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63 ASSESSMENT OF BOILING HISTOTRIPSY DOSE IN HUMAN EX VIVO KIDNEYS AND RENAL TUMOURS

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OBJECTIVES

Histotripsy is a pulsed high intensity focused ultrasound (HIFU) technology that mechanically disrupts targeted tissue without a thermal effect. Our group has developed boiling histotripsy approach (BH), a technique that utilizes millisecond-long HIFU bursts to create bubbles at the focus via rapid shock-induced boiling. Interaction of subsequent shocks in the pulse with the ensuing vapor cavity mechanically homogenizes tissue into sub-cellular micron-sized debris in a process involving acoustic fountaining. As a noninvasive, non-thermal approach, BH may have several advantages over existing clinically available thermal ablative technologies for renal masses. Preliminary data suggests differential sensitivities to the effects of histotripsy of specific locations within the kidney, while the sensitivity of human renal tumours to the effects of BH is unknown. The aim of this study was to evaluate and compare the effect of BH on samples of freshly excised human renal tissues and associated tumours *ex vivo*.

METHODS

Freshly excised human kidneys, benign renal tissue, and renal tumour tissue were obtained via IRB approved institutional rapid autopsy and tissue procurement programs. Tissue was obtained from n=11 patients: n=6 whole benign kidneys, n=5 fragments of benign parenchyma, and n=4 tumours (clear cell renal carcinoma (ccRCC): n=2, papillary RCC: n=1, oncocytoma: n=1). All specimens were acquired within 4 hours from death/nephrectomy. Tissue samples were degassed for over 30 minutes in phosphate buffered saline (PBS) and then embedded in low melting point agarose gel. Agarose embedded tissue was then placed in a holder in a bath of degassed PBS. BH exposures were performed under B-mode ultrasound guidance using a 1-MHz 7-element HIFU transducer (aperture 14.7 cm, F#=0.95) with the following pulsing protocol: pulse duration of 10 ms, pulse repetition frequency of 1 Hz, peak focal pressures of p+=88 MPa, p-=17 MPa, shock amplitude of 98 MPa. Single focal volumes within the tumour sample or the renal cortex, medulla, or collecting system were treated at various doses defined here as the number of pulses irradiated into a single focal spot (3-300 pulses/focus). Treated kidneys and tumour samples were evaluated grossly and/or formalin-fixed for histologic assessment with hematoxylin and eosin staining.

RESULTS

BH pulses produced hyperechoic bubbles at the focus in all tissue types consistent with rapid boiling induced by each pulse. Treatment within the renal cortex and tumour tissue resulted in the development of progressively hypoechoic cavities apparent between pulses, consistent with historipsy treatment effect of homogenizing tissue, while the feedback was less pronounced in the medulla and collecting system. On inspection, tumour tissue appeared more susceptible to the effects of BH than benign tissue; lesions created in tumour tissue with 10 pulses were similar in size to those created with 30 pulses in the cortex (Figure 1). Histologically, evidence of BH induced tissue homogenization was observed in tumours at much lower dose threshold of f 5 pulses/focus compared to those in benign tissues: 15-30 pulses/focus in the cortex, 45-60 pulses/focus in the medulla, and 90-120 pulses/focus in the collecting system.

CONCLUSIONS

BH mechanical ablation of human *ex vivo* renal tumours is feasible, yielding anticipated tissue homogenization. The observed increased resistance of benign renal tissue to the effects of BH compared to renal tumours, if confirmed *in vivo*, may help preserve renal function while providing a margin of safety when developing BH for clinical ablation of renal tumours. This work was supported by NIH R01 EB7643, K01 EB 015745, Urology Care Foundation and National Space Biomedical Research Institute (NSBRI) through NASA NCC 9-58.

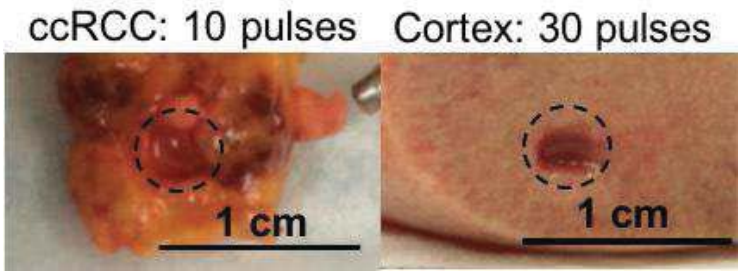

Figure 1: BH lesion produced in ex vivo human clear cell renal carcinoma (left) and benign human kidney cortex (right) with two different BH doses (10 and 30 pulses, respectively) are similar in size, demonstrating increased tumour tissue susceptibility to BH-induced damage compared to benign tissue