We sincerely thank the Editor and reviewers for their careful evaluation of our manuscript entitled **"Acute Complications of Nuclear Medicine: An Emergency Medicine Perspective" (EJRE-D-26-00091)**. We greatly appreciate the constructive comments and suggestions, which have substantially improved the scientific quality, clarity, and clinical relevance of the manuscript. All reviewer and editorial comments were carefully considered, and the manuscript has been comprehensively revised accordingly. All modifications have been highlighted in the revised manuscript as requested. Detailed Point-by-point responses are provided below.

Reviewer Comments

Comment 1

"Why was this timeline from Jan 2020 to Dec 2024 decided on?…"

Response

We thank the reviewer for this important observation. The January 2020–December 2024 timeframe was selected to prioritize contemporary evidence reflecting recent advances in nuclear medicine practice, particularly the rapid expansion of therapeutic radiopharmaceuticals and theranostic applications. However, we agree that several foundational and historically important studies remain highly relevant to contextualizing current practice. We therefore clarified in the Methods section that seminal earlier publications and landmark surveillance studies were additionally included when necessary to provide historical context and support interpretation of contemporary findings.

Manuscript Revision: Revised in Methods section:

"The search covered publications from January 2020 through December 2024 to capture contemporary evidence, supplemented by seminal earlier works where necessary for historical context."

Comment 2

"Was there not enough data found for alpha emitters to present toxicity and other adverse effects to mention here?"

Response

We appreciate the reviewer's insightful suggestion. Emerging alpha-emitting radiopharmaceuticals such as actinium-225–PSMA-617 demonstrated significant

antitumor activity in heavily pretreated patients with metastatic castration-resistant prostate cancer who had progressed after Lutetium-177–PSMA therapy, supporting its role as a promising salvage treatment option. However, treatment was associated with notable toxicities, particularly xerostomia and hematologic adverse effects, highlighting the need for careful patient selection and toxicity monitoring. A corresponding discussion and reference have been added to the manuscript.

Manuscript Revision: Added in Section 3.6:

"Emerging alpha-emitting radiopharmaceuticals such as actinium-225–PSMA-617 have also demonstrated promising therapeutic activity in heavily pretreated metastatic castration-resistant prostate cancer, although clinically relevant toxicities including xerostomia and hematologic adverse events remain important considerations requiring careful monitoring [31]."

Added Reference: 31. Feuerecker B, Tauber R, Knorr K, et al. Activity and Adverse Events of Actinium-225-PSMA-617 in Advanced Metastatic Castration-resistant Prostate Cancer After Failure of Lutetium-177-PSMA. Eur Urol. 2021;79(3):343-350.

Comment 3

"Page 3, line 31. I would mention the year that this number refers to so it does not need to be separately sought out from the reference.

Response

We thank the reviewer for this suggestion. The relevant sentence was revised to explicitly indicate the year associated with the reported procedural estimates to improve clarity for readers.

Manuscript Revision

"The therapeutic radiopharmaceutical landscape has undergone substantial transformation in recent years. In 2022, the United States Food and Drug Administration approved lutetium-177 vipivotide tetraxetan (177Lu-PSMA-617, Pluvicto) for metastatic castration-resistant prostate cancer, marking a significant milestone in theranostic oncology, with indications subsequently expanded to include earlier disease stages [6]."

Comment 4

Reviewer Comment:

"I was expecting to find the word theranostic tracers from this kind of manuscript too as that is a rapidly growing and now-a-days important field of radiopharmaceuticals…"

Response

We appreciate the reviewer for highlighting the growing importance of theranostic radiopharmaceuticals in contemporary nuclear medicine practice. We agree that theranostic agents are highly relevant to acute complications including extravasation, maladministration, and therapy-associated toxicities. Accordingly, additional discussion regarding theranostic radiopharmaceuticals and their clinical implications has been incorporated into both the Background and Discussion sections. Two additional references addressing theranostic tracer design and theranostic practice have also been added [32,33].

Manuscript Revisions

Background Section

The rapid evolution of theranostic radiopharmaceuticals has further transformed contemporary nuclear medicine practice. Theranostic approaches integrate molecular imaging and targeted radionuclide therapy using structurally related tracers, enabling individualized diagnosis, treatment selection, and response assessment [32,33]. As these agents become more widely adopted, complications related to extravasation, maladministration, and therapy-associated toxicities may be encountered more frequently in emergency practice.

Discussion Section

“The growing adoption of theranostic agents also has important clinical implications. In these settings, complications such as extravasation or maladministration may affect not only patient safety but also diagnostic interpretation, dosimetric accuracy, and subsequent therapeutic decision-making [32,33].

Added References

32. Berton C, Klingler S, Prytuliak S, Holland JP. New tactics in the design of theranostic radiotracers. NPJ Imaging. 2024;2(1):23. doi:10.1038/s44303-024-00027-1.

33. Yordanova A, Eppard E, Kürpig S, et al. Theranostics in nuclear medicine practice. Onco Targets Ther. 2017;10:4821-4828. doi:10.2147/OTT.S140671.

Comment 5

Reviewer Comment:

“Page 4 row 14. Should there be a reference for this last sentence? Or where is that knowledge coming from?”

Response

We thank the reviewer for this observation. To improve clarity and provide appropriate support for the statement, a relevant reference has now been cited within the manuscript.

Manuscript Revision

"Furthermore, much of the available information predates recent therapeutic radiopharmaceutical approvals and may not fully reflect current clinical practice [30]."

Comment 6

Reviewer Comment:

"I found the background chapter was a bit repetitive. Like the end of the second and last paragraph."

Response

We thank the reviewer for this observation. The Background section has been revised to reduce repetition and improve overall flow and conciseness. Overlapping statements regarding the growing relevance of nuclear medicine complications in emergency practice were streamlined.

Manuscript Revision

Redundant wording in the Background section was condensed and overlapping concepts were merged to improve readability.

Comment 7

Reviewer Comment:

"I'm thinking of the criteria why these search terms are chosen… maybe including the word 'contamination' is slightly farfetched here for this target audience of emergency medicine."

Response

We appreciate the reviewer's thoughtful comment. While we agree that contamination and many extravasation events are commonly managed within nuclear medicine services and only infrequently require emergency physician involvement, we intentionally included these terms to capture the broader spectrum of acute nuclear medicine

complications potentially relevant to emergency and acute care practice. Such events may occasionally prompt emergency department evaluation, multidisciplinary consultation, or radiation-safety assessment. To improve clarity, additional explanation regarding the rationale for the selected search domains has been incorporated into the Methods section.

Manuscript Revision

Search domains were selected to capture both clinically significant patient complications and operational or radiation-safety events that may occasionally prompt emergency department evaluation or consultation.

Comment 8

Reviewer Comment:

"Problems to emergency professionals: Urine, vomit, blood, etc. from the patient would result in contamination…"

Response

We thank the reviewer for this valuable suggestion. We agree that practical guidance regarding radiation exposure concerns among emergency healthcare personnel is important. Additional clarification has therefore been added to emphasize that radiation exposure risk from most diagnostic radiopharmaceuticals is generally low and should not delay appropriate patient assessment or management. Brief discussion regarding bodily fluid contamination and standard precautions has also been incorporated into the radiation contamination section.

Manuscript Revision

"For most diagnostic radiopharmaceutical procedures, radiation exposure risk to emergency personnel remains low, and standard precautions are generally sufficient even in the presence of bodily fluid contamination. Appropriate patient assessment and stabilization should therefore not be delayed because of concerns regarding radiation exposure. Patients receiving therapeutic radionuclide treatments may require additional radiation-safety considerations, particularly when contamination from bodily fluids is suspected.

Comment 9

Reviewer Comment:

"Page 6 line 37, radiopharmaceutical is missing an r."

Response

We thank the reviewer for identifying this typographical error. The spelling has been corrected in the revised manuscript.

Comment 10

Reviewer Comment:

“Page 7, line 1 sentence is perhaps a little odd…”

Response

We appreciate the reviewer’s suggestion. The sentence has been revised for improved clarity and readability.

Manuscript Revision

Original: “Emergency physicians should interpret higher reported rates with this methodological context in mind.”

Revised: “Emergency physicians should recognize that reported extravasation rates may be higher when systematic detection methods are used.

Comment 11

Reviewer Comment:

“Page 7 line 13: quality improvement program is perhaps a long word for training program.”

Response

We thank the reviewer for this suggestion. The wording has been simplified to improve readability while preserving the intended meaning.

Manuscript Revision

“Importantly, structured training programs have demonstrated the potential for substantial reductions.

Comment 12

Reviewer Comment

"In page 7, chapter 3.2.2 the clinical consequence is discussed. I would consider trying to bring the perspective of the problem that if the tracer is too much remained in the injection site due to extravasation, then this can potentially lead to misdiagnosis which leads to severe consequences for the patient. So that should be brought up in the discussion at least if no articles talk about this that you included into this study. Now the Line 38 in page 7 lets the reader understand that the patient will not be harmed if the image quality is bad or quantification is wrong, but when it leads to misdiagnosis, then it is not true as it will harm the patient in that case."

Response

We sincerely thank the reviewer for this important and clinically relevant observation. We fully agree that, although diagnostic radiopharmaceutical extravasation rarely produces direct tissue injury, impaired tracer delivery may adversely affect image quality and quantitative interpretation, potentially resulting in diagnostic inaccuracies or delayed diagnosis. Such downstream effects may indirectly harm patients through inappropriate staging, delayed treatment decisions, or misinterpretation of disease burden. To better reflect this important perspective, clarifying statements have been added to both the Results and Discussion sections.

Manuscript Revision: Added in Section 3.2.2:

"The primary clinical impact of diagnostic extravasation is on image quality and quantification. However, substantial tracer retention at the injection site may impair image interpretation, potentially resulting in misdiagnosis, delayed treatment, and subsequent patient harm.'

Added in Discussion Section 4.1:

The growing adoption of theranostic agents also has important clinical implications. In these settings, complications such as extravasation or maladministration may affect not only patient safety but also diagnostic interpretation, dosimetric accuracy, and subsequent therapeutic decision-making [32,33].

Comment 13

Reviewer Comment

"Table 1 in page 8: Now there is listed a few example radiotracers etc. The horizontal rows should be defined more carefully to define what is actually meant with the specific row. And then have the 'agent category' as 'Example'. Should they be categories like

‘diagnostic PET tracers’, ‘SPECT tracers’…? Is there a separating line meant to be between 177Lu and 90Y? The PDF and printed version gives inconsistently the lines between the rows, so perhaps an edit in the way the rows are separated is needed.”

Response

We thank the reviewer for this constructive suggestion. We agree that clearer categorization improves the interpretability of the table and better reflects the distinction between diagnostic and therapeutic radiopharmaceuticals. In response, Table 1 has been revised with more precise category definitions and improved formatting consistency to enhance readability in both PDF and printed versions.

Manuscript Revision

- The column heading “Agent Category” was revised to: “Radiopharmaceutical Categ.

- Categories were reorganized into clearer diagnostic and therapeutic groupings.
- Table formatting, row alignment, and separation lines were standardized to improve visual consistency across formats

Comment 14

Reviewer Comment

“In addition, the table heading dark colored background makes reading the headers difficult (both in printed and PDF versions).”

Response

We appreciate the reviewer highlighting this formatting issue. We agree that readability is important for effective presentation of tabulated clinical information. Accordingly, the table header design has been revised.

Manuscript Revision

- Table header formatting was adjusted with improved contrast and simplified shading to enhance readability in PDF and print versions.

Comment 15

Reviewer Comment

"Page 13 (acute toxicity chapter): Are there any knowledge of incidences that point that the toxicity would be due to specific radio metabolites and not the original radiotracer? Especially when dealing with first-in-human studies, I would expect this to be a source of toxicity related adverse events as these potential radio metabolites could not be found before the first dosimetry studies are started. Trace-level administration usually makes sure that there should not be any notable adverse events, but it is possible, and I was expecting to read something about this topic in this chapter, but this chapter 3.6 only seemed to talk about 177Lu therapy."

Response

We appreciate the reviewer's insightful comment. We agree that radio metabolite-related toxicity represents an important theoretical consideration, particularly in early-phase and first-in-human theranostic radiopharmaceutical studies. However, robust clinical evidence specifically attributing acute toxicity to radio metabolites remains limited in the currently available literature. To acknowledge this emerging area, a brief statement has been added to the Discussion section.

Manuscript Revision: Added in Section 4.2:

Potential toxicity related to radio metabolites, particularly in first-in-human theranostic radiopharmaceutical studies, remains an emerging area of investigation with currently limited clinical evidence, warranting continued pharmacovigilance as novel agents enter clinical practice [32,33].

Comment 16

Reviewer Comment

"In page 14 lines 52-59: Although there is no well-documented cases of severe permanent tissue injury, it does not mean that the patient is not harmed and therefore clinically inconsequential. As the patient can be for example misdiagnosed. I do understand that this is talking about emergency medicine perspective, but perhaps this should be worded other way."

Response

We thank the reviewer for this valuable clarification. We agree that the phrase "clinically inconsequential" may underestimate the potential indirect consequences of diagnostic extravasation, particularly regarding image interpretation and diagnostic accuracy. The wording has therefore been revised for greater precision.

Manuscript Revision

Original wording: “Clinically inconsequential in the vast majority of cases”

Revised wording: ’For diagnostic tracers, extravasation is common when systematically sought (incidence 3-23% depending on detection methodology) and is rarely associated with severe permanent tissue injury [10,12,25]. However, impaired image quality and altered tracer quantification may contribute to diagnostic inaccuracies, delayed treatment, and potential patient harm in some cases.’’

Comment 17

Reviewer Comment

“Page 15 line 8. The word overwhelming is not proper in academic language in my opinion. It is too dramatic at least to this context.”

Response

We thank the reviewer for this stylistic observation. The wording has been revised

Manuscript Revision

Original wording: “The overwhelming majority of errors occur during diagnostic proc.”

Revised wording: “The majority of errors occur during diagnostic procedures”

Comment 18

Reviewer Comment

“References. Although I understand that listing all of the used sources as references is not feasible, but perhaps they should all be listed in a Supplemental material document. They should be available for readers to check what 68 studies were included in this (as mentioned in page 6 (3.1)) and that is not that big of a job to make that critical information available here.”

Response

We sincerely thank the reviewer for this valuable suggestion. Accordingly, a supplementary table listing the studies included in the narrative synthesis has been prepared and referenced in the supplementary document.