LOCOREGIONAL DRUG DELIVERY FOR LIVER CANCER: THE IMPACT OF TUMOR BURDEN ON THE PARTICLE DISTRIBUTION IN A PATIENT-SPECIFIC LIVER

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Keywords: hepatocellular carcinoma, drug delivery, transarterial therapy, biofluid mechanics

1. Introduction

Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer and the second leading cause of cancer-related deaths worldwide [1]. WHO estimates that in 2030 over 1 million people will die from liver cancer [2]. Due to its high prevalence, HCC has become a global economic burden on society. Risk factors for HCC include Hepatitis B or C infection, excessive alcohol intake and non-alcoholic fatty liver disease [2]. In 80%-90% of patients, HCC develops from cirrhosis, a chronic liver condition that also affects the hepatic architecture [1]. In patients unfit for tumor resection, HCC can be treated by transarterial chemoembolization (TACE) or radioembolization (TARE). During these procedures, embolic microparticles are injected in a branch of the proper hepatic artery (PHA), which either emit a high-intensity beta-radiation (TARE) or carry chemotherapeutic agents (TACE) to permanently damage the tumor tissue [3]. The goal is to direct particles towards the tumor, increasing the efficiency of the therapy and limiting the offsite toxicity delivered to healthy tissue. Due to the complexity and tortuosity of the arterial network, it is often challenging to navigate catheters towards the tumor tissue. Therefore, easily accessible upstream injection locations need to be identified without compromising the target-specificity of the procedure. The goal of this research is to investigate the impact of tumor burden (i.e. tumor size, location) on the particle distribution in a patient-specific cirrhotic liver and to assess the possibility of targeting solid tumor(s) by injection from specific upstream injection locations.

2. Methods

The dataset of a patient-specific cirrhotic liver was obtained by combining vascular corrosion casting and micro-CT imaging [4]. The hepatic arterial network was segmented based on the contrast difference between parenchyma, arteries and veins using Mimics software (Materialise, Leuven, Belgium). A 3D reconstruction of the arterial network was made (see Figure 1). Arteries were truncated at the 4th or 5th generation to reduce computational complexity. A volume mesh containing $9 \cdot 10^6$ tetrahedral elements was created in ICEM CFD (Ansys Inc., Canonsburg, USA.)

The blood flow (continuous phase) and the particle mass transport (discrete phase) were simulated using Fluent (Ansys Inc., Canonsburg, USA). Six cancer cases were defined: a small (135 ml), moderate (565 ml) or large tumor (1130 ml) confined to either the left (Case 1-3) or the right lobe (Case 4-6) of the liver. Inlet and outlet boundary conditions were set according to the methodology described by Aramburu et al. [5]. Aramburu's perfusion model considers that the arterial perfusion of tumor tissue is at least four times larger than the perfusion of healthy tissue, which significantly increases arterial flow in the branches perfusing the tumor tissue (i.e. higher outflow fraction). At the inlet, a steady blood flow was imposed, depending on the tumor burden. Since tumors derive their blood supply mainly from the hepatic artery, higher tumor burden is associated with an increase in hepatic artery blood flow [5]. For a small tumor (Case 1 and 4), a blood inflow of 306 ml/min was set; for a moderate tumor (Case 2 and 5), 484 ml/min, and for a large tumor (Case 3 and 6), 718.5 ml/min. At the 21 outlets, a fractional outflow distribution was imposed.

For post-processing, Particle Release Maps (PRMs) were calculated by projecting particle destination (i.e. through which outlets of the computational domain the particles exit) on the injection plane. As visible in Figure 1, the color-coded PRMs show in which sections of the injection plane particles should be injected to target certain specific outlets of the computational domain.

3. Results and Discussion

In Figure 2, the PRMs for each of the six cancer scenarios are given (top row: tumor(s) confined to left lobe, bottom row: tumor(s) confined to

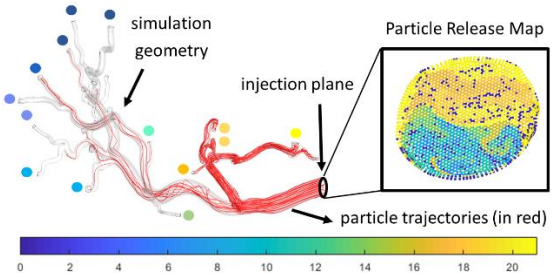

Figure 1: PRMs are color-coded projections of particle fate on the injection plane (0: no exit, 1-21: outlet through which the particles exit).

right lobe, left to right: increasing cancer burden). The PRMs for Case 1-3 (top row, Figure 2) clearly show that, as cancer burden in the left lobe increases, more particles flow to the left lobe (i.e. outlets 17-21). This effect is also evident in Table 1: particle fraction for the left lobe (LL) increases for increasing tumor burden, while the particle fraction for the right lobe (RL) decreases significantly (Case 1-3). The PRMs for Cases 4-6 (bottom row, Figure 2) also show that more particles will flow towards the right lobe (i.e. outlets 1-16) for higher tumor burden in the right lobe, but this effect is much less outspoken than in the left lobe cases. This is also visible in Table 1. The fraction of particles exiting the right lobe increases only 6.5% from low to high right tumor burden (RL, Cases 4-6), while the left lobe fraction increases almost 27% from low to high left tumor burden (LL, Cases 1-3).

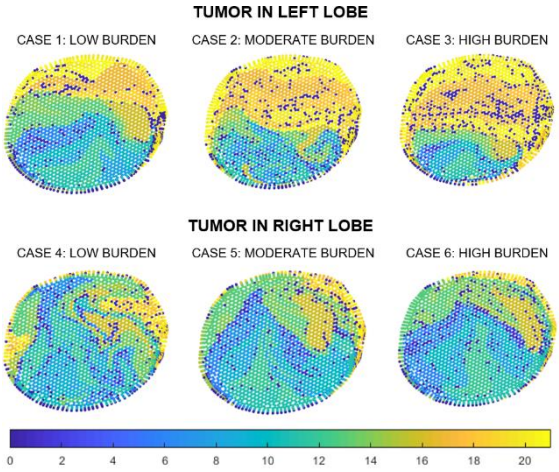

Figure 2: PRMs for the 6 cancer cases.

The results show that by carefully controlling the radial in-plane location of the catheter tip particles may be steered towards specific exit branches. Based on the patient-specific data above, targeting downstream solid tumor(s) may become easier as cancer burden and arterial flow to the tumor(s) increase. However, these results are highly patient-specific and cannot yet be generalized for other cases.

	Case 1	Case 2	Case 3
LL (%)	29.96	49.95	56.57
RL (%)	58.49	35.86	24.83
PD (%)	11.55	14.20	18.60
	Case 4	**Case 5**	**Case 6**
LL (%)	13.99	9.56	7.60
RL (%)	74.71	80.71	81.20
PD (%)	11.30	9.73	11.20

Table 1: Particle distribution fractions in left lobe (LL) and right lobe (RL) for the 6 cases. There was also significant particle deposition (PD) in the domain (i.e. particles which didn't exit through any outlet).

4. Conclusions

This work represents the first step in modelling locoregional drug delivery in the liver with the overall aim of identifying easily accessible injection locations where particles can be steered towards tumor tissue by careful control of radial catheter tip location. PRMs are helpful tools in identifying the regions of the injection plane where particle release leads to particle deposition in the tumor tissue. Future work will focus on including transient simulations and in vivo validation of the models.

5. Acknowledgements

Charlotte Debbaut is supported by a postdoctoral fellowship from the Research Foundation Flanders (1202418N), and a starting grant from the special research fund, Ghent University (BOF/STA/201909/015).

6. References

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