

# Segmental Perfusion Differences on Paired Tc-99m Macroaggregated Albumin (MAA) Hepatic Perfusion Imaging and Yttrium-90 (Y-90) Bremsstrahlung Imaging Studies in SIR-Sphere Radioembolization: Associations with Angiography

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## Abstract

Surgically unresectable primary and metastatic liver tumors have been increasingly treated with Y-90 radioembolization. In preparation for Y-90 radioembolization therapy, a baseline angiogram and a Tc-99m MAA hepatic perfusion study simulating Y-90 microsphere infusion are routinely performed, followed by a 2<sup>nd</sup> angiogram in which the catheter is positioned in the same position as during the baseline angiography. However, radiotracer distribution on paired Tc-99m MAA hepatic perfusion imaging and post-therapy Y-90 bremsstrahlung imaging studies does not always match. The purpose of this study was to examine perfusion differences or mismatch which involve hepatic segment(s) and to identify underlying causes by correlating with angiography. 81 paired Tc-99m MAA hepatic perfusion imaging and post-therapy Y-90 bremsstrahlung imaging studies and corresponding angiograms were reviewed. 31 studies showed segmental perfusion differences (SPDs). SPDs were less frequently observed with infusion into the left hepatic artery (LHA) as compared to the proper (PHA) and right hepatic artery (RHA) ( $P < 0.05$ ). Significant associations were found with differences in catheter tip position between the two angiograms ( $P < 0.001$ ), catheter tip in proximity to an arterial bifurcation ( $P < 0.01$ ) or a small branch ( $P < 0.01$ ). Differences in catheter position, in combination with proximity to an arterial bifurcation or an arterial branch showed strong association with SPDs ( $P < 0.001$ ). In conclusion, when the catheter tip is in proximity to an arterial bifurcation or a branch, subtle differences in its position can alter microsphere perfusion or trajectory to the target vessels, which can be demonstrated by segmental perfusion mismatch on paired Tc-99m MAA hepatic perfusion imaging and post-therapy Y-90 bremsstrahlung imaging studies.

**Keywords:** Yttrium-90 radioembolization; SIR-sphere; Y-90 Bremsstrahlung imaging; Tc-99m MAA hepatic perfusion imaging; Segmental perfusion differences; Angiogram; Catheter position; Microparticle trajectory selection

## Introduction

Surgically unresectable primary and metastatic liver tumors have been increasingly treated with Y-90 radioembolization, a relatively new treatment modality. Y-90 labeled microspheres are delivered directly through the hepatic arterial circulation and are preferentially localized in the peri-tumoral or intra-tumoral arterial vasculature, allowing delivery of a high radiation dose to the tumor and avoiding excessive radiation to the normal hepatic parenchyma [1-3].

In preparation for Y-90 radioembolization therapy for patients with hepatocellular carcinoma (HCC) or metastatic cancers to the liver, a baseline angiogram and a <sup>99m</sup>technetium macroaggregated albumin (Tc-99m MAA) hepatic perfusion study simulating the Y-90 microsphere infusion are routinely performed prior to Y-90 radioembolization therapy [4-6]. The purpose of these steps is to detect excessive hepatopulmonary shunting as evident by increased activity in the lungs and to look for atypical vascular anatomy which may cause intra-abdominal, extra-hepatic deposition of Y-90 microspheres and subsequently result in gastrointestinal ulcers or pancreatitis [6-9]. The intended treatment dose and radiation dose to the tumors, normal liver parenchyma and lungs can be calculated as well, on the basis of relative hepatic parenchyma and tumor volume and perfusion [5]. Subsequently, a 2<sup>nd</sup> angiogram is performed and Y-90 microspheres are infused through the indwelling catheter which is positioned at the same position as in the baseline angiogram.

It has been assumed that the distribution of radiotracer on the post-therapy Y-90 imaging and pre-therapy Tc-99m MAA hepatic perfusion imaging studies is the same. However, the distribution of radiotracer between these paired studies does not always match [10]. Since the tumor dosimetry can be obtained based on the Tc-99m MAA hepatic perfusion study, perfusion differences or discrepancy of tracer distribution between these two studies can cause significant inaccuracy in tumor dosimetry. We considered a number of possible causes, including different flow characteristics of Tc-99m MAA particles and Y-90 microspheres, and potential differences in catheter position.

Based on Couinaud and Bismuth's functional classification of the liver, the liver can be divided into eight functionally independent segments, where each segment has its own vascular inflow, outflow and biliary drainage [11]. Therefore, we hypothesize that perfusion

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**Received** December 21, 2011; **Accepted** February 15, 2012; **Published** February 20, 2012

**Citation:** Jiang M, Fischman A, Nowakowski FS, Heiba S, Zhang Z, et al. (2012) Segmental Perfusion Differences on Paired Tc-99m Macroaggregated Albumin (MAA) Hepatic Perfusion Imaging and Yttrium-90 (Y-90) Bremsstrahlung Imaging Studies in SIR-Sphere Radioembolization: Associations with Angiography. J Nucl Med Radiat Ther 3:122. doi:10.4172/2155-9619.1000122

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differences which involve hepatic segments on the paired Tc-99m MAA hepatic perfusion imaging and post-Y-90 radioembolization imaging studies are likely caused by infusion of radiotracer into non-target arterial branches or absent infusion into target vessels during the angiographic procedures. The objective of this study was to identify angiographic related factors that correlate with SPDs between the paired <sup>99m</sup>Tc MAA perfusion imaging and post-Y-90 radioembolization imaging studies.

## Patients and Methods

### Patients

A total of 81 paired Tc-99m MAA hepatic perfusion imaging and post-therapy Y-90 bremsstrahlung imaging studies in 75 patients were included and reviewed. Six patients had two separate set of studies due to a two-step treatment strategy targeting the left and right lobes respectively. All patients were treated with resin microspheres, SIR-Spheres (Sirtex Medical Inc, Wilmington, MA).

### Procedure

A baseline angiogram was performed by an experienced interventional radiologist to determine hepatic vascular anatomy for catheter placement and for identification of any aberrant or collateral vessels. Right common femoral arterial access was obtained and a 5 French (Fr) vascular sheath was placed. A 5 Fr reverse curve diagnostic catheter was used to catheterize the superior mesenteric and celiac arteries. Digital subtraction angiograms were performed using power injections of 25 ml of Isovue 300 (Bracco Diagnostics, Milan, Italy) at 5 ml per second. Interrogation of all visceral vessels supplying the liver was performed to review superior mesenteric, celiac, proper hepatic, right hepatic, left hepatic, left gastric, right gastric, and gastroduodenal arteries. A 2.8 Fr Renegade Hi-Flo microcatheter and Fathom 16 wire (Boston Scientific, Natick, MA) were used to catheterize the target vessels. Prophylactic coil embolization of extrahepatic vessels was undertaken when deemed necessary by the interventional radiologist (eg, right gastric artery or gastroduodenal artery). The microcatheter was advanced into the target treatment vessel and repeat digital subtraction angiograms were performed to confirm position. 185 MBq of Tc-99m MAA (Covidien, USA), suspended in 10 cc of normal saline were then injected through the catheter by a nuclear medicine physician in a pulsatile fashion over several minutes, with the intention of simulating the Y-90 SIR Spheres infusion. After the catheter and the sheath were removed and hemostasis at the catheter insertion site was established, the patient was transported to the nuclear medicine suite. Planar images of the whole body and Single-photon emission computed tomography-computed tomography (SPECT-CT) images of the abdomen were obtained (GE Infinia SPECT/CT scanner).

The administration of SIR-Spheres was performed in a separate session 1-3 weeks after the baseline angiogram and Tc-99m MAA hepatic perfusion imaging studies. Prior to the procedure, the following premedication regimen was administered intravenously as per standard protocol: 3.375 g piperacillin/tazobactam, 8 mg ondansetron, 50 mg benedryl, 8 mg dexamethasone and normal saline at 150 ml/hr. Repeat angiograms of the celiac and superior mesenteric arteries were performed initially. A 2.8Fr Renegade Hi-Flo microcatheter (Boston Scientific, Natick, MA) was advanced to the previously targeted vessel. Catheter position was confirmed with digital subtraction angiography and comparison to prior planning angiograms. The prepared activity of SIR-Sphere (0.5-1.8 MBq) (Sirtex Medical Inc, Wilmington, MA) was injected by a nuclear medicine physician using standard procedure,

by administration of small batches of the Y-90 SIR spheres in a gentle pulsatile fashion. The infusions of the small radioembolization batches were alternated with infusion of small amounts of IV contrast to document good flow, with infusions of sterile water in between for flushing purposes [12]. The Y-90 microsphere activity to be infused was calculated by method recommended by the Sirtex company, based on the body surface area and the percent of the perfused liver volume and percent of the liver volume occupied by tumor [12]. After the catheter and the sheath were removed and hemostasis at the catheter site was established, the patient was transported to the nuclear medicine suite. Whole body planar and SPECT-CT images of the abdomen were obtained using Y-90 bremsstrahlung imaging (GE Infinia SPECT-CT scanner) by using a medium-energy general-purpose (MEGP) collimator and an energy window of 90 keV  $\pm$  15% [13]. Y-90 SPECT images were reconstructed by using ordered subset expectation maximization (OSEM) algorithm [13]. After each treatment session, patients were observed for 3-6 hours and discharged home the same day. All patients receiving SIR-Sphere therapy at our institution received daily oral prophylactic proton pump inhibitors for 3-6 months following treatment.

### Image analysis

The images were displayed on a computer workstation (Xeleris; General Electric Medical Systems) and were interpreted by an experienced nuclear medicine physician. The distribution of the radiotracer in the liver was assessed on the SPECT-CT images. We categorized the studies into two groups; one group with segmental perfusion differences (SPDs) and the other group without SPD. SPDs were defined as mismatched tracer distribution on paired Tc-99m imaging and Y-90 imaging studies if the mismatch involved at least one hepatic segment. The group without SPD included those studies that showed close resemblances in tracer distribution as well as those studies that showed only intra-segmental perfusion differences or those differences in degree of uptake among lesions in the liver parenchyma.

The angiographic images were displayed on PACS (GE) and were reviewed by an experienced interventional radiologist. Catheter tip position, presence of arterial bifurcation or branch near the catheter tip on the baseline and 2<sup>nd</sup> angiography were assessed and compared. Differences in catheter tip position were defined as significant when greater than 5mm. The catheter tip and a bifurcation or an arterial branch was considered to be in proximity of one another if the distance was measured to be less than 10 mm. The diameter of the catheter was used as a reference for measurement.

### Statistics

Differences in frequencies of occurrences of various observations between those patients with SPDs and those who did not show SPDs were tested by the construction of 2 x 2 contingency tables, and tested for significance using the chi-squared test. A probability of the observed differences in frequencies occurring by chance equal to or less than 0.05 was considered significant.

### Results

There were total of 75 patients including 46 male and 29 female patients, with a mean age of 59 (ranges 35-82). Six patients had a two-step treatment plan targeting the tumors in the left and right lobe respectively. The diagnoses included neuroendocrine tumors metastatic to the liver (n=32), hepatocellular carcinoma (n=26) and metastatic liver tumors from other primary tumors including colon, lung, breast cancer or sarcoma (n=17).

Of the 81 paired studies, 31 paired studies were classified into the group with SPDs and 50 paired studies were without SPD. The infusion site, including proper (PHA), right (RHA) and left hepatic artery (LHA) for each study was shown in Table 1. SPDs were less frequently observed when therapy was delivered into the LHA as compared to PHA and RHA ( $P < 0.05$ ).

A difference in catheter tip position (distance greater than 5mm) along the artery between two angiograms (variable A) was observed in 24 out of 31 paired studies in the SPD group, compared to 5 out of 50 in the non-SPD group. An arterial bifurcation present in proximity to the catheter tip (variable B) was observed in 10 out of 31 studies in the SPD group, compared to 3 out of 50 in the non-SPD group. A small arterial branch present in proximity to the catheter tip (variable C) was observed in 13 out of 31 studies in the SPD groups, compared to 2 out of 50 in the non-SPD group. Each of these variables was statistically significant in association with segmental perfusion differences as compared to the non-SPD group (Table 2).

Interestingly, 21 of 31 paired studies in the SPD group showed a combination of differences in catheter tip position (variable A) and with the presence of either a small arterial branch (variable C) ( $n=12$ ) or an arterial bifurcation (variable B) ( $n=9$ ) in close proximity. On the contrary, none of the studies in the group without SPD showed a combination of variable A along with variable B or C (Table 2).

There was no significant difference between the SPD group and non-SPD group when each of the three variables was present alone without combination with any of the other variables. A difference in catheter position, without combination with either variable B or C, was found in only 3 out of 31 studies in the SPD group, as compared to 5 out of 50 in the non-SPD group. Presence of an arterial branch or bifurcation near the catheter tip, without combination with a difference in catheter tip position, was found in 2 out of 31 studies in the SPD group, as compared to 5 out of 50 in the non-SPD group (Table 2).

A sample case demonstrated mismatch of tracer distribution involving the left lobe on paired Tc-99m MAA imaging and Y-90 imaging studies. Angiogram correlation confirmed a difference in catheter tip position with a bifurcation in proximity (Figure 1). A second case demonstrated SPD involving liver segment VI. Angiogram correlation confirmed a difference in catheter tip position with an arterial branch nearby (Figure 2).

## Discussion

A baseline angiogram and a Tc-99m MAA hepatic perfusion imaging study are routinely performed in preparation for Y-90 radioembolization therapy. The purpose of these steps is to simulate Y-90 radioembolization treatment and to examine potential abnormal tracer distribution in the lungs (secondary to hepatopulmonary shunting) or abnormal extra-hepatic deposition in the intra-abdominal organs. SPECT-CT images add considerable value to the planar images due to the ability to detect tracer deposition in extra-hepatic visceral sites [8,9]. Additionally, the pre-therapy Tc-99m MAA SPECT-CT hepatic perfusion imaging studies allow calculation of the intended administered activity of SIR Spheres by the measurement of the percent perfused liver volume and the percent of the perfused volume being occupied by tumor, in combination with the patient's body surface area [12]. In addition the Tc-99m MAA SPECT-CT studies allow calculation of the radiation dosimetry to the tumors as well as to the normal hepatic parenchyma, based on the volume and gamma accounts in the regions of interest for tumors and normal liver parenchyma, respectively.

Two microsphere products are currently commercially available. TheraSpheres (glass microspheres; MDS Nordion) and SIR-Spheres (resin microspheres; Sirtex Medical Inc, Wilmington, MA) were approved by the Food and Drug Administration in 1999 and 2002, respectively. Due to differences in the physical characteristics and possible flow dynamics of the resin and glass beads, we only investigated those patients whose treatment was performed with the resin microspheres (SIR-Sphere). Therefore, our findings and conclusions are limited only to treatment with SIR Spheres and

Infusion site	Group with SPDs (n=31)	Group w/o SPD (n=50)
PHA	12	10
RHA	18	27
LHA	1*	13

\*:  $P < 0.05$

**Table 1:** Comparison of infusion sites between the groups with and without SPDs.

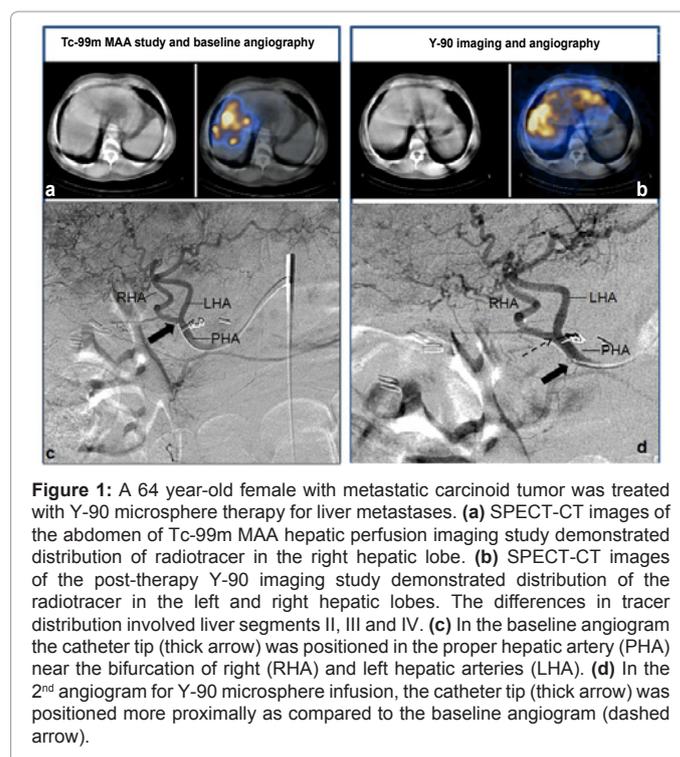
	Group with SPD (n=31)	Group w/o SPD (n=50)	P value
Variable A (with and without other variables)	24	5	<0.001
Variable B (with and without other variables)	10	3	<0.01
Variable C (with and without other variables)	13	2	<0.01
Variable A+B	9	0	<0.001
Variable A+C	12	0	<0.001
Variable A only (without combination with other variables)	3	5	>0.5
Variable B or C only (without combination with other variables)	2	5	>0.5

**Variable A:** The position of micro-catheter tip showed difference in the angiograms for the TC-99m MAA study and Y-90 treatment

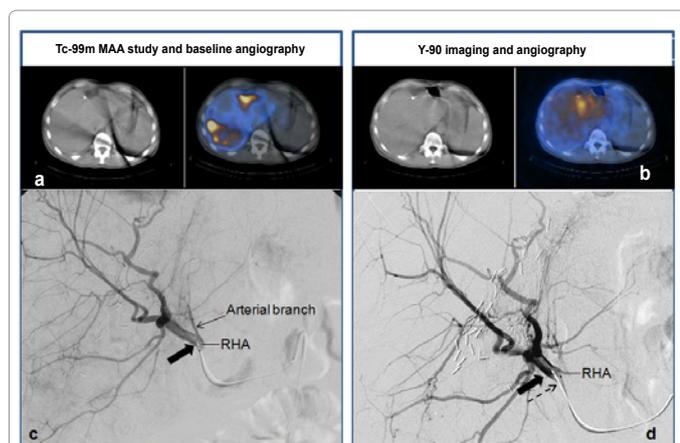
**Variable B:** A bifurcation is present near the catheter tip

**Variable C:** Small arterial branch is present near the catheter tip

**Table 2:** Comparison of three variables (singly and in combination) between the group with and without SPD.



**Figure 1:** A 64 year-old female with metastatic carcinoid tumor was treated with Y-90 microsphere therapy for liver metastases. (a) SPECT-CT images of the abdomen of Tc-99m MAA hepatic perfusion imaging study demonstrated distribution of radiotracer in the right hepatic lobe. (b) SPECT-CT images of the post-therapy Y-90 imaging study demonstrated distribution of the radiotracer in the left and right hepatic lobes. The differences in tracer distribution involved liver segments II, III and IV. (c) In the baseline angiogram the catheter tip (thick arrow) was positioned in the proper hepatic artery (PHA) near the bifurcation of right (RHA) and left hepatic arteries (LHA). (d) In the 2<sup>nd</sup> angiogram for Y-90 microsphere infusion, the catheter tip (thick arrow) was positioned more proximally as compared to the baseline angiogram (dashed arrow).



**Figure 2:** A 65 year-old male with metastatic carcinoid tumor received Y-90 microsphere therapy for hepatic metastases. (a) SPECT-CT images of Tc-99m MAA hepatic perfusion imaging study demonstrated distribution of radiotracer in the right hepatic lobe in the segment IV, V and VI. (b) SPECT-CT images of the post-therapy Y-90 imaging demonstrated distribution of radiotracer mostly in the medial aspect of the right lobe in segment IV and V. The differences in tracer distribution involved liver segment VI. (c) In the baseline angiogram, the catheter tip (thick arrow) was positioned in the right hepatic artery, with a small arterial branch nearby (thin arrow). (d) In the 2<sup>nd</sup> angiogram for Y-90 microsphere infusion, the catheter tip (thick arrow) was positioned more distally as compared to the baseline angiogram (dashed arrow). Perfusion into the small arterial branch is only minimally visualized on the 2<sup>nd</sup> angiogram.

cannot be extended to treatment with Theraspheres, which needs to be investigated separately.

Differences in distribution of radiotracer between the paired Tc-99m MAA hepatic perfusion imaging and post-therapy Y-90 bremsstrahlung imaging can present as differences in intensity of uptake among lesions and/or differences in areas of deposition, either within the same segments or involving different hepatic segments. Perfusion discrepancies involving hepatic segments usually affect a larger perfused area compared to those studies with intra-segmental perfusion differences. Therefore, these studies may have a greater impact on the calculation of tumor and liver dosimetry. Discrepancy in tracer distribution between the planning Tc-99m MAA imaging and post-therapy Y-90 imaging studies thus raised a question if tumor dosimetry data can be used to correlate tumor response if discrepancy between the two studies is significant or frequent.

It is recommended to document technical success or failure of the treatment protocol after Y-90 radioembolization treatment because “technical success or failure” has direct relevance to “clinical success or failure” and post-radioembolization patient management [14]. The term “technical success” simply addresses whether the tumor was treated according to protocol and was addressed completely [14]. Incomplete targeting of the tumors is considered as one of the criteria for “technical failure” [14]. In our experience, perfusion mismatch between the planning Tc-99m MAA study and Y-90 imaging study was not uncommon for SIR-Sphere radioembolization therapy [10].

It has been suggested that due to the inherent properties of scatter imaging, the Bremsstrahlung image was not recommended to be used to define whether the procedure was technically successful [14]. However, our study demonstrated usefulness of using both Tc-99m MAA study and Y-90 imaging study in evaluation of perfusion mismatch involving liver segments and assessment of complete or incomplete targeting of tumors for treatment. To our best knowledge, this is the first study

describing the discrepancy in tracer distribution between the paired Tc-99m MAA study and post-therapy bremsstrahlung imaging with angiographic correlations.

Differences in characteristics of resin microspheres and MAA particles, as well as differences in imaging techniques may also contribute to perfusion differences between the MAA and Y-90 images. However, these factors should be considered only after the more obvious effects of catheter position are factored in. Additionally, retrograde reflux of resin microspheres due to flow stasis during infusion may increase the area of perfused hepatic parenchyma by refluxing into the branches more proximally to the catheter tip, therefore it may contribute to segmental perfusion differences between the MAA and Y-90 images. During infusion of Y-90 microspheres, intermittent contrast angiograms are performed to examine the status of hepatic flow. Upon encountering stasis or reflux, the infusion is terminated to prevent possible reflux to the proximal arteries supplying such organs as the stomach, pancreas, or intestines. Therefore, in most cases that encountered stasis or reflux, the amount of refluxed Y-90 microsphere beads is probably small and may not cause significant perfusion differences.

Recent research in micro-particle transport and trajectory in a bifurcated / branched artery using validated computer models have shown that injected microspheres travel via predictable trajectories and the differences in microparticle trajectories are dependent on the spatial (i.e., cross-sectional position) and temporal (i.e., phase of arterial pulse) conditions of micro-particle release [15-17]. The concept of microparticle trajectory selection may be exploited for possible non-target vessel avoidance as well as for achievement of specific daughter vessel targeting by selecting a desired microparticle trajectory based on the appropriate cross-sectional spatial location and temporal injection interval timed to pulsatile arterial flow. Recently, Kao et al. [18] published a case series with significant imaging discordance between hepatic angiography versus Tc-99m-MAA SPECT-CT imaging, and a retrospective review of angiograms revealed eccentric microcatheter tip placement abutting the arterial wall in all 3 patients, suggesting that non-target microparticle trajectories were selected due to the eccentric microcatheter tip position [18].

Our results confirm that changes in catheter tip position in combination with an arterial bifurcation or a branch in proximity can contribute to changes in flow dynamics and microsphere trajectories to the target vessels. The findings are consistent with the microparticle trajectory selection model, as changes in catheter tip position along the curved pathway of an artery can readily cause changes in the spatial location of the catheter tip relative to the center-point of the target vessel. Modeling has revealed that the selection of the daughter branching artery for microsphere perfusion depends on the spatial location of the microcatheter relative to the center of the artery [15,17]. However, the distance between the injection pump to the bifurcation was a fixed parameter in those computer model studies. Our results indicated that not only the spatial location at the cross-sectional plane can determine the micro-particle trajectory, but also the distance to the bifurcation and daughter branches can also play an important role in micro-particle trajectory selection.

Our results also show that SPDs were less frequently observed when infusion was made into the LHA compared to the RHA and PHA. This may be the result of fewer branches or bifurcations arising off the LHA as compared to the RHA, although that hypothesis needs to be tested.

We recommend that the catheter tip should be maintained at the same position during the therapeutic infusion and operators should be

aware of changes in flow dynamics when the catheter tip is near the arterial bifurcation or branch. Several factors pose potential challenges for the operator to position the catheter at the exact same position during second angiogram for Y-90 microsphere infusion. The  $^{99m}\text{Tc}$  MAA and Y-90 microsphere are injected in two separate procedures which are 1-3 weeks apart. These procedures may be performed in different procedure rooms with different equipment, and by different operators. In addition, patient motion, and respiration during procedure often make it difficult to accurately place the catheter within 5 mm of the recorded position during MAA infusion. Access to the target vessel may vary slightly due to arterial spasm, tumor progression or arterial stricture secondary to prior endovascular treatments or concurrent anti-angiogenesis medication. Identification of subtle changes in catheter position in some cases required careful comparison of angiograms. Therefore, without any internal markers, subtle changes in catheter position and very small arterial branches nearby may not be easily perceived by the operator during angiogram procedure. This study highlights the need to pay close attention to catheter position and potential significant effect on flow dynamics and microsphere trajectory selection when near a bifurcation or a branch.

In summary, subtle differences in catheter position, in combination with an arterial bifurcation or branches in close proximity to the microcatheter tip in the target vessel can cause significant changes in flow dynamics and microsphere trajectory to the daughter branching vessels. These changes can present as segmental perfusion differences on paired Tc-99m MAA hepatic perfusion imaging and post-radioembolization therapy Y-90 imaging studies.

## References

1. Koshariya M, Jagad RB, Kawamoto J, Papastratis P, Kefalourous H, et al. (2007) An update and our experience with metastatic liver disease. *HepatoGastroenterology* 54: 2232-2239.
2. El-Serag HB, Marrero, JA, Rudolph L, Reddy KR (2008) Diagnosis and treatment of hepatocellular carcinoma. *Gastroenterology* 134: 1752-1763.
3. Sharma S, Camci C, Jabbour N (2008) Management of hepatic metastasis from colorectal cancers: an update. *J Hepatobiliary Pancreat Surg* 15: 570-580.
4. Salem R, Thurston KG, Carr BI, Goin JE, Geschwind JF (2002) Yttrium-90 microspheres: radiation therapy for unresectable liver cancer. *J Vas Interv Radiol* 13: S223-229.
5. Ibrahim SM, Lewandowski RJ, Sato KT, Gates VL, Kulik L, et al. (2008) Radioembolization for the treatment of unresectable hepatocellular carcinoma: a clinical review. *World J Gastroenterol* 14: 1664-1669.
6. Salem R, Parikh P, Atassi B, Lewandowski RJ, Ryu RK, et al. (2008) Incidence of radiation pneumonitis after hepatic intra-arterial radiotherapy with yttrium-90 microspheres assuming uniform lung distribution. *Am J Clin Oncol* 31: 431-438.
7. Konda A, Savin MA, Cappell MS, Duffy MC (2009) Radiation microsphere-induced GI ulcers after selective internal radiation therapy for hepatic tumors: an underrecognized clinical entity. *Gastrointest Endosc* 70: 561-567.
8. Ahmadzadehfar H, Sabet A, Biermann K, Muckel M, Brockmann H, et al. (2010) The significance of  $^{99m}\text{Tc}$ -MAA SPECT/CT liver perfusion imaging in treatment planning for  $^{90}\text{Y}$ -microsphere selective internal radiation treatment. *J Nucl Med* 51: 1206-1212.
9. Jiang M, Nowakowski SF, Wang J, Heiba H, Zhang Z, et al. (2011) Characterization of extra-hepatic distribution of Tc-99m MAA in hepatic perfusion imaging studies prior to Yttrium-90 microsphere therapy. *Cancer Biother Radiopharm* 26: 511-518.
10. Machac J, Heiba S, Zhang Z, Weintraub J, Nowakowski F, et al. (2008) Prediction of yttrium-90 Sir Sphere deposition by Tc-99m MAA SPECT/CT liver perfusion imaging. *J Nucl Med* 49: 323P.
11. Rutkauskas S, Gedrimas V, Pundzius J, Barauskas G, Basevicius A (2006) Clinical and anatomical basis for the classification of the structural parts of liver. *Medicina (Kaunas)* 42: 98-106.
12. Package insert of SIR-Spheres microspheres (2011) Sirtex Medical Inc. (Wilmington, MA, USA).
13. Kneusaurek K, Machac J, Muzinic M, DaCosta M, Zhang Z, et al. (2010) Quantitative comparison of yttrium-90 ( $^{90}\text{Y}$ )-microspheres and technetium-99m ( $^{99m}\text{Tc}$ )-macroaggregated albumin SPECT images for planning Y-90 therapy of liver cancer. *Technol Cancer Res Treat* 9: 253-262.
14. Salem R, Lewandowski RJ, Gates VL, Nutting CW, Murthy R, et al. (2011) Research reporting standards for radioembolization of hepatic malignancies. *J Vasc Interv Radiol* 22: 265-278.
15. Basciano CA, Kleinstreuer C, Kennedy AS, Dezarn WA, Childress E (2010) Computer modeling of controlled microsphere release and targeting in a representative hepatic artery system. *Ann Biomed Eng* 38: 1862-1879.
16. Kennedy AS, Coldwell D, Nutting C, Murthy D, Wertman DE, et al. (2006) Resin  $^{90}\text{Y}$ -Microsphere brachytherapy for unresectable colorectal liver metastases: modern USA experience. *Int J Radiat Oncol Biol Phys* 65: 412-425.
17. Kennedy AS, Kleinstreuer C, Basciano CA, Dezarn WA (2010) Computer modeling of  $^{90}\text{Y}$  microsphere transport in the hepatic arterial tree to improve clinical outcomes. *Int J Radiat Oncol Biol Phys* 76: 631-637.
18. Kao YH, Tan EH, Teo TK, Ng CE, Goh SW (2011) Imaging discordance between hepatic angiography versus Tc-99m-MAA SPECT/CT: a case series, technical discussion and clinical implications. *Ann Nucl Med* 25: 669-676.