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EDITORIAL

Spatial density and tumor dosimetry are important in radiation segmentectomy with ^{90}Y glass microspheres

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An important study for clinical practice

The aim of the retrospective two-arms study by the Mayo Clinic group under focus here [1] is the optimization of segmentectomy, which means treating a maximum of two liver segments with radioactive microspheres. Authors considered patients treated for hepato-cellular carcinoma (HCC) with ^{90}Y glass microspheres as neo-adjuvant therapy before transplantation. The intriguing work was split in two analyses.

The first consisted in a retrospective comparison between two groups, the baseline and the "intensified" cohort, differing for the time interval between the device calibration date and the injection day. Activity per microsphere decays with the ^{90}Y half-life of 2.66 days. Our group made hypotheses about the potential clinical implications of the choice of the injection day [2]. Considering a fixed absorbed dose, a longer decay time requires an increased number of microspheres. Typically, moving from an injection on day 4 (first week after the calibration date) to one on day 8 (second week), increases the number of microspheres per GBq three-fold.

The Mayo Clinic group adopted a different strategy. They intensified the experimental arm apparently using the same number of microspheres per cm^3, i.e., they fixed the spatial density of microspheres at about 16,500 particles/cm^3. The intensification in the experimental arm consisted in anticipating the injection day from the second week to the first week. This implied a higher activity per sphere in the intensified cohort (median 715 Bq versus 321 Bq; $p < 0.001$) and a higher absorbed dose to the injected region (median 536 Gy versus 314 Gy). Note that for a fixed spatial density, the activity per sphere and the absorbed dose to the injected region are directly proportional, i.e., they are perfectly correlated covariates. The interesting new result, obtained through a valuable ex-vivo pathological analysis, was that the complete pathologic necrosis (CPN), defined as the absence of any cell identifiable as HCC in explanted samples, was significantly higher in the intensified versus the baseline cohort (76% versus 49%; $p = 0.013$). The modified RECIST evaluation on MRI indicated a trend toward improved response rate after intensification, but not statistically significant. This first part of the study alone is of value, since it indicates that such intensification paradigm increases the CPN rate. It should therefore be adopted in clinical practice.

The second part of the work focused on CPN in the combined dataset obtained merging the two cohorts. At the univariate analysis, CPN was significantly associated with activity per sphere ≥ 327 Bq (injection in the first week after calibration), the absorbed dose to the treated region, the absorbed dose ≥ 446 Gy, the total treatment activity, the total treatment activity ≥ 2.55 GBq. At the multivariate analysis, only the activity per sphere ≥ 327 Bq (first week injection) was statistically significant, and not the absorbed dose. Again, this result alone, i.e., the importance of the injection day in the first week, deserves attention and should be applied to the clinical practice, but without forgetting the absorbed dose.

What could be further investigated

Two aspects were not investigated in the work, while they could reserve additional important findings. First, authors did not comment on the fact that CPN was also statistically associated with the spatial density of particles ($p = 0.050$ in their Table 2). This ranged from 12,600 to 26,100 microspheres per cm^3 in the baseline cohort, while from 11,000 to 20,700 in the intensified cohort. Note the higher values of

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the baseline cohort, though without statistically significant difference ($p = 0.124$). Nonetheless a significance statistical test demostrates something only when it is significant. When it is non-significant, the null hypothesis cannot be rejected, but it is not confirmed. In this case, the absence of significance cannot be used to say that the spatial density in the two cohorts was the same. It was simply not possible to demonstrate a difference.

In our first two papers about the importance of the number of spheres per GBq, or equivalently of the activity per microsphere [2, 3] the hypothesis was that the higher the number of particles per GBq, the higher the efficacy. This derives from a higher uniformity of the dose deposition pattern at microscopic level obtainable with a better coverage consequent to a higher spatial density of particles. In a more recent paper [4], contrarily to our expectations, after having decreased the activity per microsphere (shifting the injection day from day 4 to day 8), we observed a worsening of the dose–response correlation, a worse separation in terms of absorbed dose between responding and non-responding lesions, and, above all, a decreased efficacy even at 800 Gy. Unfortunately, data on day 4 had been obtained with a different dosimetric methodology, and they were not as reliable as data on day 8. Therefore a comparison study with the same methodology is necessary to investigate the dependence of efficacy on injection day, with the same absorbed dose and the same tumor size, possibly. Nevertheless, our most recent data [4] and the Mayo clinic data seem to provide an initial hint about the fact that efficacy is decreased if the spatial density of microspheres is too high, or, equivalently, if the specific activity per microsphere is too low. We are speaking about glass microspheres, without any intention of drawing any comparative conclusion with resin microspheres, which might have a completely different microscopic behavior in micro-vessels.

Our initial hypothesis [2, 3] (the higher the number of particles per GBq, the higher efficacy) holds until microspheres lodge in micro-vessels without forming too many clusters or mega-clusters, aggregates containing about 13 glass microspheres. This hypothesis was supported by the simulations by Pasciak et al. [5] about efficacy, and by Walrand et al. about non-tumoral liver tolerance [6, 7]. On the contrary, following the papers based on experiments by Hogberg et al. [8] and, above all, the study of pig livers by Pasciak et al. [9], our most recent clinical work [4] considered that mega-cluster formation is a non-linear phenomenon triggered when the spatial density of glass microspheres is too high. Pasciak et al. found mega-cluster formation only with a spatial density of 15,555 particles/cm^3. At lower particle densities, ordinary clusters contained an average of 5 particles/cluster [9]. In addition, the number of ordinary clusters per cm^3 increased abruptly from less than 500/cm^3 with 1755 particles/cm^3 to more than 1100 cm^3 with particle density higher than 5558 particles/cm^3. Therefore, for a fixed mean absorbed dose, choosing a longer decay interval (more microspheres per GBq) may cause an abrupt heterogeneity of the absorbed dose distribution at microscopic level, with a decreased biological effect.

A comparison between our data [4] and the Mayo results requires an arithmetical correction. The Mayo clinic group adopted the activity per sphere cut-off value of 327 Bq to pass from the first to the second week injection. This corresponds to the nominal value of 2500 Bq reported by the manufacturer as the initial ^{90}Y glass activity per sphere at the calibration date. Physicists [4, 10] have more confidence using the value obtained by Pasciak et al. with a direct measurement of 4354 Bq per sphere, in a paper where a representative of the company is co-author (Matthew R. Dreher) [9]. This more reliable initial value shifts up all the activity per spheres values of a factor of $4354/2500 = 1.74$ in the paper by the Mayo clinic [1]. Similarly, it reduces spatial densities of the same amount. After this correction, the Mayo clinic group used a density ranging from 7200 to 15,000 particles/cm^3 in the baseline cohort, while from 6300 to 11,900 particles/cm^3 in the intensified cohort. Note that the former cohort, with lower CPN rate, was injected with a spatial density closer to our proposed threshold for mega-cluster formation, at about 15,000 particles/cm^3 [4]. This threshold value however was derived from the study by Pasciak et al. in which the injection day proceeded by 4 days steps [9]. Mega-clusters were found on the injection day 16 (15,000 particles/cm^3), not on day 12 (5200 particles/cm^3). But we do not know if they could have been produced injecting on day 13, for instance. In other words, the mega-cluster threshold could be considerably lower than 15,000 particles/cm^3, but higher than 5200 particles/cm^3. To conclude our comments about the spatial density of particles, we believe that the reduced efficacy in terms of CPN reported by the Mayo clinic group in their baseline cohort seems in agreement with our hypotheses of mega-cluster formation.

The second important missing factor in the Mayo clinic paper is the evaluation of the tumor absorbed dose (two-compartment dosimetry). This is loosely related to the reported treated region absorbed dose. This could be the reason why, in the multivariate analysis, they did not find a significant association between CPN of the tumor and the mean absorbed dose to the treated region: they considered different regions. Note in addition that the p value in the second multivariate model was 0.084, not so far from significance. In a "gedanken experiment", the same association they found with the activity per sphere should have been obtained for the tumor absorbed dose, since the two quantities are rigorously correlated if the spatial density is rigorously the same.

The association of CPN with only the activity per microsphere neglects the main radiobiological factor, the tumor

absorbed dose. A high activity per microsphere does nothing on a tumor, if the absorbed dose is insufficient. This is confirmed by the authors themselves who, in their conclusions, propose an activity per sphere above their threshold and an absorbed dose above 446 Gy.

For these reasons, tumor absorbed dose, i.e., two-compartment dosimetry, is scientifically important even in segmentectomy, despite the indication of the panel of glass microsphere experts [11]. Of course such method is operationally more demanding than the radiological evaluation of the bulky treatment volume.

An addendum by the Mayo clinic group considering replacing the absorbed dose to the treated region (monocompartment dosimetry) with the tumor absorbed dose (two-compartment dosimetry) could provide new association of CPN with the latter parameter. Moreover, the Mayo clinic has the potential (dosimetric data, MRI follow-up, 75 explanted tumor samples) of going far beyond the studies by Hogberg et al. [8] (resin microspheres in one explanted human liver) and Pasciak et al. [9] (eight pig livers with low absorbed dose, explanted only one month after treatment). This data constitute a unique opportunity to clarify many microscopic aspects that affect efficacy besides the mean absorbed dose evaluated at macroscopic scale.

Declarations

Ethical approval Institutional Review Board approval was not required because the paper is an editorial.

Informed consent Not applicable.

Conflict of interest Carlo Chiesa was consultant for Boston Scientific and Terumo as speaker at congresses and for clinical training. In 2017, he received a research grant from Boston Scientific. Marco Maccauro was consultant for Boston Scientific as speaker at congresses and for clinical training. Stefania Mazzaglia declares no conflicts of interest.

References

1. Montazeri SA, De la Garza-Ramos C, Lewis AR, et al. Hepatocellular carcinoma radiation segmentectomy treatment intensification prior to liver transplantation increases rates of complete pathologic necrosis: an explant analysis of 75 tumors. Eur J Nucl Med Mol Imaging. 2022. https://doi.org/10.1007/s00259-022-05776-y.
2. Spreafico C, Maccauro M, Mazzaferro V, Chiesa C. The dosimetric importance of the number of 90Y microspheres in liver transarterial radioembolization (TARE). Eur J Nucl Med Mol Imaging. 2014;41:634–8. https://doi.org/10.1007/s00259-013-2674-6.
3. Chiesa C, Maccauro M, Romito R, Spreafico C, et al. Need, feasibility and convenience of dosimetric treatment planning in liver selective internal radiation therapy with 90Y microspheres: the experience of the National Cancer Institute of Milan. Q J Nucl Med Mol Im. 2011;55:168–97.
4. Romanò C, Mazzaglia S, Maccauro M, Spreafico C, et al. Radioembolization of hepatocellular carcinoma with 90Y glass microspheres: no advantage of voxel dosimetry with respect to mean dose in dose-response analysis with two radiological methods. Cancers. 2022;14(4):959. https://doi.org/10.3390/cancers14040959.
5. Pasciak AS, Bourgeois AC, Bradley YC. A microdosimetric analysis of absorbed dose to tumor as a function of number of microspheres per unit volume in 90Y radioembolization. J Nucl Med. 2016;57:1020–6. https://doi.org/10.2967/jnumed.115.163444.
6. Walrand S, Hesse M, Chiesa C, Lhommel R. Jamar F The low hepatic toxicity per Gy of 90Y glass microspheres is linked to their transport in the arterial tree favouring a non uniform trapping as observed in posttherapy PET imaging. J Nucl Med. 2014;55:135–40. https://doi.org/10.2967/jnumed.113.126839.
7. Walrand S, Hesse M, Jamar F, Lhommel R. A hepatic dose-toxicity model opening the way toward individualized radioembolization planning. J Nucl Med. 2014;55:1317–22. https://doi.org/10.2967/jnumed.113.135301.
8. Högberg J, Rizell M, Hultborn R, Svensson J, et al. Increased absorbed liver dose in selective internal radiation therapy (SIRT) correlates with increased sphere-cluster frequency and absorbed dose inhomogeneity. EJNMMI Phys. 2015;2:10. https://doi.org/10.1186/s40658-015-0113-4.
9. Pasciak AS, Abiola G, Liddell RP, Crookston N, et al. The number of microspheres in Y90 radioembolization directly affects normal tissue radiation exposure. Eur J Nucl Med Mol Imaging. 2020;47:816–27. https://doi.org/10.1007/s00259-019-04588-x.
10. Chiesa C, Sjogreen-Gleisner K, Walrand S, Strigari L, et al. EANM dosimetry committee series on standard operational procedures: a unified methodology for (99m)Tc-MAA pre- and (90)Y peri-therapy dosimetry in liver radioembolization with (90)Y microspheres. Eur J Nucl Med Mol Imaging Phys. 2021;8:77. https://doi.org/10.1186/s40658-021-00394-3.
11. Salem R, Padia SA, Lam M, Bell J, et al. Clinical and dosimetric considerations for Y90: recommendations from an international multidisciplinary working group. Eur J Nucl Med Mol Imaging. 2019;46(8):1695–704. https://doi.org/10.1007/s00259-019-04340-5.