Abstract ID: 17297 Title: Ultrasound and Microbubble Enhancement of Radiation Response in TumoursPurpose: It is now appreciated that radiation not only damages the DNA inside tumour cells *in vivo* but may act by damaging the endothelial cells of the vasculature. In this study we tested the hypothesis that microbubble agents *in vivo* may be used *apriori* to cause endothelial cell perturbations thus causing "radiosensitization" of tumours.

Materials and Methods: Human prostate cancer xenograft-bearing mice (120 animals) were exposed to combinations of ultrasound (570kPa peak negative pressure with a 3kHz pulse repetition frequency for 750 milliseconds over 5 minutes), activated-microbubbles (Definity) alone and in the presence of ultrasound at various concentrations, and radiation (160 kVp) (8 animals per group) at doses of 0, 2 and 8 Gy. In order to optimize treatments, studies undertaking the timing of the ultrasound and radiation treatments were carried out (40 animals) by introducing a time-gap between ultrasound and radiation treatments ranging from 0 to 24 hours. In another cohort of animals (n=60) insonifying pressure and radiation dose were varied to investigate the effects of these parameters on treatment effect. In order to further demonstrate the efficacy of this type of combination treatment, multiple treatments combining radiation and ultrasound were also administered to tumour bearing mice over 3-4 weeks (40 animals). Treatment effects were monitored using staining of representative tumour sections with immunohistochemistry, clonogenic assays and growth delay studies.

Results: Analyses indicated a synergistic increase in tumour cell kill due to vascular disruption caused by the combined therapies leading to endothelial cell apoptosis through the activation of the ceramide cell-death pathway caused by microbubbles. The optimal time for combining the two treatments in order to maximize treatment synergy varied with radiation dose and appeared to be within 6 hours. Effects varied with radiation dose and insonifying ultrasound pressure. Multiple treatments indicated better therapeutic outcome compared to single treatments and caused tumour regression. Analyses indicated activation of ceramide-mediated apoptotic cell death in endothelial cells leading to vascular disruption in tumours.

Conclusions: This work forms the basis for ultrasound-induced spatial targeting of radiotherapy enhancement. Results indicated a greater than 50-fold increase in tumour cell death. This type of combination treatment has the potential to increase the efficacy of radiation and should permit lower radiation doses to be used with the same treatment effect as high doses of radiation when administered alone.