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Streamlining TARE or personalizing SIRT? Different philosophies to treat different HCCs with Yttrium-90…

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The use of Yttrium-90 microspheres in liver malignancies is known by two names: Selective Internal Radiation Therapy (SIRT) and TransArterial RadioEmbolization (TARE). Interestingly, the two names reflect two representations of the therapy, and might be a reason why the role of SIRT in the field of Hepatocellular Carcinoma (HCC) treatment is still not clear in the mind of many clinicians. While some guidelines (i.e. EASL's) do not recommend its use, others (i.e. ESMO's) do recognize some space in the therapeutic armamentarium [1,2]. The negative view is clearly related to the negativity of 3 phase III trials in the advanced setting in comparison with sorafenib, and the limited prospective data in other contexts [3–5]; but the positive view of other guidelines is also based on major opportunities offered by the therapy (for example in case of macrovascular invasion) and suggested in many retrospective studies, as well as limitations of the phase III trials [6–8]. While SIRT refers to the treatment as a radiation therapy, TARE refers to the treatment as a transarterial therapy, and this has important implications as the way the treatment delivery might be conceived.

In this issue of Journal of Hepatology, Gabr *et al* from the Chicago team describe the absence of risk of significant lung shunt fraction (LSF) and consecutively the absence of risk of high lung doses and toxicity in a cohort of patients treated with TARE for small lesions (UNOS T1/T2, HCC <5cm). This is in line with their growing interest in the "radiation segmentectomy" approach of delivering TARE in a segmental approach, similarly as TACE is now given selectively rather than as a whole-liver approach [9].

From their large cohort of patients, they focused on a population with tumor <5cm who received TARE, and specifically on the population of patients without TIPS (n=410). They demonstrated in this population that the risk of significant lung irradiation is non-existent. Indeed, the maximum lung dose was 14Gy, well below what is known to be at-risk for lung toxicity with SIRT (30Gy). Overall, their results are consistent with previous works, from their team and others, that showed that tumor size and macrovascular invasion were among the most important predictive factors for LSF [10,11].

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Importantly, they clarify the clinical usefulness of previous results by clearly defining a population who might be spared LSF evaluation.

The results presented here might have important implications for TARE diffusion. TARE is often viewed as a complex treatment modality, only feasible in expert centers. In the limits of the population well defined in this paper by the Chicago team, the possibility to offer a one-day treatment, without evaluation of the MAA scan, might greatly facilitate the adoption of this treatment modality. It might spare time, hurdles and possible adverse events for the patients, as well as time and cost for the health system. Other approaches have also been developed to streamline TARE, such as faster SPECT analysis [12].

However, we believe that streamlining might not be the only way to improve the diffusion of the technique, and we would like to stress out that MAA-SPECT usefulness is not limited to the search of LSF or extra-hepatic deposit. Our team and others have for several years worked around the very straightforward notion that response to SIRT treatment is related to the dose delivered to the tumor [13,14]. As SIRT is a radiation therapy, one might be surprised to learn that the current way to prescribe the activity injected is based for glass-microspheres on the dose delivered to the injected liver (considering in the same volume tumor and non-tumoral tissues), and for resin-microspheres on the body surface area… in both case without considering the way the dose is distributed between tumoral and non-tumoral tissues. We therefore developed the “personalized dosimetry” approach, in which the activity prescribed is calculated to offer a sufficient dose to the tumor (>205Gy), at the same time ensuring that the dose to the normal liver is not excessive (<120Gy) [15].

As was recently conceptualized in an expert statement about SIRT, we should now more clearly distinguish different clinical scenarios in which SIRT is applied [16]. As exemplified in the Figure, different clinical scenarios lead to different requirement from MAA-SPECT.

Figure legend: Different clinical scenarios for the use of SIRT in HCC, with related consequences about the usefulness of MAA analysis.

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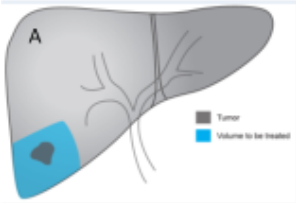
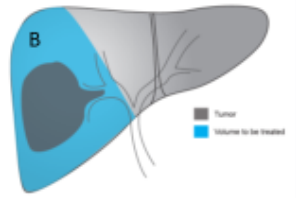
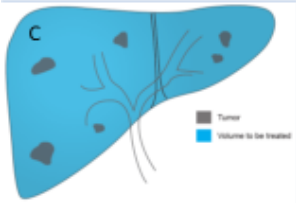
Clinical scenario	Lung shunt fraction evaluation	Extrahepatic deposit	Dosimetric considerations
	No risk of significant shunt if no TIPS	No risk if segmental infusion	**Segmental infusion** associated with: - High concentration within a small tumour - Low volume of non-tumoral liver irradiated => **Compartmental dosimetry not required**
	Significant risk of shunt	Possible risk	**High volume lesion** associated with: - 1st priority: High dose to the tumour for efficacy - 2nd priority: Dose delivered to the non-tumoral liver, relative to the hepatic reserve, for safety - In a pre-operative case, dose to the non-tumoral liver associated with contralateral hypertrophy => **Personalized dosimetry required**
	Possible shunt	Possible risk	**Whole-liver injections** (usually in 2 sessions) and multiple tumour associated with: - 1st priority: Low dose to the non-tumoral liver for safety - 2nd priority: High dose to the tumours for efficacy - Multiple lesions to delineate => **Complexity of the dosimetric approach**

When treating a small tumor using the “radiation segmentectomy” approach (Figure 1A), the current study clearly shows that MAA analysis could be spared, as there is no risk of high lung doses, low risk of extrahepatic deposit, and no role for personalized dosimetry. Conversely, when treating a high volume unilobar tumor, especially in case of macrovascular invasion (Figure 1B), the MAA analysis is not only required to ensure rule out LSF or extrahepatic deposit, but is also a requirement for adopting a personalized dosimetric approach, to ensure efficacy, and in some cases also to allow for contralateral hypertrophy in a downstaging setting [17]. In the scenario of multifocal disease (Figure 1C), which might have been a frequent occurrence in the phase III trials conducted vs sorafenib, the role of dosimetry might be more complex, as obtaining an adequate dose to every tumor might be made impossible without increasing the dose to the normal liver to an at-risk area.

The present work is important for the diffusion of TARE to allow streamlining in case of small tumors. This is important for the philosophy of TARE as an intra-arterial therapy. However, we must not forget that in other cases MAA-SPECT is an absolute requirement to improve oncological outcomes, especially in case of large tumors using personalized dosimetry SIRT. This is important for the philosophy of SIRT as a radiation therapy. Despite negative trials, there are still important avenues for research in the delivery of Yttrium-90 microspheres to strengthen its role in HCC treatment.

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Defining the adequate population, choosing the adequate philosophy to apply to this population, and using appropriate dosimetry methods to test this population/philosophy combination in future clinical trials are absolutely required if we want to achieve this goal.

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