international expert groups. Level-one evidence for the major impact of personalised dosimetry on response and overall survival in HCC is now available, bringing a new standard approach for TARE in clinical practice as for trial design. New metrics based on voxel dosimetry will likely contribute to further improvements in TARE dosimetry.

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Declarations

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Informed Consent For this type of study, informed consent is not required.

Consent for Publication For this type of study, consent for publication is not required.

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