Pharmacokinetic analysis of targeted nanonubbles for quantitative assessment of PSMA expression in prostate cancer

Pharmacokinetic analysis of targeted nanobubbles for quantitative assessment of PSMA expression in prostate cancer

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Background

- Despite showing promise, contrast enhanced ultrasound (CEUS) has yet not reached sufficient sensitivity for prostate cancer diagnosis [1]
- Molecular imaging by microbubbles (MBs) targeted to the vascular endothelial growth factor receptor 2 is promising, but the detection rate for prostate cancer in a phase-0 clinical trial was limited to 65% [2]
- Ultrasound nanobubbles (NBs) are emerging for targeted imaging and therapy. Being able to cross the vascular endothelium, NBs permit including targets beyond the vessel wall. A long-circulating NB targeted to the prostate-specific membrane antigen (PSMA) was recently developed, showing promise for selective accumulation in tumors expressing PSMA, such as prostate cancer [3].
- In this work, we propose pharmacokinetic modeling of the kinetics of PSMA-targeted NBs by the simplified reference tissue model [4] for quantitative assessment of NB binding.

Methods

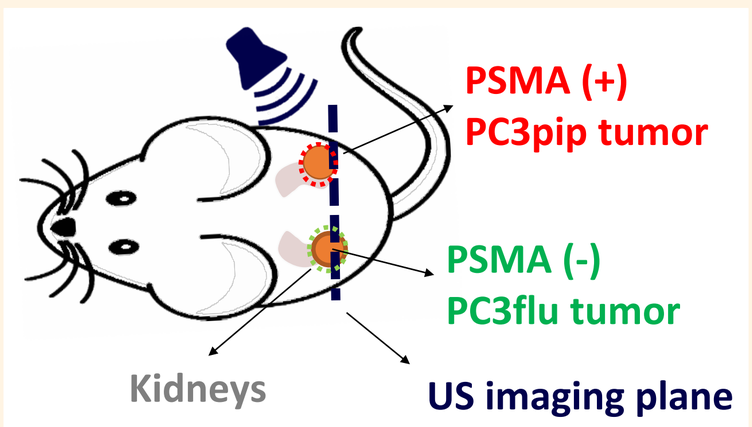
- **Pharmacokinetic modeling**

The kinetics of PSMA-targeted NBs can be described by a 3-compartment model: the plasma compartment, the "free" tissue compartment, and the "bound" tissue compartment. When a reference tissue is available, the acoustic intensity in a pixel can be described by the **simplified reference tissue model** [4] as

$$I_t(t) = R_1 I_r(t) + \left(k_2 - \frac{R_1 k_2}{1+\mathrm{BP}} \right) I_r(t) * e^{-\frac{k_2}{1+\mathrm{BP}} t}$$

- **BP**, binding potential
- $I_t(t)$, linearized acoustic intensity in the target tissue
- $I_r(t)$, linearized acoustic intensity in the reference tissue
- k_2, transfer rate from free to plasma compartment
- R_1, ratio of transfer rate from plasma to target tissue over transfer rate from plasma to reference tissue

- **Dual-tumor mouse model**



Subcutaneous implantation of
- PSMA-positive PC3pip cells in one flank,
- PSMA-negative PC3flu cells in the other flank.

- **Ultrasound acquisition**
  - Toshiba AplioXG (Toshiba Medical System, Japan) with PLT-1204BT probe working at 12 MHz (MI, 0.1; dynamic range, 65dB; gain, 70dB; imaging frame rate, 0.2 frames/s).
  - Injection of 200-μL bolus of either **non-targeted NBs** or **PSMA-targeted NBs**.
  - Repeated high-intensity flashes followed by injection of 200-μL bolus of **Lumason** (Bracco Diagnostics Inc, Switzerland).

Results

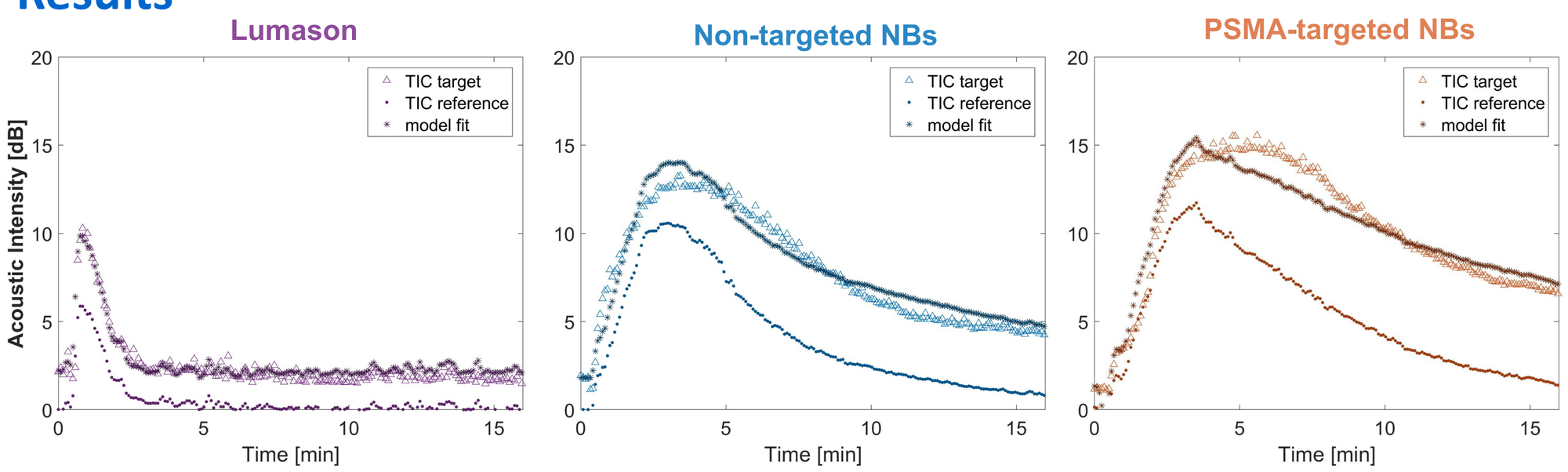


Fig. 1 Examples of TICs extracted from the reference tissue (PSMA-negative ROI) and target tissue (PSMA-positive ROI), together with corresponding model fit of the target TIC.

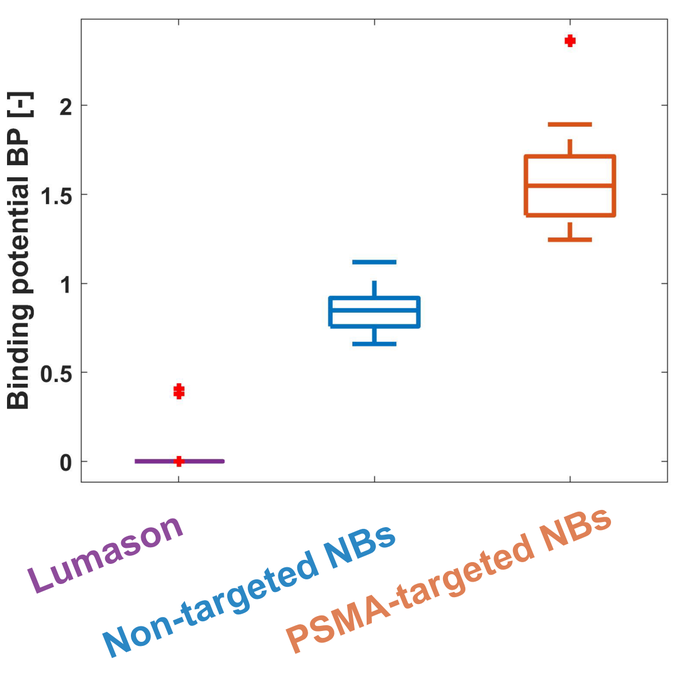


Fig. 2 Estimated BP for Lumason, non-targeted NB, and PSMA-targeted NB in a PSMA-positive tumor. The PSMA-negative is used as reference tissue.

Conclusions

The estimated BP was nearly zero for conventional MBs, while the highest BP was obtained for PSMA-targeted NBs, suggesting that these NBs are able to reach and bind to the target. The non-zero BP value obtained for non-targeted NBs may be due to the fact the BP reflects both binding and unbinding. To conclude, pharmacokinetic analysis of the kinetics of PSMA-targeted NBs by the simplified reference tissue model is feasible. The binding potential BP may represent a promising parameter for quantitative assessment of PSMA expression in prostate tumors. In the future, alternative pharmacokinetic models not requiring the presence of a reference tissue in the field of view will be investigated.

References

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