Semi-Quantitative Analysis of Post-Transarterial Radioembolization ^{90}Y Microsphere Positron Emission Tomography Combined with Computed Tomography (PET/CT) Images in Advanced Liver Malignancy: Comparison With $^{99\text{m}}\text{Tc}$ Macroaggregated Albumin (MAA) Single Photon Emission Computed Tomography (SPECT)

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Received: 8 January 2015 / Accepted: 24 August 2015 / Published online: 14 September 2015
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Abstract

Objectives The purpose of this study is to evaluate the correlation between pretreatment planning technetium-99m ($^{99\text{m}}\text{Tc}$) macroaggregated albumin (MAA) SPECT images and posttreatment transarterial radioembolization (TARE) yttrium-90 (^{90}Y) PET/CT images by comparing the ratios of tumor-to-normal liver counts.

Methods Fifty-two patients with advanced hepatic malignancy who underwent ^{90}Y microsphere radioembolization from January 2010 to December 2012 were retrospectively reviewed. Patients had undergone $^{99\text{m}}\text{Tc}$ MAA intraarterial injection SPECT for a pretreatment evaluation of microsphere distribution and therapy planning. After the administration of ^{90}Y microspheres, the patients underwent posttreatment ^{90}Y

PET/CT within 24 h. For semiquantitative analysis, the tumor-to-normal uptake ratios in ^{90}Y PET/CT (TNR-yp) and $^{99\text{m}}\text{Tc}$ MAA SPECT (TNR-ms) as well as the tumor volumes measured in angiographic CT were obtained and analyzed. The relationship of TNR-yp and TNR-ms was evaluated by Spearman's rank correlation and Wilcoxon's matched pairs test.

Results In a total of 79 lesions of 52 patients, the distribution of microspheres was well demonstrated in both the SPECT and PET/CT images. A good correlation was observed of between TNR-ms and TNR-yp (rho value=0.648, $p<0.001$). The TNR-yp (median 2.78, interquartile range 2.43) tend to show significantly higher values than TNR-ms (median 2.49, interquartile range of 1.55) ($p=0.012$). The TNR-yp showed weak correlation with tumor volume (rho=0.230, $p=0.041$).

Conclusions The $^{99\text{m}}\text{Tc}$ MAA SPECT showed a good correlation with ^{90}Y PET/CT in TNR values, suggesting that $^{99\text{m}}\text{Tc}$ MAA can be used as an adequate pretreatment evaluation method. However, the $^{99\text{m}}\text{Tc}$ MAA SPECT image consistently shows lower TNR values compared to ^{90}Y PET/CT, which means the possibility of underestimation of tumorous uptake in the partition dosimetry model using $^{99\text{m}}\text{Tc}$ MAA SPECT. Considering that $^{99\text{m}}\text{Tc}$ MAA is the only clinically available surrogate marker for distribution of microsphere, we recommend measurement of tumorous uptake using ^{90}Y PET/CT should be included routinely in the posttherapeutic evaluation.

This manuscript has not been published before and is not under consideration for publication anywhere else and has been approved by all coauthors.

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Keywords Tc-99m-MAA · Radioembolization · Y-90 · Microsphere · Liver malignancy · PET scan · Single-photon emission computerized tomography

Introduction

Yttrium-90 (^{90}Y) microsphere transarterial radioembolization (TARE) is an alternative therapy option for unresectable liver malignancies, including primary and metastatic diseases. It is also considered a tool for bridging to resection, radiofrequency ablation, and liver transplantation [1]. Several reports have shown that TARE could be beneficial in the management of advanced liver malignancy [2–5].

Technetium-99m ($^{99\text{m}}\text{Tc}$) macroaggregated albumin (MAA) liver breakthrough imaging is a tool used for the evaluation of intrahepatic and possible extrahepatic distribution and for the estimation of lung shunt fraction. The intrahepatic tracer distribution and tumor-to-normal uptake ratio (TNR) are important for dose calculation especially when using a partition model. Many reports have suggested the correlation of $^{99\text{m}}\text{Tc}$ MAA dosimetry and intraoperative estimation of radiation doses [6–11]. After the injection of the microsphere, postembolization evaluation for the distribution of ^{90}Y microspheres is essential to predict possible complications and treatment response [12]. Bremsstrahlung imaging and/or SPECT of ^{90}Y microspheres is useful not only for the evaluation of posttreatment distribution of microspheres in the liver target volume, but also for the evaluation of possible extrahepatic spillage. The poor spatial resolution of the ^{90}Y microsphere bremsstrahlung image (FWHM 12.5 mm–20 mm) and long acquisition time and reconstruction, however, are major limitations for reliable posttreatment evaluation [13–16].

Recent studies report the feasibility of high-resolution ^{90}Y positron emission tomography/computed tomography (PET/CT) imaging using time-of-flight (TOF) technology and the possibility of the posttreatment evaluation of ^{90}Y microsphere distribution with ^{90}Y PET/CT [17–19].

The characteristics of $^{99\text{m}}\text{Tc}$ MAA used in treatment planning differ from those of the ^{90}Y microspheres used in the actual treatment [20]. Some researchers reported that the distributions of microspheres between $^{99\text{m}}\text{Tc}$ MAA and ^{90}Y microspheres are not identical. It has not been fully clarified whether $^{99\text{m}}\text{Tc}$ MAA SPECT accurately represents the true delivered ^{90}Y microsphere distribution [21]. In spite of this limitation, $^{99\text{m}}\text{Tc}$ MAA SPECT is the only possible method to evaluate the pretreatment dose distribution and therapy planning. Therefore, it would be important to compare and evaluate the correlation between pretreatment $^{99\text{m}}\text{Tc}$ MAA SPECT and high-resolution posttreatment images that can show the actual distribution of microspheres.

The purpose of this study is to compare the tumor-to-normal uptake ratios between $^{99\text{m}}\text{Tc}$ MAA SPECT pretreatment images and posttreatment ^{90}Y PET/CT images by semiquantitative comparison to evaluate whether the $^{99\text{m}}\text{Tc}$ MAA SPECT image can accurately predict the posttreatment distribution of microspheres.

Materials and Methods

Patients

We retrospectively reviewed the medical records of 52 consecutive patients who had undergone ^{90}Y microsphere TARE because of unresectable hypervascular hepatocellular carcinoma or metastatic tumors from January 2010 to December 2012. Only patients with preserved hepatic function, Child-Pugh score A or B, were included. Patients who presented with extrahepatic metastasis, hepatic failure, previous history of external beam radiation, or systemic chemotherapy were excluded. The ethics review boards of our hospital approved this retrospective study.

Pretreatment Planning Angiography

Pretreatment planning angiography was performed on all patients using the transfemoral approach for celiac, superior mesenteric, and selective hepatic arteriography and was done by an interventional radiologist. For preventing possible extrahepatic arterial spillage, coil embolization was performed in the gastroduodenal, right gastric artery and/or the cystic artery if a significant opportunity for the reflux and escape of microspheres into the GI tract, gall bladder, and pancreas could be considered. Subsequent CT scanning was performed while the intraarterial catheter was in place with injection of contrast media, and tumor and nontumor liver volumes were obtained using hepatic angiography CT images. Thereafter, 100–150 MBq of $^{99\text{m}}\text{Tc}$ MAA was injected via the planned target hepatic artery. If the target tumor was located in a segment, the artery corresponding to the segment was chosen as a planned target artery.

$^{99\text{m}}\text{Tc}$ Macroaggregated Albumin Imaging

After $^{99\text{m}}\text{Tc}$ MAA injection through the planned target artery, patients were brought to the nuclear medicine department and underwent an $^{99\text{m}}\text{Tc}$ MAA breakthrough image. We used a dual-head gamma camera (Infinia; GE Healthcare, Milwaukee, WI, USA) with low-energy, high-resolution collimators. The energy window was set at 140 ± 10 keV, and 120-s planar images were acquired for anterior and posterior projections. For the SPECT, 90 projections of the step-and-shoot mode in a 256×256 matrix were acquired in 360 degrees (10 s per step). The SPECT was analyzed on a dedicated Xeleris workstation (GE Healthcare, Milwaukee, WI, USA). We displayed the $^{99\text{m}}\text{Tc}$ MAA SPECT images in transverse, sagittal, and coronal format. The slice thickness of the transverse slice was 5 mm.

We evaluated the lung shunt, extrahepatic distribution, and tumor-to-normal liver ratio using a planar image for dose calculation with a partition model. Administration doses were calculated to achieve a tumoricidal dose of 120 Gy.

^{90}Y Microsphere Administration and PET/CT Imaging

A resin microsphere (SIR-Sphere, SIRTeX™, Sydney, Australia) was used as the medium of ^{90}Y . Within 24 h after microsphere administration, the patients were scanned using a PET/CT scanner (Gemini TF PET/CT, Philips Healthcare) with a conventional ^{18}F energy window (511 keV) and time-of-flight (TOF) mode including attenuation correction. According to the liver size of the patient, one or two imaging bed positions were selected. The imaging time was 10 min per bed. Reconstruction was performed with a TOF ordered-subset expectation maximization iterative (OSEM) algorithm at a 3-iteration and 33-subset protocol. Low-dose CT was used for attenuation correction of the PET emission data.

Image Analysis

We measured the tumor volume by using hepatic angiographic CT. Because we did not use an integrated SPECT/CT machine, the exact registration of tumor $^{99\text{m}}\text{Tc}$ MAA uptake with

anatomical images is a major concern in this study. The identification of the location of tumor uptake in $^{99\text{m}}\text{Tc}$ MAA SPECT was compared with the latest anatomical images, such as liver CT or MRI, by comparing the images slice by slice. The ratios of the tumor-to-normal liver parenchymal radioactivity uptake count were measured with ^{90}Y PET/CT (TNR-yp) and $^{99\text{m}}\text{Tc}$ MAA SPECT (TNR-ms), respectively. TNR values were calculated by dividing the mean count of the tumorous volume of interest (VOI) by the mean count of normal liver. To measure the radioactivity of a tumor, we manually drew a 2-cm-diameter spherical VOI on the highest uptake portion of the target tumor and calculated a mean count value. Radioactivity of normal liver parenchyma was obtained from the mean value of two or three spherical VOIs of 2 cm diameter at the same lobe with the tumor. Selection of the normal parenchymal count was done by placing VOIs at the proximity of the tumor (Fig. 1).

To minimize the subjectivity of selecting the normal parenchymal regions and interobserver variation, two researchers independently selected VOIs and measured TNR in 20 randomly selected patients, and we compared the kappa values.

Fig. 1 Example of measurement of the tumor-to-normal ratio on the ^{90}Y PET/CT image. In this ^{90}Y PET/CT image, a 2-cm-diameter spherical VOI is marked on a tumor lesion. The three numbers of separate 2-cm-

diameter VOIs were delineated on normal liver parenchyma. Mean counts of each regions were obtained, and the tumor to normal ratio was calculated

Statistical Analysis

The commercial statistical software, Medcalc software (MedCalc Version 12.2.1.0, MedCalc Software, Mariakerke, Belgium) was used for analyzing the data. For evaluating the correlation and comparison of the TNR values, Spearman's rank correlation and Wilcoxon's matched pairs tests were used.

Results

A total of 52 patients and 79 lesions were evaluated. Hepatocellular carcinoma (HCC) was the most frequent diagnosis ($n=42$, 81 %). Other diagnoses included cholangiocarcinoma ($n=3$, 5.8 %), metastasis from colon cancer ($n=4$, 7.7 %), adrenal cancer ($n=1$), prostate cancer ($n=1$), and neuroendocrine tumor ($n=1$) (Table 1). The data regarding the treated lesions are presented in Table 2.

The median TNR-yp was 2.78 with an interquartile range of 2.43, and the median TNR-ms was 2.49 with an interquartile range of 1.55. Significant correlation was observed with a moderate Spearman's rho value of 0.648 (p value<0.001) between the TNR-yp and TNR-ms (Fig. 2). The TNR-yp showed a significantly higher value than that of TNR-ms (p value=0.0118) (Fig. 3).

The median tumor volume was 187 ml with an interquartile range of 423.75 ml (Table 2). The TNR-yp of ^{90}Y PET/CT showed borderline correlation with tumor volume measured using angiographic CT ($\rho=0.230$, p value=0.0412) (Fig. 4).

Table 1 Patient characteristics

Clinical variable	Value
Patient number	52
Age (years)	58.25±11.62
Sex	
Male	38
Female	14
Diagnosis	
HCC	42
Colon cancer	4
Cholangiocarcinoma	3
ETC	3
Treated lobe of liver	
Both lobes	15
Right lobe	31
Left lobe	6
Injection dose (GBq)	
Mean	1.60±0.81
Median	1.59
Interquartile range	1.02

Table 2 Lesion characteristics

Clinical variable	Value
Total lesions	79
Tumor region	
Involving both lobes	5
Right lobe	46
Left lobe	28
Tumor volume (ml)	
Mean	317.31±382.58
Median	187
Interquartile range	423.75
TNR from SPECT	
Mean	2.90±1.62
Median	2.49
Interquartile range	1.55
TNR from PET/CT	
Mean	4.68±9.44
Median	2.78
Interquartile range	2.43

Weighted kappa values from measurement of 20 randomly selected patients by two researchers showed 0.710 and 0.764 for ^{90}Y PET/CT and $^{99\text{m}}\text{Tc}$ MAA SPECT, respectively.

Discussion

The role of the pretreatment imaging modality in the radioembolization is to simulate the distribution of the microsphere. An $^{99\text{m}}\text{Tc}$ MAA breakthrough scan can be used as a surrogate marker of the ^{90}Y microsphere [22, 23]. Furthermore, it can predict treatment response. Garin et al. [24]

Fig. 2 Correlation between the TNR value of $^{99\text{m}}\text{Tc}$ MAA SPECT and ^{90}Y PET/CT. Positive correlation was found between the TNR values of $^{99\text{m}}\text{Tc}$ MAA SPECT and ^{90}Y microsphere PET/CT ($\rho=0.648$, p value<0.001)

Fig. 3 Comparison of TNR values between ^{90}Y PET/CT and $^{99\text{m}}\text{Tc}$ MAA SPECT. The TNR value of ^{90}Y PET/CT showed a significantly higher value than that of $^{99\text{m}}\text{Tc}$ MAA SPECT (p value=0.012)

reported that $^{99\text{m}}\text{Tc}$ MAA SPECT/CT is useful for predicting the prognosis after ^{90}Y microsphere treatment. When a higher TNR is observed in $^{99\text{m}}\text{Tc}$ MAA SPECT/CT, the patient would show a better response, progression-free survival, and overall survival than those of the patients that have a lower TNR.

^{90}Y bremsstrahlung scintigraphy is a well-established method and can be easily performed after radioembolization [25]. When combined with SPECT imaging, bremsstrahlung SPECT/CT showed more accurate anatomical localization of ^{90}Y microspheres [26]. In spite of these characteristics of the bremsstrahlung image, the major drawbacks are the low spatial resolution and long image acquisition time, which would lead to lower tumor-to-normal ratios compared to the $^{99\text{m}}\text{Tc}$ MAA images [27]. Moreover, $^{99\text{m}}\text{Tc}$ MAA images are not considered to be ideal method to predict the actual distribution

Fig. 4 Correlation between tumor volumes and TNR values of ^{90}Y PET/CT. Tumor volumes measured by angiographic CT showed a borderline correlation with TNR values of ^{90}Y PET/CT ($\rho=0.230$, p value=0.0412)

of the ^{90}Y microspheres. Recent reports have postulated that there is a discordance between $^{99\text{m}}\text{Tc}$ MAA and ^{90}Y microsphere bremsstrahlung SPECT [12, 28, 29].

Other reports revealed that ^{90}Y PET/CT after ^{90}Y microsphere treatment has better image quality than ^{90}Y bremsstrahlung SPECT images [15, 26]. The higher resolving power of ^{90}Y PET/CT might have the potential to predict treatment responses more accurately. Ng et al. [30] conducted a study comparing $^{99\text{m}}\text{Tc}$ MAA and ^{90}Y PET/CT images for the dosimetry of five cases. They reported discordance between two images. This finding raised the need for more thorough investigation in comparing between $^{99\text{m}}\text{Tc}$ MAA SPECT and ^{90}Y PET/CT with larger series of cases.

The results of our study yielded a good correlation between the TNR values of $^{99\text{m}}\text{Tc}$ MAA SPECT and ^{90}Y PET/CT. The TNR obtained with ^{90}Y PET/CT showed constantly higher values as compared to the TNR values obtained with $^{99\text{m}}\text{Tc}$ MAA SPECT, with a moderate Spearman's ρ value of 0.648. We suggest two possible explanations for this. First, the positron imaging has a lower scatter effect than the SPECT images so that the PET image has a lower background activity [15]. Second, the particle characteristics of the $^{99\text{m}}\text{Tc}$ MAA and ^{90}Y microspheres are not exactly the same. $^{99\text{m}}\text{Tc}$ MAA particles have diameters in the range of 15 to 30 μm and a density of 1.3 g/cc, whereas ^{90}Y microspheres have diameters of 35 ± 5 μm and densities of 1.6 g/cc [31]. The larger size particles would lead to embolization of more proximal vessels and the smaller size particles would preferentially deposit in more distal regions, i.e., more proximity to the tumors [32]. Therefore, a wide variation of particle size could lead to embolization of wider areas of the liver.

We followed the method of Garin et al. [24] to obtain the TNR in the tumor and normal parenchyma. To overcome the subjectivity of measuring the normal parenchymal count, we applied two or three VOIs in the normal liver parenchyma at the proximity of each tumor and compared weighted kappa values derived from two independent researchers. The kappa values for TNR-yp and TNR-ms are 0.710 and 0.764, respectively, which showed substantial agreement.

The TNR values of ^{90}Y PET/CT showed weak positive correlation with the tumor volume measured by using angiographic CT ($\rho=0.230$, p value=0.0412). This means that more microspheres may accumulate in the larger tumors. In smaller tumors, however, due to the partial volume effect, the radioactivity could be measured to be lower than the actual value, and this could lead to a lower TNR value.

The pretreatment dosimetry during the procedure of ^{90}Y radioembolization is important for safe and adequate treatment as well as predicting the occurrence of complications and treatment response. $^{99\text{m}}\text{Tc}$ MAA SPECT showed a good correlation with ^{90}Y PET/CT in the TNR. Even though the $^{99\text{m}}\text{Tc}$ MAA SPECT image consistently shows lower values of TNR compared to ^{90}Y PET/CT, the $^{99\text{m}}\text{Tc}$ MAA SPECT is

the only clinically available method for prediction of microsphere deposition before actual injection. Therefore, measurement of tumorous uptake using ^{90}Y PET/CT should be included routinely in the posttherapeutic evaluation.

Conclusions

$^{99\text{m}}\text{Tc}$ MAA SPECT showed a good correlation with ^{90}Y PET/CT in TNR values, suggesting that $^{99\text{m}}\text{Tc}$ MAA can be used as an adequate pretreatment evaluation method. However, the $^{99\text{m}}\text{Tc}$ MAA SPECT image consistently shows lower values of TNR compared to ^{90}Y PET/CT, which means the possibility of underestimation of tumorous uptake in the partition dosimetry model using $^{99\text{m}}\text{Tc}$ MAA SPECT. Considering that $^{99\text{m}}\text{Tc}$ MAA is the only clinically available surrogate marker for distribution of microsphere, we recommend measurement of tumorous uptake using ^{90}Y PET/CT should be included routinely in the posttherapeutic evaluation.

Acknowledgments This study was partly supported by a research grant for R & D for Clinical and Translational Research, HI13C1611, Korea Health Industry Development Institute, Ministry of Health and Welfare, Republic of Korea.

Conflicts of Interest Seunghong Rhee, Sungeun Kim, Jaehyuk Cho, Jukyung Park, Jae Seon Eo, Soyeon Park, Eunsub Lee, Yun Hwan Kim, and Jae-Gol Choe declare no conflict of interest.

Ethical Statement The manuscript contains a statement that the study was approved by an institutional review board or equivalent and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All subjects in the study gave written informed consent or the institutional review board waived the need to obtain informed consent.

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