DCE-MRI–Based Quantification of Tumor Transport and Microenvironment Heterogeneity Using the Cross-Voxel Exchange Model

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ABSTRACT

Tumor heterogeneity within and across tumors contributes to variable therapeutic response by altering biophysical transport barriers in the tumor microenvironment (TME). Elevated interstitial fluid pressure (IFP) and reduced hydraulic conductivity (K) generate outward convection that impedes drug delivery and influences radiation response. This study evaluated the capability of the Cross-Voxel eXchange Model (CVXM) applied to DCE-MRI to quantify transport properties across distinct TME, characterize intra- versus intertumoral heterogeneity, and detect radiation-induced TME changes.

INTRODUCTION

Among various components of the tumour microenvironment (TME), elevated interstitial fluid pressure (IFP) and low hydraulic conductivity (K) drives outward convective fluid flow, hindering therapeutic penetration and contributing to treatment resistance[1,2]. Characterizing these biophysical properties is essential for understanding the TME-mediated treatment resistance across tumour types. In this study, diverse TMEs were evaluated to assess the capability of the Cross-Voxel eXchange Model (CVXM) to quantify transport parameters and elucidate the dynamic relationship between the TME and pharmacokinetics.

METHODS AND MATERIALS

- ME180 human cervical carcinoma xenografts in NRG mice
- Implant sites: orthotopic (n=26), intramuscular (n=18), and subcutaneous (n=10)
- IFP measurements using a pressure probe (SPR-1000, Millar)
- Extravasation (Kext), convection (velocity), and diffusion were quantified using CVXM and DCE-MRI (7T Bruker).
- CVXM-derived K was quantified by applying Darcy's law, using IFP and tracer velocity
- A subset of orthotopic tumours received fractionated radiotherapy (RT) (5 x 5Gy, SmART+, Precision). Follow-up DCE-MRI at one and five days post-RT to evaluate the model's ability to capture RT-induced biological change.

RESULTS

IFP Measurements

IFP was the highest in intramuscular tumours (34 ± 2 mmHg), followed by orthotopic (20 ± 1 mmHg), and subcutaneous tumours (14 ± 2 mmHg). IFP gradient was observed as significant differences were found between central and peripheral IFP, and between tumor types.

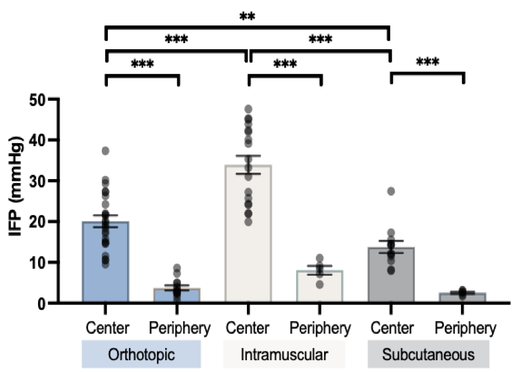

Figure 1. Bar graph of IFP values shown as mean ± SEM. (**: p<0.01, ***: p<0.001).

RESULTS

CVXM maps displayed preferential peripheral blood flow combined with the impaired core convective transport, which is a hallmark of elevated central IFP

- Mean CVXM K^{ext}: 0.028 ± 0.015 min^{-1} (orthotopic), 0.022 ± 0.015 min^{-1} (intramuscular), and 0.033 ± 0.023 min^{-1} (subcutaneous)
- Mean tracer velocity: 2.43 ± 1.0 $\mu m/s$ (orthotopic), 1.9 ± 1.0 $\mu m/s$ (intramuscular), and 2.1 ± 0.5$\mu m/s$ (subcutaneous)
- CVXM-derived K (orthotopic mean: 3.08×10^{-7} ± 1.65×10^{-7} $cm^2/(mmHg\cdot s)$) showed a strong correlation with mean tracer velocity (R^2 = 0.49–0.65, p < 0.001), and exhibited high precision within 95% confidence interval against ex vivo K (data not shown)

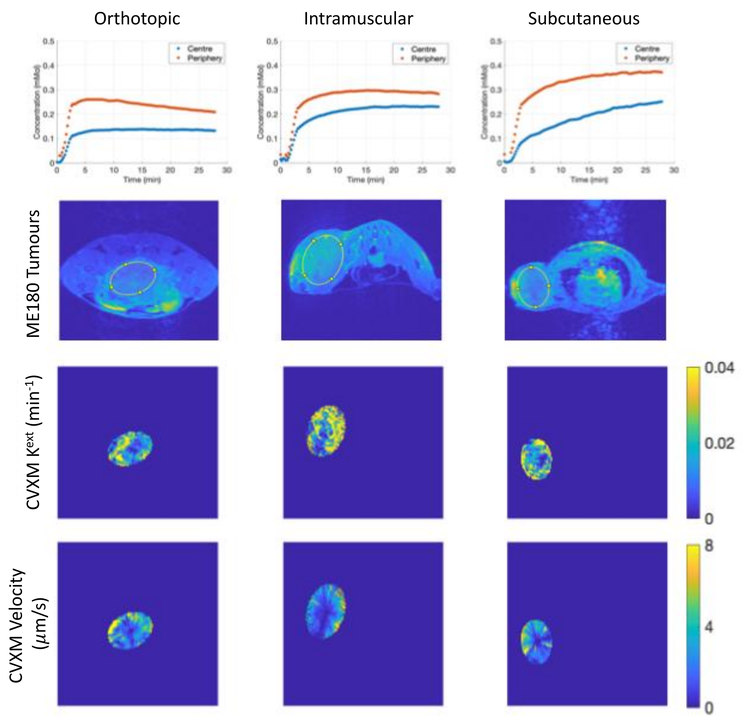

Figure 2. DCE-MRI-derived tracer kinetics and spatially resolved image-derived transport parameter (ImTP) maps

CVXM-ImTP maps reveal the radiotherapy-induced changes in the TME non-invasively in vivo

- Decrease in K^{ext} post-RT indicate vascular damage and reduced transvascular transport
- Velocity decreased by 20% 5-days post-RT. CVXM-derived K reduced by 18% at RT D+1 and by 37% at RT D+5; worsening convective transport post-RT
- IFP showed an increase by 12% and 23% at RT D+1/D+5

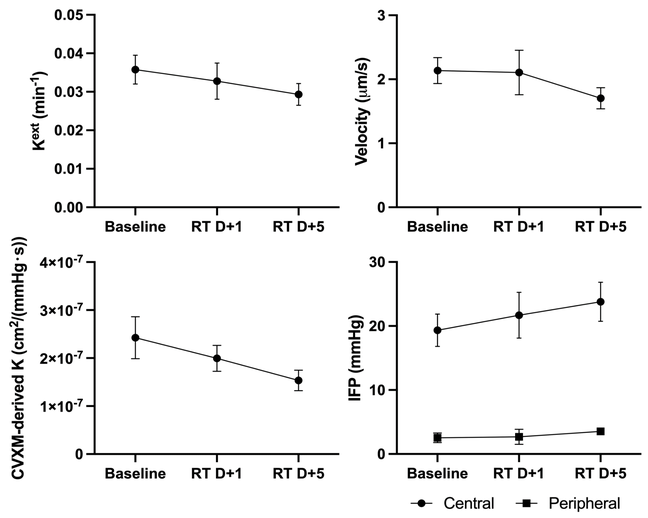

Figure 3. Changes in transport parameters post-radiotherapy. Data shown shown as mean ± SEM (n=5)

Intramuscular tumors demonstrated marked intratumoral heterogeneity phenotypically and quantitatively

- Within the IM model, CVXM captured distinct tumor microenvironments at the lobular level (p < 0.001), with intra-tumoral heterogeneity (ICC = 0.46) comparable to intertumoral heterogeneity (ICC = 0.54)
- This indicates that disregarding lobular uniqueness may obscure biologically relevant differences in the TME

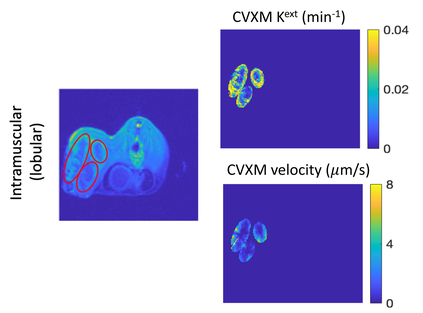

Figure 3. DCE-MR image and lobule-specific CVXM maps in intramuscular tumors

DISCUSSION

1. Understanding the interplay between tracer velocity, hydraulic conductivity, and IFP is essential for advancing CVXM toward clinical applications
2. Immunohistochemistry will be performed to validate in vivo findings using H&E, PIMO, CD31 and Mason's Trichrome staining
3. Future work includes expanding the model to 3D, allowing for a more comprehensive evaluation of tracer transport and provide a more realistic representation of tumor microenvironment dynamics.

CONCLUSIONS

CVXM non-invasively quantified tumour transport properties(extravasation, velocity, and hydraulic conductivity, across diverse TME. CVXM also captured reductions in velocity and hydraulic conductivity following radiotherapy, illustrating its sensitivity to dynamic TME changes.

REFERENCES

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