VALIDATION OF A COMPUTATIONAL FLUID DYNAMICS MODEL OF DRUG DELIVERY AND INTERSTITIAL FLUID PRESSURE IN OVARIAN CANCER XENOGRAFTS

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INTRODUCTION

Effective drug transport in tumor tissue is hindered by elevated interstitial fluid pressure (IFP). Computational fluid dynamics (CFD) models allow to analyze drug transport and its relation to IFP, offering a tool to improve anticancer efficacy. Here, we validated a CFD model by comparison with drug concentrations obtained using dynamic contrast enhanced (DCE)-MRI.

METHODS

Subcutaneous ovarian cancer (OC) xenografts (SKOV-3 cells) were created in female nude Foxn1^{nu} mice. Animals underwent DCE-MRI using a 7 T magnet (Bruker, Germany) with a FLASH sequence. At t=60 s, Gd-DOTA (Dotarem^{TM}, Guerbet, France) was intravenously (IV) injected. The resulting signal intensities were converted to drug concentrations using custom software (PMI 0.3, prof Sourbron). A 3D tumor model was reconstructed using image processing software (Mimics, Materialise, Belgium). The output was imported in COMSOL Multiphysics (Burlington, VT). The CFD model was based on applicable physical laws (mass conservation, Darcy, and Starling). Appropriate initial (zero pressure and concentration at the outer edge) and boundary conditions (mass source and reaction) were applied. Drug concentrations simulated using the CFD model at several time points were compared with DCE-MRI data in a single slice, while IFP was simulated at a single time point (t=30 min).

RESULTS

The CFD simulation showed an elevated IFP in the center of the tumor, while drug concentration rapidly decreased from the periphery to the central region (Fig.1). Comparison of DCE-MRI-measured concentrations with CFD simulations showed a good correspondence at 210, 420 and 720 seconds (Fig.2).

CONCLUSION

Drug transport in tumor tissue after IV administration is limited to the outer tumor rim, and hindered by elevated IFP. Our CFD based predictions of spatial and temporal drug distribution and IFP agree with experimental data. The model therefore allows to develop methods to improve drug delivery, and will be extended to intraperitoneal tumors.

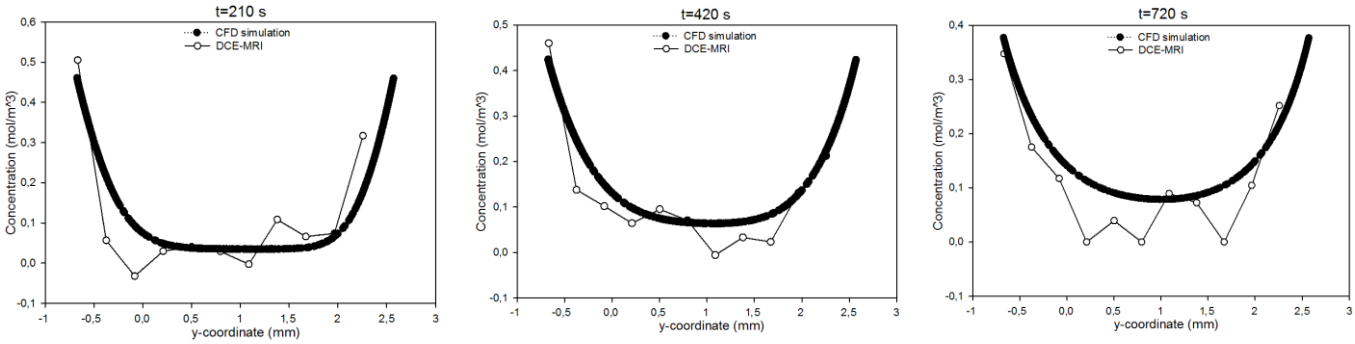

Figure 2. Comparison of measured concentration by CFD simulation and DCE-MRI in different time points, t=210, 420 and t=720 s

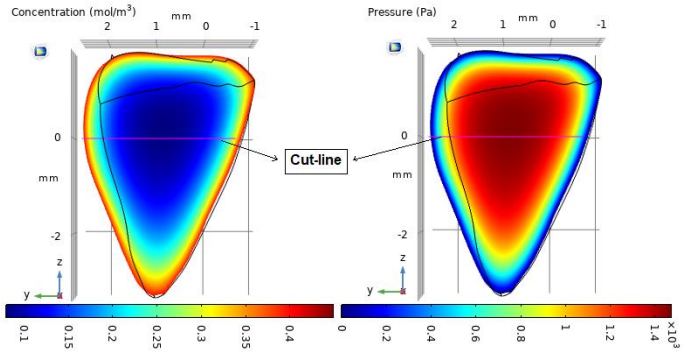

Figure 1. Concentration and pressure distribution contours (t=30 min)