European Journal of Nuclear Medicine and Molecular Imaging (2018) 45:1908–1914
https://doi.org/10.1007/s00259-018-4043-y

ORIGINAL ARTICLE

Risk-related ^{18}F-FDG PET/CT and new diagnostic strategies in patients with solitary pulmonary nodule: the ITALIAN multicenter trial

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Received: 5 February 2018 / Accepted: 26 April 2018 / Published online: 5 May 2018

Abstract

Purpose Diagnosis of solitary pulmonary nodule (SPN) is an important public health issue and ^{18}F-FDG PET/CT has proven to be more effective than CT alone. Pre-test risk stratification and clinical presentation of SPN could affect the diagnostic strategy. A relevant issue is whether thoracic segmental (s)-PET/CT could be implemented in patients with SPN. This retrospective multicenter study compared the results of FDG whole-body (wb)-PET/CT to those of s-PET/CT.

Methods ^{18}F-FDG PET/CT of 502 patients, stratified for pre-test cancer risk, were retrospectively analyzed. The thoracic part of wb-PET/CT, considered s-PET/CT, was compared to wb-PET/CT. Clinical and PET/CT variables were investigated for SPN characterization as well as for identification of patients in whom s-PET/CT could be performed. Histopathology or follow-up data were used as a reference.

Results In the study population, 36% had malignant, 35% benign, and 29% indeterminate SPN. ^{18}F-FDG uptake indicative of thoracic and extra-thoracic lesions was detectable in 13% and 3% of the patients. All patients with extra-thoracic metastases (n = 13) had thoracic lymph node involvement and highest ^{18}F-FDG uptake at level of SPN (negative predictive value 100%). Compared to wb-PET/CT, s-PET/CT could save about 2/3 of ^{18}F-FDG dose, radiation exposure or scan-time, without affecting the clinical impact of PET/CT.

Italian Tailored Assessment of Lung Indeterminate Accidental Nodule

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Conclusion Pre-test probability of malignancy can guide the diagnostic strategy of ^{18}FDG-PET/CT in patients with SPN. In subjects with low-intermediate pretest probability s-PET/CT imaging might be planned in advance, while in those at high risk and with thoracic lymph node involvement a wb-PET/CT is necessary.

Keywords Pulmonary nodule · ^{18}F-fluorodeoxyglucose · Segmental-PET/CT · Extra-thoracic lesions

Introduction

The mean prevalence of solitary pulmonary nodule (SPN) is relatively high (13–33%), but with a low prevalence of lung cancer (<2%) [1]. Its characterization represents an important public health issue, since lung cancer is the leading cause of cancer death, despite possibility of cure and a favorable 5-year survival rate after surgical resection at an early stage [2, 3].

Computed tomography (CT) is an excellent diagnostic tool, albeit affected by a suboptimal specificity. Contrast-enhanced CT may improve specificity, but the increasing dosimetry, although significantly reduced with modern technologies, is questionable in a highly benign context [4, 5] and it is not recommended where positron emission tomography (PET)/CT is an available alternative [1]. ^{18}F-fluorodeoxyglucose (FDG) PET/CT has proven to be more effective than CT [6, 7] and is fully integrated into SPN clinical guidelines [1, 8, 9].

The accurate assessment of risk before diagnostic imaging is a crucial issue in medicine and management of patients with SPN relies on likelihood of disease [1, 8, 9]. In patients with low to moderate pre-test probability of malignancy, the American College of Chest Physicians recommends the characterization of SPN (>8 mm in diameter) by PET/CT, whereas staging is reserved when malignancy is highly probable or confirmed [8]. It should be noted that there is a low prevalence of malignancy and an even lower prevalence of metastases at clinical presentation in SPN [1, 10, 11]. Recently, concerns have emerged for rising healthcare costs and the increasing medical exposure to ionizing radiation associated with hybrid imaging [12, 13]. In this regard, the first priority of the 2016–2020 International Commission on Radiological Protection (ICRP) Strategic Plan is to improve radioprotection, i.e. to reduce patient dose while maintaining diagnostic information [14].

FDG-PET/CT procedure guidelines consider limited-area tumor imaging only for some indications, such as follow-up examinations [15] or when critical abnormalities are likely to be localized in a known region (e.g., SPN or probable lung cancer) [16]. However, concerns exist on the possible disadvantage of not staging the entire body [16]. Segmental (s-PET/CT), i.e. limited to a thoracic acquisition, could be a cost-effective approach in SPN [17–19] but the absence of studies leaves several questions unanswered [20]. The aim of this retrospective multicenter study was to compare the results of thoracic s-PET/CT to those of wb-PET/CT in a large cohort of patients with SPN in order to assess: (a) the feasibility of s-PET/CT without a significant loss in clinical information, (b) the possibility to identify patients in whom wb-PET/CT is necessary, and (c) the advantages and disadvantages of s-PET/CT in SPN.

Material and methods

Study approval and data collection

The study protocol was approved by Veneto Institute of Oncology in Padova (Italy) on September 2016 (nr. 0016), in accordance with Italian Institutional Legacy. Thirteen Italian imaging centers experienced in FDG-PET/CT in lung cancer were invited to participate [21]. Each patient signed a written informed consent for the execution of PET/CT and for anonymous publication of disease-related information. All centers provided a list of anonymous cases in expressly created dedicated Excel datasheets. After combining all received datasheets, reports were generated for each variable to identify data inconsistencies. Through regular communication with all sites, resolution of all identified anomalies was achieved before analysis. Finally, the database was built, and the final data set was produced for the current analysis.

Study population

From September 2016 to May 2017, FDG-PET/CT scans of 502 consecutive patients with SPN, performed between January 2013 and December 2014, were retrospectively reviewed and collected. Patients with one or more SPN previously identified by CT images, defined as lung nodule with a size <3 cm, with no associated atelectasis or adenopathy, and sent to PET/CT for the characterization of the nodule/nodules were included. Patients with prior cancer history and those candidates to PET/CT for the staging of lung cancer were excluded. Patients were stratified in low (<5%), intermediate (5–65%) and high (>65%) risk category using the Brock model of pre-test probability of lung malignancy [8, 22]. A further category was derived from the British Thoracic Society (BTS) guidelines [1], which are more recent and extend the low probability up to 10%.

PET/CT imaging

PET/CT images were acquired in all centers by using a standard comparable protocol with integrated 3-D mode PET/CT systems, from the base or top of the skull to mid-thigh (wb-PET/CT) starting 60 min after tracer administration. All patients fasted for at least 6 h prior to imaging, and blood glucose levels were < 180 mg/dL at the time of tracer injection. All patients were instructed to avoid talking, chewing or any muscular activity before acquiring PET/CT scan. Attenuation correction was performed using CT images. CT and PET images were matched and fused into transaxial, coronal, and sagittal images. Two experienced nuclear physicians reviewed PET/CT scan, partially blinded and based on visual analysis to identify the areas of disease. A positive PET scanner was defined in the presence of significant FDG uptake in the SPN. Moreover, intra and extra-thoracic sites were defined in the presence of significant FDG uptake outside the areas of physiological biodistribution.

FDG uptake in SPN was assessed: (1) visually, using a 4-point scoring system (4PS), whereby 1 = absent, 2 = mild, 3 = moderate and 4 = intense [1]; (2) by a semi-quantitative analysis calculating maximum body-weighted standardized uptake value (SUVmax) in SPN and the ratio between SUVmax in SPN and SUV-mean in mediastinal blood pool (SUV-ratio), by isocontour volume of interest in the SPN and mediastinal blood pool [21]. In patients with more than one nodule, only the Brock highest-risk nodule was evaluated.

The transformation of the CT dose-length product (DLP in cm × mGy) and FDG dose (in MBq) in effective dose (ED, in mSv) was made according to ICRP [23].

Standard of reference

Final diagnosis was established by histopathology or imaging data at follow-up. The diagnosis of malignancy was made by: (1) histopathological analysis of surgical specimen or histology obtained by needle biopsy and (2) a significant increase in SPN diameter (≥25%) and/or number of pulmonary nodules at CT studies during follow-up [24]. Nodules were considered benign on histopathology or those that during a follow-up of ≥24 months did not change or were spontaneously resolved. In all other cases, they were defined indeterminate. Incidental findings were defined as foci of unexpected FDG uptake regardless of the presence or absence of tracer avidity in the SPN.

Comparison between wb-PET/CT and s-PET/CT

s-PET/CT was retrospectively defined as the beds of the wb-PET/CT covering the chest from the first costovertebral articulation to the entire costodiaphragmatic sinuses. The ratio between number of beds in s-PET/CT and wb-PET/CT was the basis to estimate the temporal relationship between the two modalities. Based on the time-dose equation, two alternative s-PET/CT methodologies were compared: full FDG dose (*first option*), allowing a time reduction for chest scan only and reduced FDG dose (*second option*), acquiring s-PET/CT at the same scan-time as wb-PET/CT that leaves the thoracic counts unchanged [15].

Statistical analysis

Continuous data are expressed as mean ± SD and categorical data as percentage. A commercial statistical software was used (MedCalc®). Differences between continuous data were assessed using unpaired Student's t test. Categorical data were evaluated by chi-square analysis, Fisher exact test, Mann-Whitney or Wilcoxon test, as appropriate. Receiver operating characteristic curve analysis was used to evaluate the diagnostic performance of variables. Analysis of diagnostic performance was also performed by calculating sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy, with 95% confidence interval (CI). Univariate and multivariate logistic analysis was used to evaluate significant determinants of extra-thoracic metastases. A p value <0.05 was considered statistically significant.

Results

General features of the study population are reported in Table 1. Based on standard of reference, 180 (36%) patients had malignant disease (94% histologically confirmed), 175 (35%) benign disease (34% histologically confirmed) and 147 (29%) indeterminate lung nodules. Patients were in low, intermediate and high category risk in 15%, 77% and 8%, respectively, and in BTS low-risk in 27%. FDG uptake score was 1 in 29%, 2 in 23%, 3 in 12%, and 4 in 36% of SPN. A significant relationship between FDG uptake score and risk category (chi-square 75, $p < 0.0001$) was found.

Clinical disease presentation and prediction of distant metastases

Thoracic and extra-thoracic PET/CT findings of the study population are reported in Table 2. Overall, 436 patients (87%) did not have metastases, 66 (13%) had an FDG uptake suggestive of thoracic metastases (47 lymph node, 12 both lymph node and others, and 7 others) and 13 (3%) had evidence of extra-thoracic metastases (3 both lymph node and others, and 10 only others). All 13 patients with extra-thoracic metastases had a thoracic lymph node involvement. The prevalence of extra-thoracic metastases progressively increased from patients with low risk (0%) to those with intermediate (3%) and high (5%) pre-test risk. Six (1%) of these

Table 1 Demographic data, clinical characteristics, and imaging findings of study population

Characteristic	Value
Age (years)	67±12
Male gender	300 (60)
Blood glucose levels (mg/dL)	101±19
Mean population Brock pre-test risk (%)	29±22
Lung nodule diameter (mm)	16.3±6.7
Patients with >1 pulmonary nodule	47 (9)
FDG score 1	
Low risk	47 (62)
Intermediate risk	97 (25)
High risk	3 (8)
FDG score 2	
Low risk	19 (25)
Intermediate risk	89 (23)
High risk	4 (11)
FDG score 3	
Low risk	5 (7)
Intermediate risk	50 (13)
High risk	1 (3)
FDG score 4	
Low risk	4 (6)
Intermediate risk	151 (39)
High risk	32 (79)

Values are mean ± standard deviation or number (percentage) of patients

latter patients showed incidental PET findings (rectosigmoid, cervical lymph nodes, sub-diaphragmatic lymph nodes and prostate gland). Patients with extra-thoracic lesions showed higher nodule SUVmax and SUV-ratio, higher 4PS, higher risk probability, larger nodule diameter and higher prevalence of thoracic lesions (Table 3). At univariate analysis, several variables were significantly associated with the presence of extra-thoracic lesions (Table 4). When variables significant at univariate analysis were entered at multivariate logistic analysis, only the presence of thoracic lymph node involvement (odd ratio [OR] 8.9; 95% CI 3.5–22.6; $p < 0.0001$) and nodule SUV-ratio (OR 1.3; 95% C.I. 1.0–1.6; $p = 0.04$) remained significant. The performance obtained combining these two variables was better than a model based on pre-test Brock probability (area under curve 0.94 ± 0.01 vs. 0.73 ± 0.06, $p < 0.0005$). Sensitivity, specificity, accuracy, NPV and PPV of this combined model were 100%, 91%, 91%, 100%, and 24%, respectively.

Table 3 Clinical and imaging variables in patients with and without extra thoracic lesions

Variable	With extra-thoracic lesions	Without extra-thoracic lesions	*p* value
Age (years)	68±10	67±12	0.86
Male gender	77	59	0.26
Brock pre-test risk (%)	46±18	29±22	0.006
SPN diameter (mm)	29.1±25.6	16.1±6.7	<0.0001
SUVmax	10.7±3.8	4.5±4.9	<0.0001
SUV-ratio	3.8±2.2	1.7±1.9	0.0003
FDG Score			<0.0001
1	0	31	
2	0	24	
3	0	11	
4	100	34	
Thoracic lesions	100	12	<0.0001
Emphysema	26	23	0.92

Values are mean ± standard deviation or percentage of patients

Comparison between wb-PET/CT and s-PET/CT

The comparison between the two modalities is shown in Table 5. In wb-PET/CT, the external (CT) and internal (PET) radiation components were calculated as 64% and 36% of the total, respectively. The ratio between numbers of beds on s-PET/CT and wb-PET/CT was 0.35. With the first option (i.e. full FDG dose), s-PET/CT compared to wb-PET/CT could save more than 10 min per scan (5.5 vs. 15.8 min, that is >65% of wb-PET/CT scan-time) and 42% of radiation exposure (7.7 vs. 13.2 mSv, due to decreased external

Table 2 Thoracic and extra-thoracic PET/CT findings in study population

Type		Extra-thoracic				
Thoracic		None	LN	Others	LN + others	Total
	None	436 (86.8)	0 (0)	0 (0)	0 (0)	436 (86.8)
	LN	41 (8.2)	0 (0)	4 (0.8)	2 (0.4)	47 (9.4)
	Others	7 (1.4)	0 (0)	0 (0)	0 (0)	7 (1.4)
	LN + others	5 (1)	0 (0)	6 (1.2)	1 (0.2)	12 (2.4)
Total		489 (97.4)	0 (0)	10 (2.0)	3 (0.6)	502 (100)

Values are number (percentage) of patients

LN lymph node

Table 4 Univariate logistic analysis for prediction of extra thoracic lesions

Variable	Odds ratio	95% Confidence interval	*p* value
Age	1.004	0.958–1.053	0.47
Gender	0.437	0.119–1.609	0.18
Brock pre-test risk	1.036	1.009–1.063	0.007
Diameter	1.133	1.039–1.235	0.0001
SUVmax	1.159	1.075–1.249	0.0003
SUV-ratio	1.340	1.125–1.595	0.003
FDG 4PS	3.246	1.637–6.435	<0.0001
Thoracic lesions	11.575	4.859–27.571	<0.0001
Emphysema	0.864	0.234–3.190	0.82
Family history	0.732	0.254–2.108	0.52
Nodule spiculation	0.186	0.040–0.846	0.01
Nodule type	0.916	0.403–2.078	0.83

exposure). With the second option (i.e. low FDG dose), s-PET/CT would need a dose of 101.0 MBq (2.7 mCi), which is 35% of the full dose of 288.6 MBq (7.8 mCi) to obtain the same chest counts and the same scan-time of wb-PET/CT. This option would decrease PET ED from 4.7 to 1.6 mSv (66%) and PET/CT ED from 13.2 to 4.6 mSv (65%).

Discussion

The main finding of this study is that pre-test probability of malignancy affects the extent of disease at the onset of SPN and can guide the diagnostic strategy of PET/CT. In the present study only 13 out of 502 patients (3%) showed extra-thoracic metastases and had a significantly higher Brock pre-test risk (29% vs. 46%). In patients with low-intermediate pretest probability of malignancy s-PET/CT imaging might be planned in advance, whereas in high-risk patients wb-PET/CT should be directly performed. Therefore, a key point is to identify a priori patients who may have extra-thoracic lesions. A possible role of limited region FDG-PET/CT in screening of patients at high risk of lung cancer has been suggested [25]. In our study, all patients with extra-thoracic metastases had high SPN FDG uptake as well as thoracic lymph node involvement, with NPV of 100%. These data are in agreement with the International Association for the Study of Lung Cancer staging database in which only 0.1% out of 10,410 patients in N0 had distant metastases [26]. Based on the 100% NPV, in absence of a chest lymph node involvement at s-PET/CT, wb-PET/CT can be avoided in 88% of patients, without failing to detect extra-thoracic lesions. On the other hand, in the remaining 12%, wb-PET/CT detected distant metastases in only 22% of patients.

Table 5 Comparison between s-PET/CT and wb-PET/CT

Variable	s-PET/CT	wb-PET/CT
PET beds (*n*)	2.3±0.6	6.6±0.9
PET beds time (min)	2.4±0.5	2.4±0.5
FDG dose MBq[a]	289±76	289±76
FDG dose MBq[b]	101	289±76
PET/CT scan time (min)[a]	5.5	15.8
PET/CT scan time (min)[b]	15.8	15.8
DLP (cm × mGy)	198	566±472
External ED (mSv)	3.0	8.5
Internal ED (mSv)[a]	4.7	4.7
PET/CT (mSv)[a]	7.7	13.2
Internal ED (mSv)[b]	1.6	4.7
PET/CT ED (mSv)[b]	4.6	13.2

Values are mean ± standard deviation, except for derivative parameters

ED effective dose, *DLP* dose length product

[a] *First option* full FDG dose

[b] *Second option* low FDG dose

A segmental strategy would reduce either radiation dose and administered tracer activity. However, calculation of radiation risk is imprecise and represents extrapolated estimated risk from epidemiologic data to the clinical setting. There is an ongoing debate on the incremental risk to subjects exposed to low diagnostic doses [27, 28]. Given these uncertainties, any ability to reduce radiation without sacrificing diagnostic accuracy would be a positive advancement and consistent with the principle of ALARA. In our study, the reduced exposure, up to 8.6 mSv (65%), as well as the reduced radiosensitive extra-thoracic targets due to segmental CT, did not prevent reaching the clinical goal.

The rapidly growing cost of innovative imaging imposes a careful evaluation of its cost-effectiveness [12, 29]. Adopting a segmental strategy could favorably affect productivity. Administering a "full" FDG dose (first option), s-PET/CT could save about 10 min/study, i.e. 50% of a wb scan, doubling a laboratory's workflow. Alternatively, the second option to reduce FDG dose may lead to a significant decrease in the tracer cost in addition to the dosimetry. Although the exact estimate of the economic savings is out of the scope of this study, a regional strategy may allow a significant improvement in productivity and health care costs.

The segmental approach has some clinical and practical drawbacks [16, 20]. The first is the inability to complete SPN staging. However, full staging is not always necessary according to clinical SPN guidelines [8] and its requirement should be verified in the individual clinical setting. Although incidental findings on wb-PET/CT may represent a different pathology, the risks of over-diagnosis and over-treatment should be considered [10, 30]. Some disadvantages in terms of practicability of s-PET/CT are due to "on-the-fly" decisions to complete the study with a subsequent wb-PET/CT acquisition [20]. With modern equipment this approach would

require only a few minutes. Also, the choice of the tracer dose just before imaging may produce organizational problems.

Study limitations

The segmental analysis, retrospectively extrapolated from the wb-PET/CT, though with a very strict criterion, is virtual and organizational and logistical problems have not been verified. Failure to homogeneously calibrate a center's imaging systems or centralize the imaging studies could be considered a limitation on the basis that some data (e.g. SUVmax) may be affected by technical and organizational variables. To reduce this effect, we also used SUV corrected for BP activity (SUV-ratio) to favor a relative internal standardization process. Nevertheless, a perspective study is mandatory to support the clinical application of this new protocol.

Conclusions

Pre-test probability of malignancy can guide the diagnostic strategy of ^{18}FDG-PET/CT in patients with SPN. In subjects with low-intermediate pretest probability s-PET/CT might be planned in advance, while in those at high risk with thoracic lymph node involvement wb-PET/CT is necessary. A segmental strategy can reduce radiation exposure, scan-time, and might allow individually targeted protocols other than further development of PET indications.

Acknowledgements We thank Christina A. Drace, Istituto Oncologico Veneto-IRCCS, Padova, Italia, for assistance in writing this manuscript.

Compliance with ethical standards

Conflict of interest None.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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