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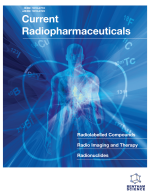
RESEARCH ARTICLE

The Multicenter Italian Trial Assesses the Performance of FDG-PET/CT Related to Pre-Test Cancer Risk in Patients with Solitary Pulmonary Nodules and Introduces a Segmental Thoracic Diagnostic Strategy



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Abstract: ***Purpose:*** The Italian Tailored Assessment of Lung Indeterminate Accidental Nodule (ITALIAN) trial is a trial drawn to determine the performance of 18F-FDG-PET/CT in patients with solitary pulmonary nodules (SPN), stratified for a different kind of risk. An additional end-point was to compare the diagnostic information and estimated dosimetry, provided by a segmental PET/CT (s-PET/CT) acquisition instead of a whole body PET/CT (wb-PET/CT), in order to evaluate if segmental thoracic PET/CT can be used in patients with SPN.

Methods: 18F-FDG PET/CT of 502 patients, stratified for pre-test cancer risk, was retrospectively analyzed. FDG uptake in SPN was assessed by a 4-point scoring (4PS) system and a semiquantitative analysis using the ratio between SUVmax in SPN and SUVmean in mediastinal blood pool (BP), and between SUVmax in SPN and SUVmean in the liver (L). Histopathology and/or follow-up data were used as a standard of reference. Data obtained on the thoracic part of wb-PET/CT, defined as s - PET/CT, were compared with those deriving from wb-PET/CT.

Results: SPNs were malignant in 180 patients (36%), benign in 175 (35%), and indeterminate in 147 (29%). The 355 patients diagnosed with a definitive SPN nature (malignant or benign) were considered for the analysis of PET performance. Sensitivity, specificity, positive (PPV) and negative (NPV) predictive values, and accuracy were 85.6%, 85.7%, 86%, 85.2%, and 85.6%, respectively. Sensitivity and PPV were higher in intermediate and high-risk patients.

18F-FDG uptake indicative of thoracic and extra-thoracic lesions was detectable in 13% and 3% of the patients. Compared to wb-PET/CT, s-PET/CT could save about 2/3 of 18F-FDG dose, radiation exposure or scan-time, without affecting the clinical impact of PET/CT.

Conclusion: In patients with SPN, the pre-test likelihood of malignancy stratification allows to better define PET clinical setting and its diagnostic power. In subjects with low-intermediate pre-test likelihood of malignancy, s-PET/CT might be planned in advance. The adoption of this segmental strategy could reduce radiation exposure, scan-time, and might allow individually targeted protocols.

Keywords: Lung cancer, single pulmonary nodules, likelihood, FDG, PET/CT.

ARTICLE HISTORY

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1. INTRODUCTION

A solitary pulmonary nodule (SPN), defined as an intraparenchymal lung lesion of less than 3 cm in diameter, without associated atelectasis or adenopathy [1], is one of the most frequent imaging incidental findings. The mean prevalence of SPN is high (13-33%), though with a low prevalence of lung cancer (<2%) [2]. Therefore, its characterization represents an important public health issue, since lung cancer is the leading cause of cancer death. Prognosis of malignant pulmonary lesions is strictly related to a tumor's dimension at diagnosis [3, 4], with a favourable 5-year survival rate, after surgical resection at an early stage [4, 5]. 18F-FDG PET/CT is more effective than CT [2, 6] and is already included in the guidelines for the management of SPN [2, 4, 7]. These recommend to characterize SPN in low to moderate pre-test likelihood of lung malignancy, reserving staging when malignancy is highly probable or confirmed [6]. Although pre-test risk assessment is the main component of

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clinical evaluation and there is extensive literature on PET in SPN, no study reported the role and performance of PET/CT related to pre-test cancer risk stratification. Moreover, there are only a few data on disease presentation in patients with SPN. Both the low prevalence of malignancy and metastases at SPN presentation [2, 8, 9] could outline alternative cost-effective PET/CT diagnostic strategies [10-12]. Finally, many published papers have a small sample size and employed old technologies [2, 13-15], thus altering the final diagnosis and staging [16]. Within this context, the Italian Tailored Assessment of Lung Indeterminate Accidental Nodule (ITALIAN) trial was conceived [17-19]. ITALIAN is a retrospective trial designed to determine the performance of 18F-FDG-PET/CT, by visual and semiquantitative data analysis, in patients with stratified risk, according to the likelihood of pulmonary malignancy [19]. As additional endpoint, ITALIAN trial aims to compare the diagnostic information and estimated dosimetry provided by a segmental PET/ CT (s-PET/CT) acquisition instead of a whole body (wb)-PET/CT, in order to evaluate if thoracic s-PET/CT is feasible in patients with an SPN. In this paper, the main contents of the ITALIAN multicentric experience are reported.

2. MATERIALS AND METHODS

The materials and methods have been previously reported in a paper published by Evangelista *et al*. [17].

3. RESULTS

180 (36%) patients had a malignant disease (94% histologically confirmed), 175 (35%) had a benign disease (34% histologically confirmed) and 147 (29%) had indeterminate lung nodules. Patients were in low, intermediate and high category risk in 15%, 77% and 8%, respectively, and in BTS low-risk category 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 the FDG uptake score and risk category was found.

355 out of 502 patients with malignant or benign SPN were considered for the analysis of PET performance. Sensitivity, specificity, positive (PPV) and negative (NPV) predictive values, and accuracy were 85.6%, 85.7%, 86%, 85.2%, and 85.6% respectively, for an FDG uptake ≥ 2. Sensitivity and PPV were higher in intermediate and high-risk patients, while specificity and NPV were higher in the low-risk group. The best cut-offs for distinguishing between benign and malignant SPN were 1.56 (sensitivity 81% and specificity 87%) and 1.12 (sensitivity 81% and specificity 86%) for SUVmaxSPN /SUVmeanBP and SUVmaxSPN /SUVmeanL, respectively. In intermediate and high-risk patients, including the SUVmaxSPN /SUVmeanBP, the specificity shifted from 85% and 50% to 100%.

436 out of 502 patients (87%) did not have metastases, 66 (13%) had an FDG uptake suggestive of thoracic metastases and 13 (3%) had evidence of extra-thoracic metastases. These latter patients 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. Patients with extra-thoracic lesions showed higher nodule SUVmax and SUVratio, higher 4PS, higher risk probability, larger nodule diameter and higher prevalence of thoracic lesions.

With respect to wb-PET/CT, the external (CT) and internal (PET) radiation components for s-PET/CT 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 CT external 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 exposure from 4.7 to 1.6 mSv (66%) and CT exposure from 13.2 to 4.6 mSv (65%).

4. DISCUSSION

The risk before imaging has an important position in lung cancer diagnosis [18]. ITALIAN is the first trial that has considered the performance of FDG-PET/CT for SPN in accordance with the pre-test likelihood of malignancy, as also set out in the international guidelines [2, 6, 7]. Moreover, the low frequency of extra-thoracic metastases correlated with pre-test cancer risk may allow to test a segmental diagnostic strategy as an alternative to wb-PET/CT in a clinically relevant public health issue. From the results obtained in 355 out of 502 patients with SPN, excluding indeterminate nodules, it emerges that, based on visual/categorical analysis, the performance of FDG-PET/CT, in terms of sensitivity, is high in all patients, but particularly in those with an intermediate-high likelihood of malignancy. The inclusion of semiquantitative data, in terms of SUV ratios, can significantly increase the specificity of the imaging modality in this setting of patients.

The performance of FDG- PET/CT for SPN has been extensively evaluated in the literature [19]. However, no data are available on the correlation between diagnostic accuracy and the likelihood of malignancy, although clinical guidelines are based on the risk stratification. In our study, we found that PET/CT had a sensitivity, specificity, PPV, NPV, and accuracy of 85.6%, 85.7%, 86%, 85.2%, and 85.6% in 355 patients with SPN. However, sensitivity reached a value > 90% in patients with an intermediate likelihood of lung malignancy (5%-65%). Furthermore, the inclusion of semiquantitative analysis as SUV ratios, particularly effective in high-risk patients, resulted in a sensitivity and specificity of 91.3% and 100%, respectively.

In many guidelines, PET/CT is mainly recommended in patients with an intermediate risk of disease. By considering SUVratio cut-offs based on the likelihood of lung malignancy, we found that a sensitivity > 80% and specificity ≥ 75% were present in each risk category. This latter finding underlines the clinical advantage of PET/CT in all patients with SPN, from a low to high probability of malignancy.

The present results suggest that in high-risk patients, the incremental information obtained with the semiquantitative analysis of the metabolic status, specifically by the ratio be-

tween SUVmaxSPN and SUVmeanBP, in indeterminate SPNs may significantly reduce the false positive rate associated with the visual examination alone. This latter concept was also reported in the recent BTS Guidelines for the investigation and management of pulmonary nodules, where the authors stated that a qualitative assessment to define FDG uptake should be advocated by determining the mediastinal BP as a baseline threshold [2].

One of the main findings of the ITALIAN trial is that the pre-test probability of malignancy affects the extent of disease at the first diagnosis of SPN and can guide the diagnostic strategy of PET/CT. In 112 patients with SPN, Tasdemir *et al*. [9] reported a 5.4% incidence of body metastases. In the present study, only 13 out of 502 patients (3%) presented extra-thoracic metastases, showing a significantly higher Brock pre-test risk (29% *vs.* 46%). These data support the ACCP recommendations to characterize, and not to stage, SPN if the pretest probability of malignancy is from low to moderate.

Therefore, in low-risk categories, in agreement with the ALARA principle, s-PET/CT imaging might be planned in advance, whereas in high-risk patients, wb-PET/CT should be directly performed. In this setting, the key point is to identify priori patients who may have extra-thoracic lesions, since only in these subjects, a wb-PET/CT is necessary.

Moreover, in the 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.

This study firstly demonstrates the potential of s -PET/TC to reduce the effective dose and scan duration without affecting the clinical impact. This is in line with: 1) the growing demand for better use of health care resources; 2) the basic principle of radiation protection and the provisions of ICRP, that state the need to reduce patient' s dose, while maintaining full diagnostic information [20]; 3) the personalization of medical care with the possibility to select, for each patient, different options, allowing a more tailored diagnostic procedure. In our study, the reduced whole exposure, up to 8.6 mSv (65%), associated with a segmental thoracic CT, did not create problems in reaching the clinical goal. Moreover, the rapidly growing cost of innovative imaging procedures imposes a careful evaluation of its cost-effectiveness [21, 22]. Adopting a segmental strategy could favorably affect productivity. Administering a "full" FDG dose, s -PET/CT could save about 10 min/study, *i.e*., 50% of a wb-scan, doubling the laboratory's workflow. Alternatively, a second option based on the reduction of the FDG dose may lead to a significant decrease in the tracer' s cost, in addition to dosimetric advantages. Thus, a segmental strategy may allow an improvement in productivity and health care costs. The segmental approach has some clinical and practical drawbacks, also with respect to the procedural guidelines [23-25]. The first is the inability to complete SPN staging. However, full staging is not always necessary, according to clinical SPN guidelines [6], 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 also be considered [8, 26]. Furthermore, 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 [8]; nevertheless, using modern performing equipment, this approach would require only a few more minutes. Segmental flexibility in acquiring PET/CT studies, based on a procedure suitable for the patient and not vice versa, is more consistent with the increasing personalization requested by healthcare. This strategy might determine a wider application of PET indications in diseases in which it is now considered inappropriate, because of an unfavorable cost-effectiveness. The result could potentially change many diagnostic imaging flow charts, not only in oncology.

4.1. Limitations

Retrospective data and the utilization of different PET scanners (Table **1**).

Table 1. Technical characteristics of PET/CT scanner.

S. No.	Center, City	Type of PET/CT Scanner	Time between FDG Administration and Start of Acquisition	Data for Imaging Reconstruction	PET Scanner Accreditation
1	S. G. Moscati Hospital, Avellino	Ge Discovery 710 64 slices	60±10 min	TOF	No
2	Veneto Institute of Oncology, Padua	Biograph 16S updated with HD software, Siemens	60±10 min	PSF	No
3	University of Naples Federico II, Naples	Discovery LS scanner GE Healthcare	60±10 min	PSF	No
4	Hospital of Bolzano, Bolzano	Philips Gemini TF 16	60±10 min	TOF	No
5	Rionero in Vulture Hospital, Rionero in Vulture, Potenza	GE VCT 64 Slices	60±8 min	PSF	Ge-68 phantom-based FDG-PET site qualification (FIL)

Table (1) contd…

S. No.	Center, City	Type of PET/CT Scanner	Time between FDG Administration and Start of Acquisition	Data for Imaging Reconstruction	PET Scanner Accreditation
6	Università Cattolica del S. Cuore, Rome	Biograph, Siemens	60±10 min	TOF	No
7	Humanitas Hospital, Rozzano, Milan	1) Biograph 6, Siemens 2) Discovery ST 690, GE	60±10 min	Measured	EARL accreditation for both the scanners
8	Azienda Ospedaliera Universitaria Integrata di Verona, Verona	GEMINI TF BIG BORE software version 3.6, Philips	60±10 min	TOF	No
9	Medicina Futura IOS, Acerra, Naples	Siemens biograph TruePoint 6 slice	60±10 min	PSF	No
10	SDN Foundation, Naples	1) GE Discovery 710 2) Philips Gemini TF 64	60±10 min	PSF, TOF TOF	No
11	San Gerardo Hospital, University of Milano Bicocca, Monza	1) Discovery 600, GE Healthcare 2) Discovery IQ 5 Rings	60±10 min	PSF	EARL accreditation
12	Policlinico S. Orsola Malpighi, University of Bologna, Bologna	E Discovery STE PET/CT system / GE Discovery D710 PET/CT System	60±5 min	PSF, TOF	No
13	University Tor Vergata, Roma	GE Discovery VCT	60±5 min	PFS	No

Center, City PET/CT scanner Imaging reconstruction Ospedale S.G. Moscati, Avellino Discovery 710 64 slices, GE Istituto Oncologico Veneto IOV - IRCCS, Padova Biograph 16, Siemens Università di Napoli Federico II, Napoli Discovery LS, GE Ospedale di Bolzano, Bolzano Gemini TF 16, Philips Centro di Riferimento per il Cancro della Basilicata-IRCCS, Rionero in Vulture (Potenza) VCT 64, GE Università Cattolica del Sacro Cuore, Roma Biograph, Siemens Ospedale Humanitas, Milano Biograph 6, Siemens and Discovery ST 690, GE Azienda Ospedaliera Universitaria di Verona, Verona Gemini TF 3.6, Philips Medicina Futura IOS, Acerra (Napoli) Biograph, Siemens SDN-IRCCS, Napoli Discovery 710, GE and Gemini TF 64, Philips Università di Milano Bicocca, Milano Discovery 600 and Discovery IQ 5 Rings, GE Università degli Studi di Bologna, Bologna Discovery 710, GE Università Tor Vergata, Roma Discovery VCT, GE TOF PSF PSF TOF PSF TOF Measured TOF PSF PSF, TOF PSF PSF, TOF PSF TOF time of flight, PSF point spread function

CONCLUSION

The ITALIAN trial fills the existing gap between clinical guidelines, articulated in cancer risk subsets, and previous PET studies. The pre-test likelihood of malignancy stratification allows to better define PET clinical setting and its diagnostic power. The 4-point scale assessment in evaluating FDG-PET/CT has an acceptable accuracy in patients with SPN. Moreover, especially in patients with an intermediate or high risk of malignancy, the diagnostic performance may further significantly improve when considering semiquantitative data, expressed in terms of SUV ratios (particularly as SUVmaxSPN/SUVmeanBP ratio). In addition, the pre-test probability of malignancy can guide the diagnostic strategy of 18FDG-PET/CT in patients with SPN. In subjects with low-intermediate pre-test likelihood of malignancy, s-PET/CT might be planned in advance; conversely, in those at high risk or with a thoracic lymph node involvement at s - PET/CT, wb-PET/CT is necessary. The adoption of this segmental strategy could reduce radiation exposure, scan-time, and might allow individually targeted protocols.

Furthermore, the achievement of a more favourable cost-effectiveness could create conditions for a wider application of PET/CT also for indications actually not considered in the clinical practice either in oncology or in non-oncologic fields.

LIST OF ABBREVIATIONS

ITALIAN = Italian Tailored Assessment of Lung Indeterminate Accidental Nodule

SPN = Solitary Pulmonary Nodules

PET/CT = Positron Emission Tomography/Computed Tomography

18F-FDG = Fluorodeoxyglucose

SUV = Standardized Uptake Value

PPV = Positive Predictive Value

NPV = Negative Predictive Value

MBq = Megabequerel

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Ethics Committee of Istituto Oncologico Veneto IOV - IRCCS, Padua, Italy (protocol number 16/2016).

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All human procedures were followed in accordance with the ethical standards

of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013 (http://ethics.iit.edu/ecodes/node/3931).

CONSENT FOR PUBLICATION

Written informed consent was obtained from all patients prior to the publication of the study.

AVAILABILITY OF DATA AND MATERIALS

All data generated or analysed during this study are included in this published article.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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