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MINI REVIEW

Radioligand therapy and tumor dosimetry: where are we and where are we going; are we in the era of personalized radioligand therapy?

F. Serani[1,2] · **M. Maccauro**[3]

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Abstract
The landscape of Nuclear Medicine is being fundamentally transformed by the theragnostic concept, which integrates diagnosis with radiopharmaceuticals and targeted radioligand therapy (RLT) for a personalized approach to cancer treatment. While European Directive 2013/59/Euratom mandates dosimetry for organs at risk, current clinical practice still largely relies on standardized, fixed-dose regimens for [177Lu]Lu-DOTATATE and [177Lu]Lu-PSMA-617. However, emerging evidence from key studies (such as LUMEN and LUTADOSE) demonstrates that tumor-absorbed dose is a powerful prognostic factor for progression-free survival, suggesting that a shift toward individualized, dosimetry-guided treatment is essential to maximize the therapeutic index. Despite these findings, significant challenges hinder routine implementation, including the methodological heterogeneity of dosimetric approaches and the logistical burden of multiple post-therapy SPECT/CT acquisitions. Innovative solutions, such as Artificial Intelligence (AI) and Deep Learning (DL), are currently being explored to facilitate pre-therapy dose prediction at the voxel level. Ultimately, the successful transition to precision dosimetry requires unprecedented multidisciplinary collaboration among nuclear medicine physicians, physicists, and regulatory bodies. Establishing unified standards and machine protocols is crucial to ensure that every patient receives optimal benefit from evolving therapeutic approaches, which will further facilitate the translation of these findings into future radiopharmaceutical developments.

Keywords Radioligand therapy · RLT · Dosimetry · Personalized therapy · [177Lu]Lu-PSMA-617 · [177Lu]Lu-DOTATATE

The RLT breakthrough

In recent years the landscape of Nuclear Medicine has been transformed by the evolution of the theragnostic concept in which diagnosis and specific targeted therapy are combined to achieve a personalized treatment approach to the patient; theragnostic is often performed utilizing the same molecule labeled with two different radionuclides; one radionuclide for imaging and another for therapy [1]. A lot has changed since the first administration of radioactive iodine to treat thyroid cancer in late '30s Saul Hertz [2], however few questions still are not answered.

Even though theragnostic is not a new concept in Nuclear Medicine, only in recent years, first with the NETTER-1 study [3] with the approval of [^{177}Lu]Lu-DOTATATE for midgut and pancreatic neuroendocrine cancers and more recently with the approval of [^{177}Lu]Lu-PSMA-617 for metastatic castration resistant prostate cancer (mCRPC) through the VISION [4], radioligand therapy (RLT) made a serious breakthrough in the oncological treatment landscape.

The theragnostic concept has made the "you see it, you treat it" motto more real than ever.

✉ F. Serani
francesca.serani@unipd.it

[1] Department of Medicine — DIMED, University of Padua, Padua, Italy

[2] Nuclear Medicine Unit, DIDAS — Integrated Diagnostic Services, University—Hospital of Padova, Padova, Italy

[3] Nuclear Medicine Department, Foundation IRCCS, Istituto Nazionale Tumori, Milan, Italy

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The dosimetry mandate and the push for personalization

Dosimetry estimation for organ at risk (OARs), always a concern in RLT, has become mandatory according to European Directive 2013/59/Euratom and even though it mandates also individualized planning and verification for radioligand therapy (RLT) to satisfy the "as low as reasonably achievable" (ALARA) principle to non-target volumes, clinical practice still largely relies on standardized dosing [5, 6]. Although international guidelines for tumor-specific dosimetry are currently lacking, a consensus is forming around the necessity of shifting toward individualized, dosimetry-guided treatments to maximize the therapeutic index [7]. Unlike external beam radiotherapy, RLT lacks agreed-upon absorbed dose thresholds for lesions, with most established constraints focusing on OARs [6, 8–10].

This review examines recent dosimetry studies to evaluate how tumor-delivered doses correlate with patient prognosis and explores ongoing trials aiming to optimize RLT through personalized treatment planning.

Post-therapy dosimetry in RLT: prognostic value and methodological divergence

In the last years few studies emerged stating the importance of SPECT/CT after RLT.

Even though not many studies have been published yet about RLT dosimetry of [177Lu]Lu-PSMA-617 Emmett et al. [11] proposed a personalized RLT strategy stratifying treatment decisions through early PSA response and visual changes in Total Tumor Volume (TTV) on post-treatment [177Lu]Lu-PSMA-617 SPECT/CT. Unlike formal dosimetry, this approach relies on visual assessment, identifying favorable responders (> 30% TTV reduction and PSA response), who could benefit from "treatment holidays" to limit cumulative toxicity, and unfavorable responders - patients who showed minimal PSA reduction and new lesions. Significant differences were noted in baseline SUVmean and delta SUVmax, which dropped sharply in favourable responders compared to unfavorable ones ($p < 0.01$). While acknowledging limitations inherent to the retrospective nature of the study the authors conclude that these preliminary results raise important questions regarding the clinical value of incorporating composite biomarkers derived from quantitative Lu-SPECT and early PSA response to rationally guide therapy management [11].

During the last year and a half three quite similar but different and independent European studies have been published on the prognostic role of SPECT/CT dosimetry after standard dose administrative treatment of Peptide Receptor Radionuclide Therapy (PRRT) utilizing [177Lu] Lu-DOTATATE.

The standard regimen of PRRT typically involves four fixed-activity injections (7.4 GBq); these three studies [12–14] explored the potential of individualized dosimetry and molecular imaging parameters to serve as early predictive biomarkers for treatment outcome, particularly Progression-Free Survival (PFS).

The most critical similarity, even though with the differences in methodology (detailed in Table 1), across the prospective LUMEN study [13], the retrospective Hebert et al. study [14], and the prospective LUTADOSE trial [12] is the conclusion that dosimetric or volumetric parameters of the SPECT/CT after the first cycle post PRRT predict patient PFS; the central finding is the association between the tumor-absorbed radiation dose and patient outcome.

Mileva et al. with the LUMEN study [13] found that patients receiving a minimal absorbed dose of at least 35 Gy across all target lesions measured at SPECT/CT after Cycle 1 (C1) had a significantly longer median PFS (48.1 months) compared to those who did not (26.2 months).

Hebert et al. [14] found that lesion dosimetric indices had prognostic value, noting that patients with a mean total absorbed dose per target lesion greater than 91.36

Table 1 Dosimetry methodology of LUMEN, LUTADOSE and Hebert et al. STUDIES.

Study	Software for dosimetry	Time Points and timing	Dosimetry Model and Partial Volume Correction (PVC) method
LUMEN (Mileva et al.) [13]	MIM Encore v6.9	After 4 h, 24 h, 168 h of each cycle	Sphere model (OLINDA/EXM 1.1) with recovery coefficient derived from NEMA phantom.
LUTADOSE(Maccauro et al.) [12]	PHILIPS IMALYT-ICS (segm.) / Olinda v1.1 (calcolo)	After Cycle 1 and Cycle 4 both at 20 h and 162 h	Sphere model (OLINDA/EXM 1.1). PVC was performed by applying recovery coefficient derived from a study specific phantom.
Hebert et al. [14]	PLANET Dose v3.1.1 (DOSIsoft)	For Cycle 1 and 2: 4 h, 24 h, 72 h, 192 h; after Cycle 3 and 4: at 24 h (single time point)	For lesions volume of interests were initially delineated on baseline contrast enhanced CT and then drawn on scintigraphy imaging. PVC was performed by applying a recovery coefficient based on previously performed calibration studies.

Table 2 Outcome comparison of the studies LUMEN, LUTADOSE and Hebert et al. studies.

Study	Predictive Index (Cut-off)	Outcome	PFS (High Dose Group)
LUMEN Mileva et al.	Minimal Cycle 1 Dose≥35 Gy	PFS	48.1 months
LUTADOSE Maccauro et al.	Mean Cycle 1 Dose (GTD1)≥10.6 Gy	PFS	>45.5 months (Not reached)
Hebert et al.	Min Total Absorbed Dose≥52.52 Gy (Cumulative)	PFS & OS	41 months (PFS)

Gy were more likely to have longer PFS (39.4 months vs. 23.6 months). Furthermore, patients with a minimum total absorbed dose greater than 52.52 Gy had a higher probability of both PFS and overall survival (OS).

Maccauro et al. [12] demonstrated that the Global Mean Tumour absorbed Dose after Cycle 1 (GTD1), when stratified by a cut-off of 10.6 Gy, was statistically associated with PFS. Patients above this threshold had a median PFS that was not reached (longer than 45.5 months), significantly better than those below the 10.6 Gy threshold (21 months).

Both Hebert et al. [14] and Maccauro et al. [12] observed that tumor-absorbed doses tend to decrease over subsequent PRRT cycles. Mileva et al. [13] also reported that the tumor-absorbed dose declined from Cycle 1 to Cycle 4. This observation reinforces the strategic importance of the data derived from early treatment cycles. This was not a new finding; the tumor-absorbed dose tend to decrease in time and this is a known issue of RTL [11, 15].

A major point of divergence in the three studies lies in the methodological approaches, particularly the complexity and timing of imaging protocols, and the specific dosimetric index chosen for predictive stratification.

Mileva et al. [13] in the LUMEN study relied on SPECT/CT acquisitions at three time points (4, 24, and 168 h) for every cycle tumor dosimetry.

For their retrospective cohort Hebert et al. [14] acquired images at four time points (4, 24, 72, and 192 h) for the initial cycles (Cycle 1 and Cycle 2) for SPECT/CT dosimetry. However, for organizational reasons, cycles 3 and 4 were simplified to a single time point SPECT/CT acquisition 24 h after injection.

Maccauro et al. in the LUTADOSE trial [12] aimed to test a feasible dosimetric schedule for routine clinical use. Dosimetry was performed only after Cycle 1 and Cycle 4, using two SPECT/CT scans for each dosimetric cycle: one at day 2 (~ 20 h post injection) and one at day 8 (~ 162 h post injection). Moreover, they specifically developed a OS-CG algorithm this purpose. The authors suggest that this simplified two-scan schedule is clinically effective.

While all studies point to dose predictability, the crucial dose threshold values differed substantially (Table 2).

Maccauro et al. specifically noted the differences in their threshold (10.6 Gy, based on mean dose) compared to the minimal dose threshold (35 Gy) found by Mileva et al. They suggest these quantitative differences likely stem from variations in patient cohort characteristics and the methodology used to calculate the mean absorbed dose.

From these studies we can notice that the three cohorts, all consisting of GEP-NET patients treated with the standard regimen, exhibited different clinical outcomes: Mileva et al. [13] reported an intermediate median PFS of 28.1 months, with a best objective response rate (PR) of 30%. Hebert et al. [14]reported a median PFS of 30.72 months, with a partial response rate of 22%.

Maccauro et al. [12] reported the longest median PFS for their overall cohort at 42 months. The high dose group's median PFS was not reached (> 45.5 months). They had a relatively low partial response (PR) rate (7%). The authors, already making comparisons with Mileva et al. and Hebert et al. suggest their patients might have been "less advanced" compared to other cohorts.

Maccauro et al. observe a seeming "paradoxical situation" where centers reporting higher objective response rates (Mileva and Hebert) tend to report shorter PFS values, suggesting that stabilization (low dose/low response) may be a more beneficial long-term strategy for this type of slow-growing tumor than high response rates followed by faster progression.

Despite the differences both for dosimetry methodology used and for differences both on the absorbed dose cut-off and the timepoint in the studies the consensus is that tumor dosimetry after the first administration of [^{177}Lu]Lu-DOTATATE is a powerful prognostic factor for patient outcome.

However, none of these three studies considered the predictive value of the pretreatment and selective potential of the pretreatment PET/CT imaging.

Moreover, in the specific cohorts of these three studies the tumor sink effect was not stated if it was considered.

Pre-treatment prediction, SUV, and the tumor-sink effect

Although few, there are some studies investigating the potential pretreatment prediction value of pre therapy PET/CT, mainly focusing on ^{68}Ga labeled radiopharmaceuticals.

One of these is the study from Violet et al. [15] published in 2019 studied radiation dosimetry using an automated voxelized dosimetry tool. The researchers specifically evaluated whether baseline [^{68}Ga]Ga-PSMA-11 imaging was predictive of the absorbed radiation dose. They also assessed the relationship between the absorbed dose in normal tissues (organs at risk) and tumor tissue, and subsequent

toxicity and clinical response. Whether a ''sink effect'' was evident, which means that an elevated tumor burden reduces the uptake on OAR, specifically salivary glands in [177Lu]Lu-PSMA-617 and kidneys and spleen fro [177Lu]Lu-DOTATATE therefore reducing the potential damages due to radiation exposure to these organs, and whether dose in normal tissues and tumor can predict toxicity and clinical response.

They performed thirty dosimetric image sets after initial therapy with serial quantitative SPECT/CT encompassing neck to pelvis performed 4, 24, and 96 h after injection.

Mean ''whole-body'' tumor volume was determined by applying a 5-Gy threshold to the voxel dose volumes and then removing regions of physiologic uptake.

The methodology aimed to define the mean "total-body" tumor dose alongside lesional tumor dosimetry, based on the hypothesis that this whole-body measure might be more clinically relevant for outcomes.

The study investigated the prognostic value of biomarkers, including PSMA PET tumor volume (PSMA-TV). In this specific cohort, Violet et al. [15] did not observe a statistically significant correlation between PSMA-TV and overall survival (OS) in the patients treated with [^{177}Lu]Lu-PSMA-617. Both soft-tissue and bone metastases separated showed a significant correlation between SUVmean and mean absorbed dose, respectively. There was a trend for a higher SUVmean to be associated with a PSA response at 12 weeks, with a median SUVmean of 8.9 (mean, 9.2; SD, 2.8; IQR 5.3–15.6) in patients achieving a decline of at least 50%, versus 7.0 (mean, 7.3; SD, 1.9; IQR 5.1–12.1) in those who did not.

The authors underlined that a similar association is reported for [^{68}Ga]Ga-DOTATOC PET/CT where the SUVmax may predict response to radionuclide therapy [16]; however in their study they were unable to determine a SUVmean below which patients are unlikely to respond, though there was a trend for a higher SUVmean to be associated with a PSA response at 12 weeks [15].

Violet et al. in their study observed that SUVmax and absorbed dose in salivary glands and kidneys decreased significantly with a greater disease burden and a larger physical size. Such finding may be relevant in predicting salivary gland and renal toxicity as stated in precedent studies on radiolabeled somatostatin analogs [17]; however they found no correlation between absorbed dose and renal function. These data suggest that it may be optimal to deliver higher administered activities to patients with a larger burden of disease and size and, conversely, to reduce activity in patients with a lower disease burden, in concordance with what has already been observed, that uptake of radionuclide in normal tissues is lower in patients with a high tumor burden because of a "tumor-sinkeffect" both in neuroendocrine tumors [18] studied with radiolabeled somatostatin analogs and prostate cancer as described by Gaertner et al. [19] in which study they described reduced uptake of [^{68}Ga]Ga-PSMA-11 in salivary glands in patients with high, medium, or low tumor burdens. At the moment, as far of our knowledge, no other considerations may be drown if the "tumor-sink effect" has different implications in the two different clinical settings.

What all the studies on dosimetry have in common, however, are the multiple SPECT/CT time points needed to calculate the absorbed dose [15]; Violet et al. [15], due to the effort needed and because of the considerable overlap in whole-body tumor dose between individual patients who responded to therapy and those who did not, would not regard routine dosimetry as mandatory in clinical application of [^{177}Lu]Lu-PSMA-617 therapy.

This has always been a drawback for clinical implementation of dosimetry, and in the current clinical practice we do not have yet any approved or official protocol nor methodic to overcome the multiple time points dosimetry or to understand from the pre therapy PET/CT what could be the tumor absorbed dose. In order to overcome this issue, we could think start using Deep Learning (DL) and Artificial Intelligence (AI) to overcome some of our issue with dose.

Overcoming methodological hurdles: the potential of AI in dose prediction

Altough not the main scope of this review we wanted to give the reader few examples of what is going on research about AI, dosimetry and dose prediction for RLT.

The integration of AI and Deep Learning (DL) is shifting personalized RLT from retroactive measurement to pre-therapy prediction. To address intra-organ pharmacokinetic heterogeneity, Xue et al. [20] developed a DL framework (3D RPT DoseGAN) for voxel-wise tumor-absorbed dose mapping. By implicitly extracting tissue-specific kinetics from baseline PET, this model significantly outperformed conventional organ-level projections (NRMSE 0.79% vs. 1.11%).

Complementing this, Yazdani et al. [21] utilized Machine Learning to integrate radiomic features from [68Ga]Ga-PSMA-11 PET/CT with clinical biomarkers (e.g., PSA, ALP). This multivariate approach achieves high reliability in dose estimation before treatment initiation.

These AI-driven strategies, although they might be time consuming at the beginning, streamline clinical workflows by reducing the logistical burden of multiple post-therapy SPECT/CT scans, facilitating a transition toward a sustainable "predict and optimize" paradigm in precision dosimetry.

Charting the future: key ongoing clinical trials

Right now, there are some clinical trials investigating the potential application of SPECT/CT tumor dosimetry and dose prediction with calculation with various PET/CT tracers.

The observational study NCT07096999 evaluates the relationship between absorbed radiation doses and clinical outcomes in mCRPC patients undergoing [177Lu]Lu-PSMA-617 therapy. By utilizing SPECT/CT imaging, the trial aims to correlate tumor-absorbed doses with clinical response and organ-absorbed doses with toxicity. This research is pivotal for establishing fundamental dose-response relationships for [177Lu]Lu-PSMA-617 therapy, providing essential data to optimize future therapeutic strategies and personalized patient management [22].

The Interventional Diagnostic Study SPECTacular Study (NCT05823402) [23] tackles the methodological reliability of dosimetry itself. Since the calculation of absorbed radiation dose is complex, this diagnostic study performs extensive serial SPECT/CT scans (six per cycle) to evaluate the accuracy and limits of agreement of simplified approximation dosimetry methods when compared to a comprehensive triexponential fitting method, enrolling patients already receiving PSMA-targeted RLT for mCRPC.

The effort to understand dosimetry importance goes on in PRRT with two trials addressing personalized PRRT using [^{177}Lu]Lu-DOTATOC for NENs. The DOBATOC study (NCT04917484) [24] is designed to evaluate whether individualized, dosimetry-based dosing, governed by kidney dose limits (targeting an accumulated kidney dose of 24 Gy), can improve clinical outcomes compared to standard fixed-dose therapy. The trial is designed as a randomized Phase 2 study with Progression Free Survival (PFS) as the primary outcome measure.

The START-NET (NCT05387603) [25] elevates personalization in NEN management by incorporating dual-tracer PET imaging ([^{68}Ga]Ga-DOTA PET/CT and [^{18}F]FDG PET/CT) to guide treatment. Patients with tumors positive for both tracers (indicating high proliferation/poor differentiation) receive a combination of dosimetry-based PRRT and Capecitabine, while those with only [^{68}Ga]Ga-DOTA PET/CT positivity receive dosimetry-based PRRT alone. This randomized Phase 3 trial compares these adaptive strategies against standard treatment to determine improved safety and efficacy, focusing primarily on PFS.

The FLEX-MRT trial (NCT06216249) [26] is a prospective, randomized phase 2 study designed to evaluate the efficacy of a response-based flexible and extended dosing schedule of [^{177}Lu]Lu-PSMA-617 in patients with mCRPC. While the current standard of care involves a fixed regimen of six cycles every six weeks, this trial investigates an adaptive approach allowing for up to 12 cycles and incorporating "treatment holidays" based on individual patient response, monitored via PSA levels and SPECT/CT imaging. The primary objective is to determine if this personalized dosing strategy can improve the 2-year survival rate compared to the standard fixed schedule, potentially optimizing therapeutic outcomes while managing toxicity through tailored treatment intervals. The exploratory objective of this study is to determine the dosimetry with SPECT/CT in organs and tumor lesions of the flexible/extended schedule of ^{177}Lu]Lu-PSMA-617 therapy.

The effort to understand dosimetry goes on also in thyroid cancer where there is the 131THEROPT124 study (NCT05299437) [27] investigates the optimization of [^{131}I] Iodide therapy for metastatic differentiated thyroid cancer, addressing the historical challenge of suboptimal outcomes from empirically fixed administered activities. The core innovation is the use of pre-treatment [^{124}I]Iodide PET/CT dosimetry to calculate the optimal therapeutic [^{131}I] dose required to achieve therapeutic absorbed doses (e.g., > 80 Gy for soft tissue lesions), while adhering to critical organ constraints (e.g., 2 Gy to blood). Furthermore, this Phase 2 study integrates molecular characterization, analyzing genetic mutations and miRNA expression to correlate biological features with iodine uptake and response to therapy.

We do have to disclose, however, that the 131THEROPT124 trial and SPECTacular trial are right now registered as "unknown status" in the NCT trials register, and that of these studies we do not know the different dosimetry methods utilized.

Conclusions

The recent literature here presented emphasizes the shifting paradigm from fixed-dose regimens to individualized, dosimetry-guided treatments to maximize the therapeutic power of radioligand therapy and for patient selection optimization. However, significant heterogeneity in dosimetric methodologies remains a challenge for clinical integration. Implementing precision dosimetry requires unprecedented collaboration between nuclear medicine physicians, physicists to establish unified standards. Such harmonized protocols are essential to ensure optimal patient outcomes and to facilitate the translation of these findings to future radiopharmaceutical therapies.

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Declarations

Competing interests The authors declare no competing interests.

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