Purpose: The aim of this study was to determine the dosimetric impact of heterogeneous cellular uptake of Lu-177 and Y-90 labelled compounds in targeted radionuclide therapy (TRT).

Methods: Fine resolution voxel S values (VSVs) were generated for Lu-177 and Y-90 using Monte Carlo simulation with the EGSnrc user-code DOSXYZnrc. The VSVs were generated to be 20 microns on edge for Lu-177 and 100 microns for Y-90. To simulate varying degrees of heterogeneous uptake, activity was randomly assigned to percentages ranging from $1 \%$ to $80 \%$ of voxels in cubic volumes chosen to be large enough so that a central region, $30 \times 30 \times 30$ voxels in size could receive a cross dose from the maximum beta range of Lu-177 and Y-90. The resulting dose distributions were determined using the VSV approach where each target voxel dose is calculated by summing the product of the activity and corresponding voxel-to-voxel S value from each source voxel.

Results: For the simulated Y-90 activity distribution, when $80 \%$ of the 100 micron voxels were labelled, the minimum and maximum voxel doses in the central region of interest were within $2.2 \%$ and $1.3 \%$ of the mean voxel dose, respectively. A percent difference of less than $10 \%$ was maintained between the minimum/maximum and mean voxel dose all the way down to $20 \%$ labelling. At $80 \%$ labelling of $\mathrm{Lu}-177$, the minimum and maximum voxel doses were within $11.1 \%$ and $5.4 \%$ of the mean voxel dose, respectively, and at $20 \%$ labelling these values increased to $21 \%$ and $40 \%$.

Conclusions: This study indicates the impact of nonuniform activity distributions of two commonly used radionuclides in TRT. Even with low percentage labelling, the relatively long range of Y-90 emissions helps to significantly smooth out the dose. The calculated dose distributions were not as uniform for $\mathrm{Lu}-177$ due to the shorter range of its emitted betas.

