# Dosimetry of 177Lu-DOTATOC First Circle Treatment in Patients With Advanced Metastatic Neuroendocrine Tumors: a Pilot Study in China

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# Dosimetry of $^{177}$Lu-DOTATOC first circle treatment in patients with advanced metastatic neuroendocrine tumors: a pilot study in China

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**Running Title:** Dosimetry of $^{177}$Lu-DOTATOC Treatment in Metastatic neuroendocrine tumors

**[Abstract] Objective**: The aim of this study was to calculate the dosimetry of $^{177}$Lu-DOTATOC in the first circle of peptide receptor radionuclide treatment (PRRT) in patients with advanced neuroendocrine tumors (NETs). **Patients and Methods**: Eight patients (4 female, 4 male) with NETs were enrolled in this study. All these patients with unresectable primary lesion and multiple metastasis received $^{177}$Lu-DOTATOC treatment with a single activity of 1.59-3.49 GBq (43.1-94.2 mCi) and underwent a series of whole-body planar scan at 0.5 h, 24 h, 48 h and 72 h and SPECT/CT scan at 24 h after injection. The region of interest (ROI) was drawn on the primary and metastatic lesion, the mediastinum served as control area. Therefore, the ratio of tumor-to-mediastinum (T/NT) was also calculated. The Hermes hybrid viewer dosimetry module together with OLINDA/EXM 2.0 was used to determine absorbed doses of organs and tumors. **Results:** No significant changes in both laboratory test was found after $^{177}$Lu-DOTATOC treatment, including renal function and blood cell analysis ($F$=0.047-1.062, $P$=0.364-0.959). Physiological uptake of $^{177}$Lu-DOTATOC was seen in the liver, the spleen and the kidneys. Focal uptake of $^{177}$Lu-DOTATOC was found in the tumors including primary tumors and metastatic lesions, the ratio of T/NT was 39.45 ± 28.83. The residence time of $^{177}$Lu-DOTATOC was 0.82 ± 0.12 h for left kidney, 0.80 ± 0.15 h for right kidney, 1.35 ± 0.89 h for spleen, 1.80± 2.70 h for tumors, and 30.21 ± 11.29 h for total body. Organs with the highest absorbed doses per injected activity were tumors (1.2936 ± 0.8625 mGy/MBq), spleen (0.4608 ± 0.4084 mGy/MBq), and kidneys (0.3843 ± 0.1120 mGy/MBq). The mean effective dose was 0.0392 ± 0.0158 mSv/MBq with the range of 0.0158-0.0674 mSv/MBq. In addition, Photon cross-irradiation was found to reach 19.46 % in adrenals, whereas photon can contribute less than 3% of the kidneys' total dose. **Conclusion:** This study demonstrates that absorbed dose in the kidneys and spleen are relatively lower, whereas the tumor shows longer retention time and higher internal radiation absorbed dose in PRRT. PRRT is a well-tolerated treatment strategy. $^{177}$Lu-DOTATOC SPECT /CT serves as independent predictor for the evaluation of response to PRRT, which contributes to predict the response to PRRT and the related adversity.

**Keywords**: $^{177}$Lu-DOTATOC; PRRT; Dosimetry; Neuroendocrine tumor

## INTRODUCTION

Neuroendocrine tumors (NETs) are a group of heterogeneous tumors originating from endocrine cells in different organs [1]. The majority of NETs express a high density of somatostatin receptors (SSTR) at their cell surfaces with different subtypes [2], such as $SSTR_{1-5}$, which is ideal target in targeted therapeutic applications. Peptide receptor radionuclide therapy (PRRT) with radiolabeled somatostatin analogue has become a promising treatment option in the management of patients with unpourable or metastatic NETs [3,4]. So far, the most extensively used $^{177}$Lu-labelled somatostatin analogue is [$^{177}$Lu-DOTA]0-D-Phe1-Tyr3-octreotate ($^{177}$Lu-DOTATATE) in the world [5,6]. Similar to DOTATATE, [DOTA]0-D-Phe1-Tyr3-Octreotide (DOTATOC) also has a high binding affinity to $SSTR_2$, revealing that the $^{177}$Lu-DOTATOC should be an alternative treatment option for PRRT. $^{177}$Lu-DOTATOC for PRRT was first reported by Forrer et al [7]. in patients with relapsed NETs. Several retrospective studies reported that $^{177}$Lu-DOTATOC was significantly less myelotoxicity than $^{90}$Y-DOTATOC, and effectively reduced specific symptoms of the neuroendocrine syndrome without significant side-effects in progressive NETs [8].

Recently, $^{177}$Lu-DOTATOC shows a particular therapeutic index-large interpatient variability in tumor and organ uptake [9], which prompted us to further evaluate the dosimetry of this compound. Patient-specific dosimetry provides absorbed dose information in organs and tumors, which is utilized to assess the risk of critical organ toxicity (kidneys and bone marrow) and predict the therapeutic response in the following treatment cycles [10]. Various dosimetry methods have been proposed for investigating absorbed doses of $^{177}$Lu-labelled PRRT [11], but most of the previous studies were based on planar imaging and conjugate-view activity quantification, leading to an overestimated absorbed dose in the organs with tumors or overlapping with tumors. The clinical dosimetry protocols with $^{177}$Lu single photon emission computed tomography (SPECT) dosimetry proved to be more accurate and reliable as mentioned before [12,13]. Although SPECT/CT imaging consumes a long acquisition time and requires sophisticated algorithms for activity quantification, SPECT/CT fused images provide insight into organ-specific 3D activity distribution, which can then be used as input data for voxel dosimetry. To make dosimetry calculation available in the

clinical, a simplified dosimetry procedure was proposed according to the medical internal radiation dose (MIRD) scheme including four serial whole-body planar scans and one SPECT/CT imaging [14]. This procedure was found to be a compromise between the calculation accuracy and practical conditions, ensuring the doses estimation in the daily clinical routine with a reasonable effort and within an acceptable collecting time.

For the last five years, $^{177}$Lu-DOTATATE for PRRT has been established only in the fewer clinical medicine centers or hospitals in the China [15-17]. To our knowledge, there are fewer study which reported $^{177}$Lu-DOTATOC PRRT and dosimetry calculation in Chinese patients. Herein, we explored the dosimetry of $^{177}$Lu-DOTATOC treatment in the Chinese patients with advanced metastatic NETs with a hybrid 2D/3D activity quantification technique, and the safety and toxicity were also addressed by laboratory examination and renal function.

## MATERIALS AND METHODS

### Patients

Eight patients (4 men, 4 women) with inoperable NETs were consecutively enrolled in this prospective study， who referred to Nanjing first hospital from November 2016 to March 2018 (Table 1). The study was approved by the institute ethical review board of Nanjing medical university, Nanjing first hospital (KY20171208-02) and performed in accordance with the principles of the declaration of Helsinki and national regulations, and all patients signed an informed consent form before entering. The mean age of the patients was 53.12 ± 12.02 years (range, 24-64 years). The patient weight was 63.00 ± 6.96 kg (range, 55-78 kg), and the height was 1.70 ± 0.07 m (range, 1.62-1.85 m).

All patients underwent $^{68}$Ga-DOTANOC PET/CT for evaluation tumor somatostatin receptors expression in the primary tumor and metastasis before treatment. Five patients were diagnosed as pancreatic NETs, three patients were diagnosed with rectal NETs with liver metastasis. All patients were administered $^{177}$Lu-DOTATOC in 6-8 weeks intervals in one to five cycles. In this study, injected activity of 2.33 ± 0.52 GBq (1.59 – 3.49 GBq) of $^{177}$Lu-DOTATOC in the first cycle was administered in 30 minutes infusion and received amino acids for kidney protection (2.5 % lysine and 2.5 % arginine in 1 L of 0.9 % NaCl, infusion rate 250 mL/h).

**$^{68}$Ga-DOTA-NOC PET/CT**

PET data acquisition was performed with a dedicated hybrid uMI 780 PET/CT scanner (Shanghai United Imaging Healthcare, China) 45-60 minutes after receiving an intravenous injection of 111-148 MBq (range, 3–4 mCi) of $^{68}$Ga-DOTANOC. PET images were reconstructed by ordered-subset expectation maximization (OSEM) with 2 iterations, 20 subsets, time of flight (TOF), point spread function (PSF) and the CT-based attenuation correction.

**$^{177}$Lu-DOTATOC radiolabeling and quality control**

$^{177}$Lu-DOTATOC was synthesized into a specific activity of 0.05 GBq/ug DOTATOC, using carrier-free lutetium-177 (ITM, Garching, Germany) and DOTATOC (Bachem, Bubendorf, Switzerland) according to a previously published procedure [17]. The product (radiochemical purity >98%) was dissolved in 0.9 % saline and passed through a 0.22-um filter to ensure sterility. The quality control was highly determined using analytical reverse-phase high-performance liquid chromatography (HPLC). Only the radiochemical purity was more than 99% will be used in the clinical.

**SPECT/CT imaging**

The acquisition protocols consisted of a series of whole-body planar scan at 0.5 h, 24 h, 48 h and 72 h and one SPECT/CT scan at 24 h after injection. All images were obtained with a dual-head Discovery NM 670 SPECT/CT system (GE healthcare, America) with medium energy general purpose collimators that have 20 % energy window width centered symmetrically over the 208 keV and 113 keV peak energy of $^{177}$Lu [18]. The scatter correction windows corresponding to the lower peak received widths of 15 % and those of the upper peak was set to 20 % adjacent to each peak. The whole-body images were acquired with a 256 × 1024 matrix at a scan speed of 20 cm/min.

SPECT scanning of the upper abdomen of patients was performed using a step and shoot mode with 120 frames at 30 s per frame following by a low dose CT. SPECT images were reconstructed using Xeleris station (version 2.0 GE healthcare) with the OSEM algorithm. The reconstruction setting was as follows: 8 subsets and 4 iterations, Hanning filter with a cutoff at 0.85 cycles/cm, triple energy window and CT attenuation correction based on automatically generated attenuation map created from a 4-slice CT

scanner (GE Discovery NM 670, 140 keV, 3.0 mA, half rotation).

**Dosimetry calculation**

The dosimetry calculation of $^{177}$Lu-DOTATOC was performed with a software package called Hermes Internal Radiation Dosimetry (HIRD) which was developed according to the European Association of Nuclear Medicine Dosimetry Guidance [19]. The HIRD was implemented to run under the HERMES data analysis applications 3.0 (HERMES, Stockholm, Sweden).

Briefly, the HIRD workflow was as follows: Firstly, the software was launched with inputted information from both planar and SPECT/CT images at each time point. Secondly, the SPECT study was co-registered to the whole-body planar image at the time point closest to the time point of the SPECT/CT. Thirdly, the activity in regions of interest (ROIs) / volumes of interest (VOIs) was drawn in critical organs on the planar images and SPECT/CT image respectively, and a smaller ROI was also drawn outside of the organs for background subtraction. The activity concentration measured on the SPECT was used to adjust the planar time-activity curves. Fourthly, curves of the fraction of injected activity against the time of each organs post-administration were determined by fitting the data using a bi-exponential model, and the residence time was calculated using the trapezoidal method. Finally, the total absorbed dose distribution can be calculated on OLINDA/EXM 2.0 software with the phantom, isotope and kinetic data, after the calibration procedure using "first whole-body (pre-excretion)" technique that equate the total counts at the first time to the activity in the patient at a given time point, and the corresponding effective dose was calculated using new tissue weighting factors based on international commission on radiological protection publication 103 (ICRP103), which were shown in the equation (1) and (2). A standard radioactive source with a well-determined $^{177}$Lu activity placed near the bottom of feet on the whole-body planar images was used to normalize the time points and provide quality control of the images acquired.

$$\mathrm{D} = A_0 \times \tau_s \times S \qquad (1)$$

$$E = D \times W_R \times W_T \qquad (2)$$

Where D is the absorbed dose, $A_0$ is the administered activity, $\tau_s$ is the time-integrated activity coefficient, $S$ is the radionuclide specific absorbed dose rate per unit of activity

in target region delivered by source region. $E$ is the effective dose, $W_R$ is the radiation weighting factor for radiation type $R$, $W_T$ is the tissue weighting factor for organ $T$.

**Safety and toxicity observation**

Antiemetic therapy with ondansetron and dexamethasone was performed in prior to the administration of PRRT, and intravenous furosemide was given after $^{177}$Lu-DOTATOC injection for enough hydration. Physical examination was performed at each cycle and 1-3 months after the treatment, and vital signs, electrocardiography, blood test, biochemistry and immunological exam were taken. Renal function was evaluated prior to each cycle and after restaging. The glomerular filtration rate (GFR) was estimated using technetium-99m diethylenetriamine pentaacetic acid ($^{99m}$Tc-DTPA), and effective renal plasma flow (ERPF) renography was determined with technetium-99m ethylenedicysteine ($^{99m}$Tc-EC).

**Statistical analysis**

Quantitative data were expressed as means ± standard deviations, range and median. The difference among groups was compared with the one-way analysis of variance test. A paired t test was used to compare the intergroup difference when the data have the normal distribution, otherwise the non-parametric test was used. In all analyses, $P$ <0.05 was considered to indicate statistical significance.

## RESULTS

**Safety evaluation**

During the entire course of $^{177}$Lu-DOTATOC administration and 3 months follow-up, no remarkable side effects or adverse symptoms were observed. No clinically significant changes in physical examination, electrocardiography parameters, and immunology were found.

At baseline, 1 month and 3 months after $^{177}$Lu-DOTATOC treatment, slight changes of hematology parameters occurred in most patients in 1 month, but recovered spontaneously in 3 months. Additionally, no significant changes were observed in white blood count ($F$=0.385, $P$=0.685), neutrophils count ($F$=0.062, $P$=0.940), red blood count ($F$=0.148, $P$=0.336), hemoglobin ($F$=0.542, $P$=0.589), and platelet count ($F$=1.062, $P$=0.364). Furthermore, hepatotoxicity marker data was also collected, there

were no significant statistical difference in alanine aminotransferase ($F$=0.192, $P$=0.827), aspartate transferase ($F$=0.550, $P$=0.585), total bilirubin ($F$=0.312, $P$=0.735), urea ($F$=0.436, $P$=0.652), and serum creatinine ($F$=0.047, $P$=0.959). Last but not least, neither glomerular filtration rate ($F$=0.188, $P$=0.830) nor effective renal plasma flow ($F$=0.172, $P$=0.843) for renal function evaluation showed significant statistical difference.

**Pharmacokinetics**

$^{177}$Lu-DOTATOC reached the maximal level in bladder and tumors at 0.5 h after injection. The normal tissues including liver, spleen, and kidneys showed moderate uptake of $^{177}$Lu-DOTATOC, whereas no significant uptake was observed in the blood circulation (Fig. 2A). $^{177}$Lu-DOTATOC showed fast clearance in kidneys and spleen over time, while the tumor uptake was in a relatively slow decline (Fig. 2).

Since the whole-body counts from the first planar scan (with full bladder) represent the total administered activity, whole-body kinetics start with an initial uptake of 100 %, hereby the other activities at other time points were expressed as the percentage of injected activity [IA (%)][20]. These percentages were used to describe the uptake of radioactivity about temporal changes. The IA (%) of target organs and tumors in patients treated with $^{177}$Lu-DOTATOC was given in figure 3. The maximum uptake (presented as IA (%)) of $^{177}$Lu-DOTATOC was found on the first measurement which was 2.07 ± 0.92 (range, 1.05-4.24) for left kidney, 1.81 ± 0.92 (range, 0.83-1.08) for right kidney, 1.84 ± 0.80 (range, 0.60-3.11) for spleen, 1.59 ± 1.03 (range, 0.57-3.99) for tumors. The distribution pattern of time-activity curves for all organs and tumors showed a rapid decline during the first two scans, then appeared a slower decrease tendency with time prolonged. At 24 h or so, the mean IA(%) was decline to be 22.15 ± 7.60 (range, 10.35-35.89,) for total body, 0.77 ± 0.24 (range, 0.38-1.08) for left kidney, 0.74 ± 0.22 (range, 0.35-1.08) for right kidney, 0.76 ± 0.49 (range, 0.1-1.7) for spleen, 1.15 +10.75 (range, 0.32-3.33, median, 2.07) for tumors. The activity in the left kidney was almost equal to those in the right kidney due to the correction of SPECT/CT, and the uptake in the spleen was comparable with kidneys in the whole four days. Moreover, there was still more than 10 % of radioactivity retained in the whole body (11.98 %) after 72 h, and only less than 0.5 % activity was retained in the kidneys (0.405 %,

0.403 %) and spleen (0.441 %), which was lower than that of tumors (0.816 %). Note that, in terms of IA (%) dispersion, the standard deviation was comparable to the mean value in spleen and tumors at different time points. The time-activity curves of normal organs and tumors were all fitted to a biexponential function, which was used to the calculated residence time of $^{177}$Lu-DOTATOC according to MIRD schema. The results were shown in table 2.

**Dosimetry**

On the basis of the quantification of serial planar and SPECT/CT images, the absorbed dose and effective dose for $^{177}$Lu-DOTATOC were calculated using OLINDA/EXM 2.0 software. Among individual target organs, the tumors received the highest absorbed dose per injected activity (1.2936 ± 0.8625 mGy/MBq) with a range of 0.2730-3.2340 mGy/MBq, secondly in spleen (0.4608 ± 0.1590 mGy/MBq) with a range of 0.0632-1.1798 mGy/MBq, thirdly in kidneys (0.3843 ± 0.1120) mGy/MBq with a range of 0.2770-0.6452 mGy/MBq (table 3), thus the corresponding total absorbed doses were calculated to be 3258.1 ± 2374.3 mGy, 868.4 ± 996.1 mGy, and 875.5 ± 295.5 mGy, respectively. The ratio of photo-to-total absorbed dose was shown in Figure 4.

As shown in Figure 5, NET lesions were identified with $^{68}$Ga-DOTANOC PET/CT imaging. The lesions showed a high local accumulation of radioactive signal at 45 minutes after injection, and the average $SUV_{max}$ of tumors was 39.62 ± 24.82 (range, 8.17-115.38, median, 32.97). Most of the lesions seen by $^{68}$Ga-DOTANOC PET were also visualized on $^{177}$Lu-DOTATOC planar images and SPECT/CT images. The radioactivity rate between tumors and muscle in SPECT/CT images was 39.45 ± 28.31 with a median of 27.89 (range, 5.83-94.58). The absorbed mass doses of the $^{177}$Lu-DOTATOC were 0.0004 ± 0.0002 MBq-h/MBq/g in whole body, 0.0067 ± 0.0018 MBq-h/MBq/g in kidneys, and slightly higher in spleen (0.0099 ± 0.0071 MBq-h/MBq/g), which was shown in table 4.

## DISCUSSION

PRRT has been well validated and recommended as a standard treatment strategy for metastatic or inoperable SSTR-positive NETs by national comprehensive caner

network (NCCN) and European society for medical oncology (ESMO) guideline [22]. Dosimetry was systematically performed in some European nuclear medicine centers. However, due to complicated procedure of dosimetry calculation, the clinical value was limited in the NETs. Herein, the present study is to the first quantitative dosimetry analysis of $^{177}$Lu-DOTATOC in Chinese patients with advanced NETs. During and after the $^{177}$Lu-DOTATOC treatment, no serious adverse effects were observed, and no significant change was noticed in hematology parameters and renal function, which indicates safety and well tolerance of $^{177}$Lu-DOTATOC treatment.

Regarding $^{177}$Lu-DOTATOC treatment, physiological uptake of $^{177}$Lu-DOTATOC was found in the main organs such as kidneys, spleen and liver. With the enough hydration and clearance, the activity of $^{177}$Lu-DOTATOC in the kidneys, liver and spleen significantly decreased with time. The ID (%) of $^{177}$Lu-DOTATOC in kidneys declined to 0.4 % after 72 h. In comparison, it takes 168 h to reach the same level for $^{177}$Lu-DOTATATE in the study of Gupta [23], which explains the faster clearance of $^{177}$Lu-DOTATOC. Moreover, tumor uptake was found higher than that of kidneys and spleen with considerably more variation for $^{177}$Lu-DOTATOC, and comparing with $^{177}$Lu-DOTATATE, tumor-to-kidney uptake ratios were higher for $^{177}$Lu-DOTATOC in most lesions, this finding is consistent with Wehrmann et al. [24]. The residence time of total body for $^{177}$Lu-DOTATOC was ranged from 14.5 h to 50.3 h with a median of 26.8 h which is comparable with the study by Schuchardt et al. [12] who reported 14.6 h to 66.2 h (median 23.3 h). Furthermore, the average residence time in our study was highest for tumors, secondly for spleen, lowest for kidneys, longer retention to NETs than normal organs may lead to better outcome and fewer adversity. Valerie et al. [11] found significantly longer kidneys, spleen and tumor residence time for $^{177}$Lu-DOTATATE rather than $^{177}$Lu-DOTATOC in a study using seven patients, and the result was consistent with our findings with $^{177}$Lu-DOTATOC.

In PRRT with $^{177}$Lu, significant correlation between tumor absorbed dose and the response to the treatment was reported in pancreatic neuroendocrine tumors (pNETs) [25]. In this study, relatively low dose treatment (range, 1.59-3.49 GBq), rather than a standard administration activity of 7.4 GBq, was performed in the first circle of PRRT for the prediction of response and toxicity. As showed in the previous studies [26,27], the

tumor absorbed dose per injected activity of $^{177}$Lu-DOTATATE revealed a wide inter-variability with a range of 0.1-56 mGy/MBq, and variable difference was observed between pretherapeutic dosimetry and post therapeutic dosimetry. Now similar evidence seems to be happening in our study using $^{177}$Lu-DOTATOC (range, 0.273-3.234 mGy/MBq), even though the discrete degree of absorbed dose was relatively small. This phenomenon was interpreted by the first analysis of uncertainty in molecular radiotherapy based on a cohort of clinical cases [28], uncertainties associated with quantity were throughout the whole absorbed dose calculation process (i.e. volume, activity, calibration factor, recovery coefficient, time-activity curve fitting), which further emphasizes the necessity of individualized dosimetry in PRRT.

Regarding kidney toxicity, the maximum accepted dose was set in the range of 23-29 Gy on the basis of data derived from external-beam therapy [27]. Renal irradiation is mainly caused by reabsorption of radiolabeled peptides in the proximal tubule. Another reason is the high endogenous expression of SSTR in vasa recta, distal tubule cells, and tubular cells of the cortex. Compared with $^{177}$Lu-DOTATOC, Esser et al [29]. found a 1.4 times longer kidneys residence time after $^{177}$Lu-DOTATATE, resulting in a higher absorbed kidneys dose. The same result was also obtained by Schuchardt et al [12]., they found the renal uptake, residence time, and absorbed dose were calculated to be higher in 25 patients treated with $^{177}$Lu-DOTATATE. From a clinical review for PRRT dosimetry [22], it's clear that the average absorbed dose per injected activity of kidneys in our study (0.3843 mGy/MBq) was lower than most all other studies using $^{177}$Lu-DOTATATE for treatment, which inferred that $^{177}$Lu-DOTATOC was likely to have lower renal toxicity than $^{177}$Lu-DOTATATE. Similarly, the absorbed dose of kidneys (0.542–1.480 Gy) was far less than the permissible renal threshold, which contributes to predict the maximum cumulative activity of $^{177}$Lu-DOTATOC in the following treatment cycles.

Concerning the bone marrow dosimetry, the total absorbed dose (0.026–0.139 Gy) in our study was far less than the generally accepted maximum absorbed dose (2 Gy). Moreover, the effective dose of bone marrow for $^{177}$Lu-DOTATOC in our study was (0.0036 ± 0.0015 mSv/MBq) which was approximately equivalent to that for $^{177}$Lu-DOTATATE used in Zhang' study (0.0032 ± 0.0004 mSv/MBq). However, because of

the moderate correlation between the mean absorbed dose of bone marrow and the development of hematologic toxicity, the therapy protocol has to be carefully planned. Radiation exposure of spleen also influences the changes in splenic volume and the development of hematologic toxicity [30]. Zhang et al. [21] found the spleen was the organ that received the highest absorbed dose from $^{177}$Lu-DOTATATE (1.769 ± 0.945 mGy/MBq) which was almost 4-fold higher than that of $^{177}$Lu-DOTATOC in our study (0.4612 ± 0.4093 mGy/MBq). This result was consistent with Schuchardt's study [12] in which $^{177}$Lu-DOTATOC exhibited the lowest dose delivered to spleen in the three peptides.

Moreover, compare with kidneys and spleen, PRRT with $^{177}$Lu-DOTATOC showed lower absorbed dose in other normal organs. With respect to whole-body dosimetry, the absorbed dose was 0.1735 ± 0.0722 mGy/MBq for $^{177}$Lu-DOTATATE [21], which is almost 4-fold higher than that of $^{177}$Lu-DOTATOC (0.0412 ± 0.0164 mGy/MBq). Meanwhile, the effective dose (0.0392 ± 0.0158 mSv/MBq) of $^{177}$Lu-DOTATOC is half of that in $^{177}$Lu-DOTATATE (0.0693 ± 0.0317 mSv/MBq). These inferred that PRRT with $^{177}$Lu-DOTATOC may bring relatively lower radiation to patients' body.

Because of the relatively low abundance of gamma radiation from $^{177}$Lu emission, photon cross-irradiation dose has been neglected in many previous published $^{177}$Lu clinical dosimetry studies. Sandstrom et al [31]. found that photon cross-irradiation can occur in organs with high activity concentration and low activity concentration in $^{177}$Lu-DOTATATE-treated patients. We quantified photon cross-irradiation in each target organs, the average photon dose to the adrenals was up to 19.46 % of the total absorbed dose, and relatively high photons contribution was found in metastatic livers (11.91 ± 1.37 %). We also found that photons can contribute 2.92 ± 0.55 % of kidneys' total absorbed dose and 3.95 ± 1.99 % of spleen's total absorbed dose, which was lower than previously believed (5-15 %) [31], partly because of no high-uptake lesions close to these organs.

One limitation of this study is that the number of patients is rather small. A study with more patients is necessary to evaluate the therapeutic efficacy and potential toxicity of $^{177}$Lu-DOTATOC. Moreover, the dosimetry of PRRT should be promoted

to the whole therapy course, which might be improve the accuracy of absorbed dose estimates.

## CONCLUSION

$^{177}$Lu-DOTATOC showed favorable biodistribution as well as high affinity to the tumors with high expression of somatostatin receptors. The dosimetric estimations demonstrated large interpatient variability of tumors and normal organs uptake, which indicated the need for accurately personalized therapy planning, rather than in a fixed-dose therapy in the whole treatment cycles. $^{177}$Lu-DOTATOC had lower doses in the kidneys than $^{177}$Lu-DOTATATE as reported before, which allowed higher $^{177}$Lu-DOTATOC activities to be administered in NETs therapy. In summary, $^{177}$Lu-DOTATOC is safe, well-tolerated and appropriate in Chinese NETs patients for PRRT.

## ACKNOWLEDGMENTS

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## CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests regarding the publication of this paper. This clinical study was performed with the approval of Nanjing first hospital ethical committee, and its results did not influence any further therapeutic decision making.

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# Figures

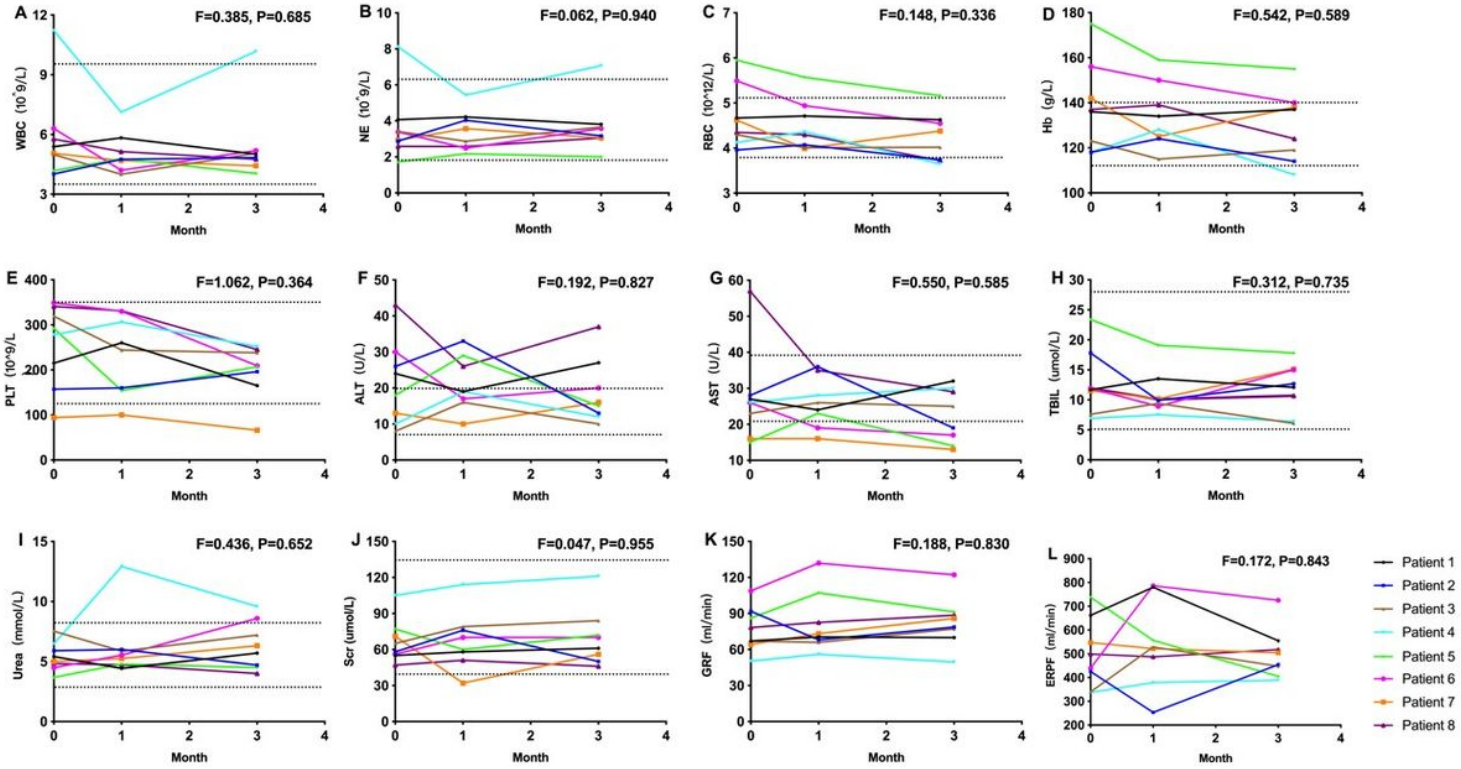



**Figure 1**

The changes of indicator of hemotoxicity (A-D), hepatotoxicity (E-H), nephrotoxicity (I, J), and renal function (K, L) at baseline, 1 month and 3 months after the 177Lu-DOTATOC treatment. The two dotted lines on each graph represent the upper and lower limits of the reference range. No significant change was observed in hematology parameters, kidney and liver function by one-way repeated measures analysis of variance. WBC: white blood counts; NE: neutrophils counts; RBC: red blood counts; Hb: hemoglobin; PLT: platelet counts; ALT: alanine aminotransferase; AST: aspartate transferase; TBIL: total bilirubin; Scr: serum creatinine; GFR: glomerular filtration rate; ERPF: effective renal plasma flow

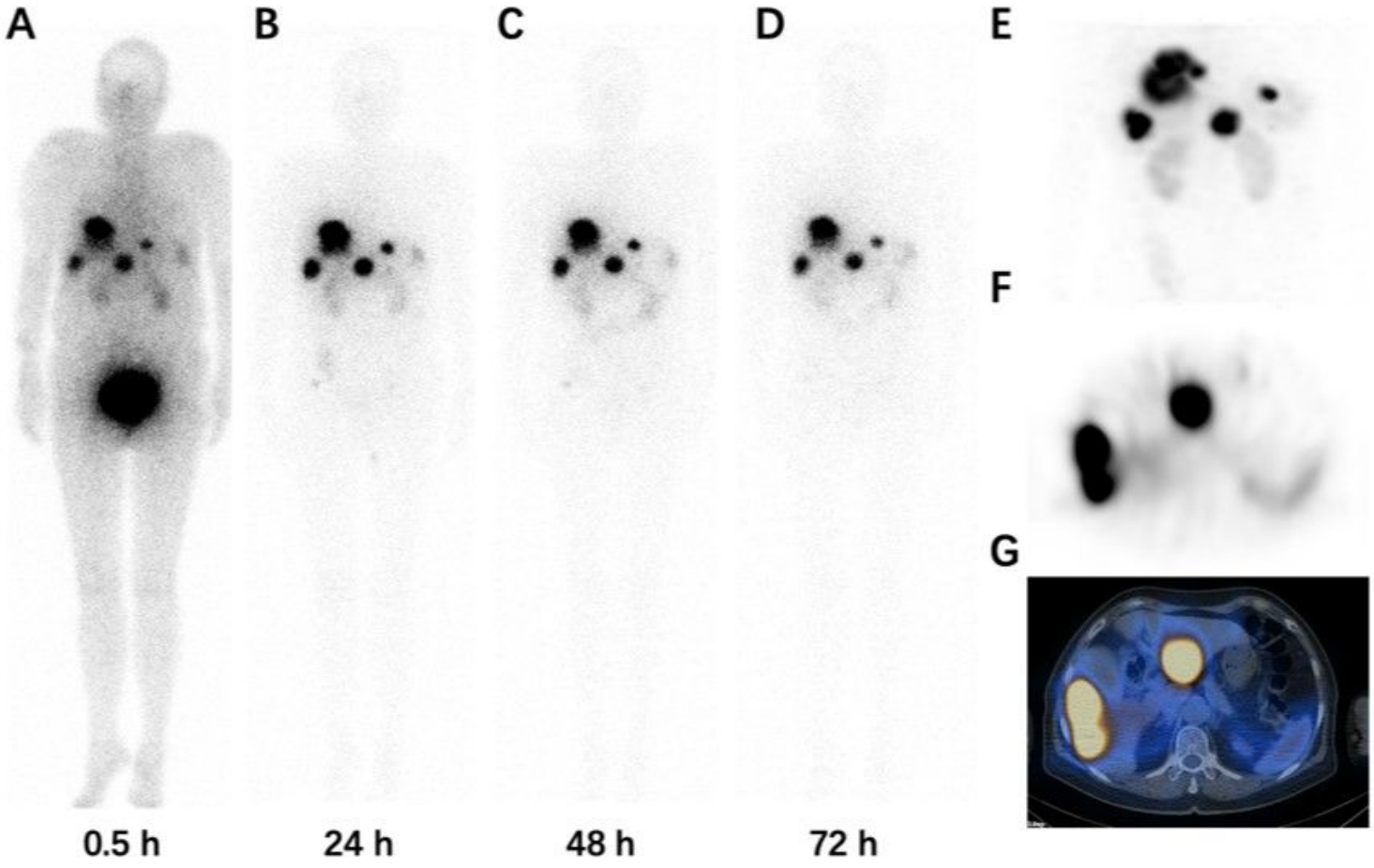
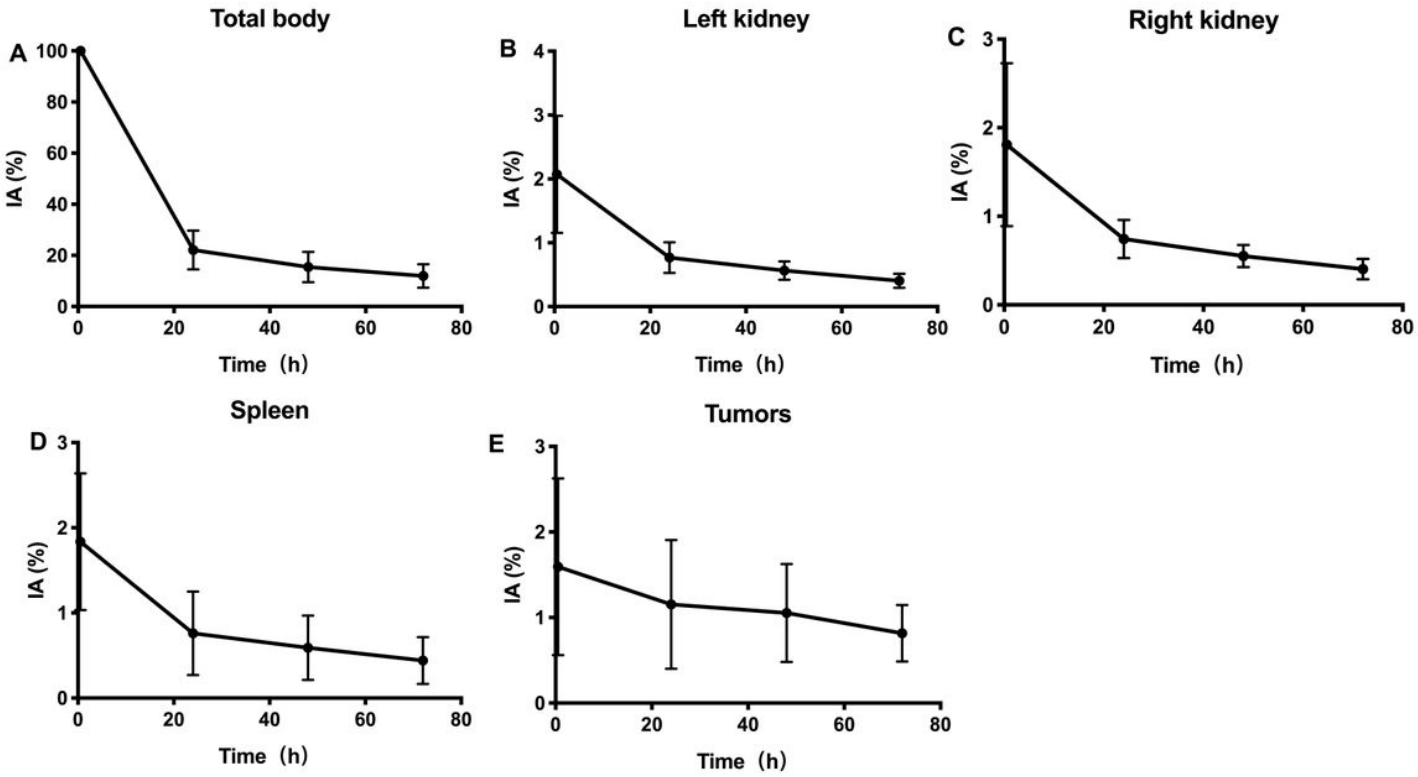



**Figure 2**

177Lu-DOTATOC whole-body planar imaging and SPECT/CT of a 63 years old female patient with NET liver metastases. (A), (B), (C) and (D) were anterior whole-body planar images at 0.5, 24, 48 and 72 h after intravenous administration of 177Lu-DOTATOC respectively. (E), (F) and (G) were SPECT tomography image, axial SPECT image and SPECT/CT at 21.6 h after intravenous administration of 177Lu-DOTATOC respectively




## Figure 3

IA(%) of target organs and tumors in patients treated with 177Lu-DOTATOC

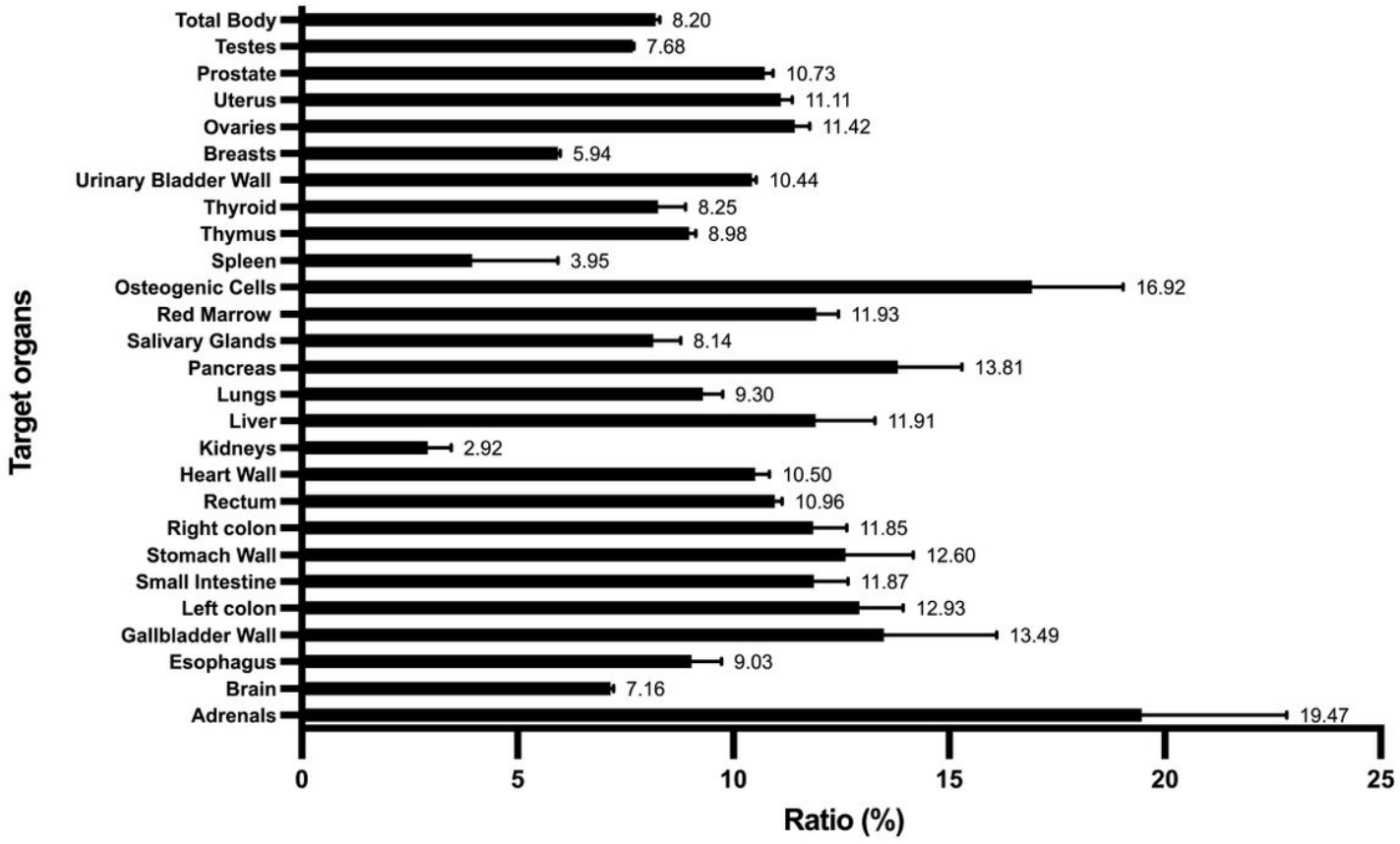


**Figure 4**

Photon to total absorbed dose ratio in each target organs

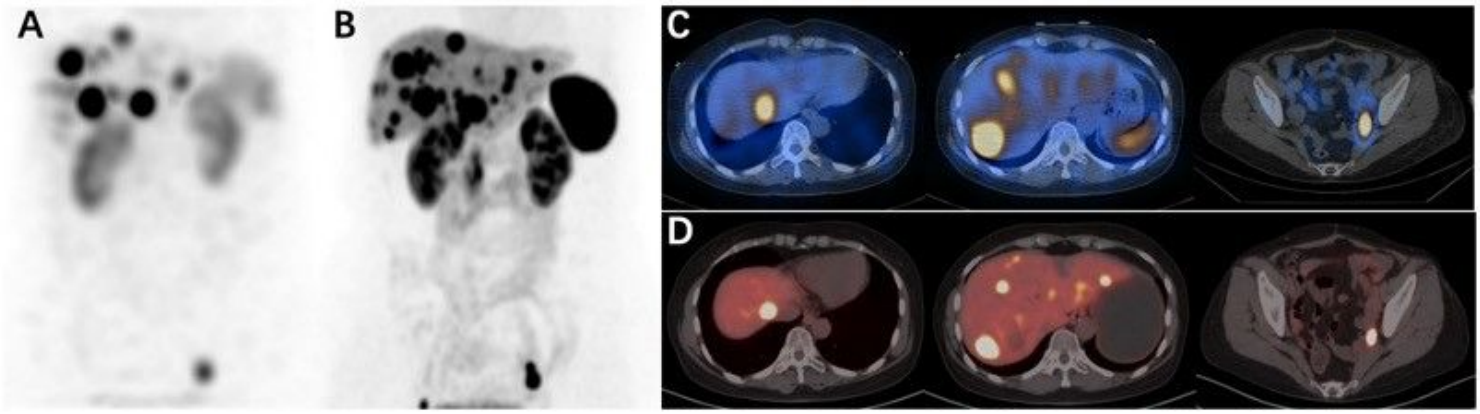



**Figure 5**

177Lu-DOTATOC SPECT/CT images and 68Ga-DOTANOC PET/CT images of a 64 years old female NET patient with advanced NET (G2). Multiple metastases were shown on SPECT (A) and SPECT/CT (C) images at 24 h after administration of 177Lu-DOTATOC. The same metastases were shown on coronary MIP view of PET (B) and PET/CT (D) images at 60 minutes after intravenous injection of 68Ga-DOTANOC

## Supplementary Files

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