Changes in the Tumor Microenvironment during Brachytherapy Treatment

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Introduction: Slowly-growing malignant tumors such as prostate cancer are often treated with permanently implanted radioactive Iodine-125 seeds (low dose rate brachytherapy). Unfortunately, little is known about how the tumor microenvironment (partial pressure of oxygen, perfusion, etc.) responds to this kind of radiation treatment. Without such knowledge, it may be very difficult to optimize treatment strategies, especially when combining brachytherapy with external beam radiation or chemotherapy (1,2). The purpose of this work was to measure changes in oxygen partial pressure (pO2) and perfusion in an experimental TLT mouse tumor, as a function of both time and distance from an implanted Iodine-125 seed.

Methods: The iodine seeds were provided by IBt, Inc. The activity of each seed was 0.5 mCi at the time of implantation (0.0 mCI for inactive control seeds). The dose rate was ~6 Gy per day at a distance of ~2 mm from the seed and ~0.7 Gy per day at ~5 mm. The pO2 in tumors was monitored by EPR oximetry (3) using a low frequency EPR spectrometer (1.2 GHz). Paramagnetic particles of charcoal, used as oxygen sensors, were implanted at well defined distances from the Iodine-125 seed. Dynamic Contrast-Enhanced Magnetic Resonance Imaging (DCE-MRI) was performed at 4.7 Tesla using P-792 (Guerbet) as the contrast agent. The kinetics analysis was performed according a protocol previously described (4).

Results: For days 1-3 after implantation, a significant (P=0.01) increase in pO2 was observed when the radioactive I-125 seed was located at 4-6 mm from the oxygen sensor (N=6). For all other EPR pO2 experiments, tumors remained hypoxic at all times (pO2 < 3 mm Hg, N=11 total). For days 1-3, the radioactive I-125 seeds also appeared to cause perfusion to increase (~20%, relative to control values) far (4-6 mm) from the I-125 seed but to decrease (~ 25%) near (0-2 mm) the seed.

Figure 1: EPR pO2 measurements

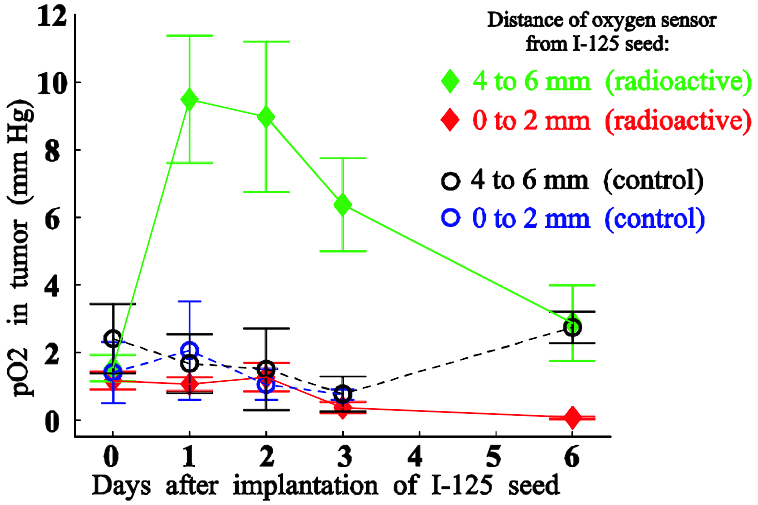
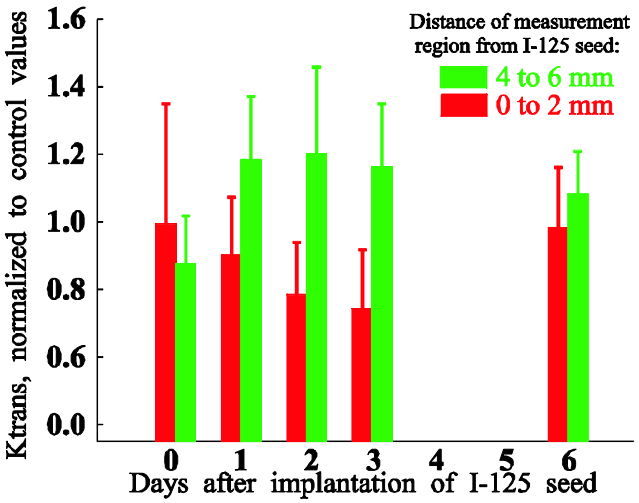


Figure 2: MRI perfusion measurements



Discussion: We observed that the tumor pO2 only increased when the radioactive I-125 seed was implanted at a substantial distance (~4-6 mm), where the dose rate is very low (~0.7 Gy per day). One possible explanation is that, at short range (~0-2 mm), the dose rate is high enough to damage vasculature, thus reducing the O2 supply (1). This explanation is consistent with the DCE-MRI data, which showed that perfusion tended to increase far from the radioactive implant and to decrease near the implant. Another possible explanation for the pO2 results is that the very low dose rate may avoid the triggering of induced radioresistance in the tumor cells (5). This could enhance cell killing, thereby reducing oxygen consumption and increasing the available pO2.

Conclusions: Our data clearly indicate changes in the tumor microenvironment after implantation of radioactive seeds used in brachytherapy. These changes are very dependent on the distance from the seed and the dose rate. A transient increase in oxygenation and perfusion was observed for some areas in the tumors. This suggests that these areas of the tumors may be more sensitive at that time to an external radiation beam or to the administration of a chemotherapeutic agent.

References:

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