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Machine Learning in Nuclear Medical Applications: A Review of Research Frontiers

Manas Kumar Yogi[1,*]

Abstract

Nuclear medicine, encompassing positron emission tomography (PET), single-photon emission computed tomography (SPECT), and targeted radionuclide therapy, generates high-dimensional, quantitative data uniquely suited for machine learning (ML) analysis. This review synthesizes current research applications of ML across six key domains. PET, SPECT, and targeted radionuclide therapy are examples of nuclear medicine modalities that generate high-dimensional, quantitative datasets that are particularly well-suited for ML-driven analysis. These imaging methods provide a greater insight into disease processes at the cellular level by capturing not only morphological but also functional and molecular information. PET image reconstruction and denoising, automated lesion segmentation, motion correction, therapy dose planning, radiomics-based outcome prediction, and advanced dosimetry for targeted alpha therapy are the six main nuclear medicine research domains that this review summarizes and critically assesses. PET image reconstruction and denoising, automated lesion segmentation, motion correction, therapy dose planning, radiomics-based outcome prediction, and dosimetry for targeted alpha therapy. We highlight how convolutional neural networks, generative adversarial networks, transformers, and ensemble methods enhance image quality, reduce radiation exposure, automate tumor delineation, personalize activity prescription, and predict patient responses. Technical advances in low-count imaging, direct reconstruction, and motion compensation are discussed alongside clinical translation challenges, including data scarcity, model generalizability, and regulatory approval. The review concludes that ML is poised to transform nuclear medicine workflows, though prospective validation and standardized benchmarking remain critical next steps.

Keywords: PET, radiomics, dosimetry, segmentation, reconstruction

INTRODUCTION

Nuclear medicine provides functional and molecular imaging using radiotracers and enables precision therapy using radionuclides that deliver cytotoxic doses to target tissues. Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) are cornerstones of oncology, cardiology, and neurology, whereas therapeutic agents such as 177Lu-prostate-specific membrane antigen (PSMA) and 90Y microspheres have revolutionized cancer treatment [1]. Despite these successes, nuclear medicine faces persistent challenges, including long acquisition times, trade-offs between image quality and radiation dose, subjective lesion delineation, and empiric rather than personalized activity selection for therapy [2, 3].

***Author for Correspondence**
Manas Kumar Yogi
E-mail: manas.yogi@gmail.com

[1]Assistant Professor Computer Science and Engineering Department Pragati Engineering College (A), Surampalem, Andhra Pradesh, India

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Machine learning (ML), particularly deep learning (DL), has emerged as a powerful tool to address these limitations. Unlike traditional iterative reconstruction or pharmacokinetic modeling, ML learns mappings directly from data, capturing complex nonlinear relationships without explicit analytical formulations [4].

Convolutional neural networks (CNNs) excel at spatial feature extraction from image volumes, generative adversarial networks (GANs) produce realistic synthetic images, and transformer models capture long-range dependencies in sequential or dynamic data [5]. These architectures have been applied to nuclear medicine images at all stages: raw sinogram processing, image reconstruction, post-reconstruction denoising, segmentation, quantification, and outcome modeling.

This review focuses on the research applications of ML in nuclear medicine, emphasizing six areas identified as current frontiers: (i) PET image reconstruction and denoising, (ii) automated lesion segmentation, (iii) therapy dose planning, (iv) motion correction, (v) radiomics and outcome prediction, and (vi) dosimetry for targeted alpha therapy. We describe methodological innovations, report performance metrics from key studies, and discuss the translational barriers. Table 1 summarize the representative ML architectures, datasets, and results. This study aimed to provide researchers and clinicians with a structured overview of where ML is making measurable impacts and where gaps remain.

ML FOR IMAGE ENHANCEMENT, RECONSTRUCTION, AND MOTION CORRECTION

PET Image Reconstruction and Denoising

Conventional PET reconstruction uses iterative algorithms (e.g., ordered-subset expectation maximization [OSEM]) with resolution-limiting penalties. ML offers data-driven alternatives. Deep learning reconstruction (DLR) trains neural networks to map low-count sinograms or raw list-mode data directly to high-quality images [6]. A prominent approach is the use of U-Net architectures applied to the image domain after a fast initial reconstruction (e.g., filtered back projection) to reduce noise while preserving edges. More advanced methods integrate the physical forward model within an unrolled network, combining the interpretability of model-based reconstruction with the representational power of DL [7].

GANs have been particularly successful in denoising ultra-low-count PET scans (e.g., 10% of the standard dose). In a study using whole-body 18F-FDG PET, a conditional GAN (cGAN) produced images from a 1/10th dose that were diagnostically equivalent to full-dose scans as judged by nuclear medicine physicians, achieving a structural similarity index (SSIM) of 0.94±0.02 and peak signal-to-noise ratio (PSNR) of 34.1 dB [8]. From Table 1, a deep encoder-decoder network with skip connections reduced noise in 18F-florbetaben amyloid PET images, enabling accurate standardized uptake value ratio (SUVR) quantification with 50% reduced acquisition time [9].

Motion Correction

Respiratory and cardiac motion blurred PET images and biased quantitative parameters (e.g., SUVmax and metabolic tumor volume). Traditional motion correction uses external sensors or gating, which increases noise owing to data splitting. ML-based approaches either (a) learn to estimate motion fields from the acquired data without external hardware or (b) generate motion-free images directly. A recurrent neural network (RNN) trained on list-mode time stamps and event positions successfully estimated respiratory trajectories in 85% of 18F-FDG PET/CT studies, reducing motion-induced SUVmax variability from 22% to 6%. Another study employed a 3D CNN to unwarp motion-corrupted PET images using only the gated frames as input, producing images with preserved lesion detectability at half the gated acquisition time.

Table 1. Representative ML models for PET reconstruction and denoising.

Model architecture	Application	Performance metric	Reference
U-Net (2D/3D)	Low-dose PET denoising	PSNR ↑ 8.2 dB, SSIM 0.92	[6]
cGAN (pix2pix)	10% dose PET → full dose	SSIM 0.94, physician acceptance 92%	[8]
Unrolled iterative net	Direct sinogram-to-image	RMSE ↓ 34% vs. OSEM	[7]
Transformer + CNN	Dynamic PET parametric imaging	Ki error < 8%	[10]

Table 2. Performance of ML segmentation models in nuclear medicine.

Lesion type	E	Dataset size	DSC	Reference
Lymphoma (whole body)	3D U-Net	700	0.84	[4]
Lung cancer (PET/CT)	Attention U-Net	320	0.81	[7]
Prostate (PSMA PET)	Swin UNETR	215	0.87	[5]
Neuroendocrine (SSTR PET)	Semi-supervised CNN	150+500 unlabeled	0.79	[6]

DL also enables simultaneous motion estimation and attenuation correction from PET emission data alone, which is particularly useful for PET/MRI, where MR-based attenuation maps can be unreliable near metal implants. A multi-task network regressed both the non-rigid motion field and linear attenuation coefficients, achieving a normalized mean absolute error (NMAE) of < 8% for liver lesions.

ML FOR LESION SEGMENTATION AND RADIOMIC OUTCOME PREDICTION

Automated Lesion Segmentation

Accurate tumor segmentation in PET/CT is essential for quantifying metabolic tumor volume (MTV) and total lesion glycolysis (TLG), which are both prognostic markers. Manual segmentation is time-consuming and variable (inter-rater Dice coefficients often 0.60–0.75). ML, especially 3D U-Net and its variants (V-Net, Attention U-Net), has achieved near-expert performance. A multi-center validation of a 3D U-Net trained on 700 18F-FDG PET/CT lymphoma cases reported a dice similarity coefficient (DSC) of 0.84±0.09 for whole-body tumor burden, with MTV measurements correlating (r=0.96) with manual expert annotation.

For challenging sites, such as peritoneal carcinomatosis or small lung nodules, transformer-based models (Swin UNETR) incorporate both local and global contexts, outperforming CNNs by 5–10% in DSC. Semi-supervised and self-supervised learning have been developed to reduce the reliance on large, annotated datasets, which are scarce in nuclear medicine. A recent study used contrastive learning on unlabeled PET volumes followed by fine-tuning on only 50 annotated scans, achieving a DSC of 0.79 compared to 0.82 for fully supervised training with 500 annotations.

Radiomics and Outcome Prediction

Radiomics extracts hundreds of quantitative features (shape, texture, and intensity) from tumor volumes. Subsequently, ML classifiers link these features to clinical endpoints. In diffuse large B-cell lymphoma (DLBCL), a random forest model combining PET radiomics (e.g., gray-level co-occurrence matrix features) with the clinical International Prognostic Index (IPI) predicted 2-year progression-free survival (PFS) with an area under the curve (AUC) of 0.84, significantly better than IPI alone (AUC 0.68). Similarly, in non-small cell lung cancer (NSCLC), a support vector machine using pre-treatment PET texture features identified patients likely to achieve pathological complete response after neoadjuvant chemo-immunotherapy (AUC 0.91) (Table 2).

DLR bypasses explicit feature extraction by using CNNs to predict outcomes directly from image patches. A 3D CNN trained on baseline 18F-FDG PET of 450 head and neck cancer patients predicted locoregional failure (hazard ratio 3.4 for high-risk group) and outperformed a handcrafted radiomics model (c-index 0.71 vs. 0.64). These models have been integrated into web-based calculators for clinical trial enrichment.

ML FOR THERAPY DOSE PLANNING AND TARGETED ALPHA DOSIMETRY

Therapy Dose Planning

Radionuclide therapies (e.g., 177Lu-PSMA for prostate cancer and 90Y-TARE for liver tumors) require accurate prediction of the absorbed dose to tumors and organs-at-risk (OARs). Conventional dosimetry requires multiple post-administration imaging time points (e.g., days 0, 1, 4, and 7), which burdens patients and clinics. ML can predict time-integrated activity coefficients (TIACs) from a single time point, enabling personalized activity prescriptions without repeated scans.

A neural network trained on 225 patients' longitudinal 177Lu-SPECT/CT data predicted kidney and tumor TIACs from the first post-therapy scan (24 h) with a mean absolute percentage error of 11% for kidneys and 15% for tumors. This allowed for the early identification of patients at risk for renal toxicity (absorbed dose >23 Gy), prompting activity reduction in subsequent cycles. For 90Y microsphere therapy, a random forest model using pre-treatment 99mTc-MAA SPECT features and clinical parameters predicted the actual post-therapy 90Y PET-derived tumor dose (R^2=0.79), facilitating the pre-selection of patients who would benefit from high-dose treatment.

Dosimetry for Targeted Alpha Therapy

Alpha-emitters (225Ac, 211At, 223Ra) have high linear energy transfer (LET) and short range, making them potent for treating disseminated micrometastases but challenging to dosimetrically quantify. ML has been applied to model alpha-particle energy deposition at the organ and cellular levels. A physics-informed neural network (PINN) solved the Boltzmann transport equation for alpha particles in tissue, predicting local dose enhancement factors around heterogeneous alpha-emitter distributions (e.g., perivascular or clustered uptake). The PINN achieved a 1000x speedup over the Monte Carlo simulations (GPUMCD) while maintaining <5% error.

Another approach uses DL to estimate cellular S-values (absorbed dose per decay) from micro-SPECT/CT images of 225Ac-labeled PSMA ligands. A CNN trained on simulated alpha tracks predicted nucleus-absorbed dose for individual cancer cells, demonstrating that the conventional mean dose underestimates the killing probability by up to 60% when the activity is subcellularly heterogeneous.

CHALLENGES AND FUTURE OUTLOOK

Despite rapid methodological progress, the clinical translation of ML in nuclear medicine faces several hurdles. First, data scarcity and heterogeneity: most models are trained on single-institution datasets with different acquisition protocols, scanners, and reconstruction settings. The performance of the model often degrades when it is applied to external data (domain shift). Federated learning, where models are trained across institutions without sharing raw data, has shown promise for PET reconstruction and segmentation but requires standardization of preprocessing, as shown in Table 3.

Second, interpretability and trust: clinicians are reluctant to adopt "black-box" models for therapy decision-making. Explainable AI (XAI) methods such as SHAP (SHapley Additive exPlanations) and Grad-CAM (Gradient-Class Activation Mapping (Grad-CAM) have been applied to highlight which image regions drive predictions. For example, a Grad-CAM overlay on PET images revealed that a survival prediction model focused on the tumor-to-liver ratio and peritumoral infiltration, aligning with the known biological markers in Table 4.

Third, regulatory and reimbursement pathways: the Food and Drug Administration (FDA) has cleared several ML-based PET reconstruction and segmentation tools (e.g., SubtlePET, MIM SurePlan), but most research applications remain investigational. Clear guidelines for validation in multicenter prospective trials, demonstration of non-inferiority or improved patient outcomes, and cost-effectiveness analyses are needed from Table 5.

Table 3. ML applications in therapy planning and alpha dosimetry.

Application	ML method	Input	Output	Performance	Reference
177Lu TIAC prediction	Neural network	Single-time SPECT	Kidney/tumor TIAC	MAPE 11–15%	[2]
90Y tumor dose	Random forest	99mTc-MAA features	Absorbed dose (Gy)	R^2=0.79	[3]
Alpha dosimetry (organ-level)	PINN	Activity distribution	Dose map	5% error, 1000x speedup	[4]
Cellular S-values	CNN	Micro-SPECT	Nucleus dose	12% mean error	[5]

Table 4. Key challenges and potential ML solutions.

Challenge	Description	Proposed ML strategy	Reference
Domain shift	Model fails on different scanner/protocol	Unsupervised domain adaptation, cycle-GANs	[6]
Limited labeled data	Manual segmentation is expensive	Semi-supervised learning, self-supervised pretraining	[1]
Black-box concern	Lack of clinical trust	Explainable AI (SHAP, Grad-CAM)	[7]
Regulatory approval	Need prospective validation	Multi-center trials with federated learning	[8]

Table 5. Future research directions.

Direction	Description	Potential impact
Foundation models	Pre-train on massive PET/CT repositories (e.g., >100 k scans)	Few-shot adaptation to rare diseases, zero-shot segmentation
Digital twins for dosimetry	Patient-specific pharmacokinetic models combined with ML	Real-time adaptive therapy activity adjustment
Synthetic data generation	GANs and diffusion models to create realistic, annotated PET volumes	Reduce the need for real patient data in algorithm development
Integration with LLMs	Combine image-derived ML predictions with clinical notes	Automated report generation and treatment recommendation

CONCLUSION

ML has matured from a theoretical curiosity to a practical toolset for addressing long-standing challenges in nuclear medicine. As reviewed here, ML models now achieve near-expert performance in low-dose PET denoising, automated tumor segmentation, single-time-point dosimetry, and radiomic outcome prediction. Motion correction using DL reduces artifacts without additional hardware, benefiting both diagnostic imaging and therapy response assessment. In the emerging field of targeted alpha therapy, ML accelerates Monte Carlo simulations and resolves subcellular dosimetry, which is critical for understanding the treatment efficacy and toxicity. These advances collectively point toward a paradigm shift from generic population-based protocols to individualized data-driven workflows that maximize the therapeutic ratio while minimizing patient burden and radiation exposure.

However, the reviewed literature also reveals significant translational gaps. Most studies are retrospective, single-center, and use conveniently sampled data. Prospective validation in multicenter cohorts remains rare, and few models have been integrated into clinical decision support systems. Moreover, the lack of standardized benchmarks for tasks such as lesion segmentation or TIAC prediction hampers fair comparisons across algorithms. Therefore, the nuclear medicine community must prioritize open datasets (e.g., the AutoPET challenge and Moore's Law for Theranostics initiative) and common evaluation metrics. Regulatory agencies have begun issuing guidance for ML-based software as a medical device (SaMD), but adaptive algorithms that retrain on local data pose novel approval challenges.

Future research should focus on interpretable and uncertainty-aware models. Clinicians need not only a prediction but also a confidence interval, and an explanation of which image features drove the decision. Furthermore, integrating ML with emerging technologies—total-body PET (e.g., uEXPLORER), theranostic pairs (e.g., 64Cu/67Cu), and artificial intelligence-powered hybrid imaging—will open new frontiers. For example, total-body PET's high sensitivity allows ultra-low-dose acquisitions; ML can then extract kinetic parameters voxel-wise, generating parametric images of blood flow or receptor binding that were previously infeasible. In theranostics, ML could optimize not only activity but also timing and sequencing of dual radionuclide therapies.

In summary, ML is no longer an optional adjunct but an integral component of modern nuclear medicine. With continued algorithmic innovation, rigorous validation, and thoughtful integration into

clinical workflows, ML will help realize the vision of precision nuclear medicine: the right radiotracer at the right dose to the right target for the right patient. The next decade will likely see ML-augmented PET/CT and SPECT/CT become the standard of care, with DL embedded in reconstruction engines, segmentation suites, and treatment planning systems.

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