Cell-Level Dosimetry and Biologic Response Modeling of Heterogeneously Distributed Radionuclides: A Step Forward

Historically, clinical response to internal radionuclides has been related to the macroscopic (i.e., whole-tumor or whole-organ) absorbed dose, implicitly assuming uniform distributions of activity and energy deposition (1,2). However, the actual biologic response among cells within a tumor or organ can vary substantially, depending on spatial nonuniformities of these distributions at the multicellular, cellular, and subcellular levels (3–9). The macroscopic, or mean, absorbed dose thus may not be a reliable descriptor of the biologic effect of internally deposited

radionuclides, and its use may actually confound the derivation of clinically meaningful (i.e., predictive) dose–response and dose–toxicity relationships (2,4,10). For example, Behr et al. (3) reported a preclinical study comparing in mice the myelotoxicity of monoclonal antibody CO17-1AA (directed against human gastrointestinal malignancies) labeled with a β-particle emitter (^{131}I or ^{90}Y), an Auger- or conversion-electron emitter (^{125}I or ^{111}In), or an α-particle emitter (^{213}Bi). The maximum tolerated blood dose (as a surrogate of the marrow-absorbed dose) differed by nearly 3-fold among the foregoing radiations: predictably, the radionuclides emitting the shortest (subcellular)-range radiations (namely,

Auger or conversion electrons) and therefore having the lowest dose per decay to hematopoietic stem cell nuclei had the highest maximum tolerated blood dose (>2,400 cGy). O'Donoghue (4) modeled the impact of dose nonuniformity on radiocurability of tumors, demonstrating that overall tumor response is poorer (i.e., tumor cell survival is greater) as dose nonuniformity increases. The calculated dose–response curve was concave upward, indicating that the tumor-sparing effect of such nonuniformity is actually greater at higher doses. Although some cells will receive supralethal doses with increasing tumor dose, others will still receive sublethal doses and remain clonogenic. The tumor may therefore not regress even with mean tumor doses sufficiently high to otherwise bring about expectation of a significant therapeutic response. The foregoing studies illustrate that, in light of dose nonuniformity, clinically predictive dose–response and dose–toxicity relationships based on the mean absorbed dose may be difficult or impossible to derive.

Tissue culture models can be used to grow cells in vitro in a manner that simulates, to varying degrees, in vivo tissue structure, and such models can be used to characterize the impact of nonuniform distributions of activity and energy deposition on biologic response. The study by Rajon et al. (11) in this issue of *The Journal of Nuclear Medicine* presents a theoretic 3-dimensional tissue-culture model that more realistically recapitulates the variability of cell activity than previous models and, combined with dose–response models, provides new and important insights into the radiation dose distribution and biologic effect of heterogeneously deposited internal radionuclides.

Previously published cell culture studies of biologic response to radionuclides in situ have used 2-dimensional (2D) (i.e., monolayer) or microscopic 3-dimensional (3D) (i.e., spheroid) models. Although yielding important dosimetric and radiobiologic insights, both such cell culture models have notable limitations in terms of accurately simulating in vivo tissue structure and response. Carlin et al. (12), for example, assessed the potential of expression of the sodium iodide symporter (NIS) by genetic transduction of the NIS gene as a means of therapeutically targeting radioiodine to tumor cells, assaying the clonogenic survival of NIS-transduced UVW (UVW-NIS) glioma cells after exposure to ^{131}I iodide ($^{131}I^-$). Exposure of UVW-NIS cells to $^{131}I^-$ at an activity concentration of 4 MBq/mL reduced survival of 2D monolayer cultures and of 3D spheroid cultures to 21% and 2.5%, respectively. The 10-fold-lower cell killing in 2D cultures is likely attributable to the lack of β-particle cross-fire (because there are no β-particle–emitting cells in planes above and below the cell monolayer) (13) and of a radiologic bystander effect (14), effects that are likely important in vivo. Although 3D spheroid cultures may recapitulate the radiobiologic response of avascular micrometastases more accurately than 2D cultures (15–20), the response of more macroscopic structures (such as organs or bulk tumors) is likely not reliably modeled by spheroids. Spheroids are typically only 100–200 μm in diameter, considerably shorter than the range of most β-particles, and therefore a relatively large portion of a β-particle's energy is deposited outside the spheroid. In addition, spheroids typically approximate a hexagonal close-packed array of water-equivalent spheres (i.e., cells)

with water-equivalent intercellular space. The actual microscopic structure of tissue may differ widely from such an idealized configuration.

In the current study, a theoretic model of a macroscopic, heterogeneous 3D cell population (specifically, a cylinder 1.32 mm in diameter and 1.25 mm in height) was constructed, and cell-level Monte Carlo radiation transport simulations were performed to assess self- and cross (nonself)-doses to individual cell nuclei for monoenergetic 10-, 30-, 100-, 300-, and 1,000-keV electrons and for uniform and nonuniform activity distributions among the cells. Novel features of this cell culture model and dosimetric analysis include a structurally heterogeneous, more realistic milieu comprising water-equivalent cells, a Cytomatrix carbon scaffold (mass density, 2 g·cm^{-3}) in the form of irregular ligaments, and a water-filled extracellular space; empirically validated modeling of the differential radiobiologic effectiveness between cell self- and cross-doses (corresponding to mean lethal doses D_{37} of 400 and 120 cGy, respectively, for low–linear-energy-transfer radiations) (21–23); and a lognormal distribution of activity among cells, with quantitative assessment of the effect on overall survival of varying degrees of nonuniformity of the activity per cell (i.e., corresponding to values of 0.6, 1.0, and 2.0 of the so-called shape parameter σ of the lognormal probability density function) (22,24,25). On the basis of the calculated cell nuclei doses and previously published models of cell killing, survival curves were derived and characterized in relation to the electron energy and the nonuniformity of the activity distribution. Nonuniformity of the cell activities and the finite ranges of particulate radiations produce dose nonuniformity at the cellular level, which in turn results in variations in the overall survival fraction of the cell population. Energy-dependent changes in the shape of the survival curves—increasingly concave up (consistent with the results of O'Donoghue (4))—are most pronounced at low electron energies, at which attenuation is significant even at microscopic dimensions and self-dose thus predominates. At high electron energies, cross (or nonself)-dose dominates and mitigates the dependence of the survival curves on energy. This significant cross-dose contribution, particularly at higher electron energies, represents a notable difference dosimetrically between the current macroscopic model and the more microscopic spheroid models, for which the β-particle cross-dose contribution is minimal.

It is unrealistic to suggest that the analysis by Rajon et al. (11) is adaptable to individualized planning of radionuclide therapy; the necessary input data are not available, and perhaps unknowable, in a routine clinical setting, and the computations times are prohibitively long. Nonetheless, this analysis does provide some practical guidance for targeted radionuclide therapy of bulky tumors with specific patterns of uptake of a particular radiopharmaceutical. For example, for tumors with cells that exhibit a relatively uniform uptake (corresponding to a shape parameter σ of 0) and for radionuclides emitting low-energy electrons (i.e., Auger or conversion electrons with energies on the order of 10 keV), mean tumor cell nuclei doses of only 10 Gy can achieve a highly significant therapeutic effect (several logs of cell killing), with minimal irradiation of hematopoietic stem cells in marrow. On the other hand, if tumor cell uptake is notably nonuniform (corresponding to a shape parameter σ of 1 or 2), radionuclides emitting β-particles with mean energies of at least 100 keV and mean tumor cell nuclei doses of at least 30 or 40 Gy, respectively, are required to achieve therapeutically effective tumor cell killing overall. Projecting forward, a catalog of shape parameter values for different histologic types of tumors and different radiopharmaceuticals could perhaps be compiled by quantitative autoradiography of tumor specimens surgically harvested after tracer administrations to a limited number of patients. The individually optimized radionuclide or cocktail of radionuclides (25), tumor dose, and administered activity could then be prescribed for a patient's specific histologic tumor type (i.e., shape parameter value) using mean tumor doses per unit of administered activity derived on a case-by-case basis from routine quantitative imaging studies. With increasingly realistic dosimetric analyses—such as the method proposed by Rajon et al. (11)—and the biologic insights they provide, such a hypothetical leap forward warrants at least some consideration.

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