Directing Local Hypoxia Radiation Boosts in a Third Tumor Model, SCC7 Squamous Cell Carcinomas, with Low- and High-frequency EPR pO_2 Imaging

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Purpose: Hypoxia is a leading cause of tumor cell resistance to radiation. Our previous studies using ten-minute Electron Paramagnetic Resonance (EPR) pO_2 images in murine FSa fibrosarcomas and MCa4 mammary adenocarcinomas to locate hypoxia for radiation boosts showed significantly improved tumor control when boosting hypoxic *vs* oxygenated tumor regions (p=0.01 for MCa4 and p=0.04 for FSa). Experiments were performed using a low-frequency pulse EPR (LFEPR) imager at 250 MHz, with a penetration depth sufficient to image humans. A high frequency pulse EPR imager at 720 MHz (JIVA-25^{TM}, O2M Technologies) allows for higher pO_2 resolution using less oxygen sensitive spin probe with 5-minute images. Here we present *preliminary data* in a third murine tumor model – squamous cell carcinoma – in both low and high frequency EPR instruments.

Methods and Materials: Female C3H mice with leg-bearing SCC7 squamous cell carcinoma tumors were imaged with EPR to locate hypoxic tumor regions ($pO_2 \leq 10$mmHg) in the 250 MHz LFEPR (N=41) and 720 MHz JIVA-25^{TM} (N=27). In the ongoing study, tumors are entirely treated with a 20% tumor control dose (TCD_{20}) and receive a boost dose treatment randomly assigned to either hypoxic or oxygenated tumor regions for a total TCD_{95} + 5Gy. Conformal blocks are printed based on EPR pO_2 tumor hypoxia to locate the boost choice of equivalent integral volume. By completion of the study, 50 mice in each group will be assessed for local tumor control by recurrence free survival over 180 days and compared between boost treatments using Kaplan-Meier analysis and log-rank test.

Preliminary Results: *LFEPR:* For 25 of 41 mice that completed their study, we observe a trend of increased local tumor control for hypoxia boosts vs well-oxygenated tumor boosts. At 115 days, estimated survival probability (ESB) for hypoxic boosts = 0.73, and for oxygenated boosts = 0.62. *JIVA-25^{TM}:* 0 out of 28 mice completed their study, though a strong trend of increased local tumor control for hypoxia boosts is apparent. At 115 days, ESB for hypoxic boosts = 0.89, and for oxygenated boosts = 0.44. Upon completion of the study, a reported p-value via log-rank test will be reported.

Conclusions: We are investigating a 3rd mammalian tumor type to confirm the ability of EPR pO_2 images to define tumor hypoxia for boosting hypoxic regions to increase local tumor control. Preliminary results show trends that imply improved tumor control with hypoxic boosts relative to well oxygenated tumor boosts.

Clinical Relevance: This shows potential enhanced therapeutic index from dose painting using pO_2 imaging in three mammalian tumors.

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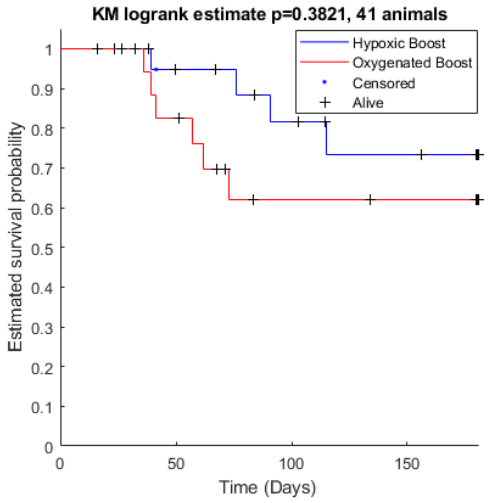
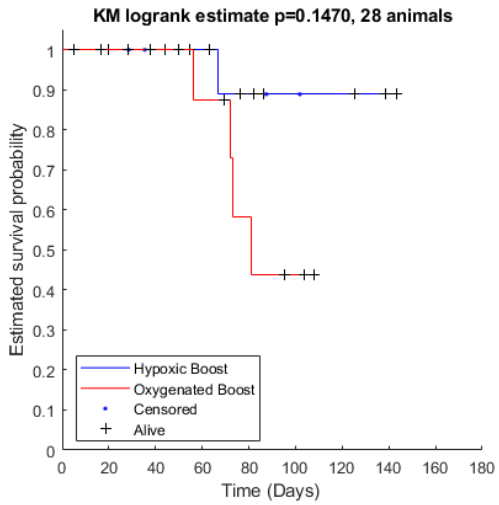
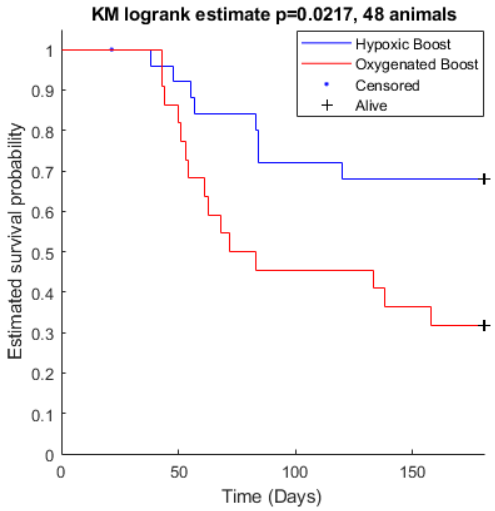
LFEPR (250 MHz) SCC7 squamous cell carcinomas



JIVA-25^{TM} (720 MHz) SCC7 squamous cell carcinomas



LFEPR (250 MHz) MCa4 mammary carcinomas



LFEPR (250 MHz) FSa fibrosarcomas

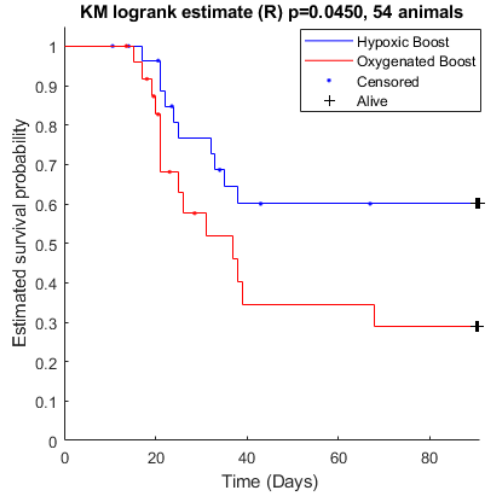


Figure 1: The two Kaplan-Meier curves at the top show SCC7 squamous cell carcinoma tumor control probabilities for 250 MHz Pulse EPR (LFEPR, left) and high-frequency 720 MHz Pulse EPR (JIVA-25^{TM}, right). Blue lines indicate Hypoxia Boost treatment; red lines indicate Oxygenated Boost treatment. Crosshairs indicate where animals are in the 180-day experiment as of April 29th, 2021. The study is expected to be nearly complete by the end of 2021.
The two Kaplan-Meier curves at the bottom show completed studies with MCa4 mammary carcinomas (left) and FSa fibrosarcomas (right), both imaged with the LFEPR. Both completed studies show a significantly higher survival probability for tumors treated with a Hypoxia Boost vs. Oxygenated Boost treatment.