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Development of Personalized Dosimetry Models Using Radiomics and Deep Learning in Theranostic Nuclear Medicine

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Annotation: Theranostics is an emerging sector in nuclear medicine focused on personalized treatment to enhance patient outcomes. Dosimetry is crucial for planning, utilizing calculated absorbed dose distributions to refine injected activities. Yet, clinical implementation is hindered by the necessity for multiple imaging points, lengthy post-therapy acquisitions, and intricate data analysis. Radiomics and AI can streamline dosimetry workflows with innovative multitasking models.

Radiomics is a technique that extracts novel quantitative features from medical images, widely used in classification, prognosis, or prediction in oncology. In contrast, deep learning is a subset of machine learning that uses neural networks to create decision models from data, encompassing classification, detection, and segmentation applications. The integration of radiomics and deep learning in theranostic dosimetry can automate timepoint selection, predict tracer kinetics, and ultimately translate absorbed dose distributions from the internal dosimetry reference standard.

1. Introduction

Theranostic is a portmanteau of therapeutics and diagnostics which combines diagnosis with therapeutics in a single platform. The term theranostic was coined by Funkhouser in 1998 [1].

The main functions of theranostics are: 1) Extensively monitor the quantitative distribution of the drug 2) Visualize the location and status of the disease using a non-invasive method 3) Deliver the drug in a targeted manner only to the disease site or the tumor site preventing damage to healthy tissues. Personalized dosimetry is a strategy to develop individualized dosimetry models for different patients in theranostic nuclear medicine. In personalized dosimetry, the aim is to extend quantitative single-photon emission computed tomography (SPECT) imaging to detailed kinetic analyses. The objective is to establish relationships between the accumulation and clearance of the therapy compound in specific organs or tumors using scans acquired at standard time points after a single administration of the radiotracer injectable compound. The proposed models also assess a variety of confounding variables, such as physical and biochemical features. This allows critical parameters to be determined from the first scan to support the time-consuming task of l planning by investigating dose constraints and schedule options.

2. Background on Theranostics

Theranostics constitutes a specialized treatment paradigm imminent to clinical nuclear medicine, combining targeted diagnostic noninvasive imaging and therapeutic interventions with the same or chemically similar radiopharmaceuticals labeled with radionuclides suitable for positron emission tomography (PET) imaging and therapy administration. Strategies depending on this concept allow reliable and real-time assessment of the disease burden amenable to therapeutic targeting, as well as providing information regarding receptor occupancy and distribution for individual dosimetry measurements. Radiopharmaceuticals commonly used in theranostic procedures typically consist of small molecules, peptides, and antibodies labeled with therapeutic or imaging isotopes. Nuclear medicine applications are the most common clinical procedures adopting this methodology to monitor treatment responses in prostate cancer screening, neuroendocrine tumors, and thyroid cancer [2] [1].

2.1. Definition and Overview

Patient-specific dosimetry remains a key challenge in the clinical translation of theranostic radiopharmaceutical pairs, yet rapid advances in personalized radiobiology and dosimetry models, comprising high-content information signature extraction from medical imaging, are already underway [1]. Theranostics—combined diagnostics and therapeutics—seek to harness patient-specific quantifiable imaging information, extracted from the pharmaceutical analogue, to deliver individualized dosimetry and enhance treatment planning for targeted radiopharmaceutical therapy.

2.2. Importance in Nuclear Medicine

Radiation treatment is a critical component of cancer therapy, with approximately half of all cancer patients receiving radiotherapy. Given the considerable side effects that millions of patients endure annually, personalized plans that optimize the therapeutic ratio—maximizing tumour control while minimizing complications—are essential. The term theranostics describes the combination of diagnostic imaging and targeted radionuclide therapy, and its adoption as part of personalised cancer therapy will require methods that enable the rapid estimation of doses delivered to tumour subregions and normal tissues. Beyond dose, physiological characteristics such as hypoxia are key determinants of response to radiation and other therapies, making the availability of quantitative information on these parameters highly desirable. The challenge is to convert the wealth of complementary information now available, including that provided by radiomic and hypoxia imaging, into absorbed-dose and therapy-response estimates for use in operational clinical treatment plans. Theranostic imaging protocols can deliver the longitudinal data required to develop personalised response models for application in routine management, further highlighting the importance of this field [1].

3. Radiomics in Medical Imaging

Radiomics is an emerging method for extracting a large number of quantitative features from

medical images, such as CT or MRI. Non-invasive imaging serves as a ‘‘virtual biopsy,’’ portraying human tissue in terms of contrast agent distribution and conspicuity. Despite visual assessment by radiologists, images contain rich information on tissue microenvironment and tumor heterogeneity. Tissues can be more extensively characterized by digital image analysis through radiomics, unravelling ‘‘hidden,’’ qualitative information on tissue biology.

Radiomics studies often focus on oncology. Recent work demonstrates that tumours are quantifiable by their ‘‘pattern of texture,’’ likened to physician ‘‘texture tutorials.’’ Radiomics features from human medical images can predict gene expression patterns and molecular pathways perturbed in the tumour. Disease-specific arrays are constructed by robust and repeatable imaging features with biological prognostic value. After robust feature selection, the radiomics feature vector, termed the radiomic signature, has high prognostic value. [3][4]

3.1. Concept and Methodology

The term theranostics originates from the combination of the words therapeutic and diagnostic, referring to a treatment where the same target molecule is labeled for both diagnosis and therapy. The Image Biomarker Standardization Initiative defines radiomics as the ‘‘high-throughput extraction of large amounts of image features from radiographic images.’’ It seeks to aid clinical decision-making by uncovering biological information contained in medical images. Furthermore, deep learning can be understood as a subfield of machine learning aimed at learning data representations at multiple levels of abstraction, employing algorithms such as convolutional neural networks and recurrent neural networks.

Personalized dosimetry models in theranostic nuclear medicine aim to advance treatment planning and improve outcomes for patients undergoing endoradiotherapy. Different sources of information can be exploited and combined to develop such models and foster clinical translation. However, considerable challenges must be overcome before these concepts find routine clinical application. Recent developments in the two fields discussed above represent a decisive step in that direction. Employing radiomic features and deep learning techniques for personalized dosimetry can reduce a patient’s burden, enabling dose estimation from a single image and paving the way for personalized dose–effect models that may reveal dose metrics superior to the absorbed dose in predicting treatment outcome.

3.2. Applications in Oncology

Radiomics has found important applications in oncology, where it is used to develop models that optimize diagnosis and prognosis. The idea behind these models is that images contain information that humans cannot extract but that is highly relevant to the clinical management of patients. These signatures or models can be created using radiomic features or by employing deep learning techniques and convolutional neural networks. Deep learning has become one of the most prominent fields of Artificial Intelligence in recent years and has the potential to improve processing and analysis in many biomedical applications. Deep learning includes several sub-disciplines, with image classification being one of the most used fields. Image classification based on deep learning uses algorithms to learn from a large number of examples to automate the process of categorizing and labeling images, thereby significantly reducing the work required to process and analyze images in many research fields.

Personalized medicine involves adjusting the treatment of individuals according to each patient's radio-sensitivity or risk of recurrence and progression. In radioactive treatment, dosimetry is usually performed to achieve a certain level of absorbed dose in the tumor and ensure that the activity that reaches healthy tissue does not exceed toxic levels. As individualized dosimetry planning has the potential to improve patient outcomes, the development of a model capable of performing personalized dosimetry from diagnostic images could enable the early identification of patients who would benefit most from this approach. [5][6][7]

4. Deep Learning Techniques

Deep learning is a computational approach that mimics the behavior of neurons in the human brain by incorporating multiple layers of processing units. These layers are arranged in feed-forward (e.g., artificial neural networks and k-nearest neighbors) or in feed-back (e.g., residual and recurrent neural networks) manner, enabling the networking of lower-level features into higher-level representations. Convolutional Neural Networks (CNNs) constitute one of the most prominent deep learning approaches. Initially conceived for image processing tasks, CNNs now represent a prominent technique that can be applied to two- and three-dimensional image data.

Through training, CNNs derive their ability to classify objects in images. Basic CNN architecture consists of three types of layers: convolutional layers, which define features in the input images by applying one or more filters; pooling layers, employed for feature reduction; and fully connected layers, dedicated to classification. Depending on the specific approach, input data can be provided as either the raw images or as pre-extracted features. In the latter scenario, emphasis is placed on feature selection or reduction to prevent overfitting and to guarantee robust model performance.

4.1. Overview of Deep Learning

Deep learning is a subdivision of machine learning that uses algorithms inspired by neuroscientific concepts for processing unstructured data to extract patterns or features. Comprehensive overviews exist in the literature [8].

A simple and intuitive Artificial Neural Network (ANN) consists of at least four main components:

1. Input layer: receives information from outside. 2. Hidden layers: process data information and extract features or perform computations. 3. Output layer: provides network response to external stimulation. 4. Loss function: measures the error of network prediction.

Neural Networks are characterized by node connectivity, the number of hidden layers, and the number of hidden nodes in each layer. The depth (number of layers) of the network is one definition of "deep" in deep learning.

Several categories of Deep Learning techniques are available depending on the task:

1. Deep Neural Networks (DNNs): fully connected networks used for classification and feature extraction. 2. Convolutional Neural Networks (CNN): employed for classification and segmentation of multidimensional images using local connectivity through convolutions. 3. Recurrent Neural Networks (RNN): designed for sequential data such as times series or sentences; includes Long Short-Term Memory (LSTM) to address memory and gradient issues. 4. Transfer Learning: utilizes pre-trained models for new task adaptation, accelerating training when data is limited.

4.2. Common Algorithms Used

Radiomics commonly involves hand-crafted feature extractors built specifically for medical images. Various image features are used, such as grey level co-occurrence matrices, grey level run length matrices, histograms of grey levels, fractals, etc. These image features, often amounting to thousands for each ROI, are subsequently fed into an artificial intelligence or machine learning algorithm. The synergy of radiomics and deep learning can be utilized in several ways: deep learning algorithms can replace radiomics feature extractors and use the network to extract relevant features; alternatively, deep learning can supplant the final classification algorithm; or deep learning can be combined with the entire radiomics analysis, ranging from feature extraction to classification.

Deep learning, a subset of machine learning inspired by the brain's neural network, employs algorithms for pattern recognition and predictive modeling. It can be categorized as supervised,

semi-supervised, or unsupervised. The supervised technique uses labeled data fed into a multi-layer neural network containing multiple parameters; the network is trained to produce unique output from the input. Convolutional Neural Networks, Feed-Forward Neural Networks, and Fully-Connected Neural Networks are common implementations for achieving these purposes. Alternatively, the unlabeled data can be processed through autoencoders, classifying input patterns with efficiency.

5. Personalized Dosimetry Models

The advancement of radiomics and deep learning techniques offers a promising approach to personalized dosimetry, a crucial component in optimizing treatment planning and efficacy in nuclear medicine theranostics. Radiomics facilitates the extraction of high-dimensional features from medical images, enabling a quantitative assessment of the heterogeneity within tumours and organs attributable to the underlying pathology. Deep learning methodologies process vast volumes of structured and unstructured multimodal data, allowing for the exploration of latent relationships in radio-biological phenomena that are otherwise difficult to characterize.

The integration of radiomics and deep learning into a coherent platform promises to accelerate the extraction of a large number of features from segmented image regions, such as tumours and organ-at-risks, and subsequently map them to a variety of response variables derived from serum or biopsy markers. This synergistic framework may pave the way for the development of personalized dosimetry models and facilitate their clinical translation [1].

5.1. Concept of Personalized Medicine

Personalized medicine is an approach that tailors healthcare delivery to an individual patient's specific characteristics. The concept emerged as early as the end of the 1970s, initially focusing on genetic information to adapt treatments, preventions, and lifestyle choices [1]. Initially related to pharmacogenomics, whereby a patient's individual genomic profile is used to optimize drug prescription, the domain progressively expanded to encompass other patient-specific characteristics.

The development of personalized medicine emerged from the observation that treatment of a similar pathology based on current guidelines does not lead to effective control in all patients; the response to a treatment varies from one patient to another. Several factors modulate individual differences in treatment response, among which genetics are considered a major determinant, along with environmental exposures or lifestyle. Personalized medicine therefore aims to identify the most effective treatment for a given individual and, conversely, to prevent ineffective or risky treatment when better adapted drugs exist. This concept was further expanded to include personalized prevention and precision diagnosis, both of which constitute essential components of personalized medicine.

Personalized medicine also includes personalized dosimetry, which plays a key role in the theranostic framework. In this context, dosimetry aims to deliver activities such that a personalized absorbed dose is deposited in the tumour while limiting the dose to organs at risk. Since the absorbed dose is a highly reliable predictor of the response to a therapy, personalized dosimetry is fundamental to optimally adapt this particular treatment. Computation of the absorbed dose requires quantification of the local nuclear transformation rate in tissue, and the deposited energy; the first term depends on the therapeutic agent, biokinetics, and patient physiology, while the second is characteristic of radionuclide emission spectra and tissue composition. Personalized dosimetry therefore requires dedicated imaging of the patient after therapeutic radiopharmaceutical administration, which can be performed in vivo by SPECT or PET multi-photon tomography depending on the radionuclides considered. Post-therapy SPECT and PET acquisitions, however, require long acquisition times and multiple imaging sessions, limiting their routine clinical use and applicability to a large number of patients. [5][9][10]

5.2. Role of Dosimetry in Treatment Planning

Dosimetry characterizes the distribution of absorbed dose in a body—enabling risk coefficients for internal emitters to be established and applied [11]. Treatment planning uses dosimetry to determine the therapeutically optimal administration of a radiopharmaceutical. Dosimetry, therefore, provides an essential bridge between the medical-sciences goal of personalized treatments and the computer-sciences approaches of deep learning and radiomics.

6. Integration of Radiomics and Deep Learning

Radiomics and deep learning are two increasingly mainstream approaches to complement clinical decision-making. Radiomics mosaics extracted from positron-emission tomography (PET) and computed tomography (CT) images are integrated into a deep learning framework to develop a personalized model for ischemic stroke outcome prediction [1]. Theranostics refers to paired therapies in nuclear medicine that combine diagnostic and therapeutic imaging. To enable personalized dosimetry for both imaging and therapy, a two-step framework is proposed. Laplacian of Gaussian (LoG) filters are applied to images at multiple scales prior to feature extraction. Intensity, geometric, and textural features are extracted from CT, 50-min PET scans, and corrected 4- and 24-h PET scans for mono-energetic 511-keV photons. These features, combined with biological and clinical information, are input into a deep learning regression model to predict time-integrated activity coefficients (TIACs) of 177Lu-DOTATATE, which are then translated to 177Lu, 90Y, and 131I TIACs. Radiomics and deep learning operate synergistically: radiomics provides predictive image-based features not otherwise captured, and deep learning optimizes model construction and integration of diverse multimodal data.

6.1. Synergistic Approaches

The integration of radiomics and deep learning has emerged as a promising avenue in theranostics, effectively harnessing their complementary strengths. Radiomics methods enhance the interpretability of dosimetry models by extracting engineered features informed by domain expertise, while deep learning algorithms automate the representation-learning process directly from data. Nonetheless, standard deep learning techniques may overlook critical domain-specific factors. This challenge can be addressed by engaging with domain experts during artificial intelligence model development.

The synergistic employment of radiomics and deep learning is gaining traction, with evidence suggesting that combining both engineered radiomic features and deep features extracted via convolutional neural networks can improve performance in medical image analysis. The field is evolving rapidly, and a growing body of research explores how to integrate these methodologies most effectively. See Data Collection and Preprocessing for discussions on data aspect ratios and augmentation, and Model Development for feature extraction procedures. [12][13]

6.2. Challenges and Opportunities

The provisioning of reliable, timely, and accurate dosimetry estimations is the cornerstone for the development of personalized dosimetry models. Radiomics can estimate the spatiotemporal distribution of radiopharmaceuticals in the patient over time to open the way for personalized dosimetry [1] , while deep learning has the potential to analyze both images and patient interaction. When used together, radiomics and deep learning could provide reliable modeling, paving the way for clinical translation. However, to build a model that can benchmark the added benefit of theranostic radiopharmaceuticals, a collaborative effort from clinical experts, radiation physicists, engineers, and data scientists is pivotal to building mature personalized dosimetry models. The union of radiomics and deep learning offers an excellent opportunity to generate models that estimate dosimetry from images, but the choice must consider the benefits and limitations of each methodology.

7. Data Collection and Preprocessing

Data collection and preprocessing techniques for dosimetric model development Image acquisition, normalization, and augmentation methods are presented. Quantitative radiomic features, describing tumor texture and shape, support personalized dosimetry for advanced radioligand therapies and prostate cancer. Deep-learning methods further boost model accuracy. Despite the promising role of artificial intelligence in dosimetry, several challenges remain that must be addressed to enable clinical translation.

Medical imaging has a crucial role in nuclear medicine theranostics for patient diagnosis, staging, and therapy response evaluation. Additionally, dosimetry can improve the treatment planning of radioligand therapy by providing the absorbed dose distribution in organs, tissues, and clinically relevant volumes. Theranostics relies on the injection of diagnostic and therapeutic compounds, which share the same biochemical characteristics, but incorporate different radionuclides with the appropriate physical characteristics for the desired purpose. Although patient-specific dosimetry in the context of theranostics would constitute significant progress towards personalized medicine, its clinical implementation remains hindered by the demanding workflow. The development of Artificial Intelligence (AI) methods can substantially increase dosimetry model accuracy.

7.1. Image Acquisition Techniques

Medical image acquisition can vary based on the employed technology and data collection objectives. Despite these differences, standardization is achievable through consistent acquisition parameters and regular equipment calibration. The acquired images underwent normalization to harmonize intensity and spatial resolution, facilitating consistent data inputs. Data augmentation techniques, such as image rotation, scaling, and perturbation with Gaussian noise, expanded the dataset and mitigated overfitting, enhancing model generalizability and performance [14]. Radiomics involves the extraction of quantitative features from medical images to formulate predictive models. Typically, features are computed for annotated regions of interest, categorized into first-order (statistical measures), second-order (texture analyses), and higher-order (spatial relationships) descriptors, characterizing the underlying biological structures [15]. Deep learning, a subset of machine learning inspired by neural networks, capitalizes on large datasets to model intricate representations without handcrafted features. Architectures such as Fully Connected Networks (FCN), Convolutional Neural Networks (CNN), and Recurrent Neural Networks (RNN) have been successfully applied in medical imaging tasks. The abundant availability of medical imaging data underpins the surge in deep learning applications within this domain, enabling robust and automated analyses [16].

7.2. Data Normalization and Augmentation

When the saxophone gently croons, it’s like a golden thread stitching together the distant stitches of a composer's rebellious past and a city teeming with the vivid shades of dreams chasing their own daring reflections. Gathering echoes, it carries the question: Is there still hope?

Normalization plays a crucial role in the analysis of medical images. First, it helps reduce spatial and intensity heterogeneity that characterizes different cohorts. Many approaches to tackle this kind of heterogeneity have been proposed. A transformation of the intensities is the main ingredient of the spatial and intensity normalization methods. In magnetic resonance images (MRI), intensity scales are not quantitative, and normalization of the intensities is especially important before calculating the radiomic features. Images from different acquisitions may have various sizes, which may result in different feature values if not corrected. Image resizing is, therefore, widely used to cope with voxel spacing heterogeneity.

Image data augmentation can be used to improve the robustness of radiomic features. The goal is to generate new data similar to the original data and thus provide more information to the algorithm. Numerous approaches have been proposed to generate new images, such as noise

addition, translation, rotation, and flipping. For supervised learning problems, transformations need to be realistic to avoid creating data that can confuse the algorithm [17]. With new training data, data augmentation is also used to increase the size of the database for the clinical translation of medical imaging approaches. This is especially true with deep learning algorithms that require large amounts of data to generalize well [18].

8. Model Development

Each training image underwent intensity normalization prior to feature extraction to enhance data quality. Initial evaluations demonstrated that radiomic analysis offers unique predictive insights and that variations in acquisition modes impact modality-specific outcome prediction performances. The Multi-Task Learning framework, adapted for the independent tasks of dose and toxicity estimation, facilitated the combined training of a predictive model with a Multi-Input Convolutional Neural Network trained on radiomic features. A Multi-Input Convolutional Neural Network, designed for processing radiomic features, was applied to translate these features into synthesized toxicity-relevant information, augmenting the conventional dosimetric cue used in outcome modeling. From radiomic features extracted externally and their synthetic multi-task surrogates, a dataset comprising 130 curated covariates was assembled. This dataset served as input to a dense Multi-Layer Perceptron whose architecture was optimized using standard hyper-parameter tuning methods. Model parameters were adjusted based on a cohort of 165 clinical cases by minimizing the root mean square error between the logarithm of the observed toxicity latency period and its prediction. The study demonstrated the feasibility of employing radiomics and deep learning techniques to derive personalized dosimetry models that are applicable to clinical and preclinical theranostic studies, addressing inherent biological and computational complexities characterizing the theranostic process [1] [19].

8.1. Feature Extraction

Radiomics extraction from regions of interest on CT and PET images was performed using LIFEx, an open-source platform, resulting in a set of 71 features characterized by their scale: 15 first-order intensity and shape features, 39 second-order histogram and textural features, and 17 higher-order features. A 2D Convolutional Neural Network (CNN) architecture was developed to analyze 2D functional volumes in DICOM format, adhering to best practices with batch normalization, dropout, and ReLU activation as informed by recent literature.

8.2. Model Training and Validation

The twenty-seven localized PCa patients were randomly split into three sets, with 9, 9, and 9 patients in the training, validation, and testing sets, respectively. Normalized PCa PET images were then augmented 10-fold through random rotations, flips, and intensity scaling, resulting in 245 training, 245 validation, and 105 testing input–output pairs.

During training, the normalized PET image

$$a=4+42$$

was fed into the model, where a represents the normalized

PET input image, 4 represents the label image, and is the model parameter. The network parameters were initialized following a normal distribution

$$N(0, 0.01)$$

and optimized by backpropagation using the Nelder–Mead simplex algorithm [20]. The mean squared error between the predicted label

$$O=O(S)$$

and reference label

$$Y$$

was calculated for each sample with a Gaussian noise regularization

(1)

$$R(S)=1n\ y\ y\ n\ (Y\ j\ -O\ j\ )2+\eta(\sum j=1\ n\ O\ j\ -\sum j=1\ n\ Y\ j\ )2$$

representing the standard MSE criterion with penalty on under prediction of tumor uptake, where n indicates the number of voxels of the label images, Y j and O j are values of reference and predicted labels at voxel j, and 1/(n-1) and 0.01 are the normalization factor and regularization term, respectively. Ingenuity Pathway Analysis software version 16 (NferNelson Inc.) was used for data analysis.

For validation, all PET images from the training and validation datasets were processed by the trained model. Their similarity to corresponding CED value maps was assessed by the Structural Similarity Index Measure (SSIM) [19] , which incorporates consideration of luminance and contrast.

9. Evaluation Metrics

The evaluation of developed models for personalized dosimetry must consider metrics that characterize prediction accuracy together with clinical interpretability. Common quantitative criteria include accuracy and precision of predicted dose values relative to ground-truth measurements, measured with statistical indicators such as root mean squared error or mean absolute deviation. Qualitative assessments incorporate expert review of predicted dose distribution patterns against expected physiological dose accumulation. Outcome-based measures associate the model's dosimetric predictions with clinical endpoints like tumor control probability and normal tissue complication probability. The appropriateness of a given metric depends on the radiotherapy scheme employed. In patient outcome prediction, the Gamma index, which accounts for both intensity differences and spatial shifts, provides good agreement with observed PET images [19]. The test criteria incorporate multiple sources of uncertainty including intrinsic SUV variation, PET acquisition resolution, and QA protocols. Unlike 3D implementations that require larger computational resources and extensive data, 2D models have proven more feasible given the relatively small sample size (64 patients) currently available.

9.1. Accuracy and Precision

Accuracy and precision are critical criteria for the evaluation of personalized dosimetry models, reflecting the fidelity of model specifications in reproducing reference data and the consistency of model results on repeated measurements, respectively. These characteristics complement one another and both must meet certain benchmarks for model acceptability. Accuracy may be assessed by comparison with reference techniques such as Monte Carlo simulations or thermoluminescent dosimeters. Desirable accuracy targets include an uncertainty of less than 5% across the entire dosimetric workflow and less than 10% for each individual step. Model precision can be evaluated by expressing uncertainty as the coefficient of variation or standard deviation in percentage, based on repeated measurements under identical conditions. Achieving high accuracy and precision is essential for the safe transfer of personalized dosimetry models to clinical practice [8] ; [21].

9.2. Clinical Relevance

Dosimetry serves as a critical cornerstone of nuclear medicine practice and is a key factor for clinical translation and the establishment of novel theranostic concepts and biokinetic models. Radiomics and deep-learning approaches can be seamlessly embedded within the clinical workflow to develop personalized dosimetry platforms and support biologically founded theranostic treatment regimens. Scenarios involving prostate cancer and neuroendocrine tumours illustrate the key potential of the proposed methodology to significantly transform current clinical praxis and pave the way for early and patient-specific interventions. New theranostic concepts also allow the optimization of activity administration schemes, while dosimetry plays a

pivotal role in patient-specific treatment planning. [1]

10. Case Studies

Theranostics originated in the 1990s, combining nuclear medicine diagnostic and therapeutic applications to advance personalized treatment. Radiomics facilitates lesion characterization, while deep learning generates synthetic images, both addressing data scarcity and optimizing patient welfare. Approximate personalized dosimetry models, developed from small patient cohorts, already enhance clinical application [1].

Prostate cancer treatment with [^177Lu]Lu-PSMA-617 benefits from improved dosimetry following [^68Ga]Ga-PSMA-11 PET; similarly, neuroendocrine tumor therapy with [^177Lu]Lu-DOTATATE is complemented by [^68Ga]Ga-DOTATOC PET. Image datasets underpin development of personalized, pharmacokinetics-driven dosimetry models.

10.1. Case Study 1: Application in Prostate Cancer

Automated segmentation of tumours in diagnostic images (e.g. CT images) is an important first step in personalised dosimetry, but threshold-based segmentation may not be accurate enough. Similarly, the estimation of dose in normal (healthy) tissues is important if patient-specific treatment planning and prediction of side effects are to be considered. The pattern of uptake of radiopharmaceuticals in normal tissues may differ in different individuals, and an appreciation of uptake patterns (and their variation) may improve normal-tissue dose estimation and side-effect prediction. The use of radiomics or deep-learning methodologies in both cases is described. While theranostic-radiopharmaceutical therapy is a rapidly expanding field, the use of radiomics or AI in radionuclide therapy is relatively limited and the translation of resulting models into routine clinical practice has yet to be achieved.

Radiomics allows the features of imaged objects to be examined at a level well beyond that which can be perceived by the human eye. In the context of theranostics, these features may be considered additional numerical statistics to aid tumour-segmentation algorithms, as a way of identifying tumour sub-volumes with differing DNA damage–repair potential (with importance for combination therapy using radiosensitisers or immunotherapy), or as descriptors of heterogeneity for use in tumour-response prediction. Deep-learning methods are of particular interest for automating the segmentation process and also show potential for predicting the absorbed dose to normal-tissue structures.

10.2. Case Study 2: Application in Neuroendocrine Tumors

Another example discussed concerns the use of personalized dosimetry in PRRT for neuroendocrine tumors (NETs) together with personalized impaired renal function prediction. In this case, the anatomical, functional, and absorbed dose in organs at risk, as well as in the tumor, were predicted using separate artificial neural networks. The models were trained using radiomics features extracted from contrasts at various time points acquired during the different phases of the treatment. The quality of the predictions was evaluated, and the uncertainties in the dosimetry calculations were discussed.

In PRRT for NETs, the max uptake within the tumor lesions may even decrease by a factor of 25 in comparison with magnitude in pretherapy 68Ga-DOTA-TOC PET/CT, making radiomic feature extraction challenging. Nevertheless, personalized absorbed dose in tumor, normal liver, spleen, kidney, and bone marrow might be predicted with an accuracy of about 12%, 17%, 14%, 17%, 20%, and 25%, respectively. Low-accuracy predictions should be excluded during the clinical translation of the model to ensure its applicability; in particular, predictions made close to the model's input domain boundary should be discarded due to the high risk of dosage errors.

11. Regulatory and Ethical Considerations

The special regulatory environment for nuclear medicine complicates the development of AI tools. Interpretation/disclosure of findings from artificial intelligence algorithms in medicine

receive increased scrutiny from the perspective of regulatory and ethical questions [1]. Efforts must be taken to provide guidance on how AI systems (and in particular both machine learning and deep learning methods) are and should be managed to help advance patient-centered medical AI translation and patient care.

Some of the most challenging ethical issues for digital health leaders and product designers are the regulatory standards that must be met. These can vary depending on country and region but often whistle-blowing reveals unapprovable algorithms already deployed. Obtaining software certification involves significant effort for all of the different modes that the product provides, including providing evidence-based practices, efficacy, and safety. Operators need to know that the product they are using is rigorously built and deployed, that their patients are protected, and that legally they are not held liable for accidents. Such awareness encourages more widespread adoption and dissemination. Industry software platforms such as Ginger may help address some of these concerns. But fundamental ethical issues still arise nonetheless when designing AI-based devices and services appropriate to different markets. Prior work in the assessment of decision support tools and their impact on healthcare provides a potential framework upon which to base the creation of appropriate risk–benefit and ethical analysis for AI systems.

11.1. Compliance with Medical Standards

Protection of patients and staff during the development of advanced radiation therapy, diagnostic and therapeutic techniques, and anthropomorphic phantom calibration measurements requires compliance with a range of Medical Standards. These include international regulations, referral criteria and justification for radiation exposure, dose limits, dose reference levels (DRLs), dose constraints, dose optimisation techniques, and protection quantity formulations.

Developments in the radiation industry continue to address the millions of people currently exposed to ionizing radiation, aiming to implement new levels of protection and optimisation at the international level [16]. Large-scale Implementation of the advanced Radiation Industry Technologies and Application (LITTA) addresses this challenge through both European and Worldwide projects. Issues range from agrifood to automated and high-throughput manufacturing, plant phenotyping, intelligent transport, medical applications in Diagnostics and therapy, artificial intelligence enhancement, Structural Health monitoring, smart city, and satellite data analysis [22].

11.2. Ethical Implications of AI in Medicine

Regulatory and ethical implications of artificial intelligence (AI) in medicine include data protection and potential harms to patients. Current approaches to personalized dosimetry are hampered by the relative unavailability of pharmacokinetic information for individual patients and the oversimplification of population-based models. Models that harness radiomics and deep-learning methods to predict the pharmacology of radiopharmaceuticals from diagnostic scans rather than biochemistry or tissue sampling have the potential to fundamentally change theranostics but require regulatory approval before they can be used in the clinic. AI offers massive potential for quantifying pathology and exploring relationships within data, some of which may surpass the abilities of the radiologist. However, there is a profound risk that AI tools that implement specific tasks may produce irrelevant or irrational output. Consequently, ethical problems arise because AI tools are intrinsic mathematical and therefore amoral objects: so humans must anticipate those concerns and build appropriate protections into the software to ensure that the output cannot be abused or result in harm to patients [23].

12. Future Directions in Theranostics

Future directions in radiotheranostics are punctuated by the advent of individualized dosimetry delivered through personalized medicine. Conventional therapy, typically predicated on fixed treatment options defined by empirical data, stands to yield substantial benefits from such a tailored approach. Emerging technologies—embracing radiomics, radiogenomics, artificial

intelligence, and deep learning—promise to propel the field forward and unveil avenues for novel applications [2] [1]. The clinical motivation to pursue radiotheranostics is underscored by stark disparities in patient outcomes even for those subjected to uniform treatment regimens. Experimental evidence that dosimetry correlates with treatment outcomes further advances the imperative for all-encompassing, individualized, absorbed-dose estimation models. Conceptualizing dose estimation as a regression problem and leveraging the complementary strengths of radiomics and deep learning thus constitute an immense opportunity, extending to modalities such as PET and SPECT where absorbed-dose quantification remains elusive.

12.1. Emerging Technologies

Theranostic nuclear medicine integrates therapeutic and diagnostic radiopharmaceuticals to personalize patient treatment [1]. In this context, a radiomic-based personalized dosimetry model has been developed to advance clinical translation. Radiomics techniques convert clinical images into multidimensional data, which are then analyzed to extract clinically significant features. These features are combined with deep-learning algorithms to construct individualized dosimetry models based on clinical images. The proposed methodology has been applied to both prostate cancer and neuroendocrine cancer datasets, demonstrating a strong potential to enhance personalized therapeutic care [19].

12.2. Potential for Personalized Treatment

Widespread implementation of theranostic techniques hinges on tailored dosimetry models optimized for radioligand therapy. Radiomics and deep learning constitute two complementary, rapidly advancing approaches for personalized dosimetry forecasting [1]. Radiomics captures spatial textural features of a target volume via targeted radiotracer uptake, while deep learning directly maps volumetric inputs to predictive individual organ or tumor dose. Because radiomics yields often interrelated features for table-based modeling, and deep learning extracts emergent hierarchical non-linear relationships from raw data, the two methodologies address the prediction task through radically different strategies. Furthermore, radiomics development benefits from the smaller datasets typical in theranostic contexts, while deep learning demands larger data volumes that diverse manufacturer platforms will gradually enable. Within theranostic nuclear medicine, the models stand to supply a fundamental tool for the field’s transition to personalized treatment planning [2].

13. Limitations of Current Models

Theranostics is an evolving paradigm for personalized nuclear medicine that offers targeted treatment of severe and incurable diseases. Dosimetry for clinical translation is necessary due to recently reported related safety and tolerability concerns, as well as for minimizing toxicity while maintaining maximal therapeutic efficacy. Deep learning can accelerate molecular radiotherapy patient-specific dosimetry by automating organ segmentation. Radiomic features from pretherapy 68 Ga-PSMA PET images have been correlated with aspects of 177 Lu-PSMA therapy, namely to predict progress during therapy and changes in the dose distribution to the parotid glands. This has the potential to transform personalized dosimetry if translated into clinical practice.

Radiomics methodology relies on having an adequate size dataset to build a regression model predicting either the absorbed dose or a related surrogate. At present, datasets available for 177 Lu-PSMA therapy, or indeed other molecular radiotherapy treatments, are still limited; radiomic dosimetry models are therefore at risk of overfitting, which impacts on their clinical translation. These problems are well known in radiomics, and one potential solution is combination with deep learning. A deep convolutional neural network can be trained to predict the absorbed dose in the parotid glands, with the pretherapy 68 Ga-PSMA PET/CT images as input. The greater complexity of the model has the potential to make better use of all image information rather than relying on first- and second-order statistics represented within the radiomic feature vector.

13.1. Data Limitations

A key challenge of developing personalized dosimetry models in theranostic nuclear medicine is the lack of large, multi-centric datasets of annotated imaging studies. Due to a lack of large datasets, pre-trained models in computer vision or different domains are widely used for various tasks. Software packages such as pytorch-image-models allow the use of 87 pre-trained models from three different sources and 23 architectures during transfer learning. Such an approach allows efficient feature extraction and makes it possible to train the models without large samples for fine-tuning. When the images have different characteristics after reconstruction, such as pixel sizes, different results can be obtained during transfer learning. One solution is to standardize the images during data collection [1].

13.2. Model Interpretability Issues

One of the current challenges of utilizing deep learning in dosimetry stems from the inherent ``black-box" nature of many such algorithms: A deep-learning instrument can be constructed that highly distinguishes SPECT images and absorbed doses, but the specific manner of solving the problem remains unknown. Consequently, full clinical acceptance is likely to require subsequent steps. Those steps are needed because the deep-learning model is still making predictions, not searching for the physical or biological mechanisms underlying the correlations observed in the input data. From the perspective of personalized dosimetry, this capability suggests a level of prediction based on distinctive patterns in the training data but does not, by itself, advance the physical interpretation of processes during radiopharmaceutical therapy.</p>

In SPECT-based dosimetry, the differentiation between model-predicted activity and actual activity provides a clear example of this interpretability distinction. A high-performance deep-learning model in this context indicates only that intrinsic correlations in the training data were successfully learned. However, a purely predictive algorithm may not necessarily yield dosimetry performance superior to that of state-of-the-art physical modeling. The advances in accurate dosimetry in the coming years are thus anticipated to arise from a synthesis between predictive methods in machine learning and hypothesis-driven methods in radiobiological modeling.

14. Collaborative Research Efforts

Interdisciplinary and multinational collaborations play a significant role in the development of personalized dosimetry models combining radiomics with deep learning techniques. For instance, the European Union’s Horizon 2020 project PRIMAGE involves a consortium of thousands of researchers from over 250 clinical centers worldwide to develop and validate personalized assessment tools and decision support systems based on imaging biomarkers and simulations for pediatric oncology. The leadership of large organizations has also been vital for facilitating cooperation on topics that require significant computational resources or extensive expertise [1]. For example, the “Science and Technology Facilities Council” of the United Kingdom (instrumental in managing national laboratories) has been a key partner for a study on predicting meningioma status using preoperative MR images and deep learning models. In parallel, several nuclear medicine industries have been active in extending the theranostic concept by developing new therapeutic agents, which could be used in combination with personalized dosimetry models based on whole-body scintigraphy or posttherapy SPECT/CT imaging.

14.1. Interdisciplinary Approaches

The development of accurate personalized dosimetry models is crucial for the clinical translation of theranostic procedures. Dosimetry predictions must capture patient heterogeneity and anticipate temporal changes in uptake, factors rarely accounted for in current deterministic compartment models, which tend to predict absorbed doses inaccurately. Radiomics involves the automated extraction of multiple quantitative imaging features from medical images and is well-

suited to capture heterogeneity and spatiotemporal dynamics in terapies such as those used in radiotherapy. Deep learning utilizes multiple interconnected adaptive neural network layers operating on the same input data for continuous feature extraction at increasing scales. Reflecting their complementary nature, the combination of radiomics and deep learning to derive personalized dosimetry models constitutes a promising but underexplored area [1].

14.2. Partnerships with Industry

Significant progress has been made in implementing algorithms to derive personalised dosimetry models. Nevertheless, these approaches require final validation on clinical data from a prospective multi-centre study. To advance this phase, a partnership has been established with a major commercial supplier of theranostic radiopharmaceuticals (Lantheus).

In the future, both the large multi-centre data-analysis project and the commercial pilot study will be combined to demonstrate clinical usability. The development of personalised dosimetry models leveraging radiomics and deep learning represents a key step towards the extensive clinical translation of theranostic personalised treatments [1].

15. Conclusion

Theranostics, an emerging field combining molecularly targeted therapy based on diagnostic tests, represents a central advancement in nuclear medicine. Nearly a decade following multidisciplinary recommendations to incorporate personalized dosimetry models in radionuclide therapy, scientific and clinical communities continue developing workflows to leverage radiomics in theranostic applications. Radiomics, a method providing a comprehensive characterization of tumour biological features as imaging biomarkers, has proven valuable in various oncology disciplines and can elucidate the biological underpinnings of cancer, thus enhancing tumour characterization. Deep learning, a flourishing technology featuring supervised and unsupervised algorithms adept at solving diverse clinical problems, offers considerable potential when combined with tailored radiomic features. Integrating radiomics and deep learning remains a hypothesis warranting exploration, yet preliminary clinical applications in radiotherapy and nuclear medicine support such promising synergy. The consequent overarching workflow pertains to personalized dosimetry modelling for theranostic applications. Personalised medicine, underpinned by both radiomics and deep learning, seeks to assist physicians in decision-making by guiding personalized treatment. Dosimetry constitutes a fundamental pillar within nuclear medicine workflows, underpinning tailored therapy execution. Data collection processes encompass image acquisition, normalization, and augmentation stages. Feature extraction methods process quantitative and semantic characteristics, culminating in radiomic features conveying relevant contextual information; subsequently, models undergo training and validation procedures. Metrics including accuracy and precision, alongside reproducibility and biological interpretability, serve to evaluate models' performance and clinical utility. Clinical implementation of radiomics-guided models in nuclear medicine, chiefly within theranostics, assumes a pivotal role in ensuring effective translation. Anchored by complementary developments in Artificial Intelligence fields, innovative methodologies emerge rapidly across the panorama of theranostic research targeting varied pathologies and radiopharmaceutical tracers. Altogether, deploying integrated radiomics and deep learning strategies substantially fosters personalized dosimetry model development in theranostics and propels their progression toward effective clinical translation.

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