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REVIEW ARTICLE

Fluorine-18 fluorodeoxyglucose positron emission tomography in the management of solitary pulmonary nodule: a review

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ABSTRACT

Solitary pulmonary nodules are common radiologic findings and their detection has increased due to the introduction and improvement of diagnostics. Since a nodule can be an expression of early lung cancers, a proper classification and management are required because its treatment might lead to decreased morbidity and mortality. In this regard, prominent guidelines are available although they are characterized sometimes by discordant and misleading evidences. Furthermore, the same results of studies in the literature appear conflicting. Aim of this work is to evaluate the role of imaging through an extensive literature review but focusing on 18-fluorine fluorodeoxyglucose positron emission tomography combined with computed tomography (^{18}F-FDG-PET/CT) in order to assess the limits and future perspectives of solitary pulmonary nodule characterization in early detection of lung cancer.

KEY MESSAGES

- Detection of solitary pulmonary nodules has increased.
- Management of solitary pulmonary nodules is still debated.
- Future perspectives of early solitary pulmonary nodule characterization.

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KEYWORDS
Solitary pulmonary nodule; 18F-FDG PET/CT; computed tomography; ground glass opacities

Introduction

Solitary pulmonary nodule is defined as an intrapulmonary lesion of diameter from 5 to 30 mm, completely surrounded by aerated lung and without any lymphadenopathy [1]. Normally, it is found in 0.9–2% of chest X-rays and 90% is incidentally detected [2]. The advent of new technologies, such as spiral computed tomography with multi-layer technique (SCTT) or thin-section computed tomography (TSCT) and 18-fluorine fluorodeoxyglucose positron-emission tomography combined with computed tomography (^{18}F-FDG-PET/CT) have increased pulmonary nodule detection rates for lesions up to 1–5 mm in diameter, allowing a reduction of false images resulting from artifacts due to cardiac and respiratory movements. As a consequence, lung nodule frequency has considerably increased with occurrences from 8 to 51% [3,4]. According to our clinical experience, we believe that pulmonary nodules should be divided into: solitary pulmonary micronodule (SPMN) for a lesion between 1 and 5 mm in diameter and solitary pulmonary nodule (SPN) for a 6–20 mm lesion. For SPN, CT highlights morphology and peripheral structures as well as ^{18}F-FDG-PET/CT allows to distinguish benign from potential malignancy features. Fiber-optic bronchoscopy (FBS, with or without fluorescence), endobronchial ultrasound (EBUS) associated with trans-bronchial biopsies (TBB), pulmonary CT-guided needle biopsy (CTNB) as well as video-assisted thoracoscopy (VAT) ensure a histologic diagnosis, thus influencing surgical approach [5]. The management of solitary pulmonary nodules is still debated. The increased incidence diagnostic findings has determined the necessity of guidelines in order to optimize patient's treatment. Currently, according to the third edition of ACCP guidelines, annual screening with LDCT should be offered for smokers and former smokers who are age 55–74 years and who have smoked for 30 pack-years or more and either continue to smoke or have quit within the past 15 years; while, in individuals who have accumulated fewer than 30 pack-years of smoking or are either younger than age $\geq$55 years than 74 years, or individuals who quit smoking more than 15 years ago, and for individuals with severe comorbidities that would preclude potentially curative treatment and/or limit life expectancy, a LDCT screening program should not be performed. A screening program should include counseling with a complete

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description of potential benefits and harms and conducted in a center with a multidisciplinary coordinated group. However, the same guidelines states the most effective duration or frequency of screening was not known. Concerning with the effects of LDCT screening on the rate of death from lung cancer in the screened population, a significant reduction in mortality was reported [6]. However, in the setting of a screening program, the most serious concern is the risk of death or major complications as a result of it. Referring to the National Lung Screening Trial (NLST) [7], the overall frequency of deaths that occurred within 2 months of a diagnostic evaluation of a detected finding was 16 per 26,722 (0.06%) individuals screened by LDCT scan versus 10 per 26,732 (0.04%) individuals screened by CXR. Although it was not known whether the complications from the diagnostic procedure caused the deaths, the low frequency of death within 60 days after the procedure suggested that death, as a result of the diagnostic evaluation of positive screening tests, was a rare occurrence. Moreover, there was an appreciable increase in the rate of death or major complications resulting from investigation of screening findings from LDCT imaging and specifically in individuals who had only benign lesions. Nevertheless, in the highly organized NLST setting, the rate of such events was quite low. Another concern is the amount of radiation. An appropriately performed LDCT scan (~1.5 mSv) is less than the average annual background radiation; however, nodules requiring further imaging rapidly drive up the dose these patients receive; but, the benefit in preventing lung cancer deaths in NLST was considerably greater than the radiation risk [6]. A close surveillance for detected lesions is thus advocated because, if cancerous, they may benefit from surgical resection in pre-clinical stage, correlating a better prognosis [8]. In fact, the 5-year survival for Stage I NSCLC is respectively between 63 and 83.7% (Stage IA) and between 46 and 76% (Stage IB) after radical resection [9–11]. For SPN <5 mm, no radiological findings enable to assess benign or malignant features and minimally invasive diagnostic techniques (FBS, EBUS-TBB, CTNB, VAT) are contraindicated due to size of the nodule. In 2005, the Fleischner Society [12] established guidelines for the management of SPN and SPMN. Henscke [13], in a study conducted on 1000 patients with no history of malignancy undergoing screening programs for lung cancer, showed $<1\%$ of the nodules with a diameter ≤ 5 mm presented a malignant behavior. In these cases, the American College of Chest Physician (ACCP) guidelines [14] suggest anyway a follow-up of 24 months. On the other hand, the Fleischner Society states [12] patient enrollment without any dimensional cut-off would result in a series of disadvantages such as: (i) an increased false positive patients undergoing surgery; (ii) an increased health care costs; (iii) a prolonged patient psychological discomfort; (iv) loss of confidence in radiologists and (v) an increased radiation exposure for patients. Swensen et al. [15,16] reported that half of ≥ 50 years smokers, undergoing CT "screening" programs, showed at least one SPN and that 10% developed new lesions during the follow-up period. Therefore, a development of mathematical risk models needed in order to validate clinical algorithms for the management of SPN patients. The 2005 Fleischner Society guidelines stratified patients according to risk of cancer and size. In our opinion, this may expose patients both to neoplastic lesion development during the follow-up period and to diagnostic delay. In part, this attitude changed with the 2013 edition [16] by the introduction of six recommendations for the management of sub-solid pulmonary nodules (SSNs) due to their relationship with lung adenocarcinoma, whose incidence is up to 35% of cases [17]. The third edition of the ACCP guidelines [7,18] emphasized that a solitary pulmonary nodule evaluation cannot disregard risk factors and size of lesion. In patients with a solid nodule >8 mm and a likelihood of malignancy between 5 and 65%, PET/CT could be considered for characterization of lesion but, at the same time, for malignancy risk exceeding 65%. However, PET scan estimates of sensitivity ranged from 72 to 94%, because a limitation of most studies of diagnostic accuracy was the use of a single threshold [e.g. standardized uptake value (SUV) $= 2.5$] for distinguishing malignant from benign nodules. Notwithstanding the increased likelihood ratio (LR) for benign and malignant PET results (0.03 versus 9.9, respectively), false-negative findings on PET scan could be seen in patients with less metabolically active tumors, such as lepidic-predominant adenocarcinomas (minimally invasive or *in situ*), mucinous adenocarcinomas and carcinoid tumors. On the other hand, false-positive findings often could be the result of infections or inflammatory conditions, including mycoses, TB, rheumatoid nodules, and sarcoidosis. Paradoxically, false-positive PET scan results could sometimes be helpful because they alert the clinician to the presence of an active infectious or inflammatory conditions requiring specific treatment. In some circumstances, FDG-PET scan could be helpful in directing tissue biopsy. As a metabolic biopsy tool, PET scan could identify metabolically active lesions to yield a definitive tissue result. In this setting, Authors reported FDG-PET scanning might be most cost-effective when clinical pretest probability

and CT scan results were discordant, especially with low probability and CT indeterminate characteristic patterns. Otherwise, ACCP's guidelines favored for further diagnostic work-up among patients with indeterminate and high pretest probability nodules, due to negative PET scan results did not reliably exclude malignancy. Hence, patients with solid nodules and non-hypermetabolic PET scan results required continued surveillance for at least 2 years to confirm benignity or even a needle-biopsy. For these reasons, although Authors considered nodule characterization and lung cancer staging as separate indications for PET scanning, they favored PET scan over other functional imaging modalities for solitary pulmonary nodule characterization due to the presence of addictional informations provided by PET scans itself. Purpose of this work is to analyze the role of imaging through an extensive literature review focusing on ^{18}F-FDG-PET/CT in order to assess the limits and future perspectives of early SPN characterization in early lung cancer.

^{18}F-FDG-PET with and without CT in solid pulmonary nodule characterization

^{18}F-FDG-PET exploits the impairment cellular metabolism and the relative cytoplasmic glucose level uptake both in neoplastic and non-neoplastic diseases [19–21]. The radiopharmaceutical absorption is evaluated from a qualitative and quantitative point of view, allowing firstly an avidity-morphological study of the lesions and secondly an absolute evaluation of substance absorbed. SUV is the ratio between the surveyed area uptake and the normal tissue uptake and a SUV $\geq$2.5 a parameter of malignancy is considered [19,22]. For solitary pulmonary nodules (SPNs), ^{18}F-FDG-PET sensitivity, accuracy and specificity contextually increases as the size of the nodule itself, but it is poorly diagnostic for nodules $\leq$1 cm [4–6]. Herder et al. [23] analyzed 35 patients for a total of 36 SPN $\leq$1 cm. They found ^{18}F-FDG PET sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) rate of 93, 77, 72 and 94%, respectively. Diagnostic accuracy was 30%. Khalaf et al. [24] reported their experience in 173 patients with 202 lung nodules. They conducted a four-braced cohort study according to lesion diameter and a SUV = 2.5 as a cut-off of malignancy. Sensibility, specificity and accuracy were respectively: (i) 85, 36 and 54% in the first group (28 nodules $\leq$1 cm); (ii) 91, 47 and 79% in the second (58 nodules between 1.1 and 2 cm); (iii) 94, 23 and 76% in the third (47 nodules between 2.1 and 3 cm); (iv) 100, 17 and 82% in the fourth one (69 nodules $>$3 cm). Author showed that ^{18}F-FDG PET specificity was relatively low. For these reasons, sequential uptake levels (Dual Time Point PET, DTP-PET) were investigated. Lan et al. [25] evaluated 96 patients both 45–55 min and 150–180 min after ^{18}F-FDG intravenous infusion, deeming a variation of the radiopharmaceutical avidity of at least 10% as a positive result. Sensitivity, specificity, accuracy, PPV and NPV were 91.5, 67.6, 82.3, 81.8 and 98.3% at the first measurement and 98.3, 75.7, 89.6, 86.6 and 96.6% at the second one. Zhang et al. [26] conducted a meta-analysis including 415 patients and 430 lung nodules by comparing results both in "Dual Time Point PET" and "Single Time Point PET". Sensitivity and specificity were 79 versus 77% and 73 versus 59%, but no significant difference between these two techniques was found. Furthermore, the high incidence of infectious diseases producing "PET-avid" pulmonary lesions aroused the interest of several authors about the reliability of this examination. Deppen et al. [27] performed a meta-analysis including 70 studies from 1923 articles, for a total of 8511 nodules, 5105 of which were malignant. Average specificity was 16% inferior in lung infectious endemic regions (61%) rather than in non-endemic ones (77%) although sensitivity presented overlapping values between these groups. In a further study, Deppen et al. [28] reported 279 patients with lung nodules form an area with high incidence of granulomatous disease of USA. Two-hundred eleven respected the criteria of eligibility (SUV $>$2.5) and results showed high sensitivity values (92%) but low specificity (40%). ^{18}F-FDG-PET was improved by the association with CT, allowing a simultaneous evaluation of different parameters such as the size of nodule, metabolic activity and diameter uptake ratio [29]. Kim et al. [30] observed 42 patients with 7–30 mm SPNs with SUV_{max} between 0.5 and 17.2. Sensitivity and specificity of ^{18}F-FDG-PET and ^{18}F-FDG-PET/CT were 69 and 85% versus 97 and 85%, respectively, with a ^{18}F-FDG-PET/CT diagnostic accuracy of 93%. Opoka et al. [31] reported an experience on 82 SPN patients in order to evaluate PET/CT the differential diagnosis of pulmonary nodules. Forty patients presented lung cancer and 38 with $SUV_{max}>2.5$ nodules (9.1 average). The remaining had benign disease and 37 with $SUV_{max}<2.5$ lesions (average of 1.9). Sensitivity, specificity, accuracy, PPV and NPV were 95, 88, 91.5, 88.4 and 94.8%. Therefore, the possibility of studying a $SUV_{max}<2.5$ lung nodule seemed to be an additional benefit of PET/CT. Sim et al. [32] examined 641 PET/CT, whose sensitivity, specificity, accuracy, PPV and NPV were 86.7, 50, 81.2, 90.7 and 40%. These values have been positively influenced by the possibility of studying malignant lesions with $SUV_{max}<2.5$, which

were correctly diagnosed in 62% of cases. Li et al. [33], analyzing 96 patients with SPN <30 mm in an area with high incidence of TB, noticed PET/CT reduced the number of false positives. In fact, they reported a sensitivity, specificity, accuracy, PPV and NPV of 88.3, 61.1, 79.1, 79.1 and 75.9% versus 96.7, 75.7, 88.5, 88.1 and 94.4%, respectively comparing PET and PET/CT. Moreover, the quantitative analysis of sequential radiopharmaceutical uptake levels also increases PET/CT diagnostic accurancy. Demir et al. [34], in a retrospective study on 48 SPN patients SPN, performed previous PET/CT scan after 1 h from the radiopharmaceutical administration and a second one after 2 h, considering SUV_{max} threshold values both 2.5 and 2.75. Sensitivity, specificity and accuracy were 94 versus 75%, 75 versus 80% and 83 versus 78% after the first survey, while 94 versus 100%, 77 versus 80%, 83 versus 88% after the second one. Furthermore, the authors optimized SUV_{max} according to body surface area (BSA-SUVmax), lean body mass (LBM-SUV_{max}) and glucose (Glc-SUV_{max}), but these parameters showed no advantages in both phases. Nevertheless, PET/CT advantages are not universally shared. Li et al. [35] retrospectively studied 298 SPN patients, reporting an overall sensitivity, specificity, accuracy, PPV and NPV for lung cancer of 80.2, 38, 73.1, 86.5 and 27.9%. Of 219 patients with NSCLC, false negative results were 19.6% (43 cases). Authors concluded that size ≤3 cm, histologic diagnosis of adenocarcinoma, absence of pleural invasion, peripheral location of the tumor and absence of smoking history were the reasons of those low specificity and NPVs (Table 1).

^{18}F-FDG-PET/CT versus CT in solid solitary pulmonary nodule characterization

Computed tomography and ^{18}F-FDG-PET/CT result in a reduction of radiological artifacts due to cardiac and respiratory movements with a detection rate between 1 and 5 mm [5]. Moreover, the latter positively contributes to the identification of sub-centimeter pulmonary neoplasms because their low necrotic areas favor the SUV and thus overall specificity [5,36].

According to 2015 BTS Guidelines for the investigation and management of pulmonary nodules, PET-CT has shown a sensitivity of 93.9% and specificity of 88.5% for determining malignancy from a pooled cohort of studies including solitary pulmonary nodule patients with low to high risk, with more limited evidence for nodules 10% (Brock model) where the nodule size is greater than the local PET-CT detection cut-off. However, a qualitative assessment to define FDG uptake should be advocated by determining the mediastinal blood pool as a baseline threshold [37]. Ultimately, these guidelines emphasize the importance of a revision of the uptake cut-off, towards a qualitative dual-time assay rather the absolute SUV value. However, the high sensitivity has to be referred to a pooled cohort of patients with an adjusted stratified risk stratified according to a predefined model (Brock's or Herder's ones), and then, although it would be in conflict with those reported in the general analysis from ACCP **[**18**]** in a reduction of the occurrences of false positives (e.g. inflammatory diseases) and false negatives (e.g. lepidic adenocarcinoma), stratified rates of occurrence are in agreement with those published in other large series. Yi et al. [38] evaluated 119 SPNs patients with diameters between 6.2 and 30 mm who underwent both helical dynamic computed tomography (HDCT) and ^{18}F-FDG-PET/CT. Cut-off malignancy index were an enhancement ≥25 Hounsfield Units (HU) for the previous and a SUV_{max}≥3.5 for the latter. Sensitivity, specificity, diagnostic accuracy, PPV and NPV were 81 versus 96%, 93 versus 88%, 85 versus 93%, 96 versus 94% and 71 versus 92%, respectively. Authors concluded that^{18}F-FDG-PET/CT can be used as a first level diagnostic investigation (i.e. first-line evaluation tool) but HDCT remains a viable alternative according to its high specificity and acceptable diagnostic accuracy. Kagna et al. [39] retrospectively analyzed 307 SPN patients, of whom 93 at high risk for lung cancer, comparing visual ^{18}F-FDG-PET-low-dose chest CT (LDCT), semi-quantitative ^{18}F-FDG-PET/LDCT and LDCT. Thirty-eight percent of patients highlighted a histological diagnosis of malignancy. Visual PET/LDCT analysis displayed sensitivity of 94%, specificity of 70%, accuracy of 80%, a PPV of 66%, and NPV of 95% compared to 77, 83, 81, 73 and 86% for semi-quantitative PET/LDCT and 97, 48, 66, 53 and 96% for LDCT respectively. Authors suggested that integrated PET scans could be a valuable diagnostic tool for lung cancer screening in high risk patients. Harders et al. [40] reported 168 patients with SPN ≤30 mm in order to verify multi-detector computed tomography (MDCT) and integrated PET clinical reliability in the detection of malignant lung lesions. ^{18}F-FDG-PET/LDCT and MDCT showed a sensitivity of 97 versus 93%, a specificity of 47 versus 53%, a diagnostic accuracy of 81 versus 82%, a PPV of 89 versus 89% and a NPV of 79 versus 63%, respectively. Results seem to be slight in contrast with previous reports, especially in diagnostic accuracy and sensitivity. Moreover, referring to cost-benefits and to radiological risks, the Authors concluded that the integrated PET should not be advocated as a first-line diagnostic exam in high risk patients but rather MDCT should be considered. In this

Table 1. ^{18}F-FDG-PET with and without CT in solid pulmonary nodule.

	Imaging	Threshold	*N*	Sensitivity	Specificity	Accuracy	PPV	NPV	Conclusions
Herder et al. (2004)	^{18}F-FDG-PET	$SUV_{max}>2.5$	36 (SPN <1 cm)	93.0	77.0	30.0	72.0	94.0	FDG PET imaging could be useful in differentiating benign from malignant SPNs ≤10 mm
Kim et al. (2007)	^{18}F-FDG-PET versus ^{18}F-FDG-PET/CT		42 (7–30 mm SPNs)	69.0 versus 97.0	85.0 versus 85.0				PET/CT demonstrates an excellent performance in classifying SPNs as benign or malignant
Kalaf et al. (2008)	^{18}F-FDG-PET	$SUV_{max}>2.5$	202	85.0	36.0	54.0			
			Group A (nodules <1 cm)						
			Group B (nodules between 1.1 and 2.0 cm)	91.0	47.0	79.0			SUVmax cutoff of 2.5 is a useful tool in the evaluation of large pulmonary nodules (>1.0 cm), but it has no or minimal value in the evaluation of small pulmonary nodules
			Group C (nodules between 2.1 and 3.0 cm)	94.0	23.0	76.0			
			Group D (nodules >3 cm)	100.0	17.0	82.0			
Lan et al. (2008)	DTP-PET (45–55 min) (150–180 min)	SUV_{max} >2.5	96	91.5	67.6	83.2	81.8	98.3	Dual time point ^{18}F-FDG PET imaging is an important noninvasive method for the differentiation of malignant and nonmalignant lesions
				98.3	75.7	89.6	86.6	96.6	
Li et al. (2011)	^{18}F-FDG-PET/CT		298	80.2	38.0	73.1	86.5	27.9	PET/CT can improve the diagnostic accuracy in the differentiation of an SPN.
Zang et al. (2013)	DTP-PET versus STP-PET		439	79.0 versus 77.0	73.0 versus 59.0				Dual time point ^{18}FDG-PET/CT appears to be more specific than single time point ^{18}FDG-PET/CT
Opoka et al. (2014)	^{18}F-FDG-PET/CT		82	95.0	88.0	91.5	88.4	94.8	PET-CT appeared to have high sensitivity (95%), but lower specificity (88%) for predicting the malignant character of solitary pulmonary lesions.
Demir et al. (2014)	DPT-^{18}F-FDG-PET/CT								
	1 h	SUV_{max} 2.5 versus 2.75	48	94 versus 75	75 versus 80	83 versus 78			Dual-phase PET/CT may increase the diagnostic potential of PET/CT in the characterization of SPNs
	2 h			94 versus 100	77 versus 80	83 versus 88			

regard, Dabrowska et al. [41] reported 71 SPN patients with diameter between 8 and 30 mm. Radiological assessment was carried out by contrast-enhancement (CE) CT (enhancement cut-off of 19 HU) and ^{18}F-FDG-PET/CT (SUV_{max} cut-off of 2.5), in order to assess the accuracy of the two radiological methods in characterizing benign or malignant lesion. Sensitivity was 100 versus 77%, specificity 37 versus 92%, diagnostic accuracy 0.58 versus 0.9, PPV 32 versus 83% and NPV 100 versus 89%. According to sensitivity and NPVs, the authors concluded that CECT should be preferred in low risk patients, while PET should be recommended in high-risk ones due to high specificity and PPV levels (Table 2).

^{18}F-FDG-PET/CT in sub-solid solitary pulmonary nodule characterization

Sub-solid pulmonary nodules (SSNs) include pure ground glass (pGGN) and part-solid (PSN) nodules. A pGGN is defined as a parenchymal opacity characterized by the presence of interstitial focal attenuation in which vessels or bronchial structures can be observed [42], while PSNs present ground-glass areas in which the underlying lung cyto-architecture cannot be displayed [43]. The "Early Lung Cancer Action Project" (ELCAP) study reported that the probability of malignancy for SSN is higher than solid solitary pulmonary nodules (34 versus 7%) [44]: up to 63% for part-solid nodules and 18% for pure ground glass ones [45]. Moreover, the literature data shows [46,47]: (i) a higher rate of incidental malignant tumors in partially solid nodules when compared to solid ones and (ii) adenocarcinomas in the most persistent GGNs. Histologically, solitary pulmonary sub-solids nodules can be expression of a variety of diseases. The screening programs as well as clinical and radiological correlations have allowed an accurate etiological definition of SSNs [48–50], embracing both benign and malignant conditions. Among the first group, focal or desquamative interstitial fibrosis, eosinophilic pneumonia, endometriosis chest, focal hemorrhage areas are reported [51]. On the other side, many studies have focused on the pre-cancerous nature of these radiological findings. Travis et al. [52], in conclusion of the 2004 International Association for the Study of Lung Cancer/American Society of Clinical Oncology consensus workshop, notified that sub-solid nodules can be an expression of hyperplasia areas and atypical adenomatous hyperplasia (AAH). This latter was found in NSCLC patients with an incidence rate from 10 to 23% [53]. However, the presence of a sub-solid pulmonary nodule is often associated with bronchioloalveolar

Table 2. ^{18}F-FDG-PET/CT versus CT in solid solitary pulmonary nodules.

	Imaging	Threshold	*N*	Sensitivity	Specificity	Accuracy	PPV	NPV	Conclusions
Yi et al. (2006)	HDCT versus PET-CT	>25 HU versus SUV_{max}>3.5	119 (79 malignant and 40 benign)	81/96	93/88	85/93			PET/CT is more sensitive and accurate than HDCT for malignant nodules characterization and may be performed as the first-line evaluation tool for SPN characterization
Kagna et al. (2009)	Visual PET-ldCT versus Semiquantitavite PET/ldCT versus ldCT		93 (high risk for LC)	94/77/97	80/83/48	80/81/66	66/73/53	95/86/96	Integrated PET scans is a valuable diagnostic tool for lung cancer screening in high risk patients
WalbomHandersat al (2012)	^{18}F-FDG PET/CT versus MDCT		168	97/93	47/53	81/82	89/89	79/63	Integrated PET should be not advocated as a first-line diagnostic exam in high risk patients, but MDCT should be considered
Dabrowska et al. (2015)	CECT versus 18-F-FDG PET/CT	19 HU versus SUV_{max}>2.5	71	100/77	37/92	0.58/0.9	32/83	100/89	CECT should be preferred in low risk patients, while PET should be recommended in high-risk ones due to high specificity and PPV levels.

carcinoma (BAC), characterized by a lepidic growth-model along the inter-alveolar septa in absence of stromal invasion [54]. In 2011, the WHO proposed a revised lung adenocarcinoma classification, providing different pathologic patterns for BAC and its subtypes (mucinous, non-mucinous and mixed one): adenocarcinoma in situ (AIS), mini-invasive adenocarcinoma (MIA), lepidic pulmonary adenocarcinoma (LPA), papillary non-mucinous adenocarcinoma with or without lepidic component and invasive adenocarcinoma [55]. This classification enables a better differentiation between pre-invasive, minimally invasive and invasive lesions and their prognostic effects. Noguchi et al. [56], evaluating 174 cT1 adenocarcinoma patients including 28 with SSNs, reported a better prognosis in patients with GGNs than those with solid nodules (100 versus 74.8% at 5 years). In the 1999 and 2004, WHO classification on lung cancer [57,58] introduced ^{18}F-FDG PET/CT as routine exam in the assessment of NSCLC patients [59], whose radiopharmaceutical uptake also correlates with patient prognoses [60–62]. However, the role of ^{18}F-FDG-PET/CT for sub-solid pulmonary nodules is not defined and still debated. Kim et al. [59], evaluating 89 patients with 134 pGGNs, pointed out the absence of a clear advantage in malignant GGN staging due to the low incidence of lymph node and distant metastases. Lee et al. [63], analyzing 160 patients, focused on the limited role of ^{18}F-FDG PET/CT in cT1 SSN nodal staging due to lower sensitivity and diagnostic accuracy when compared with CT (81.9 versus 91.9%). Moreover, the ^{18}F-FDG-PET/CT was not recommended in patients with a less than 50% solid pattern due to the absence of lymph node metastases [64]. Nomori et al. [65] reported 136 SSNs characterized by PET and then surgically sampled. Of 10 adenocarcinoma GGNs, nine showed no PET uptake (90% false negative) while of five benign nodules, four were false positive (80% false positive). PET/CT overall sensitivity and specificity for pGGNs and solid one was thus 10 versus 90% and 20 versus 71% for solid nodules, respectively. The authors concluded that in presence of non-solid or partially solid nodules, PET/CT does not allow a proper assessment of the nature of the lesion itself. Kim et al. [30] studied 89 ground glass opacity (GGO) patients. Fifty-six presented GGNs and in 93% of them, an early stage lung cancer was diagnosed (7 ex bronchioloalveolar adenocarcinomas and 45 adenocarcinomas with bronchioloalveolar areas). Average radiological diameter was 15 mm (range: 5–37 mm) and a positive correlation between size and SUV_{max} (range: 0.2–5.2) was found. A negative one was indeed reported between ground glass percentage ratio (mean value observed: 77%) and SUV_{max} itself. Results were confident with Goudarzi et al. ones [66]. The Authors, after an evaluation of 53 patients, underlined absence of a diagnostic role of PET/CT in the T-parameter staging process due to the low radiopharmaceutical uptake. In fact, in only 24% of lepidic or papillary adenocarcinomas, a significant and identifiable metabolic rate was detected; results which are inferior to other primitive tumor uptake values [67]. However, SUV_{max} appears to be an independent predictor of lymph node metastasis in early stage adenocarcinoma and a preoperative prognostic parameter (disease-free survival and overall survival) both in part-solid and in solid nodules [68,69]. Despite the 2013 Fleischner Society recommendation [17] on the use of PET/CT in lung part-solid nodules $<$10 mm, its role is still under discussion. In fact, the Fleishner Society suggested no role for the PET/CT in solitary GGNs smaller than 10 mm (level of evidence 1B) and in multiple GGNs with the dominant one having a diameter between 5 and 8 mm, because of the low proportion of lymph node metastases. Yap et al. [70], studying 46 surgically treated sub-solid lesions with histologic diagnosis of adenocarcinoma, have found that 32 were ground glass and of which 67% were PET/CT negative. Similar results were observed by Heyneman and Patz [71], reporting an overall PET/CT sensitivity of 38%. Moreover, the Fleishner Society recommended considering PET/CT in the case of partially solid multiple lesions with dominant nodule size of between 8 and 10 mm (grade of evidence 1C). The recent British Thoracic Society [37] guidelines suggested PET/CT execution for sub-solid lesions with size $>$10 mm or $<$10 mm if the risk stratification of malignancy is higher than 10% (Brock's model). For pGGNs, the examination can only be considered by reducing the 2.5 SUV_{max} malignancy index (level of evidence 3).

Conclusions

The management of solitary pulmonary nodules is still debated. The increased incidence diagnostic findings determined the necessity of guidelines in order to optimize the treatment of patient but it is difficult to propose a single and schematic diagnostic algorithm for solitary pulmonary nodule management. Although ^{18}F-FDG-PET/CT is the most sensitive non-invasive diagnostic procedure for prediction of malignancy of $<$10 mm-solid solitary pulmonary nodules, CT alone cannot be considered superfluous due to its characteristics and peculiarities for a proper evaluation of these lesions. The sub-solid solitary pulmonary nodule radiological management, indeed, remains controversial, despite prominent published guidelines.

The malignancy-related risk and the controversial role of imaging could turn into misleading behaviours resulting in diagnostic delay. In our opinion, in sub-centimeter lesions, a correct stratification of risk and PET/CT execution allow for a comprehensive patient assessment. On the other hand, in the case of a dimensional increase or a morphological modification, surgical biopsy is mandatory.

Disclosure statement

No potential conflict of interest was reported by the authors.

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