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Quantification of Tc-99m macroaggregated albumin liver perfusion as a predictor of tumor response to intra-arterial therapy with yttrium 90 spheres

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ABSTRACT

Objectives: It remains unclear whether quantifying the pre-therapy tumor Technetium 99m macro aggregated albumin (Tc 99m MAA) localization can accurately predict the response to Yttrium 90 (Y-90) spheres therapy. Present studies are limited and with contradictory results. The aim of this study is to determine if quantification of Tc-99m MAA in hepatic tumor lesion(s) on pretherapy planning nuclear scan can predict the degree of tumor response after radioembolization using Y-90 Spheres.

Material and Methods: We retrospectively included patients with primary liver cancers or metastases who were treated with SirSpheres or TheraSpheres. All patients had a Tc-99m MAA scan with an average dose of 5.0mCi injected aseptically in either the right, left, or common hepatic artery. The patients were subsequently transferred for imaging using planar and single-photon emission computed tomography (SPECT) of the abdomen and planar images of the chest. We calculated geometric mean of radiotracer counts in the largest lesion in the lobe to be treated by placing same size region of interest (ROI) around the largest lesion on the anterior and posterior planar images. Subsequently, an irregular ROI around the liver or lobe to be treated were drawn to calculate the geometric mean of counts in the liver. The percent tracer accumulation in the largest lesion was calculated by dividing the geometric mean of counts in the largest lesion by the geometric mean of counts in the liver or lobe and multiplying by 100%. The size of this largest lesion was obtained on the most recent CT or magnetic resonance imaging (MRI) in cm in 2 directions prior to treatment with Y-90 Spheres. The extent of the response to Y-90 Spheres therapy was re-evaluated with 3 months follow-up MRI or CT by measuring the decrease in the largest lesion size. Comparison of the percent Tc-99 MAA count accumulation in the largest lesion on the pre-therapy scan with the reduction in size using anatomic imaging was performed.

Results: A total of 30 patients were included (16 hepatocellular carcinoma, eight colorectal, three breast, one neuroendocrine, one cholangiocarcinoma, and one cervical metastases). There were 14 patients in stable disease or progressive disease group (SD/PD gp) and 16 patients in partial response or complete response group (PR/CR gp). The median lesion size was 3.5 cm in the PD/SD gp versus 2.8 cm in the PR/CR gp ($P = 0.31$). Additionally, the median delivered Y90 Spheres treatment dose was 51.3 mCi in the PD/SD versus 43.2 mCi in the PR/CR gp ($P = 0.22$). The percent median largest lesion to liver concentration was 21.9% in the PR/CR gp versus 23.3% in the PR/CR gp ($P = 0.74$). There was no significant difference in percent Tc-99m MAA distribution in the largest liver lesion between the SD/PD gp and the PR/CR gp.

Conclusion: The degree of Tc-99m MAA localization in the largest tumor lesion in the liver compared to the remainder of the liver as quantified from planar images does not predict the response to Y-90 spheres therapy.

Keywords: Liver malignancy, Quantification of Tc-99m macro aggregated albumin scan, Response prediction, Y-90 pretherapy planning, Y-90 spheres therapy

INTRODUCTION

Radioembolization is becoming a widely available treatment option for liver masses, commonly due to hepatocellular carcinoma and metastatic disease. It is also accepted as a safe procedure with limited and tolerable side effects. Patients who are not candidates for surgical resection or liver transplantation are often candidates for targeted liver therapies. This is true for both intermediate-stage hepatocellular carcinoma and nonresectable vascular hepatic metastatic disease.[1,2] Options for intra-arterial therapy include chemoembolization transarterial chemoembolization or radioembolization. Yttrium 90 (Y-90) radioembolization has been found to be an effective treatment to downstage tumor burden, with a milder post-embolization syndrome compared to systemic chemotherapy or chemoembolization.[3]

Two agents available in the U.S for radioembolization are Y-90 SirSpheres (Y-90 SS) by SIRTeX Medical Incorporated, Woburn, Massachusetts, USA, and Y-90 TheraSpheres (Y-90 TS) by Boston Scientific, Marlborough, Massachusetts, USA. Y-90 is a pure beta emitter with a half-life of 64.2 h. The Y-90 can be integrated into glass beads (Y-90 TS) or embedded in polymer beads (Y-90 SS) and injected into vessels supplying liver tumors where high doses of beta radiation provide therapeutic effect.[4] Both radiopharmaceuticals are introduced in a trans-arterial fashion to deliver the dose preferentially to the liver malignant lesions because of their higher vascularity.

Prior to administration of Y-90 spheres, a treatment planning angiogram is performed. One key component is arterial injection of Technetium 99m macro-aggregated albumin (Tc-99m MAA) to evaluate for hepatic arterial shunting to other organs and to ensure adequate localization of Tc-99m MAA particles in malignant lesions as a predictor of Y-90 spheres localization.[5] It remains unclear whether quantifying the tumor Tc-99m MAA uptake can accurately predict the response to radioembolization therapy. Studies regarding this concept are limited with contradictory results.[6-13]

The goal of this study is to determine if quantification of Tc-99m MAA in the tumor lesion(s) can predict the degree of tumor response.

MATERIAL AND METHODS

After obtaining the institutional review board approval of this study, we retrospectively reviewed all patients who underwent Y-90 spheres treatments between May 2014 and November 2016. Patients with either primary liver cancers or liver metastases treated with intra-arterial injection of Y-90 SS or Y-90 TS in the same artery and location as the pre-therapy Tc-99m MAA mapping injections were included in the study.

All patients had a Tc-99m MAA pre-treatment planning scan with an average dose of 5.0 mCi (range 4.3–5.8 mCi) injected in either the right, left, or common hepatic artery according to the lobe to be treated. Scintigraphic anterior and posterior planar images of the abdomen were obtained for 500K counts followed by anterior and posterior images of the chest for the same time as the abdomen images. The images are acquired in a 256 × 256 matrix using low energy high-resolution collimator. The percent shunting to the lungs was quantified using geometric means of the counts in the chest divided by the geometric mean of the counts in the liver. We also evaluated the images visually for extrahepatic organ perfusion in the abdomen. Planar images were followed by the acquisition of single-photon emission computed tomography (SPECT) images of the abdomen using 360° arc, 64 stops/20 s/stop.

Quantitation of Tc-99m MAA counts was calculated using geometric mean counts in the largest lesion in the lobe to be treated. Same size squared regions of interests (ROI) around the largest lesion was placed both on the anterior and posterior images and counts were recorded from these ROIs to calculate the geometric mean. Subsequently, an irregular ROI around the liver or lobe to be treated was drawn to calculate the geometric mean counts in the liver. The percent tracer accumulation in the largest lesion was calculated by dividing the geometric mean of the counts in the largest lesion by the geometric mean of the counts in the treatment lobe or whole liver and multiplying by 100% [Figure 1]. In addition, the size of this largest lesion was obtained on the most recent computed tomography (CT) or magnetic resonance imaging (MRI) in cm in two directions prior to treatment with Y-90 Spheres.

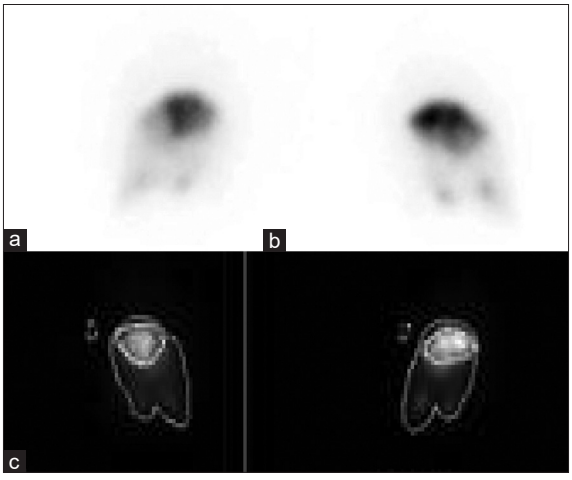

Figure 1: 63-year-old female presenting with abdominal pain and found to have hepatocellular cancer at the dome of the liver. Scintigraphic Tc-99m macro-aggregated albumin planar images, anterior view (a) and posterior view (b). Regions of interest around the lesion and the right lobe of the liver to obtain tracer uptake percentage (c).

The extent of response to Y-90 Spheres therapy was re-evaluated by 3 months follow-up anatomic imaging with MRI or CT by measuring the decrease in the size of the largest lesion. Comparison of Tc-99m MAA count accumulation in the largest lesion on the pre-therapy scan compared to tracer distribution in the remainder of the liver lobe with the percent reduction in size using anatomic imaging was performed. The patients were categorized according to their response to therapy, patients with partial or complete shrinkage of their lesions were categorized in the partial response or complete response group (PR/CR gp), and patients with no change in the size of their lesions or increased in the size of their lesions were categorized as no response group (PD/SD gp). At our institution, we use the modified RECIST criteria to evaluate for anatomic response on CT imaging as per Yaghmai *et al*. guidelines.[14]

RESULTS

A total of 30 patients were included in the study (19 males, 11 Females) with average age 63.7 years, (range 43–91). There were 16 patients with hepatocellular carcinomas and 14 patients with metastatic disease. Metastatic origins were from colorectal (8), breast (3), neuroendocrine (1), cholangiocarcinoma (1), and cervical metastases (1). There were 14 patients in stable disease or progressive disease group (SD/PD gp) and 16 patients in PR/CR gp.

There is no statistically significant difference in the percent of the Tc-99 MAA count uptake and accumulation in the largest lesion compared to the rest of the liver. In the SD/PD gp the median was 21.9% (14.2, 34.0) (mean ± SD [25.7 ± 18.3]). The median of the percent in the PR/CR gp was 23.3% (14.6, 33.3) (mean ± SD [25.5 ± 16.6]). *P*-value for medians is 0.7419, while *P*-value for means is 0.9733.

Smaller pre-therapy lesion size was noted in the PR/CR gp with a mean 3.4 ± 2.9 cm and median 2.8 cm (range 1.8–3.3 cm) than with the SD/PD gp which had a larger pre-therapy lesion size with a mean 4.7 ± 3.7 cm and a median 3.5 cm (range 2.2–6.3 cm). Examples of different responses with different lesion sizes are demonstrated in [Figures 2 and 3]. The difference in lesion size did not reach statistical significance with *P*-values 0.29 for mean lesion size and 0.31 for median lesion size.

Patients in the SD/PD gp received a higher mean Y-90 spheres dose with a mean ± SD of 61.2 ± 30.8 mCi and a median 51.3 mCi (range 38.9–88.9 mCi) than the PR/CR gp that had a mean ± SD 46.2 ± 26.2 mCi and a median 43.3 mCi (range 25.2–55.2 mCi) with a $P = 0.16$ for mean doses of the two groups and $P = 0.22$ for the median doses [Table 1].

DISCUSSION

Our study indicates that quantification of counts using geometric mean in the largest malignant liver lesion using the pre-therapy Tc-99m MAA scan does not predict the degree of response to treatments with Y-90 Spheres. Our study results add information in this controversial concept with contradicting results in the literature. For example, in the setting of colorectal liver metastasis, angiographic studies

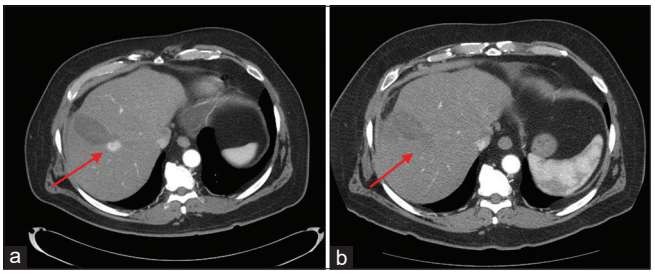

Figure 2: 61-year-old male presenting with fatigue and vague abdominal pain. Computed tomography (CT) images show enhancing liver lesion (red arrow) at baseline CT of the abdomen (a) and complete response post Y90 spheres treatment with no residual enhancement (b).

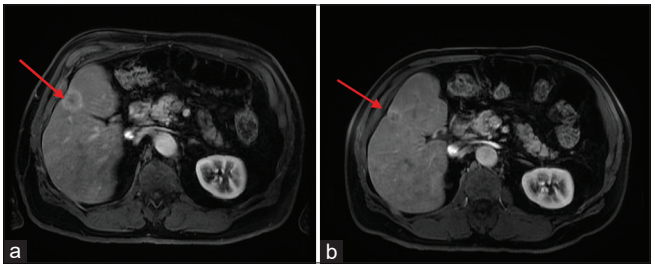

Figure 3: 72-year-old patient presenting with right upper quadrant abdominal pain. Computed tomography images show malignant liver lesion with peripheral enhancement (red arrow) at baseline (a) and partial response with decrease in diameter of peripherally enhancing metastatic lesion after Y-90 radioembolization (b).

Table 1: Comparison of lesion size, treatment dose and degree of Tc-99m MAA accumulation in the two treatment groups according to response status to Y90 radioembolization.

Variable	PD/SD Group (CI)* (14 patients)	PR/CR Group (CI) (16 patients)	*P*-value
Median of pretherapy largest lesion size (cm)	3.5 (2.2, 6.3)	2.8 (1.8, 3.3)	0.31
Median of Y-90 therapy dose (mCi)	51.3 (38.9, 88.9)	43.2 (25.2, 55.2)	0.22
Median percent lesion/liver Tc-99m MAA accumulation	21.9 (14.2, 34.0)	23.3 (14.6, 33.3)	0.74

PD: Progressive disease, SD: Stable disease, PR: Partial response, CR: Complete response, MAA: Macro-aggregated albumin

have shown vascularity was a poor predictor of response to Y-90 radioembolization.[6] Additional studies showed no correlation between Tc-99m MAA uptake and either Y-90 microsphere distribution or response to therapy.[7-9] Although we have used the planar images for Tc-99m MAA scan quantitation, other studies used SPECT images and have reached the same conclusion.[7] More recent studies in patients with hepatocellular carcinoma have shown that Tc-99m MAA uptake and Tc-99m MAA-based tumor dosing did correlate with a positive response to therapy, progression-free survival, and overall survival.[10-13] These studies used either SPECT-CT or dual tracer SPECT for better pre-therapy planning.

Differences between Tc-99m MAA particles size and Y-90 TS and Y-90 SS sizes result in different flow patterns. Van de Wiele *et al*. demonstrated that arterial flow to liver metastases is most pronounced in the hypervascular rim, followed by the smaller metastases, and finally within the central hypoperfused region of the larger metastases.[15] Because of the wide variability in size of Tc-99m MAA particles and because of the skimming effect, existing differences in flow between metastatic lesions of variable size are likely exaggerated on Tc-99m MAA scintigraphy when compared to Y-90 TS and Y-90 SS.

Our study also suggests that lesions <3 cm in size is more likely to respond to radioembolization. Although our results did not reach statistically significance difference, yet there was a trend towards better outcome with smaller lesions. This is supported by prior results from Kennedy *et al*., who found that the highest dose concentration and dose delivery is at the periphery of the lesion.[16] Extensive efforts and quantitative methods have been used to accurately evaluate response to therapy in malignant lesions, but there is a paucity of effort are directed towards predicting response to therapy prior to initiation of treatment plan.[17,18]

Limitations of our study include small sample size and the use of both Y-90 resin and glass spheres for the treatments. This is due to the retrospective nature of our study but the authors feel it is more representative of clinical outcomes from these treatments.

CONCLUSION

Quantification of Tc-99m MAA counts in tumor lesions using planar imaging is not sufficient to predict tumor response to Y-90 radioembolization for malignant liver lesions.

Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet 2003;362:1907-17.
2. Saxena A, Bester L, Shan L, Perera M, Gibbs P, Meteling B, *et al*. A systematic review on the safety and efficacy of yttrium-90 radioembolization for unresectable, chemorefractory colorectal cancer liver metastases. J Cancer Res Clin Oncol 2014;140:537.
3. Murthy R, Mutha P, Gupta S. Yttrium-90 radioembolotherapy for hepatocellular cancer. In: Hepatocellular Carcinoma: Targeted Therapy and Multidisciplinary Care. New York: Springer; 2011. p. 319-335.
4. Salem R, Thurston KG. Radioembolization with 90yttrium microspheres: A state-of-the-art brachytherapy treatment for primary and secondary liver malignancies. Part 1: Technical and methodologic considerations. J Vasc Interv Radiol 2006;17:1251-78.
5. Mosconi C, Cappelli A, Pettinato C, Golfieri R. Radioembolization with yttrium-90 microspheres in hepatocellular carcinoma: Role and perspectives. World J Hepatol 2015;7:738-52.
6. Sato KT, Omary RA, Takehana C, Ibrahim S, Lewandowski RJ, Ryu RK, *et al*. The role of tumor vascularity in predicting survival after yttrium-90 radioembolization for liver metastases. J Vasc Interv Radiol 2009;20:1564-9.
7. Ilhan H, Goritschan A, Paprottka P, Jakobs T, Fendler W, Todica A, *et al*. Predictive value of 99mTc-MAA SPECT for 90Y-labeled resin microsphere distribution in radioembolization of primary and secondary hepatic tumors. J Nucl Med 2015;56:1654-60.
8. Ulrich G, Dudeck O, Furth C, Ruf J, Grosser O, Adolf D, *et al*. Predictive value of intra-tumoral 99mTcmacroaggregated albumin uptake in patients with colorectal liver metastases scheduled for radioembolization with 90Y-microspheres. J Nucl Med 2013;54:516-22.
9. Wondergem M, Smits ML, Elschot M, de Jong HW, Verkooijen HM, van den Bosch MA, *et al*. 99mTc-macroaggregated albumin poorly predicts the intrahepatic distribution of 90Y resin microspheres in hepatic radioembolization. J Nucl Med 2013;54:1294-301.
10. Garin E, Lenoir L, Rolland Y, Edeline J, Mesbah H, Laffont S, *et al*. Dosimetry based on 99mTc-macroaggregated albumin SPECT/CT accurately predicts tumor response and survival in hepatocellular carcinoma patients treated with 90Y-loaded glass microspheres: preliminary results. J Nucl Med 2012;53:255-63.
11. Garin E, Rolland Y, Pracht M, Le Sourd S, Laffont S, Mesbah H, *et al*. High impact of macroaggregated albumin-based tumor dose on response and overall survival in hepatocellular

carcinoma patients treated with 90Y-loaded glass microsphere radioembolization. Liver Int 2017;37:101-10.
12. Grain E, Rolland Y, Laftont S, eldeline J. Clinical impact of (99m)Tc-MAA SPECT/CT-based dosimetry in the radioembolization of liver malignancies with (90)Y-loaded microspheres. Eur J Nucl Med Mol Imaging 2016;43:559-75.
13. Demirelli S, Erkilic M, Oner AO, Budak ES, Gunduz S, Ozgur O, *et al*. Evaluation of factors affecting tumor response and survival in patients with primary and metastatic liver cancer treated with microspheres. Nucl Med Commun 2015;36:340-9.
14. Yaghmai, V, Yaghmai V, Besa C, Kim E, Gatlin JL, Siddiqui NA, *et al*. Imaging assessment of hepatocellular carcinoma response to locoregional and systemic therapy. AJR Am J Roentgenol 2013;201:80-96.
15. Van de Wiele C, Maes A, Brugman E, D'Asseler Y, De Spiegeleer B, Mees G, Stellamans K. SIRT of liver metastases: Physiological and pathophysiological considerations. Eur J Nucl Med Mol Imaging 2012;39:1646-55.
16. Kennedy AS, Nutting C, Coldwell D, Gaiser J, Drachenberg C. Pathologic response and microdosimetry of (90)Y microspheres in man: Review of four explanted whole livers. Int J Radiat Oncol Biol Phys 2004;60:1552-63.
17. Gonzalez-Guindalini FD, Botelho MP, Harmath CB, Sandrasegaran K, Miller FH, Salem R, Yaghmai V. Assessment of liver tumor response to therapy: Role of quantitative imaging Radiographics 2013;33:1781-800.
18. Chung WS, Park MS, Shin SJ, Baek S, Kim Y, Choi J, *et al*. Response evaluation in patients with colorectal liver metastases: RECIST version 1.1 versus modified CT criteria. AJR Am J Roentgenol 2012;199:809-15.

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