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Computational Fluid Dynamics Modeling of ^{90}Y Microspheres in Human Hepatic Tumors

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Abstract

The number of patients afflicted with liver tumors continues to rise being a major concern of international healthcare. Yttrium-90 microsphere radioembolization can be an effective and safe treatment of unresectable primary and secondary liver tumors, and has the potential to be a forefront treatment option for tumor-afflicted patients. Computational fluid-particle dynamics is a powerful research tool that can be used to understand the underlying physics of Yttrium-90 microsphere transport and deposition, leading to improved clinical strategies and ultimately to a better treatment of tumor-afflicted patients. Two representative, patient-inspired three-dimensional geometries of the hepatic arterial system with assumed connections to liver tumors have been considered. Experimentally-validated computational fluid-particle dynamics modeling results have shown the significant influence of vessel morphology, downstream resistance to flow, catheter radial and axial location associated with microsphere injection time interval, and injection velocity on microsphere transport through the hepatic arterial system. Moreover, the computational investigations have identified the ability to preferentially deliver microspheres to a specific arterial vessel outlet, presumably connected to a tumor, by selecting appropriate temporal and spatial parameters of the microsphere injection. As the computational findings are extended to additional experiments as well as next-generation smart micro-catheters, clinicians can implement a refined set of treatment strategies that utilize the aforementioned physical phenomena. Computational fluid-particle dynamics models have thus provided valuable physical insight as well as suggestions for the improvement of current Yttrium-90 microsphere radioembolization treatment. Additional computational investigations are needed to create more encompassing conclusions from a large collection of patient-specific analyses plus the design, prototyping, and testing of a new smart micro-catheter and high-resolution imaging devices that give radiation and interventional oncologists new degrees of control and precision when administering Yttrium-90 microsphere radioembolization.

Keywords: Computational fluid-particle dynamics; Mathematical modeling; ^{90}Y-microspheres; Radioembolization; Blood flow; Particle transport

Abbreviations: ^{90}Y: Yttrium-90; GDA: Gastroduodenal Artery; WK: Windkessel; SMC: Smart Micro-Catheter

Introduction

The widespread and rapidly increasing cases of hepatic malignancies require effective clinical treatment of unresectable hepatic tumors which make up the vast majority of hepatic malignancies. Despite the increasing and existing prevalence of hepatic tumors, they remain among the more difficult tumors to treat with methods such as surgical resection, external beam radiation, ablation, and system-wide chemotherapy. Yttrium-90 (^{90}Y) microsphere radioembolization has been shown to be an effective and safe treatment for patients with unresectable liver tumors and/or tumors that are irresponsive to chemotherapy [1]. Computer simulation of ^{90}Y-microsphere transport in the hepatic arteries is a powerful tool that can determine appropriate conditions for the preferential directing/targeting of ^{90}Y-microspheres to the tumor sites. The clinical relevance of such computational analyses, are to provide recommendations for microsphere delivery that would enable the clinician to administer a controlled radiation dose to the tumor sites while sparing the surrounding healthy liver tissue from radiation damage.

Patruno et al. [2] was among the first to computationally analyze ^{90}Y microsphere transport and simulated ^{90}Y microspheres traversing through a single axisymmetric bifurcation. Kennedy et al. [3] documented the first computational analysis of ^{90}Y-microsphere transport through a steady flow field in a representative hepatic artery system. In a more complex study, Basciano et al. [4] performed the first transient analysis of microsphere transport in the representative hepatic arterial system and identified conditions such as injection time and location as primary influences on microsphere transport. This paper provides a description of the experimentally-validated computational model that has been used to investigate ^{90}Y-microsphere transport in hepatic artery models and reviews the resulting scientific observations and clinical implications of the computational fluid-particle dynamics analyses.

Materials and Methods

Radioembolization technique

Detailed accounts of the recommended clinical procedures and patient indicators for ^{90}Y-microsphere radioembolization can be found in publications [5-10]. Briefly stated, a patient must exhibit sufficient liver function to undergo the treatment and the clinician must have

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sufficient access to the hepatic arteries to inject the ^{90}Y-microspheres. Specific attention is also placed on connections between the hepatic arterial system and the surrounding organs (lungs, stomach, gallbladder, etc.) via shunting between the local capillaries and/or accessory hepatic arterial vessels. Currently, medical practitioners administer the microspheres using systems of hand-held syringes organized into a delivery apparatus, where a radiation oncologist controls the delivery of microspheres by hand.

Computational fluid-particle dynamics modeling procedure

Following the procedures and detailed descriptions in Kleinstreuer [11,12] and Basciano [13], a one-way coupled system of partial differential equations used to describe Eulerian fluid dynamics and Lagrangian particle transport was solved over a three-dimensional spatial domain (the hepatic arterial lumen). To ensure clinical relevance, the spatial domain was defined from population-representative, patient-inspired, or patient-specific anatomical and/or morphological data of the hepatic arterial system. The hepatic hemodynamics were calculated prior to the microsphere transport, using conservation equations of mass and momentum plus boundary conditions of arterial flow rate and pressure. To maintain clinical relevance, the arterial flow rate and pressure values implemented at the domain boundaries were again derived from patient-specific or population-averaged data. Figure 1 depicts two computational domains inspired by population averaged and patient-specific hepatic arterial vessel morphologies with corresponding arterial flow and pressure waveforms.

Subsequent to the calculated arterial flow-field, the ^{90}Y-microsphere trajectories through the spatial domain (the arterial lumen) were calculated using Newton's second law of motion, where the net forces acting on each particle were derived from the previously calculated hemodynamics and the spatial domain's boundaries. While a large number of forces eventually act on the particles, Basciano [13] identified the most influential as the total drag, pressure gradient and gravitational forces. Different particle-to-wall collision model parameters collisions were shown by Basciano et al. [4] to not have a significant influence on microsphere transport in a representative hepatic arterial system. Thus, all particle-to-wall collisions were modeled to conserve both kinetic energy and momentum. Particle-to-particle collision forces were not included because the injected ^{90}Y-microspheres form a dilute suspension in the flow field of larger hepatic vessels [3,13]. Prior to utilizing the computational model to analyze clinically-relevant cases, the model must be shown to reproduce known experimental and clinical data. To ensure that this requirement was met, multiple validations of the one-way coupled, computational fluid-particle model implemented in the commercial finite volume solver CFX (ANSYS Inc., Canonsburg, PA) were completed and documented by Basciano [13].

Results

Local hemodynamics and arterial vessel morphology

The local hemodynamics and flow distribution of the hepatic arterial system are the primary factors that determine particle transport through the hepatic arteries. Thus, factors that have a profound influence on the arterial fluid dynamics will have direct implications for particle transport through that flow field. The most critical parameter influencing flow distribution is the downstream resistance to flow in each arterial branch; where a smaller resistance will result in larger flow through that arterial branch. Figures 2a and 2b illustrate the relationship between flow distribution, local flow-field, and downstream resistance. In this case, the flow field is constant over time and the increased resistance is depicted by an elevated pressure at the representative hepatic geometry's branch vessel (which simulates the gastroduodenal, GDA, artery). Specifically, the 20% increase in arterial pressure at the branch vessel redirects flow such that 80% of flow entering the domain now traverses through the daughter outlets resulting in increased velocity magnitudes in the daughter vessel region. To capture more accurate clinical hemodynamics, Nichols and O'Rourke [14] incorporated high frequency pressure wave reflections into flow resistance by using the physical quantity of impedance, which can potentially be extended to computational fluid-particle dynamics through fractal modeling.

While steady flows can illustrate fundamental relationships between resistance and flow, physiologic hemodynamics are not constant and exhibit periodic behavior in the time domain. Transient waveforms of

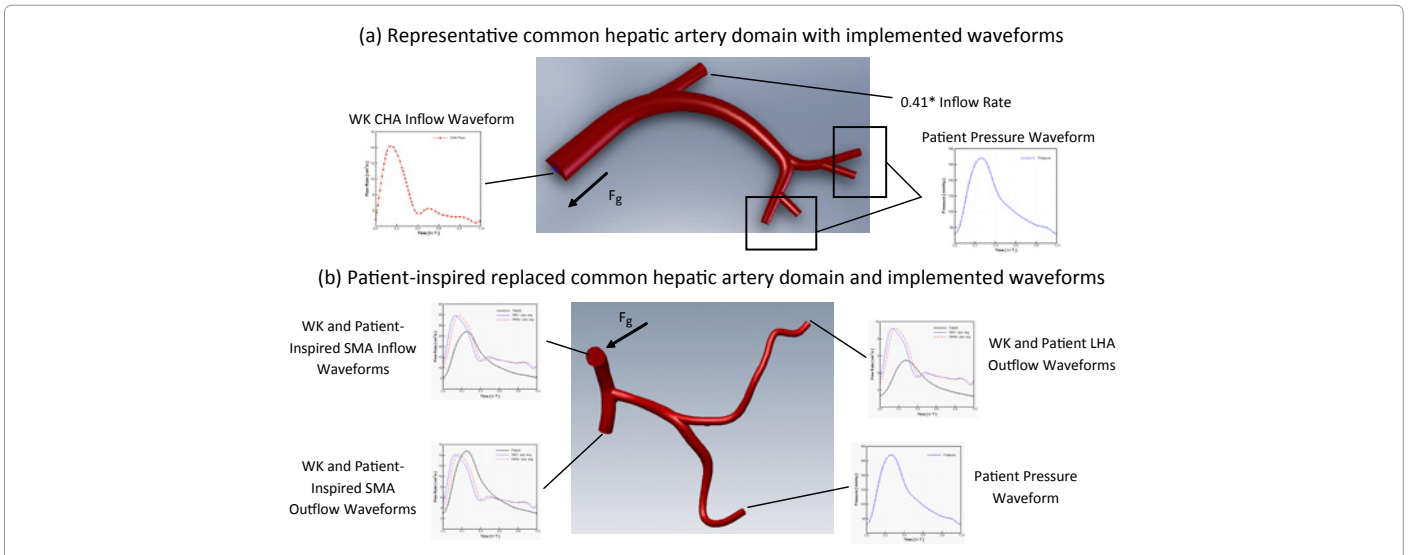

Figure 1: (a) Representative hepatic arterial system created from population averaged anatomical and morphological data with accompanying flow rate and pressure boundary conditions **(b)** Patient-inspired replaced common hepatic arterial system created from diameter and centerline data from a patient CT-scan with accompanying flow rate and pressure boundary conditions.

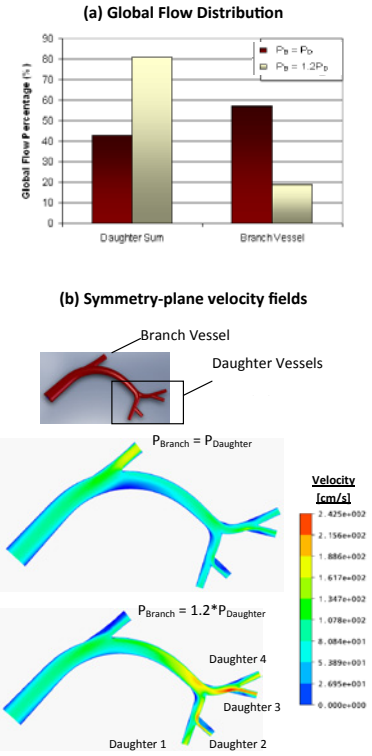

Figure 2: (a) Global flow distribution in a representative hepatic arterial system under equal and increased degrees downstream pressure in the branch (GDA) vessel **(b)** Velocity magnitude contours in the symmetry plane illustrating increased flow and velocity in the daughter vessel region of the representative hepatic arterial system.

arterial flow rates and pressures are thus needed to conduct the more complicated transient, hemodynamic analyses. However, such transient data is not always readily available for a particular patient or even a population average. In an attempt to create representative waveforms, Basciano [13] utilized a hepatic pressure waveform, Windkessel (WK) circuit models, and population-averaged mean and maximum flow rates to estimate physiologically plausible flow rate waveforms. To assess the influence of the different waveforms, the WK waveforms and patient-inspired waveforms were implemented in fluid flow analyses of the patient-inspired geometry illustrated in Figure 1b. Figure 3 depicts the differing velocity contours from each flow waveform throughout a periodic pulse, and while the waveforms created subtle differences in the local velocity profiles, notable difference can be seen in the velocity magnitudes. Because similar regions of the arterial lumen exhibited elevated and diminished velocity for both waveforms, the local vessel morphology (e.g., vessel centerline curvature, changes in lumen cross-sectional area, bifurcation angles, etc.) played a more influential role than the arterial waveforms in quantifying the patient's transient hemodynamics.

Microsphere characteristics, injection time, and location

In the upstream regions of the hepatic arteries, the maximum Stokes numbers of both clinically available ^{90}Y-microspheres (SIR-Spheres from Sirtex Medical Ltd in Lane Cove, Australia and TheraSpheres from MDS Nordion in Kanata, Canada) are less than one and implies that both microspheres will primarily follow fluid streamlines. Basciano [13] showed that the particle density had to be on the order of ten times greater than the carrier fluid density to noticeably influence microsphere trajectories through a steady flow field with an inlet Reynolds number of 1150 in the representative hepatic artery system shown in Figure 1a. However, when the particle diameter is a substantial fraction of the artery lumen diameter (i.e., in the arterioles

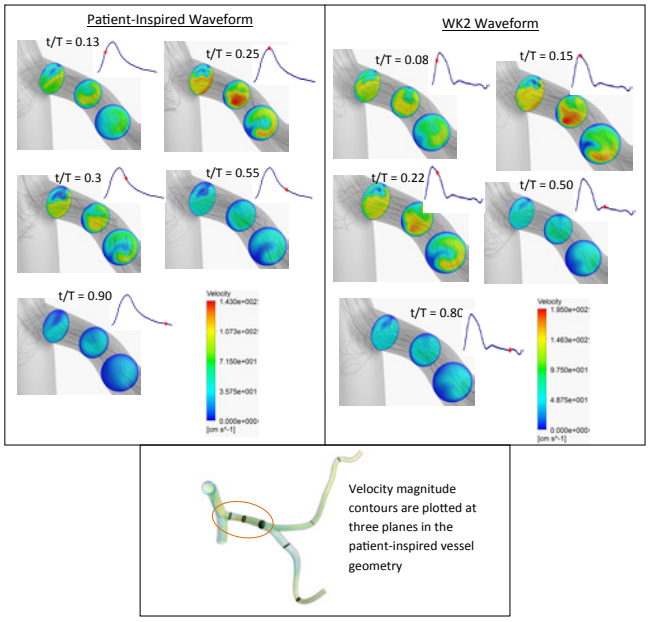

Figure 3: Transient velocity contours in a patient-inspired replaced common hepatic arterial system with patient-inspired and windkessel (WK) inflow waveforms.

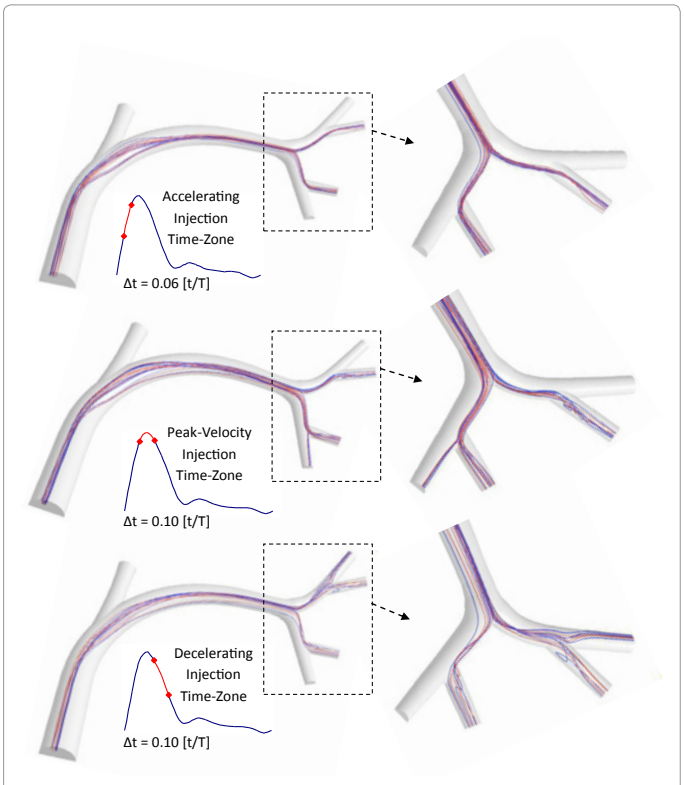

Figure 4: Influence of the microsphere injection timeframe on the microsphere trajectories and dispersion through a representative hepatic arterial system.

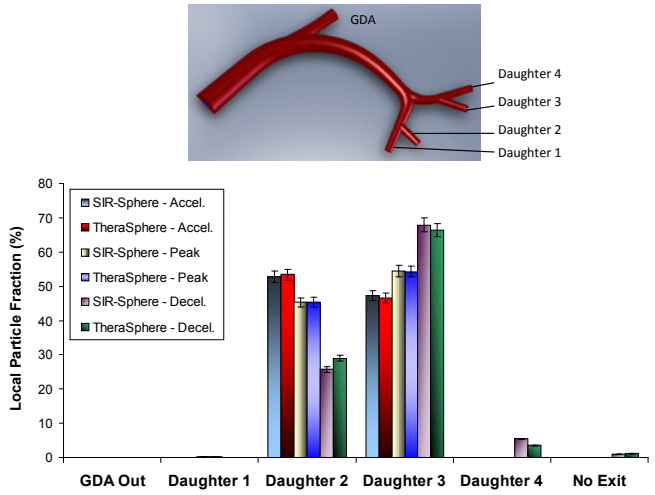

Figure 5: Influence of the microsphere injection timeframe on the microsphere trajectories and dispersion through a representative hepatic arterial system.

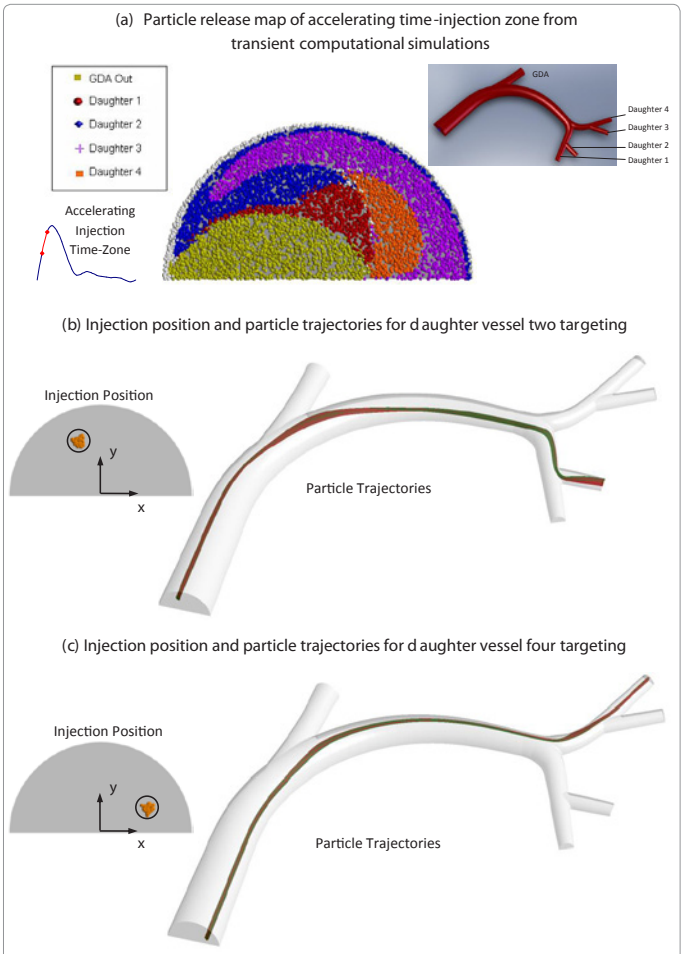

Figure 6: Influence of the microsphere injection timeframe on the microsphere exit fractions in a a representative hepatic arterial system (error bars represent an arbitrary ±3% range).

close to the liver tumor), the Stokes number can become larger than one and the tendency of the microspheres to cross fluid streamlines is greatly elevated (see Kleisntreuer [11]). Thus, investigations are needed of microsphere transport in the arterioles near the tumor periphery to ensure that the microspheres do not deviate from the desired final locations around the liver tumors.

A method for greatly reducing the influence of microsphere characteristics such as particle diameter and particle density is to select appropriate microsphere injection time and location. Basciano et al. [4] showed that by introducing microspheres into the representative hepatic artery geometry during the accelerating region of the arteriole pulse (with the same velocity as the surrounding blood), microsphere dispersion and transit time is greatly reduced. Interestingly, their results also showed that microspheres introduced into the domain during the peak velocity and decelerating portions of the arterial pulse, resulted in the microspheres ricocheting off the arterial walls and increased microsphere dispersion, respectively. Figures 4 and 5 illustrate the influence of the microspheres entrance timeframe on the microsphere trajectories and microsphere exit fractions, respectively. The exit fraction is defined as the percentage of injected particles exiting the selected domain outlet/opening. A specific characteristic of the exit fractions in Figure 5 is that none of the injected microspheres exited through the GDA branch artery. Such a result highlights another influential injection parameter which is the cross-sectional and axial position of the microsphere injection. To utilize the dependence on microsphere injection location, Kennedy et al. [3], Basciano et al. [4], and Basciano [13] created a map of microsphere exit locations (entitled a particle release map) at the microsphere injection cross-sectional plane. Basciano et al. [4] was the first to demonstrate that by combining the appropriate microsphere injection timeframe, axial location, and cross-sectional position, up to 100% of the injected microspheres can exit a predefined outlet location. Figure 6a displays a particle release map created during the accelerating phase of the arterial pulse, while

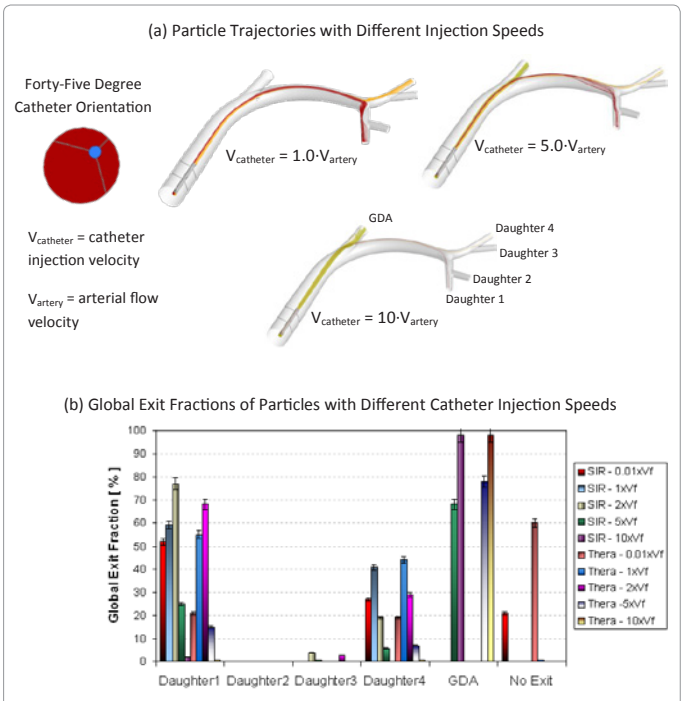

Figure 7: (a) Particle release map of microspheres released during the accelerating portion of the arterial pulse **(b)** Targeting daughter vessel two by releasing microspheres in the accelerating portion of the arterial pulse and appropriate cross-sectional position **(c)** Targeting of daughter vessel four by releasing microspheres in the accelerating portion of the arterial pulse and appropriate cross-sectional position.

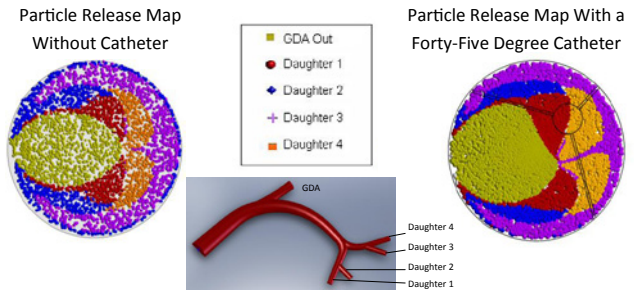

Figure 8: (a) Influence of catheter injection velocity on microsphere trajectories through steady flow in a representative hepatic arterial system **(b)** Influence of catheter injection velocity on microsphere exit fractions in a representative hepatic arterial system under steady flow (error bars represent an arbitrary ±3% range).

Figures 6b,c illustrate targeting specific daughter vessels by selectively releasing microspheres at specific cross-sectional positions derived from the particle release map.

Influence of microsphere delivery catheter

In current clinical practice, ^{90}Y-microspheres are injected via a standard 3 French diameter microcatheter. Because the injection is driven by hand, there is a large amount of variability in the potential injection velocity of the administered ^{90}Y-microspheres. To provide clinicians with greater understanding of microsphere injection velocities, Basciano [13] calculated microsphere trajectories through a steady flow field in a representative hepatic arterial system with a stationary 3F catheter. Figures 7a,b illustrate the catheter injection velocity has a prominent influence on microsphere trajectories and the microsphere exit fractions respectively. More specifically, when the momentum of the injected particles is large enough to cross fluid streamlines, the majority of injected particles will exit the domain through the GDA due to the small bifurcation angle of the GDA branch. Thus, the catheter injection velocity and arterial morphology can yield conditions that reduce the effectiveness of daughter vessel targeting from cross-sectional release positions. Furthermore, Figure 8 shows that the presence of a catheter shifts the particle release map into a slightly modified orientation, but distinct regions still exist which can be used for daughter vessel targeting.

Discussion

Clinical implications

This article provides an overview of an experimentally-validated computational model which has been used to investigate ^{90}Y-microsphere transport in the hepatic arteries and to highlight specific findings which can improve the effectiveness of ^{90}Y-microsphere radioembolization. While mathematical modeling and computational fluid-particle dynamics are not the most common clinical research tools, both techniques have provided valuable insight to the underlying physics of ^{90}Y-microsphere transport. The increased knowledge and known influence of the injection time interval, specific daughter vessel targeting via smart radial positioning of the catheter, microsphere injection velocity, and vessel morphology enable radiation and interventional oncologists to improve ^{90}Y-microsphere radioembolization by utilizing computer simulation results. Moreover, the previous computational studies are paving the way for a new generation of medical devices such as a smart micro-catheter (SMC), which would give clinicians the ability to visualize and remotely control the cross-sectional release position of the microspheres (see Kleinstreuer [15]).

Model limitations

Some fundamental limitations exist with the removal of certain forces in the particle transport calculation (e.g., particle-to-particle collision forces when high microsphere concentrations are being delivered). Particle-to-particle collisions do occur in the therapy and there is no data to determine their potential impact on the clinical response of the therapy. Additionally, the computational models exhibit long calculation times on the order of days to weeks. A clinical limitation to the modeling approach is the availability of clinical data to build more refined models. Current resolutions of standard CT-scans have enough definition and clarity to generate three dimensional arterial geometries up to the right and left hepatic arteries, which is the current standard release position for most ^{90}Y-microsphere treatments.

Future work

As mentioned in the model limitations, the ability to create three-dimensional domains from the microsphere injection site to the tumor periphery is a continued area of intense research. Furthermore, benchtop experimental demonstrations of selective daughter vessel targeting via cross-sectional positioning are underway, and computational research is being conducted to improve the microsphere supply apparatus. Research needs exist beyond the mentioned items by collecting new clinical data on transient hemodynamics in the hepatic arterial system (see Morgan et al. [16]). Such data is vital to the computational model's ability to maintain clinical relevance and continue to help clinicians save lives through more effective treatments.

Conclusions

Experimentally validated computational fluid-particle dynamics models were utilized to analyze ^{90}Y-microsphere transport in representative and patient-inspired hepatic arterial system geometries. Key parameters that greatly influence microsphere transport (and hence tumor targeting) include downstream flow resistance, arterial vessel anatomy and morphology, microsphere injection timeframe, microsphere injection position (cross-sectional and axial positions), and microsphere injection velocity. Optimization of the aforementioned parameters and the associated designed of next-generation smart micro-catheters will increase ^{90}Y-microspheres effectiveness through refined clinical practice that gives new levels of control and precision to the clinicians. In the end, patients afflicted with liver tumors will have a more positive outlook of treatment options from the fusion of clinical research, physics, and engineering that is aimed at improving effective clinical therapies such as ^{90}Y-microsphere radioembolization.

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