

# The ten commandments of hepatic radioembolization: expert discussion and report from Mediterranean Interventional Oncology (MIOLive) congress 2017

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**Abstract.** – Microsphere and particle technology represent the next-generation agents that have formed the basis of interventional oncology, an evolving subspecialty of interventional radiology. One of these platforms, yttrium-90 microspheres, is increasingly being used as a treatment modality for primary and secondary liver tumors. Due to the widespread use of radioembolization, a comprehensive review of the methodologic and technical considerations seems to be mandatory. This article summarizes the expert discussion and report from Mediterranean Interventional Oncology Live Congress (MIOLive 2017) that was held in Rome, Italy, integrating evidence-reported literature and experience-based perceptions, to assist not only residents and fellows who are training in interventional radiologists but also practicing colleagues who are approaching to this intra-arterial treatment.

*Key Words:*

Liver, Radioembolization, HCC, Metastases, Locoregional treatment.

## Introduction

Microsphere and particle technology represent the new-generation agents that have developed the basis of interventional oncology, an evolving subspecialty of interventional radiologists. One of these platforms, yttrium 90 (Y90) microspheres, is increasingly being used as a treatment modality for primary and secondary liver tumors<sup>1-4</sup>.

Due to the widespread use of radioembolization, a comprehensive review of the methodologic and technical considerations seems to be mandatory. In particular, to help achieve maximal technical success and limit complications, a series of tips and tricks of the trade should have to be underlined.

This work summarizes the expert discussion and report from Mediterranean Interventional Oncology Live Congress (MIOLive 2017) that was held in Rome, Italy.

The aim of this paper is to integrate evidence-reported literature and experience-based perceptions, attempting to make the information easy to access using a point format, to assist not only residents and fellows who are training in interventional radiologists but also practicing colleagues who are approaching to this intra-arterial treatment. Accordingly, we have organized these principles into a “ten commandments” framework.

### ***I. Accurate Selection of Patients: Radioembolization (RE) Must be Administered to the Most Appropriate Candidates***

Discussions within multidisciplinary board (MDB) should be based on published scientific evidence, as well as a personalized approach to each patient's circumstance. There is now increased evidence (SIRFLOX study) that RE with Sir-Spheres provides a remarkable increase in the Progression-Free Survival (PFS) in the liver (7.9 months in median PFS, from 12.6 to 20.5 months) in patients with metastatic colorectal carcinoma (mCRC), with 31% reduction in risk of progression and 3-fold increase in complete response rate in the liver<sup>5</sup>. The study, however, failed to show a significant improvement in the overall PFS. Yet, it is important to consider that almost 10% of the RE arm (intention to treat) did not receive RE and that approximately 50% of the cases had synchronous liver metastases and/or an unresected primary tumor. In spite of these unfavorable characteristics, RE has demonstrated control of the liver metastases. The inclusion of the SIRFLOX data with respect to the overall survival (OS), a secondary objective of the study, will be incorporated into another two randomized trials (Foxfire and Foxfire Global) which are designed to obtain data, concerning OS, based upon a target recruitment of more than one thousand patients. The information will be achieved in 2017 and will help facilitate defining the role of RE in the first line treatment of mCRC. RE has demonstrated a definitive increase in OS and in PFS in patients in whom RE has been incorporated after several lines of chemotherapy (refractory cases) when compared with best supportive care (BSC).

Three articles published in 2010-2011 (comprising >700 patients) offered important information with respect to RE (both glass and resin) for the treatment of hepatocellular carcinoma (HCC). They showed differences according to the BCLC

staging, gave better results in Child-Pugh A and remarkably demonstrated, not only that RE could be safely administered in patients with tumoral portal vein thrombosis (PVTT), but also that if PVTT was segmental or subsegmental, outcomes were similar to the group without PVTT. These series, together with several clinical trials that compare RE with Sorafenib, will definitively give light to understanding in which subgroups of BCLC B and BCLC C should be the first option of treatment<sup>6-14</sup>.

Furthermore, several reports have also demonstrated the clear benefit in terms of OS, PFS and clinical and analytical improvement of the use of RE for the treatment of liver metastases from neuroendocrine tumors<sup>15</sup>. They have proven a marked increase in the tumoral response in patients with other metastatic disease such as breast, pancreas, and melanoma<sup>16</sup>.

### ***II. Preserve as much Healthy Liver as is Possible: Any Patient Could Potentially Become a Surgical Candidate***

While discussing in the Multidisciplinary Tumor Board how to design the treatment strategy for every particular patient, some of them will be allocated to receive a palliative treatment depending on the staging, the tumor burden, and the presence of comorbidities. Some others will be guided towards a curative method (surgery and/or percutaneous ablation) and some will be initially treated by non-curative methods, but, depending on the response and if correctly downstaged/downsized, could in theory ultimate once again become candidates to receive surgery/ablation. Taking into consideration the above, when defining how RE should be administered if selected, it is highly recommend to treat just the tumoral area and avoid, as much as possible, to irradiate healthy tissue. The reasons for this strategy are, basically, two: first by sparing healthy liver, the possibility of provoking RadioEmbolization Induced Liver Disease (REILD) (ascites and, with the absence of bile obstruction, jaundice) markedly decreases, and second because RE will trigger a mechanism of hypertrophy of the remnant liver quite similar (8 weeks) to that obtained with Portal Vein Embolization (PVE)<sup>7,18</sup>. However, it should be noted that RE is a treatment option for liver tumors (radiation lobectomy) whereas PVE is a technique to increase the volume of healthy liver parenchyma<sup>19,21</sup>. As said, sparing healthy liver allows its hypertrophy and if the tumor is correctly downstaged the patient can receive a cu-

rative treatment, something that, for sure, would not be so easy if the whole liver has been treated with RE and the remnant liver is insufficient<sup>22,23</sup>.

### **III. Careful Evaluation of Liver Anatomy, Using Angio-CT/MR, to Avoid Undertreated Areas**

The technical improvement of sectional imaging methods (CT and MR) currently allows obtaining accurate and precise informations about the visceral vascular anatomy. It is highly recommended to carefully analyze the vascular anatomy before performing the angiographic evaluation<sup>24-27</sup>. The reasons for this is twofold: firstly, to define the vascular pattern of the liver, with the predictable hepatic arterial variants, identifying aberrant vessels, classified as accessory or replaced, according to the Michels classification; secondly, to detect/exclude eventual extra-hepatic non-predictable aberrant vessels. In particular, inferior phrenic, right and left internal mammary, right and left gastric, cystic, and omental arteries are well known extrahepatic collateral pathways supplying HCC<sup>28,29</sup>. In clinical practice, certain configurations of aberrant hepatic arteries may be missed when radiologists do not use a systematic approach to identify these anatomical variants. This may compromise the treatment efficacy of RE, due to inadequate biodistribution of radioactive microspheres, with a high rate of residual tumor that could be erroneously diagnosed as a recurrence in a follow-up study. The lack of the accuracy of identifying the precise vascular afferents may render under-treatment with poor consequences both for the patient and for the credibility of the method itself.

### **IV. Use Microcatheters: You Want to Avoid Vascular Spasm/Damage**

Most patients with metastatic liver disease have received multiple prior courses of therapy prior to the indication to interventional oncologic treatment. Some of them may have received anti-angiogenetics, such as Bevacizumab, that can modify the vascular humoral network, also potentially changing the response to any direct stress of the hepatic vessels<sup>30-33</sup>.

To improve the Y90 tumoral uptake, it is highly recommended to perform RE at least 6 weeks after the last administration of Bevacizumab. Similarly, in such cases the diagnostic catheters (4 or 5 Fr) should be placed just at the origin of the visceral trunks (celiac and superior mesenteric) and the complete angiographic work-up

carried out just with microcatheters. Moreover, to avoid any endothelial damage, in patients in whom the right gastric artery needs to be occluded, it may be recommended to access to its origin using a reverse approach via the left gastric, taking advantage of the connections between the left and the right gastric arteries<sup>34</sup>.

### **V. Embolize Only if Needed: Over Embolization or Unneeded Occlusions may Provoke the Opening of Collaterals**

The selection of the treatment strategy has evolved over the last several years. RE was initially applied, in many cases, as a rescue procedure once several lines of chemotherapy were already given. In such a palliative setting, RE was administered as a whole liver treatment by a single injection from the common/proper hepatic artery. In order to avoid complications, the gastroduodenal and the right gastric arteries were systematically embolized by placing occlusion devices (coils, microcoils, etc.) at their origins. Both RE indications, as well as the methodology used, have evolved and now treatments are delivered from more distal (lobar, segmental) arteries and whole liver treatments are administered in a multilobar setting<sup>35,36</sup>.

The unnecessary occlusion of major gastro-intestinal arteries may facilitate the undesired re-opening of collaterals, from distant/smaller pedicles, which may, at the moment of the treatment, allow the passage of particles to undesired allocations. Thus, it is a clear recommendation to avoid the indiscriminate occlusion of vessels, and not just because it increases costs and procedural time<sup>37-39</sup>.

### **VI. Participate in the Calculation of the Dose: You Have Unique Information About the Patient**

Several techniques that have been incorporated along the past years have allowed an increase in the image accuracy as well as in the understanding of the angiographic information. The use of Cone-Beam Computed Tomography (CBCT) has certainly increased the effectiveness of a wide variety of procedures and, undoubtedly, those targeted to liver tumors<sup>40-42</sup>.

In the case of RE, CBCT allows the detection of any extrahepatic (abdominal) uptake and some authors have documented sensitivities greater than even that of (99m)Tc-macroaggregated albumin (MAA) SPECT-CT. In segmental treatments, as well as in cases of bilobar infusions for which

the activity has been divided in two or more vials, it is a unique method to identify the tumoral arterial afferents that need to be specifically targeted<sup>43-46</sup>.

It is, thus, quite relevant to include angiographic information and not just volumetric or laboratory data, for deciding the treatment strategy that is going to be applied to each specific patient.

### ***VII. Pay Attention to the Flow: You Want to Deliver the Treatment to the Right Place***

Liver tumors, mainly HCC, are hypervascular. In a wide variety of patterns, they contain a complex vascular network with dilated and tortuous arteries replete with arterio-venous shunts. These peculiarities have a direct impact in the amount of blood flow that is diverted towards the tumor even stealing flow to the healthy/non tumoral liver parenchyma. These circumstances, together with some characteristics (such as morphology of a bifurcation or vessel angulations) that are inherent to the vascular morphology create a scenario in which, sometimes, the accurate prediction of the dose that a precise tumor volume is going to receive becomes difficult<sup>47-51</sup>.

It is fundamental to familiarize oneself with the above said conditions and to interact with them as much as possible. Just as the selection of the device that is going to be used (such as microcatheters) becomes very relevant, so too the same can be said for the velocity of the injection of the particles or the convenience to specifically divide the activity in super-selective branches.

### ***VIII. Try to Perform the Whole Procedure in One Day: You Want to do it Quicker and Safer***

RE is a two-step procedure. The selection of the specific candidates as well as the calculation of the personalized activity requires an angiographic/gammagraphic work-up that needs to be performed prior to the administration of Y90. Classically, it has been established that the planning procedure is usually scheduled around 7-10 days before. To avoid the shortcomings that the strategy renders (delay in the treatment and need to hospitalize the patient twice), it is becoming more common to perform both procedures on the same day<sup>52,53</sup>. The implementation of this approach requires three basic conditions. First, a well-trained multidisciplinary team that works together in a short time period. Second, the need

to hold an interventional radiology suite while the patient is being imaged in nuclear medicine. Third, the preselection of which patients may be good candidates for such a strategy. In detail, a same-day procedure can be applied to almost any case with non-primary tumors that do not present any sign (CT/MR) of vascular infiltration. In these cases, the work-up will most probably not preclude the later administration of Y90 and its valuable information will be focused towards the final calculation of the activity. Primary tumors, mainly with vascular infiltration, must require a careful and personalized evaluation because some of them are likely to have a high hepato-pulmonary shunt which could preclude the administration of Y90<sup>54-56</sup>.

Finally, adoption of the multiple vial approach for RE, summing to the overall desired activity (for example, two vials of 15 GBq and 5 GBq instead of a single 20-GBq vial) permits flexibility and adjustment on the day of treatment once the actual lung shunting fractions (LSF) and on-site dosage adjustments are complete.

### ***IX. Evaluate the Post Y90 Imaging: You Want to Know Where the Treatment Has Been Finally Delivered***

Tc99 MAA SPECT-CT as well as CBCT, although essential for the pre-procedural RE work-up, can only provide an approximate calculation of the final dose that the tumor is going to receive. The acquisition of Y90/PET-CT, obtained within 24 hours following treatment, is now becoming as a commonly accepted standard for more accurate quantification of the dose received. The information obtained is also very relevant for knowing in which patients there has been extra-hepatic delivery of Y90, rendering that particular patient theoretically exposed to post-procedural complications<sup>57-61</sup>.

### ***X. Follow-up of the Patient: You Want to Know the Efficacy of What You Have Done***

The participation of an interventional radiologist in the treatment of a patient does not finish with the correct performance of the procedure or the early detection of possible related complications. Their commitment must continue not just for clinical implications, but also for increasing the understanding of the method itself. If tumor recurs it is very important to know in which specific areas (tumoral or non-tumoral liver) has it occurred<sup>62-66</sup>.

## Conclusions

Transcatheter Arterial RadioEmbolization is a minimally invasive procedure with an established role for the management of primary and secondary hepatic tumors. Factors that contribute to clinical success include appropriate patient selection, a comprehensive work up and enrolment in a MDB management program. Factors that contribute to technical success include careful attention to hepatic as well as extra hepatic arterial anatomy and a conservative approach to embolization. Finally, long-term follow up is mandatory not just for clinical implications, but also for increasing the understanding of the method itself.

In conclusion, radioembolization requires familiarization and practice of all these aspects to provide an effective and safe treatment.

## Conflict of interest

The authors declare no conflicts of interest.

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