Determining the Cesium Limit-of-Detection in Quantitative Image-Guided DECT Interventions: A Potential New Theranostic for Thermochemical Ablation

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Purpose:
Thermochemical ablation (TCA) is a minimally invasive therapy under development for hepatocellular carcinoma, the most common type of primary liver cancer. TCA utilizes acid/base chemistry delivered simultaneously directly into the tumor to induce local ablation when administered. When delivered via a mixing catheter, acid (AcOH) and base (NaOH) react to completion at the catheter tip before delivery into tumor, producing acetate salt, water, and releasing heat (Δ>50°C) in sufficient quantities to induce lethal osmotic and thermal stress in tumor cells. The challenge is that these reagents are not distinguishable from tissues, which makes monitoring delivery of TCA difficult. We address this issue by developing CsOH as a novel theranostic component of TCA that can be quantified with dual-energy CT (DE CT) and used as a tool to track TCA during delivery and post-procedural follow-up. However, to ensure accurate product mapping, the limit-of-detection and attenuation-enhancement relationship must first be established in phantoms before performance testing in *ex vivo* and *in vivo* models.

Methods:
Phantom Experiments: Seven serial dilutions of CsOH (Sigma-Aldrich) were made in 30mL centrifuge tubes with concentrations ranging from 0.195mM-125mM using standard dilution techniques. Standards were placed in an elliptical phantom (Multi-Energy CT Phantom, Sun Nuclear Corporation) and scanned using a split-filter dual-energy system (SOMATOM Edge, Siemens Healthineers) with the following DE CT protocol: 120kVp, Au/Sn filter, 25mGy CTDIvol, 5 consecutive scans. Images were reconstructed at 1.5mm slice thickness and 1.0mm interval, processed with Siemens VNC software, and reformatted to a 5mm image thickness per quantitative imaging protocol. The attenuation-enhancement relationship for each CsOH concentration was established and evaluated for linearity using a linear fit model. The limit of detection was determined according to the method published by Jacobsen et al.[1]

Ex Vivo Experiments: Low concentration detectability of CsOH was evaluated using porcine tissue purchased at a local grocery store using the same imaging and reconstruction protocol as for phantom experiments. Three 0.50mL injections of 5 different CsOH concentrations (6mM, 8mM, 12.5mM, 25mM, and 50mM) were performed approximately 1.5cm deep. Images were processed with a two-material decomposition algorithm (Virtual Unenhanced - Syngo.via) with a low/high energy ratio of 1.43, a value determined from phantom data. 20mm line profiles were drawn on 70keV monoenergetic images through the ablation center (ImageJ, NIH). The resulting concentration gradient was calculated using the attenuation-enhancement relationship from phantom measurements and validated with standards in the FOV.

In Vivo Experiments: VX2 tumor fragments (0.3mL) from carrier animals were inoculated into the flank of New Zealand white rabbits and allowed to grow for 10 days until tumor diameter reached 1-2cm. Catheters were placed under ultrasound guidance and TCA was delivered as 5M AcOH and 5M NaOH doped with 250mM CsOH. Concentration selection was informed by previous studies. Using a similar imaging and reconstruction protocol as in previous experiments, images were acquired the pre-and post-TCA treatment. Using the same workflow established in *ex vivo* experiments, reconstructed images were processed with a two-material decomposition algorithm, 20mm line profiles were drawn through the ablation center, and cesium concentration was estimated from data gathered in phantom experiments.

Results:
Results from phantom experiments serve as the basis of this work. In phantoms, the lowest concentration of CsOH detected was 7.8mM, which is sufficiently low to serve as a viable quantitative mapping technique given the molar concentrations of reagents used in TCA. Cesium signal correlated strongly with CsOH concentration and resulted in an attenuation-enhancement relationship with strong linearity (R^2=0.999). In *ex vivo* models, concentrations as low as 25mM were detected, although it is expected that lower concentrations can be imaged in different tissue types with lower background signal. *In vivo* rabbit flank VX2 models exhibited a resulting line profile with maximum CT number of 692HU (220mM) near the center of the injection site and decreases to approximately 40HU (12mM) at the periphery of the ablated region. This demonstrates higher cesium concentration near the center, decreased concentration at the periphery, and negligible concentrations beyond the ablation zone.

Conclusion:
DECT has sufficient sensitivity to spatially track injected CsOH as determined in this proof-of-concept study. With the use of linear attenuation-enhancement curves, injection profiles can be correlated to the concentration of CsOH with the use of standards or asynchronous calibration. Quantitative assessment of CsOH distribution enables use of DECT as a viable technique to track injectable image-guided ablations, such as TCA, and ensure therapeutic delivery.

References
1. Jacobsen MC, Cressman ENK, Tamm EP, et al. Dual-Energy CT: Lower Limits of Iodine Detection and Quantification. *Radiology*. 2019;292(2):414-419.