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Pre-therapeutic dosimetry evaluation and selective internal radiation therapy of hepatocellular carcinoma using yttrium-90-loaded microspheres

To the Editor:

We have read with great interest the recent review article by Sangro *et al.* published in the *Journal of Hepatology* [1], which demonstrated that selective internal radiation therapy (or radioembolisation) with yttrium-90-loaded microspheres constitutes a promising therapeutic approach for the management of hepatocellular carcinoma.

The authors judiciously recollect that the concept of radioembolization is based on the delivery of a tumoricidal dose to the tumor, while sparing healthy liver tissue. This point is of paramount importance, as the chief active principle of radioembolization is associated with ionizing radiation, making it necessary to reach a threshold tumor absorbed dose in order to achieve good efficacy. As reminded by the author, the absorbed dose depends on: (i) injected activity; (ii) tumor vessel density; (iii) arterial flow. These last two features are tumor characteristics that cannot be modified, except, possibly, when combining radioembolization with the administration of antiangiogenic substances. However, the injected activity is modifiable. It is thus crucial to be able to retain reliable dosimetry models for therapeutic planning.

Sangro *et al.* claimed that there is no correlation between the scintigraphic distribution of technetium-99m-labeled macroaggregates of albumin (Tc-99m-MAA) and that of microspheres, and thus there is no reliable dosimetry model. However, this is only the case for resin microspheres (SIR Sphere, SIRTex Medical Limited, Sydney, Australia). The study conducted by Knesaureck *et al.* [2], which is referenced in the Sangro publication, clearly showed that only resin microspheres had no correlation. Data relating to glass microspheres was not provided.

The Milan team [3], revealed a strong correlation between the tumor-absorbed dose, which is based on Tc-99m-MAA hepatic arterial perfusion scintigraphy, and tumor responses for treatments using glass microspheres (TheraSphere, MDS Nordion, Ontario, Canada). Therefore, contrary to Sangro's conclusion, MAA-based dosimetry appears reliable when using glass microspheres. These results have been confirmed by our research team [4].

This difference in the prognostic value of Tc-99m-MAA dosimetry using either glass microspheres or resin microspheres prior to performing radioembolisation may be accounted for by fundamental differences between the two products.

As highlighted by the authors, the specific activity of glass microspheres is 50 times higher than that of resin microspheres (2500 Bq per sphere *vs.* 50 Bq per sphere). Consequently, for the same injected activity, the embolic effect is much higher and well-recognized with resin microspheres, requiring slow administration, with repeated angiographic controls for detecting reflow during the procedure. The consequences include an increased risk of gastric ulcer [5], intrahepatic reflux (accidental injection of total liver during selective injection into the liver lobe that was not detected on angiography), and reflux from the treated liver area into the non-tumor liver tissue.

Therefore, the injection of small amounts of MAA appears to exhibit a good predictive value of response when using glass microspheres, which have a low embolic effect, and a poor predictive value of response when using resin microspheres, which have a high embolic effect.

It is also important to stress that the maximal activity significantly differs between the two products, which is crucial from a radiobiological point of view: 3.2 GBq for resin microspheres *vs.* 20 GBq for glass microspheres. Previously, we established a mean tumoral threshold dose of 205 Gy in order to achieve a response [4]. This threshold dose of 205 Gy enables response prediction with an accuracy of 91%. In this study, overall survival of patients having received a tumor dose $\geqslant$205 was significantly higher compared to that of those having received a tumor dose <205 Gy (18 months [95% CI: 11–∞ months] *vs.* 9 months [95% CI: 2–31 months], respectively, $p = 0.0322$) [4]. These findings contradict Sangro's observation stating, "*a cut-off point has not been yet established*".

This dose-response concept is of major interest, since the availability of a reliable predictive model makes it possible to model the response. In a preliminary study, this approach resulted in treatment intensification in 25% of patients, along with good tolerance [4]. A study to confirm these findings is currently in progress.

From a radiobiological point of view and as recently highlighted [6], we conclude that resin and glass microspheres are different products, with probably differing efficacy and toxicity profiles. At present, reliable and predictive dosimetry is possible when using glass microspheres but not when using resin microspheres. As a result, in the future, using glass microspheres is likely to be associated with a significant improvement in clinical outcomes, as this tumor dosimetry approach renders the clinical application of treatment intensification possible.

Conflict of interest

E.G. received lectures fees from MDS Nordion.

References

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Reply to: "Pre-therapeutic dosimetry evaluation and selective internal radiation therapy of hepatocellular carcinoma using yttrium-90-loaded microspheres"

To the Editor:

We have read with interest the comments made by Garin *et al.* to our recently published review on yttrium-90 radioembolization (RE) for hepatocellular carcinoma (HCC) [1]. Yet, while they raise relevant questions regarding the dosimetric approach to RE using yttrium-90 microspheres, they also convey erroneous messages regarding pretended advantages of glass *vs.* resin microspheres that should be clarified.

We never claimed that no correlation exists between the distribution of radiolabeled macroaggregated albumin (MAA) and therapeutic microspheres. The referred study by Knesaureck *et al.* shows that when such correlation between MAA and resin microspheres was analyzed, it ranged from high to very poor, and the average correlation was not the ideal one. A more recent study by the same group indicates that differences in catheter tip position are likely to be the main contributor to this mismatch [2]. No study has been done with glass microspheres so unless Garin *et al.* may provide additional data, there is no evidence to suggest that a better correlation exists for glass microspheres. In any case, these sorts of data have to be considered cautiously since the actual distribution of beta radiation cannot be accurately quantified *in vivo* after RE.

Furthermore, we made it clear that the MAA scan could be used to anticipate the average dose of radiation that can be delivered to tumor areas. The statement made by Garin *et al.* that MAA only predicts response when using glass microspheres is unfounded and it can be misleading for the inexperienced reader. Several retrospective studies have shown that unsurprisingly, the average dose received by tumors was higher for those that showed an objective response after therapy, both for resin [3,4] and for glass microspheres [5,6]. Nevertheless, a significant overlap was also observed and a consistent cut-off value has not been reported. For glass microspheres, proposed thresholds for aimed tumor absorbed doses range from 205 Gy in the Rennes series [5] to 500 Gy in the Milano series [6]. According to the manufacturer's instructions, the prescribed activity of glass microspheres is based on a 2-compartment dosimetry model with the aim of delivering a radiation dose of 120 Gy to the targeted liver (irrespective of the tumor burden). For resin microspheres, users have to choose between an empiric formula based on body surface area and tumor burden, or by a 3-compartment dosimetry model with the aim of delivering a radiation dose of 70–80 Gy to the targeted non-tumoral liver. However, experienced centers have described different attempts to use other dosimetry models to improve the efficacy of RE with both resin [7] and glass microspheres [8]. The statement that the dosimetry approach developed by Garin *et al.* resulted in treatment intensification in 25% of patients, along with good tolerance has to be taken with caution since it is based on only 4 patients that received a dose higher than that prescribed by the conventional method of activity calculation for glass microspheres [5]. This early experience from their and other groups with these dosimetry models is certainly encouraging but only prospective studies in large series of patients will tell us if this approach proves to preserve safety while they increase efficacy.

It is well know that with a comparable size range but a different activity per sphere, the number of particles used in a typical RE treatment is higher for resin than for glass microspheres. Garin *et al.* invalidly derive from this fact that resin microspheres are associated with a higher embolic effect and a higher chance of intrahepatic reflux without providing any scientific support to these assertions. Furthermore, they sustain that resin microspheres carry an increased risk of gastric ulcer, which again is a misleading statement. Gastric ulcers result from the unnoticed presence of collateral vessels and therefore, they are much dependent on the experience of the interventional radiologist performing the procedure and on the site of injection. The higher number of studies reporting gastric ulcers after RE using resin microspheres is most likely due to the fact that glass microspheres are almost invariably delivered by a selective lobar or sublobar injection while resin microspheres are quite often injected into the proper hepatic artery (particularly for unresectable liver metastases). When glass microspheres were injected into the hepatic artery in an early series of HCC patients, 13.6% of them developed gastric ulcerations [9]. For resin microspheres, in the study referenced by Garin *et al.*, the Mount Sinai group reported an incidence of 2.6% among 270 RE-treated patients [10].

Finally, Garin *et al.* conclusion that "*resin and glass microspheres are different products, with differing efficacy and toxicity profiles*" is against all available scientific evidence. As shown in Fig. 5 of our review, the overall survival of patients treated with glass or resin microspheres across the different HCC tumor stages is very consistent. The incidence of liver-related adverse events