Editorial

Solitary pulmonary nodule: Is positron emission tomography/computed tomography radiomics a valid diagnostic approach?

Artificial intelligence techniques (machine learning, deep learning, and radiomics) have gained an increasing role in radiology and nuclear medicine to diagnose oncological and neurodegenerative disorders.[1-9] Radiomics provides the possibility to build classification and/or regression models based on quantitative features extracted from imaging data such as computed tomography (CT), magnetic resonance, and positron emission tomography (PET).[1-5] The typical workflow in radiomics includes six sequential steps: acquisition, preprocessing, segmentation, feature extraction, postprocessing, and data analysis.[2]

Feature extraction, the crucial phase of the process, consists of computing a set of quantitative parameters (image features or, simply, features) from the region of interest. The features should correlate with the clinical outcome of the disease. Two main classes of features are available: "hand-crafted" and deep learning based. Hand-crafted features, such as shape and texture features, are computed by mathematical functions essentially designed by hand, while deep learning features are obtained implicitly by training on large datasets of images.

Lung cancer is one of the most studied oncological disorders; radiomics from PET and CT images has been advocated as a potential mean to identify primary versus metastatic lesions, contribute to the histological classification, predict survival and response to treatment.[1-6] Among the possible applications, the discrimination between benign and malignant solitary pulmonary nodule (SPN) is noteworthy. The different therapeutic strategy to manage a benign SPN (only follow-up) comparing with a malignant nodule (surgery or radiotherapy) makes necessary a correct diagnosis.[3,4,10] Although biopsy is the option of choice, this is not always feasible for the anatomic SPN site and/or the clinicopathological conditions of the patients. In this scenario, radiomics could potentially provide an *in vivo* classification of disease, thus avoiding invasive diagnostic techniques.[3,4]

Many papers described the significance of CT radiomic features in characterizing SPNs,[5,10,11] while the role of features extracted by PET/CT images is less widely studied. The aim of this editorial is to discuss the use of PET/CT radiomic features to investigate the differential diagnosis among benign and malignant SPNs.

The maximum standardized uptake value (SUV_{max}) is the most common parameter used in clinical practice. It is, in a way, a radiomic feature, capable of discriminating between benign and malignant lung nodules[12] and able to correlate with lesion diameter and tumor proliferation index MIB-1 in lung cancer.[6]

Other radiomic features related to radiopharmaceutical uptake have also been investigated, such as minimum and mean SUV (SUV_{min} and SUV_{mean}, respectively), metabolic tumor volume (MTV), and total lesion glycolysis (TLG). These can be considered jointly with typical CT-derived imaging features, as for instance volume, skewness, kurtosis, entropy, and uniformity.

An interesting paper by Chen *et al*.[13] investigated the discriminant power of dual time point (DTP) 18F-fluorodeoxyglucose (^{18}F-FDG) PET/CT to differentially diagnose malignant and benign ^{18}F-FDG-avid SPNs through neighborhood gray tone difference matrix (NGTDM) texture features.

The authors evaluated DTP ^{18}F-FDG PET/CT of 116 retrospective patients with SPNs, being 35 benign and 81 malignant. Image acquisition was performed 1 and 3 h after radiopharmaceutical injection and SUV_{max}, and NGTDM texture features (coarseness, contrast, and busyness) of each nodule were calculated on DTP images.

The patients were randomly divided into training and validation datasets, and receiver operating characteristic (ROC) curve analysis was carried out on all texture features in the training dataset to obtain the optimal threshold to differentiate malignant and benign SPNs. For each lesion in the testing dataset, a 5-point scale interpretation score was made by two nuclear medicine physicians (1: definitely benign; 2: likely benign; 3: equivocal; 4: likely malignant; 5: definitely malignant) based on the PET/CT images with and without reference to the texture features.

In the training dataset, the area under curves (AUCs) of delayed busyness, delayed coarseness, early busyness, and early SUV_{max} were 0.87, 0.85, 0.75, and 0.75, respectively; while in the validation dataset, the AUCs of visual interpretations with and without texture features were 0.89 and 0.80, respectively. AUCs showed that texture features helped the physicians to improve diagnosis between malignant and benign lesions. By applying the best performance threshold, visual interpretation with

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texture features had higher specificity (90.63%) than without (75.00%).

The authors concluded that NGTDM features, particularly those extracted from delayed PET/CT images, were useful to differentiate malignant and benign SPNs and that SUV_{max} and visual interpretation performance could be improved by adding busyness from delayed PET/CT images. In conclusion, NGTDM features from delayed PET/CT scans could be considered as a good predictor of SPN malignancy.

Nakajo *et al*.[14] investigated the ability of texture analysis from DTP ^{18}F-FDG PET/CT to differentiate ^{18}F-FDG-avid benign and malignant pulmonary lesions. The authors compared SUV-related (SUV_{max} and SUV_{mean} [g/ml]), volumetric (MTV [cm^3] and TLG [g]), and texture (entropy, homogeneity, dissimilarity, intensity variability [IV], size-zone variability [SZV], and zone percentage [ZP]) (MTV ≥5.0 cm^3 and SUV ≥2.5 g/ml) parameters between 13 benign and 46 malignant lesions using the Mann–Whitney U-test. Diagnostic performance was investigated by ROC analysis, and stepwise logistic regression was performed to identify and use the independent variables useful to correctly discriminate benign and malignant lesions. The results showed that significantly higher SUV_{max}, SUV_{mean}, MTV, TLG, entropy, dissimilarity, IV, and SZV and significantly lower homogeneity and ZP were present in malignant pulmonary lesions compared with benign pulmonary lesions in both early and delayed images. The AUCs ranged between 0.69 and 0.94, and diagnostic accuracies varied between 64.4% and 93.2%. Entropy-early ($P = 0.014$), SUV_{mean}-delay ($P = 0.039$), and dissimilarity-delay ($P = 0.027$) were independent parameters, but the combined use of them allowed to reach the highest AUC (0.98) having 100% sensitivity (46/46), 84.6% specificity (11/13), and 96.7% (57/59) accuracy in the discrimination between benign and malignant lesions. The authors concluded that individual early and delayed SUV-related, volumetric, and texture parameters disclosed a wide range of accuracy. Although the combination of independent parameters extracted from DTP imaging might ensure a high diagnostic accuracy to differentiate between benign and malignant ^{18}F-FDG-avid pulmonary lesions, a further study should be necessary to confirm the usefulness of SUV-related, volumetric, and texture analysis of DTP imaging.

Zhang, *et al*.[15] investigated the diagnostic value of a support vector machine (SVM) model built on texture features from ^{18}F-FDG PET scans in 82 subjects with SPNs larger than 5 mL in volume.

PET images were retrospectively analyzed and the volumes of interest (VOIs) were automatically segmented using threshold techniques from PET images. After a large number of texture features were extracted from the VOIs an optimized SVM machine-learning model was trained on PET scans using texture features to obtain the optimal differentiation between malignant and benign nodules. Diagnostic models based on SUV_{max} and MTV were compared with the SVM model to evaluate SPN diagnostic power.

Compared with the SUV_{max} and MTV models, the texture-based SVM model improved (of approximately 20%) diagnostic accuracy, positive predictive value, negative predictive value, and the area under the operating characteristic curve. The ROC curve of the SVM model resulted significantly better than the MTV model ($P = 0.0345$, $P < 0.05$) and the SUVmax model ($P = 0.01$ $P < 0.05$). In conclusion, ^{18}F-FDG PET imaging was useful to better differentiate benign and malignant SPNs with volumes larger than 5 mL using an SVM model based on texture features.

In a recent work, we assessed the ability of shape and texture features from PET/CT to improve discrimination between benign and malignant SPN compared with standard imaging features such as lesion size, density, and radiotracer uptake.[4] Cross-sectional data from 111 patients with histologically confirmed benign ($n = 39$) or malignant ($n = 72$) SPNs were retrospectively investigated.

Prediction models based on different feature sets and three classification strategies (Classification Tree, k-nearest neighbors, and Naïve Bayes) were evaluated to assess the potential benefit of shape and texture features beyond conventional imaging features. Eight features from CT and 15 from PET significantly differed in benign versus malignant groups. The radiomic features derived from PET obviously showed that radiotracer uptake (SUV_{min}, SUV_{max}, and SUV_{mean}) was higher in the malignant group and as for the shape features, only the flatness computed on PET significantly differed between the two groups, being higher in the malignant one.

The addition of shape and texture features increased the performance of both the CT-based and PET-based prediction models with overall gain of 3.4–11.2 and 2.2–10.2 pp, respectively.

This study indicates that shape and texture features from ^{18}F-FDG PET/CT can be useful to identify benign versus malignant lung nodules by increasing the accuracy of the prediction models by an appreciable margin.

In summary, PET/CT radiomics is a promising approach to improve the differential diagnosis among benign and malignant pulmonary nodules, providing the possibility to obtain an *in vivo* evaluation of the aggressiveness of disease. However, further studies (ideally prospective and multicentric) are necessary to support these conclusions. The definition of standardized procedures for extracting radiomic features as well as internationally recognized guidelines for their use is also needed before the method can be translated into clinical practice.

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