Theranostiek en dosimetrie

Wetenschappelijke najaarsvergadering van de NVNG

De drukbezochte wetenschappelijke vergadering van de Vereniging voor Nucleaire Geneeskunde stond in het teken van theranostiek en dosimetrie, twee snel ontwikkelende pijlers binnen de moderne nucleaire geneeskunde. Ook deze keer werd de bijeenkomst in het Postillion hotel te Bunnik gehouden. De grote opkomst onderstreepte het toenemende klinische en wetenschappelijke belang van deze thema's.
Tijdens de bijeenkomst werd uitgebreid ingegaan op de integratie van diagnostiek en therapie binnen theranostische concepten, met bijzondere aandacht voor radionuclidentherapie bij oncologische aandoeningen zoals prostaatkanker en neuro-endocriene tumoren. Sprekers benadrukten hoe gepersonaliseerde theranostiek bijdraagt aan effectievere behandelingen en betere patiëntuitkomsten.
Een centraal onderwerp was dosimetrie, waarbij zowel technische als klinische aspecten aan bod kwamen. Er werd gediscussieerd over methoden voor patiëntspecifieke dosisbepaling, de rol van beeldvorming (zoals SPECT/CT en PET/CT) en de noodzaak van standaardisatie binnen de klinische praktijk. Verschillende presentaties lieten zien dat nauwkeurige dosimetrie essentieel is om therapieën te optimaliseren en toxiciteit te beperken.
Daarnaast kwamen regelgeving, implementatie in de kliniek en multidisciplinaire samenwerking aan bod. Sprekers gaven aan dat verdere scholing, harmonisatie van protocollen en samenwerking tussen artsen, klinisch fysici en radiochemici cruciaal zijn voor een succesvolle toepassing van theranostiek.
De vergadering werd afgesloten met een vooruitblik op toekomstige ontwikkelingen, waaronder nieuwe radiofarmaca, automatisering van dosimetrische berekeningen en de toenemende rol van kunstmatige intelligentie. De algemene conclusie was dat theranostiek en dosimetrie zich snel ontwikkelen en een steeds centralere plaats innemen binnen de nucleaire geneeskunde.

Voorzitters van de eerste sessie waren Tineke van de Weijer en Dennis Vriens. De bijeenkomst werd geopend met een keynote over de basisbeginselen van radiobiologie en dosimetrie, verzorgd door radiobioloog Julie Nonnekens (Erasmus MC) en klinisch fysicus Sasha Ivashchenko (UMCG). Vanuit hun respectieve expertises legden zij de relatie tussen externe radiotherapie en radionuclidentherapie, en benadrukten zij het belang van radiobiologische inzichten voor een verantwoorde dosisbepaling.
Vervolgens ging klinisch fysicus Steffie Peters (Radboudumc) in op de politieke en regelgevende kaders rondom dosimetrie, waarbij zij duidelijk maakte hoe wetgeving en richtlijnen de klinische implementatie van patiëntspecifieke dosimetrie beïnvloeden.
In de sessie over klinische toepassingen, onder voorzitterschap van Anke de Vries en Steffie Peters, kwamen diverse theranostische behandelvormen aan bod. Klinisch fysicus Roel Wierts (MUMC) besprak de praktische toepassing van dosimetrie bij I-131-therapie, terwijl nucleair geneeskundige James Nagarajah (Radboudumc) liet zien hoe theranostiek en dosimetrie worden ingezet bij PSMA-radionuclidentherapie. Aansluitend gaf technisch geneeskundige Linda de Wit-van der Veen (NKI-AvL) een overzicht van dosimetrische benaderingen bij andere vormen van radionuclidentherapie.

Aan het einde van de ochtend werd de Woldring prijs uitgereikt aan Pascalle Mossel voor haar proefschrift *F-18MC225 and PET: in vivo measurements of the P-glycoprotein function at the human blood-brain barrier.* Een samenvatting van dit proefschrift is reeds gepubliceerd in nummer 2025(3) van het Tijdschrift voor Nucleaire Geneeskunde.
Na de pauze volgde een keynote over uitdagingen en kansen in de theranostiek, waarin nucleair geneeskundige Marcel Stokkel (NKI-AvL) reflecteerde op de balans tussen innovatie, klinische meerwaarde en praktische haalbaarheid. Hij benadrukte dat grondige klinische kennis bij de huidige opleiding onontbeerlijk is voor goede theranostiek. Daarna belichtte nucleair geneeskundige Arthur Braat (UMCU/NKI-AvL) de specifieke dosimetrische aspecten van Selectieve Interne Radiatie Therapie (SIRT), met aandacht voor behandelplanning en uitkomstoptimalisatie. De vergadering werd afgesloten met een beschouwing door nucleair geneeskundige Dennis Vriens (Radboudumc). In deze afsluitende presentatie werd op kritische wijze stilgestaan bij de toegevoegde waarde van dosimetrie, maar ook bij de praktische beperkingen, tijdsinvestering en klinische haalbaarheid.
In de middagsessie waren er vier voordrachten van wetenschappelijke inzendingen.
De algemene conclusie van de vergadering was dat theranostiek en dosimetrie onmisbare bouwstenen zijn van gepersonaliseerde nucleaire geneeskunde, maar dat verdere standaardisatie, scholing en multidisciplinaire samenwerking essentieel blijven voor brede klinische implementatie.

Vrije inzendingen wetenschappelijke voordrachten in de middagsessie

In de middagsessie werden vier wetenschappelijke voordrachten gepresenteerd, waarin actuele onderzoeksresultaten op het gebied van theranostiek, dosimetrie en beeldvorming centraal stonden.
In de presentatie *Dosimetry LuPSMA I&T* besprak Jessie Jaspers (Meander MC) de dosimetrische evaluatie van LuPSMA I&T-therapie, met aandacht voor dosisverdeling, meetmethoden en klinische implicaties.
Mara Veenstra (Erasmus MC) presenteerde het abstract *[^{68}Ga]Ga-FAPI-46 versus [^{18}F]FDG PET/CT in HPB-kankers*, waarin de diagnostische meerwaarde en verschillen tussen beide tracers bij hepatopancreatobiliaire maligniteiten werden onderzocht.
In de voordracht *LuPSMA exposure and neutrophil dynamics* liet Debra van Asten (NKI-AvL) zien hoe

blootstelling aan LuPSMA-therapie samenhangt met veranderingen in neutrofielen, wat relevante inzichten biedt in therapiegerelateerde hematologische effecten.
Tot slot ging Remco Poelarends (Isala) in op *Reconstruction SUV variability PSMA*, waarbij de invloed van reconstructieparameters op SUV-variabiliteit bij PSMA-PET werd geanalyseerd, met implicaties voor zowel diagnostiek als dosimetrie.

Pascalle Mossel

Uitreiking Woldring prijs

Sprekers van de vrije inzendingen van wetenschappelijke voordrachten. Van links naar rechts: Jessie Jaspers, Remco Poelarends, Mara Veenstra en Debra van Asten.

Samenvattingen vrije inzendingen middagprogramma

Dosimetry method simplification for [^{177}Lu]Lu-PSMA-I&T treatment of castration-resistant prostate cancer

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Background

The kidneys are one of the organs at risk for absorbing high dose in [^{177}Lu]Lu-PSMA-I&T treatment of castration-resistant prostate cancer. Dosimetry can be used to assess the absorbed dose. However, this is resource intensive and demanding for both patients and the nuclear medicine department, requiring dedicated SPECT/CT scans and manual image processing. The current dosimetry protocol at the Meander Medical Centre consists of a single time-point SPECT/CT at 24h, for each treatment cycle. This study evaluates simplified sampling strategies, in which imaging is only performed at key treatment cycles, estimating the dose for all other cycles while keeping absorbed kidney dose uncertainty within acceptable limits.

Method

Dosimetric data from 63 patients were analysed. First, inter-patient variability in absorbed kidney dose across treatment cycles was assessed. Second, longitudinal dose trends were evaluated in a subset of 20 patients who underwent at least four consecutive treatment cycles, each followed by SPECT/CT imaging at 24 hours. Finally, two simplified dosimetry methods (SM) were tested: SM1, excluding cycles 4, 5 and 6 by duplicating cycle 3; and SM2, similar to SM1 but also replacing cycle 2 with the mean of cycles 1 and 3. These simplified methods were compared with the reference protocol using Bland–Altman analysis.

Results

The mean absorbed kidney dose is 0.64±0.21Gy/GBq, with the largest inter-patient variability in cycle 1. Both simplified methods showed good agreement with a bias of 1.56% (SM1) and 0.71% (SM2), with no data-points outside of the limits of agreement (LOA). The width of the LOA was +5,40% to -8,51% for SM1 and +8.56% to -9.99% for SM2. Scatter analysis shows no systematic pattern in any of the SM.

Conclusion

These preliminary results show imaging at cycle 1 remains essential due to the largest range between patients, likely due to tumour sink effects. Imaging reduction limited to cycle 1 and 3 (SM2) appears feasible if the limits of agreement are deemed acceptable, potentially decreasing the imaging burden to only 2 of 6 cycles. Validation in larger cohorts and across different institutional protocols is warranted.

Comparative Diagnostic Accuracy of [^{68}Ga]Ga-FAPI-46 and [^{18}F]FDG PET/CT in Hepatopancreatobiliary Cancers: A Large Single-Centre Study

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Background

Accurate detection of hepatopancreatobiliary (HPB) malignancies remains challenging, as conventional imaging often struggles to distinguish between malignant and inflammatory processes. ^{18}F-fluorodeoxyglucose (FDG) PET/CT has variable performance in this setting, whereas fibroblast activation protein inhibitor (FAPI) PET/CT has emerged as a promising alternative. This study compared the diagnostic performance of [^{18}F]FDG and [^{68}Ga]Ga-FAPI-46 PET/CT in patients with suspected HPB malignancies.

Methods

A retrospective analysis was conducted of patients identified from a prospectively maintained institutional registry at AIG Hospitals, Hyderabad, India, who underwent both [^{18}F]FDG and [^{68}Ga]Ga-FAPI-46 PET/CT for suspected HPB cancer. Histopathology and/or clinical follow-up served as the reference standard. [^{18}F]FDG PET/CT results were classified using an SUV_{max} cut-off derived from receiver-operating characteristic (ROC) analysis, whereas [^{68}Ga]Ga-FAPI-46 PET/CT classification followed expert clinical interpretation as recorded in the original reports. Diagnostic accuracy metrics were calculated for each tracer and compared using paired statistical methods.

Results

A total of 204 patients were included in this study. [^{68}Ga]Ga-FAPI-46 PET/CT demonstrated higher sensitivity for HPB malignancies than [^{18}F]FDG PET/CT (92.9% [95% CI, 0.87–0.96] vs 75.9% [95% CI, 0.68–0.82]; p<0.001), with the most pronounced differences observed in cholangiocarcinoma (92.9% vs 70.2%) and pancreatic

carcinoma (100% vs 79.0%). Overall diagnostic accuracy was 80.0% for FAPI (95% CI, 0.74–0.85) compared with 68.7% for FDG (95% CI, 0.62–0.75; p<0.001). In discordant cases (n=55), FAPI-only positivity was more frequent (n=41), of which 78.0% were malignant, compared with 57.1% of FDG-only positive cases. A dual-tracer approach improved diagnostic accuracy compared to FDG alone (78.3% [95% CI, 0.72–0.84] vs 68.7% [95% CI, 0.62–0.75]; p<0.001), but not compared to FAPI alone (78.3% [95% CI, 0.72–0.84] vs 80.0% [95% CI, 0.74–0.85]; p=0.720).

Conclusions

[^{68}Ga]Ga-FAPI-46 PET/CT outperformed [^{18}F]FDG PET/CT for the detection of HPB malignancies, particularly in cholangiocarcinoma and pancreatic cancer. Discordant analyses demonstrated that FAPI provided additional true-positive findings, whereas FDG added limited value. These results highlight [^{68}Ga]Ga-FAPI-46 PET/CT as a superior diagnostic modality in this patient group and suggest that dual-tracer imaging may not offer advantages beyond FAPI alone.

Quantifying the relationship between [^{177}Lu]Lu-PSMA-I&T exposure and neutrophil dynamics using a population pharmacokinetic-pharmacodynamic analysis

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Rationale

[^{177}Lu]Lu-PSMA is a radioligand therapy that prolongs survival in metastatic castration-resistant prostate cancer (mCRPC) patients. While well tolerated, some patients experience dose-limiting hematological toxicities, potentially due to considerable variability in bone exposure. This study aimed to quantify the impact of [^{177}Lu]Lu-PSMA-I&T exposure in bones and bone metastases on neutrophil levels using a semi-physiological population pharmacokinetic-pharmacodynamic (PK-PD) model.

Methods

SPECT/CT scans (4h, 24h, 6 days post-treatment) and neutrophil counts (up to 3 months post-treatment) were retrospectively collected from mCRPC patients receiving 1-8 cycles of ~7.4GBq [^{177}Lu]Lu-PSMA-I&T (September 2019-March 2024). Organ (aorta, bones, kidneys, salivary glands) and tumour segmentation was performed semi-automatically using MIM (version 7.3.6) to obtain volumes (L) and mean uptake (MBq/mL) in organs and tumours (≥2.5mL). An existing PK-model (NONMEM 7.5) was optimized with seven compartments representing blood, salivary glands, kidneys, bones, bone metastases, other tumours and a rest compartment. Structural parameters included volume of distribution (V_1), renal excretion (k10) and rate constants (k_{in}, k_{out}) between compartments. A previously developed PD-model was sequentially used to link bone PK (healthy and metastatic tissue) to neutrophil data and included a delayed linear or sigmoidal effect-relationship, resulting in reduced neutrophil proliferation. The model was used for simulations (n=1000) to predict clinically relevant neutropenia (≤1.5×10^9/L) compared to observations.

Results

Data from 139 patients were analysed (average 3.2 cycles). The PK-model demonstrated good fit and precision (RSEs<40%). Uptake rates varied between compartments, with relative faster rates for bone metastases and kidneys (0.031 and 0.035h^{-1}) and slower rates for salivary glands, other tumours and healthy bone (0.004, 0.007, 0.018h^{-1}, respectively). High inter-individual variability (IIV) was estimated for uptake in bones, bone metastases and other tumours (51%, 151%, 67%, respectively). A linear PK-PD relationship best captured neutrophil dynamics, with a baseline neutrophil count of 4.2×10^9/L (41% IIV). The estimated impact of [^{177}Lu]Lu-PSMA-I&T (slope: 0.0006MBq^{-1}) led to a maximum neutrophil proliferation reduction of 15% (median 1.8%). Simulations predicted a median 8.0% of patients (80% prediction-interval: 5.1%-10.9%) would experience clinically relevant neutropenia, aligning with the observed 7.2% (≤1.5×10^9/L). These results demonstrate the feasibility of predicting individual neutrophil levels.

Conclusions

Our PK-PD model quantified the [^{177}Lu]Lu-PSMA-I&T exposure-neutrophil relationship of mCRPC patients, highlighting substantial variability in bone exposure and feasibility of predicting individual neutrophil levels. These findings suggest that with further optimization the model could help.

Reconstruction-Dependent SUV Variability in Unspecific Bone Uptake: A Risk for Threshold-Based Staging in ^{18}F-PSMA-1007 PET/CT

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Introduction

Interpreting ^{18}F-PSMA-1007 PET scans can be challenging due to the occurrence of unspecific bone uptake (UBU), defined as focal PSMA uptake without a clear CT morphological correlate and uncertain clinical significance. Although Standardized Uptake Value (SUV) in PET is commonly used to distinguish physiological uptake from metastases, SUV can be affected by technical factors such as the applied reconstruction algorithm. Our aim was to evaluate the impact of different iterative reconstruction settings on SUV measurements and lesion classification in ^{18}F-PSMA-1007 PET.

Methods

We retrospectively included 33 patients who underwent ^{18}F-PSMA-1007 PET/CT (Vereos, Philips) and in whom UBUs were identified by expert nuclear medicine physicians. For each patient, three Ordered Subset Expectation Maximization (OSEM) reconstructions with increasing image noise were performed: an EARL2-compliant reconstruction (3 iterations, 7 subsets, point spread function (PSF) modelling with 6 relaxation steps, 4mm Gaussian post-filter), a high-resolution (HR) reconstruction (3 iterations, 13 subsets, without PSF or filtering) routinely used in our institute, and an ultra-high-resolution (UHR) reconstruction with still diagnostic image quality (4 iterations, 24 subsets, without PSF or filtering). A maximum of three UBUs per patient were identified using the HR-reconstruction. SUVmax and SUVmean were measured using a 50%-isocontour for the UBUs on each of the three reconstructions. Impact on SUV measurements was assessed using the HR-reconstruction as reference. Reclassification rates between reconstructions were evaluated using three groups: likely benign (SUVmax<7), equivocal (SUVmax 7-11), and likely metastatic (SUVmax>11).

Results

A total of 56 UBUs were identified. Compared to the HR-reconstruction, the EARL2-reconstruction yielded lower SUV: SUVmax decreased by 16% (6.5 vs. 5.5, p<0.001) and SUVmean by 15% (4.1 vs. 3.5, p<0.001). Conversely, the UHR-reconstruction showed higher values compared to HR: SUVmax increased by 8% (7.0 vs. 6.5, p<0.001) and SUVmean by 6% (4.4 vs. 4.1, p<0.001). Compared to HR, 10 of 56 UBUs (18%) were reclassified from equivocal to likely benign when using EARL2-reconstruction. Using UHR-reconstruction, reclassification occurred in 11 of 56 UBUs (20%) in comparison to HR, including seven from likely benign to equivocal, two from equivocal to likely benign, and two from equivocal to likely malignant (table 1).

Conclusion

In this study, we demonstrated that different OSEM reconstruction settings significantly affect SUVmax and SUVmean of UBUs, leading to reclassification of UBUs when using threshold-based criteria. Consequently, clinicians should use SUV-based thresholds and quantitative PET measurements with caution. Standardization of reconstruction protocols is essential to ensure consistent and reliable quantitative PET interpretation. ♦

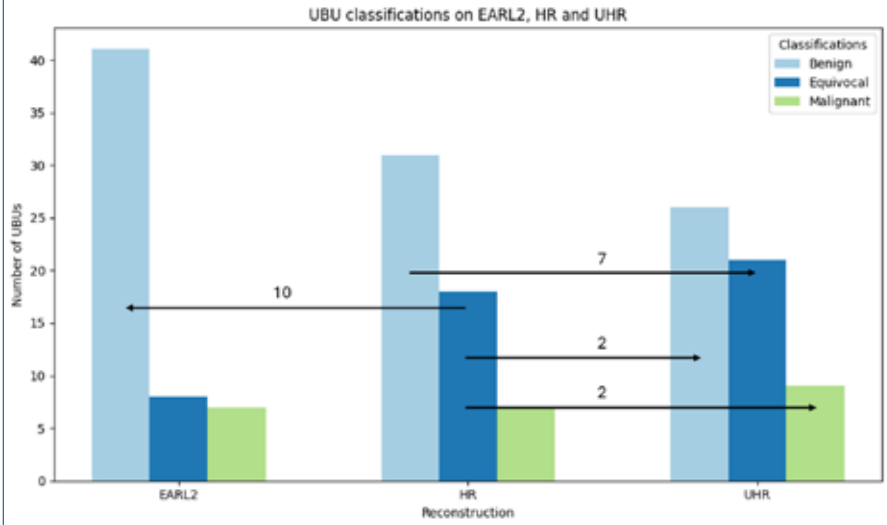

Table 1: UBU classification transitions between the EARL2, HR and UHR reconstructions.