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EDITORIAL

^{166}Ho microsphere scout dose for more accurate radioembolization treatment planning

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Radioembolization is nowadays dominated by ^{99m}Tc MAA for pretreatment study of biodistribution and dosimetry, and by ^{90}Y microspheres for therapy Physical properties of such radionuclide are: 64 h half-life, beta emission maximal energy 2280 keV, beta abundance 99.9%, no gamma, and 32 positron emissions per million of transformations. A new kind of medical device available for therapy recently became commercially available also for planning: polylactic acid (PLLA) microspheres labeled with ^{166}Ho. Such radionuclide has a 26.8 h half-life, dual beta emission with maximal energy of 1770 keV (49%)–1850 keV (50%) and, new aspect, it is paramagnetic and it emits gamma photons at 81 keV, with low abundance (6.7%). Gamma photons allow SPECT/CT imaging and dosimetry (some days after therapy to avoid gammacamera saturation) [1], while paramagnetism gives the additional possibility of post-therapy MRI evaluation. Publications about the use of ^{166}Ho in therapy are available [2, 3], but this application is not under discussion here.

We are rather focusing on the just published work by the Utrecht centre [4], which demonstrated higher accuracy of intra-liver dosimetric prediction using a tracer injection of ^{166}Ho microspheres (the so-called ^{166}Ho scout dose) with respect to ^{99m}Tc MAA. Scout dose consists in the angiography-guided administration of 250 MBq of ^{166}Ho microspheres (about 3 million of particles) instead of some hundred thousand of ^{99m}Tc MAA particles. The activity was fixed on one side in order to be safe even in case of lung shunt during simulation [5], and on the other side to be sufficiently high to allow ordinary gamma camera imaging (planar + SPECT/CT scan), despite the low photon abundance. Medium energy collimators are needed to reduce the remarkable amount of bremsstrahlung photons impinging on the detector.

Readers used to simulations with MAA might argue which advantages could be provided by ^{166}Ho scout dose. Several authors investigated the problem of accuracy of prediction with ^{99m}Tc MAA. This is obviously a crucial factor for an accurate dosimetric treatment planning. The first evidence of differences between MAA prediction and the actual microspheres biodistribution were published studying ^{90}Y resin particles with bremsstrahlung SPECT [6, 7]. Those papers indicated the first reasons for discrepancy: bad catheter tip repositioning, above all in proximity of an arterial bifurcation. The Utrecht group confirmed this, but remarked the importance of the difference in number and size between MAA and ^{90}Y resin spheres [8]. They further investigated the problem with a key work comparing prediction of lung absorbed dose with MAA versus ^{166}Ho scout dose, having as gold standard the true lung absorbed dose obtained with ^{166}Ho SPECT/CT after therapeutic infusion [9]. The lung dose overestimation with MAA was systematic, huge with planar imaging, but still large even if evaluated on fully corrected 3D ^{99m}Tc SPECT/CT images. Median lung absorbed dose was 0.2 Gy evaluated both pretherapy (scout dose) and post-therapy with ^{166}Ho SPECT/CT, while it was overestimated to 2.5 Gy according to ^{99m}Tc MAA SPECT/CT.

A major reason for such a large discrepancy is the difference in size and material between the simulation and therapy particles. MAA are not solid, and, above all, their size distribution extends from 10 μm to more than 100 μm [10]. The problem of the large lung shunt overestimation with MAA probably derives from the portion of MAA with small size (10 μm). These have higher penetrability in capillaries with respect any kind of therapeutic microspheres (resin, glass, and PLLA), which are more than twice larger in diameter. MAA can therefore more easily pass through arterious to venous capillaries, and reach lungs.

As a first note about methodology found in publications, correlation and concordance tests are not the best statistical

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tools to perform comparison between pre- and peri-therapy dosimetry. They are poor tools in pointing out individual differences, which are important in individualized treatment planning for the most aggressive and crucial therapy in nuclear medicine. Bland–Altmann developed a simple way focused on testing the agreement in individual cases between two methods of quantitative evaluation [11, 12]. In our case, this method considers the set of differences between pre- and peri-therapy evaluations. It plots each absorbed dose comparison as a dot having the difference as *Y*-coordinate, and their mean value as *X*-coordinate. The global analysis is summarized by two parameters: the bias, which is the average over all differences, and most important, the 95% C.I., i.e., the dispersion of such differences, measured as ± 1.96 times their standard deviation. The ideal simulation, and the ideal interventional radiologist, would result in the ideal Bland–Altmann plot with bias = 0 and standard deviation = 0, where all dots should lie on the *X*-axis, without any individual difference between prediction and therapy.

The Ssecond note about the application of Bland–Altman methodology concerns the sample size. The accurate determination of the 95% C.I. evidently requires to observe the 5% of improbable cases. Since these happens on the average in the 1/20 ratio, we cannot expect to have a good evaluation of the 95th percentile using 10 or 20 patients. A similar sample size will statistically provide only the "good" cases, i.e., those within the 95% C.I.. A rigorous statistical analysis would require to estimate the uncertainty about the extreme values of the 95% C.I.

Coming back to the reliability of MAA absorbed dose prediction, in more recent literature, dosimetric comparison exploited the more quantitatively accurate ^{90}Y PET imaging. Gnesin et al. studied 7 patients treated with glass and 20 patient studied with resin spheres [13]. On tumors, authors obtained a ratio between MAA and ^{90}Y PET-absorbed dose ranging from 0.6 to 2.5. These astonishing values mean that MAA prediction differed from − 40% to 250% with respect to the true absorbed dose, both for glass and resin spheres, with a median ratio ^{99m}Tc/^{90}Y of 1.46 for glass and 1.16 for resin spheres. Jadoul et al. [14] compared MAA evaluations to resin spheres on 20 primary HCC and 20 metastatic patients, while for other 20 HCC patients they used glass spheres. They obtained bias and (95% C.I.) with resin spheres of − 11 Gy (− 68 Gy, 46 Gy) for HCC and − 8 Gy (− 69 Gy; 52 Gy) for metastases, and 16 Gy (− 144 Gy, 175 Gy) for HCC with glass spheres. Kafrouni et al. [15], with glass spheres on 24 patients, obtained lower but still important C.I., of about (− 50 Gy, + 40 Gy) for lesions. Richetta et al. [16] with 10 patients treated with resin spheres obtained − 6 Gy (− 80 Gy, 68 Gy).

According to all these studies, the situation is definitely better for normal liver, with a median (range) ratio of 0.88 (0.56, 1.00) for glass, and 0.86 (0.58, 1.35) for resin spheres according to Gnesin et al. [13], while bias and (95% C.I.) of − 1.4 Gy (− 16 Gy, 13 Gy) for HCC with glass spheres, with resin spheres 0.2 Gy (− 6 Gy, 6 Gy) for HCC, and − 1.4 Gy (− 12 Gy ; 9 Gy) for metastases according to Jadoul et al. [14], about 0 Gy (− 12 Gy, + 11 Gy) for Kafrouni et al. [15], and 1 Gy (− 7 Gy, 9 Gy) for Richetta et al. [16].

It is evident that, beyond some authors' conclusive statements like "*for HCC there is a good correlation between the predicted dose to the tumour estimated on ^{99m}Tc-MAA SPECT/CT*" or mentioning "*good correlation and no significant differences*", their plots and 95% C.I. show for lesions indisputably marked differences between predicted and actual absorbed dose in several patients, especially for lesions. The problem was further enlightened for glass spheres by Haste et al. [17] who report for lesions of 63 patients a bias of − 14 Gy (− 355 Gy, 327 Gy), and for parenchyma, a zero bias and a 95% C.I. of 0 Gy (− 15 Gy, 15 Gy). Their data were obtained with a pure SPECT system, without CT-based attenuation correction. This is not a major limit on dosimetric accuracy, as long as the patient relative calibration method is adopted [18, 19], as authors did. With this method, the conversion from counts to activity in a VOI is based on the ratio between the intended or administered net ^{90}Y total therapeutic activity divided by the total technecium or therapy counts in each patient.

The above reported confidence intervals (or range of ratios by Gnesin et al.), are unacceptably large for lesions and suboptimal for non tumoral liver, if compared to the thresholds of toxicity and efficacy proposed in literature, which are for resin spheres of 50–70 Gy to liver [20] and 150 Gy to lesions [21], and for glass spheres of about 75 Gy for parenchyma [22, 23] or 120 Gy to the injected volume if its fraction is larger than 70% [24], and 205 Gy for lesions [24, 25]. Beyond that, since nuclear medicine therapy is a kind of radiotherapy, it could be worth recalling that our colleagues in external beam have a limit of ± 5% on the treatment dosimetric uncertainty [26]. The above reported uncertainty of MAA prediction for lesions casts a serious shadow on the possibility of a reliable individual planning based on tumor-absorbed dose, while a more predictive MAA planning can be obtained to the non-tumoral tissue.

The above statement about poor MAA prediction for lesions should not be intended as "MAA dosimetry is totally useless." The optimal good correlation between MAA predicted lesion absorbed dose and response, progression-free survival, overall survival [27–29] are explained by the low bias values reported by all authors. This means that MAA planning works on the average over many patients. Response rate, tumor control probability, progression-free survival, and overall survival are average properties of a studied cohort. We could think that for each underestimated lesion value, there is an overestimation with another, giving a balance. Therefore, ^{99m}Tc MAA dosimetry is useful indeed to optimize treatment on the average; but for instance, the choice of treating or not

an individual patient depending on the MAA predicted lesion absorbed dose is debatable.

The novelty of the ^{166}Ho scout dose in the paper under focus [4] is the demonstrated improvement in accuracy prediction with respect to ^{99m}Tc MAA. 95% C.I. for lesions were reduced from (− 164 Gy, 197 Gy) with MAA, to (− 90 Gy, 105 Gy) with ^{166}Ho scout dose. Authors properly evaluated the uncertainty on the extreme of the 95% C.I. to assess the significance of the improvement.

The study is limited to colorectal metastases. However, on the basis of the results obtained by Jadoul et al. (better MAA prediction for HCC than for metastases), we can believe that, similarly, ^{166}Ho scout dose could improve prediction on HCC even more than obtained on metastases [4]. The use of the same particle for simulation and therapy is in principle promising in all applications.

Accuracy of ^{166}Ho scout dose prediction is however not free from limits. It cannot solve all problems of radioembolization, which shows the highest operator dependence among all nuclear medicine therapies, with additional problems of catheter kind, vasospasm [30], etc. Even the problem of the different number of injected particles in the two sessions is not solved. Moreover, consider that in this kind of comparison, the reproducibility of VOI positioning or an imperfect image co-registration has a role. Therefore, the Bland–Altman plot with ^{166}Ho scout dose is still not ideal [4], i.e., differences between simulation and therapy are still present, but by sure reduced for lesions with respect to MAA. After the papers by Smits et al. [4], and by Elshot et al. [9], nobody can deny that using MAA instead of therapeutic microspheres introduces important differences between pre- and peri-therapy biodistribution and dosimetry.

As always, the diffusion in the clinical practice of ^{166}Ho microspheres planning and therapy will be influenced by the tradeoff between pro and cons. Remember that, despite the low photon abundance, the exposure rates close to a patient after ^{166}Ho therapeutic administration [31] make it difficult to avoid at least one night of hospitalization in a shielded room, while this is not necessary with the 10 times lower exposure rates from patients treated with ^{90}Y microspheres [32]. Moreover, the high bremsstrahlung photon emission forces to use medium energy collimators for SPECT/CT, with unavoidable loss of spatial resolution.

Beyond the specific considerations about the use of the ^{166}Ho scout dose, we remark the importance of this additional step forward towards personalized treatment planning by a microsphere producer. All microsphere companies are making efforts in the same direction, either reconsidering the impact of missing optimization in the failure of their phase III studies [33], or producing specific software for optimization (Simplicity^{TM}, Velocity Rapidsphere^{TM}, Qsuite^{TM}).

To conclude, we do not know which is “the best particle” for radioembolization [34], but by sure we now know which is the best one nowadays for individual treatment planning, both on liver and lung.

Compliance to ethical standards

This paper did not involve research on humans nor on animals.

Conflict of interest In the last three years, Carlo Chiesa and Marco Maccauro received fees as speakers from Biocompatibles Uk Ltd, producer of ^{90}Y glass microspheres, and from TERUMO, producer of ^{166}Ho microspheres. They received honoraria as consultant from Biocompatibles UK Ltd. Carlo Chiesa received a grant for an Investigator Initiated Study from the same Company. He is consultant of Alfasigma S.p.A.

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