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Evaluation of uncertainties in pre-clinical cellular dosimetry of 111In-labeled radiopharmaceutical

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Introduction.
Preclinical studies provide detailed information to evaluate the efficacy and safety of a new radiopharmaceuticals for diagnostic and therapeutic applications. In molecular radiotherapy (MRT) it is essential to calculate absorbed doses to the various structures of interest. Uncertainties in external beam radiotherapy are around 2% to 4%. In contrast, dosimetry for MRT suffers from different sources of uncertainties and is challenging to assess. This study tried to characterize the uncertainty related to absorbed dose calculations in preclinical cellular internal dosimetry.
Method
Based on the pre-Clinical Dosimetry Workflow for in-vitro studies and according to EANM guideline, the different sources of fractional uncertainty in preclinical studies were extracted and analyzed from the individual terms of a generic equation of absorbed dose, and then their potential effect on the global uncertainty were evaluated.
These variables were applied to calculate the fractional and total uncertainty related to nucleus absorbed dose for 111In-labelled radiopharmaceuticals distributed in three different regions of A431CEA cells; cell surface, cell nucleus and cytoplasm. The total uncertainties associated to absorbed dose were obtained by propagating the standard deviations and the systematic uncertainties related to each step of the dosimetry in all parts of experiments. The contribution of each cell area on total uncertainty of absorbed dose was also evaluated.
Results
The specific aspects of uncertainty within the cellular dosimetry chain include the combination of standard deviation of measurements and other uncertainties related to cell counting, calibration factor of gamma counter and dose calibrator, time activity curve fitting to calculation of the cumulated activity and uncertainty on S-value calculations.
Results showed that the main source of fractional uncertainty at cellular level was the standard deviation associated to repeated experiments. For cumulated activities calculation in different regions of the cells, the maximum uncertainties were 65%, 39% and 25% for cytoplasm, nucleus and cell surface, respectively. Using the standard propagation method, the maximum total uncertainties of nucleus absorbed dose were 37%, 31% and 36% for single cell, cell cluster and monolayer models, respectively. However, the contribution of different areas of the cells to total uncertainty of nucleus absorbed dose strongly depends on the cell models and the specific type of vectors. This is because of different internalization capabilities of the vectors to the cell and cell nucleus, resulting in different contributions of cell regions to total nucleus absorbed doses for different radiopharmaceuticals. Discussion and Conclusion
The greatest source of uncertainty in preclinical dosimetry involves the need to longitudinally measure the spatial distribution of the radiopharmaceutical in vivo and in vitro. In this study, random errors seem to be the major contributor to the global uncertainty; systematic uncertainties had a lesser impact, but should be considered to improve the reliability of the obtained results.

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