Editorial

Comments on characterization of solitary pulmonary nodules with 18F-FDG PET/CT relative activity distribution analysis

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Submitted Sep 30, 2015. Accepted for publication Oct 10, 2015.
doi: 10.3978/j.issn.2072-1439.2015.10.61
View this article at: http://dx.doi.org/10.3978/j.issn.2072-1439.2015.10.61

Background

The solitary pulmonary nodule (SPN) is defined as focal parenchymal opacity of the lung, <3 cm in size, generally discovered incidentally during an X-rays examination (1), with a prevalence of 2.1% in non-selected populations. Subsequently, SPNs may be classified by computed tomography (CT), allowing better radiographic criteria as margins, size, density, contrast enhancement and calcification pattern (2), in order to ensure the diagnosis and correct identification between malignant lesions (metastases, primary tumors) and benign nodules (granulomas, abscess, vascular malformations). Despite these forewords, the correct diagnosis of SPNs by means of morphological criteria still represents a diagnostic dilemma (3).

As a matter of debate, the attention of the researchers has been focused during the time on the best diagnostic tool with the highest accuracy in distinguishing SPNs with a benign behavior from those with a prospective of malignancy, setting undeniable repercussions regarding the choice of the best treatment option, patients prognosis and overall costs of management for the community (4). In particular, these forewords are of the utmost importance when we account that a SPN can be a primary localization of lung cancer: one of the most diffuse causes of death in the United States and in the rest of the world (5), with evident social repercussions linked to the cause-effect relationship with tabagism and environmental exposure and the high costs in the overall sanitary management of this disease. In fact, lung cancer remains in the top leading cause of cancer death in both men and women, despite an extensive list of risk factors has been well-characterized with variability between leading causes (6).

On the other hand is intuitive, prior to be scientifically proven, the absolutely negative impact that could sort a wrong diagnosis on the life quality of patients with benign lung lesions not correctly identified.

In this scenario, it is evident that the early correct identification of SPN can sort positive effects on the patients care, in terms of correct choice of the best treatment option and on the disease-free survival in patients with malignant lesions, considering that an important percentage (30-40%) of SPNs is malignant (7).

As a matter of fact, the attention of researchers is focused on the early diagnosis of malignant SPNs, by means of the best imaging modality option. Beyond the limited utility, X-rays, due to the widely diffusion and the easily reproducibility, still remain the first imaging step in diagnosing SPNs, although often the diagnosis occur as an incidental finding during the asymptomatic phase. The CT of the thorax has become the best imaging tool for a rapid, relatively not-expensive correct anatomical characterization of the whole thoracic district, from the pulmonary interstitium to the upper airways, offering a rapid, high resolution multi-planar evaluation of lungs and mediastinal tissues. Furthermore, the use of contrast agent can improve the visualization of the lung parenchyma by increasing the absolute CT attenuation difference between the target and surrounding tissues, helping to depict lesions with more accuracy (8). Despite this fact, are also well known the limits of CT in depicting lung lesions smaller

than 3 cm, by assessing only the morphological, especially in some complicated radiologic scenarios as the "honeycomb lung" (9). In the last two decades, positron emission tomography (PET) has been tested to enlarge the field of the early diagnosis and correct identification of SPN with a better depiction of the molecular processes at the basis of the metabolic behavior of the lesions. PET with 18F-FDG is widely useful for SPNs characterization due to the intrinsic properties of the tracer as analogue of the glucose, surrogate marker of cells vitality and biological cells behavior. Therefore, the metabolic assessment of SPNs was one of the first useful indications of this 18F-FDG PET (10), showing promising results in the correct diagnosis of SPNs, by means of both visual assessment and semi-quantitative evaluation with calculation of the "differential uptake ratio" (DUR) in the lesions, allowing a sensitivity of 95% and a specificity of 80% (11). Despite these data were obtained on a non-hybrid PET scanner, often using as standard of reference the clinical criteria of Bayesian analysis, the probability of diagnosing cancer using the "standard criteria" available in literature ("*based on patient's age*, *history of previous malignancy*, *smoking history*, *size and age of nodule and presence or absence of calcifications*") also using histologic sample as the gold standard (12). Therefore, PET alone was more accurate in depicting the likelihood of malignancy of lung nodules, in comparison with standard criteria.

During the time, the development of hybrid PET/CT scanners allowed to define more accurate exams, in order to take advantages of the high sensitivity provided by PET with a more specificity with the morphologic characterization of CT, the "hybrid scanners era" started with the encouraging results, in terms of global accuracy, of the experiences of various group of researchers (13,14), improving the added value of an integrated evaluation between metabolic data and morphologic features of the lesions. More specifically, the evaluation of PET data ensured the usefulness of semi-quantitative analysis of the maximum standardized uptake value (SUVmax) (15), a measure of the metabolic activity inside the lesions, provided by the ratio between administered tracer and weight of the patient, obtained by the following Eq [1] (16):

[Radioactivity (kBq)–tissue volume (mL)]/[dose administered (kBq)/body weight (g)] [1].

In particular, a large series of studies demonstrated that a SUVmax cut-off value of 2.5 was able to discriminate between malignant from benign lesions, since malignant lesions show an increased metabolic activity, with a SUVmax generally higher than 2.5, allowing an increase of the positive predictive value of 18F-FDG PET (17-20).

Despite these promising results, the aim of the researchers was focalized in reducing the rate of false negative and false positive cases in PET/CT, by using both semi-quantitative analysis and morphologic criteria of the CT component of the exam, with the help of the measurement in Hounsfield Units of the enhancement of the iodinate contrast agent inside the cells, allowing a relatively cost-effective approach to evaluate the SPNs (4) and a rise of specificity.

Moreover, based on the evidence that metabolic activity of cancer cells tends to rise during the time, various groups of researchers tried to better depict SPNs behavior with a dual time PET acquisition protocol, since in the late acquisition it was possible to observe that benign lesions moderately 18F-FDG avid, such as pulmonary mycobacteriosis (21), present lower SUVmax than in the early scan while cancer cells can display a rise of the uptake (22).

In particular, in the experience of our group with dual-time acquisition point 18F-FDG and concomitant contrast enhanced CT, the early and delayed SUVmax of malignant lesions were higher than those of benign nodules, the contrast enhanced CT did not show meaningful accuracy whereas the dual-time point SUVmax was associated only with the better value of sensitivity (83%) (23). Therefore, also the role of the dual time point PET and of the enhanced CT is still under exam and better non-invasive methods of assessment are still required.

18F-FDG PET/CT relative activity distribution (RAD) analysis of SPNs: our comments

Another chapter in the molecular imaging of SPNs was recently provided by the work of Zhao *et al.* (24): the aim of this study was to compare the capability of a new semi-quantitative index of 18F-FDG uptake in the cells, the relative activity distribution (RAD), with the typical markers, in differentiating benign and malignant SPNs, by means of 18F-FDG PET/CT.

Foremost, the authors developed the concept of RAD. Since cancer cells tend to invade blood vessels, they supposed that the metabolic activity detectable by 18F-FDG uptake should be higher in the proximal part than in the distal part of malignant SPNs, using the ipsilateral hilar angle as the reference point. To verify this hypothesis, they analyzed a population of 175 patients, measuring in all cases: the RAD-index, SUVmax, SUVmax corrected for partial volume (corrSUVmax) and retention index (RI),

correlating these data also with the visual assessment.

Therefore, the malignant lesions showed a meaningful lower RAD index than benign lesions. Furthermore, the area under the curve (AUC) was significantly larger and specificity was significantly higher for RAD than for SUVmax, corrSUVmax and visual assessment. Moreover, the RAD analysis showed the best sensitivity value (92%), with the exception of visual assessment, performed by two physicians with more than 8 years of experience in this field. Consequently, the analysis of RAD index showed meaningful differences between malignant and benign nodules.

For our opinion, the best added value improved by this index is the better value of specificity, that is the goal of the hybrid PET/CT evaluation of lung nodules, it being well understood that the visual or semi-quantitative analysis of the 18F-FDG inside the cells is usually associated with satisfying values of sensitivity (20). Moreover, the RAD analysis takes into account the heterogeneity of the cancer lesions, showing different phenotypically and functionally cells, with a dynamic approach in depicting the biological heterogeneity of the lesions.

An important feature of the RAD analysis is the tendency to remain an accurate semi-quantitative index of objective analysis of the uptake in the cells, without invalidate the evaluation of the lesion, considering the rigid adopted inclusion criteria and the easily reproducibility of the exams. The only potential limit of this approach is the measure of the ipsilateral pulmonary hilar angle, which can present intra-observers variations, especially when we consider some errors potentially induced by the respiratory movement, in particular in those SPNs localized in the inferior lobes of the lungs, particularly interested by respiratory excursion.

However, the development of respiratory-gated PET imaging (25) could improve this aspect, allowing a better accuracy of the overall metabolic evaluation of SPNs, particularly with the measurement of RAD index, improving the detectability and semi-quantitative evaluation of even small SPNs, especially considering the high number of SPNs smaller than 1.5 cm in diameter (34%) evaluated in the present study by Zhao *et al.* (24).

Despite the promising results, another potential limit of this cited paper is the relatively high number of examined malignant lesions (65%), in comparison with the experience of other groups in this field (10,11,13,14). This high percentage of malignant lesions was also recently reported in a paper by van Gómez López *et al.* (26). The authors examined 55 patients with 18F-FDG PET/CT. Among these, 40 (72.7%) were malignant. Similar to the paper of Zhao *et al.* (24), the aim of this study was to assess the capability of new semi-quantitative methods of quantization of the metabolic activity inside the cells. Otherwise, they did not find meaningful diagnostic impact for these new parameters, as SUVmax threshold depending on SPN diameter or ratio SUVmax/diameter of the lesion (26), conversely, similarly to the experience of Zhao *et al.*, confirmed the undisputed role of visual evaluation of detectable metabolism as the "method" with the best accuracy in discriminating between malignant and benign lesions.

For these reasons, we need to underline two important features: as first, the necessity of an adequate visual evaluation of PET/CT scans of patients with SPNs by nuclear physicians or radiologists with expertise in the field of thoracic disease, in order to take advantage of the overall amount of data or clinical suggestions provided by PET and CT simultaneously, in a way of mutual strengthening of diagnostic accuracy between the two techniques. Of course, it is also important the knowledge of morphological features on CT and radiological criteria to correctly identify non-18F-FDG-avid lesions with characteristics of malignancy as well as avid 18F-FDG nodules showing high tracer uptake, with benign behavior (27).

The second consideration concerns the improvement of the specificity provided by RAD index analysis in evaluating SPNs, probably the main suggestion provided by the work of Zhao *et al.* (24). In fact, the attempts of researchers on this topic were focused on the necessity to rise the global accuracy of PET/CT evaluation, it being clear the evident high sensitivity of 18F-FDG PET/CT since the first studies (10,11).

However, future studies on larger populations are needed to define results and to deep the scientific reputation of this new semi-quantitative approach to clearly split malignant SPNs, needing of rapid use of surgical and/or systemic therapy, from benign lesions, in whom medical therapy is requested or long-term follow-up can be sufficient for the health of the patients. In particular, the field of interest of this new approach should be extended to the study of lung cancer with associated infectious lung diseases, a topic where the 18F-FDG PET/CT traditionally may not accurately descript malignant lesions (28).

As a future trends, we must consider that the recent fast increasing availability of hybrid PET/magnetic resonance imaging (MRI) scanners will also improve this trend of research, permitting to take advantage of the best quality of images provided by MRI and its highest power resolution

limit, to develop more accurate methods of quantization of the tracer uptake inside the cells, also permitting a more precise placing of regions of interest for calculating RAD index or other semi-quantitative parameters of uptake, with or without the contrast agent administration, as recently described (29,30). In fact, the added value of MRI lies in its multiplanar capabilities, which may allow for a better depiction of lung structures, with the advantage of a higher spatial resolution. In addition, any morphological abnormality may also be better depicted after the administration of contrast agent. About this trend, an important suggestion could be to improve the impact of RAD analysis with a dual time point PET/MRI scan.

Finally, once confirmed its usefulness in the management of SPNs, as future field of application, it would be interesting to deep the knowledge of the role of RAD index in identifying the T component of somatic tumors in order to ensure features as the exact recognition of the site of the biopsy or, considering the intrinsic considerations linked to the potential better depiction of the tumor vitality, to define the response to therapy of particular lung lesions, in particular referring to radiotherapy.

In conclusion, we can state that the variable panorama of semi-quantitative models of tracer uptake quantization in tumor lesions has been enhanced by a novel promising approach, the RAD index, which needs to be rapidly further evaluated. The challenge is open.

Acknowledgements

None.

Footnote

Provenance: This is a Guest Editorial commissioned by the Guest-Editor Lihua Chen [Department of Radiology, Taihu Hospital (PLA 101 Hospital), Wuxi, Jiangsu, China].
Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Schillaci O, Calabria FF. Comments on characterization of solitary pulmonary nodules with 18F-FDG PET/CT relative activity distribution analysis. J Thorac Dis 2015;7(10):1708-1712. doi: 10.3978/j.issn.2072-1439.2015.10.61