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ORIGINAL ARTICLE

^{18}F-FDG PET/CT diagnostic performance in solitary and multiple pulmonary nodules detected in patients with previous cancer history: reports of 182 nodules

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Abstract

Purpose In oncological patients, ^{18}F-FDG PET/CT performance for pulmonary nodules' characterization is not well-established. Thus, the purpose of this study was to evaluate the ^{18}F-FDG PET/CT diagnostic performance in pulmonary nodules detected during follow-up in oncological patients and the relationship between malignancy and nodules' characteristics.

Methods We retrospectively evaluated 182 pulmonary nodules (121 solitary, 61 multiple; mean size = 16.5 ± 8.1 mm, mean SUVmax = 5.2 ± 5.1) in 148 oncological patients (89 males; mean age = 69.5 ± 8.4 years). Final diagnosis was established by histology or radiological follow-up. Diagnostic performance of ^{18}F-FDG visual analysis (malignancy-criterion: uptake ≥ mediastinal activity), ROC curve analysis for SUVmax and nodules' characteristics were assessed.

Results In 182 nodules, the prevalence of malignancy was 75.8%; PET/CT provided sensitivity = 79%, specificity = 81.8%, accuracy = 79.7%, PPV = 93.1%, NPV = 55.4%; ROC analysis (SUVmax cut-off = 1.7) provided sensitivity = 85.5%, specificity = 72.7%. In 121 solitary nodules, the prevalence of malignancy was 87.6%; PET/CT provided sensitivity = 82.1%, specificity = 73.3%, accuracy = 81%, PPV = 95.6%, NPV = 36.7%; ROC analysis (SUVmax cut-off = 2) provided sensitivity = 84%, specificity = 80%. In 61 multiple nodules, the prevalence of malignancy was 52.5%; PET/CT (nodule and patient-based analysis, respectively) provided sensitivity = 68.7% and 88.9%, specificity = 86.2% and 55.6%, accuracy = 77% and 77.8%, PPV = 84.4% and 80%, NPV = 71.8% and 71.5%; ROC analysis (nodule-based, SUVmax cut-off = 1.8) provided sensitivity = 71.9%, specificity = 82.8%. Malignant nodules were prevalent in males, in solitary pattern and in upper lobes, and had significantly greater size and metabolic activity (SUVmax and TLG) than benign ones, with no differences in interval-time between previous cancer diagnosis and nodule detection, patients' age or other nodules' features (lung side, central/peripheral). When comparing solitary and multiple patterns, malignant nodules had significantly greater size and metabolic activity than benign ones in both groups.

Conclusions In oncological patients, ^{18}F-FDG PET/CT provides good diagnostic performance for ruling in the malignancy in pulmonary nodules detected during follow-up, even at small size and especially when solitary. In multiple patterns, PET seems useful in the perspective of a personalized management, for identifying the "reference" nodule deserving histological assessment.

Keywords Pulmonary nodule · PET/CT · ^{18}F-FDG · Metabolic characterization · Previous cancer history

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Introduction

In patients with previous cancer history, the detection of solitary or multiple pulmonary nodules is a common finding due to the regular oncological surveillance and the technical evolution of computed tomography (CT) [1]. In oncological patients, pulmonary nodules have a high probability of malignancy (either a metachronous lung cancer or a lung metastasis), also increased (up to 85%) when compared to non-oncological subjects, even if their benign nature cannot be

completely excluded [2–6]. In literature, the prevalence of malignancy is widely variable, mainly depending on patient's risk factors (smoking history, genetic predisposition, environmental factors, etc.), previous cancer characteristics (histotype, stage and anatomical site in relation to venous drainage) [4, 5, 7–10], as well as on nodules' features such as size (from few millimeters to masses) and number (solitary or multiple) [4, 7–9, 11]. To differentiate malignant nodules from benign ones is of supreme importance because it impacts both on subsequent therapeutic strategies and prognosis; moreover, it seems a harder challenge when multiple nodules are detected. Indeed, it is not clearly established if multiple patterns are associated with an increased or reduced risk of cancer when compared to solitary patterns [12, 13], considering that metastases remain a leading hypothesis even if inflammatory processes—common sequelae of anticancer treatment—cannot be excluded [8].

^{18}F-FDG PET/CT is a well-established and accurate diagnostic tool for the metabolic characterization of solitary pulmonary nodules in non-oncological subjects [2, 3, 14, 15], whereas its diagnostic performance in oncological patients, especially in the setting of multiple nodules, is less established. Indeed, few data are available and most of them derive from mixed populations, oncological and non-oncological [8, 16–19].

Aims of this study were to evaluate the ^{18}F-FDG PET/CT performance for the characterization of pulmonary nodules detected during follow-up in a population of exclusively oncological patients and the relationship between malignancy and main nodules' characteristics, with particular reference to the solitary and multiple nodules' pattern.

Materials and methods

Study population

From a single-institution database, we retrospectively reviewed medical records of all consecutive patients referred from a local Unit of Thoracic Surgery to our PET/CT center between September 2009 and August 2017 to perform ^{18}F-FDG PET/CT for evaluation of pulmonary lesions. We included only patients with: (1) a history of previous cancer, considered to be disease-free at the time of PET/CT; (2) pulmonary nodules detected at CT during oncological follow-up and ranging from 5 mm to 40 mm in maximum axial diameter; and (3) availability of histopathological evidence or a radiological follow-up of at least 24 months as reference standard for nodules' final diagnosis. Oncological patients with history of prior pulmonary metastases or with pulmonary abnormalities described as "ground glass" (GGO) were excluded. Finally, 148 oncological patients (89 males; mean age = 69.5 ± 8.4 years) with a total of 182 pulmonary nodules were included: 121 patients had a solitary nodule (n = 121), and 27 patients had multiple nodules (n = 61). Nodules were finally classified as malignant or benign according to histopathological diagnosis or radiological follow-up (CT technique performed according to clinicians' judgment considering patient's oncological history and radiation exposure): benign if they resolved or remained stable over 24 months after the initial detection, and malignant if they increased in size. The following data were retrospectively collected for all included patients: age, gender, primary cancer site, date of previous cancer diagnosis, disease free interval (DFI) considered as the time between the diagnosis of primary cancer (in patients with only one cancer)/the diagnosis of most recent previous cancer (in patients with more than one cancer) and the nodule detection, nodules' characteristics including ^{18}F-FDG uptake, size, number, location (i.e. right or left lung, upper or lower lobes, central or peripheral), and result of final diagnosis. According to the ethical standards of our institution, an informed consent for PET/CT examination and for evaluation of clinical records was obtained from all patients.

^{18}F-FDG PET/CT image acquisition

All patients fasted for at least 6 h before ^{18}F-FDG administration. PET images were acquired 60 ± 10 min after an intravenous injection of a mean of 240 MBq (185-333 MBq) of ^{18}F-FDG, according to body mass index. At the time of tracer injection, all patients presented blood glucose levels <150 mg/dl and they were in optimal hydration state (i.v. administration of 500 ml of saline solution). All studies were performed using an integrated PET/CT device (Gemini GXL by Philips Medical System, Cleveland, Ohio or Biograph mCT by Siemens Healthineers, Chicago, Illinois). An X-ray scout to precisely define the spatial range of acquisition and a low-dose unenhanced CT scan from the skull base to mid-thighs (120 kV, 50–80 mA) for anatomical localization, photon attenuation correction and fusion with PET images were acquired. PET emission scans were acquired in 3D mode with an acquisition time of 2 to 3 min per bed position over the same spatial range as defined at scout view and reconstructed using iterative algorithms.

^{18}F-FDG PET/CT image interpretation

To analyze the images, PET and CT datasets were transferred to an independent computer workstation by DICOM (Digital Imaging and Communications in Medicine) transfer. PET images were qualitatively evaluated by two independent nuclear medicine physicians (ST, VS), partially blinded (aware of the clinical indication of PET/CT but blinded to the nodules' final diagnosis), using a dedicated fusion and display software (Syngo.via; Siemens Medical Solutions) and scored as follows: negative if the ^{18}F-FDG uptake in the lung nodule was

lower than the mediastinal background activity; positive if the ^{18}F-FDG uptake was equal to or higher than the mediastinal background activity. Any disagreement was resolved by consensus. The maximum standardized uptake value (SUVmax) was measured for all nodules, applying the EQ·PET reference-based quantification technology (developed by Siemens Healthineers) [20]. The total lesion glycolysis (TLG) was calculated as the product of the SUVmean and the metabolic tumor volume defined using a threshold of 50% of the SUVmax; the success of tumor delineation was visually checked.

Statistical analysis

Statistical analysis was performed for all pulmonary nodules and for the two groups of solitary and multiple nodules; in this latter group, both a nodule-based and a patient-based analysis (malignancy criterion: at least one ^{18}F-FDG-positive nodule) were performed. Continuous variables were expressed as mean (with standard deviation, SD) or median (with range) and categorical data as a percentage. The level of agreement between the two observers who performed the visual analysis was evaluated using the Kappa-test. Diagnostic performance of ^{18}F-FDG for the detection of malignancy was calculated in terms of sensitivity, specificity, accuracy, positive and negative predictive values (PPV and NPV, respectively) for a qualitative analysis. PPV and NPV were calculated assuming that the individual pre-test probability of malignancy was equal to the prevalence of disease found in our study population. In addition, ^{18}F-FDG diagnostic performance was calculated for a semi-quantitative analysis, at the optimal SUVmax cut-off provided by the receiver operating characteristic (ROC) curve analysis. Results were reported with 95% confidence intervals (CIs). Comparison between malignant and benign nodules in clinical, anatomical and functional parameters were performed using Mann-Whitney test (the Shapiro-Wilk test showed a not normal distribution) and chi-square test for continuous and categorical data, respectively. Statistical significance was set at p value <0.05. Data were analyzed by MedCalc Statistical Software version 16.8.4 (https://www.medcalc.org; 2016).

Results

Detailed characteristics of the study population are reported in Table 1. In the 148 oncological patients (121 patients with a solitary nodule and 27 with multiple nodules), previous cancer sites were: urological tract (kidney, bladder, prostate; $n = 42$), breast ($n = 29$), colon-rectum ($n = 24$), lung ($n = 12$), others ($n = 32$); nine patients had more than one previous cancer. Final diagnosis was obtained by histology in 128/182 (70%) nodules, by radiological follow-up in 54/182 (30%). Malignancy was proven in 138/182 nodules (23 metastases, 96 primary lung cancers, 19 increased at radiological follow-up); 44/182 nodules were benign. Table 2 reports the diagnostic performance (sensitivity, specificity, diagnostic accuracy, PPV and NPV) of ^{18}F-FDG PET/CT visual analysis in all ($n = 182$), solitary ($n = 121$) and multiple ($n = 61$) nodules. The level of agreement between the two observers who performed the visual analysis was almost perfect (K = 0.964; 95% CI = 0.92-1.0). ROC curve analysis (SUVmax cut-off = 1.7) provided 85.5% (95% CI = 78.5-90.9%) sensitivity and 72.7% (95% CI = 57.2-85%) specificity (see Fig. 1).

Regarding 121 solitary nodules, 106 were malignant (20 metastases, 75 primary lung cancers, 11 increased at follow-up) and 15 were benign. ROC curve analysis (SUVmax cut-off = 2) provided 84% (95% CI = 75.6–90.4%) sensitivity and 80% (95% CI = 51.9–95.7%) specificity (see Fig. 1).

Regarding 61 multiple nodules, 32 were malignant (3 metastases, 21 primary lung cancers and 8 increased at radiological follow-up) and 29 were benign. ROC curve analysis (SUVmax cut-off = 1.8) provided 71.9% (95% CI = 53.3–86.3%) sensitivity and 82.8% (95% CI = 64.2–94.2%) specificity (see Fig. 1). Eighteen patients out of 27 (66.6%) had at least 1 malignant nodule. On patient-based analysis, ^{18}F-FDG PET/CT provided the following diagnostic performance: sensitivity = 88.9% (95% CI = 67.2–96.9%), specificity = 55.6% (95% CI = 26.7–81.1%), diagnostic accuracy = 77.8% (95% CI = 59.2–89.4%), PPV = 80% (95% CI = 56.3–94.3%), NPV = 71.5% (95% CI = 29.2–96.4%).

Comparison between malignant and benign nodules

Comparison between malignant and benign nodules in clinical, anatomical and metabolic characteristics is detailed in Table 3. Among 148 oncological patients, the malignancy was prevalent in males ($p = 0.0446$) and in patients with solitary pattern compared to the multiple one (malignancy rate 87.6% vs 52.5%, respectively; $p < 0.0001$). No significant differences between the group with malignant and the group with benign nodules were observed in terms of patient's age and DFI.

Among 182 nodules, significant differences were observed in size ($p < 0.0001$), SUVmax and TLG ($p < 0.0001$) and in lung lobes' location ($p = 0.01$), whereby malignant nodules were larger, with higher metabolic activity and more frequently located in the upper lobes than benign ones. No significant differences were observed in the other nodules' location features.

Analyzing patients with solitary nodules and patients with multiple ones, in both groups malignant nodules had significantly larger size and higher metabolic activity than benign ones, whereas no differences in patients' characteristics or nodules' location were found.

Table 1 Main characteristics of the study population (patients and pulmonary nodules)

Characteristic	All patients (N = 148)	With solitary nodules (N = 121)	With multiple nodules (N = 27)
Age (years)			
Mean (SD)	69.5 (8.4)	69.6 (8.5)	69.2 (8)
Median (range)	71.1 (44.1–85.5)	71.1 (44.1–83.2)	71.1 (55.8–82.6)
Gender			
Male, n (%)	89 (60.1)	75 (62)	14 (51.8)
Female, n (%)	59 (39.9)	46 (38)	13 (48.2)
DFI (years)			
Mean (SD)	5.4 (6)	5.1 (5.5)	6.5 (7.6)
Median (range)	3 (1–34)	3 (1–30)	4 (1–34)
Nodules	All (n = 182)	Solitary pattern (n = 121, 66.5%)	Multiple pattern (n = 61, 33.5%)
Size (mm)			
Mean (SD)	16.5 (8.1)	18.2 (7.7)	13 (7.7)
Median (range)	15 (5–40)	16 (6–40)	10 (5–37)
Location			
Right lung, n (%)	97 (53.3)	64 (52.9)	33 (54.1)
Upper lobes[a], *n* (%)	115 (63.2)	79 (65.3)	36 (59)
Central[b], *n* (%)	56 (30.8)	35 (28.9)	21 (34.4)
SUVmax			
Mean (SD)	5.2 (5.1)	6.1 (5.5)	3.5 (3.9)
Median (range)	3.5 (0.5–38)	4.5 (0.5–38)	1.7 (0.8–18.7)
TLG			
Mean (SD)	10.83 (19.72)	13.88 (22.92)	4.78 (8.14)
Median (range)	3.32 (0.05–122.26)	4.51 (0.09–122.26)	1.1 (0.05–52.26)

SD standard deviation, *DFI* disease free interval, *SUVmax* maximum standardized uptake value, *TLG* total lesion glycolysis

[a] The right middle lobe was included in the upper lobes location

[b] The nodule was defined as central if located in the inner one-third of the lung parenchyma, and as peripheral if located in the outer two-thirds of lung parenchyma

Discussion

Literature data on diagnostic performance of ^{18}F-FDG PET/CT for the metabolic characterization of pulmonary nodules detected in oncological patients mostly derive from mixed populations in whom the number of oncological patients is a minor proportion [18, 19, 21, 22]. Only few papers evaluated the role of ^{18}F-FDG PET/CT in a population of exclusively oncological patients [8, 16, 17]. To our knowledge, our study evaluated and compared the ^{18}F-FDG PET/CT performance

Table 2 Diagnostic performance of ^{18}F-FDG PET/CT visual analysis

Measure	All nodules (N = 182)	Solitary pattern (N = 121)	Multiple pattern (N = 61)
Malignant nodules (%)	*n* = 138 (75.8)	*n* = 106 (87.6)	*n* = 32 (52.5)
TP/FN	109/29	87/19	22/10
Benign nodules (%)	*n* = 44 (24.2)	*n* = 15 (12.4)	*n* = 29 (47.5)
TN/FP	36/8	11/4	25/4
Sensitivity (95% CI)	79% (71.5–85)	82.1% (73.7–88.2)	68.7% (51.4–82)
Specificity (95% CI)	81.8% (68–90.5)	73.3% (48.1–89.1)	86.2% (69.4–94.5)
Accuracy (95% CI)	79.7% (73.2–84.9)	81% (73.1–87)	77% (65.1–85.8)
PPV (95% CI)	93.1% (86.9–97)	95.6% (89.1–98.8)	84.4% (64.7–95.3)
NPV (95% CI)	55.4% (42.6–67.8)	36.7% (20–56.2)	71.8% (54.1–85.6)

TP true positive, *FN* false negative, *TN* true negative, *FP* false positive, *CI* confidence interval, *PPV* positive predictive value, *NPV* negative predictive value

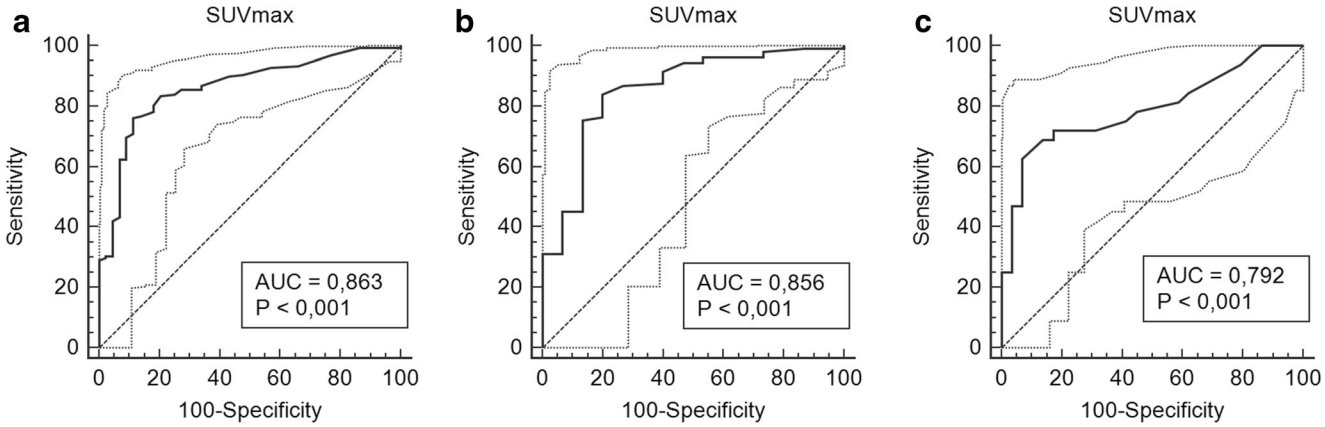

Fig. 1 Receiver operating characteristic (ROC) curves for semi-quantitative ^{18}F-FDG PET analysis by maximum standardized uptake value (SUVmax) in all 182 pulmonary nodules (**a**), in 121 solitary pulmonary nodules (**b**), and in 61 multiple ones (**c**). Area under the curve (AUC) and *p* value are reported. *Solid line* represents the ROC curve. *Dotted lines* represent the 95% confidence intervals. *Dotted diagonal line* represents the line of equality

in the largest sample of both solitary and multiple nodules detected in an oncological population, mainly using the histological proof as final diagnosis.

In our study, the prevalence of malignancy was >75%, higher than that reported in non-oncological populations [2–4, 15] and within the range (from 20% to 98%) of that reported in oncological populations [4, 6–9, 17]. The wide range described in oncological populations mainly depends on the heterogeneous characteristics and risk factors among patients, such as smoking status, and on the features of investigated nodules, such as number (solitary or multiple) and size. The prevalence of malignancy rises with the increasing of smokers and of nodule size, and with solitary pattern [3, 4, 8, 9, 11, 16, 17]. In addition, it strongly depends on the institutional dataset from which the investigated nodules have been collected: when collected from archives of nodules sent to surgical diagnosis, they are generally more likely malignant when compared to those that had been sent to radiological follow-up. This represents a "potential selection bias" in all studies [4], as well as in our study since we chose only patients referred from a unit of thoracic surgery (that, obviously, does not include all patients with previous cancers). Therefore, our population may not be representative of all patients with previous cancers. In our sample, the relatively high rate of malignancy can be explained considering that most of the nodules were solitary, that all patients referred to our PET/CT center from thoracic surgeons and most nodules were sent to invasive diagnosis (surgery or biopsy). The mean size did not seem to unbalance the probability of malignancy since we included nodules with a wide size range. Moreover, when considering the malignant nodules, we observed a higher prevalence of metachronous lung cancers compared to metastases. As previously reported [4, 5, 10], the likelihood that a pulmonary nodule is a metachronous cancer or a metastasis mainly depends on the anatomical site of the previous cancer: the nodule is more likely to be a lung cancer in patients with previous head and neck, bladder, breast, and prostate cancers; it has a fairly equal probability in previous colon and kidney cancers; it is more likely to be a metastasis in previous melanoma, soft tissue sarcomas, and testicular cancers. So, the high rate of metachronous malignancies we observed does not seem an unexpected finding when considering that most previous cancers sites were represented by urological tract, breast, colon-rectum and lung.

Visual analysis of ^{18}F-FDG PET/CT images provided good diagnostic performance with high and balanced sensitivity and specificity values (80%). This finding is even more interesting when considering the overall small size of nodules suggesting that, in an oncological population, PET/CT may be able to characterize a nodule just after its radiological detection. The diagnostic accuracy of ^{18}F-FDG PET/CT provided in our study is in line with that reported in the few papers available in literature in the same setting of oncological populations [16, 17]. ^{18}F-FDG PET/CT is of clinical value for ruling in the malignancy, as supported by our only eight false positive results (7 inflammations and 1 amarthocondroma) and by the very high positive predictive value. From a clinical point of view, PET positive results should deserve, when possible, further histological assessment not only to confirm the malignancy, but especially to define whether the malignant nodule is a metastasis or a metachronous lung cancer. This differential diagnosis has important implications on the personalized subsequent therapeutic approach and on the prognosis. Conversely, ^{18}F-FDG PET/CT performance for ruling out the malignancy is suboptimal, as supported by the low negative predictive value. This result can be explained by the following reasons: the low number of benign lesions; the restrictive image analysis criterion; the relative high amount of false negative results (17 adenocarcinomas, 2 carcinoids, 4 metastases [2 from mucinous colorectal adenocarcinomas, 2 from

Table 3 Comparison between malignant and benign nodules in clinical, anatomical and metabolic characteristics

Characteristic	All nodules ($n = 182$)			Solitary nodules ($n = 121$)			Multiple nodules ($n = 61$)		
	Malignant ($n = 138$)	Benign ($n = 44$)	p value	Malignant ($n = 106$)	Benign ($n = 15$)	p value	Malignant ($n = 32$)	Benign ($n = 29$)	p value
Patients' age (years)									
Median (range)	71.0 (44.1–85.5)	71.1 (54.8–82.6)	$p = 0.93$	70.8 (44.1–85.5)	73.1 (54.8–79.8)	$p = 0.28$	71.7 (56.1–80.4)	63.8 (55.8–82.6)	$p = 0.11$
Male gender									
n (%)	79 (63.7)	10 (41.7)	$p = 0.04$	69 (65.1)	6 (40)	$p = 0.06$	10 (55.5)	4 (44.4)	$p = 0.59$
DFI (years)									
Median (range)	3.5 (1–34)	2.5 (1–22)	$p = 0.75$	3 (1–30)	2 (1–22)	$p = 0.69$	5.5 (1–34)	3 (1–11)	$p = 0.67$
Size (mm)									
Median (range)	17 (5–40)	10 (5–28)	$p < 0.0001$	18 (7–40)	11 (6–25)	$p = 0.0001$	12.5 (5–37)	8 (5–28)	$p = 0.006$
Location									
Right lung, n (%)	78 (56.5)	19 (43.2)	$p = 0.12$	58 (54.7)	6 (40)	$p = 0.28$	20 (62.5)	13 (44.8)	$p = 0.16$
Upper lobes[a], n (%)	94 (68.1)	21 (47.7)	$p = 0.01$	72 (67.9)	7 (46.7)	$p = 0.10$	22 (68.8)	14 (48.3)	$p = 0.10$
Central[b], n (%)	38 (27.5)	18 (40.9)	$p = 0.09$	28 (26.4)	7 (46.7)	$p = 0.10$	10 (31.2)	11 (37.9)	$p = 0.58$
SUVmax									
Median (range)	4.7 (0.5–38)	1.3 (0.6–7.7)	$p < 0.0001$	5.1 (0.5–38)	1.4 (0.6–7.5)	$p < 0.0001$	2.9 (1–18.7)	1.3 (0.8–7.7)	p = 0.0001
TLG									
Median (range)	5.46 (0.12–122.26)	0.64 (0.05–19.01)	$p < 0.0001$	6.1 (0.26–122.26)	0.69 (0.09–5.34)	$p < 0.0001$	4.94 (0.12–52.26)	0.61 (0.05–19.01)	$p = 0.0008$

DFI disease free interval, *SUVmax* maximum standardized uptake value, *TLG* total lesion glycolysis

[a] The right middle lobe was included in the upper lobes location

[b] The nodule was defined as central if located in the inner one-third of the lung parenchyma, and as peripheral if located in the outer two-thirds of lung parenchyma

clear cell renal cell carcinomas] and 6 increased at radiological follow-up). Regarding the latter aspect, we believe that our false negative results were mainly due to the high prevalence of well-known low ^{18}F-FDG-avid tumors [19] and to the small nodules' size that implies the partial volume effect [23]. Therefore, in order to avoid delays in diagnosis and treatment, we suggest to consider even a nodule with faint ^{18}F-FDG uptake suspicious for malignancy. This concept is supported by the results obtained from ROC analysis, identifying a very low SUVmax cut-off (from 1.7 to 2), and also by other authors [17]. When comparing patients with solitary and multiple nodules, in multiple ones we found a lower prevalence of malignancy (67% vs 88%), in line with that reported in literature [9, 11, 16], and a suboptimal ^{18}F-FDG PET/CT sensitivity on nodule-based analysis. However, the improved sensitivity of PET on a patient-based analysis suggests its significant relevance in the perspective of a personalized patient management, allowing to identify the "reference" nodule which deserves to be histologically assessed. Our results are not completely comparable with those reported by Evangelista et al. in multiple nodules [16]. Indeed, the authors found similar sensitivity but higher specificity on a patient-based analysis, although they analyzed only the largest lesion, whereas we considered all nodules of all sizes. From a clinical point of view, the detection of multiple nodules in oncological patients seems a harder issue compared with solitary ones, because there is a general tendency to consider multiple patterns as metastases. However, it is not clearly established if multiple patterns are associated with an increased or reduced risk of cancer, even in non-oncological populations [6, 12, 13]. In our study, half of multiple nodules were benign and likely due to inflammatory processes since they had disappeared or were reduced at follow-up. This finding in oncological patients is explainable by the increased lung toxicity or lung susceptibility to pathogenic agents, both as possible sequelae of anticancer treatments [8].

When comparing malignant and benign nodules, malignant ones had a larger size and higher metabolic activity (in terms of SUVmax and TLG) than benign ones in both solitary and multiple groups, as expected. Indeed, the relationship between malignancy and both nodules' size and SUVmax is a well-established concept, regardless of the evaluated population (oncological or non-oncological) [4, 15, 24]. In addition, when considering our overall population, malignancy was more associated with the upper lobes location, as expected since cancers occur more frequently in upper lobes [13, 14], and with the male gender. In literature data, the possible role of gender as a risk factor in non-small-cell lung cancer is less established; nevertheless, the increased incidence over the recent decades of adenocarcinoma histotype, as well as the higher incidence of adenocarcinoma in female non-smokers compared to male non-smokers, has moved the risk toward the female gender [13, 25, 26]. No other feature (lung side or central/peripheral nodule location, patient age, DFI) seems useful to differentiate malignant nodules from benign ones.

Limitations of our study are represented by the retrospective nature and the unavailability of information on the prevalence of smokers. Regarding this latter point, smoking history is a well-recognized risk factor for malignancy in pulmonary nodules. Although we cannot evaluate this additional factor in our population, in previous similar reports focusing on oncological populations, no difference in smoking status between malignant and benign pulmonary nodules has been observed [8, 11, 16].

Conclusions

In a population of exclusively oncological patients, ^{18}F-FDG PET/CT provides good diagnostic performance for the metabolic characterization of pulmonary nodules detected during follow-up, and in particular in solitary nodules compared with multiple ones. In this latter group, PET seems still useful in the perspective of a personalized patient management, allowing to identify the "reference" nodule deserving histological assessment. PET/CT is clinically relevant for ruling in malignancy, even when pulmonary nodules are still small in size. However, since PET/CT performance for ruling out malignancy is suboptimal (mainly related to small nodule sizes), a lower than mediastinal ^{18}F-FDG uptake should be explored as visual criterion for malignancy in oncological patients, in order to avoid delays in diagnosis and treatment.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All patients gave a general written informed consent for PET/CT examination and for retrospective evaluation of their data.

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