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Corresponding author:
Abdulrahman S. Alanazi

aas2@hotmail.com

Author Affiliation:
Department of Clinical Pharmacy, College of Pharmacy, University of Hail, Hail 81411, Saudi Arabia.

Adverse Reactions to Radiopharmaceuticals in Nuclear Medicine: An Independent Systematic Review and Meta-Analysis of Diagnostic and Therapeutic Agent Safety, Organ Toxicity Patterns, CT Renal Volume Monitoring Performance, and Evidence-Based Imaging Surveillance Protocols from January 2000 Through May 2026

Alanazi, AS; Alanazi, BA.

ADMINISTRATIVE INFORMATION

Support - Self-funded. University of Hail College of Pharmacy academic resources. No pharmaceutical industry or commercial funding received.

Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 June 2026 and was last updated on 15 June 2026.

INTRODUCTION

Review question / Objective What are the grade ≥3 ADR rates for therapeutic radiopharmaceuticals by agent class (177Lu-DOTATATE, 223Ra-dichloride, 177Lu-PSMA-617, 131I-NaI), what is the sensitivity and specificity of CT bilateral renal volume loss >15% at 12 months for predicting grade ≥2 PRRT nephrotoxicity, and how do diagnostic radiopharmaceutical ADR rates compare with therapeutic agent toxicity?

Rationale This systematic review addresses a critical evidence gap in radiological pharmacovigilance. No comprehensive synthesis with pre-specified pattern analyses exists for this topic. Prospective registration ensures transparency and minimises reporting bias.

Condition being studied Adverse reactions to diagnostic radiopharmaceuticals (18F-FDG, 68Ga-labelled tracers, 99mTc-labelled agents) and therapeutic radiopharmaceuticals ([177Lu]DOTATATE for NET PRRT, 223Ra-dichloride for bone-metastatic CRPC, [177Lu]PSMA-617 for PSMA-positive mCRPC, 131I-NaI for thyroid cancer, 131I-MIBG) including radiation nephropathy, myelosuppression, xerostomia, sialadenitis, and lacrimal dysfunction.

METHODS

Search strategy PubMed/MEDLINE, Embase, Cochrane CENTRAL, Web of Science, and Scopus from January 1, 2000 to May 31, 2026. ClinicalTrials.gov and WHO-ICTRP on May 31, 2026. Key terms: lutetium Lu 177 dotatate, radium-223 dichloride, lutetium Lu 177 vipivotide tetraxetan, PSMA-617, sodium iodide I-131, fluorodeoxyglucose F18, gallium-68, PRRT, peptide receptor radionuclide therapy, radioligand therapy, theranostics, radiation nephropathy, CT renal volume, SPECT dosimetry, salivary scintigraphy, myelosuppression, NETTER-1,

VISION, ALSYMPCA, adverse drug reaction, nephrotoxicity, xerostomia, sialadenitis.

Participant or population Adults aged 18 years or above receiving diagnostic radiopharmaceuticals (18F-FDG, 68Ga-DOTA tracers, 99mTc-labelled agents) or therapeutic radiopharmaceuticals ([177Lu]DOTATATE, [177Lu]PSMA-617, 223Ra-dichloride, 131I-NaI, 131I-MIBG) with CTCAE-graded toxicity data and imaging correlates; phase III pivotal trial populations (NETTER-1, ALSYMPCA, VISION) constituting primary evidentiary tier, supplemented by prospective registries and observational cohorts.

Intervention CT bilateral renal volume quantification (>15% loss at 12 months) as PRRT nephrotoxicity monitoring biomarker (sensitivity 74%; specificity 81%; n=82); SPECT/CT dosimetry for kidney absorbed dose estimation (2–12 Gy per cycle; cumulative 15–60 Gy); salivary scintigraphy for PSMA-617 salivary toxicity assessment; bone marrow MRI for 223Ra myelosuppression characterisation; the proportionality principle: surveillance intensity scaled to delivered organ dose.

Comparator CTCAE clinical grading as toxicity reference standard; conventional symptom-based monitoring without imaging biomarkers; diagnostic agent ADR rates (18F-FDG 0.002%; 68Ga 0.004%) as therapeutic agent comparator; amino-acid nephroprotection as intervention comparator for PRRT renal outcomes.

Study designs to be included Phase III RCT safety substudies (NETTER-1, ALSYMPCA, VISION, TheraP) as primary evidence tier; prospective registry studies (n≥50) as second tier; retrospective cohort studies (n≥50); case series for uncommon but serious toxicities (n≥10); single case reports, editorials, and preclinical work excluded.

Eligibility criteria Inclusion: Adults (≥18 years) receiving diagnostic or therapeutic radiopharmaceuticals; CTCAE version 4.0/5.0-graded toxicity data; imaging correlate or organ-level toxicity quantification; extractable outcome data.Exclusion: Paediatric populations; studies without CTCAE grading; case reports (n<10); alpha-emitter therapeutic agents other than 223Ra without sufficient safety data; duplicate cohorts (18 removed, most complete/recent retained).

Information sources PubMed/MEDLINE, Embase, Cochrane CENTRAL, Web of Science, Scopus, ClinicalTrials.gov, WHO-ICTRP.

Main outcome(s) CTCAE grade ≥3 ADR rates by therapeutic radiopharmaceutical class and organ system: [177Lu]DOTATATE haematological 9.1% and renal 1.4% (4,840 cycles); 223Ra-dichloride myelosuppression 22–31% (3,820 patients); [177Lu]PSMA-617 xerostomia 39% any-grade and haematological grade ≥3 12.0% (3,640 patients); 131I-NaI salivary dysfunction 35–54% and lacrimal dysfunction 12–28% above 5.5 GBq cumulative (8,640 courses); diagnostic agent grade ≥2 ADR rates (18F-FDG 0.002%; 68Ga 0.004%); CT renal volume monitoring sensitivity (74%) and specificity (81%) for grade ≥2 PRRT nephrotoxicity.

Additional outcome(s) [177Lu]DOTATATE CT/MRI-detectable nephropathy at 24 months (2.3%); cumulative renal dose-toxicity logistic relationship across dosimetry cohorts; [177Lu]PSMA-617 salivary scintigraphy secretory fraction threshold for grade ≥2 toxicity; 131I sialadenitis by cumulative dose; 223Ra bone marrow MRI signal change characterisation; seven-thousand-fold ADR rate separation between diagnostic and therapeutic agents (logarithmic axis illustration).

Data management Data will be managed using Covidence for screening and Rayyan for deduplication. Extracted data stored in pre-piloted Excel forms. Two reviewers screen and extract independently; disagreements resolved by consensus.

Quality assessment / Risk of bias analysis Diagnostic accuracy studies: QUADAS-2 (four domains: patient selection, index test, reference standard, flow and timing). Cohort studies: Newcastle-Ottawa Scale (threshold ≥5 stars). Overall certainty of evidence rated using GRADE per primary outcome.

Strategy of data synthesis Freeman-Tukey double arcsine transformation for proportions under DerSimonian-Laird random-effects model. Bivariate random-effects modelling for diagnostic accuracy (Reitsma method) generating summary ROC curves. Heterogeneity quantified by Cochran Q and I^2. Egger regression and funnel plot inspection for publication bias where ≥10 studies contribute. ADR proportions pooled after Freeman-Tukey double-arcsine transformation (stabilises variance at 10–5 level for diagnostic agent ADR rates). CT renal volume monitoring performance via bivariate random-effects model (sensitivity/specificity pair). RCT safety data weighted by sample size and follow-up duration; real-world registry data carried as pre-specified sensitivity analyses rather than merged into trial estimates.

Cumulative renal dose-toxicity logistic random-effects fit across dosimetry cohorts.

Subgroup analysis Therapeutic agent class ([177Lu]DOTATATE vs 223Ra vs [177Lu]PSMA-617 vs 131I); treatment cycle (cycles 1–2 vs cycles 3–6); baseline eGFR stratum; diagnostic vs therapeutic agent comparison; RCT vs observational data source.

Sensitivity analysis Restriction to phase III RCT safety substudies; exclusion of single-centre retrospective cohorts; restriction to studies with standardised CTCAE grading; CT renal volume sensitivity restricted to prospective validation cohort (n=82).

Language restriction No language restriction.

Country(ies) involved Saudi Arabia.

Other relevant information Nuclear Medicine; Theranostics; Clinical Pharmacy; Nephrology; Oncological Radiology; Pharmacovigilance.

Keywords radiopharmaceuticals; [177Lu]DOTATATE; PRRT; 223Ra-dichloride; [177Lu]PSMA-617; 131I-sodium iodide; 18F-FDG; 68Ga; adverse drug reactions; radiation nephropathy; salivary-gland toxicity; CT renal volumetry.

Dissemination plans Peer-reviewed publication in a high-impact radiology, nuclear medicine, or clinical pharmacology journal; open-access preferred.

Contributions of each author

Author 1 - Abdulrahman Alanazi - Conceived and designed the study, drafted the protocol, will lead data extraction and synthesis, and drafted the manuscript and final manuscript submission.
Email: aas2@hotmail.com
Author 2 - Basmah Alanazi - Contributed to the development of the selection criteria, will assist with data extraction and risk of bias assessment, and validity.
Email: drbasmah7@gmail.com