Contrast-Enhanced Detection and Quantitative Molecular Imaging of Breast Microcalcifications with Spectral Photon-Counting Computed Tomography

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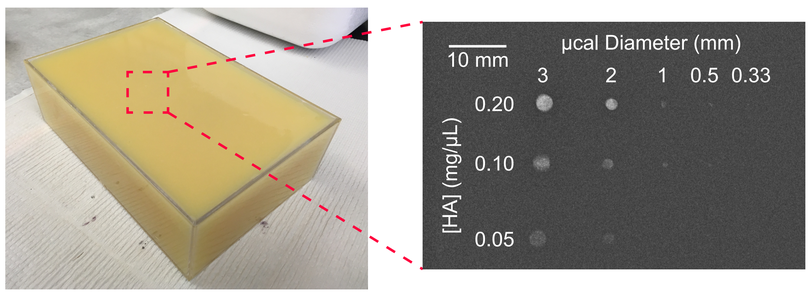
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Introduction

- Breast microcalcifications (μcals) are biomarkers of early, nonpalpable breast cancer lesions [1] that exhibit high X-ray attenuation compared to surrounding soft tissue for detection via mammography.
- Mammographic detection sensitivity and specificity is dramatically decreased with elevated breast tissue density [2] as mammography is unable to discriminate overlapping μcal and tissue compositions.
- Bisphosphonate-functionalized gold nanoparticles (BP-Au NPs) were able to target μcals and enhance X-ray contrast for the detection of μcals that were otherwise undetectable in murine models of both normal and radiographically dense breast tissue [3-5].
- Spectral photon-counting computed tomography (PCCT) is an emerging imaging modality that is capable of multi-material quantitative molecular imaging of spatially coincident contrast agent and tissue compositions [6,7].
- ***Therefore, the objective of this study was to investigate contrast-enhanced detection and quantitative molecular imaging of model μcals targeted by BP-Au NPs with spectral PCCT compared to mammography.***

Imaging Phantom Preparation

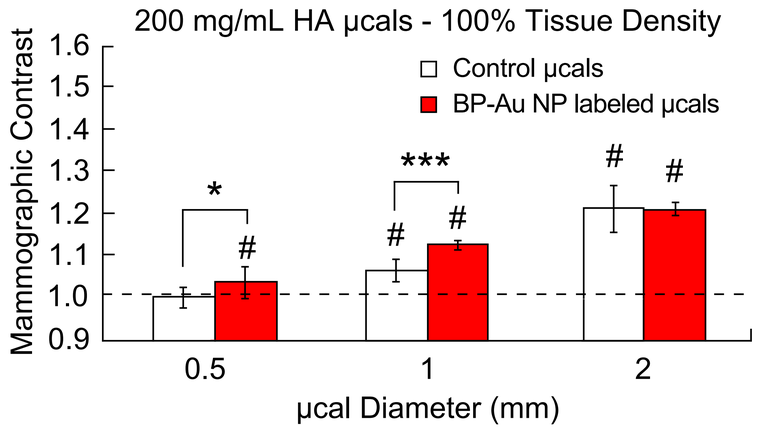
- BP-Au NPs were synthesized using the citrate reduction method and surface functionalized with BP (alendronate) using a HS-PEG-COOH linker [3].
- Microscale hydroxyapatite (HA) crystals were incubated in 50 mg/L BP-Au NPs in DI water to allow targeting and binding.
- Model μcals of finite size and varying HA composition with and without targeting by BP-Au NPs were placed within 1% agarose in trays for mammography or Eppendorf tubes for PCCT imaging.



- The tissue model comprised canola oil and an albumin-agarose hydrogel in separate layers of varying volumetric proportions to mimic combinations of adipose (0% density) and fibroglandular tissue (100%), which was calibrated to an American College of Radiology (ACR) clinical tissue phantom at 50% tissue density.

Mammographic Imaging

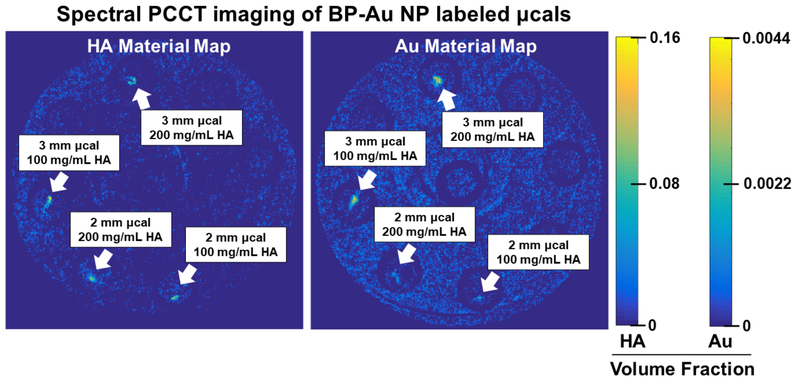
- Phantoms were imaged by mammography at 42 kVp (Hologic Selenia Dimensions) and 40 mAs with a 0.050 mm rhodium filter. The mammographic contrast of μcals was measured as the ratio of the μcal X-ray attenuation to the X-ray attenuation of the background model tissue phantom.
- Model μcals were imaged in arrays of varying size and HA concentration, which resulted in a range of detectable and undetectable μcals for mammography.
- BP-Au NPs enabled contrast-enhanced mammographic detection of 0.5 and 1 mm diameter model μcals that were otherwise undetectable from 100% dense background tissue.



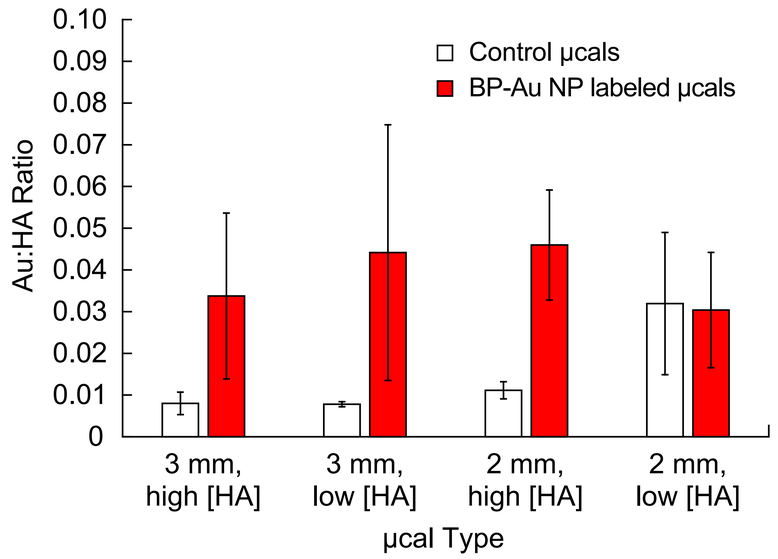
PCCT Imaging and Material Decomposition

- Images of targeted and untargeted μcals were acquired with a commercially-available PCCT (MARS Bioimaging) equipped with a polychromatic X-ray source operating at 120 kVp and 24 μA and a photon-counting detector comprising a 2 mm thick CdZnTe sensor bonded to a Medipix 3RX chip with 110 μm pixel pitch and 5 energy bins in charge-summing mode.
- Energy thresholds were chosen at 30, 43, 55, 65, and 120 keV to normalize photon counts and leverage the *k*-edge of Au.
- Material decomposition of contrast (Au), ucal (HA), and tissue (water) compositions was performed using constrained maximum likelihood estimation (MLE) in the image domain [6].
- MLE was calibrated by an *M x N* material basis matrix, where *M* is the number of energy bins and *N* is the number of materials.
- The material basis matrix was estimated by multiple linear least squares regression of the X-ray attenuation measured in each energy bin versus known concentrations of each material composition.
- Spectral PCCT with material decomposition enabled detection and volumetric quantification of HA and Au NP content within control and labeled μcals.
- However, the presence of false Au signal within control μcals hindered the use of molecular concentration alone for discrimination between control and labeled μcals.

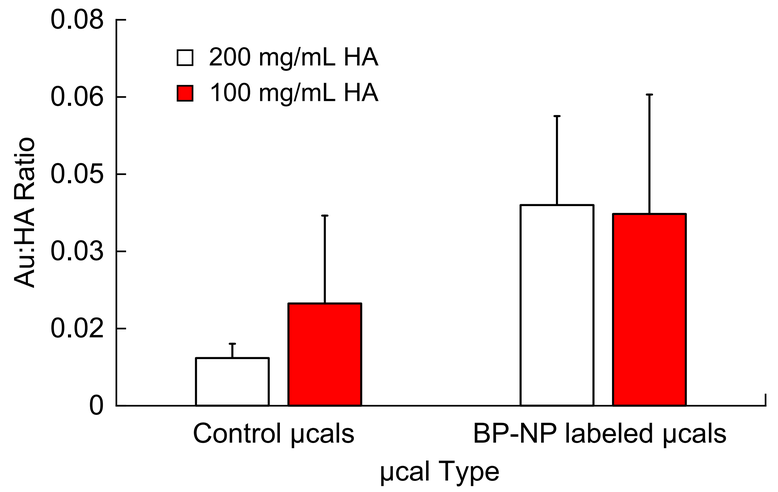
Spectral PCCT imaging of BP-Au NP labeled μcals



- The ratio of Au to HA content in material density maps provided a metric for 3 mm μcal discrimination at both 200 and 100 mg/mL HA concentration. The Au:HA metric also demonstrated robust μcal discrimination at 2 mm size and 200 mg/mL [HA], but not for 2 mm μcals at 100 mg/mL HA concentration.
- Spectral PCCT combined with material decomposition enabled discrimination between control and Au NP labeled μcals by measuring the volumetric ratio of Au to HA.



- HA concentration did not have a pronounced effect for discriminating μcals regardless of μcal size and BP-Au NP labeling, as measured by the Au:HA ratio in spectral PCCT.
- The primary limitation of this study is that spectral PCCT was unable to discriminate between control and BP-Au NP labeled 2 mm μcals at 100 mg/mL HA concentration. This was most likely due to material decomposition falsely assigning HA as Au, causing artificially high Au:HA ratios in 2 mm control μcals.



Conclusions

- Mammographic imaging enabled contrast-enhanced detection of μcals targeted by BP-Au NPs against elevated tissue density.
- Spectral PCCT enabled both contrast-enhanced detection and quantitative molecular imaging of contrast agent, μcal, and tissue compositions.

Acknowledgments

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References

[1] Ferranti C, *Br. J. Radiol.*, 2000; 73:698. [2] Pu H, *Clin. Breast Cancer*, 2020; 20:317. [3] Cole LE *et al.*, *Acta Biomaterialia*, 2018; 82:122. [4] Cole LE *et al.*, *ACS Nano*, 2015; 9:8923. [5] Cole LE *et al.*, *ACS Nano*, 2014; 8:7486. [6] Curtis TE and Roeder RK, *J. Med. Imaging*, 2019; 6:013501. [7] Curtis TE and Roeder RK, *bioRxiv* 2020, 300509.