State-driven mathematical model simulations of tumor response to radiotherapy: how does high FDG uptake relate to classical radiobiological principles?

**Background:** As the most commonly used functional imaging modality in radiation oncology, $^{18}$F-FDG PET has played a valuable role in detecting, staging and monitoring tumor. Many clinical studies have shown that the uptake of FDG, usually measured as a standardized uptake value (SUV), can be a significant predictor of prognosis. Also the region of high FDG uptake is known to be radioresistant and correlated with increased local failure. Many studies have been carried out to correlate FDG uptake with physiological parameters, such as hypoxia, proliferation, blood flow, histology and differentiation, using PET, immunohistochemical method and histology. Although several studies have shown the relationship between the FDG uptake and hypoxia or proliferation, the underlying mechanism of FDG uptake in a tumor is still unclear.

**Innovation/Impact:** The FDG uptake mechanism was explored using a state-driven mathematical model for tumor response, in which classical radiobiological mechanisms were incorporated. Three different FDG uptake patterns were hypothesized and tested in the model to find a relevant FDG uptake mechanism, which is consistent with the clinically observed radioresistance of high FDG uptake region.

**State-driven mathematical model:** The model is comprised of three sub-populations of cells based on the level of proliferation, hypoxia and cell loss, which is thought to be related to the available amount of oxygen and glucose as shown by Kiran et al. [1]. The model focused on a small tumorlet that has comparable size of a typical PET voxel ($4 \times 4 \times 4$ mm$^3$), which is the smallest in-vivo imaging unit that can reveal the microenvironment within a tumor. Figure 1(a) shows three compartments before RT. Proliferation takes place only in P compartment and cell loss in H. Cells in I compartment neither proliferate nor die. The transition of cells between compartments is determined by the size of each compartment, not by fixed transfer rates. After RT begins, the damaged cells (calculated by L-Q model) become doomed with compartment-specific radiosensitivity and mitotic cell death takes place in $P_d$ sub-compartment (Fig. 1(b)). As doomed cells die out, the hypoxic cells move toward P compartment and, in this process, reoxygenation occurs, while viable cells in P compartment still proliferate and cause repopulation.

**Estimation of $TD_{50}$ in the model:** The tumor doses for 50% control ($TD_{50}$’s) in 2 Gy/fx (5 fx/week) were estimated for all possible initial conditions of the model, which are determined based on growth fraction (GF) and cell loss factor (CLF) as shown in figure 2. Relevant parameter values for head and neck squamous cell carcinoma (HNSCC) were used for the simulation, including radiosensitivity of P compartment ($\alpha_p=0.41$ & $\alpha/\beta=10$) [2]. The hypoxic cells in I and H are considered to be only in G0/G1 phase and the OER values for I and H were assumed to be 2 and 1.4, respectively, considering lower OER of G0/G1 phase and reduced repair capability of chronically hypoxic cell [3].

![Figure 1](image1.png)

**Figure 1.** Schematic diagram of the model: (a) just prior to the initiation of radiation therapy and (b) after radiation therapy begins with doomed sub-compartment in each compartment.

![Figure 2](image2.png)

**Figure 2.** Model predicted tumor dose for 50% control ($TD_{50}$) in 2 Gy/fx for all possible initial conditions given by growth fraction (GF) and cell loss factor (CLF).
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Three hypotheses of FDG uptake pattern: The sub-populations of tumor cells in the model were distinguished based on oxygen and glucose availability [1], and only P and I compartments were thought to be associated with FDG uptake. Three different FDG uptake patterns were assumed: (1) The FDG uptake is proportional to the total number of metabolically viable cells; (2) The FDG uptake is associated mainly with the proliferating cells with minor contribution from intermediate cells; or (3) The FDG uptake is associated mainly with the intermediate cells with minor contribution from proliferating cells as shown in figure 3 (insert plots).

Correlation between FDG and TD₅₀: For each initial condition of the model, the FDG uptake value was quantified and correlated with model predicted TD₅₀ value, depending on the assumed FDG uptake patterns. For the first assumed pattern (fig. 3(a)), only weak positive correlation was observed. When the uptake pattern was assumed to be associated with cell proliferation (fig. 3(b)), significant negative correlation existed between FDG uptake and TD₅₀, which is opposed to the clinical observation. For the hypothesis that metabolically-viable hypoxic cells are avid for FDG uptake (fig. 3(c)), strong positive correlation was acquired, which is consistent with the clinical observation. In the model, the number of cells in I compartment is a deterministic factor on tumor response and this sub-population seems to be associated with FDG uptake.

Figure 1. Model predicted tumor dose for 50% control (TD₅₀) in 2 Gy/fx vs. FDG uptake (normalized to maximum) for three hypothetical uptake patterns: (a) proportional to total number viable cells, (b) associated mainly with proliferation, (c) associated mainly with intermediate hypoxia. In subplot (d), contribution from extreme hypoxia was also included as a reference.

Reference: