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Short Communication

Dosimetric evaluation of NET treatment with somatostatin analogs labeled with ^{177}Lu

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Abstract

Introduction: A reliable dosimetric assessment in internal radiotherapy is a key element in ensuring the effectiveness and safety of the treatment. The aim of the presented work was to perform model dosimetric calculations in patients undergoing treatment with a somatostatin analog labeled with radioactive lutetium-177, [^{177}Lu]Lu-DOTA-TOC, for GEP-NET.

Material and Methods: Dosimetric modeling was performed for 17 patients (11 women, 6 men, aged 32–77). Each patient received 2-4 injections of the radiopharmaceutical [^{177}Lu]Lu-DOTA-TOC during treatment, with an activity range of 2–8 GBq. Subsequently, patients underwent SPECT-CT scanning. The obtained images were segmented and quantitatively analyzed using the GE Dosimetry Toolkit software package. VOIs were delineated for the liver, kidneys, spleen, heart, and areas of pathological radiopharmaceutical accumulation. Model TAC were determined for these areas. Dosimetric calculations were performed using the OLINDA/EXM version 2.1 software.

Results: The average absorbed dose values in a single therapeutic cycle were 2.5 Gy for the liver, 3.8 Gy for the kidneys, 2.9 Gy for the spleen, and 28 mGy for the heart. The calculated absorbed dose from these organs for the bone marrow averaged 11.6 mGy. The average cumulative absorbed dose values for these organs were: 6.9 Gy, 10.6 Gy, 7.8 Gy, and 72.3 mGy, respectively. Areas of localized, non-physiological accumulation of [^{177}Lu]Lu-DOTA-TOC received an average absorbed dose of 16.2 Gy in a single therapy cycle and 48 Gy in total over the entire treatment process.

Conclusion: The results of internal dosimetry in the studied group of patients are characterized by high variability. The kidneys were the organs most exposed to high radiation doses, and their function was monitored during treatment using biochemical markers. The good tolerance of high absorbed doses may be due to the microscopic characteristics of the dose distribution from the ^{177}Lu radionuclide radiation. The highest absorbed doses were observed in areas of pathological radiopharmaceutical accumulation.

Keywords: dosimetry; PRRT; radiotherapy; NET.

Introduction

Radionuclide internal radiotherapy, while sharing the concept of introducing a radioactive source into the body with brachytherapy, is a distinct treatment modality that relies on open radioactive sources, which are distributed within the body according to pharmacokinetic principles. Such implantation occurs by incorporating an atom with a radioactive nucleus into a molecule that exhibits affinity for a specific molecular target, being a particular receptor. When the guiding molecule (ligand) is a protein molecule, the therapy is referred to as Peptide Receptor Radionuclide Therapy (PRRT).

Neuroendocrine tumors account for 2-3% of all malignant tumors. Typically, in 55-70% of cases, they are localized in the organs of the gastrointestinal tract.[1]

In this study, dosimetric calculations were performed for internal radiotherapy of neuroendocrine tumors located in the digestive system organs (GEP-NET) using the radiopharmaceutical [^{177}Lu]Lu-DOTA-TOC.

The radiopharmaceutical [^{177}Lu]Lu-DOTA-TOC consists of the chelator DOTA, which binds the radioactive nuclide ^{177}Lu, and an octapeptide composed of eight amino acids known as octreotide. Octreotide exhibits affinity for somatostatin receptors SSTR2, and to a lesser extent SSTR3 and SSTR5.

Authors' contribution:
A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article.

Overexpression of these receptors is characteristic of neuroendocrine tumor cells,[2] which allows for the use of somatostatin analogs labeled with radioactive elements for the treatment of these diseases.

The radionuclide ^{177}Lu is a beta-minus emitter with a maximum energy of 497 keV and a half-life of 6.65 days. The decay product of the ^{177}Lu nucleus is the stable nuclide ^{177}Hf in its ground state (76% of decays) or in one of the excited states. The transition of the ^{177}Hf nucleus from an excited state to the ground state may be accompanied by the emission of gamma photons with energies of 113 keV or 208 keV,[3] which are used for imaging the distribution of radioactivity with a gamma camera.

Dosimetry plays a crucial role in ensuring the safety and efficacy of radiotherapy. Knowledge of the dose absorbed by critical organs allows for the assessment of the risks associated with the therapy, while determining the absorbed doses in the treated areas enables the evaluation of its effectiveness.

Material and Methods

Patients

The patient group included in the study consisted of 21 individuals with histopathologically confirmed non-surgical GEP-NET stage III/IV. Comparable and repeatable dosimetry modeling was performed for 17 patients (11 women and 6 men, aged 32-77). Detailed information about patients' demographics and clinical conditions is summed in the table below (**Table 1**).

Treatment protocol and imaging

The treatment protocol for each patient involved 2-4 radiotherapy courses, in which an activity of 2.4-8 GBq [^{177}Lu]Lu-DOTA-TOC was administered. The administration method was intravenous or intraarterial infusion. The time interval between the following therapy courses was 8-12 weeks. Between radiotherapy courses, patients underwent chemotherapy with capecitabine and temozolomide (CAPTEM). The activities averaged for a group of patients are shown in the table below (**Table 2**).

The imaging of radiopharmaceutical distribution in patient's body was performed using a GE NM/CT 860 gamma camera with a MEGP collimator installed. The energy windows for SPECT were 113 keV and 208 keV widths of 15% and 20% respectively. The energy window for scatter correction was set at 183 keV with a width of 8%. Acquisition was performed using the step-and-shoot technique, with 60 frames and a duration of 25 s per frame. The image matrix was set 128 × 128 pixels. The applied reconstruction algorithm was OSEM with attenuation and scatter corrections and a resolution recovery algorithm enabled for PVE minimization.

Table 1. Demographic and clinical data of the patient group included in the presented study.

Parameter		All	Pancreatic	Intestinal
Number		17 (100%)	13 (76%)	4 (24%)
Mean age ± SD		58.7 ± 13.2	53.9 ± 13.5	66.8 ± 5.3
range [y]		32 - 77	32 - 77	62 - 74
Sex	F	11 (65%)	8 (62%)	3 (75%)
	M	6 (35%)	5 (38%)	1 (25%)
BMI, median		26.6	26.9	25.7
Time between diagnosis to treatment start [months]		12	9	27
Tumor endocrinal active	Y	4 (24%)	2 (15%)	2 (50%)
	N	13 (76%)	11 (85%)	2 (50%)
Tumor differentiation state (G)	1	7 (41%)	5 (38%)	2 (50%)
	2	8 (47%)	6 (46%)	2 (50%)
	3	2 (12%)	2 (15%)	0
Clinical stage	III	2 (12%)	1 (8%)	2 (50%)
	IV	15 (88%)	12 (92%)	2 (50%)

Table 2. Activity dosage averaged in patient group in a single therapy course and cumulatively. The activities administered in individual courses for each patient were averaged and the medians are presented in the table.

Parameter	All	Pancreatic	Intestinal
Cumulated activity in whole therapy [GBq]	26.5	25.5	27.3
Activity in single therapy course [GBq]	6.5	6.4	6.9

Image quantitative analysis

After each radiopharmaceutical administration, the patients underwent at least three SPECT-CT examinations to track the distribution of radioactivity in the body and its changes in time. The mean time intervals were 6.03 h, 27.39 h, 83.56 h, and 126.93 h after [^{177}Lu]Lu-DOTA-TOC administration.

In order to enable quantitative analysis of SPECT images, it is necessary to calibrate the gamma camera's volumetric sensitivity. For this purpose, SPECT imaging of a phantom was performed using the same protocol applied to patients. The NEMA NU-2 phantom, without spherical components, was uniformly filled with an activity of 1 GBq of ^{177}Lu and scanned. The sensitivity correction factor:

$$SF = \frac{C}{\frac{t \cdot n \cdot V}{A_C}} \left[\frac{cps}{Bq}\right] \quad \text{Eq. 1}$$

where C is the count number in the reconstructed VOI with a volume V, t denotes the acquisition time of a single frame, n is the number of angular projections (frames), and A_C corresponds to the known activity concentration in the phantom. A value of SF equal to 3.5 cps/MBq was obtained.

For the quantitative analysis of the obtained images, the GE Dosimetry Toolkit software was used.[4] After image preparation, including overlap control and correction, manual organ segmentation was performed. The liver, kidneys (left and right individually), spleen and heart were outlined (see **Figure 1**). The most prominent areas of focal radiopharmaceutical accumulation were also outlined for dosimetry calculations in these regions.

Based on the successive SPECT-CT scans, the Dosimetry Toolkit was used to determine the time-activity curves (TAC) for each studied VOI, along with their parameters, such as effective half-life, volume, fraction of injected activity and particularly the residence time (see **Figure 2**).

Dosimetry calculations

The dosimetry calculations were performed using OLINDA/EXM version 2.1. The input data for the calculations were obtained from the analysis of images performed in the Dosimetry Toolkit. The OLINDA/EXM software implements the RADAR internal dosimetry calculation model, in which the absorbed dose is calculated according to:

$$D = N \cdot \frac{k \sum_i n_i E_i \phi_i}{m} [Gy] \quad \text{Eq. 2}$$

where D is an absorbed dose, N - number of nuclear decays (cumulated activity) in volume, k - proportionality factor, n_i denotes a number of particles emitted with energy E_i, ϕ_i is an absorbed fraction and m is the mass of VOI.

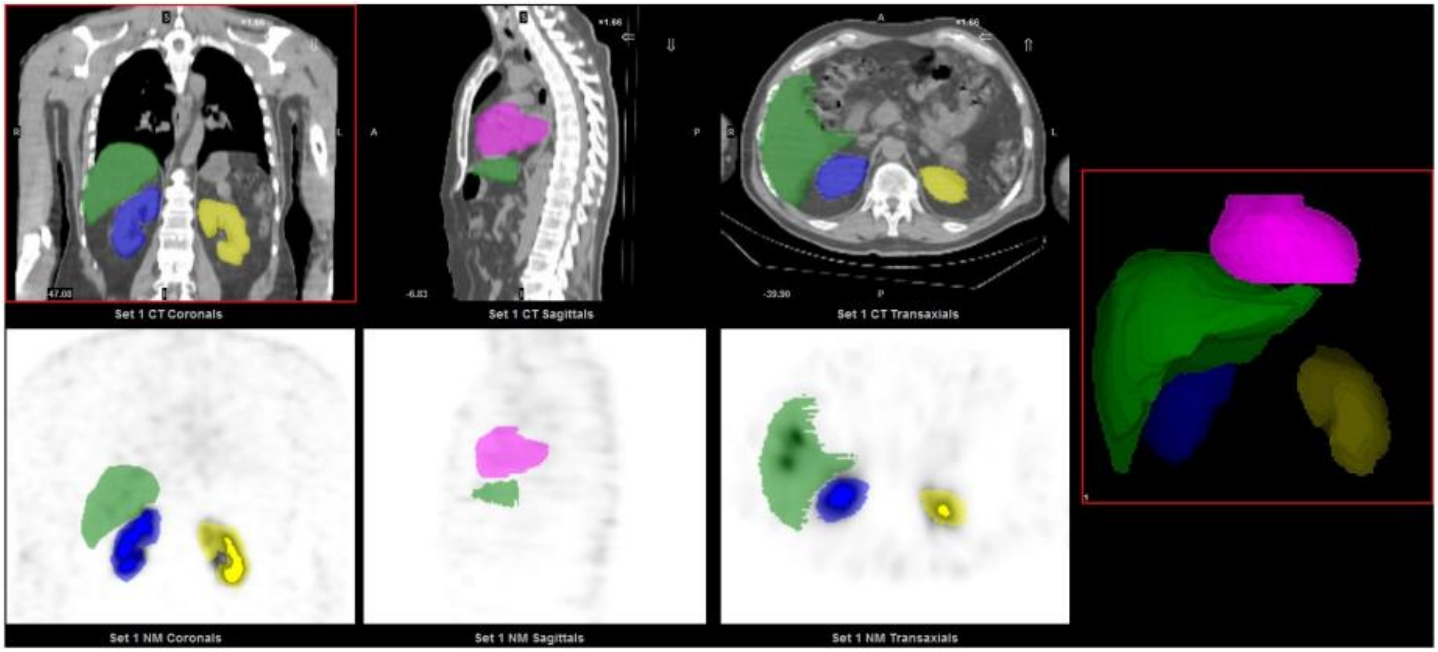

Figure 1. Image segmentation performed in Dosimetry Toolkit software. The liver, kidneys and heart are outlined.

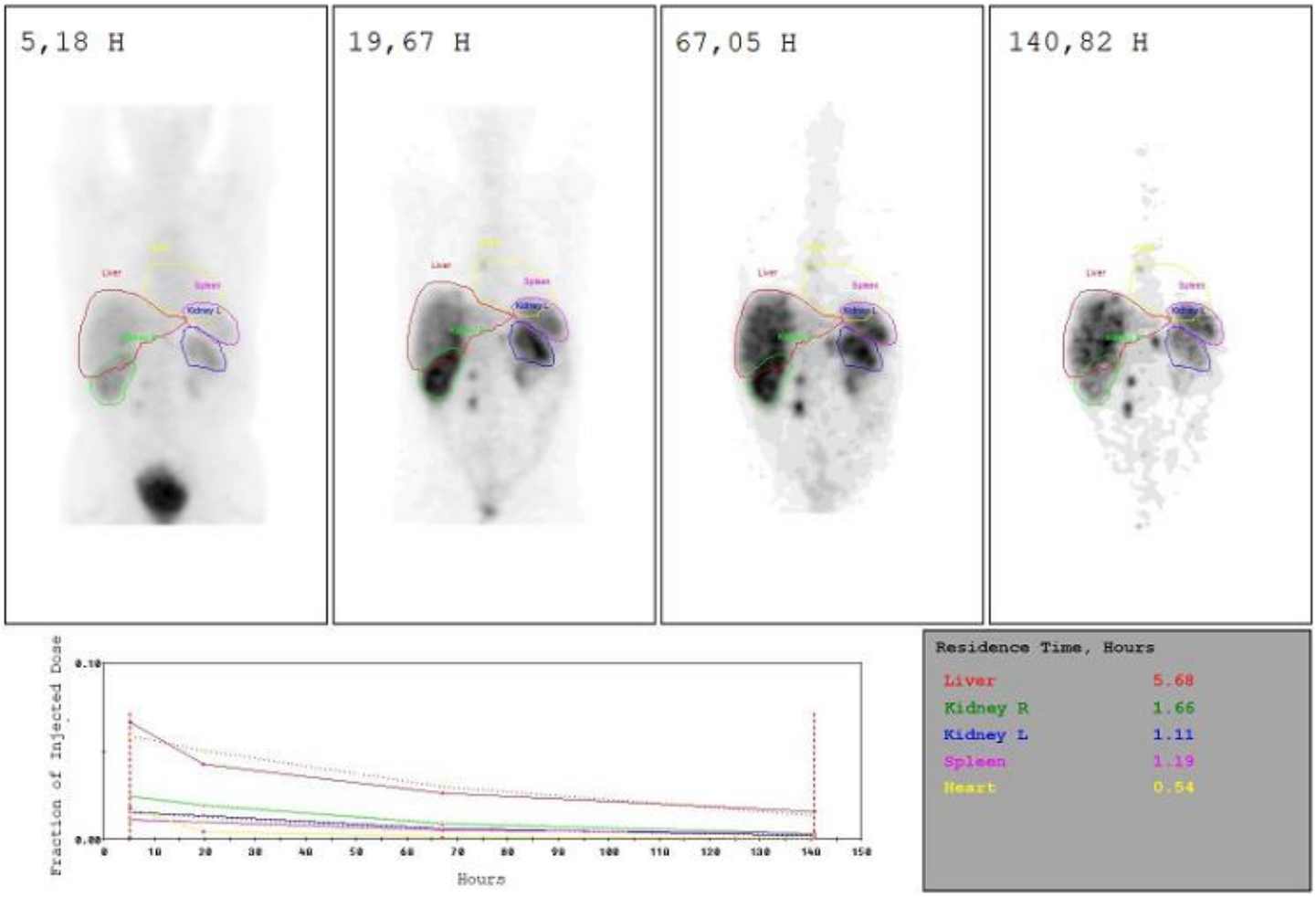

Figure 2. Quantitative analysis was performed using the GE Dosimetry Toolkit. The figure presents coronal SPECT images at successive time intervals after the administration of the radiopharmaceutical, with the contours of the regions of interest highlighted. The graph illustrates changes in activity in these areas, while the table next to the graph contains the residence time (in hours) for each VOI.

Results

Table 3 presents the organ dosimetry results for a single course of therapy. The next table (**Table 4**) contains the dosimetry results for areas of pathologically increased hot-spots of [^{177}Lu]Lu-DOTA-TOC accumulation.

Discussion

Staanum et al.[5] published the results of kidney dosimetry in peptide receptor radionuclide therapy using [^{177}Lu]Lu-DOTA-TOC and [^{177}Lu]Lu-DOTA-TATE. The study utilized 59 courses of TOC therapy. A specific dose of 0.38 Gy/GBq was obtained. In the presented work, a result of 0.66 Gy/GBq for the kidneys was obtained.

The article by Grassi et al.[6], dedicated to the influence of imaging registration methods on absorbed dose calculations in [^{177}Lu]Lu-DOTA-TOC therapy, also includes dosimetry data comparable to the results obtained in this work. In the cited study, the group consisted of 11 individuals for whom dosimetry modeling of the kidneys and pathological lesions exhibiting radiopharmaceutical accumulation was performed.

Table 3. Organ dosimetry results for individual therapy courses.

Parameter	Liver	Kidneys	Spleen	Heart
Mean	2.5 Gy	3.8 Gy	2.9 Gy	0.028 Gy
SD	3.1 Gy	3.5 Gy	2.9 Gy	0.035 Gy
Range	0.1 - 14.9 Gy	0.3 - 18.0 Gy	0.1 - 11.9 Gy	0.0013 - 0.149 Gy
Median	1.3 Gy	3.1 Gy	1.9 Gy	0.012 Gy
Q1	0.6 Gy	1.8 Gy	1.1 Gy	0.005 Gy
Q3	3.1 Gy	4.3 Gy	3.4 Gy	0.038 Gy

Table 4. Lesion dosimetry results for individual therapy courses and cumulative.

Parameter	Single course	Cumulative
Mean	16.2 Gy	48.0 Gy
SD	13.2 Gy	27.9 Gy
Range	1.4 - 71.1 Gy	9.3 - 120.6 Gy
Median	13.8 Gy	40.5 Gy
Q1	6.2 Gy	24.6 Gy
Q3	20.4 Gy	64.4 Gy

The specific absorbed dose obtained in Grassi's study was 0.65 Gy/GBq for kidneys and 1.36 Gy/GBq for tumors (in this paper for tumors obtained 2.46 Gy/GBq).

In the study by Goetz et al.[7], the authors performed Monte Carlo dosimetry for [^{177}Lu]Lu-DOTA-TOC therapy on 14 patients, encompassing a total of 39 cycles. The results obtained in the cited study were 3.41 Gy for kidneys, 4.4 Gy for spleen and 9.7 Gy for tumors, whereas in the study discussed here, there were 3.8 Gy, 2.9 Gy and 16.2 Gy respectively.

Conclusions

The dosimetric assessment of radionuclide internal radiotherapy conducted in this work contributes to extensive research aimed at improving and simplifying the determination of dose distributions in such therapy. A personalized approach to internal radiotherapy is necessary in light of the significantly varied results of dosimetric calculations. Performing dosimetric modeling in areas of abnormal radiopharmaceutical accumulation provides a quantitative and easily comparable parameter for evaluating the safety and efficacy of radionuclide internal radiotherapy.

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Editor's comment

The abstract of the work was submitted to the 18th Congress of the Polish Society of Medical Physics (held in Poznań, Poland, 19-21 September 2024). The authors of the work were invited by the Scientific Committee of the Congress and the Editor-in-Chief of the Polish Journal of Medical Physics and Engineering to present their work in the form of a Short Communication in the Journal.

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