Original Article

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Validation of Simplified Renal Dosimetry Protocols for ^{177}Lu-DOTATATE Therapy Using the IDAC-dose Software

IDAC-dose Yazılımı Kullanılarak ^{177}Lu-DOTATATE Tedavisi için Düzenlenmiş Basitleştirilmiş Böbrek Dozimetri Protokollerinin Doğrulanması

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Abstract

Objectives: The multi-time-point imaging method for renal dosimetry in lutetium-177 (^{177}Lu)-DOTATATE therapy imposes a significant burden. This study aimed to validate simplified two-time-point (2TP) and three-time-point (3TP) protocols using the International Commission on Radiological Protection-compliant IDAC-Dose 2.1 software.

Methods: This retrospective study analyzed 28 kidneys obtained from 17 patients with neuroendocrine neoplasms. Renal absorbed doses from a reference four-time-point (4TP) schedule (4, 24, 72, and 120 hours) were compared with ten simplified protocols using statistical analyses of error and agreement.

Results: Protocols that included the 120-hour time point demonstrated significantly higher accuracy. The 2TP (4, 24) protocol showed a profound underestimation [mean percentage error (MPE): -14.3%] and a high error. In contrast, the 2TP (24, 120) protocol showed excellent agreement [MPE: 0.57%, mean absolute percent error (MAPE): 5.5%]. Among 3TP methods, the 3TP (24, 72, 120) protocol yielded the highest accuracy (MAPE: 1.97%).

Conclusion: Accurate renal dosimetry in ^{177}Lu-DOTATATE therapy can be achieved with simplified protocols. Incorporating a late-phase time point (around 120 hours) is essential for reliable estimation. The 2TP (24, 120) and 3TP (24, 72, 120) combinations are suggested as feasible alternatives to the standard 4TP method.

Keywords: ^{177}Lu-DOTATATE, renal dosimetry, peptide receptor radionuclide therapy, neuroendocrine neoplasms, simplified dosimetry

Öz

Amaç: Lutetyum-177 (^{177}Lu)-DOTATATE tedavisinde böbrek dozimetresi için çok zamanlı görüntüleme yöntemi önemli bir yük oluşturur. Bu çalışma, Uluslararası Radyolojik Koruma Komitesi'ne uygun IDAC-Dose 2.1 yazılımını kullanarak basitleştirilmiş iki zamanlı (2TP) ve üç zamanlı (3TP) protokollerinin doğruluğunu doğrulamayı amaçlamıştır.

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Yöntem: Bu retrospektif çalışma, 17 hastadan alınan 28 böbreği analiz etmiştir. Bir referans dört zamanlı (4TP) takviminden (4, 24, 72 ve 120 saat) böbrek emilen dozlar, hata ve uyum istatistiksel analizleriyle on basitleştirilmiş protokolle karşılaştırılmıştır.

Bulgular: Yüz yirmi saatlik zaman dilimini içeren protokoller, anlamlı şekilde daha yüksek doğruluk göstermiştir. 2TP (4, 24) protokolü, derin bir düşük tahmin [ortalama yüzde hatası (MPE): %-14,3] ve yüksek hata göstermiştir. Buna karşılık, 2TP (24, 120) protokolü mükemmel bir uyum göstermiştir [MPE: %0,57, ortalama mutlak yüzde hatası (MAPE): %5,5]. 3TP yöntemleri arasında, 3TP (24, 72, 120) protokolü en yüksek doğruluğu elde etmiştir (MAPE: %1,97%).

Sonuç: ^{177}Lu-DOTATATE tedavisinde doğru böbrek dozimetresi, basitleştirilmiş protokollerle elde edilebilir. Geç evre bir zaman noktasının (yaklaşık 120 saat) dahil edilmesi, güvenilir bir tahmin için önemlidir. 2TP (24, 120) ve 3TP (24, 72, 120) kombinasyonları, standart 4TP yöntemine alternatif olarak uygun seçenekler olarak önerilmektedir.

Anahtar Kelimeler: ^{177}Lu-DOTATATE, böbrek dozimetresi, peptit reseptör radyonüklid tedavisi, nöroendokrin neoplaziler, basitleştirilmiş dozimetri

Introduction

Peptide receptor radionuclide therapy (PRRT) is a therapeutic approach that selectively delivers radiation to target organs in patients with somatostatin receptor-positive neuroendocrine neoplasms (NENs). The radiopharmaceutical lutetium-177 (^{177}Lu)-DOTATATE, representative of those used in PRRT, has been reported to significantly improve progression-free survival and overall survival (1,2). In PRRT, achieving high absorbed doses to tumors while minimizing radiation to normal organs such as the kidneys and bone marrow is essential (3,4,5,6,7). This principle is underscored in established international treatment guidelines (8). The kidneys are particularly radiosensitive, and a renal absorbed dose threshold of 23 Gy originally derived from external beam radiotherapy, is widely applied in clinical practice to avoid the risk of nephropathy (9). Renal absorbed dose estimates have directly influenced treatment modifications, as demonstrated in one cohort where 8 of 13 patients (62%) have discontinued the PRRT before completing the planned four cycles due to exceeding projected kidney tolerance doses (10). Furthermore, long-term follow-up studies have shown that renal dysfunction can appear several years after therapy, highlighting the importance of early dose assessment and individualized treatment planning (4). The established standard for individualized dosimetry is the multi-time-point (MTP) imaging method. This method involves generating a time-activity curve (TAC) from single photon emission computed tomography/computed tomography (SPECT/CT) images acquired at multiple time points over several days to accurately calculate the absorbed dose (11). However, this approach imposes a substantial burden on both patients and medical staff because it requires multiple days of outpatient care and prolonged SPECT acquisition. Indeed, a recent consensus statement from the Society of Nuclear Medicine and Molecular Imaging has highlighted the critical importance of personalized dosimetry in PRRT, while simultaneously acknowledging the logistical necessity of developing practical, simplified imaging schedules (12). Consequently, single-time-point (STP) methods applicable to PRRT have been proposed (13,14), and the accuracy of these methods has been evaluated in numerous studies (15,16,17). On the other hand, STP methods have also been reported to be less stable in terms of accuracy and reproducibility compared with MTP methods (18,19). The acquisition timing for renal dose assessment using SPECT is commonly based on a three-time-point (3TP) protocol, with imaging completed within 72 hours post-injection (15,16); however, this schedule may mischaracterize the critical terminal clearance phase of ^{177}Lu-DOTATATE from the kidneys. Specifically, omitting direct measurement at later time points necessitates extrapolation of the tail of the TAC, which can introduce substantial errors in the calculated time-integrated activity and, consequently, the final absorbed dose estimate. This is particularly relevant because approximately 70% of renal time-integrated activity occurs after 24 hours (20). To establish robust and reliable dosimetry, international guidelines, such as those from the European Association of Nuclear Medicine/Medical Internal Radionuclide Dose (MIRD) Committee, recommend a comprehensive imaging schedule. For radiopharmaceuticals with pharmacokinetics similar to ^{177}Lu-DOTATATE, this typically involves three to five acquisitions over a period of up to seven days to accurately characterize the TAC, including both uptake and washout phases. Therefore, a four-time-point (4TP) protocol spanning this period is widely considered the reference standard for validating simplified methods (21).

In recent years, numerous studies have investigated reduced time-point strategies, such as two-time-point (2TP) and 3TP protocols, to alleviate the clinical burden associated with MTP dosimetry. These studies have successfully demonstrated that simplified schedules can provide reliable dose estimates (10,15,22). However, these crucial validations have predominantly been performed using software based on the traditional MIRD formalism (e.g., OLINDA/EXM), which utilizes older, stylized anatomical phantoms (23).

The field of dosimetry is transitioning to a more modern, standardized framework proposed by the International Commission on Radiological Protection (ICRP). This transition represents a substantial shift from previous MIRD-based approaches, as the ICRP framework employs a new generation of anatomically realistic adult and pediatric reference phantoms alongside updated, nuclide-specific S-values. This modern framework is implemented in IDAC-Dose 2.1, an open-source, freely accessible software platform (24). The advantage over commercial and original software programs is accessibility, which is designed to promote a harmonized, internationally standardized approach to dosimetry. Removing software cost barriers and using a common ICRP-based calculation engine have the potential to unify dosimetry practices across institutions worldwide. However, to our knowledge, the performance and reliability of simplified dosimetry protocols have not yet been extensively evaluated using an ICRP-compliant platform. This validation provides additional evidence for moving the field towards genuine international standardization.

The aim of this study was to systematically evaluate, against a robust 4TP reference standard, various 2TP and 3TP combinations for renal dosimetry in ^{177}Lu-DOTATATE therapy using the ICRP-compliant, open-source software IDAC-Dose.

Materials and Methods

Patients and Treatment Protocol

PRRT in this study was performed using ^{177}Lu-DOTATATE, with a typical administered activity of 7.4 GBq per cycle. The mean administered activity was 7.47±0.17 GBq for 15 patients, while two patients received reduced doses of 5.8 GBq and 3.8 GBq, respectively. Antiemetics, including serotonin receptor antagonists, were administered prophylactically to mitigate radiation-induced nausea and vomiting. Subsequently, an amino acid solution (LysaKare, Novartis Pharma K.K, Tokyo, Japan) was administered to competitively inhibit reabsorption of the radiopharmaceutical in the renal proximal tubules, thereby reducing the renal radiation dose. ^{177}Lu-DOTATATE was administered intravenously after the LysaKare infusion.

The study Ethics Committee of Kanazawa University School of Medicine was approved by the institutional review board (approval no: 114507-1, date: 13.03.2024), and the requirement for written informed consent was waived. Clinical data were collected from 17 NEN patients who underwent four SPECT/CT scans during their first cycle of PRRT at our institution. A total of 33 kidneys were evaluated: 32 were obtained from 16 patients with bilateral kidneys, and 1 was obtained from a patient with a single kidney. However, 5 kidneys were excluded from the analysis due to severe difficulties in accurately delineating the volume of interest (VOI) and subsequently generating TACs. The specific reasons included: massive spill-in from intense physiological liver uptake compressing the right kidney, with an unclear boundary (n=1); massive spill-in from a liver tumor to the right kidney (n=1); splenic contact causing left kidney deformation and massive spill-in, complicated by a renal cyst (n=1); a right renal tumor obscuring the organ boundary (n=1); and a giant right renal tumor combined with intense liver uptake (n=1). Furthermore, because of the curve-fitting characteristics of IDAC-Dose, fluctuating activity plots caused by such spill-in or poorly defined boundaries result in variable and unreliable calculations of the time-integrated activity coefficient (TIAC). Therefore, these kidneys were excluded to ensure overall dosimetric accuracy. Consequently, twenty-eight kidneys (6 of 17 patients had only a single evaluable kidney) were included in the final analysis. Because a substantial proportion of evaluations involved a single kidney, individual kidneys were analyzed as independent samples in the statistical analysis. The baseline characteristics of the patients were as follows: the mean age was 61 years (range, 34-82 years); there were 10 male and 7 female patients. According to the World Health Organization classification (25), tumor grades were G1 in one patient, G2 in eleven patients, G3 in two patients, and unknown in three patients. The baseline estimated glomerular filtration rate was 70.8±21.8 mL/min (range: 28.4-108.0 mL/min). Diabetes mellitus and hypertension were each present in seven patients.

SPECT/CT Imaging and Image Reconstruction

SPECT/CT imaging was performed at four time points: approximately 4-, 24-, 72-, and 120-hours post-administration of ^{177}Lu-DOTATATE. The equipment used was either a Symbia Intevo 16 or a Symbia Intevo Bold (Siemens Healthineers, Erlangen, Germany), each fitted with a medium-energy, low-penetration collimator. The acquisition parameters were a matrix size of 128, a pixel size of 4.8 mm, a zoom of 1.0, and 60 views. The time per view was 10 seconds for early post-administration scans and was appropriately extended, up to a maximum of 40 seconds, for later time points as counts decreased. The energy peak was set at 208 keV with a 20% main energy window. For the triple energy window (TEW) method, two adjacent 10% scatter windows (lower and upper) were also set.

Image reconstruction was performed using xSPECT Quant (Siemens Healthineers, Erlangen, Germany) (26), employing an algorithm based on the ordered subsets

conjugate gradient minimization method. Reconstruction parameters were set as follows: iterations: 24-60; subsets: 1; Gaussian filter full width at half maximum: 16 mm. Corrections for attenuation and scatter were applied using CT-based attenuation correction and the TEW method, respectively.

Imaging Point Combinations

The various imaging point combinations evaluated in this study are illustrated in Figure 1. A total of ten simplified protocols were assessed against the 4TP reference standard: six 2TP combinations and four 3TP combinations.

TAC Generation and Absorbed Dose Calculation

Kidney VOIs was defined on the CT images of the SPECT/CT datasets. To strictly account for potential organ motion, deformation, and positional shifts between scans, VOIs were manually delineated at each imaging time point (4, 24, 72, and 120 hours), rather than propagating a single VOI from the baseline scan. Using the co-registered CT images (3-mm slice thickness) as an anatomical reference, the VOIs were drawn slice-by-slice to encompass the entire renal parenchyma while excluding the renal pelvis and cysts. To ensure consistency and minimize intra-operator variability, all delineations were performed by a single experienced operator. From these time-point-specific VOIs, activity concentration values were extracted for each time point and decay-corrected to generate a TAC. To calculate the TIAC, the TAC data was input into the integrated curve-fitting module of IDAC-Dose 2.1 (Lund University, Sweden), a publicly available internal dosimetry program (24). To formally assess intra-observer variability, a repeatability analysis was conducted. A subset of 10 kidneys, selected via computer-generated random sampling, was re-segmented at all four time points by the same operator after an interval of more than one year to eliminate recall bias. The intraclass correlation coefficient (ICC) was calculated to assess the reliability of the quantified renal radioactivity, which is the most critical determinant of dosimetric accuracy. To generate TACs and subsequently calculate TIACs, we used the software's internal compartmental system. A standard "1 uptake, 2 retention" phase model was selected to fit the data points accurately and extrapolate the terminal clearance.

The final renal absorbed dose was calculated using the IDAC-Dose software (version 2.1) based on the methods and reference phantoms described by the ICRP (27). The software settings were specifically configured for the ^{177}Lu isotope. To ensure anatomically accurate dosimetry, the ICRP Publication 110 adult male or adult female reference voxel phantom was selected according to each patient's sex. The resulting TIAC was used by the software to calculate the absorbed dose by multiplying it by the ICRP Publication 133-compliant S-values for ^{177}Lu and the administered activity for the kidneys based on the adult model described in ICRP Publication 133.

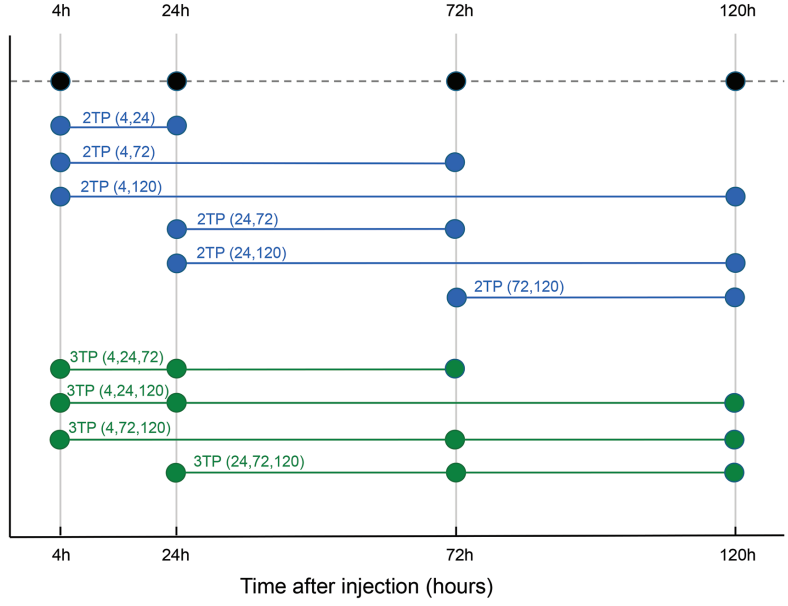

Figure 1. Schematic of the evaluated dosimetry protocols, comparing the reference 4TP schedule with six 2TP and four 3TP combinations
4TP: Four-time-point, 2TP: Two-time-point, 3TP: Three-time-point

Statistical Analysis

The accuracy of the 2TP and 3TP methods was evaluated by comparing their estimated renal absorbed doses with the reference values calculated using the 4TP method (imaging at 4, 24, 72, and 120 hours). In addition to identifying the optimal combination for each reduced-time-point method, we compared the accuracy across methods with varying numbers of imaging points. Specifically, by comparing the results of the most accurate 2TP combination with those of the least accurate 3TP combination, we assessed the importance of selecting appropriate imaging time points rather than simply increasing the number of imaging points for the accuracy of renal absorbed dose estimation. The accuracy of absorbed dose estimation for each combination of imaging points was assessed using the mean percent error (MPE), the mean absolute percent error (MAPE), and the root mean square error (RMSE). These metrics were calculated using the following equations:

Where pred is the absorbed dose calculated by each reduced-time-point method such as 2TP and 3TP methods, ref is the reference value from the 4TP method, and N is the total number of kidneys evaluated.

Additionally, Bland-Altman analysis was performed to assess agreement between each reduced-time-point method and the 4TP method by calculating the mean difference (fixed bias) with its 95% confidence interval (CI) and the limits of agreement (LoA), thereby statistically evaluating differences between the protocols. Furthermore, to formally test the differences in absolute absorbed doses among the protocols, a non-parametric Friedman test was conducted because the data consisted of repeated measurements on the same kidneys. Because the Friedman test indicated a significant overall difference, pairwise comparisons between the reference 4TP protocol and the simplified protocols were performed using the Wilcoxon signed-rank test with Holm's adjustment. An adjusted p-value of <0.05 was considered statistically significant. An acceptable accuracy threshold was predefined for the objective evaluation of the clinical viability of the simplified methods. In clinical internal dosimetry, absolute absorbed dose calculations inherently encompass various sources of methodological uncertainties, including camera calibration, image segmentation, and partial volume effects, which are generally estimated at 10% to 20% even with MTP imaging (21). Given this inherent noise floor, a predefined MAPE threshold of <10% was established as a conservative criterion for acceptable clinical equivalence. This threshold ensures that the simplification does not substantially degrade dosimetric reliability and is consistent with the optimal MAPE values reported in recent simplified PRRT dosimetry studies (22).

Results

The mean renal volume for the 28 kidneys included in the analysis was 163.2±42.4 cm³ (range: 101-279 cm³). The mean reference absorbed dose, calculated using the 4TP method, was 3222.5±1173.4 mGy (range: 1490-6040 mGy). The repeatability analysis of a randomly sampled subset of 10 kidneys demonstrated excellent intra-observer reliability for quantification of radioactivity, yielding an ICC of 0.998 (95% CI: 0.996 to 0.999). A summary of the absolute absorbed dose estimations [mean, standard deviation (SD), and range] for the reference (4TP) protocol and all ten simplified (2TP and 3TP) protocols is presented in Table 1.

Table 1. Renal volumes and absolute absorbed dose estimations for the 4TP reference and simplified 2TP and 3TP protocols

Parameter	Mean ± SD	Range (min-max)
Renal volume (cm³)	163.2±42.4	101-279
Absorbed dose (mGy)		
Reference (4TP)	3162.5±1090.3	1490-5690
2TP (4, 24)	2713.0±1313.1	955-5910
2TP (4, 72)	3309.6±1269.8	1290-6590
2TP (4, 120)	3196.4±988.6	1620-5610
2TP (24, 72)	3335.0±1274.5	1280-6400
2TP (24, 120)	3156.8±1040.2	1620-5630
2TP (72, 120)	3292.1±1203.9	1710-5790
3TP (4, 24, 72)	3219.6±1256.4	1260-6290
3TP (4, 24, 120)	3146.8±1071.1	1610-5510
3TP (4, 72, 120)	3205.4±1057.1	1490-5590
3TP (24, 72, 120)	3204.3±1118.9	1500-5820

SD: Standard deviation, 4TP: Four-time-point, 2TP: Two-time-point, 3TP: Three-time-point

Evaluation by 2TP Method

To formally evaluate the absolute absorbed doses, a Friedman test was performed. For the 2TP methods, a statistically significant overall difference was observed among the protocols (p=0.0047). However, the post hoc pairwise comparison with Holm's adjustment demonstrated no significant difference between the reference 4TP and the recommended 2TP (24, 120) protocols (adjusted p=1.000) (Figure 2).

As detailed in Figures 3 and 4, the 2TP (4, 24) protocol, which omits late-phase imaging, performed the worst across all error metrics. It exhibited a large negative bias (MPE: -14.3±30.5%) alongside the highest MAPE (29.6%) and RMSE (1271.9 mGy). Its MPE distribution was skewed towards negative values with a wide interquartile range. In stark contrast, protocols incorporating the 120-hour time point demonstrated significantly improved accuracy. Specifically, the 2TP (24, 120) combination yielded the highest precision, displaying the smallest MPE (0.57±5.8%) and a remarkably low MAPE (5.5%). Both 2TP (24, 120) and 2TP (4, 120) maintained MAPE values well below our predefined 10% clinical threshold and RMSE values below 400 mGy.

The Bland-Altman analysis of the 2TP methods is shown in Figure 5. The 2TP (4, 24) protocol showed a large, statistically significant negative fixed bias (mean difference: -603.2 mGy, 95% CI: -991.2 to -273.1 mGy) and wide LoA. For these two protocols, 2TP (4, 120) and 2TP (24, 120), the 95% CIs for the mean difference included zero (95% CI: -33.4 to 125.9 mGy and -161.2 to 44.6 mGy, respectively), indicating no statistically significant systematic bias. The 95% CIs for the other 2TP protocols were: 2TP (4, 72) (-5.4 to 227.8 mGy), 2TP (24, 72) (59.7 to 354.6 mGy), and 2TP (72, 120) (19.1 to 234.4 mGy) (Figure 5).

Evaluation by 3TP Method

For the 3TP methods, the Friedman test also revealed a significant overall difference in absolute absorbed doses (p=0.019) (Figure 6). The post-hoc analysis indicated that the high-precision 3TP (24, 72, 120) protocol showed a statistically significant difference compared with the 4TP reference (adjusted p=0.0057), whereas the 3TP (4, 24, 72) and 3TP (4, 24, 120) protocols did not show significant differences (adjusted p=1.000 for both).

The MPE, MAPE, and RMSE for the 3TP combinations are summarized in Figures 7 and 8. While all 3TP methods demonstrated clinically acceptable error margins based on our predefined threshold (MAPE ≤10%), the 3TP combination (24, 72, 120) outperformed the other combinations. It achieved the smallest bias (MPE: 1.24±2.2%) with the narrowest interquartile range, the lowest MAPE (1.97%), and an exceptionally low RMSE (58.1 mGy).

The Bland-Altman analysis of the 3TP methods is shown in Figure 9. The 3TP (4, 24, 72) protocol, which omits imaging beyond 72 hours, exhibited a large SD of differences (340.3 mGy) and wide LoA, ranging from -632.7 to 701.2 mGy.

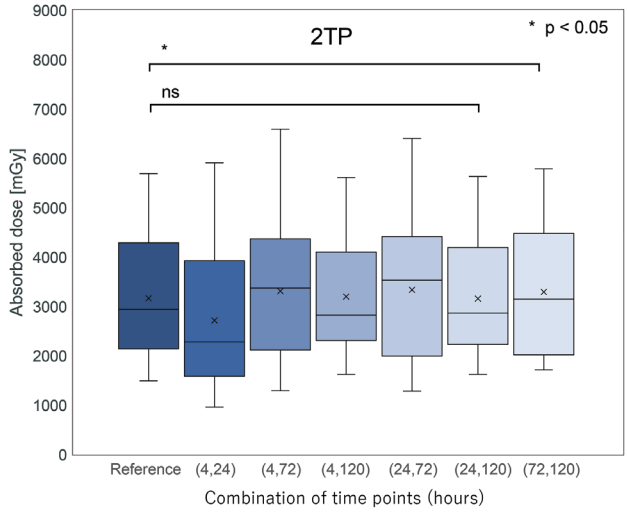

Figure 2. Absolute renal absorbed doses for the reference 4TP and simplified 2TP protocols. Boxes show the interquartile range, the median (line), and the mean ("x"); whiskers indicate the minimum and maximum values. *adjusted p<0.05 vs. 4TP (Friedman test followed by Wilcoxon signed-rank test with Holm's adjustment); not significant
4TP: Four-time-point, 2TP: Two-time-point

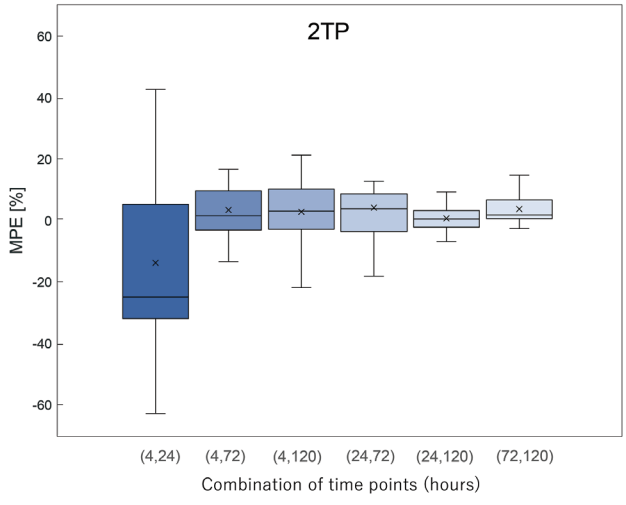

Figure 3. Mean percent error of each 2TP protocol relative to the 4TP reference. Box plot elements as in Figure 2
4TP: Four-time-point, 2TP: Two-time-point

In contrast, replacing the 72-hour time point with the 120-hour time point in the 3TP (4, 24, 120) protocol reduced the SD of the differences to 189.3 mGy. The smallest SDs of the differences were observed for 3TP (4, 72, 120) and 3TP (24, 72, 120), with values of 63.6 mGy and 78.0 mGy, respectively; these yielded the narrowest LoAs. For these two high-precision protocols, the 95% CIs for the mean differences did not include zero. The 95% CIs for the mean differences in the 3TP combinations were as follows: 3TP (4, 24, 72) (-81.9 to 132.9 mGy), 3TP (4, 24, 120) (-75.8 to 43.7 mGy), 3TP (4, 72, 120) (21.6 to 61.8 mGy), and 3TP (24, 72, 120) (19.8 to 68.9 mGy) (Figure 9).

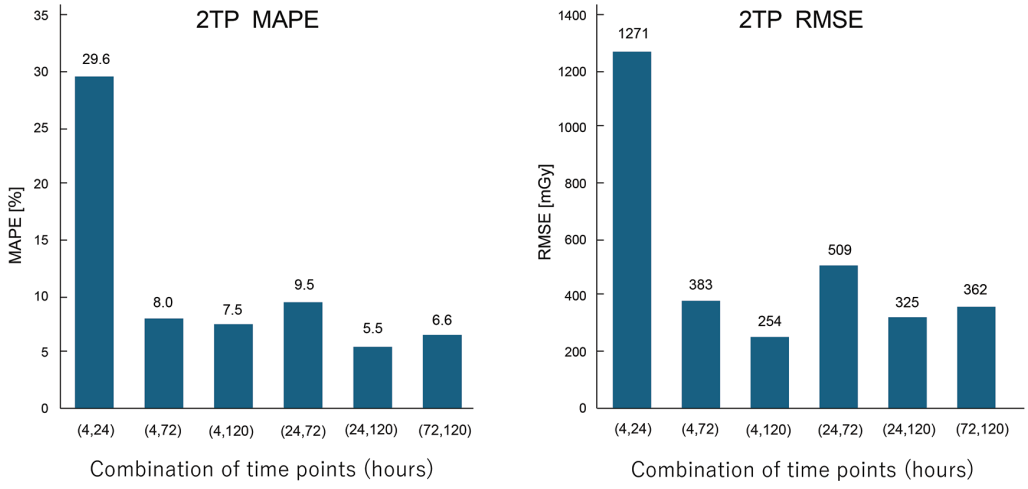

Figure 4. MAPE and RMSE for each 2TP protocol
MAPE: Mean absolute percent error, RMSE: Root mean square error, 2TP: Two-time-point

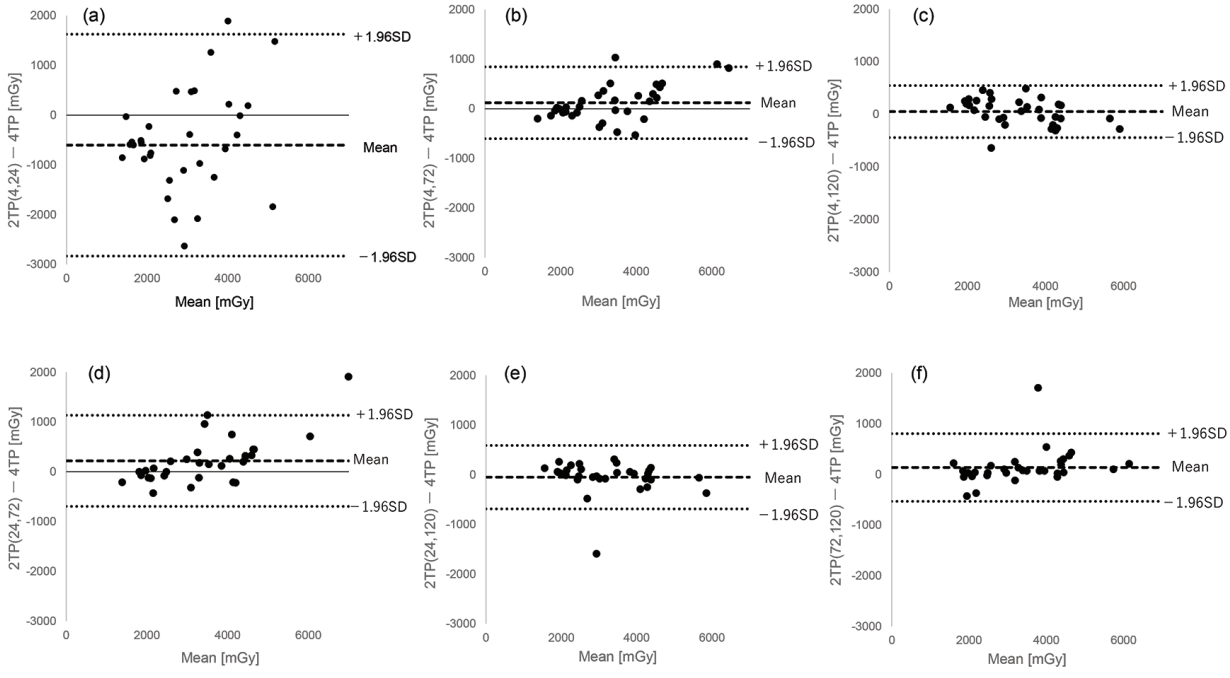

Figure 5. Bland-Altman plots comparing absorbed doses from 2TP protocols with the 4TP reference. Solid lines indicate the mean difference (bias); dashed lines indicate the 95% limits of agreement
4TP: Four-time-point, 2TP: Two-time-point, SD: Standard deviation

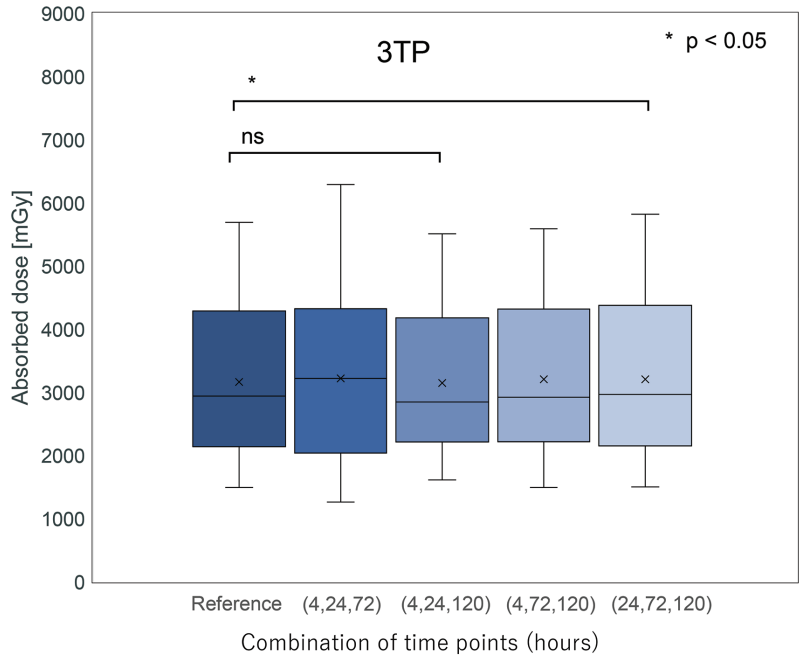

Figure 6. Absolute renal absorbed doses for the 4TP and simplified 3TP protocols. Box plot elements and statistical tests as in Figure 2. *adjusted p<0.05, **adjusted p<0.01 vs. 4TP; not significant
3TP: Three-time-point, 4TP: Four-time-point

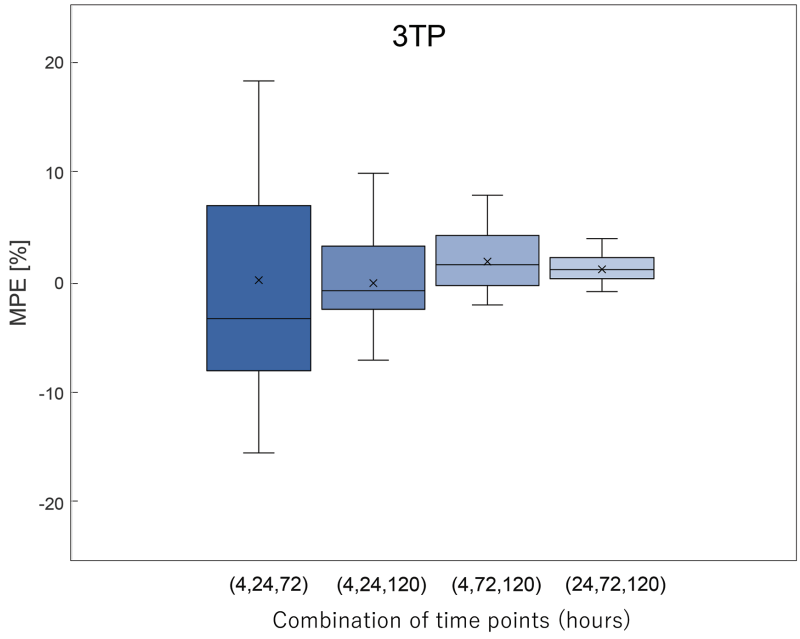

Figure 7. MPE of each 3TP protocol relative to the 4TP reference. Box plot elements as in Figure 2
MPE: Mean percent error, 3TP: Three-time-point, 4TP: Four-time-point

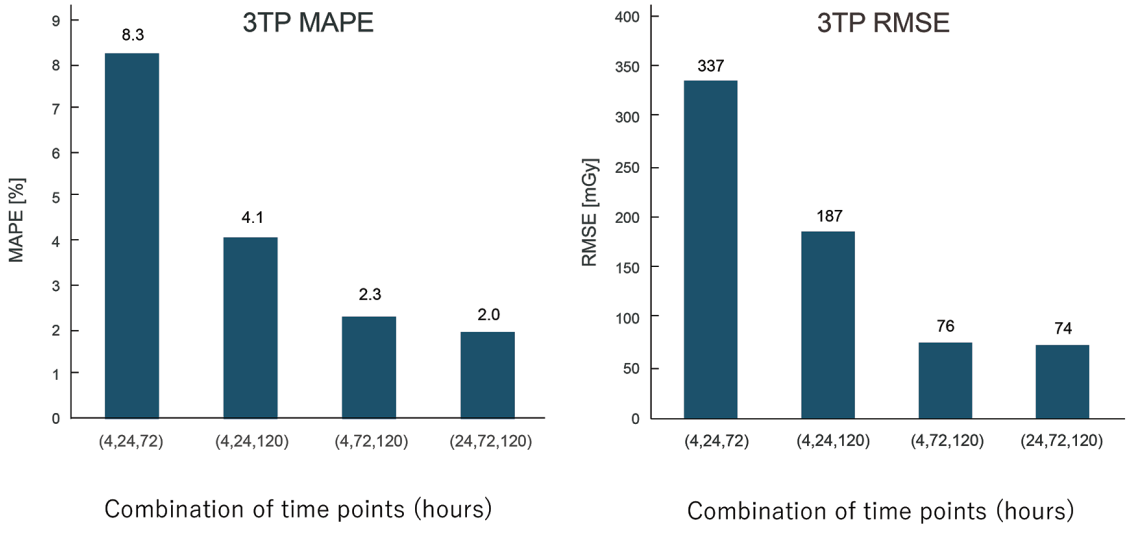

Figure 8. MAPE and RMSE for each 3TP protocol
MAPE: Mean absolute percent error, 3TP: Three-time-point, RMSE: Root mean square error

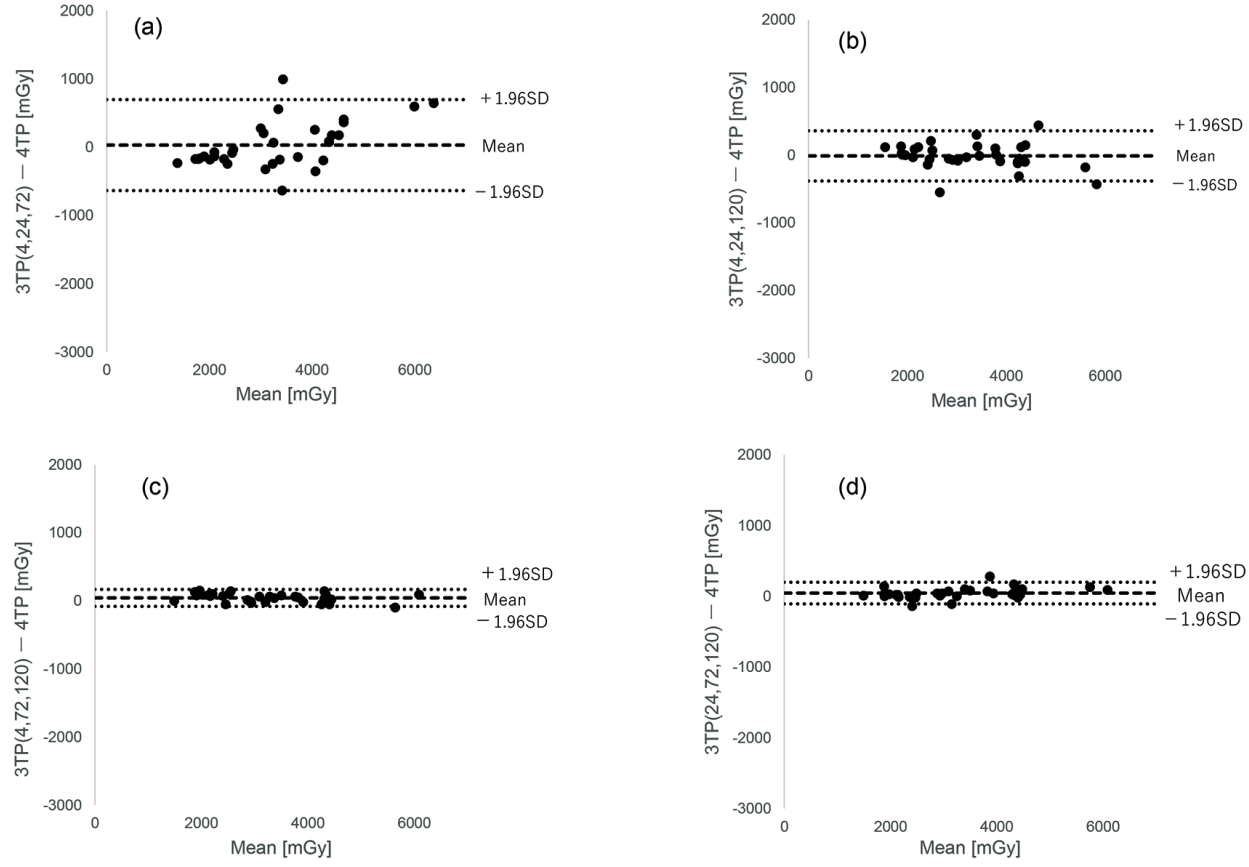

Figure 9. Bland-Altman plots comparing absorbed doses from 3TP protocols with the 4TP reference. Lines are defined as in Figure 5
3TP: Three-time-point, 4TP: Four-time-point, SD: Standard deviation

Discussion

The optimization of ^{177}Lu-DOTATATE therapy depends on patient-specific dosimetry to balance tumor control against toxicity to organs such as the kidneys and bone marrow. Conventional MTP protocols are accurate but clinically burdensome, motivating research into simplified approaches. The primary determinant of accuracy is not the number of acquisitions but the choice of imaging times (22,28,29,30).

This study shows that accurate renal dosimetry can be achieved with simplified protocols if they include a late-phase acquisition. Our results highlight the necessity of an imaging point around 120 hours post-injection to capture terminal renal clearance. For example, the 2TP (4, 24) protocol substantially underestimated the dose (RMSE: 1271 mGy) because it relied solely on early distribution data, thereby overestimating washout and underestimating the absorbed dose. In contrast, protocols incorporating a late point—2TP (24, 120) and 2TP (4, 120)— successfully met our predefined acceptable threshold of MAPE <10% (RMSE: 325 mGy and 254 mGy). The combination of a 24-hour baseline and a 120-hour terminal point enabled robust estimation of the effective half-life using the selected compartmental model. Notably, the 2TP (24, 120) protocol outperformed the 3TP (4, 24, 72) (RMSE: 325 mGy vs. 337 mGy), underscoring that late data are more valuable than additional early points. Since ~70% of renal time-integrated activity occurs after 24 hours (29), omission of late acquisitions critically undermines reliability.

The Bland-Altman analysis provided further critical insights beyond average error metrics. It confirmed that the poor performance of protocols lacking late data, such as 2TP (4, 24), was not due to random error but to a significant systematic bias that consistently underestimated the absorbed dose. Similarly, the 3TP (4, 24, 72) protocol, despite a modest mean error, exhibited wide LoA, indicating poor precision and making it unreliable for individual patient dosimetry. In stark contrast, the 2TP (24, 120) protocol showed no significant systematic bias and had narrow LoA, demonstrating good agreement with the 4TP reference standard in this cohort. The high-precision 3TP protocols further narrowed these limits, confirming their robustness for providing reliable, patient-specific dose estimates.

The statistical testing of the 3TP methods highlighted an important distinction between statistical significance and clinical relevance. The 3TP (24, 72, 120) protocol, despite yielding the lowest error metrics (MAPE of 1.97% and RMSE of 58.1 mGy), demonstrated a statistically significant difference from the reference standard (adjusted p=0.0057) with a narrow 95% CI (19.8 to 68.9 mGy) that did not cross zero. This statistical significance is observed because the protocol is exceptionally precise; the systematic bias is so consistently small across all kidneys that it is detected by the paired test. However, considering our predefined clinically acceptable threshold of <10% MAPE, this minimal absolute difference (~50 mGy on average) is negligible in the context of clinical dosimetry. Therefore, the 3TP (24, 72, 120) method remains a highly robust and clinically reliable alternative despite minor statistical variation.

From practical and logistical perspectives, the 2TP (24, 120) schedule is highly feasible and patient-centered. The 24-hour acquisition conveniently aligns with the typical time of hospital discharge following the administration of the radiopharmaceutical. The 120-hour acquisition requires only a single outpatient follow-up visit a few days later. Compared with the standard 4TP schedule, eliminating two intermediate SPECT/CT sessions significantly reduces the physical, logistical, and financial burdens for patients. Simultaneously, it frees valuable gamma camera time and reduces workload for clinical staff. Furthermore, while our study validated the 120-hour point, this specific timing may not be a strict, universal optimum for every institution. Depending on specific facility workflows and scheduling constraints—such as avoiding weekend imaging—other late-phase acquisitions (e.g., 144- or 168-hours post-injection), when combined with the 24-hour baseline, may offer similar dosimetric utility. These alternative late-point combinations represent viable and flexible options that should be explored in future studies to further accommodate diverse institutional needs.

Our focus on simplifying the imaging schedule aligns with the contemporary trend toward favoring routine clinical use of PRRT dosimetry. For example, a recent study by Pirozzi Palmese et al. (31) demonstrated that simplified longitudinal protocols—specifically, performing dosimetry only at the first and fourth cycles—provide cumulative absorbed dose estimates in excellent agreement with full four-cycle dosimetry, thereby significantly improving the cost-benefit ratio. While their work successfully optimized the number of evaluated treatment cycles, our study complements this effort by optimizing the number of imaging time points per cycle. Together, such streamlined strategies offer an optimal balance between clinical feasibility and quantitative accuracy, reducing the burden on both patients and hospital resources.

Validating simplified renal dosimetry protocols within the modern ICRP-based framework represents a primary focus of this work and provides additional evidence to the field. IDAC-Dose 2.1 (24) incorporates the ICRP Publication

110 adult reference voxel phantoms, thereby enabling anatomically accurate dose assessment from real patient CT data. This approach provides a distinct advantage over legacy MIRD-based systems, such as OLINDA/EXM version 1.0 (10, 15, 22), which were based on stylized mathematical phantoms defined by analytical equations and possessed inherent limitations in representing realistic human anatomy.

Software accessibility is a critical factor for broad clinical implementation and multi-center standardization. IDAC-Dose eliminates economic and administrative hurdles as an open-source and freely available platform (24). Commercial platforms such as OLINDA/EXM often impose significant financial and licensing barriers to initial implementation and subsequent upgrades, potentially hindering the widespread adoption and inter-institutional harmonization of dosimetry protocols.

Dosimetric results obtained using IDAC-Dose 2.1 for the adult cohort in this study are methodologically equivalent to those of the latest version. The primary advancement of the recently released IDAC-Dose 2.2 is the inclusion of pediatric reference phantoms. The computational methodology for adult phantoms remains consistent between versions 2.1 and 2.2, ensuring the continued validity of the findings presented here. Software choice is known to affect dose estimates due to differences in phantoms, S-values, and curve fitting (32,33,34). A key question was whether principles derived from MIRD-based systems remain valid in an ICRP-compliant setting. Our results confirm that the fundamental requirement for late acquisition also holds for IDAC-Dose. This reflects the sensitivity of its compartmental fitting model to accurate characterization of the terminal clearance phase (19).

The dosimetry accuracy depends on the entire workflow, including imaging, reconstruction, VOI delineation, and dose calculation (29,35). This study should therefore be considered a pilot study establishing proof of concept. Nonetheless, by demonstrating a simplified, efficient, and accurate protocol within an ICRP-compliant framework, our work provides the foundation for large, multicenter studies needed to establish standardized protocols and to promote broader clinical adoption of individualized dosimetry in PRRT.

Study Limitations

This study has several limitations. First, VOIs were delineated manually at each time point. While this approach ensures anatomical precision for each specific scan, it is labor-intensive and may introduce operator-dependent variability compared to automated segmentation methods. Although our intra-observer repeatability analysis, performed by a single experienced operator, demonstrated excellent consistency in radioactivity quantification (ICC =0.998), the absence of an inter-observer variability assessment remains a limitation. Furthermore, our findings are based on a uniform workflow using a single scanner type, specific reconstruction algorithms, and a standard amino acid protocol. Because variations in these technical factors can influence absolute dosimetric quantification, future multicenter studies evaluating diverse clinical setups are necessary to fully establish the generalizability of these simplified methods. Second, this study should be considered a proof-of-concept pilot, and larger cohorts are needed for further validation. Third, we acknowledge a unit-of-analysis limitation regarding statistical independence. Because 6 patients had only one evaluable kidney, we treated each kidney as independent samples to maximize the use of available data. However, for patients with bilateral evaluations, the pharmacokinetics in the two kidneys of the same individual are likely to be correlated. A more robust statistical approach in larger future studies would be to apply a mixed-effects model treating patients as random effects.

Finally, because this was a retrospective pilot study establishing proof-of-concept for the IDAC-Dose 2.1 framework, a formal a priori sample-size calculation was not performed. The cohort size was determined by the available clinical data that met our strict inclusion and segmentation criteria during the study period. We acknowledge this lack of a formal justification of power as a limitation. Nevertheless, the quantitative data, variances, and effect sizes generated in this study will serve as an essential and reliable foundation for accurate power calculations in future, larger-scale prospective multicenter trials designed to standardize these simplified protocols.

Conclusion

This study demonstrates that accurate renal dosimetry in ^{177}Lu-DOTATATE therapy can be achieved with simplified protocols. Incorporating a late-phase time point (specifically the 120-hour time point used in our study) is essential to improve the accuracy of bi-exponential curve fitting and to reduce dose-estimation errors. Our findings, which, to our knowledge, are among the first to be evaluated in an ICRP-compliant framework, identify the 2-time-point (24, 120 h) and 3-time-point (24, 72, 120 h) combinations as robust and practical alternatives. Adopting these pharmacokinetic-driven schedules provides a clear pathway for reducing patient and institutional burdens while maintaining high-quality, personalized dosimetry for PRRT.

Ethics

Ethics Committee Approval: The study Ethics Committee of Kanazawa University School of Medicine was approved by the institutional review board (approval no: 114507-1, date: 13.03.2024).

Informed Consent: This is retrospective study.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: A.Y., T.K., H.Y., H.W., Concept: A.Y., T.S., T.K., H.W., Design: A.Y., T.S., T.K., H.I., Data Collection or Processing: A.Y., Analysis or Interpretation: A.Y., T.S., T.K., H.Y., H.I., H.W., Literature Search: A.Y., T.S., T.K., Writing: A.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

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Availability of Data

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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