

Value of Individualized Dosimetry in Peptide Receptor Radionuclide Therapy (PRRT) by Lutetium-177 [$^{177}\text{Lu} - \text{Dota}^0, \text{Tyr}^3$] Octreotate

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Abstract

Response and toxicity prediction is essential to the implementation of Peptide Receptor Radionuclide Therapy (PRRT) for neuroendocrine tumors. Radiolabelled somatostatin analogue [$^{177}\text{Lu-DOTA}^0, \text{Tyr}^3$] octreotate stands as a promising therapy tool. Specific dosimetry is a crucial factor in patient treatment planning.

In our Institution, neuroendocrine tumor treatment, by radiopeptide infusion via intrahepatic arterial catheterization, is a well established technique. Kidney protective agents are also included in our protocol. The individualized patient dosimetry calculations were based on planar and SPECT scintigraphy images. Counts were determined in a region of interest (ROI) around the tumor, liver, kidneys and spleen. In planar technique, the ROIs were drawn in both anterior and posterior images while in SPECT counts measured per slice. For counts conversion to activities, calibration factors were calculated. Planar and SPECT images of cylindrical water - filled phantom, with five different known amounts of activity, were obtained. Corrections for scatter attenuation, collimator efficiency and detector response were calculated. Absorbed doses were calculated using MIRD formalism and S values were calculated using the RADAR system.

The absorbed doses to organ per unity administered activity were comparable for both planar and SPECT techniques. On average, the absorbed dose was in tumor [4-40] mGy/ MBq, in kidneys [0.25-1.05] mGy/ MBq, in the spleen [0.3-2.1] mGy/ MBq and in the liver [0.05-0.34] mGy/ MBq.

In order to deliver higher dose to tumor and avoid kidneys and red marrow toxicity, accurate individualized dosimetry is obligatory. Furthermore, the results quantitatively confirm the therapeutic efficacy of transhepatic administration and introduce ^{177}Lu labeled peptide as an ideal for peptide receptor radiotherapy.

Key words: Individualized Dosimetry, $^{177}\text{Lu-DOTA}$ -octreotate, Neuroendocrine Tumors, Peptide Receptor Radiotherapy.

Introduction

Peptide receptor radionuclide therapy known as PRRT is a well established method for treatment of cancer, especially when chemotherapy, radiotherapy or surgery is excluded. The real challenge of internal targeted radionuclide therapies is to deliver the highest possible dose to the tumor while sparing normal organs from damage. Toxicity in kidneys and red marrow is a common problem. For the determination of the risk and therapeutic benefit of such internal therapies, patient-specific dosimetry is an essential prerequisite. The radiopharmaceutical $^{177}\text{Lu} - \text{DOTA}^0, \text{Tyr}^3$ octreotate is a somatostatin analogue with a higher affinity for the

somatostatin receptor subtype-2. Thereby, a chelator, DOTA, is used in order to ensure a more stable binding of the intended β -emitting radionuclide [1]. Somatostatin receptor imaging is considered an important technique for the localization and staging of neuroendocrine tumors [2]. Infusion of a diagnostic In-111 octreotide permits physician to confirm sufficient tumor uptake as a patient inclusion criterion in PRRT [3] (fig 1). Newer positron emission tomography radiopharmaceuticals such as ^{68}Ga -labeled peptides [4] have been developed for diagnostic somatostatin receptors. Due to the need for kidney protection [5, 6], infusion of amino acid 30-60 min before treatment is mandatory. In our institution, Aretaieion hospital, radionuclide infusions are performed by a nuclear physician via an angiographic catheter [7-9] that has been inserted in the hepatic artery by a radiologist. By this application method, uptake of radiopharmaceutical by the tumor is enhanced, compared with uptake after antecubital administration, because of the high concentration of activity that reaches the target tissue. The aim of this study was the estimation of patient specific dose for the tumor and healthy tissue as this is the most precise way to designate an administered dose to the best therapeutic result. It is also assistance to the physician in order to avoid side effects of the therapy and compare the treatment results to other related therapies.

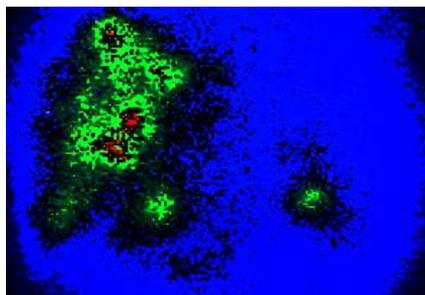


Figure 1: Planar anterior image immediately after In-111-octreotide infusion demonstrating the abundance of somatostatin receptors.

Materials and Methods

Patients

In present study, 9 patients in Aretaieion hospital were infused with 7,4GBq in average per treatment. To be included in the therapeutic cycle, the patient had to have a histologically confirmed exclusively neuroendocrine tumor, normal kidney function, and somatostatin receptor overexpression of the tumor lesions, as scintigraphically assessed. The infusion was performed through a port attached to the hepatic artery. The hepatic artery port makes the therapy more comfortable for the patient as in this way the hepatic artery angiography catheterization, at each therapeutic session, is avoided. The treatment cycles were 3 to 4, based on a calculated maximal tolerated absorbed dose of 27 Gy to the kidneys (according to the consensus protocol). The time interval between the treatment cycles was usually 6 to 8 weeks.

γ -Scintigraphy

Scintigraphy was performed at 30min, 24h, 72h and 96h after radiopharmaceutical infusion. Planar images were obtained using an APEX SPX4 ElScint gamma (General Electric) camera equipped with a medium energy all-purpose collimator, 20 % energy

window centered at 208 keV ¹⁷⁷Lu photo peak and 1 minute time to acquire an image.

Gamma-camera calibration

In order to convert count rate that was measured from planar images to activity a cubic tank filled with water was used and placed on the examination bed simulating patient's body [10]. A series of vials were placed in phantom consecutively, filled with ¹⁷⁷Lu radionuclide. The activity in each vial was measured in a well-type scintillation counter (Curiementor 3, model 12001; PTW). Planar views of each vial were obtained with ¹⁷⁷Lu activity varying from 72 to 610 MBq. A linear fit function was applied to correlate measured count rate with source organ activity. A second-degree polynomial function was introduced in all the measurements. The true counting rate (TCR) and the measured counting rate (MCR) were calculated using the linear function and the polynomial function, respectively. The TCR/MCR ratio corresponds to the counting rate correction factor (CRCF). The CRCF and MCR were graphically presented, and the fitting process resulted in a second-degree polynomial.

Patient-specific dosimetry

Patient's body absorbs radiation emitted from organ sources. The count rates were measured by manually drawn regions of interest for liver, spleen, kidneys and tumor. Background count rate was measured close to regions of interest and a simple background subtraction method was performed. Activity was calculated from the planar anterior and posterior images 30min after radiopharmaceutical infusion, at 24h, 72 h and 96 hours later. Activity was calculated for the tumor, liver, kidneys and spleen. Curves of activity as a function of time were drawn for each source organ. The area between each curve and time axis is the cumulative activity [13]. Cumulative activity A_c is measured in MBq hr for each source organ using MatLab code (MathWorks Ltd). The MIRD (Medical Internal Radiation Dose) schema calculates the mean absorbed dose, assuming an average tissue deposition of energy and a uniform distribution of the radiopharmaceutical. The dose is calculated for the target region (T), by summing up the contribution of each source region (S) to the target and the contribution of the target region itself. Any region containing activity greater than the average concentration of activity in the total body is accepted as source region. On the other hand, penetrating radiation emitted by all source regions, including radiation emitted by the target region itself, contributes to the absorbed dose to the target region. RADAR software (Stanford Dosimetry, LLC) calculates absorbed dose per cumulative activity (S values) using anthropomorphic phantoms [11]. A Microsoft Excel calculation sheet is developed so that count rate was converted to activity in a simple way.

Cumulative activity was then measured for tumor, kidneys, spleen and pancreas. Finally absorbed doses for each organ were calculated in mGy/ MBq according to the following formula [12-15]

$$D_{target} = \sum_{source} A_{cum}^{source} * S(t_{target} \leftarrow source)$$

Where, D_{target} : absorbed dose of each target, A_{cum} : cumulative activity of each source, S values: absorbed dose per cumulative activity for each activity for each pair source-target.

Liver, spleen, kidneys, and bladder contents were considered target organs because they showed significant radiopharmaceutical uptake on the scintigrams.

Results and Discussion

Mean absorbed dose was estimated at 0.23 mGy/ MBq for kidneys, 2.22 mGy/ MBq for liver, 1.64 mGy/ MBq for spleen. Minimum and maximum estimated absorbed dose values were 0.18-0.32mGy/ MBq for kidneys, 0.15-2.26 mGy/ MBq for liver and 0.3-3.4 mGy/ MBq for spleen. [fig 2-4].

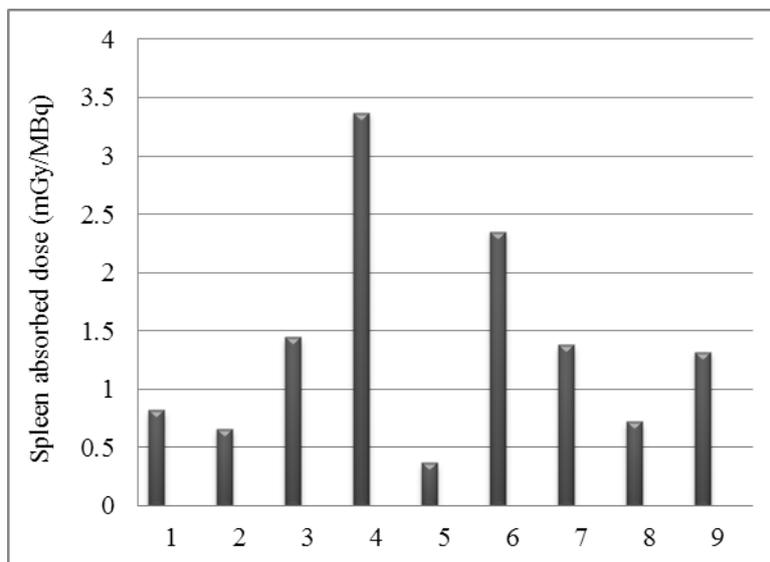


Figure 2: The mean spleen absorbed dose per unit administered activity for each patient

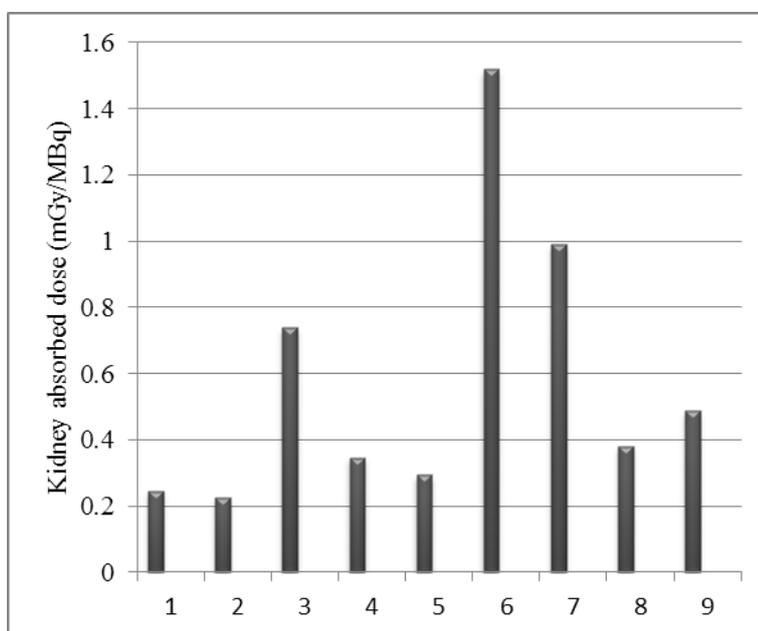


Figure 3: The mean kidney absorbed dose per unit administered activity for each patient.

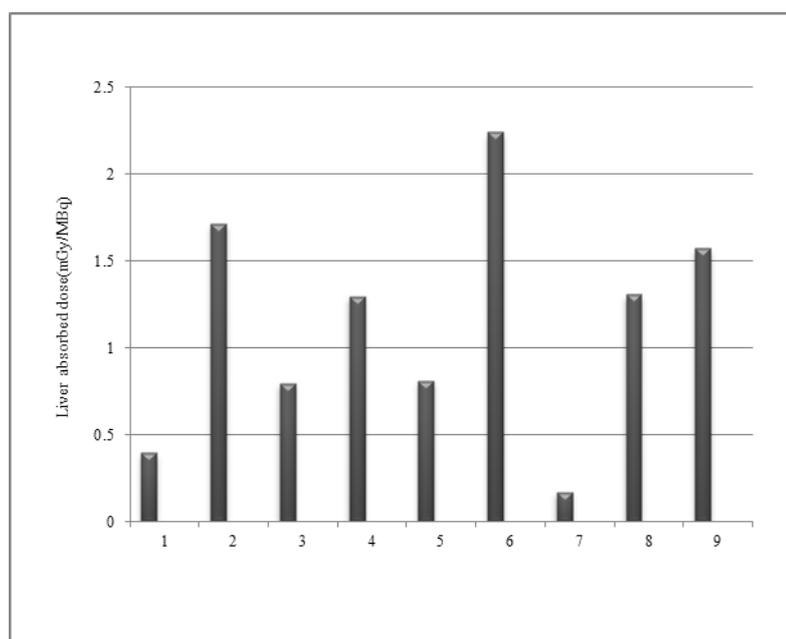


Figure 4: The mean liver absorbed dose per unit administered activity for each patient.

Radiopharmaceutical-therapy dosimetry differs significantly of the dosimetry of diagnostic radiopharmaceuticals scintigraphy. There is a greater risk for the healthy tissue since organ absorbed dose is much higher during radiopharmaceutical therapy than based on the MIRDA schema [16]. For radiopharmaceutical therapy, patient, specific dose calculation is essential because each patient has different pharmacokinetic and his anatomy deviates from anatomic averages. Measured absorbed doses for tumor and kidneys are in good agreement with absorbed doses measured by Kwakkeboom et al [17], 0.88 mGy/ MBq for kidneys, 0.21 mGy/ MBq for liver and 2.15 mGy/ MBq for spleen. Also comparable results with Cremonesi et al [18], 0.62 mGy/ MBq for kidneys ,0.18 mGy/ MBq for liver and 0.64 mGy/ MBq for spleen. At this study certain deviations of absorbed dose between patients were observed. This verifies the importance of patient specific dosimetry in radiopharmaceutical routine therapy, as a useful tool for the determination of the therapeutic activity dose with maximum biological effect to the tumor avoiding great risks for the healthy tissue [19].

Conclusion

The results of the present study quantitatively confirm the potent therapeutic efficacy of transhepatic administration. Indeed, it reinforces uptake of radiopharmaceutical by tumor, consequently reducing the radiation burden to healthy organs. The patient-specific dosimetric protocol introduced here helps optimize the planning of trans-hepatic administered radioisotope therapy. Besides objective tumor responses, the median progression-free survival is more than 40 months. The patients' self-assessed quality of life increases significantly after treatment with ¹⁷⁷Lu-DOTATATE [19].

References

1. Zaknun J.J., Bodei L., Mueller-Brand J., Pavel M.E., Baum R.P., Hörsch D., O'Dorisio M.S., O'Dorisiol T.M., Howe J.R., Cremonesi M., Kwekkeboom D.J., "The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours", *European Journal Nuclear Medicine Molecular Imaging*. DOI 10.1007/s00259-012-2330-6,2013.
2. Kam BL, Teunissen JJ, Krenning EP, de Herder WW, Khan S, van Vliet EI, Kwekkeboom DJ, "Lutetium-labelled peptides for therapy of neuroendocrine tumours" ,*European Journal Nuclear Medicine Molecular Imaging*, 39 Suppl 1:S103-12,February 2010.
3. Maecke HR, Reubi JC, "Somatostatin receptors as targets for nuclear medicine imaging and radionuclide treatment", *Journal Nuclear Medicine*, 52:841-4, 2011.
4. Bal C.S, Gupta S. K. and Zaknun J.J., "Rdiolabeled somatostatin analogs for radionuclide imaging and therapy in patients with gastroenteropancreatic neuroendocrine tumors",*Tropical Gastroenterology*,31(2):87-95,2010.
5. Rolleman E.J., Melis M., Valkema R., Boerman O.C, Krenning E.P., De Jong M., "Kidney protection during peptide receptor radionuclide therapy with somatostatin analogues", *European Journal Nuclear Medicine Molecular Imaging*,37:1018-31,2010.
6. Rolleman E.J., Valkema R., De Jong M., Kooij P.P., Krenning E.P., "Safe and effective inhibition of renal uptake of radiolabelled octreotide by a combination of lysine and arginine", *European Journal Nuclear Medicine Molecular Imaging*,30:9-15,2003.
7. Limouris G.S., "Neuroendocrine tumors: a focus on liver metastatic lesions", *Frontiers in Oncology*, 2:20. doi: 10.3389/fonc.2012.00020.
8. Limouris G.S., Dimitropoulos N., Kontogeorgakos D., et al, "Evaluation of the therapeutic response to In-111-DTPA-octreotide based targeted therapy in liver metastatic neuroendocrine tumors according to CT/MRI/US findings", *Cancer Biother Radiopharm*,20:215-217,2005.
9. Limouris G.S., Chatziioannou A., Kontogeorgakos D., Mourikis D., Lyra M., Dimitriou P., et al, " Selective hepatic arterial infusion of In-111-DTPA-Phe1-octreotide in neuroendocrine liver metastases", *European Journal Nuclear Medicine Molecular Imaging*,35 :1827-1837,2008.
10. Vamvakas I.,Lagopati N.,Andreou M., Sotiropoulos M., Gatzis A., Limouris G.S,Antypas C., Lyra M., "Patient specific computer automated dosimetry calculations during therapy with 111In Octreotide", *European Journal of Radiography*, 1(4):180-183, December 2009.
11. RADAR (RAdition Dose Assessment Resource) [*Internet*]. Available from:www.doseinfo-radar.com.
12. Sgouros G., "Dosimetry of internal emitters", *Journal Nuclear Medicine*,46 Suppl 1:18S-27S,2005.

13. Stabin M.G., Siegel J.A., “Physical Models and Dose Factors for Use in Internal Dose Assessment” ,*Health Physics*, **85** (3) ,pp 294-310 ,September 2003.
14. Stabin G.M., “The importance of patient-specific dose calculations in nuclear medicine” ,*Nuclear Engineering and Technology*, 40(7) ,2008.
15. Lyra M.,Phinou P., “Internal dosimetry in nuclear medicine:A summary of its development,applications and current limitations” ,*Radiation Protection Management*,16(6):17-30,1999.
16. Lassmann M. , Chiesa C., Flux G., Bardiès M., “EANM Dosimetry Committee guidance document: good practice of clinical dosimetry reporting” ,*European Journal Nuclear Medicine Molecular Imaging*, DOI 10.1007/s00259-010-1549-3.
17. Kwekkeboom D.J, Teunissen J. J., Bakker W.H., Kooij P.P., De Herder W.W., Kam B.L., Feelders R.A., Van Eijck C.H., Esser J-P, Kam B.L., Krenning E.P, “Radio-labeled Somatostatin Analog [177Lu-DOTA0,Tyr3]Octreotate in Patients With Endocrine Gastroenteropancreatic Tumors” , *Journal of Clinical Oncology* 23(12):2754-2762,2005.
18. Cremonesi M., Botta F., Di Dia A., Ferrari M., Bodei L., De Cicco C.,et al. “Dosimetry for treatment with radiolabelled somatostatin analogues”. A review. *Quarterly Journal Nuclear Medicine Molecular Imaging*,54:37–51, 2010.
19. Kwekkeboom J.D., Wouter W. de Herder, Boen L. K., Casper H. van Eijck, Martijn van Essen, Peter P. Kooij, Feelders A.R, Maarten O. van Aken, and Krenning P.E. “Treatment With the Radiolabeled Somatostatin Analog [177Lu-DOTA0,Tyr3]Octreotate: Toxicity, Efficacy, and Survival” , *Journal of Clinical Oncology*,26(13) ,2008.