A study of the Effects of Vascular Damage On Tumor Volume After Hypo-Fraction Radiotherapy by Using a Cellular Automata model

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INTRODUCTION

The mechanisms of tumor growth in vivo involves many different processes[1], such as the supply of nutrient, the local oxygen concentration, the behaviors of immune system, the mechanical pressure inside the tumor. Our previous study introduced a novel automaton model of tumor growth in response to irradiation[2].

In our previous study, we optimized the fractionation scheme of SRS by using a cellular automata model including the indirect cell death, in which the blood vessels receive the lethal damage causing less oxygen supply to tumor after irradiation in addition to the direct cell damage by which radiation directly induces the death of cancer cells[3].

METHODS

- Cancer cells died by direct and indirect death from the radiation, which was quantified by the LQ-model. Direct death was caused by mitotic death and apoptotic death due to the lack of nutrients.
- The radiation caused increased oxygen permeation through the blood vessel or the breakdown of the vasculature resulting in a decrease of oxygen and nutrients. The cell death by this ischemia was defined as indirect death. It leads to apoptotic death by hypoxia and necrotic death by nutrient deprivation.
- The dead cells did not consume the oxygen. Instead, the oxygen was distributed only to the survived cells.

Figure 1 shows the block diagrams of the cellular automata (CA) model The entire simulation process is summarized as follows:

(1) Generate blood vessels and get the oxygen distribution.
(2) A cancer cell proliferates with probability Pc and the lattice rules.
(3) A cancer cell, which cannot proliferate, turns to a necrotic cell or an apoptotic cell. If the nutrient level is smaller than the threshold value and the random probability is smaller than necrosis probability P_{nd}, the cancer cell is replaced with a necrotic cell. If the oxygen level is smaller than the threshold value and the random probability is smaller than apoptotic probability P_{O2}, the cancer cell is replaced with an apoptotic cell.
(4) A cancer cell turns to a doomed cell by radiation damage (direct death). Here, the doomed cell is a cancer cell, which is damaged by radiation and will die eventually in the future. If the random probability of death was smaller than the probability of the radiation damage P_{LQ} and the random probability is smaller than apoptotic death P_{ap}, the cancer cell is replaced with a doomed cell. If the random probability of death was smaller than the probability of the radiation damage P_{LQ} and the random probability is smaller than $(1\text{-}P_{ap})$, the cancer cell is replaced with a doomed cell.
(5) An arrested cell can be repaired and become a cancer cell if the random probability of death P_{id} is smaller than apoptosis repair probability P_{ar}. In the current study, the repair is not considered, thus P_{ar} was set to 0.
(6) A necrotic cell is replaced by a dead cell if the random probability is smaller than the necrotic death probability P_{necro}. The apoptotic cell and doomed cell for apoptotic death are replaced by a dead cell with a constant rate and its half-life T_{icd}. The doomed cell by the direct death is replaced by a dead cell with a constant rate and its half-life T_{dd}.
(7) A dead cell does not consume the oxygen. So, there is an extra amount of oxygen, some of which can be redistributed to the remaining cancer cells. The ratio of the redistribution is defined as Λ.

The optimal model parameters were determined by matching the simulation results with experimental data of the mice tumor volume for various doses. We did 1000 simulations per case.

AIM

1. To improve a cellular automata model by including necrotic death by vessel damage. The vessel damage was assumed to cause by lacking the nutrient or oxygen.
2. To investigate the mechanism of the vessel damage for treatment outcome.

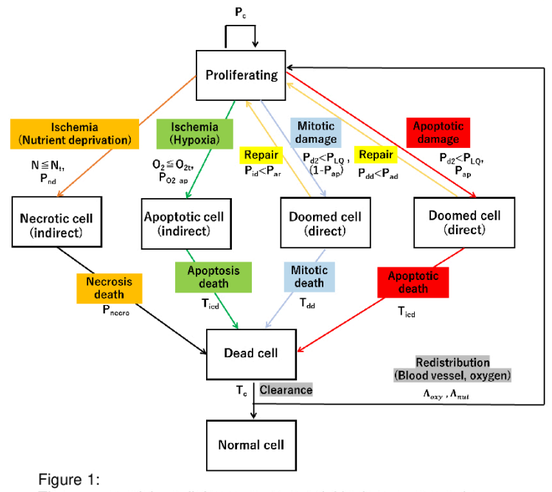

Figure 1:
The process of the cellular automata model in the current study

RESULTS

Figures 2(a-c) shows the cell distributions of the cellular automata simulation for before irradiation, immediately after irradiation, and 10 days after irradiation with a uniform dose over the entire volume. The parameters used in the simulation were shown in Table 1. Figures 3(a)(b) show the volumes of proliferating cancer cells ("Tumor")(a) and the whole tumor "Total" (b) vs. the time in days for P_{nd}=0.00 and 0.06 with a single dose of 20 Gy on day 100. The number of cancer cells decreased immediately after irradiation, then it increased. On the other hand, the tumor volume ("Total") decreased until the 26th day. The volumes of Total and Tumor for P_{nd}=0.0 are larger than that for P_{nd}=0.06, demonstrating the effect of necrosis caused by the lack of nutrients.

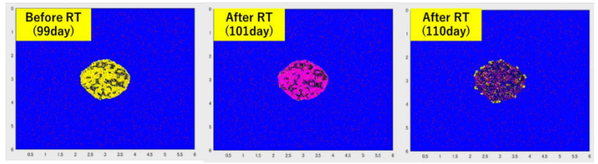

Fig. 2: The cellular automata model of the tumor (a) before irradiation, (b) immediately after irradiation, and (c) 10 day after irradiation with a uniform dose over the entire volume.

Parameters	Value
α/β	5
P_0	0.6
N_1	1.0
P_{nd}	0.00,0.02,0.06,0.1
P_{O2_ap}	0.0
N_1	1.0
O_{2t}	0.2
P_{ar}	0
P_{ap}	0
P_{necro}	0.1
T_{icd} (day)	10
T_{dd} (day)	5
T_c (day)	6
Vessel density (g/cm^3)	0.038
L_{oxy}, L_{nut}	0.3

Table 1 The cell parameters.

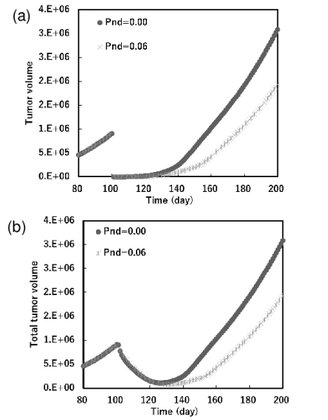

Fig. 3: The tumor volume vs. time in days. The closed black shows the total tumor volume without necrotic death (P_{nd}=0). The grey plus shows the total tumor volume with necrotic death (P_{nd}=0.06).

Figure 4 shows the relation of the dose and the ratio of tumor volume at day 200 (V200day) to day 100 (V100day). Figure 5 shows the relation of the dose and the tumor control ratio (TCP). Here, the tumor control probability (TCP) was defined as the ratio of the number of histories in which all cancer cells died after the irradiation to the total number of the histories per simulation. The ratio,V200day/V100day, and TCP decreased with increasing dose. The comparison of curves of P_{nd} = 0.0 and non-zero values indicates that ***the radiation damage of blood vessels causes higher cell death.***

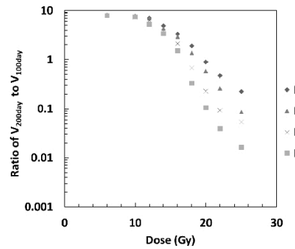

Figure 4: Ratio of the tumor volume at day 200 (V200day) to day 100 (V100day) vs. dose in Gy for Pnd=0.0, 0.02, 0.06, and 0.1.

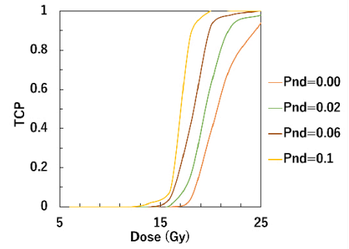

Figure 5: TCP vs. dose in Gy for Pnd=0.0, 0.02, 0.06, and 0.1.

Figure 6 shows the concentration of the nutrients in the cancer cells with a single dose of 6, 10, 16, and 20 Gy. The concentration of the nutrients in the tumor cells decreased immediately after irradiation. We can observe the level of the nutrients is lower for larger doses because there is more damage to the blood vessels with increasing dose.

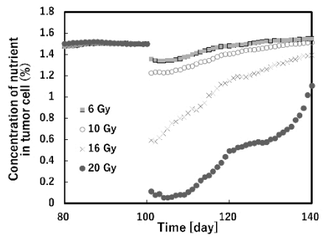

Figure 6: The concentration of the nutrients in cancer cells in % from day 80 to day 140 with a single dose of 6, 10 16 and 20 Gy on day 100.

CONCLUSIONS

We showed that the necrosis induced by the lack of nutrients, which in turn caused by the vascular damage by high dose, enhanced the radiation cell kill ability by explicitly modeling the nutrient supply and the damage of blood vessels by radiation in a CA simulation.

REFERENCES

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