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Short Communication

Individual dosimetry and monitoring response to treatment in tandem PRRT with [^{177}Lu/^{90}Y]-DOTA-TATE

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Abstract

Introduction: The Duonen project aims to test the efficacy of tandem PRRT therapy of neuroendocrine tumors with DOTA-TATE labeled with ^{177}Lu and ^{90}Y radionuclides compared to conventional mono-radionuclide therapy using ^{177}Lu with a fixed activity of 7.4 GBq. The paper presents the dosimetric procedure used and preliminary results obtained from the treatment of 40 patients and 113 cycles of therapy.

Material and Methods: Dosimetry is performed using the QDose program based on 4 SPECT/CT scans and 5 blood samples taken for bone marrow dosimetry. Calculation of the dose to the kidneys is done by segmenting them on images, fitting the corresponding activity versus time (TAC) curves and calculating the dose using the Voxel-S method. The dose to the red marrow is calculated based on the IDAC2 model using the TAC curve for blood obtained from the measurements (self-dose) and the segmented organs from images (cross-dose). In addition, the time-integrated activity coefficients of activity in selected tumors or high uptake areas in four consecutive cycles of therapy were calculated for several patients as a measure of response to therapy.

Results: Large variability of individual doses to kidneys is observed. The average specific dose for ^{177}Lu was equal to 0.76 Gy/GBq, SD = 0.29 Gy/GBq, and for ^{90}Y: 3.26 Gy/GBq, SD = 1.26 Gy/GBq. With the standard activity equal to 7.4 GBq in the first cycle, the activity in the next cycle could be increased by > 10% in 60% of cases and had to be decreased in 16% of cases.

Conclusion: Individual dosimetry is an important part of PRRT, leading to significant dose modifications in subsequent cycles in more than 80% of the cases studied.

Keywords: radionuclide therapy; PRRT; individual dosimetry; tumor response.

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.

Introduction

The Peptide Receptor Radionuclide Therapy (PRRT) of neuroendocrine tumors is well established and validated for its efficacy in disease control and relatively mild toxicity.[1-3] In many studies, individual dosimetry has been performed along the PRRT, showing a large variability of individual doses to critical organs.[4-6] However, due to the cost and complexity of the dosimetry, the therapy in most cases is based on the administration of the empirically established fixed activity of approximately 7.4 GBq ^{177}Lu- or 3.7 GBq ^{90}Y-DOTA-TATE in 3 – 5 cycles.[7] These values have been chosen in order to keep the total absorbed dose to kidneys below the critical level of 23 Gy and to the red bone marrow below 2 Gy. The critical values, adopted from the external beam radiotherapy, have been questioned in several studies suggesting that, at least in the case of ^{177}Lu, the critical dose to the whole organ could be higher, due to the highly non-uniform dose distribution in the radioisotope therapy.[8]

In this paper, the preliminary results of the individual dosimetry carried out in the framework of the Duonen project[9] are presented. The primary objective of this clinical trial is to test the efficacy of tandem PRRT of neuroendocrine tumors with mixed doses of ^{177}Lu- and ^{90}Y-DOTA-TATE, compared to the conventional mono-nuclide therapy using ^{177}Lu with a fixed activity of 7.4 GBq. Patients who meet the eligibility criteria are randomly assigned to one of the four arms of the study with the following activity administration scheme: The first arm A is the control group receiving 7.4 GBq ^{177}Lu in 4 cycles. Arm B: 3.7 GBq ^{177}Lu + 1.85 GBq ^{90}Y in the first cycle, and variable activity of ^{90}Y in the following cycles. Arm C: 3.7 GBq ^{177}Lu + 1.85 GBq ^{90}Y in the first cycle, and variable activity of ^{177}Lu in the following cycles. Arm D: 7.4 GBq ^{177}Lu in the first cycle, and variable activity of ^{177}Lu in the following cycles. The variable activities are adjusted according to the results of individual dosimetry in the previous cycles, to ensure that the critical doses to the kidneys and red marrow are not exceeded after all four cycles. Individual dosimetry is therefore one of the key elements of the study, determining whether the activity of one of the radionuclides should be increased or decreased in subsequent cycles. The following sections outline the dosimetry procedure employed and present preliminary findings regarding the variability of individual doses to kidneys obtained from the treatment of 40 patients across 113 cycles of therapy. Examples of tumor dosimetry are also shown. Apart from the tumor-absorbed doses, other quantities, such as time-integrated activity coefficients and the biological half-lives of the radiopharmaceutical, are derived from the post-therapeutic images. These may prove valuable in determining the patient's response to the therapy.

Material and Methods

Individual dosimetry procedure

The dosimetry is conducted with the aid of the QDose software (ABX-CRO). Four SPECT/CT scans are acquired at 4, 24, 48, and 192 hours post-administration of the radiopharmaceutical. The patients are scanned on the NM/CT 870 gamma camera (GE Healthcare), fitted with a medium-energy (MEAP) collimator. The scan duration is 40 minutes, with 60 projection angles. The counts are acquired in the main energy window at 208 keV ± 10% and in two scatter windows for the triple energy window (TEW) scatter correction. A CT scan is performed with standard clinical parameters to obtain attenuation correction and precise organ localization and segmentation. The images are reconstructed using the ordered subset expectation maximization (OSEM) algorithm, with two iterations, ten subsets, and attenuation and scatter corrections, as well as modelling of the collimator response function. The camera has been calibrated using point sources and a phantom with a known activity, enabling the acquisition of quantitative images.

Furthermore, five blood samples are collected: up to 5 min, 10 ± 5 min, 40 ± 10 min, 210 ± 20 min and 24 ± 3 h post administration for bone marrow dosimetry. The dose to the kidneys is calculated by segmenting the kidneys on images, fitting the corresponding activity versus time (TAC) curves, and calculating the dose using the Voxel-S method.[10] The dose to the red marrow is calculated based on the IDAC2 model utilizing the TAC curve for blood obtained from the measurements and the activities in the hot organs (liver, kidney, spleen) and the rest of the body, which are estimated from SPECT images.[11] The SPECT imaging is performed for the ^{177}Lu. The doses from ^{90}Y are calculated on the assumption of identical metabolism and activity distribution of ^{90}Y- and ^{177}Lu-DOTA-TATE. With the known injected activities of both radionuclides and their physical half-lives, the activity distribution of ^{90}Y can be computed.

Tumor metabolic activity

In addition to the dosimetry of critical organs, the absorbed doses to selected tumors or active metastatic masses in the liver are evaluated. This is done on the basis of SPECT images at four time points, similarly to the kidney dosimetry described above. However, the primary challenge lies in the accurate delineation of the tumor region of interest (ROI) through anatomical segmentation. In most cases, the precise outline of the tumor is not discernible on the CT image. Accordingly, the tumor region of interest (ROI) is selected based on the hot region visible on the SPECT image. However, the finite spatial resolution of SPECT images (7–9 mm FWHM) and the partial volume effect can result in the significant overestimation of the ROI size , particularly in the case of small tumors. Additionally, due to the short range of β radiation in tissue, the dose distribution within the tumor can be highly non-uniform. Consequently, the

calculated dose represents merely the average over the selected ROI, whereas the actual doses to active cells may be considerably higher.

In addition to the absorbed dose, other quantities that characterize tumor metabolic activity can be calculated from the time-activity curves (TAC) obtained from the images. One such quantity is the time-integrated activity coefficient (TIAC), also called the residence time, which is defined as

$$\mathrm{TIAC} = \frac{\int A(t)dt}{A_0} \qquad \text{Eq. 1}$$

where *A(t)* is the activity in ROI as the function of time, and A_0 is the injected activity. It is thus the area under the TAC, normalized to the administered activity. As a single value for a tumor, it is not particularly meaningful; however, it may be useful when the molecular activities in consecutive cycles of therapy are to be compared. To ensure the comparability of the calculated values, the region of interest (ROI) was selected as the set of pixels with the highest activity within a predefined broad boundary in the first time point image of the first cycle. This approach was then applied consistently to all subsequent images and cycles, maintaining the volume of the ROI fixed by adjusting the activity threshold to ensure that the ROI volume remained the same as in the first image. The size and shape of the active region may change over time, but by choosing the ROI of a fixed volume as described above, the computed TIAC will reflect the change in the total molecular activity of the tumor.

The TIAC may be regarded as the analogue of the Total Lesion Glycolysis used in PET FDG.[12] The widely used SUV is also a related quantity, however, it is calculated on a single time-point image, while the TIAC takes into account the whole TAC. The TAC can be fitted with a bi-exponential function, however, one of the exponentials is usually dominant, so a monoexponential also yields a good and more numerically stable fit. The biological half-life of the radiopharmaceutical in tumors, which is derived from the TAC, can provide valuable information about their molecular activity.

Results

Figure 1 shows the doses to kidneys obtained in the subgroup of patients who received ^{177}Lu at the standard activity of 7.4 GBq in a cycle. The average dose was 4.92 Gy, SD = 1.35 Gy, with a maximum value of 8.12 Gy and a minimum value of 0.97 Gy.

The obtained average dose is 17% lower than the critical dose per cycle. In 60% of cases, the kidney doses were found to be more than 10% below the critical value per cycle. Consequently, the administered activity could be increased in the subsequent cycle to achieve a more optimal therapeutic effect. In 16% of cases, the kidney doses were more than 10% higher than critical, indicating the necessity for a decrease in activity in the subsequent cycle to prevent overexposure of the kidneys. Overall, individual dosimetry resulted in alterations to the administered activity in 76% of cases, whereas only in 24% of cases the standard activity of 7.4 GBq would be continued without modification.

In the group of patients who received a combination of 3.7 GBq ^{177}Lu and 1.85 GBq ^{90}Y in one cycle the variability of the kidney doses was even greater, as illustrated in **Figure 2**.

The mean absorbed dose to the kidneys was 8.73 Gy, SD = 4.21 Gy, indicating that the majority of patients (68%) required a reduction in the administered activity in subsequent cycles. In 21% of cases, the activity could be increased.

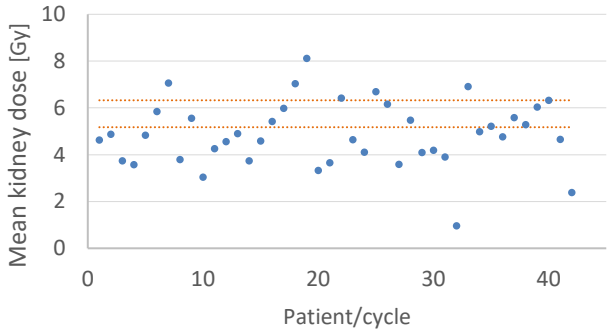

Figure 1. Doses absorbed by kidneys following the administration of the standard activity of 7.4 GBq (± 5 %) ^{177}Lu-DOTA-TATE. Results of 42 cycles (18 patients) are shown. The dotted lines indicate the range of doses corresponding to the critical dose of 5.75 Gy/cycle ± 10%.

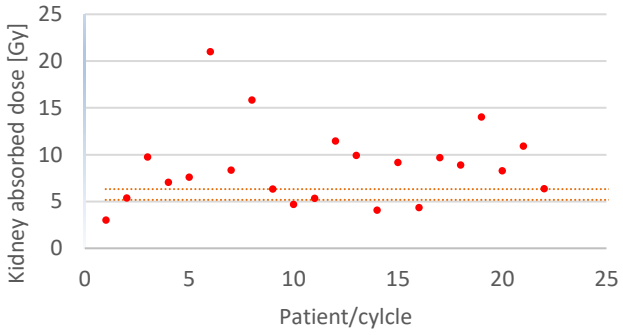

Figure 2. Doses absorbed by kidneys following the administration of the standard activity of 3.7 GBq (± 5%) ^{177}Lu + 1.85 GBq (± 5%) ^{90}Y-DOTA-TATE. Results of 22 cycles (18 patients) are shown. The dotted lines indicate the range of doses corresponding to the critical dose of 5.75 Gy/cycle ± 10%.

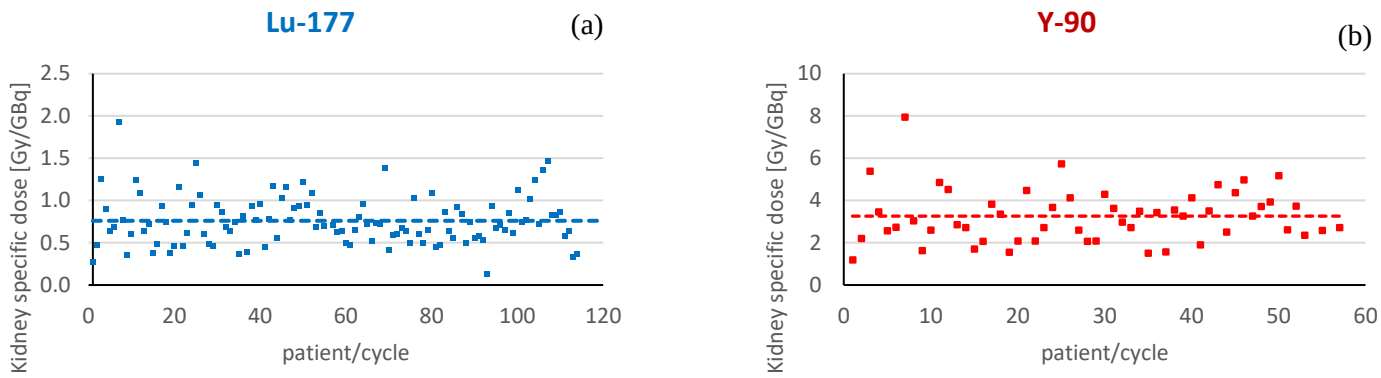

Figure 3. Specific doses per injected activity absorbed by the kidneys for ^{177}Lu-DOTA-TATE (a), and ^{90}Y-DOTA-TATE (b).

The specific doses per unit of injected activity of ^{177}Lu and ^{90}Y were calculated for all analyzed PRRT cycles, including both mixtures and ^{177}Lu-only cycles. The results are presented in **Figure 3**.

The mean kidney specific dose for ^{177}Lu-DOTA-TATE was 0.76 Gy/GBq (standard deviation (SD) = 0.29 Gy/GBq), and for ^{90}Y-DOTA-TATE, it was 3.26 Gy/GBq (SD = 1.26 Gy/GBq). It was observed that there was a considerable degree of inter-individual variability in the absorbed doses among different patients. However, the variability in dose per unit of administered activity for the same patient in different cycles was found to be considerably less.

In no case did the doses to red bone marrow exceed the critical value of 2 Gy/4 cycles, with the majority of doses being considerably lower. For the standard administered activity of 7.4 GBq ^{177}Lu, the mean red marrow dose was 0.113 Gy (SD = 0.074 Gy).

Tables 1 and **2** present the dosimetry outcomes for a selection of tumors in two patients. **Figure 4** shows the TIACs for the aforementioned tumors. In patient 1, a favorable response to the treatment was observed. The TIAC in the final cycle is reduced by a factor of four in comparison to the initial cycle, although, for tumor 1, this reduction is not observed until the third cycle. Tumor 2 has nearly disappeared in the images acquired following the fourth cycle. In contrast, patient 2 exhibits a relatively poor response, despite the high activities administered in all cycles. The TIAC in the intestinal tumor decreased by approximately 20% in the fourth cycle, following an increase in cycles two and three. In the case of an extensive metastatic mass in the liver, the TIAC in the last cycle was comparable to that of the first cycle, following an increase in cycles two and three. The favorable response to treatment also appeared to be correlated with lower biological half-lives of the radiopharmaceutical.

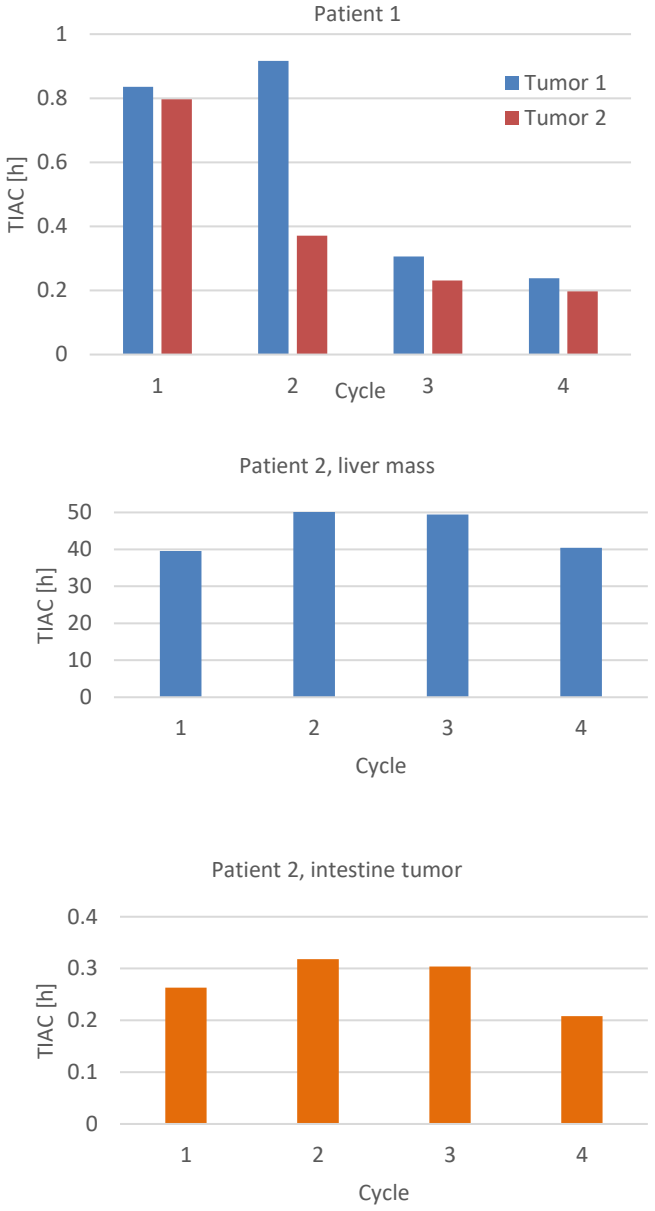

Figure 4. Time-integrated activity coefficients of selected tumors in two patients over the four therapy cycles.

Table 1. Example of dosimetry results for two selected liver tumors in patient 1, treated with 4 cycles of ^{177}Lu- + ^{90}Y–DOTA-TATE.

Cycle		1	2	3	4
Administered activity [GBq]	^{177}Lu	3.58	3.56	3.71	3.99
	^{90}Y	1.68	1.62	1.39	1.66
Dose [Gy]	Tumor1 19 ml	28.56	32.54	10.62	9
	Tumor2 30 ml	17.28	7.92	4.68	4.8
$\tau_{1/2\ biol}$ [h]	Tumor1 19 ml	248	406	196	54
	Tumor2 30 ml	256	417	295	219

Table 2. Example of dosimetry results for the active liver mass of 1500 ml and an intestine tumor, 25 ml in volume, in patient 2, treated with 4 cycles of ^{177}Lu + ^{90}Y–DOTA-TATE.

Cycle		1	2	3	4
Administered activity [GBq]	^{177}Lu	3.63	3.65	3.58	3.7
	^{90}Y	1.72	3.6	3.5	5.46
Dose [Gy]	Liver mass	18.01	39.09	35.16	42.35
	Intestine tumor	6.73	13.66	12.35	13.09
$\tau_{1/2\ biol}$ [h]	Liver mass	625	642	960	729
	Intestine tumor	524	345	1250	379

Discussion

The findings of our study unequivocally demonstrate the necessity of individual dosimetry in PRRT. A large variability in individual doses to critical organs was observed, resulting in significant dose modifications in subsequent cycles in over 70% of the cases studied. In the majority of cycles with a standard activity of 7.4 GBq ^{177}Lu, the activity administered in subsequent cycles could be increased without exceeding the critical dose to the kidney. This is a crucial aspect of the effectiveness of the treatment.

On the other hand, the dosimetry procedure is time-consuming, costly and places an additional burden on the patient. For these reasons, the fixed-dose approach is still preferred in the majority of centres. It is therefore necessary to establish a reasonable compromise in terms of the accuracy of the dosimetry in order to facilitate the provision of more personalized treatment to a greater number of patients. One potential avenue for exploration, based on the findings of our study, is the elimination of red marrow dosimetry, which represents a significant portion of the overall computational burden and patient inconvenience (requiring additional blood samples). In our patient cohort, the critical red marrow dose per cycle has not been exceeded in any case, with the average doses being 2–4 times below the critical value. Additional options include reducing the number of SPECT scans[13] to 3 or even 2, as well as improving the kidney segmentation technique, which remains somewhat cumbersome within the utilized software.

The absorbed doses to selected tumors appear to fall below the target values established for external beam therapy. However, as previously stated, the values are dependent on the selected ROI and may be influenced by the partial volume effect, rendering them less reliable. Conversely, the time-integrated activity coefficients, calculated on the fixed volume ROIs, provide a robust representation of tumor activity, exhibiting variation across cycles.

Conclusions

Individual dosimetry should be an indispensable component of the PRRT of neuroendocrine tumors with somatostatin analogues. The observed variability of doses to critical organs suggests that the fixed-dose approach may result in inadequate treatment of some patients or, less frequently, may lead to excessive kidney toxicity. Following the principles of theranostics, the post-therapeutic images can be utilized to assess the patient's response to the administered therapy. The TIAC in tumors, computed on fixed volume ROIs proposed in the paper, provides a reliable and sensitive quantitative measure of the molecular activity. The proposed method of defining the ROIs circumvents the challenge of precise anatomic delineation of the tumor, which may undergo significant alterations in consecutive cycles of therapy.

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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.

References

1. Fani M, Maecke HR, Okarvi SM. Radiolabeled Peptides: Valuable Tools for the Detection and Treatment of Cancer. Theranostics. 2012;2(5):481-501. https://doi.org/10.7150/thno.4024
2. Loharkar S, Basu S. Peptide receptor radionuclide therapy in neuroendocrine neoplasms and related tumors: from fundamentals to personalization and the newer experimental approaches. Expert Review of Precision Medicine and Drug Development. 2023;8(1):1-32. https://doi.org/10.1080/23808993.2023.2211090
3. Gabriel M, Nilica B, Kaiser B, Virgolini IJ. Twelve-Year Follow-up After Peptide Receptor Radionuclide Therapy. J Nucl Med. 2018;60(4):524-529. https://doi.org/10.2967/jnumed.118.215376
4. Sandström M, Garske-Román U, Johansson S, Granberg D, Sundin A, Freedman N. Kidney dosimetry during 177Lu-DOTATATE therapy in patients with neuroendocrine tumors: aspects on calculation and tolerance. Acta Oncologica. 2017;57(4):516-521. https://doi.org/10.1080/0284186X.2017.1378431
5. Marin G, Vanderlinden B, Karfis I, et al. A dosimetry procedure for organs-at-risk in 177Lu peptide receptor radionuclide therapy of patients with neuroendocrine tumours. Physica Medica. 2018;56:41-49. https://doi.org/10.1016/j.ejmp.2018.11.001
6. Santoro L, Mora-Ramirez E, Trauchessec D, et al. Implementation of patient dosimetry in the clinical practice after targeted radiotherapy using [177Lu-[DOTA0, Tyr3]-octreotate. EJNMMI Res. 2018;8(1). https://doi.org/10.1186/s13550-018-0459-4
7. Zaknun JJ, Bodei L, Mueller-Brand J, et al. The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2013;40(5):800-816. https://doi.org/10.1007/s00259-012-2330-6
8. Haug AR. PRRT of neuroendocrine tumors: individualized dosimetry or fixed dose scheme? EJNMMI Res. 2020;10(1). https://doi.org/10.1186/s13550-020-00623-3
9. Opalińska M, Kamiński G, Dedecjus M, et al. DUONEN multicenter study - personalized PRRT treatment with 177Lu- or 177Lu/90Y-DOTA-TATE in patients with neuroendocrine tumors based on individual dosimetry. Endocrine Abstracts. 2023;90:P440. https://doi.org/10.1530/endoabs.90.P440
10. Siegel JA, Thomas SR, Stubbs JB, et al. MIRD pamphlet no. 16: techniques for quantitative radiopharmaceutical biodistribution data acquisition and analysis for use in human radiation dose estimates. Journal of Nuclear Medicine. 1999;40(2):37S-61S.
11. Hindorf C, Glatting G, Chiesa C, Lindén O, Flux G. EANM Dosimetry Committee guidelines for bone marrow and whole-body dosimetry. Eur J Nucl Med Mol Imaging. 2010;37(6):1238-1250. https://doi.org/10.1007/s00259-010-1422-4
12. Hwang SH, Jung M, Jeong YH, et al. Prognostic value of metabolic tumor volume and total lesion glycolysis on preoperative 18F-FDG PET/CT in patients with localized primary gastrointestinal stromal tumors. Cancer Metab. 2021;9(1). https://doi.org/10.1186/s40170-021-00244-x
13. Chicheportiche A, Ben-Haim S, Grozinsky-Glasberg S, et al. Dosimetry after peptide receptor radionuclide therapy: impact of reduced number of post-treatment studies on absorbed dose calculation and on patient management. EJNMMI Phys. 2020;7(1). https://doi.org/10.1186/s40658-020-0273-8