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Abstract: Background: The Italian Tailored Assessment of Lung Indeterminate Accidental Nodule (ITALIAN) is a retrospective, multicenter trial designed to compare the diagnostic information provided by segmental positron emission tomography (PET)/computed tomography (CT) (s-PET/CT) with those of whole body (wb)-PET/CT in patients with single pulmonary nodules (SPN). This report describes the details and implications of the ITALIAN trial design.

Methods and Results: Between September 2016 and May 2017, 502 consecutive patients (302 men, mean age 67±12 years) with SPN undergoing ¹⁸F-fluorodeoxyglucose (FDG) PET/CT were enrolled. PET/CT images will be visually and semiquantitatively evaluated. For visual analysis, a 4-point scoring system (1=absent; 2=mild; 3=moderate and 4=intense) will be used; for semiquantitative analysis, maximum standardized uptake value (SUV) in the SPN and mean SUV in the mediastinal blood pool and in the liver will be computed.

Conclusion: The results of this trial might help to define the role of s-PET/CT in patients with SPN. This trial will also evaluate the impact on radiobiology and costs subsequent the introduction of this alternative imaging acquisition modality.

Keywords: Single pulmonary nodule, diagnostic performance, FDG PET/CT, radiobiology, cost-analysis, SUV, SPN.

1. INTRODUCTION

The characterization of a solitary pulmonary nodule (SPN) incidentally detected represents a major public health issue. The American College of Chest Physicians (ACCP) recommends the use of thoracic computed tomography (CT) scan as one of the main modalities when screening for lung cancer in high-risk populations [1]. However, the management of the SPN varies in accordance with nodule characteristics (i.e. size, doubling time, morphology and density) and the risk of populations [2, 3]. ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography (PET) scan is recommended only for nodules that are >8 mm in diameter because the sensitivity decreases for the smaller pulmonary nodules. Nodules <1 cm and ground glass nodules have a high rate of false negative interpretation (2). Furthermore, PET scan is indicated in patients with an “intermediate” range of risk (5%-60%) [3]. This likelihood can be assessed qualitatively or using algorithms [4]. The ACCP categorizes patients into 3 groups: very low likelihood (<5%); low to moderate likelihood (5-65%); and high likelihood (>65%) [5]. The utility of whole-body FDG PET/CT in intermediate category of patients and in those with a high likelihood risk of malignancy is the ability to detect the presence of extra-thoracic disease, otherwise missed by chest CT. However, in a recent paper, it has been demonstrated that the incidence of extra-thoracic metastases in SPN is very low, ranging from 0.9% in the brain to 2.7% in the abdomen [6]. Recently, the opportunity to introduce an alternative PET/CT acquisition protocol for the definition of SPN has been discussed [7, 8].

PET/CT offers semiquantitative values that can be considered as parameters able to predict patient survival. The main parameter used in clinical practice to estimate FDG uptake is the maximum standardized uptake value, SUVmax (defined as the value of the voxel showing the highest uptake) [9]. Since SUVmax is underestimated for small nodules owing to the partial-volume effect, and for nodules located in the lower lungs due to respiratory motion, some authors recommend the use of relative analysis by comparing the SUV for the SPN to mediastinal pool or liver background noise [10].

It is within this context that the Italian Tailored Assessment of Lung Indeterminate Accidental Nodule (ITALIAN) trial was conceived. ITALIAN is a retrospective, multicenter trial designed to 1) compare the diagnostic information provided by segmental PET/CT (s-PET/CT) with whole body (wb)-PET/CT; 2) estimate dosimetry and cost impact of segmental imaging; 3) determine the performance of FDG...
PET/CT in discriminating between benign and malignant nodules, by considering categorical data and continuous data analysis in all patients and in accordance with the likelihood of malignancy; 4) evaluate if continuous data were correlated with intra- and extra-thoracic pathological FDG uptake; and 5) assess if clinical, demographical or morphological variables are correlated with the presence of pathological FDG uptake (intra- and extra-thoracic) other than the lung nodule. The purpose of this report is to discuss the details and implications of the ITALIAN trial design.

2. METHODS

The organizational structure of the ITALIAN trial, including principal investigators and co-investigators at participating centers and by-center recruitment, is contained in the Appendix. The study population will include consecutive patients with one or more SPN previously identified by CT images, defined as lung nodule with a size ≤3 cm who were send to PET/CT for the characterization of the nodule/nodules. Patients with prior cancer history and those candidates to PET/CT for the staging of lung cancer will be excluded. For each patient, at the time of PET/CT study and/or during follow-up, the following variables will be collected: demographical data (age and gender), risk factors (smoking history, familiarity, emphysema), pre and post-test probability of malignancy (Brock and Herder model, respectively), CT parameters (morphological characteristics of the lung nodule, such as size, solidity, margins and site), PET/CT acquisition data (bed number for the entire whole-body and for the thorax, glycaemia, FDG dose and dosimetric parameters), PET/CT interpretation data (FDG uptake) and histopathological and/or follow-up data. For the retrospective nature of the study, the approval by ethical local committee has already been obtained from one out of all involved Institutions (IOV-IRCCS; September 2016, approval number 0016).

2.1. Study Protocol

**PET/CT imaging.** PET/CT images were acquired in all centers, by using a standard comparable protocol. 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. To minimize FDG uptake in skeletal muscles, all patients were instructed to avoid talking, chewing or any muscular activity before acquiring PET/CT scan. PET/CT studies were acquired with integrated PET/CT systems, according to different injected dose, PET/CT scanner and image analysis method. PET data of the whole-body tracer distribution were then acquired in 3-D mode starting 60 minutes after the FDG administration. Attenuation correction was performed using CT images.

**Image acquisition and interpretation.** CT and PET images were matched and fused into transaxial, coronal, and sagittal images. Two experienced nuclear medicine physicians will review PET/CT scan, partially blinded and based on visual analysis to identify the areas of disease. A positive PET scanner will be defined in the presence of: 1) significant FDG uptake in the SPN and 2) significant FDG uptake outside the areas of physiological biodistribution (intra and extra-thoracic sites), later confirmed by co-registered CT ab- normalities. Conversely, the absence of FDG uptake in the lung nodule and in the other sites will be used for the definition of a negative scan. Moreover, FDG uptake in SPN will be visually assessed by: 1) a 4-point scoring system (1 = absent; 2 = mild; 3 = moderate and 4 = intense) and 2) a semiquantitative analysis in terms of SUVmean in the SPN and mean SUV (SUVmean) in the mediastinal blood pool and in the liver. For the evaluation of SUVmean, an isocountour volume of interest (VOI) will be drawn in the SPN. For the SUVmean calculation, VOI will be drawn in mediastinal blood pool (2.0 cm² VOI within the emergency of big vessels) and in the liver (3.0 cm² VOI within right lobe). The ratios between SUVmax of SPN and SUVmean of mediastinal blood pool and liver will be also calculated.

2.2. Likelihood of Malignancy

For the purpose of analyzing patients in different risk subsets, the solitary pulmonary nodule malignancy risk will be calculated by using the Brock University cancer prediction equation [11] (as pre-PET probability of malignancy) and the Herder Solitary Pulmonary Nodule Malignancy Risk Calculator [4] (as a post-PET probability of malignancy). The Brock model estimates the probability that a lung nodule described above will be diagnosed as cancer within a two to four year follow-up period. It will be analyzed as aggregate descriptors of proven prognostic importance of the following patient data: age, gender, family history of lung cancer, presence of emphysema, nodule size, nodule type, nodule in the upper lung, nodule count and speculation. The post-PET likelihood of malignancy (Herder model) will be obtained by considering the following characteristics: age, history of smoking, extrathoracic cancer, diameter of the lung nodule, speculated edge, upper lobe and FDG uptake. According to the pre-PET and post-PET likelihood of single pulmonary nodule malignancy, patients will be classified into low-likelihood (<5%), intermediate-likelihood (5%–65%), and high-likelihood (>65%) subsets [5].

2.3. Standard of Reference

Final diagnosis will be established by histopathology and/or by other imaging data at follow-up. The diagnosis of malignant lung lesions will be made in the following situations: 1) histopathological analysis of surgical specimen or histology obtained by needle biopsy was positive for a primary cancer; and 2) an increase in diameter >2 mm at imaging studies (i.e. CT or further FDG PET/CT) during follow-up. The nodules that will not change during the follow-up or spontaneously resolved without employing therapy will be considered benign lesions.

2.4. Radiobiological Analysis

The PET/CT radiation dose depends on several issues, such as dose of the injected radiotracer, X-ray energy and the extension of CT scanned area. A reduction of both FDG administered dose and X-ray exposure may have important implications with respect to the basic pillars of radiation protection (ALARA criteria): radiation doses should be kept as low as reasonably achievable. The mean effective dose by s-PET/CT will be compared to that by wb-PET/CT. The reduction in cancer risk will be assessed on the basis of Biological Effects of Ionizing Radiation Phase II report [12].
2.5. Cost Analysis

The cost analysis will be performed by applying a cost-differential analysis. Differential cost will be computed as the difference in total costs between s-PET/CT and wb-PET/CT. All potential variables relative to the costs will be considered (i.e. FDG dose, acquisition time, time recovery and others). When the change in costs will occur due to change in the activity from one level to another, it will result in incremental [i.e., increase in costs] or decremental [i.e., decrease in costs] cost.

2.6. Statistical Analysis

For the purpose of the ITALIAN trial, different statistical analyses will be used: 1) descriptive analyses; 2) contingency tables, t-student test and non-parametric analysis for the comparison between categorical and continuous variables; 3) analysis of diagnostic performance (sensitivity, specificity, positive and negative predictive values and accuracy, with 95% confidence interval) for the evaluation of PET/CT in discriminating between benign and malignant nodules, both considering visual and semiquantitative analysis; 4) ROC analysis for the identification of the cut-off value of semiquantitative analysis, able to determine the benign or malignant behavior of the nodule and to predict the presence of intra and extra-thoracic FDG uptake; and 5) logistic regression analysis for the identification of the independent predictors of extra-thoracic FDG uptake in patients with SPN.

2.7. Sample Size

Sample size and power calculation were performed using G*Power software [13]. Power was computed under the hypothesis that the extra-thoracic disease had a 2% incidence in the population and a 5% incidence in our sample. A priori, the alpha level was set at 0.05 and the power level at 80%, corresponding to a probability of type II error of 20%. With these criteria and with an estimated effect size at least of 0.10, the calculated sample size is 200 patients. Since we already enrolled 500 participants, the same power calculation was performed a posteriori. We always obtained a power >0.80, for simple and multivariate logistic models. It means that, under standard inferential conditions, the analysis performed by the present sample will be able to detect an effect if it shows an effect size at least of 0.10. We will also report the effect sizes obtained for all the analyses.

3. STATUS OF STUDY

From September 2016 to May 2017, a total of 502 patients were recruited at 13 sites. The demographic characteristics, clinical data, and preliminary PET results of the patient population are reported in Table 1. The core laboratory is performing the statistical analysis of data.

Table 1. Characteristic of patients enrolled in trial (n = 502).

<table>
<thead>
<tr>
<th></th>
<th>67 ± 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td></td>
</tr>
<tr>
<td>History of smoking</td>
<td>249 (50)</td>
</tr>
<tr>
<td>Familiarity history of lung cancer</td>
<td>47 (9)</td>
</tr>
<tr>
<td>Emphysema</td>
<td>106 (21)</td>
</tr>
<tr>
<td>Pre-test probability of malignancy</td>
<td>29 ± 22</td>
</tr>
<tr>
<td>Post-test probability of malignancy</td>
<td>45 ± 37</td>
</tr>
<tr>
<td>Involved lung</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>283 (56.4)</td>
</tr>
<tr>
<td>Left</td>
<td>219 (43.6)</td>
</tr>
<tr>
<td>Involved site of lung</td>
<td></td>
</tr>
<tr>
<td>Superior</td>
<td>252 (50)</td>
</tr>
<tr>
<td>Middle</td>
<td>46 (9.2)</td>
</tr>
<tr>
<td>Inferior</td>
<td>204 (40.6)</td>
</tr>
<tr>
<td>Nodule size (mm)</td>
<td>16.2 ± 6.7</td>
</tr>
<tr>
<td>Nodule type</td>
<td></td>
</tr>
<tr>
<td>Solid</td>
<td>390 (77.7)</td>
</tr>
<tr>
<td>Non-solid</td>
<td>36 (7.2)</td>
</tr>
<tr>
<td>Partially solid</td>
<td>76 (15.1)</td>
</tr>
<tr>
<td>Speculation</td>
<td>258 (51)</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD or number of patients (%).
CONCLUSION

The results of this trial might help to define the role of s-PET/CT in patients with SPN. This trial will also evaluate the impact on radiobiology and costs subsequent the introduction of this alternative imaging acquisition modality.

APPENDIX: ORGANIZATIONAL STRUCTURE

Study Coordinators: Marco Spadafora, MD, San Giuseppe Moscati Hospital, Avellino; Leonardo Pace, MD, University of Salerno, Salerno; Luigi Mansi, MD, University Luigi Vanvitelli, Naples; Laura Evangelista, MD, PhD, Veneto Institute of Oncology IRCCS, Padua; and Alberto Cuocolo, MD, University of Naples Federico II, Naples.

Participating Clinical Centers

Cesare Gridelli, MD and Paolo Miletto, MD, San Giuseppe Moscati Hospital, Avellino (n=56); Giorgio Saladini, MD, Veneto Institute of Oncology IRCCS, Padua (n=77); Silvana del Vecchio, MD, University of Naples Federico II, Naples (n=54); Mohsen Farsad, MD and Arber Fracchetti, MD, Hospital of Bolzano, Bolzano (n=10); Giovanni Storto, MD, Hospital of Rionero in Vulture, Potenza (n=34); Salvatore Annunziata, MD, Daria Ripani, MD, and Alessandro Giordano, MD, Catholic University, Rome (n=20); Giovanna Pepe, MD, Arturo Chiti MD, and Giovanni Cusato, MD, Humanitas, Rizzuto, Milan (n=47); Marco Ferdeghini, MD and Michele Zuffante, MD, University of Verona, Verona (n=23); Maria Grazia Giuliano, MD and Giuseppe Pelo, MD, Medicina Futura IOS, Acerra, Napoli (n=38); Marco Salvatore, MD and Emanuele Nicolai, MD, IRCCS SDN, Napoli (n=37); Stefano Fanti, MD, Alessandro Lamberti, MD and Silvia Sanfilippo, MD, University of Bologna, Bologna (n=59); Luca Guerra, MD and Maurizio Arosio, MD, University of Milano Bicocca, Monza (n=47); Agostino Chiaravalloti, MD and Orazio Schillaci, MD, University Tor Vergata, Rome.

Core Laboratory for Data Analysis: Leonardo Pace, MD, University of Salerno, Salerno; Francesco Del Prete.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

For the retrospective nature of the study, the approval by ethical local committee has already been obtained from one out of all involved Institutions (IOV-IRCCS; September 2016, approval number 0016).

HUMAN AND ANIMAL RIGHTS

No animals were used in this study. 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.

CONSENT FOR PUBLICATION

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

CONFLICT OF INTEREST

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

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REFERENCES