0.3 *mm* deviation for localization and 6.5% quantitative deviation at 640 *nm* wavelength based on the heterogeneous mouse model.

There are some new understandings from the comparison of reconstruction deviations came from the heterogeneous model and the homogeneous models in the first experiment. The deviation of 2.37 *mm* in homogeneous is much larger than 0.30 *mm* in heterogeneous model. Especially, we found that the main localization deviation is about 1.8 *mm* in the Z-axis direction in the homogeneous mouse model, while it is only 0.1 *mm* deviation in the heterogeneous mouse model. The similar deviation trends can be observed in the second experiment. Both of the experimental results show that the great difference of the heterogeneous organs in spatial distribution may be the intrinsic reason which causes the great deviation in Z-axis direction. Consequently, the reconstruction deviation in the heterogeneous mouse models may be simultaneously determined by the spatial distribution of heterogeneous organs relative to the actual position of source and corresponding optical properties of organs.

The experiments also show that the method is computationally efficient and of almost equivalent time cost between the heterogeneous and homogeneous mouse models. The quantitative *hp*-finite element reconstruction method can handle a complex heterogeneous geometrical model, suitable for small animals that have complicated anatomies.

There are several limitations of this study. First we have to admit that the post-processing of semi-automatic segmentation is rather time-consuming. Another limitation of the second experiment is that super-early tumors cannot be accurately positioned with the assistance of MicroCT, due to the poor density contrast between the tumor tissue and normal hepatic tissue. The issue of semi-automatic segmentation may be solved by developing effective ways and the localization of actual position of super-early tumors may be solved if we consider using appropriate contrast agent enhancing method. Certainly, further studies of actual source location of super-early tumor are still needed.

In conclusion, we have developed a highly sensitive dual modality BLT/MicroCT system, with which the mouse experiments demonstrated that heterogeneous reconstructions have higher accuracy both in localization and quantification than the homogeneous mouse models with appropriate optical parameters. Moreover, the tumor tomographic reconstruction based on heterogeneous mouse model suggested that BLT technology is feasible for the localization and quantification of very small number of tumor cells. Overall, BLT/MicroCT imaging method offers the advantages of cost-effectiveness, good molecular specificity and sensitivity for noninvasive 3D imaging, and consequently enormous potential in drug development and preclinical oncological investigations.

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