

Safety and Efficacy of Dosimetry-Guided ^{177}Lu -DOTATATE Peptide Receptor Radionuclide Therapy in Advanced GEP-NETs: A Systematic Review and Meta-Analysis

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Abstract

Purpose

Currently, standard peptide receptor radiation therapy (PRRT) with ^{177}Lu -DOTATATE is used with a fixed-dose regimen ($4 \times 7.4 \text{ GBq}$) that aims to help limit radiation exposure to vital organs but often undertreats patients. [1] In addition, the use of personalized therapeutic doses is thought to be highly toxic. We conducted a systematic review and meta-analysis to evaluate the safety and efficacy of PRRT with personalized, dose-guided doses in patients with advanced gastrointestinal neuroendocrine tumors (GEP-NETs).

Methods

An extensive and systematic literature search was conducted in accordance with PRISMA guidelines to identify fit-for-purpose trials, using personalized doses based on the PRRT organ. The primary outcomes were severe nephrotoxicity and hematology (grades 3–4), objective response rate (ORR), and progression-free survival (PFS). The methodological and research reliability of the selected trial was evaluated using the RoB 2 and MINORS tools. The aggregate rate was calculated using a random effect model with the Freeman-Tukey dual arc transformation.

Results

Two prospective clinical trials (randomized phase 2, single-handed phase II) included 152 patients who met the inclusion criteria. Both studies increased the cumulative biologic dose (BED) to the kidneys up to 27–40 Gy, which still showed safety. The overall rate of grade 3–4 nephrotoxicity was 0.0% (95% confidence interval: 0.00–0.00; $I^2 = 0\%$). The overall rate of grade 3–4 hematological toxicity was 9.2% (95% confidence interval: 0.05–0.15; $I^2 = 0\%$). Long-term efficacy from the phase II group showed an ORR of 16%, a disease control rate of 78%, a median PFS of 29 months, and an overall survival of 47 to 53 months.

Conclusion

Dosimetry-guided ^{177}Lu -DOTATATE therapy with individualized doses has been shown to be safe and feasible. By safely and controllably exceeding conventional nephrotoxic threshold limits, personalized PRRT helps optimize radiation therapy for tumors, prevent insufficient dose treatment, and provide long-term, sustainable life benefits without increasing severe toxicity.

Introduction

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are a heterogeneous group of malignancies characterized by the overexpression of somatostatin receptors (SSTRs).[2] For patients with inoperable or metastatic disease, and who continue to progress despite first-line therapy (somatostatin analogues), peptide receptor radiotherapy (PRRT) using the radioisotope ^{177}Lu -DOTATATE has become a cornerstone treatment. The landmark NETTER-1 phase 2 trial established the current standard of care: a fixed-dose regimen comprising four cycles of 7.4 GBq (200 mCi) administered at 8-week intervals.[1]

Although fixed-dose treatment provides safety and prolongs non-progressive survival, it is associated with limiting the maximum therapeutic potential of PRRT. The fixed-dose regimen is established to ensure that radiation exposure to critical organs, namely the kidneys and bone marrow, will not exceed the toxicity thresholds of 23 Gy and 2 Gy, respectively. However, these thresholds are initially inferred from external irradiation therapy and may not accurately reflect the radiobiology of internal irradiation in a continuous manner at low doses.[3] Therefore, significant disparities among patients in radiopharmacokinetics indicate that a fixed-dose course will result in systemic dose deficiency treatment for patients whose organs can tolerate higher cumulative activity.

In the era of molecular medicine and theranostics, personalized PRRT based on post-treatment organ dosage has been proposed to optimize treatment. By adjusting the dose used per cycle or the total number of cycles to reach the true safety threshold for each patient, clinicians can maximize the uptake dose for the tumor, thereby improving control. This systematic review and meta-analysis is intended to evaluate the safety, rigor, feasibility, and clinical efficacy of the personalized, dose-guided ^{177}Lu -DOTATATE therapy in advanced GEP-NET patients.

Materials and methods

Study Design and Registration

This systematic review and meta-analysis was carried out in strict compliance with the guidelines of the Priority Reporting Section for Systematic Overview and Meta-Analysis (PRISMA) 2020.[4] The study protocol was registered in the PROSPERO international registry of systematic overviews.

Search Strategy and Selection Criteria

An extensive document search was conducted on major electronic databases, including PubMed/MEDLINE, Embase, and Google Scholar. The search strategy utilized a combination of Medical Subject Headings (MeSH) and free-text keywords: (" ^{177}Lu -DOTATATE" OR "PRRT" OR "peptide receptor radionuclide therapy") AND ("dosimetry" OR "personalized" OR "individualized") AND ("neuroendocrine tumors" OR "NETs").

Selected studies based on the PICO framework:

- P - Patient (Population): Patients diagnosed with Neuroendocrine Tumors (NETs/GEP-NETs). Adult patients with advanced GEP-NET, positive for SSTR.
- I&C - Intervention & Comparison: Peptide receptor radiotherapy (PRRT) treatment using ^{177}Lu -DOTATATE (or ^{177}Lu -DOTATOC). Most important: The paper should mention the measurement of personalized/individualized doses or have a direct comparison between individualized doses and fixed doses.
- O - Outcomes: Safety (nephrotoxicity and hematological grade 3–4 according to CTCAE criteria), objective response rate (ORR), and progression-free survival (PFS).
- S - Study Design: Clinical trials (RCTs), prospective or retrospective cohort studies, and observational studies with clear clinical data.

Criteria for exclusion when ONE of the following signs appears:

- Wrong Population: Studies on animals (mice, dogs), cells (in vitro, in vivo), or patients with prostate cancer (often with the keyword PSMA), or thyroid cancer.
- Wrong Intervention: Use of other isotopes (^{90}Y , ^{131}I only) or treatments that do not involve PRRT.
- Wrong Publication Type: Case reports (usually less than 10 patients), reviews/meta-analyses (we do not include other reviews in our data), letters/editorials, and conference summaries with incomplete data.

Data Extraction and Quality Assessment

Data extraction was independently performed using a standardized extraction form. Extracted variables included study characteristics, patient demographics, dosimetric parameters (kidney and bone marrow absorbed doses), and clinical outcomes (efficacy and safety).

Methodological quality and risk of bias were assessed according to study design. The Cochrane Risk of Bias 2 (RoB 2) tool was utilized for randomized controlled trials.[5] For non-randomized, single-arm prospective trials, the Methodological Index for Non-Randomized Studies (MINORS) criteria were applied.[6]

Statistical Analysis

All meta-analytical calculations were performed using R statistical software (R Foundation for Statistical Computing) via the RStudio environment, utilizing the *meta* package. Pooled proportions for adverse events (Grade 3–4 renal and hematological toxicities) were calculated using a random-effects model to account for anticipated clinical heterogeneity.

To appropriately handle studies with zero events (e.g., no reported grade 3–4 renal toxicity), the Freeman-Tukey double arcsine transformation ($sm = \text{PFT}$) was applied to stabilize variances before

pooling.[7] Statistical heterogeneity among the included studies was evaluated using the I^2 statistic. Efficacy outcomes derived from single-arm prospective data were synthesized narratively.

Results

Study Selection and Characteristics

The initial database search and screening process identified 379 reports. After removing 372 irrelevant records during title/abstract screening, 7 reports were sought for full-text retrieval (one was inaccessible). Following full-text assessment of 6 articles, 4 studies were excluded (missing dosimetric data [$n = 2$], inappropriate study design [$n = 2$]). Ultimately, 2 clinical trials (Kolodziej et al., 2025; Sundlöv et al., 2022) met all eligibility criteria and were included in the quantitative and qualitative synthesis.

The included studies comprised a total of 152 patients with advanced, somatostatin receptor-positive GEP-NETs. Kolodziej et al. (2025) reported an interim safety analysis of the DUONEN trial, a multicenter, randomized phase 3 trial involving 56 patients.[8] Sundlöv et al. (2022) reported the final results of the ILUMINET trial, a prospective phase II study involving 96 patients.[9]

Methodological Quality and Risk of Bias

The risk of bias for the randomized controlled trial (Kolodziej et al., 2025) was assessed as having "some concerns" overall using the RoB 2 tool, primarily due to the interim nature of the report. The prospective phase II trial (Sundlöv et al., 2022) achieved a high methodological score of 14 out of 16 using the MINORS criteria, demonstrating robust prospective data collection and a 0% loss to follow-up rate.

Safety Outcomes: Renal and Hematological Toxicity

Both studies pushed the cumulative biological effective dose (BED) to the kidneys beyond the conventional 23 Gy threshold (up to 27–40 Gy). Despite the escalated dosimetric thresholds, the meta-analysis of grade 3–4 renal toxicity demonstrated a pooled proportion of 0.0% (95% CI: 0.000–0.000), with perfect statistical homogeneity ($I^2 = 0\%$, $p = 0.85$).[10]

Hematological toxicity was the most frequent dose-limiting factor but remained manageable. The meta-analysis of grade 3–4 hematological adverse events revealed a pooled proportion of 9.2% (95% CI: 0.05–0.15). No statistical heterogeneity was detected ($I^2 = 0\%$, $p = 0.93$).[11] These findings strongly indicate that dosimetry-guided individualized PRRT effectively protects critical organs even when cumulative activities exceed standard regimens.

Efficacy Outcomes

Efficacy endpoints were reported in the ILUMINET trial (Sundlöv et al.). Individualized PRRT yielded an objective response rate (ORR) of 16% and a disease control rate (DCR) of 78%. The median progression-free survival (PFS) was 29 months, and the overall survival (OS) ranged from 47 to 53 months.[9] Time to maximum response increased sequentially with higher delivered kidney BED levels, suggesting that extended cycles contribute to prolonged tumor shrinkage without compromising safety.

Discussion

The primary objective of this systematic review and meta-analysis was to evaluate the safety and clinical efficacy of individualized, dosimetry-guided ¹⁷⁷Lu-DOTATATE PRRT in advanced GEP-NETs. Our pooled analysis yielded a compelling safety profile: the pooled incidence of grade 3–4 renal toxicity was 0.0%, and severe hematological toxicity occurred in only 9.2% of patients.

Historically, the standard PRRT regimen used a fixed cumulative activity of 29.6 GBq. Although safe, it ignored variability among patients in organ radiation tolerance. [12] The trials in our analysis challenged the traditional renal threshold of 23 Gy. Sundlöv et al. pushed the safe cumulative renal BED to 27 Gy (and 40 Gy in a select number of patients), while Kolodziej et al. reported a maximum renal dose of 29.1 Gy. The complete absence of severe nephrotoxicity in our meta-results reinforces the emerging consensus that the traditional limit of 23 Gy is too conservative for PRRT.[3]

By safely and controllably exceeding conventional nephrotoxic threshold limits, individualized dose measurement allows doctors to safely increase the radiation dose. This is evident in the treatment results in Sundlöv et al.'s study, where the median progression-free survival (PFS) reached 29 months. Moreover, their findings that the higher the radiation dose accumulated in the kidneys, the longer the time to achieve the maximum tumor atrophy effect, highlighted the practical clinical benefits of the infusion of additional drug cycles to patients.[9]

Our review had limitations. The strict inclusion criteria limited our data aggregation to two trials. Furthermore, the DUONEN trial only contributed interim safety data, which did not allow meta-analysis for long-term outcomes.

Conclusion

Personalized therapeutic dose PRRT is a safe, feasible, and radiationally correct step forward from the standard fixed-dose regimen. By maximizing the safe absorption dose for tumors without increasing the risk of serious renal or hematological damage, personalized PRRT is fully aligned with the core principles of modern theranostics. Strong current evidence supports the integration of routine organ doses into clinical practice.

Declarations

Author Contribution

A.T.P.D. contributed to the study conception and design. Literature search, study selection, and data extraction were performed by L.P.H.K. and T.N.N.T. Statistical analysis was performed by A.T.P.D. and L.P.H.K. The first draft of the manuscript was written by A.T.P.D., and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability

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

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Figures

Figure 1. PRISMA 2020 Flow Diagram

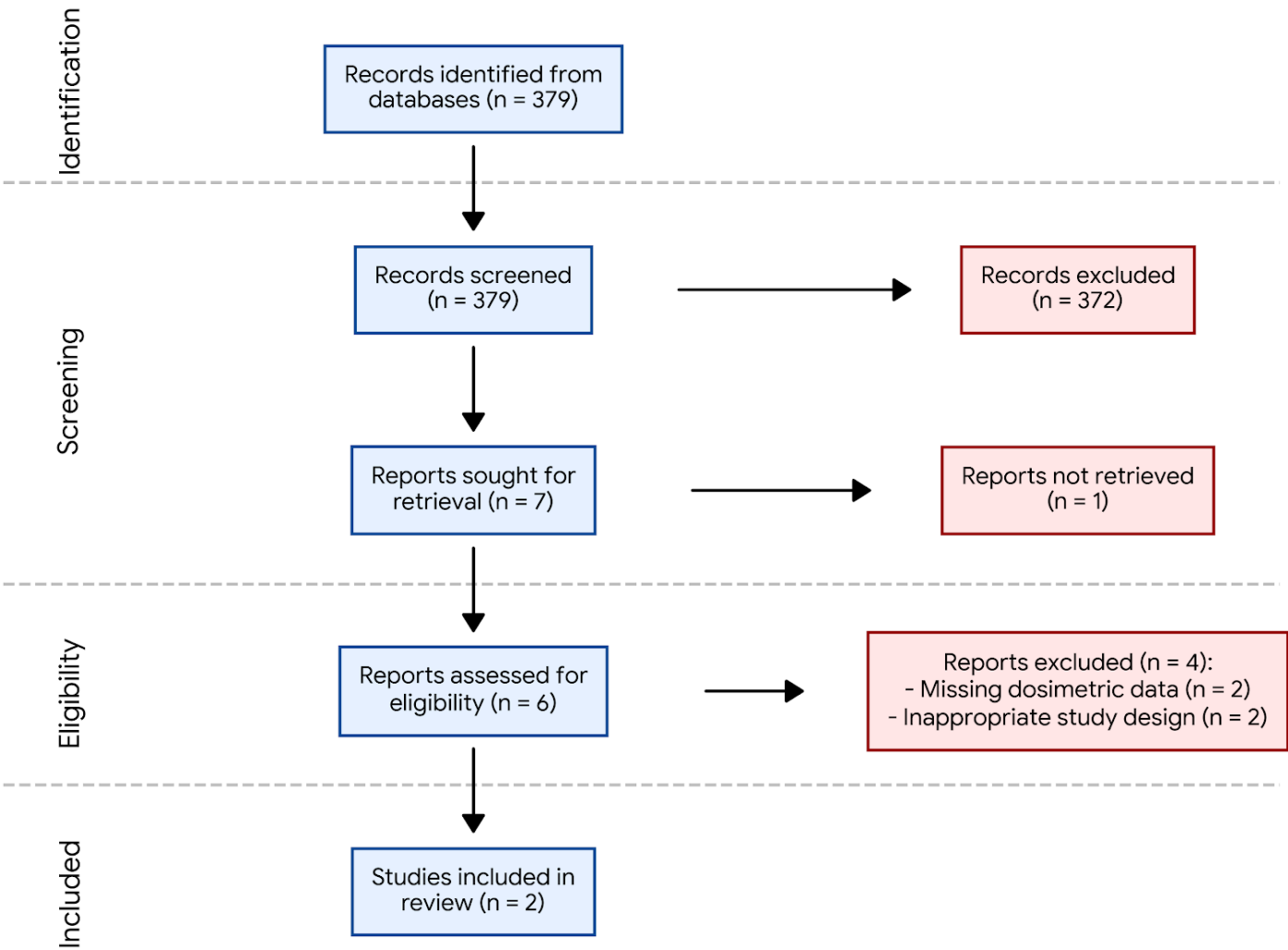


Figure 1

PRISMA 2020 Flow Diagram detailing the literature search, screening, and study selection process.

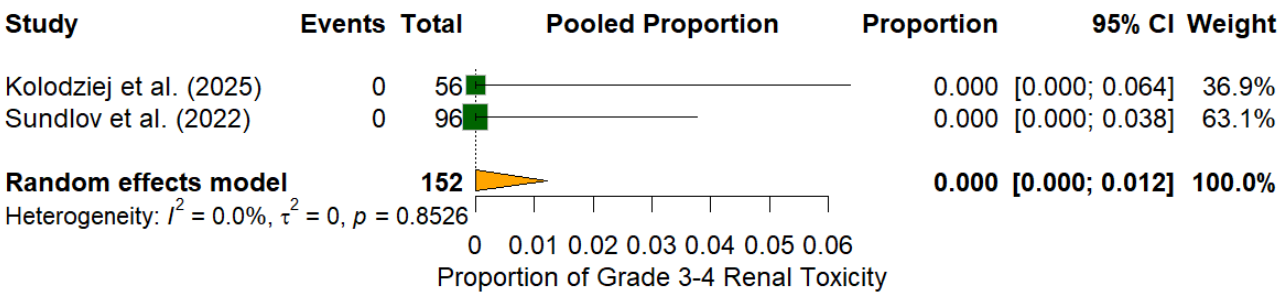


Figure 2

Forest plot illustrating the pooled proportion of grade 3-4 renal toxicity.

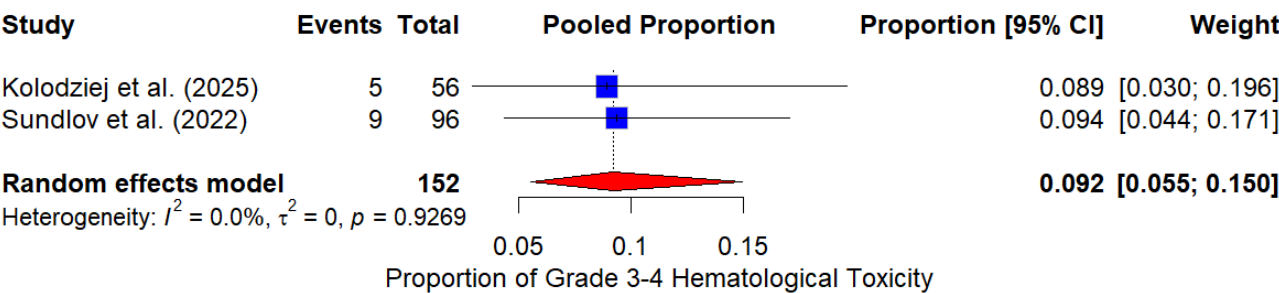


Figure 3

Forest plot illustrating the pooled proportion of grade 3-4 hematological adverse events.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [MINORSSundlov2022.pdf](#)

- [RoB2Kolodziej2025.pdf](#)