Unravelling the distribution of holmium microspheres following transarterial radioembolisation

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Transarterial radioembolisation (TARE) is a locoregional therapy used in the treatment of both primary and secondary liver malignancies. The procedure involves the intra-arterial injection of radioactive microspheres into the hepatic artery via a microcatheter. These microspheres travel with the arterial blood flow and become lodged in the arterioles due to their size, where they deliver a high local radiation dose to the tumour(s). This therapeutic strategy exploits the unique dual blood supply of the liver: while liver tumours are predominantly supplied by the hepatic artery, healthy liver parenchyma receives most of its blood from the portal vein. This anatomical distinction enables semi-selective targeting of liver tumours via intra-arterial microsphere injection.

Given the passive nature of microsphere delivery, which relies on blood flow rather than active targeting, it is plausible that the resulting dose distribution is inherently heterogeneous. In non-tumorous liver tissue, such heterogeneity may be advantageous, allowing for partial tissue sparing and subsequent regeneration. In contrast, dose heterogeneity within tumours is undesirable, as underdosed regions may persist and compromise therapeutic efficacy.

Accurate assessment of dose heterogeneity is essential for understanding and improving TARE outcomes. However, in current clinical practice, the dose distribution following TARE is assessed with positron emission tomography (PET) or single-photon emission computed tomography (SPECT) imaging. These nuclear imaging modalities offer limited spatial resolution and are susceptible to motion artefacts. These limitations hinder the reliable detection of dose heterogeneity. The dose distribution can be assessed at a higher resolution using magnetic resonance imaging (MRI) when holmium microspheres are employed. Moreover, MRI facilitates intraprocedural imaging, allowing for real-time assessment and potential adjustment of microsphere administration.

To investigate microsphere distribution in detail, a novel MRI-conditional machine-perfused ex vivo liver model was developed and fluorescent holmium-loaded microspheres were utilised. This enabled controlled simulation of TARE procedures and high-resolution imaging of the microsphere distribution and resulting dose distribution. Specifically, the heterogeneity of the dose distribution was examined, as well as the influence of consecutively administered microsphere fractions on both microscopic and macroscopic levels. In addition, physiological parameters influencing microsphere distribution were studied, with a focus on the role of hepatic arterial blood flow rate. Finally, in the absence of a gold standard for quantifying hepatic arterial blood flow in vivo, the feasibility of three-dimensional time-resolved phase-contrast MRI with three-directional velocity encoding (4D flow MRI) was explored.

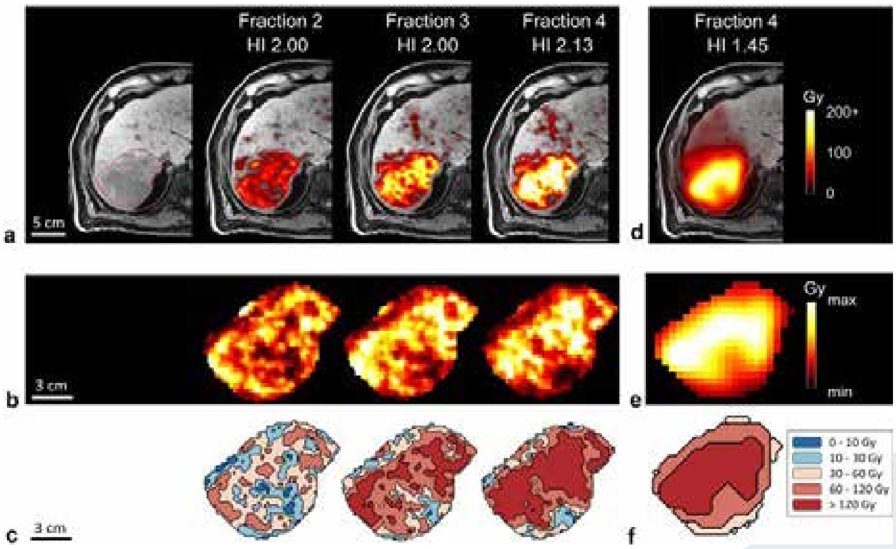
In the first study, the *ex vivo* liver model was used to investigate the distribution of fractionally administered fluorescent holmium microspheres in non-tumorous human liver tissue. The results revealed a heterogeneous distribution at both macroscopic and microscopic levels. Administering consecutive microsphere fractions from a fixed catheter position reduced macroscopic dose heterogeneity, although the overall spatial pattern remained consistent. These findings were validated against clinical data from patients treated with holmium-based TARE under MRI. Fluorescence microscopy revealed that the observed decrease in macroscopic dose heterogeneity with each additional microsphere fraction was primarily driven by the formation of new microsphere clusters in close proximity to existing clusters.

A subsequent study extended this investigation to human tumour-bearing livers. Heterogeneous dose distributions were observed in both non-tumorous liver tissue and liver tumours at macroscopic and microscopic levels. Overall, heterogeneity was more pronounced in non-tumorous tissue than in tumour tissue, although this difference was strongly associated with microsphere concentration. As before, each consecutively administered microsphere fraction reduced macroscopic heterogeneity, and findings were validated against clinical data. Fluorescence microscopy once more confirmed the formation of new clusters adjacent to existing clusters with each additional microsphere fraction. Another study examined the influence of hepatic arterial blood flow rate on microsphere distribution in healthy porcine livers using the MRI-conditional ex vivo setup. Higher flow rates were associated with more homogeneous dose distributions in non-tumorous liver tissue.

In the final study, the feasibility and repeatability of 4D flow MRI for quantifying hepatic arterial blood flow rate were explored in healthy volunteers and patients with liver disease (cirrhosis and/or malignancy). While it was feasible to quantify hepatic arterial blood flow rates with 4D flow MRI, substantial scan-rescan variability was observed. These results underscore the potential of 4D flow MRI for pre-procedural planning, while also emphasising the need for further optimisation before clinical implementation.

This thesis demonstrates that dose heterogeneity is a consistent phenomenon following TARE, in both liver tumours and non-tumorous target liver. However, as dose heterogeneity typically occurs at a scale below the resolution of nuclear imaging (see figure), it often remains unnoticed in clinical practice. To overcome the limited spatial resolution of current nuclear imaging modalities, it is recommended to use higher-resolution imaging modalities to evaluate the microsphere distribution and resulting dose distribution. Moreover, it is advised to not only report the mean absorbed dose, but also incorporate a measure of dose heterogeneity. Ideally, the dose distribution should be assessed during the TARE procedure after administering each microsphere fraction, enabling real-time adjustments to optimise the dose distribution, for example by quantifying the hepatic arterial blood flow rate and altering or accounting for this flow rate during TARE.

Future research should explore the relationship between TARE dose heterogeneity and treatment response. Moreover, the influence of the hepatic arterial blood flow rate and other patient- and treatment-related parameters on dose heterogeneity should be further investigated. A deeper understanding of these relationships may enable the optimisation or individualisation of TARE treatment parameters, with the aim of achieving a high and homogeneous dose within liver tumours, while preserving a low dose with adequate dose heterogeneity in non-tumorous liver tissue. ♦



Magnetic resonance imaging (MRI)-based and single-photon emission computed tomography (SPECT)-based dosimetry in a liver tumour following transarterial radioembolisation. (a) T1-weighted MRI, in which the tumour is delineated with a red contour, fused with MRI-based dose maps scaled from 0 to 200 Gy, revealing mainly an increase in existing hotspots with each consecutive microsphere fraction; the tumour homogeneity index (HI) was largely stable across fractions, suggesting that it approached a plateau; (b) MRI-based dose maps of the tumour, scaled from minimum to maximum, revealing largely similar distribution patterns across all microsphere fractions; (c) MRI-based isodose maps of the tumour, emphasizing the spatial heterogeneity of the dose distribution; (d) T1-weighted MRI fused with SPECT-based dose map resulting from the last microsphere fraction, scaled from 0 to 200 Gy; the SPECT-based dose map was more homogeneous (i.e., has a lower HI) than the corresponding MRI-based dose map; (e) SPECT-based dose map of the tumour, scaled from minimum to maximum, revealing a more homogeneous distribution than the corresponding MRI-based dose map; (f) SPECT-based isodose map of the tumour, revealing a more homogeneous distribution than the corresponding MRI-based isodose map.