Microspheres in motion: investigating the parameters that influence radioembolization

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Transarterial radioembolization (TARE) is a treatment method for liver tumours, during which radioactive microspheres are injected in the hepatic artery (HA) via a microcatheter. The HA blood flow will transport the microspheres predominantly towards the hepatic arterioles supplying the tumours. This technique relies on the liver's unique dual blood supply, where tumour tissue is primarily supplied by the HA, while normal liver parenchyma receives most of its blood supply via the portal vein (PV). At the time this research was conducted, three types of microspheres were commercially available: two incorporating the radionuclide yttrium-90 and one containing holmium-166. This thesis concentrates on holmium microspheres, which offer unique imaging capabilities, particularly enabling quantitative analysis through MRI. In terms of size, density, and clinically administered quantities, holmium microspheres are very similar to yttrium resin microspheres. Therefore, the results presented here are likely to be applicable to yttrium resin microspheres as well.

Maximizing microsphere delivery to tumorous tissue while sparing healthy liver tissue – achieving a high tumour to non-tumour (T/N) ratio – is very important for TARE efficacy. Achieving this requires control over microsphere distribution, potentially through adjusting treatment parameters, such as microsphere injection technique.

This PhD project investigated which parameters influence the microsphere distribution during TARE using *in vitro* and *ex vivo* experiments, to contribute in the development of patient-specific treatment plans for TARE.

Parameters influencing microsphere distribution

The thesis started with providing a systematic overview of the intraprocedural parameters that influence microsphere distribution during TARE and the resulting dose distribution. The main conclusion of the review is that solely the blood flow distribution cannot accurately predict microsphere distribution. Instead, treatment parameters play a more decisive role, with injection rate and radial and axial catheter position being the most influential parameters. Higher injection rates enhances mixing between microspheres and blood, promoting uniform distribution across downstream branches, which is advantageous for lobar or whole-liver treatments. Conversely, lower injection rates favour selective delivery to specific branches, potentially improving T/N ratios when super selective catheterization is not feasible. Radial catheter position also influences targeting, but current clinical practice lacks tools for precise visualization and control of this parameter.

Insights from an *in vitro* model

To experimentally assess relevant parameters, a successively bifurcating phantom mimicking hepatic arterial branching was developed. The model bifurcates symmetrically three times into eight outlets. Investigations into catheter behaviour under pulsatile flow demonstrated that microcatheter displacement, up to 0.87 mm in a vessel with a diameter of 3.6 mm, significantly affects microsphere distribution. Variability in manual injection patterns amplified this motion. Strategies to stabilize catheter position and standardize injection profiles could therefore improve reproducibility.

Further experiments focused on the injection technique of the microspheres. In clinical practice, holmium microspheres are injected manually as pulsed bolus injections, using a conventional administration device. It was found that these pulsed injections are in current clinical practice commonly administered at rates ranging from 24 to 48 mL/min, and that it is difficult to perform consistent injections. To investigate the effect of different injection profiles, several patterns were tested by injecting microspheres into the *in vitro* model (figure 1). At 24 mL/min, a continuous injection resulted in a more homogeneous microsphere distribution over the eight outlet vessels (outlet 5-8 received 16.5-23.1 % of the microspheres per outlet) compared to clinically recommended pulsed injections (outlet 5-8 received 11.3-40.1 % of the microspheres per outlet). Continuous profiles may therefore be advantageous for lobar or whole-liver TARE, where uniform coverage of downstream branches is desired. Lower injection rates were tested using a newly designed controlled administration device, which maintained a homogeneous microsphere suspension, allowing to apply and investigate lower injection rates. At 10 mL/min and 5 mL/min, distributions became highly targeted (outlets 5-8 received 2.5-68.8 % and 1.0-80.0 %, respectively). Such lower rates could improve T/N ratios in cases where super selective TARE is not feasible due to complex vascular anatomy, and large portions of healthy liver would otherwise be irradiated.

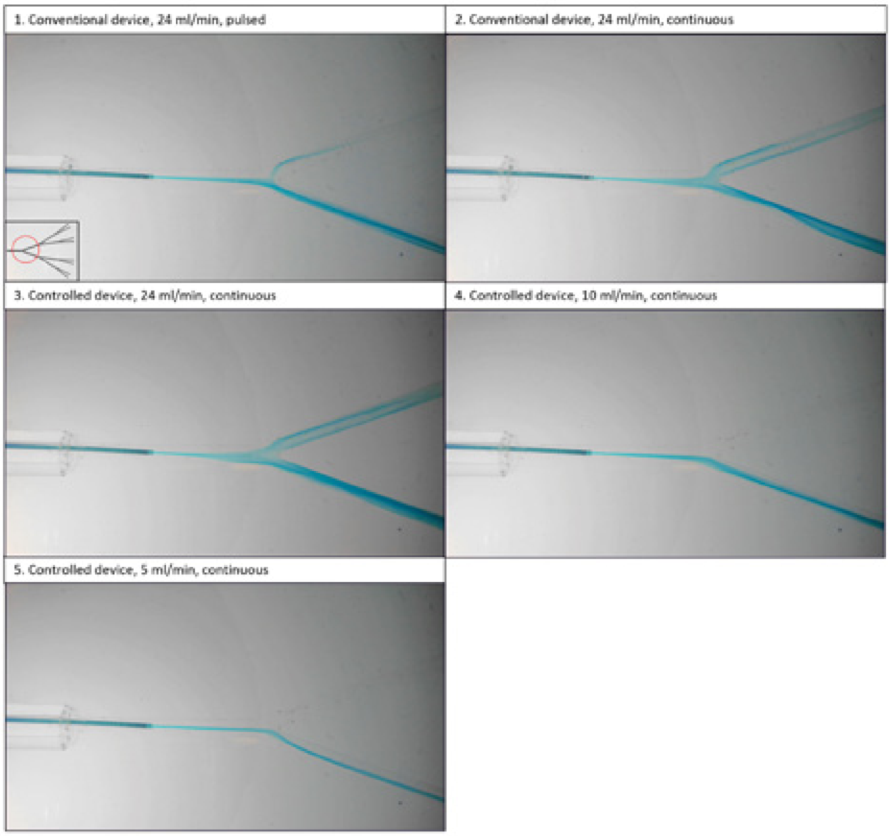

Figure 1. Outflow patterns at the catheter tip in the successively bifurcating phantom for different injection patterns (pulsatile vs continuous, 24-10-5 mL/min) after microsphere administration with a conventional and controlled administration device.

Insights from an *ex vivo* liver perfusion model

In an MRI-compatible *ex vivo* machine perfusion model the impact of the parameter HA blood flow rate on the distribution of microspheres was investigated within the porcine health liver. Nine porcine livers were perfused under oxygenated normothermic conditions in three groups (n=3) at HA flow rates of 0.02, 0.15 and 0.22 mL/min per gram of liver tissue, corresponding to mean HA pump settings of 51, 440 and 583 ml/min. Dose distribution was assessed using the homogeneity index (HI), with lower values indicating a better dose homogeneity. Higher HA flow rates resulted in more homogeneous microsphere distributions compared to lower flow rates (figure 2), with HIs ranging from 3.68-4.72 at low flow, 2.01-2.66 at medium flow, to 1.60-2.36 at a high HA flow rate. It is known that the HA flow rate is highly variable in diseased livers (220-813 mL/min) and according to the results of this study it might result in different microsphere distribution patterns. Mapping the HA flow rate before TARE and adjusting the treatment accordingly may help to improve TARE outcomes. However, its impact on tumorous tissue should first be further investigated.

Conclusions

In this thesis, we investigated parameters that influence the microsphere distribution during TARE. Our findings indicate that catheter motion, injection technique, and HA blood flow rate affect the mixing of microspheres with the blood flow. The injection technique is currently the most important parameter, as this is a potential modifiable parameter within existing clinical practice. High continuous microsphere injection rates promote uniform microsphere distributions, whereas low injection rates enable more targeted microsphere delivery. Establishing more detailed guidelines regarding the injection rate and profile, as well as increasing awareness among clinicians that the predictive value of CBCTs and ^{99m}Tc-MAA scout doses might be limited due to different injection rates and profiles is important in this. However, as our studies were limited

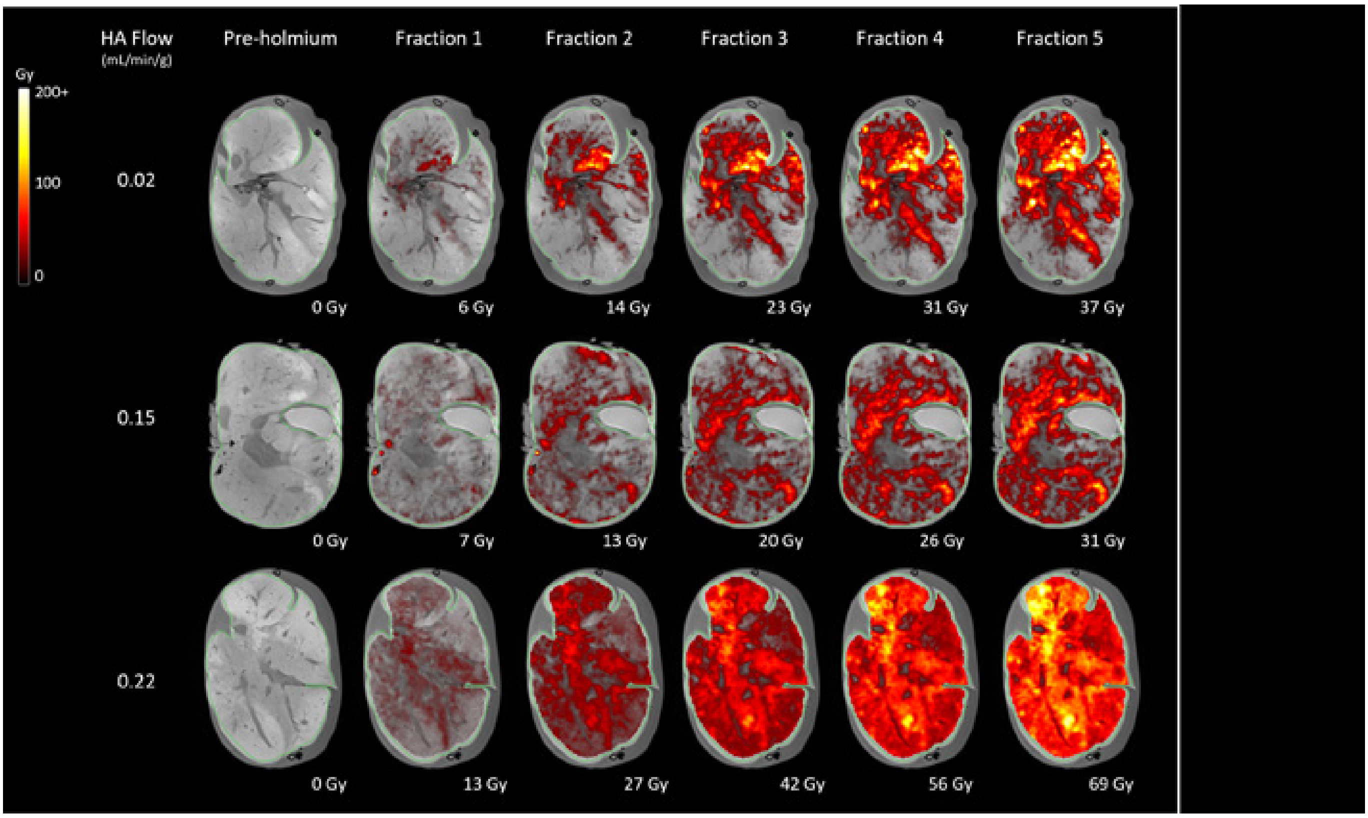

Figure 2. MRI-based dose maps of three *ex vivo* porcine livers after administering multiple fractions of microspheres under various hepatic arterial (HA) blood flow rates (0.02, 0.15, 0.22 mL/min per gram of liver tissue). Dose maps were scaled from 0 to 200 Gy. Corresponding homogeneity indices (HI): 3.68 for 0.02 mL/min/g, 2.90 for 0.15 mL/min/g, 1.60 for 0.22 mL/min/g.

to *in vitro* and *ex vivo* models without tumour simulations, future work should examine *in vivo* correlation of the investigated parameters and actual TARE outcomes. ♦