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Understanding Radiotherapy-Induced Second Cancers

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There is increasing concern regarding radiation-related second-cancer risks in long-term radiotherapy survivors, and a corresponding need to be able to predict cancer risks at high radiation doses. While cancer risks at moderately low radiation doses are reasonably understood from A-bomb survivor studies, there is much more uncertainty at the high doses used in radiotherapy. It has generally been assumed that cancer induction decreases rapidly at high doses due to cell killing. However, most recent studies of radiation-induced second cancers in the lung and breast, covering a very wide range of doses, contradict this assumption. A likely resolution of this disagreement comes from considering cellular repopulation during and after radiation exposure. Repopulation / proliferation with a significant number radiation-induced pre-malignant cells, tends to counteract the effect of cell killing, and keeps the induced cancer risks higher at high doses. We describe and apply a biologically based, minimally parameterized model of dose-dependent cancer risks, incorporating carcinogenic effects, cell killing and, additionally, proliferation / repopulation effects. The situation is somewhat different for radiation-induced leukemia, as repopulation via the blood stream tends to be with cells that originated far away from the treatment volume than is the case for solid second cancers, thus containing a smaller proportion of radiation-damaged cells. The model predictions agree well with recent data on second cancer risks, both for radiation-induced solid cancers and for radiation-induced leukemias. Incorporating repopulation effects provides both a mechanistic understanding of cancer risks at high doses, as well as providing a practical methodology for predicting, and therefore potentially minimizing, cancer risks in organs exposed to high radiation doses during radiotherapy.