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Reply: As clearly stated in the title of our manuscript, the goal of our study was to compare overall survival between the two different approaches used to treat metastatic thyroid cancer with radioactive iodine at our respective institutions: empiric vs. a personalized whole body/blood clearance (WB/BC) based approach (1). The Maximal Tolerated Activity formalism (MTA) used at MSKCC is based on the standard Benua method as reported in our paper (2). The references citing previous studies of the same group on the specific recent use of rhTSH in this setting are more than adequate.

What is probably not fully addressed in our paper is that the MTA determined for each patient is only one of the critical factors that are used at MSKCC to determine the actual administered activity. The prescribed administered activity and the timing between additional activities at MSKCC was based on MTA and multiple other factors: age, metastases size, histology, FDG avidity, response to previous RAI treatments, cumulative RAI activity, co-morbidity and toxicities from previous RAI therapies. We consider MTA as a valuable piece of information that sets the upper limit of administered activity that can be safely given with respect to lung and bone marrow toxicity but in many cases an administered activity less than the MTA is selected as we strive to maximize benefit and minimize risks. Indeed, the criticism that "optimizing quality of life and minimizing the side effects are not addressed in this work" is incorrect because the selection of administered activity on the basis of MTA and other clinical factors demands a consideration of both the risks and benefits of radioactive iodine therapy for each individual patient.

The choice of empiric fixed 100 mCi at GR is historical since the early 1950's and was later confirmed by the reported favorable outcome of metastatic patients with RAI avid metastases . In previous published series a complete remission was achieved in 40-50% of patients and 96% of complete responses were reported after the administration of a cumulative activity of less than 600 mCi (3). Additional administered activities would potentially expose the patient to greater toxicity without an expectation of significant long term clinical benefit (4). We are not aware of any clinical data demonstrating that any method of dose assessment might produce better clinical outcomes.

Jentzen et al comment on inter patients and intra patients lesion heterogeneity. This comment points out, as discussed in our reply to Tulkchinski and Flux comments, the critical importance of lesional dosimetry in patients with large tumor burden to define the optimal administered activity to achieve a therapeutic tumoricidal dose, rather than the maximum activity that can be safely delivered (5). WB/BC studies would only be required if the administered activity exceeded safe empiric activities to optimize the therapeutic efficacy while minimizing treatment related side effects. In our experience using 124I-PET lesional dosimetry, we commonly see metastatic foci that would receive a lesional dose of only a few Gray with administered activities of 200-300 mCi. In such cases, doubling or tripling the administered activity would still produce a lesional dose that is sub-therapeutic while exposing the patient to higher risks. Therefore, further prospective studies are needed to define the actual administered activities to achieve therapeutic effect and to test the hypothesis that larger administered activities will achieve long term better clinical outcomes. Finally, 124I PET scanning can only estimate the dose delivered at a macroscopic level but cannot take into account the heterogeneity of the dose distribution in tumor foci at the cell level that may increase with the lesion size. This may be a major factor of radioresistance that can be reverted by redifferentiation therapies (6).

In conclusion, science based on theoretical thoughts needs to be confirmed by prospective clinical trials that are still dramatically lacking seventy years after the initial use of radioactive iodine.

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