Technical note: simultaneous ⁹⁰Y and ^{99m}Tc-MAA injection for two-stage selective internal radiation therapy (SIRT) of liver metastases

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Abstract: Transarterial Radioembolization (TARE) with 90-Yttrium (⁹⁰Y) microspheres has been established in the management paradigm of a number of primary and metastatic liver neoplasms. Prior to treatment, angiographic assessment and ^{99m}Tc-macroaggregated albumin (Tc-MAA) hepatic arterial perfusion should be performed to detect extrahepatic shunting to the gastrointestinal tract or the lungs. Whole-liver radioembolization is not desirable in subjects with compromised hepatic reserve due to the increased likelihood of RE induced liver disease. In cases with diffuse hepatic involvement, superselective segmental and/or sequential lobar TARE is often utilized to decrease the side-effect profile with intra-arterial Tc-MAA injection playing a critical role in confirming pulmonary shunt fraction and the possibility of non-targeted embolization. Given the complexities of treatment planning, and in order to improve on the efficiencies of treatment without compromising safety, the feasibility of simultaneous ⁹⁰Y RE and Tc-MAA injection into another segment/lobe for subsequent (second stage) treatment planning would be desirable to minimize additional angiography sessions. Here we present our initial experience with two patients undergoing sequential staged TARE therapy for diffuse hepatic metastases.

Keywords: Transarterial Radioembolization (TARE); ⁹⁰Y microspheres; ^{99m}Tc-MAA; two-stage; liver neoplasms

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Introduction

Hepatocellular carcinoma (HCC) represents the sixth most common cancer worldwide (1). The liver is a common site of metastasis from malignancies such as colorectal carcinoma (CRC), neuroendocrine tumors (NETS), pancreatic carcinoma, and breast cancer (1). It creates a need for multimodal strategies in dealing with both primary liver cancer, as well as liver dominant or liver only metastatic disease. One technique is 90-Yttrium Transarterial Radioembolization (⁹⁰Y TARE), commonly known as selective internal radiation therapy (SIRT) of liver malignancies. The therapy, consisting of a multistep, minimally invasive procedure with the aim to deliver a high dose of selective radiation using an intra-arterial infusion of microspheres loaded with ⁹⁰Y is designed to be an outpatient based single cycle therapy. This catheter-based, tumor selective modality can be used for patients with primary or metastatic liver cancer, having a lower toxicity profile compared with traditional therapies (2,3). The appropriate selection of patients, meticulous planning and targeted delivery result in an acceptable incidence of complications (4). The most commonly reported complications arise from the excess deposition in extrahaptic sites or excess dose delivered to the liver (non-targeted embolization), which may include gastritis/duodenitis, gastrointestinal ulceration/bleeding, cholecytitis, pancreatitis, and radiation pneumonitis. Excessive exposure of radiation to non tumorous liver parenchyma may lead to radioembolization induced liver disease (REILD), histopathologically similar to venoocclusive disease and may be associated with underlying Translational Cancer Research, Vol 3, No 2 April 2014



Figure 1 Arterial phase CT of liver demonstrates multiple hypervascular metastasis (arrows) in medial and lateral left lobe of the liver. Prior partial right hepatectomy has been performed.

cirrhosis (1,5-12). Furthermore, candidates with diffuse hepatic disease involvement often have concomitant impaired hepatic function. Sequential treatments are safer and therefore preferable to single-session wholeliver therapy. In practice, the therapies are administered at 30-45 days' intervals (13,14).

Prior to radioembolization, hepatic arteriography and hepatic arterial perfusion (Tc-macroaggregated albumin, Tc-MAA) studies are performed to confirm particle localization and rule out extrahepatic shunting to the gastrointestinal tract and lungs (15). If the hepatic arterial anatomy precludes safe delivery or if ^{99m}Tc-MAA perfusion imaging demonstrates significant extrahepatic activity, selective permanent embolization of the relevant arteries can be performed. Generally, prophylactic embolizations of all extrahepatic vessels (gastroduedenal, right gastric) are performed before ^{99m}Tc-MAA scanning to avoid extrahepatic deposition (16). If extrahepatic accumulation of radiopharmaceutical is detected, repeat angiogram and coil embolization of aberrant arteries should be repeated until no extrahepatic accumulation is detected (15).

Generally, planar imaging and single photon computed tomography (SPECT) of the upper abdomen are performed to assess ^{99m}Tc-MAA distribution. Studies have shown that ^{99m}Tc-MAA SPECT/CT provides additional information when compared to planar and SPECT images alone and is therefore the modality of choice. ^{99m}Tc-MAA SPECT/ CT can also be utilized to accurately evaluate the exact distribution of activity in the liver (15,17).

Recently, Ahmadzadehfar et al. have shown the feasibility

of combined post-therapy Bremsstrahlung (BS) and ^{99m}Tc-MAA perfusion scan in a small case series (13). Here we present two cases of patients with diffuse NET hepatic metastases undergoing staged therapy for each lobe of the liver. We investigated the clinical role and potential applications of simultaneous TARE and injection of ^{99m}Tc-MAA.

Patient A

Patient A presented with multiple NET metastases to left lobe of the liver with no known primary site identified. Prior right hepatectomy had been performed (Figure 1). Interventional radiologists in the Department of Radiology performed the planning angiograms. The right gastric and gastroduodenal arteries were embolized to isolate and optimize hepatic perfusion. The microcatheter was retracted back to the proximal CHA and 185 MBq of ^{99m}Tc-MAA was administered (*Figure 2A*). The patient was transferred to the Department of nuclear medicine for 99mTc-MAA perfusion scan and pulmonary shunt analysis. Whole-body, planar and SPECT/CT images of the abdomen were obtained in the Nuclear Medicine Department approximately one hour after intra-arterial injection of 99mTc-MAA. A dual-detector gamma camera with a mounted single-row CT scanner (Symbia T, Siemens Healthcare) was utilized. Attenuation and scatter correction were performed on the SPECT images. The SPECT images were reconstructed into axial, sagittal and coronal planes. The co-registered CT and SPECT images were fused on OSIRIXMD software (version 1.4). Pulmonary shunt fraction was 3% and no gastrointestinal accumulation of activity was identified (Figure 2A-C). Two weeks later, the patient returned for first stage therapy. Super selective catheterization of left hepatic artery supplying Couinaud's segments II and III was performed. Single administration of 1.4 GBq of ⁹⁰Y impregnated glass microspheres utilizing an 'EX' protocol was applied, (TheraSphere, MDS Nordion Inc., Ottawa, Canada) for a total estimated absorbed dose of 80 Gy (Figure 3A). Selective catheterization of Couinaud's segment IV of the liver was then performed. Tc-MAA (185 MBq) was injected intra-arterially into segment IV for subsequent therapy planning (Figure 3B) primarily to confirm shunt fraction of segment IV due to possible concerns of anatomical variation that was missed on the preprocedural CT and angiograms. Within two hours of the procedure, the patient was transferred to nuclear medicine for simultaneous 90 Y BS and 99m Tc-MAA SPECT/



Figure 2 (A) Selective catheterization of the CHA and injection of Tc-MAA post-embolization of GDA (long arrow) and right gastric (short arrow) arteries; (B) Anterior and posterior whole body planar images post intra-hepatic injection of Tc-MAA demonstrates uptake in entire left lobe of the liver. Regions of interest (ROI) were placed on the lungs and right flank, utilizing the geometric mean method; the lung shunt fraction was 3%; (C) Axial fused SPECT/CT image demonstrates heterogeneous activity within segments II, III and IV of the liver. No gastrointestinal accumulation was noted. CHA, common hepatic artery; MAA, macroalbumin aggregate; GDA, gastroduodenal artery.



Figure 3 (A) Selective LHA catheterization and RE of segments II and III of the liver. Note hypervascular tumor blushes (arrows); (B) Selective catheterization and injection of Tc-MAA into segment IV for subsequent (second stage) therapy planning. Multiple hypervascular tumors are seen. Coil embolization of the GDA, RGA and phrenic branches were performed. In addition, two coils were placed internally within segment IV for internal redistribution; (C,D) Axial and coronal fused Tc-MAA SPECT/CT images demonstrate localized uptake in tumors within segment IV of the liver. LHA, left hepatic artery; RE, radioembolization; GDA, gastroduodenal artery; RGA, right gastric artery.

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CT imaging (*Figure 3C*,*D*). The images did not show any gastrointestinal deposition of activity and the pulmonary shunt fraction was 4%.

Patient B

Patient B presented with metastases to both lobes of the liver and carcinoid syndrome, again no primary site was identified (*Figure 4*). Mesenteric angiogram with coilembolization of the GDA was performed. We took note of prominent communicating collaterals between the right and left gastric arteries; thus we decided to embolize the branch of the left gastric artery. ^{99m}Tc-MAA was injected into the



Figure 4 Axial portal venous phase CT demonstrates multiple metastasis in both lobes of the liver with washout (arrows).

CHA and the patient underwent planar and SPECT/CT imaging. Heterogeneous activity was noted predominantly within the left lobe and spleen. The pulmonary shunt fraction was 2% (Figure 5). Two weeks later, the patient returned for first stage right lobe treatment. After selective right hepatic artery catheterization, 1.1 Gbq of ⁹⁰Y glass microspheres (TheraSpheres) utilizing 'EX' protocol was administered for a total dose of 80 Gy (Figure 6A). The left hepatic artery was then catheterized and Tc-MAA was injected for planning of subsequent left lobe therapy (second stage) (Figure 6B). The patient underwent simultaneous ⁹⁰Y BS and Tc-MAA SPECT/CT as per protocol detailed above. No significant pulmonary shunting was detected (<2%). The SPECT/CT images demonstrated accumulation of activity in multiple arterialized left lobar tumors with no gastrointestinal/splenic activity (Figure 6C,D).

Discussion

Whole-liver TARE is not desirable in candidates that present with an increased likelihood of REILD due to compromised hepatic reserve (1). In cases with diffuse hepatic involvement, superselective segmental TARE (radiation segmentectomy) has been shown to selectively deliver high dose to the tumor with minimal normal liver exposure (18). After optimization of hepatic vasculature, intraarterial ^{99m}Tc-MAA is injected in the target bed in order to confirm uptake of the tumor, determine pulmonary shunt fraction and exclude the possibility of non-targeted embolization of radioembolic. Commonly in order to establish total shunt perfusion fraction, ^{99m}Tc-MAA is



Figure 5 (A) Selective catheterization and injection of Tc-MAA into CHA after optimization with embolization of GDA (long arrow) and branch of LGA (short arrow); (B) Geometric mean calculations performed on planar images demonstrate pulmonary shunt fraction of 2%; (C) SPECT/CT images did demonstrate accumulation of activity in the spleen. CHA, common hepatic artery; GDA, gastroduodenal artery; LGA, left gastric artery.



Figure 6 (A) Selective RHA catheterization and administration of ⁹⁰Y microspheres. Embolization coilds are seen within the GDA, accessory left gastric and an escaped coil from attempted accessory LGA embolization; (B) LHA catheterization and injection of 185 ^{99m}Tc-MAA; (C,D) Axial and coronal fused Tc-MAA SPECT/CT images demonstrating heterogeneous uptake of activity in left lobar tumors. RHA, right hepatic artery; GDA, gastroduodenal artery; LGA, left gastric artery; LHA, left hepatic artery; MAA, macroalbumin aggregate.

injected in the proper hepatic artery with an assumption of uniform homogeneous distribution (and shunt) throughout the entire liver with the assumption that ^{99m}Tc-MAA must be injected into the hepatic artery similar to the application of microspheres. Neovascularity of tumors can lead to the formation of arteriovenous anastamoses or shunts, which can allow direct entry of microspheres into the venous system (19). ^{99m}Tc-MAA SPECT/CT is superior to SPECT or planar imaging alone for demonstration of gastrointestinal Tc-MAA deposition (17). ^{99m}Tc-MAA SPECT/CT is also valuable in accurate depiction of intrahepatic distribution of Tc-MAA (15,17). SPECT/CT can be particularly valuable in cases with heterogeneous intrahepatic Tc-MAA and when spare segments (segments without activity) are visualized. Subsequent test angiogram and Tc-MAA perfusion imaging of spare segments prior to

treatment is necessary to exclude aberrant vessel to other organs (*Figure 7*) (15).

Inherent in this method are fundamentally incorrect assumptions based on a single compartment model. As regional target areas will demonstrate specific shunt fractions that may effect the ability to deposit high amounts of activity in disease active regions (radiation segmentectomy, radiation lobectomy). Therefore, in situations where geographical areas require interrogation with intended multisession therapy (e.g., radiation segmentectomy on the background of planned whole liver therapy) a dual acquisition technique such as herein described would prove valuable in the determination of actual compartment shunt fraction as opposed to estimation based on whole liver ^{99m}Tc-MAA injection, also allowing for more advanced two compartment and dose kernel



Figure 7 (A) Tc-MAA injected into the CHA post-embolization of GDA and branches of LGA demonstrated accumulation of activity in the spleen likely secondary to an aberrant vessel. We decided not to carry on any further embolization due to the long pedicle of left hepatic artery assuming that no reflux of MAA would occur but anticipated application of the techniques described in this manuscript to confirm our suspicions; (B) Subsequent selective injection of Tc-MAA in LHA demonstrates no accumulation within spleen. RE of left lobe was safely carried out. CHA, common hepatic artery; GDA, gastroduodenal artery; LGA, left gastric artery; MAA, macroalbumin aggregate; LHA, left hepatic artery; RE, radioembolization.

modelling of tumor uptake (20).

Furthermore, it has been documented that embolized vessels/organs can revascularize quickly (6). Thus planning angiogram and SIRT should be performed in a narrow time frame. Confirming vascular optimization of the non-treated segment(s) can be advantageous in terms of savings in- time, dose, resources and limiting risks of extra-procedures.

Other applications may be in determining optimal treatment strategy for large volume tumors with several vascular supplies, for large volume tumors in various segments can have differing hypervascularity. Simultaneous administration of ⁹⁰Y and the injection of Tc-MAA into another lobe or segment for subsequent treatment planning may provide more accurate assessment of geographic uptake and shunt. In incidents where radiation doses to tumors are inferred from the partition model, this technique may provide a more accurate prediction of response rate and survival (21). Differential tumor burden and sequential treatment is not accounted for within the partition model for radiation dose to the lungs. RE with concurrent Tc-MAA injection could play a role in the confirmation of non-dose limiting exposure to the lungs in such cases. SPECT/CT images of Tc-MAA can also provide accurate 3D maps of MAA biodistribution at a lobar/segmental level. These quantitative 99mTc-MAA images can be used for 3D dosimetry calculations resulting in 3D maps of dose distribution arising from heterogeneous distribution

of activity in the liver (22,23). Recently, several studies investigating feasibility of ⁹⁰Y PET imaging reported very promising results in visualizing ⁹⁰Y microsphere distribution (24-27), even attempting activity quantification (28) and dosimetry (29). Quantitative segmental/lobar ^{99m}Tc-MAA SPECT/CT can be used as a validation tool for ⁹⁰Y PET.

The feasibility of TARE of a lobe/segments of a liver with simultaneous test angiogram/Tc-MAA of another has been demonstrated (15). The Tc-MAA SPECT/CT images in our two patients demonstrated pure Tc-MAA distribution. Exclusion of lower intensity BS radiation during SPECT/CT reconstruction of higher Tc-MAA gamma radiation resulted in elimination of scatter artifacts (15). We did not evaluate the distribution of ⁹⁰Y in our candidates. However, Ahmadzadehfar *et al.* have shown that accurate BS scan can be performed at 48 hours when "washout" of technetium has occurred (15). We believe that any robust future sequential segmental/lobar therapy protocol should include simultaneous Tc-MAA and Y-90 BS SPECT/CT.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE

uniform disclosure form (available at http://dx.doi. org/10.3978/j.issn.2218-676X.2014.01.01). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethical committee. Written informed consent was obtained from the patients.

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