Clinical Applications of AI and Radiomics in NENs

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Nuclear medicine has acquired a crucial role in the management of patients with neuroendocrine neoplasms (NENs) by improving the accuracy of diagnosis and staging as well as their risk stratification and personalized therapies, including radioligand therapies (RLT). Artificial intelligence (AI) and radiomics can enable physicians to further improve the overall efficiency and accuracy of the use of these tools in both diagnostic and therapeutic settings by improving the prediction of the tumor grade, differential diagnosis from other malignancies, assessment of tumor behavior and aggressiveness, and prediction of treatment response.

neuroendocrine tumor NET machine learning nuclear medicine

1. Introduction

Neuroendocrine neoplasms (NENs) comprise a wide variety of heterogeneous tumors, originating from the diffuse neuroendocrine system. These tumors are considered rare, with an incidence of about 3–5 new cases/100,000 inhabitants/year, although new data from the *US Surveillance Epidemiology and End Results Program (SEER)* show an increase in the incidence of the disease of about 520% over the last 32 years (1973–2005), with an annual rate of 5.8% [1]. This increase in incidence can be partially attributed to the introduction of new and/or more sophisticated diagnostic tools, such as single-photon emission computed tomography (SPECT), positron emission tomography (PET) combined with computed tomography (PET/CT), or magnetic resonance imaging (PET/MRI).

Although ubiquitous, these tumors most frequently affect the gastro-entero-pancreatic (GEP) tract (33%) and the bronchopulmonary system (25%). The survival of NET depends on the site and the stage according to the 2022 Tumor, Node, Metastasis (TNM) classification and the World Health Organization (WHO) histopathological classification, which expresses both the morphological appearance of the tumor and its proliferative activity in terms of the number of mitoses and the proliferation index (by assessing the Ki-67 index and thus the disease grading) [2][3].

In vivo imaging of SSTR expression in well-differentiated NENs (G1 and G2 with low-intermediate levels of the Ki-67 index, <10%) is feasible with both [^{111}In]DTPA-octreotide scintigraphy (Octreoscan®) SPECT and somatostatin analog PET ([^{68}Ga]Ga-DOTANOC, [^{68}Ga]Ga-DOTATATE, and [^{68}Ga]Ga-DOTATOC) [4][5]. In cases of high levels of the Ki-67 index (>10%), high-grade NET (G3) and NEC, or in cases of [^{68}Ga]Ga-DOTA-peptide imaging of SSTR-

negative lesions, patients are also candidates for 2-[^{18}F]F-fluoro-2-deoxy-D-glucose ([^{18}F]FDG) PET/CT, a glucose analog [6][7][8][9]. NENs usually grow slowly with a low rate of glucose metabolism; indeed, [^{18}F]FDG PET/CT scans are more likely to detect more aggressive and poorly differentiated NENs, which correlate to worse clinical outcomes [10].

In 2017, Chan et al. [11] proposed a staging protocol by means of [^{18}F]FDG and [^{68}Ga]Ga-DOTA-peptides PET/CT, resulting in the formulation of a new score, the “NETPET grade”, which could help in the prognostic evaluation of NEN patients and the resulting therapeutic decisions. However, to date, this protocol is hardly applicable in the clinical setting; imaging with multiple radiotracers, although potentially providing the most accurate biological characterization of the disease, is not feasible/reimbursed in all patients and should only be considered in selected cases.

This drawback might be partially solved using new artificial intelligence (AI) approaches to extract data from both [^{68}Ga]Ga-DOTA-labelled somatostatin analogs and/or [^{18}F]FDG PET/CT images [12][13][14][15][16]. Indeed, radiomics uses bioinformatics and data-characterization algorithms to extract several quantitative characteristics (features) from medical images. These characteristics, known as radiomics features (RFs), may be able to identify disease characteristics that are invisible to the human eye, opening the door to the prospect of quantifying particular tumor characteristics and phenotypes [15][17]. There are a large number of radiomic features, related to morphological properties, the intensity distributions of the image voxels, or to the properties of the image texture. Standardized definitions of principal RFs are provided in the reference manual of the Imaging Biomarker Standardization Initiative (IBSI) [18][19]. According to the EANM/SNMMI guidelines on radiomics in nuclear medicine [20], there are three categories of radiomics-based approaches: hand-crafted radiomics (with explicit extraction of pre-designed radiomics features from the images followed by univariate or multivariate analysis), representation-learning based radiomics (with automatic discovering of features and patterns inherent in the images) and hybrid radiomics (a combination of the two other frameworks), AI comprises different types of algorithms that can perform complex tasks by learning from available data, similar to human intelligence. Under the general category of “AI”, deep learning (DL), reinforcement learning, supervised machine learning, and unsupervised machine learning are all included [21][22][23][24][25].

2. Staging

As already mentioned, the use of dual PET/CT with [18F]FDG and [68Ga]DOTA-peptides could help to detect intratumor heterogeneity, facilitating the identification of the best target lesions for diagnostic biopsy and histological subtypes, which have a strong correlation with the prognosis of NEN [2][11][26]. The performance of dual PET for the characterization of histological patterns and prognosis of NEN lesions may be further enhanced by radiomics.

In 2017, Giesel et al. [27] published a study on the correlation between SUV_{max} and CT radiomics analysis using lymph node density in the CT component of the PET/CT examination to differentiate malignant from benign lymph nodes. The authors used a sample size of 1,022 lymph nodes extracted from the PET/CT examinations of 148

patients with different tumor types: 327 lymph nodes from 40 patients with lung cancer; 224 lymph nodes from 33 patients with malignant melanoma; 217 lymph nodes from 35 patients with GEP-NET; 254 lymph nodes from 40 patients with prostate cancer. Despite the large heterogeneity of the population evaluated, in terms of pathology and PET radiopharmaceutical analysis ([^{18}F]FDG, [^{68}Ga]Ga-DOTATOC, and [^{68}Ga]Ga-PSMA-11), the study showed that PET-positive lymph nodes had significantly higher CT densities than PET-negative ones, irrespective of the type of cancer, identifying a CT density threshold of 7.5 Hounsfield units to differentiate between malignant and benign infiltration of lymph nodes and 20 Hounsfield units to exclude benign lymph nodes processes.

In 2020, Weber et al. [28], sought to determine whether conventional PET and MRI parameters and RFs derived from simultaneous [^{68}Ga]Ga-DOTATOC PET/CT and MRI were related to the proliferative activity of NETs, potentially allowing for a non-invasive tumor grading. The authors evaluated 304 lesions from 100 NET/NECs patients. They showed that differences between G1 and G2 tumors in conventional PET parameters, MRI ADC values, and RFs determined from both modalities were statistically significant. However, the correlation between the aforementioned parameters and Ki-67-index was weak, suggesting that RFs extracted from combined PET/MRI may not be reliably used for accurate non-invasive tumor grading in patients with Ki-67 < 30%. Further insights have been presented by Thuillier et al. [29] who assessed if conventional PET parameters and RFs extracted by [^{18}F]FDG PET/CT could differentiate among different histological subtypes (NETs vs NECs) of lung-NENs in forty-four naïve-treatment patients (15 TC, 11 AC, 1 TC or AC, 16 LCNEC and 3 SCLC). Namely, conventional PET parameters resulted to be able to distinguish Lu-NECs from Lu-NETs (SUV_{max} cut-off = 5.16; AUC = 0.91; $p < 0.001$), but not TC from AC. In fact, stratifying TC and AC according to Ki-67 level, SUV_{max} and SUV_{mean} showed a positive correlation with Ki-67, without statistical significance ($p = 0.05$ and 0.07, respectively). Regarding the TNM status, SUV_{max}, MTV, and TLG of the primary lesion were significantly associated with N+ status ($p < 0.05$). On the contrary, RFs did not provide additional information.

More recently, Fonti et al. [30] aimed to test the ability of the coefficient of variation (CoV) derived from [^{68}Ga]DOTA-peptides PET/CT imaging in the evaluation and quantification of the heterogeneity of SSTR2 expression within 107 tumor lesions (including 35 primary tumors, 32 metastatic lymph nodes, and 40 distant metastases) of 38 NENs patients (25 GEP-NENs, 7 lung-NENs and 6 from other anatomic districts). Among the RFs for the assessment of tumor heterogeneity, CoV is a simple first-order parameter that indicates the percent variability of SUV_{mean} within the tumor volume reflecting the heterogeneity of tracer distribution. Average CoVs were 0.49 ± 0.20 for primary tumors, 0.57 ± 0.26 for lymph node metastases, and 0.44 ± 0.20 for distant metastases. The CoVs of malignant lesions were up to 4-fold higher than those of normal tissues ($p \leq 0.0001$). Among malignant lesions, the highest CoV was found for bone metastases (0.68 ± 0.20), and it was significantly greater than that of primary lesions ($p = 0.01$) and liver metastases ($p < 0.0001$). The lowest CoV was observed for liver lesions (0.32 ± 0.07), probably because of the high background uptake. On the other hand, no statistically significant differences were found between the SUV_{max} of primary lesions, lymph node metastases and distant metastases, although the SUV_{max} of distant metastases tended to be higher than that of primary lesions ($p = 0.0573$).

Three studies focused on evaluating the role of radiomics parameters extracted by [^{68}Ga]DOTA-peptides PET images in predicting histopathological prognostic factors in pancreatic NEN tumors (PanNETs) patients. In 2020,

Mapelli et al. [31] retrospectively extracted conventional and tumor burden PET parameters and radiomics parameters (using Chang-Gung Image Texture Analysis software package, version 1.3; digitalization method: 4; digitalization bins: 64) on the primary tumor lesion from both [^{18}F]FDG and [^{68}Ga]Ga-DOTATOC PET/CT scan images of 61 treatment-naive PanNET patients undergoing surgery. Intensity variability, SZV, homogeneity, SUV_{max} and MTV were predictive for tumor dimension in [^{18}F]FDG images. From principal component analysis (PCA), 4 elements were extracted: PC1 correlated with all [^{18}F]FDG variables, while PC2, PC3 and PC4 with [^{68}Ga]Ga-DOTATOC variables. The only significant predictor of angioinvasion was PC1 (p = 0.02), while the only significant predictor of lymph node involvement was PC4 (p = 0.015). All principal components except PC4 significantly predicted tumor dimension (p < 0.0001 for PC1, p = 0.0016 for PC2 and p < 0.0001 for PC3). The same group [32] extracted conventional PET and MRI parameters, and radiomics parameters from hybrid [^{68}Ga]Ga-DOTATOC PET/MRI of 16 treatment-naive PanNET patients undergoing surgery, using another open-source Python package Pyradiomics 3.0.1 (https://www.radiomics.io/pyradiomics.html; accessed on 24 July 2023). They discovered a moderately significant, inverse connection (rho = 0.58, p = 0.02) between SUVmax and LN involvement. SUVmax proved to be a reliable indicator of LN involvement, with an AUC of 0.850 (95% CI: 0.60–1.00), an optimal cut-off value of 90.960, sensitivity of 60%, and specificity of 100%. Potential correlations between radiomics characteristics and tumor grade, LN involvement and vascular invasion were analyzed. After adjustment for multiple comparisons, only second-order radiomics parameters Gray-Level-Variance (GLV) and High-Gray-Level-Zone-Emphasis (HGLZE) extracted from T2 MRI demonstrated significant correlations with LN involvement (adjusted p = 0.009), also showing a good predictive performance (AUC = 0.992), with an optimal cut-off value of 0.145 for GLV (correspondent sensitivity and specificity of 90% and 100%, respectively) and of 1.545 for HGLZE (correspondent sensitivity and specificity of 90% and 100%, respectively). Finally, Bevilacqua et al. [33] extracted conventional PET and radiomics parameters from [^{68}Ga]Ga-DOTANOC PET/CT imaging of 51 patients with primary G1-G2 treatment-naive PanNET to investigate their ability to predict G1 versus G2 patients. Patients were grouped according to the method of tumor grade assessment: histology on the entire primary excised lesion (HS) or biopsy (BS). Three radiomics models were evaluated: A (trained on HS, validated on BS), B (trained on BS, validated on HS) and C (using cross-validation on the entire dataset). HS group SUV_{max} values did not significantly differ between G1 (36.9 ± 23.5, [6.9–84.8]) and G2 (45.3 ± 28.6, [15.0–95.7]) (p-value = 0.60). On the contrary, the grade of the primary lesion was accurately determined when using RFs: the best RF pairs for predicting G2 and G1 were second-order normalized homogeneity and entropy (p-value = 0.0002 with AUC = 0.94 (95% CI, 0.74–0.99). Model A had the best performance (test AUC = 0.90, sensitivity = 0.88, specificity = 0.89) whereas Model C had the worst performance (test median AUC = 0.87, sensitivity = 0.83, specificity = 0.82).

In 2022, Noortman et al. [34] investigated the use of [^{18}F]FDG-PET/CT radiomics, SUV_{max}, and biochemical profile for the identification of the genetic clusters of 40 paragangliomas (PPGLs) patients (13 cluster 1, 18 cluster 2, 9 sporadic). The dataset was split into five equal-sized folds, stratified for the genetic clusters. Each subgroup consecutively served as a test set and the remaining four-fifths of patients served as the training set. The biochemical profile alone was the lowest performing model with an average multiclass AUC of 0.60. The three-factor PET model showed the best classification performance to distinguish cluster 1 from cluster 2 of PPGL (multiclass AUC of 0.88), however comparable to the performance achieved by SUV_{max} alone (multiclass AUC of

0.85), which could therefore be preferred to the radiomics analysis model in a clinical scenario being more handleable.

3. Restaging

Radiomics and AI may emphasize the role of radiological and functional imaging as prognostic biomarkers, especially to identify patients eligible for targeted therapies, such as RLT, and to evaluate their response to such therapies, facilitating patient-tailored treatments [16][35][36][37]. Several studies have already been published in this field in NEN patients.

In 2017, Nogueira et al. [38] developed an artificial neural network (ANN) approach to automatically assess the treatment responses of patients suffering from NENs (34 patients) and Hodgkin lymphoma (29 patients) based on image features extracted from pre- and post-treatment [^{18}F]FDG and [^{68}Ga]Ga-DOTANOC PET/CT scans, respectively. Cases were divided into four classes of treatment response: negative (malignancy increased), neutral (no response), positive incomplete (malignancy decreased but lesion did not disappear), and positive complete (the lesion disappeared). Four standard ANN architectures were explored: multilayer perceptron (MLP), radial basis function neural network (RBFNN), probabilistic neural network (PNN), and learning vector quantization neural network (LVQNN). After synthetic data generation and PCA-based dimensionality reduction to only two components, the LVQNN assured classification accuracies of 100%, 100%, 96.3%, and 100% regarding the four response-to-treatment classes.

In 2016, Wetz et al. [39] compared the Krenning score, tumor/lesion (T/L) ratio, and asphericity (ASP) between responding and non-responding lesions (total n = 66) segmented on baseline [^{111}In]DTPA-octreotide scintigraphy (Octreoscan®) SPECT. According to their analysis, a greater ASP level was related to a worse response to RLT. Additionally, ASP outperformed both the Krenning score and the T/L ratio, being the parameter with the greatest AUC (>0.96), at 4 and 12 months of follow-up to distinguish responding from non-responding lesions. In 2020, the same group [40] evaluated the lesional asphericity (ASP), extracted from the pre-therapeutic Octreoscan, as the first imaging-based prognostic marker for progression-free survival (PFS) in 30 GEP-NEN patients that were candidates for therapy with mTOR inhibitor everolimus and with metachronous or progressive liver metastases. Only ASP > 12.9% (hazard ratio, HR), 3.33; p = 0.024) and prior RLT (HR, 0.35; p = 0.043) resulted as statistically significant in multivariable Cox analysis. Moreover, when the ASP was above 12.9%, the median PFS was 6.7 months (95% CI: 2.1–11.4 months), whereas when it was below 12.9%, it was 14.4 (12.5–16.3) months (log-rank, p = 0.028).

Further studies evaluated the application of AI on the assessment of responses to RLT in PET images; the assessment of response to RLT is still challenging, despite the fact that it seems to be one of the most successful treatment choices for metastatic, inoperable, well-differentiated GEP NETs. Particular attention has been paid to the evaluation of RFs capable of describing tumor heterogeneity, which is usually associated with a worse prognosis as a result of more aggressive biological behavior and treatment failure. In 2020, Weber et al. [41] aimed to assess changes in semiquantitative [^{68}Ga]Ga-DOTA-TOC PET/MRI parameters, including ADC, after different

types of treatment including RLT. Although the study's sample size was too small to be statistically significant (only nine patients underwent RLT), responding patients showed a significant decrease in lesion volume on ADC maps and a borderline significant decrease in entropy after RLT, even if non-statistically significant.

In two subsequent studies, Werner et al. [42] evaluated the prognostic value of baseline [^{68}Ga]Ga-DOTA-SSTa PET/CT RFs before RLT. RF entropy predicted both PFS and overall survival (OS) in a heterogenous cohort of 141 NET patients who were eligible for RLT (cut-off = 6.7, AUC = 0.71, p = 0.02), whereas conventional PET parameters did not show significant impacts. In a consecutive study [43] on a smaller, more homogeneous cohort of 31 pan-NET patients (G1/G2), the authors discovered a similar outcome: entropy was a predictor of overall survival (OS) at ROC analysis (cutoff = 6.7, AUC= 0.71, p = 0.02). Indeed, higher entropy indicated longer survival (OS = 2.5 years, 17/31, entropy > 6.7), whereas standard PET parameters did not.

In 2020, Önner et al. [44] evaluated tumor heterogeneity using the parameters skewness and kurtosis on pre- and post-treatment [^{68}Ga]Ga-DOTATATE PET/CT to assess the therapy responses of 326 lesions (137 lesions responded partially or completely to the treatment; 189 lesions did not respond to treatment, remained stable, or progressed) delineated from PET images of 22 GEP-NET patients treated with 2–6 therapy cycles of [^{177}Lu]Lu-DOTATATE. Lesions that did not respond to RLT had significantly higher skewness and kurtosis values than responding lesions (p < 0.001 and p = 0.004, respectively). However, ROC curves provided a moderate AUC value for skewness and a slightly lower value for kurtosis (0.619 and 0.518, respectively). Moreover, the authors did not compare the RF parameters with conventional PET parameters.

Subsequent studies have better analyzed this aspect, attempting to highlight the possible added value of radiomics parameters compared to conventional ones. In 2021, Ortega et al. [45] aimed to determine whether quantitative PET parameters (mean SUV_{max}, ratio tumor to liver/spleen, T/L and T/S ratio, SUV_{max}, SUV_{mean}, and heterogeneity parameters, such as CoV, kurtosis, and skewness) on baseline [^{68}Ga]Ga-DOTATATE PET/CT (bPET) and interim PET (iPET) performed prior to the second RLT cycle were predictive of therapy response and PFS in ninety-one NET patients (71 responders and 20 non-responders). At bPET, higher mean SUV_{max} and mean SUV_{max} (tumor/liver ratio) were predictors of the therapy response (p = 0.018 and 0.024, respectively); while higher SUV_{max} and SUV_{mean} and lower kurtosis were predictors of favorable responses (p = 0.025, 0.0055, and 0.031, respectively) and correlated with longer PFS. From the multivariable analysis adjusted for age, primary site, and Ki-67, the mean SUV_{max} (p = 0.019), SUV_{max} T/L (p = 0.018), SUV_{max} T/S (p = 0.041), SUV_{mean} liver (p = 0.0052), and skewness (p = 0.048) remained significant predictors of PFS. On the other hand, iPET parameters were not predictive of PFS, even if iPET was performed only for a subset of patients.

The same year, in a pilot report on two NET patients who experienced discordant responses to RLT (responder vs. non-responder) according to RECIST1.1, Liberini et al. [46] aimed to assess whether both tumor burden and radiomics parameters may have an added value over conventional parameters in predicting RLT response. They found that 28 RFs extracted from pre-therapy [^{68}Ga]Ga-DOTATOC PET/CT showed significant differences between the two patients in the Mann–Whitney test (p < 0.05), and the modifications of the tumor burden parameter obtained from pre- and post-PRRT PET/CT correlated with the RECIST1.1 response. Moreover, the authors

concluded that seven second-order features with poor correlation with SUV_{max} and PET volume, identified by the Pearson correlation matrix, might have a role in defining inter-patient heterogeneity and in the prediction of therapy response.

The prognostic potential of tumor heterogeneity and tracer avidity in NET patients through a radiomics analysis of pre-RLT [^{68}Ga]Ga-DOTATATE PET/CT images has also been evaluated by Atkinson et al. [47] in 44 metastatic NET patients (carcinoid, pancreatic, thyroid, head and neck, catecholamine-secreting, and unknown primary NET). Measures of heterogeneity (higher kurtosis, higher entropy, and lower skewness) on coarse texture scale CT and unfiltered PET images predicted shorter PFS (CT coarse kurtosis: $p = 0.05$, PET entropy: $p = 0.01$, PET skewness: $p = 0.03$) and shorter OS (CT coarse kurtosis: $p = 0.05$, PET entropy: $p = 0.01$, PET skewness $p = 0.02$). Multivariate analysis identified that CT-coarse kurtosis (HR = 2.57, 95% CI = 1.22–5.38, $p = 0.013$) independently predicted PFS, while PET-unfiltered skewness (HR = 9.05, 95% CI = 1.19–68.91, $p = 0.033$) independently predicted OS. Conventional PET parameters, such as SUV_{max} and SUV_{mean}, showed trends toward predicting outcomes but were not statistically significant.

Finally, in 2022, Laudicella et al. [48] retrospectively analyzed and compared the predictive value of conventional parameters, radiomics, and Δradiomics parameters in 324 SSTR-2-positive lesions from 38 metastatic well-differentiated GEP-NET patients (nine G1, twenty-seven G2, and two G3) who underwent restaging [^{68}Ga]Ga-DOTATOC PET/CT before complete RLT. The disease status for each lesion was determined by [^{68}Ga]Ga-DOTATOC PET/CT follow-up using the same scanner for each patient (progression vs. response in terms of stability, decrease, or disappearance). The k-fold approach was used to divide the data into training and validation sets, and discriminant analysis was utilized to create the predictive model. Once again, SUV_{max} could not predict responses to RLT ($p = 0.49$, AUC 0.523), while radiomics parameters proved to be superior to conventional quantitative parameters. From the reduction and selection process, HISTO_Skewness and HISTO_Kurtosis were able to predict the RLT response with AUC, sensitivity, and specificity levels of 0.745, 80.6%, 67.2% and 0.72, 61.2%, 75.9%, respectively.

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