Temporal Assessment of Regional and Remote Non-tumor Microvascular Response to High-Dose Radiation Therapy Using Contrast-enhanced Ultrasound

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Purpose

• High-dose radiation therapy (RT) produces multifactorial microvascular injury in both tumor targets and normal tissue.
• Contrast-enhanced ultrasound (CEU) is a high-resolution perfusion imaging technique that is able to quantify microvascular blood flow and volume by using microbubble (MB) contrast agents that are confined in the vascular space.
• CEU molecular imaging is also possible by using MBs bearing targeting ligands.
• We hypothesized that CEU could characterize alterations in microvascular blood flow in normal tissues exposed to RT.

Methods

• Proximal hindlimb muscle of C57BL/6J mice were irradiated in a single fraction.
• Regions for analysis included: high-dose (HD) RT (15 Gy), an immediately adjacent area of lower-dose (LD) RT (12 Gy), and a region on the unirradiated contralateral limb (Figure 1).
• Control mice not undergoing any RT were also studied.
• CEU of the hindlimb muscle was performed during intravenous infusion of lipid-shelled decafluorobutane microbubble contrast at day 1 and 8 after RT.
• CEU time-intensity data were analyzed to quantify microvascular blood flow, microvascular blood transit rate (β), and microvascular blood volume.
• Molecular imaging of endothelial activation was performed using MB targeted to P-selectin by virtue of surface conjugation of mAb RB40.34 (Figure 2).

Results

• Examples of CEU perfusion imaging from a wild type limb, an unirradiated contralateral limb and irradiated limb at day 1 are illustrated in Figure 3. These images show that the primary deficit were from reduced microvascular flux rather than blood volume.
• On day 1, there was a significant reduction in microvascular blood flow in the RT versus unirradiated contralateral limbs, the degree of which was dose-dependent (Figure 4).
• On day 8, flow in the RT limbs was reduced to a similar degree irrespective of dose (Figure 5). There was also a decrease in flow in the unirradiated contralateral limb, which was reduced compared to wild type mice.

Conclusion / Discussion

• CEU perfusion imaging can spatially and temporally quantify dose-dependent radiation-induced microvascular alterations.
• The perfusion deficit is due largely to reduced microvascular flux rate, suggesting that vasomotor dysregulation plays a greater role than vaso-occlusion or microvascular rarefaction.
• The delayed reduction in perfusion at sites distant from local RT suggests a systemic, or abscopal, microvascular response to high-dose RT.
• Acute (day 1) but not late (day 8) perfusion deficits are correlated with evidence for microvascular endothelial inflammatory response.

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