Editorial

^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography characterization of solitary pulmonary nodules: can we do better?

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Solitary pulmonary nodules (SPNs) are discrete, well-marginated, rounded opacities less than or equal to 3 cm in diameter that are surrounded by lung parenchyma, do not touch the hilum or mediastinum, and are not associated with adenopathy, atelectasis, or pleural effusion. These structures have a high prevalence, being visualized in up to 69% of patients screened using low-dose computed tomography (CT) (1).

Whether detected serendipitously or during routine investigations, SPNs raise the questions of their benign or malignant character and what are the optimal actions to perform: observation, investigation or resection.

In the early 1990s, it was hypothesized that malignant and benign pulmonary nodules have distinctly different physiologic, metabolic, and pharmacokinetic characteristics. Many attempts have been made to differentiate these two nodule types with dynamic single-detector helical and multi-detector CT, dynamic magnetic resonance imaging (MRI), positron emission tomography (PET) or combined PET/CT with use of fluorine ^{18}F-fluorodeoxyglucose (FDG). However, despite many studies considering the problem, the correct diagnosis of SPNs remains a challenge to clinicians, radiologists and nuclear medicine physicians. Up to now, neither their morphology, contrast enhancement properties nor metabolism are specific enough to discriminate benign from malignant lesions (2,3). This explains why malignant lesions account for only 60% of resected pulmonary nodules in some series (4).

With respect to the diagnostic accuracy of imaging techniques, no differences have been found among dynamic contrast-enhanced CT, MRI, FDG-PET and technetium 99 m (99 mTc) depreotide single photon emission computed tomography (SPECT), for evaluation of SPNs (5). Although all of those diagnostic methods have high sensitivities, their specificities are intermediate (5,6), what limits the application of the techniques.

In order to improve the specificity, some dynamic aspects of perfusion and metabolism have been explored with the development of new imaging procedures. Dynamic first-pass contrast enhanced perfusion area-detector CT has been described as more specific and accurate technique for the differentiation between malignant and benign pulmonary nodule groups than MRI and integrated PET/CT (7,8). With respect to metabolism, a meta-analysis by Barger *et al*. (9) found the additive value of dual time point FDG-PET questionable because of significant overlap of benign and malignant nodule characteristics.

Focusing on metabolism, the evaluation of pulmonary nodules by FDG-PET has been limited because of several factors involved in the FDG distribution: (I) the maximum standardized uptake value (SUVmax), as reflection of the degree of FDG uptake, is not a specific marker of malignancies; (II) SUVmax is affected by a large number of methodological factors, which are difficult to control (10); (III) small lesions are challenging due to PET's limited spatial resolution, resulting in partial-volume effect; (IV) lung fields are in continuous movement, what causes an important detriment in the metabolic detection of SPNs, especially in smaller lesions; (V) the biological characteristics of malignant and benign lesions affect FDG

distribution.

The referred conditions influence the lesion metabolic detection and its interpretation. This has resulted in a lack of consensus criteria for defining quantitative thresholds to classify SPNs as malignant or benign. Much research has been devoted to overcome the above mentioned limitations. However, the attempts to palliate respiratory movement effect, as 4-dimensional FDG PET/CT or deep-inspiration breath-hold PET/CT, or methods of correction of partial volume effect to obtain the corrected (corr) SUVmax, have not reported a significant advantage and do not take into account other factors such as tumor density, FDG avidity, and background activity, that play a role in semiquantitative parameters (11-13). Furthermore, although these procedures provide a more realistic semiquantitative value in SPNs, SUVmax increases both in malignant and benign lesions. Therefore, lesion classification using semiquantitative approaches is still controversial.

In principle, although controversy exists, FDG uptake could be expected naively to be correlated with the biological aggressiveness and clinical behavior of malignant lesions. Thus, this is another factor to consider, adding complexity to the metabolic evaluation of SPNs (10,14).

In a recent work, Zhao *et al*. (15), conjecture that cell's metabolic activity may be expected to be higher in the proximal part than in the distal part of malignant SPNs due to the vascular supply of hilar region. To test their hypothesis they analysed the intralesional FDG distribution and introduced a novel semi-quantitative measure: the relative activity distribution (RAD) index, in order to assess its goal for SPNs characterization. To calculate the RAD index, Regions of interest (ROIs) were placed first on hilar angle in order to define a reference point in its center. ROIs were also placed on the SPNs. For the SPN, all voxels with activity ≥90%, ≥80% and ≥70% of SUVmax were automatically segmented and their average coordinates set the lesion reference points as O90, O80 and O70. Distances (*d*) from the lesion reference points O90, O80 and O70 to the hilar reference point were calculated and divided to obtain the RAD index as the first quotient in the series *d*90/*d*80, *d*80/*d*70, … that was possible to compute. Geometrically, this index intends to measure in a very simple way, the asymmetry of the peak of the FDG distribution with respect to the direction of the hilar reference point.

Zhao and co-workers (15) claim that the RAD index enables a more specific and accurate differentiation between malignant and benign SPNs than SUVmax, corr SUVmax and retention index. In their study they find no significant differences in sensitivity and accuracy compared with visual assessment, but the main advantage of the method is that it was more specific than visual assessment. Furthermore, RAD index calculation can be easily automatized, and is reproducible and objective. They stated that the cited index might be beneficial for SPNs characterization with the best statistical cut-off value of 0.99, in order to differentiate malignant and benign SPNs.

However, before this index can move into mainstream use in the clinics, some considerations about the study and/or the definition of the RAD index should be addressed in further works by researchers in this field.

First, RAD index is defined as a quotient of two distances that are very close (a fraction of the SPN size) in relation to their absolute values (distance to the lesion to the hilar reference point). This implies that index values are all clustered around 1, slightly below 1 for malignant nodules and slightly above 1 for benign ones. A definition of the index taking differences of distances in units of the SPN size [e.g., (d90-d80)/SPN size)] would provide better spread values and have a direct interpretation as a fractional deviation of the high FDG uptake peak from the "geometrical" center.

Also, from the statistical point of view, the RAD values for malignant nodules were 0.98±0.03 while for benign RAD indexes were 1.01±0.02. Although the authors claim that statistical differences were significant, that assertion seems to contradict the fact that both confidence intervals are fully overlapping. More evidences and a deeper statistical analysis should be provided in support of the author's claims.

As a third comment, the lesion points taken as reference (O90 and O80 or O80 and O70) are locations of high FDG metabolic activity. According to our understanding, these selected points have similar metabolic characteristics and the effect of noise, the fact that small nodules have a very limited number of voxels, and other factors might substantially influence the results. It would be interesting to understand why those factors did not influence Zhao *et al.*'s data and if other, in principle more robust definitions of similar indexes could be constructed. For instance definitions accounting for ratios between regions of high and medium metabolic activities could lead to alternative definitions of similar indexes. Also, indexes defined by integrals over the whole metabolic activity distribution along the line pointing to the hilar reference point would probably be more robust definitions of asymmetry.

On the other hand, the hypothesis that malignant nodules grow towards blood vessels needs further study because although in the avascular phase, malignant tumors do not have the potential to generate vessels and contain only a few preexisting vessels encased by the tumor growth, new tumor vessels develop as the result of stimulation of angiogenic factors. Thus neoangiogenesis plays an important role in the tumor growth. Besides, the effects of such functional mechanism cannot be spatially uniform throughout the tumor, what causes multiple vascular patterns (16,17). Furthermore, in inflammatory nodules, the processes of increased blood flow and permeability of vessels depend on the stage of the inflammatory process.

Additionally, although the most prevalent malignant group was constituted by adenocarcinomas, different biologically malignant lesions were analysed (minimally invasive adenocarcinomas, adenocarcinomas *in situ*, invasive adenocarcinomas, squamous cell carcinomas, neuroendocrine tumor, sarcomatoid carcinoma, and metastatic lung tumors) what may lead to a wide variety of growth patterns. This heterogeneity in the population of malignant SPNs studied is an important limitation to obtain reliable results. May be some types of cancers are more prone to satisfy the authors hypothesis?

It is also important to point out that the locations of SPNs were not reported. In centrally located SPNs, the mean SUVmax value could be significantly higher than in peripherally located ones. This higher SUVmax value may be associated with higher blood flow in central regions or higher ground activities of lung hilus and mediastinal organs (18). Thus lesion location, for example a central predominant location of malignant lesions, could have some influence in the intralesional distribution of FDG and hence in the obtained results.

Finally, respiratory movement can cause blurring. This effect averages out the measures uptake values of the voxels with higher uptake and can change the isocenter or the average coordinates locations, especially in small lesions. Thus, in addition to the potential difficulty in determining with precision the O90, O80, … points, the blurring induced by respiration may limit the applicability of the method to small lesions. Zhao *et al*. comment that their sample had high percentage of malignant nodules with a large median lesion size, thus a larger sample is required to clarify the potential applicability of the method to small malignant lesions.

In summary, the interesting theory developed by Zhao *et al*. (15) that the tumor metabolic activity will be higher in the proximal part than in the distal part of malignant SPNs due to the vascular supply of hilar region, deserves more investigation. Although vascularity of tumor tissue and intratumoral microvessel density may be an important component in determining the glucose metabolic rate of a neoplasm, it is neither the only one nor it is exclusive of malignant lesions (19,20). The novel methodology and the RAD index or other similar ones to follow, when validated in more complete studies, may provide useful tools to solve the problem of identifying the malignancy of SPNs. Thus Zhao *et al.* work has the potential to have a substantial impact on the management of these diseases.

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Footnote

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