

Good Voxel Dosimetry with a Simplified Study Design Resulted in Improvable Safety Limits

TO THE EDITOR: In a paper recently published by *The Journal of Nuclear Medicine*, Watanabe et al. claimed theirs was “the first study to show superiority for voxel-based dosimetry over multicompartiment dosimetry in the prediction of liver decompensation of [hepatocellular carcinoma] patients undergoing radioembolization with ^{90}Y glass microspheres” (1). As dosimetrists we cannot be anything but glad for this success, which pursued a methodology that Carlo Chiesa defended in a point-counterpoint debate with objective difficulty due to the scarce available evidence (2). As a matter of fact, previous efforts by our group (3) were not able to demonstrate a significant “superiority for voxel-based dosimetry in the pretherapeutic prediction of hepatotoxicity in [hepatocellular carcinoma] patients undergoing radioembolization of the whole liver,” as written by Watanabe et al. (1), nor in the prediction of response (4). Therefore, the achievement by Watanabe et al. might be regarded as an important step forward not only in dosimetric planning in radioembolization but also in nuclear medicine dosimetry in general, as one of the first evidences of superiority of voxel dosimetry over the mean-dose approach.

However, as often happens in science, opening new scenarios raises additional questions and the need for further clarification. We think that the nuclear medicine community would appreciate some general clarification to properly compare results to progress as a community. Some additional notes by Watanabe et al. would be welcome, since the rather simplified design of their study might have led to improvable safety thresholds.

Let us focus first on the whole-liver treatment subgroup of 98 patients, in which Watanabe et al. obtained a brilliant area under the curve (AUC) of 0.84 with a 40-Gy volume (V40) variable in terms of separation between toxic and nontoxic treatments. Then, with a standard methodology in the receiver-operating-characteristic curve analysis (Youden index), they found the best toxicity threshold at a 40-Gy volume of 72%. In their dose volume histogram, the 40-Gy volume variable is the percent volume of whole nontumoral liver tissue receiving an absorbed dose higher than 40 Gy. The obtained threshold means that if this percentage is larger than 72%, there is a certain risk of liver decompensation. The other limit of an absorbed dose to 30% of volume (AD30) means that we have risk if 30% of the nontumoral liver volume receives an absorbed dose of at least 43 Gy (AUC, 0.823). Using the mean absorbed dose on whole nontumoral liver tissue (AD-WNTLT), they obtained an apparently less brilliant AUC value of 0.633, with a safety threshold of 55.6 Gy.

Watanabe et al., however, did not report the uncertainty nor the 95% CI of the AUC values. Without this error estimate, it is impossible to demonstrate the significance of differences between different AUC values. Their mean AD-WNTLT can be compared with our finding, in contrast to the 40-Gy volume and 30% absorbed dose, which were not calculated in our work (5). The result, 55.6 Gy, is quite close to our 59 Gy, and the authors' AUC of 0.633 is not so different from our AUC of 0.68.

Neither sensitivity nor specificity associated with such thresholds was mentioned.

The toxicity endpoint definition was different from our definition. We included other symptoms as indicators of liver decompensation: a prothrombin time international normalized ratio greater than 2.2, clinically detectable ascites, encephalopathy, esophageal varices bleeding, and death. The timeline was the same (≤ 6 mo).

All our patients were Child–Pugh A, whereas Watanabe et al.'s Table 1 reports that 109 patients were Child–Pugh A, 6 were Child–Pugh B7, and the remaining 61 were undefined. Should these patients be Child–Pugh C? This could explain toxicity at low AD-WNTLT.

We treated 96% of our patients with the lobar approach, and we extrapolated the tolerance to a whole-liver approach according to the Lyman formalism for a pure parallel organ. In our analysis, we censored patients on the day of the second treatment, in order to observe the effect and to calculate the dose for a single administration. Watanabe et al. obtained their best results in the group whose whole liver was treated, but “in cases of whole-liver treatment with 2 or more injections (e.g., separate injections for left and right lobes), injections were performed in 2 sessions, approximately 4–6 wk apart” (1). This whole-liver approach is therefore a sort of hybrid between a real simultaneous whole-liver treatment and 2 sequential right lobe–left lobe treatments, separated by a time interval insufficient to fully obtain radioinduced contralateral hypertrophy (5.9 ± 3.4 mo (6)). The dosimetric tolerance calculation is biased by this interval because we cannot rigorously consider the treatment as a single one, nor could we assume to have a new organ, as we assume once contralateral hypertrophy is completed. When considering these 2 models, one would choose the former because a time frame of 4–6 wk is short compared with 5.9 mo. Therefore, these 2-step treatments could (hardly) be considered as whole-liver treatments.

Watanabe et al. did not apply any analysis of the cause of toxicity introduced by Garin et al. (7). This aspect is important. In a hepatocellular carcinoma patient, liver decompensation happens, even without treatment, as a natural progression of cirrhosis or tumor growth. Furthermore, hyperbilirubinemia could derive from bile-duct compression by the tumor. Without a cause analysis, the authors included as toxicity cases those not derived from treatment. These events are observed even at a low absorbed dose. For this reason, the optimal threshold determination is impaired. Confirmation is provided by the normal-tissue complication probability experimental points reported by Strigari et al. (8). They also did not apply analysis of toxicity causes. Their point at the lowest biologic effective liver dose (20 Gy, corresponding to a 16-Gy whole-liver–absorbed dose) gave about a 20% risk of toxicity of at least grade 2 according to Common Terminology Criteria for Adverse Events (version 4; National Cancer Institute). In our experience (5), almost half of the observed liver decompensations within 6 mo were not related to treatment.

The second important aspect is that Watanabe et al. did not stratify patients on the basal bilirubin level. This risk factor is stronger than with AD-WNTLT (5) and heavily influences the safety threshold obtained. In Table 1, Watanabe et al. report a baseline bilirubin distribution of 0.8 ± 0.4 mg/dL. This means that, within 1 SD, 68% of the bilirubin level was within the interval of 0.4 and 1.2 mg/dL, whereas 32% are outside such an interval, with a nonnegligible percentage above 1.2 mg/dL (16% if the distribution was normal, that is, symmetric). In our steps toward optimal planning criteria, we started with a safety limit of 75 Gy (9), but after advances in knowledge, we were forced to split this limit into 50 Gy versus 90 Gy after we observed the importance of basal bilirubin levels greater than or less than 1.1 mg/dL, respectively (5).

The normal-tissue complication probability analysis is absent. This is the standard in external-beam radiobiologic modeling. Once the normal-tissue complication probability curve is obtained, it is possible to predict the quantitative level of risk of liver decompensation

given an intended AD-WNTLT value. We decided to fix the limits to keep the liver decompensation risk lower than 15%. Just to clarify the difference, our receiver-operating-characteristic curve analysis with this bilirubin stratification gave optimal thresholds of 59 and 65 Gy, whereas the normal-tissue complication probability-based limits are 50 and 90 Gy.

In the lobar treatment group, Watanabe et al. reported 4 of 78 toxicity cases (5%) and 74 nontoxic cases. In the whole-liver approach, they had 16 of 98 liver decompensations (16%) versus 82 nontoxic treatments. Note that the difference in toxicity incidence was found to be significant using the exact Fisher test ($P = 0.03$). The mean AD-WNTLT was 42 Gy in the lobar treatment group (lower than our more conservative limit of 50 Gy), whereas it was 70 Gy in the whole-liver group. In addition, without a second contralateral treatment, radioinduced hypertrophy was free to develop. Therefore, the combination of lower AD-WNTLT and partial treatment resulted in a significantly lower toxicity incidence in the lobar approach. It was so low that the authors could not obtain statistical significance, nor was a meaningful threshold found, given the small number of toxic treatments, as was our experience with lobar treatment (4).

In conclusion, the voxel dosimetry method by Watanabe et al. might be an important advance to safely plan radioembolization. However, before being used in clinics by other centers, the proposed safety thresholds for whole-liver treatment (hybrid) should be revised according to the above comments, mainly introducing analysis of causes, stratification on the basal bilirubin value, and normal-tissue complication probability analysis.

DISCLOSURE

In the last 3 y, Carlo Chiesa and Marco Maccauro were consultants for Boston Scientific, the producer of ^{90}Y glass microspheres; for Terumo, the producer of ^{166}Ho microspheres; and for AAA, the producer of Lutathera (^{177}Lu -DOTATATE). He received a research grant from Boston Scientific. Matteo Bagnalasta is a resident supported by a scholarship from Boston Scientific. No potential conflict of interest relevant to this article was reported.

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Unraveling the Hypocalcemic Response to ^{177}Lu -Prostate-Specific Membrane Antigen Therapy

TO THE EDITOR: We read with great interest the recent article by Kumar et al. published in *The Journal of Nuclear Medicine* (1). The authors presented an intriguing finding of clinically significant hypocalcemia and osteosclerosis as rare but important side effects of ^{177}Lu -PSMA-I&T therapy in patients with high-volume osseous metastatic disease who showed a significant treatment response. The paper provides valuable insights and stimulates thought; however, there are still certain aspects that require further clarification and discussion. Although Kumar et al. shed light on the potential side effects of ^{177}Lu -PSMA-I&T therapy, additional investigation is necessary to fully comprehend the underlying mechanisms and optimize patient management.

Hungry bone syndrome was initially described by Albright and Reifenstein in relation to the removal of parathyroid adenomas (2). This procedure triggers an increase in osteoblastic activity, resulting in excessive deposition of calcium and phosphate in the bones (3). The calcium sink effect in metastatic prostate cancer, which is also associated with hungry bone syndrome, is actually caused by tumor-induced osteoblastic activity (4). These cases generally do not respond well to aggressive medical treatment but may show improvement after successful tumor control (1,5,6).

We posit that the findings of Kumar et al. may differ from the tumor-induced calcium sink effect. According to their study, patients who were previously normocalcemic experienced hypocalcemia after ^{177}Lu -PSMA therapy, specifically when there was significant tumor suppression. The authors hypothesized that the remaining minority of tumoral cells may have increased the release of osteoblastogenic growth factors. However, we propose that the underlying pathophysiology might be explained by considering the fact that prostate cancer cells have the ability to secrete parathyroid hormone–related peptide, thereby stimulating osteoclast activity. Tumor suppression consequently results in significant suppression of parathyroid hormone–related peptide in the microenvironment, leading to hypocalcemia that closely resembles hungry bone syndrome (7,8). Unfortunately, Kumar et al. did not provide any data regarding the levels of parathyroid hormone–related peptide in the cases to assess this hypothesis. Furthermore, it would have been