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LETTER TO THE EDITOR

Hepatic supraselective radioembolization, today and new horizons

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Dear Sir,

We read with great interest the article by Jafargholi Rangraz et al. recently published in EJNMMI Research [1], which invites reflection on the evolution of hepatic radioembolization in recent times.

Selective arterial irrigation of liver tumors, unlike portal irrigation of healthy parenchyma, served the basis for the initial intra-arterial therapies around the 1950s with the first radioembolization with Yttrium-90 (Y90) through the celiac axis not actually practiced until 1965 [2]. Then, a homogenous intra-abdominal distribution of the ceramic microspheres was indicative of therapeutic success with, surprisingly, good tolerability, low rate of complications, and symptomatic improvement [3].

It was not until the late 1980s, however, that first glass and resin microspheres were developed, and first phase 1 trials launched. Since then, transarterial radioembolization (TARE) has been used for the local treatment of primary and metastatic liver disease.

In recent decades, progress in the knowledge of liver pathology and radioembolic therapy has brought continuous change of therapeutic indications, activity calculation models, pre- and post-treatment dosimetric models, and, overall, a whole redefinition of the therapeutic objective of TARE.

Initially, the tissue to be treated included the whole liver parenchyma in cases of bilobar involvement but observation of radiation-dependent liver damage, especially in multi-treated patients or in those with low functional reserve, led to a more conservative approach of separate management of each hepatic lobe.

More recently, new research into the concept of radiation segmentectomy, especially suitable for lesions smaller than 5 cm, has shed light into the suitability of this treatment for patients with small lesions confined to ≤ 2 segments.

In the pivotal study describing this technique, researchers were able to selectively deliver Y90 microspheres to ≤ 2 segments of the liver with median doses of 512 Gy and 210 Gy assuming uniform and non-uniform distributions, respectively [4]. These ultra-high doses greatly exceeded the tumoricidal dose of 120 Gy recommended to treat hepatocellular carcinoma. Importantly, toxicities remained low with no signs of radiation-induced liver disease.

The activity calculation model takes into account the volume to be treated. To calculate this volume, different segmentation and volumetric software have been developed to enable establishing a minimum of a segment containing the whole tumor. However, it is not uncommon that a lesion does not respect the expected vascular anatomy or is not included in the angiosome of the corresponding segment, leading to undertreatment if it is excluded from the irrigation of the segment to which it belongs.

New radiological techniques like cone beam computed tomography (CBCT) allow to define, prior to the administration of the macro-aggregated albumin technetium-99m, the area irrigated by the segmental artery and even reach the tumor-feeding vessels. These supraselective treatments allow (with smaller gauge catheters) for a more distal approach and delivery of higher radiation doses. Furthermore, the image obtained in the radiological study offers the possibility of quantifying the intrasegmental volume to be treated, permitting subsegmental treatments or even radiotumorectomies. These procedures offer actual dosimetric and, therefore, a much more accurate therapeutic result. Additionally, this greater selectivity reduces post-radioembolization liver damage while it broadens the scope to

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patients with limited liver function. In our experience, supraselective treatment has represented a clear improvement, allowing to increase up to 100% the administered activity in selected patients, with clearly higher response rates.

In conclusion, TARE has seen an incessant evolution in recent decades, always aimed at maximizing therapeutic customization, seeking greater radiotherapeutic effect, and lowering iatrogenic risk. This progress has also facilitated the design of more accurate dosimetric pre-treatment models. We face, therefore, a phenomenon of rapid renewal in which is essential the commitment of the multidisciplinary medical team and the application of the most modern and specific software. As authors of the article of multi-modal imaging for TARE software, that gives rise to this reflection, suggest, new molecular and radiological imaging technologies like CBCT, will let for more accurate planning of radioembolic treatment. Any health institution that has these technologies should take advantage of them for the benefit of the patient and the development of the technique.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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

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