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Death and Repopulation of Tumor Cells and Reoxygenation of Hypoxic Tumor Cells after High-Dose Irradiation (SFR,SBRT,SRS)

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OBJECTIVES: The objective of our study was to determine the cell death, cell reproliferation and reoxygenation of hypoxic cells in tumors after an exposure to high-dose irradiation employed in Spatial Fractionated Radiotherapy (SFR,GLID), Stereotactic Body Radiotherapy (SBRT) and Stereotactic Radiosurgery (SRS).

METHODS: FSaII tumors grown S.C. in the legs of C3H mice were irradiated with 10-30 Gy in a single dose and the numbers of surviving cells in each tumor were determined on days 0-18 with the in vivo-in vitro excision assay method. Hypoxic cell fractions on days 0-10 after irradiation with 10, 15, 20 Gy were determined based on the cell survival in tumors exposed to 10 Gy test-irradiation while the host mice were breathing air or 5 min after the host mice were killed with nitrogen gas.

RESULTS: The cell survivals 3-5 days after 10-30 Gy irradiations were markedly less than that immediately after irradiation by as much as 1.0-2.0 logs indicating significant additional cell deaths occurred when the irradiated tumors were left in situ. After reaching a nadir in about 5 days, the surviving cell population began to increase. The hypoxic cell fraction increased from 32% before irradiation to 100% immediately after irradiated with 10, 15 or 20 Gy. Fractions of hypoxic cells were then reoxygenated over several days after irradiation. For example, after 20 Gy irradiation, the hypoxic cell fraction decreased to 60% and 45%, on days 1 and 7, respectively. The reoxygenation after irradiation with 15 or 10 Gy was slower than that after 20 Gy irradiation. Hypoxic cell fraction began to rise from day 7 after 15 or 20 Gy irradiation.

CONCLUSIONS: High-dose irradiation triggers secondary/additional cell death in tumors over several days most likely by causing massive vascular destruction. At the same time, paradoxically, some of the residual hypoxic cells are reoxygenated. It is hypothesized that the drastic decline in oxygen consumption due to massive tumor cell death leads to reoxygenation of some of the residual hypoxic cells. The reoxygenation of hypoxic cells may be effectively exploited by allowing 2-5 days interval between fractions in hypo-fractionated high dose irradiation.

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