

The use of ^{90}Y -PET imaging in evaluation of ^{90}Y -microspheres distribution in the liver: initial results

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[Received 3 IV 2015; Accepted 3 VII 2015]

Abstract

BACKGROUND: Selective internal radiation therapy (SIRT) with ^{90}Y -microspheres infusion into the hepatic artery is a novel method for palliative treatment of primary and metastatic liver cancer. The post-procedural ^{90}Y dose estimation in the liver is very difficult because direct measurement of β particles is not possible with SPECT/CT. New methods are needed to assess the ^{90}Y -microspheres liver distribution. In the present paper we evaluate the ^{90}Y -PET for these purposes.

MATERIALS AND METHODS: A GE Discovery ST PET/CT scanner with a copper ring protected the gantry was used for images acquisition. For SPECT/CT imaging, a GE Infinia VCHWK4 with HEPG collimators was used.

The liver ^{90}Y -microspheres (SIR-Spheres, SIRTEX, Australia) dose distribution after selective internal radiotherapy treatment was evaluated in three patients (9 lesions in total). The activity of ^{90}Y -microspheres delivered into the liver ranged from 1.0 GBq to 2.2 GBq. The correlations between liver lesions detected with ^{90}Y -PET, $^{99\text{m}}\text{Tc}$ -MAA and ^{90}Y -bremsstrahlung were investigated and compared with CT images obtained before and after the procedure.

RESULTS: The mean T/N ratio was 2.7 in $^{99\text{m}}\text{Tc}$ -MAA, 2.3 in ^{90}Y -bremsstrahlung and 3.6 in ^{90}Y -PET. The mean ^{90}Y absorbed dose in tumor was 133 Gy, 112 Gy, and 187 Gy, respectively. The mean liver tissue radiation was 15.5 Gy. According to RECIST criteria, one PR (mCRC) and two SD were observed (mCRC and PC). Time to progression was 217 and 117 days in two patients with mCRC and 214 days in the patient with PC.

CONCLUSIONS: ^{90}Y -PET/CT images give crucial information regarding ^{90}Y -microspheres distribution and dosimetry and may serve as a predictor of efficiency of radioembolisation.

KEY words: radioembolisation, PET, yttrium-90

Nuclear Med Rev 2015; 18, 2: 92–96

Background

Selective internal radiation therapy (SIRT) with direct ^{90}Y -microspheres infusion into the hepatic artery is a novel, promising method for palliative treatment of primary and metastatic liver cancer [1, 2]. The most important problem associated with this therapy is to calculate an adequate activity of ^{90}Y -microspheres, which can destroy liver tumors while sparing healthy liver tissue [3, 4]. The $^{99\text{m}}\text{Tc}$ -MAA scans are performed in order to calculate a ^{90}Y dose and to predict a post infusion ^{90}Y -microspheres distribution profile between the

liver parenchyma and tumor compartments (the T/N ratio). The post procedural ^{90}Y dose estimation in liver is very difficult because direct measurement of β particles is not possible with SPECT/CT. Thus, ^{90}Y bremsstrahlung single-photon emission computed tomography/computed tomography (SPECT/CT) is performed to assess post-treatment ^{90}Y -microspheres distribution [3, 5]. In reality, there are two ways to calculate dosimetry after SIRT. The first one is the MIRDOSE equation based on the assumption of uniform ^{90}Y distribution between the tumor and liver tissue compartments [6]. The second one is Monte Carlo simulation in which SPECT/CT images are used to obtain the isodoses curves and histograms of the target liver lesions [7]. For improvement of SIRT treatment results a detailed knowledge about ^{90}Y -microspheres distribution within the liver is required [3]. This way patients prone to potential radiation-induced liver disease (RILD) or patients with non-curative tumor dose may be selected immediately after a SIRT procedure. In

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the present paper, we assessed the ⁹⁰Y-PET/CT method as an alternative for the ^{99m}Tc-MAA and ⁹⁰Y-SPECT (bremsstrahlung) images in clinical studies.

Materials and methods

Patient studies

Three patients (2 males, 1 female) were treated with ⁹⁰Y microspheres selective internal radioembolisation. All patients with unresectable liver metastases had adequate performance status and acceptable liver and renal function. Two patients had colorectal liver metastasis (mCRC) and one had metastasis from pancreatic cancer. A total of nine tumors was evaluated, 7 mCRC and 2 pancreatic cancer cases. The study was approved by Ethics Committee. All the patients were included in the study after signing a written informed consent.

Image evaluation

The patients were assessed before and after selective internal radioembolisation (SIRT) with computed tomography (CT). The whole liver volume, the liver tumors longest diameter and volume were collected. The ⁹⁰Y-PET studies were performed between 8 and 48 hours after resin microspheres administration into the liver. The Response Evaluation Criteria in Solid Tumors 1.1 (RECIST) were used to evaluate liver tumors response [8]. The correlations between the target liver lesions detected with ⁹⁰Y-PET, ⁹⁰Y-SPECT and ^{99m}Tc-MAA were investigated and compared with CT images obtained one month before and two or three months after procedure. The tumor to normal liver tissue ratio (T/N ratio) in ^{99m}Tc-MAA, in ⁹⁰Y-SPECT and in ⁹⁰Y-PET for each selected lesion was calculated. Based on the data, the absorbed dose for the liver parenchyma and for each target liver tumor was calculated using the internal dosimetry schema of the Medical Internal Dose (MIRD) Committee of Society of Nuclear Medicine [6]. The absorbed dose was calculated using the T/N ratio in ^{99m}Tc-MAA, in ⁹⁰Y-bremsstrahlung and in ⁹⁰Y-PET. The target lesion in the liver was described as a lesion with the longest diameter of minimum 10 mm and clearly visible on CT, ⁹⁰Y-PET, ^{99m}Tc MAA SPECT and ⁹⁰Y-SPECT. A GE Discovery ST PET/CT scanner with a copper ring protected the gantry was used for images acquisition. The ring thickness was 2 mm. The ring width was sufficient to cover the area of the detector (and equal to the axial FOV). The time of a single ⁹⁰Y-PET scan was 20 min (one patient) and 30 min (two patients). The role of the copper ring was to absorb the bremsstrahlung photons and to prevent saturations of the detectors. A GE Infinia VCHWK4 with HEPG collimators was used for SPECT/CT imaging. The energy window was 140 keV ± 100%.

SIRT procedure

The radioembolization procedure was conducted in line with guidelines approved by panel experts [3, 5].

Candidates for radioembolization therapy were qualified by a multidisciplinary team consisting of interventional radiologists, oncologists, nuclear medicine specialists and surgeons in line with strict inclusion and exclusion criteria, which were published previously [3, 5].

During the pre-treatment procedure, selective coil embolization of the gastroduodenal artery, right gastric artery and gallbladder artery were performed. The hepatopulmonary shunt, a potential

gastrointestinal leak and the tumor to liver ratio were assessed after SPECT ^{99m}Tc-MAA. An activity of 4mCi ^{99m}Tc MAA was administered into the hepatic artery. The Body Surface Area Method was used for the patients' ⁹⁰Y-microspheres dose calculation [5]. All the patients were treated with ⁹⁰Y biocompatible, not biodegradable SIR-Spheres microspheres (Sirtex Medical Inc., Australia). The ⁹⁰Y is a pure beta emitter with a liver tissue penetration of 2.5 mm and average energy of 0.94 MeV and a half-life of 2.67 days. The average resin microspheres' diameter is 35 ± 5 mm [3, 5]. The SIRT procedure was performed after superselective catheterization of hepatic artery branches by a slow, controlled ⁹⁰Y microspheres injection. All the patients received whole liver treatment. After the therapy, bremsstrahlung with SPECT and ⁹⁰Y-PET images were made to check ⁹⁰Y-microspheres liver dose deposition.

Results

All SIRT procedures were made with technical success. The whole dose prescribed for each patient was administered. There were no serious adverse events (SAE) observed. After the therapy, two patients had transient nausea, vomiting and mild pain in the liver region which required only symptomatic treatment. The details of clinical and treatment data are summarized in Table 1.

A total of nine tumor target lesions were evaluated with imaging methods. Taking into consideration the response rate for each solid tumor, two CR, two PR and three SD were observed for seven mCRC at first follow-up. For two pancreatic lesions SD was found. The ⁹⁰Y absorbed dose in the liver tissue ranged from 8.5 Gy to 25.8 Gy (mean 15.5 Gy). The mean T/N ratio was 2.7 in ^{99m}Tc-MAA, 2.3 in ⁹⁰Y-SPECT and 3.6 in ⁹⁰Y-PET. The mean ⁹⁰Y absorbed dose in tumor was 133 Gy, 112 Gy, and 187 Gy, respectively. All the tumors except one had sufficient (> 70 Gy) absorbed dose calculated using the T/N ratio revealed in imaging. Only one mCRC lesion (No 2) had absorbed dose lower than 70 Gy (based on MAA T/N ratio). In this case a complete response was confirmed in the first follow-up. The image response parameters, the T/N ratio and the estimated (MIRD) dose calculations for each tumor are summarized in Table 2.

Table 1. Patients' data

Parameter	Patient 1	Patient 2	Patient 3
Gender	Woman	Man	Man
Age	49	61	38
Liver metastases	mCRC	mCRC	Pancreatic
Number	4	3	2
Diameter [cm]	21 (10–36)	54 (22–85)	98 (80–117)
Cancer volume [ml]	36	420	339
Liver volume [ml]	920	2376	1689
Delivered dose of ⁹⁰ Y [GBq]	1.0	1.9	2.2
AE			
SAE	0	0	0
Mild (nausea, pain)	1	1	0
RECIST			
First follow-up	PR	SD	SD
Time to progression (days)	217	117	214

Table 2. The T/N ratio and estimated adsorbed dose for each tumor

No	TUMOR	SIZE [mm]	T/N 1	T/N 2	T/N 3	AD 1	AD 2	AD 3	RECIST
1	mCRC	36	1.6	1.9	3.8	85	101	201	PR
2	mCRC	20	1.2	1.4	3.4	63	74	174	PR
3	mCRC	20	1.4	1.8	4.2	74	95	223	CR
4	mCRC	10	1.7	1.4	2.5	90	74	132	CR
5	mCRC	79	3.2	2.5	4.0	174	95	152	SD
6	mCRC	75	2.9	2.4	3.9	121	91	148	SD
7	mCRC	32	5.0	2.9	3.8	110	110	144	SD
8	PC	80	5.7	3	2.8	359	189	226	SD
9	PC	117	1.9	3.6	4.4	120	182	283	SD

T/N 1 — T/N in MAA, T/N 2 — T/N in ^{90}Y SPECT, T/N 3 — T/N in ^{90}Y -PET, AD 1 — adsorbed dose in MAA, AD 2 — adsorbed dose in ^{90}Y -SPECT, AD 3 — adsorbed dose in ^{90}Y -PET

Discussion

In the recent years, there has been a growing interest observed in the use of ^{90}Y microspheres for regional liver tumor therapy. Promising treatment results such as improvements of time to progression, median overall survival and safety profile are an encouragement for further development of this method [1, 9–11]. Although we are aware that one of the main limitations of our study is a small group of patients, we can also confirm high efficiency of this therapy. We noticed one partial response and two stable diseases in our study. The time to progression ranged from 117 to 217 days in colorectal metastases and 214 days in pancreatic cancer metastases. There are no serious adverse events associated with the therapy. In our opinion, there is still room for improvement of results in this treatment. The first way is to treat patients as soon as possible. At present, results of prospective randomized multicenter trials are expected (i.e. SIRFLOX), in which radioembolisation in first line treatment is evaluated [12]. The second way is to improve knowledge on ^{90}Y -microspheres liver distribution, especially ^{90}Y liver dosimetry. The background for intra-arterial ^{90}Y -microspheres therapy is a special type of vascular anatomy of the liver. The majority of liver tumors' blood supply originates from the hepatic artery branches, then the portal vein (about 80–100% of their supply for tumors >3 mm) [13]. It is estimated that a dose higher than 70 Gy is required to destroy most of the liver tumors. High ^{90}Y -microspheres concentration within liver cancer leads to their destruction by way of ionizing radiation and embolization. The former has a crucial importance for the therapy [14]. The main limitation of radioembolisation is low liver tissue tolerance to radiation, with a possibility of serious adverse events after irradiation higher than 30 Gy [14, 15]. In our study, the radiation of the liver was estimated from 8.4 Gy to 25.8 Gy (mean 15.5 Gy) based on the MIRD formula and no serious side effects were reported (i.e. RILD). To predict post-infusion ^{90}Y -microspheres' distribution within the liver parenchyma $^{99\text{m}}\text{Tc}$ -MAA scans are taken. Nevertheless, the real distribution of the ^{90}Y -microspheres might be different from the $^{99\text{m}}\text{Tc}$ -MAA because of a higher albumin diameter and intra-hepatic blood flow variations [3, 5, 16]. After the therapy, ^{90}Y -bremsstrahlung single-photon emission computed tomography/computed tomography (SPECT/CT) is performed to evaluate the real distribution of ^{90}Y -microspheres [3, 5]. Unfortunately, insufficient spatial resolution of ^{90}Y -bremsstrahlung images is a main limitation of this method and can lead to inaccurate evaluation of ^{90}Y -microspheres dis-

tribution [17]. To evaluate intra-hepatic ^{90}Y administration some authors use a $^{99\text{m}}\text{Tc}$ -MAA injection immediately after a SIRT procedure [18]. However, in our opinion, embolic effects of resin microspheres may lead to inaccurate $^{99\text{m}}\text{Tc}$ -MAA deposition in the liver and conclusions based on this method may therefore be misleading. A novel approach to assessment of radioembolisation effects consists in taking ^{90}Y PET images [19, 20]. Although ^{90}Y is traditionally considered a pure β -emitter, its decay has a minor branch to the 0^+ first excited state of ^{90}Zr at 1.78 MeV. De-excitation consists in emission of either a conversion electron or an internal e^-e^+ pair creation. It happens in 32 out of 1 million decays and might be imaged with PET [20, 21]. We assessed the ^{90}Y -PET method as an alternative for the $^{99\text{m}}\text{Tc}$ -MAA and bremsstrahlung SPECT/CT images in clinical studies. We performed a ^{90}Y -PET test between 8 to 24 hours after SIRT and we did not observe deterioration of image quality over time. As the ^{90}Y half-life is 2.67 days, the PET scan should be taken within this time limit in our opinion [3, 13, 21]. The time of a single PET imaging was 20 min in one case and 30 min in the next two patients. To obtain better image results we suggest taking a PET scan lasting 30 min for an administered dose ranging 1.2–2.2 GBq of ^{90}Y -microspheres. In order to protect the gantry detectors, we used a copper ring to absorb photons of low energy and we observed that 2 mm thickness of the ring is sufficient to achieve this aim. However, some authors do not use any protection and they have not noticed its saturation with total activity of 2.0 GBq. Yet, sometimes a higher dose may be needed for a patient's treatment and we suggest more caution in such cases [22].

We noticed a similar T/N ratio calculated using $^{99\text{m}}\text{Tc}$ -MAA and bremsstrahlung SPECT/CT images for most liver tumors and considerable differences when we compare them with the ^{90}Y -PET-revealed T/N ratio. The mean T/N ratio was 2.7 in $^{99\text{m}}\text{Tc}$ -MAA, 2.3 in ^{90}Y -SPECT and 3.6 in ^{90}Y -PET. The mean ^{90}Y absorbed dose in tumor was 133 Gy, 112 Gy, and 187 Gy, respectively. It leads also to significant differences between the calculated ^{90}Y liver tumors' absorbed doses. We can see doses, which are 2–3 times higher when estimated with the ^{90}Y -PET T/N ratio. It means that the dose required to destroy the tumor (approximately 70–90 Gy) is significantly exceeded [14, 15]. According to our study, tumor absorbed doses calculated with ^{90}Y -PET ranged from 144 Gy to 283 Gy, but when we consider tumor treatment results we can see mostly stable disease in overall response rate. Therefore, the absorbed doses calculated on the basis of the $^{99\text{m}}\text{Tc}$ -MAA and bremsstrahlung SPECT/CT ratio ranging from 64 Gy to 183 Gy (except tumor

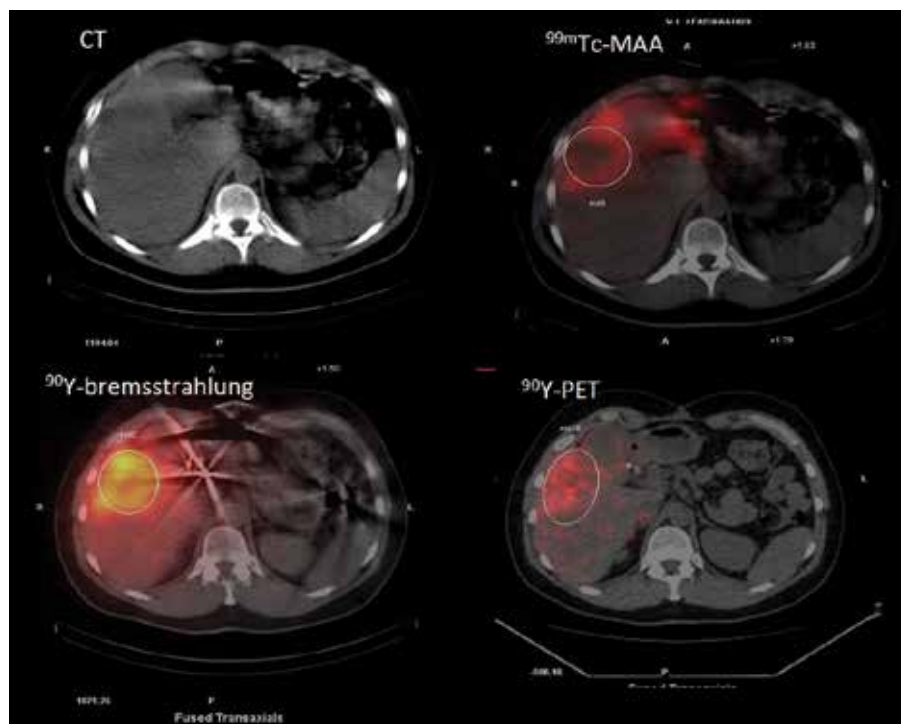


Figure 1. The same liver lesion in CT, $^{99\text{m}}\text{Tc}$ -MAA, ^{90}Y -bremsstrahlung and ^{90}Y -PET scans

No. 8) seem to be more close to reality. One of the explanations of these results may be lower sensitivity of ^{90}Y -PET/CT compared to ^{90}Y -bremsstrahlung [20]. Thus, to assess the real T/N ratio based on ^{90}Y -PET/CT, further studies are necessary (Figure 1). On the other hand, its resolution and contrast are much better and ^{90}Y -PET/CT imaging may be used not only to detect liver lesions after radioembolisation, but also to distinguish a necrosis area within solid tumors. Better resolution of this method may help to find out leaks of ^{90}Y microspheres to the digestive tract in our opinion [17, 20]. From our point of view, the possibility of estimation of radiation dose in liver lesions is very interesting.

Conclusion

^{90}Y -PET/CT images give crucial information regarding ^{90}Y -microspheres distribution and dosimetry and may serve as a predictor of efficiency of radioembolisation.

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