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POINT/COUNTERPOINT

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Voxel-based dosimetry is superior to mean absorbed dose approach for establishing dose-effect relationship in targeted radionuclide therapy

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OVERVIEW

It is becoming evident that patient-individualized dosimetry in targeted radionuclide therapy (TRT) is a must and not a luxury in the era of precision medicine. It is often argued that patient-specific absorbed dose assessment should be the standard and become routine in TRT, similar to other forms of radiation therapy to improve the correlations between the administered activitiy and the clinical outcome and enable better understanding of the absorbed dose-response relationship. This is commonly performed using the medical internal radiation dose committee (MIRD) formalism, which consists of calculating the mean absorbed dose to organs/tissues and lesions to be treated. Substantial progress has been achieved by a number of academic groups that developed the required tools that have been used in clinical trials. This has stimulated the emergence of commercial (expensive) software enabling to compute absorbed dose rate maps at the voxel level from anatomo-functional data derived from advanced hybrid imaging technologies for each individual patient. However, it is not clear yet how this should be performed and implemented in the clinic.

While some advocate that voxel-based dosimetry is superior to the mean-absorbed dose approach for establishing absorbed dose-effect relationship in TRT, others believe that there is no evidence in the literature that such relationship is substantiated by reliable clinical studies and that the mean absorbed dose is largely sufficient owing to limitations in spatial sampling. This is the topic addressed in this month's Point/Counterpoint debate.

Arguing for the proposition is Carlo Chiesa, PhD. Dr. Chiesa is medical physics expert in nuclear medicine of the National Cancer Center in Milan, working since 1993 on patient internal dosimetry in TRT, quality control of equipment, cyclotron-based tracer production, and teaching of technologists and nuclear medicine specialization university courses. He is the national coordinator of the medical physicists group working in nuclear medicine and a member of the board of the Italian Association of Medical Physics. He is a senior advisor to the Dosimetry Committee of the European

Association of Nuclear Medicine (EANM). His research interests lie in the dosimetric optimization of TRT. He was hired three times by the International Atomic Energy Agency (IAEA) to teach dosimetry courses and is a consultant for BTG Biocompatibles in dosimetry of ^{90}Y microspheres therapy for liver cancer. He conceived and led an Investigator Initiated Study in this field funded by the same company. He is a principal investigator in a 5 yr study funded by the Italian Association for Cancer Research (AIRC) where ^{124}I positron emission tomography (PET) dosimetry is used to plan optimal activity administration of radioiodine in metastatic thyroid cancer. He coauthored 103 papers, including four EANM dosimetry guidelines.

Arguing against the proposition is Manuel Bardiès, PhD. Dr. Bardiès obtained his Doctorate in radiopharmaceutical dosimetry from Paul Sabatier University (Toulouse III) in 1991. He has been developing his research in radiopharmaceutical dosimetry within INSERM (National Institute of Health and Medical Research) since 1992, in Nantes then in Toulouse (2011). Manuel Bardiès was one of the founders of the EANM Dosimetry Committee (member from 2001 to 2013, chair 2009-2011). He also chaired the European Federation of Organizations for Medical Physics Science Committee between 2014 and 2016. He has developed an increasing interest in education and is now a member of the European School of Multimodality Imaging & Therapy (ESMIT) and the European School for Medical Physics Experts (ESMPE). The team led by Manuel Bardiès in Toulouse is primarily involved in radiopharmaceutical dosimetry, at various scales (cell, tissue, organ). This requires the ability to assess radiopharmaceutical pharmacokinetics *in vivo*, through quantitative single-photon emission computed tomography (SPECT) or PET small-animal imaging. An important part of research activity is related to Monte Carlo modeling of radiation transport through biologic structures of interest to give account of energy deposition within tumor targets — or critical nontumor tissues/organs. The objective is to improve TRT by allowing patient-specific treatments (personalized medicine).

FOR THE PROPOSITION: CARLO CHIESA, PH.D

Opening Statement

For a medical physicist used to plan external beam radiation therapy (EBRT), the application of voxel dosimetry methods to TRT is obvious. However this immediate transposition should be careful, since nuclear medicine images are affected by two major problems absent in EBRT:

1. Each voxel value is affected by an intrinsic uncertainty, given by the image noise, which distorts the differential and the cumulative dose volume histogram (DVH)[1] (Appendix in Chiesa et al.[2]).
2. Realignment of the same voxel in sequential scans is difficult.

For these reasons, in the past I was skeptical about voxel dosimetry in TRT, but recent papers changed my opinion to that of prudent voxel-dosimetry promoter. A single scan in radioembolization dosimetry argues in favor of voxel dosimetry. First, the simplified radioactivity uptake kinetics, that is, permanent trapping of microspheres, allows evaluation with a single tomographic scan, which does not require voxel-to-voxel coregistration, and has unique time-activity curve for all voxels (half-life of the radionuclide).

The lesions typically evaluated in liver cancer are often large, necrotic, heterogeneous, and usually much larger than those treated with systemic radiopharmaceuticals (except neuroendocrine). Such lesions typically exhibit macroscopic regions unevenly filled with microspheres, depending on their vascularization (differently from cells taking up a metabolite). In such situations, the evaluation of mean absorbed dose alone may lack predictive value. The fair but still suboptimal dose-response correlations reported by many authors exist since radiological response assessment evaluates only mean parameters (dimension, mean density). If within the category of responding lesions those with complete response were to be characterized, a voxel dosimetry approach could be necessary to check for single under-dosed voxels.

Kao et al.[3] indicated that complete response/local failure of HCC (hepatocellular carcinoma) treated with ^{90}Y resin microspheres was correlated with D_{70} higher/lower than 100 Gy as evaluated on post-therapy ^{90}Y PET/CT imaging. Chiesa et al.[2] found that in a receiver operating characteristic (ROC) analysis, radiobiological Equivalent Uniform Doses (EUD)[4] evaluated on ^{99m}Tc MAA SPECT/CT gave significantly, but only slightly higher values of the area under the curve (AUC), indicating that this voxel-based metric better discriminated responding and non-responding lesions than the mean absorbed dose. According to D'Abadie et al.,[5] EUD gave rise to more consistent survival curves from resin and glass microspheres than did mean effective absorbed dose. These and similar results obtained with the voxel approach in Trans-Arterial Radio-Embolization (TARE) cannot be

disregarded and show its added value over the mean dose approach.

In sequential SPECT, various authors demonstrated with simulations that good accuracy in cumulative DVH images can be obtained using nonrigid coregistration.[6] Remarkable intra-lesion heterogeneity of absorbed dose deposition was reported in ^{124}I PET dosimetry of metastatic differentiated thyroid cancer,[7] but its potential impact on response was not fully investigated.

The characterization of nonuniform absorbed dose deposition can be extracted from nuclear medicine images, though with limited accuracy. As in many other examples of this discipline, even an approximate evaluation might add clinical value. Therefore the impact of this information should be tested in dose-effect studies.

AGAINST THE PROPOSITION: MANUEL BARDIÈS, PH.D

Opening Statement

The relevance of dosimetry is not questioned in external beam radiotherapy, where treatment planning is routinely performed. However, in TRT the need for dosimetry is still a matter of debate.[8–10] The difficulty[11] to establish absorbed dose-effect relationship (ADER) is often given as an argument for not implementing dosimetry in TRT. This further motivates the need for demonstrating that voxel-based dosimetry yields improved ADERs that predict tumor response better than mean organ dose for clinical acceptance of the former.[12]

Voxel-based dosimetry can be seen as an attempt to increase the accuracy of energy deposition determination, in the hope to extract more predictive ADERs. The parallel with external beam radiotherapy also motivates the generation of absorbed dose volume histograms. Indeed, voxel-based absorbed dose-calculation algorithms are available, and current academic or commercial software usually supports voxel-based dosimetry.

However, the relevance of voxel-based dosimetry for clinical applications can be questioned:

-The determination of activity can only be made using the spatial resolution of clinical scintigraphic devices, well above 1 cm in most situations (SPECT/CT), regardless of the usual voxel spatial sampling (4–5 mm). Voxel-based activity determination is therefore associated with huge uncertainties.[13]

-In addition, registering voxels and performing time integrated activity calculation at the voxel level appears at best to be extremely challenging. Therefore the calculation of absorbed doses in that context, even based on accurate algorithms and refined approaches (for example Monte Carlo modeling of radiation transport) will only result in a *false feeling of accuracy.* It also must be mentioned that Monte Carlo radiation-transport accuracy may also be impacted by spatial sampling.[14]

-Then, even if accurate absorbed dose determination at the voxel level was possible, this would still be an average in a large volume when compared to radiation range (few mm at best for beta particles, and less than 0.1 mm for alpha emitters in soft tissues). This means that *even voxel-based dosimetry may not be refined enough* to give account of absorbed dose gradients at the scale relevant to biological phenomena that condition ADER.

In conclusion, the literature supports that ADER based on absorbed doses averaged over volumes of interest (conventional dosimetry) can predict tumor response. However, there is little evidence of the added predictive value of voxel-based dosimetry — at least in clinical TRT and for voxel dimensions encountered in clinical nuclear imaging. Conventional dosimetry, possibly supplemented by autoradiography or small-scale dosimetry obtained from preclinical experiments[15] is more likely to improve our understanding of ADER in TRT.

REBUTTAL: CARLO CHIESA, PH.D

I partially agree with the statement by Dr. Bardies that *nowadays*, "there is little evidence of the added value of voxel dosimetry." My main message in this discussion is to avoid *a priori* disregard of voxel dosimetry.

In radioembolization, the spatial resolution is nowadays around 5 mm for ^{99m}Tc SPECT and ^{90}Y PET. This application is free from sequential registration problems. Therefore, from one side, the superiority of voxel dosimetry could be found here. On the other side, the inaccessibility of DVH at the microscopic scale and noise are the real substantial issues. A pragmatic approach could be followed, as done for instance by Allimant et al.[16] who reported after a multivariate analysis that the coverage of a lesion in TARE is by far much more important for response than the mean absorbed dose, with an odds ratio of 37 versus 1.027. Coverage is not accounted for by mean dose evaluation. In work conducted by our group, it was unclear why the improvement in AUC was so small passing from mean dose to EUD. I think that our ignorance of the microscopic DVH played a major role.

In the field of sequential SPECT/CT scans, Flux et al.[17] obtained a significant difference between successful and unsuccessful thyroid remnant ablation with ^{131}I by considering the single voxel maximal absorbed dose.

This single voxel approach was probably inspired by SUV$_{max}$ in FDG-PET. Beyond SUV$_{max}$, radiomics in nuclear medicine is based on reliability of single voxel counts. With a "reduction to absurdity", neglecting the reliability of single voxel counts would invalidate both concepts of SUV$_{max}$ and radiomics. This conceptual link could also indicate that, in order to obtain reliable voxel dosimetry results, careful methodological check and standardization could be necessary as in radiomics.[18]

Therefore, dose-effect studies using accurate voxel dosimetry should be undertaken.

REBUTTAL: MANUEL BARDIÈS, PH.D

It is striking to see that our opening statements both agree on the necessity to investigate absorbed dose-effect relationships in TRT via clinical studies. We differ in the appraisal of the means to reach that objective. In my opinion, clinical dosimetry is not able (yet?) to give account of absorbed dose heterogeneities at the scale that allows observing voxel-based ADER superior to those derived from mean absorbed doses.

In a famous article, Konijnenberg[15] demonstrated how absorbed dose gradients observed at the microscopic scale based on autoradiography of kidney slices provided a satisfactory explanation of the variable toxicity of peptides labeled with different isotopes.

More recently, Marnix Lam[19] presented examples of ADERs in Selective Internal Radiotherapy (SIRT) of liver cancers with radioactive microspheres. The study of hepatic toxicity, as normal tissue complication probability vs absorbed dose presented an inflexion point around 100 Gy for Chiesa[2] and 50 Gy for Strigari.[20] These seemingly discordant results could in fact be explained by the differences between glass and resin microspheres: average absorbed doses should be higher for glass microspheres to make up for absorbed dose gradients present at the microscopic scale. This means that, even in a favorable situation (i.e., one imaging time-point, no pharmacokinetics, long-range beta emitter, and possibility to perform postadministration PET-based dosimetry) absorbed dose gradients evaluated from clinical imaging cannot explain the observed effects, as relevant phenomena occur at a smaller scale. How much smaller? The reference to d'Abadie[5] provided by my esteemed colleague goes indeed in the right direction — with the limitation that this is probably the best clinical situation (SIRT) and available methodology (time-of-flight PET).

This means that we should not stop searching for dosimetric indexes that better correlate with the effect. The absorbed dose "at a relevant scale," associated with an objective clinical endpoint will provide the key to absorbed dose-effect relationship. We just need to be cautious regarding the limitations of current technologies/methodologies in order to avoid generating disappointing results that would be counterproductive in the long quest for dosimetry-based TRT optimization.

CONFLICT OF INTEREST

Dr. Chiesa received in the last 3 yr a research grant and honoraria for consultancy from BTG Biocompatibles L.t.d., a producer of ^{90}Y glass microspheres. He is also a consultant for Alfasigma S.p.A. Dr. Bardiès was a consultant and received honorarium from Bayer, INPEN, Roche, BTG.

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