Radioembolization with ^{90}Y -loaded microspheres: high clinical impact of treatment simulation with MAA-based dosimetry

Etienne Garin^{1,2,3}

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Radioembolization with ^{90}Y -loaded glass or resin microspheres is being increasingly used in the treatment of primary and secondary liver cancers. However, no randomized phase III studies have so far been conducted providing proof of this technique's effectiveness. In colorectal metastatic disease refractory to chemotherapy, its efficacy has been proven by two randomized studies using ^{90}Y -loaded resin microspheres [1, 2]. In hepatocellular carcinoma (HCC), the efficacy of radioembolization in patients with portal vein thrombosis (PVT) was demonstrated a long time ago using ^{131}I -Lipiodol [3], and the results of this large patient cohort are encouraging [4, 5].

The goal of radioembolization is to deliver a tumouricidal absorbed dose to tumours while sparing healthy liver tissue. As radiobiological effects are a crucial factor in this, it is more than likely that the tumour dose (TD) and healthy injected liver dose (HILD) play a crucial role. Despite this, current recommendations are still not based on TD and HILD.

When using glass microspheres, the activity of the ^{90}Y -loaded microspheres to be injected (IA) is calculated in order to deliver a radiation dose of 120 ± 20 Gy to the injected liver volume (ILD), with a dose calculation based on the accepted simplified medical internal radiation dose (MIRD) equation [6]:

$$\text{ILD}_{(\text{Gy})} = \text{IA}_{(\text{GBq})} \cdot (1-S) \cdot 50/W_{(\text{Kg})}$$

where IA represents the activity to be injected, S the percentage of pulmonary shunt, as measured by $^{99\text{m}}\text{Tc}$ -macroaggregated albumin (MAA) liver perfusion scan, and W the mass of the liver volume to be treated.

When using resin microspheres for whole-liver injection, the body surface area (BSA) method is currently the most commonly used approach in ongoing phase III studies, calculating the activity to inject as follows:

$$\text{IA}(\text{GBq}) = \text{BSA}(\text{m}^2) - 0.2 + \text{tumour liver involvement}$$

Applying a partitioning model using the MIRD formula has recently been recommended by a group of experts [7] for delineable tumours with the goal of achieving a TD of 120 Gy and limiting healthy liver irradiation to a dose of 50–70 Gy.

The study by Lam et al. [8], recently published in the *European Journal of Nuclear Medicine and Molecular Imaging*, has provided new evidence of the high clinical impact of MAA-based dosimetry in a large cohort of 122 patients treated primarily with resin microspheres in a whole-liver approach (80 %). TD was significantly correlated to response at 3 months in univariate ($p=0.026$) and multivariate analyses ($p=0.004$). Responders at 3 months had received a median TD of 60.1 Gy, compared to only 32.7 Gy for non-responders ($p=0.026$). Stratified for tumour type, TD was independently associated with overall survival (OS) ($p=0.004$). The authors also evidenced a correlation between total functional liver dose (with 80 % of patients receiving whole-liver injection in this study) and liver toxicity, reporting a median total functional liver dose of 41.2 Gy for the five patients suffering from radioembolization-induced liver disease (REILD), compared to only 27.9 Gy for patients without REILD, ($p=0.01$).

Similar results have already been described while using glass microspheres. In particular, a clear TD-response

✉ Etienne Garin
e.garin@rennes.unicancer.fr

¹ Department of Nuclear Medicine, CS 44229, Cancer Institute Eugène Marquis, 35042 Rennes, France

² University of Rennes 1, 35043 Rennes, France

³ INSERM, U-991, Liver Metabolisms and Cancer, 35033 Rennes, France

relationship in HCC has been independently reported by two studies [9, 10]. A TD exceeding 205 Gy has also been reported as the only parameter associated with response on multivariate analysis, correlating with OS, especially in PVT patients [10]. In the case of unilobar treatment, HILD alone was not correlated with liver toxicity, yet a HILD > 120 Gy combined with a small hepatic reserve (<30 %) highly correlated with permanent liver toxicities ($p < 0.0001$) [11].

Due to the high effectiveness achieved with MAA single photon emission computed tomography (SPECT)/CT-based dosimetry, the concept of personalized dosimetry, with intensification when necessary, in order to achieve a TD > 205 Gy has recently been reported with interesting results [11]. In this study, response rate was significantly higher when using personalized dosimetry, at 86 % compared to only 55 % while using the standard dosimetric approach aiming to deliver 120 ± 20 Gy to the treated liver, regardless of the TD ($p = 0.001$) [11]. In a cohort of 41 PVT patients treated with personalized dosimetry, with intensification in 37 %, the median OS was 18 months [95 % confidence interval (CI) 11–25 months], highly impacted by TD. For patients with a TD < 205 Gy and no PVT MAA targeting, the median OS was only 3 months (95 % CI 3–3.7 months), compared to 20.2 months (95 % CI 12–25.1 months) for patients with a TD ≥ 205 and good PVT MAA targeting ($p < 0.0001$).

Two other points that are of special interest were explored in the Lam et al. study [8]. First of all, their results were primarily obtained with resin microspheres in a metastatic disease context, for which several previous studies reported disappointing results [12, 13], probably due to several parameters, including the disease's multifocality. This difference can be explained by the fact that Lam et al. took care to only include patients with exactly identical catheter positioning between diagnostic and therapeutic angiography. This point has to be rigorously controlled in order to achieve an accurate dosimetric simulation while injecting a tracer during the diagnostic angiography. From this, we can confidently deduce that, in cases of bilobar involvement and sequential treatment in first one lobe then the other, MAA simulation cannot be performed with one sole injection in the common hepatic artery, but has to be performed twice at the precise catheter position.

The second point of interest, which can also explain Lam et al.'s positive results [8], is the tumour segmentation process used. As their population was composed of either multifocal disease or infiltrative tumour cases, namely situations where tumour segmentation was not achievable using a morphological approach, the authors interestingly proposed using a functional dual-tracer semiautomated tumour segmentation technique combining MAA SPECT, for the simulation of ^{90}Y -loaded microsphere distribution, with $^{99\text{m}}\text{Tc}$ -sulphur colloid (SC) SPECT, for identifying functional liver parenchyma, applying a fixed threshold of 10 % for both tracers. This point is

of major interest, as tumour segmentation is highly challenging. Several teams have used mixed functional and anatomical segmentation (anatomico-functional), where the volume of interest (VOI) is delineated using SPECT/CT while ensuring that the VOI boundaries delineated with SPECT correspond to the anatomical boundaries of the structure of interest [10]. With both functional [8] and anatomico-functional [10] methods, SPECT provides the volume and activity count in the VOI. Tumour necrosis (volume and count) is not included in the tumour volume and count analysis, meaning the TD reflects the dose of the vascularized part of the tumour. Other teams have used morphological VOI delineation based on CT and applied this anatomical VOI on SPECT imaging [9]. In this situation, the VOI is defined by means of CT, with SPECT solely providing the activity count. Here, the TD takes into account tumour necrosis, leading to it being underestimated compared to functional or anatomico-functional methods. We strongly believe that further studies are warranted to optimize tumour segmentation and dosimetric evaluation.

Lam et al. [8] also rightly underlined the fact that dosimetric results and threshold should be interpreted with caution, given the numerous confounding factors that can be encountered, such as the different radiobiological properties of available ^{90}Y -loaded microspheres [14], histological tumour types with different radiosensitivity profiles, underlying hepatic disease, the different dosimetric tools used, as mentioned above, and so on. These points must be kept in mind when analysing study results.

We conclude that MAA simulation using MAA-based dosimetry is, if properly performed, a highly accurate pre-therapeutic factor correlated with response, hepatic toxicity and survival. This point is of particular significance for three main reasons. First of all, given that MAA dosimetry is available prior to therapy initiation, it can lead to a fully personalized approach with a better selection of responders, improved identification of patients at risk of liver failure, and can even be used for treatment intensification, as recently suggested [11, 15]. Secondly, a more personalized oncological approach is believed to potentially yield superior clinical results. This last point certainly appears to be true when using MAA SPECT/CT dosimetry and intensification for PVT patients, with an OS rate reaching 20 months for good candidates [15]. Lastly, the availability of this predictive factor of response and survival prior to therapy initiation is a clear advantage for radioembolization, as this is not the case with other therapeutic approaches used for liver cancer, such as chemotherapy, targeted therapies or chemoembolization. Even if further studies still need to be performed in order to improve MAA dosimetry effectiveness, this technique should be included in prospective trials aiming to evaluate radioembolization efficacy, as this has never before been investigated.

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