Author's response to reviews

Title: Pathways for definitive diagnosis of solitary pulmonary nodule: a multicentre study in 18 French districts

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Author's response to reviews: see over
Thank you for your email dated 10 October 2007. We are very grateful for the reviewers comments and feel they have substantially improved the quality of the manuscript. Enclosed please find our specific responses to these comments.

We hope that the revised manuscript will be considered suitable for publication.
Reviewer: Michael Gould

Major Compulsory Revisions

1. In the discussion, the authors should acknowledge that some variability in management may be justified. Management of SPN is not amenable to a one-size-fits-all approach. Different strategies are called for depending on the clinical probability of malignancy.

Answer

We recognize that the evaluation of a solitary pulmonary nodule is complex process. Management decisions are based on clinical history, size and appearance of the nodule, and feasibility of obtaining a tissue diagnosis, so some variability in management may be justified as many considerations must be taken into account in diagnosing SPN. We added this proposal in the discussion.

2. TTNAB is not necessarily less invasive than bronchoscopy. The risk of PTX is ~25%. Please modify the sentence in the 2nd paragraph of page 4.

Answer: We apologized for this mistyping error the sentence is modified in the 2nd paragraph of page 4.

3. ~30% of patients had "mediastinal involvement" and many underwent procedures for lung cancer staging including brain imaging and bone scans. This suggests that, technically speaking, many of these patients did not have a SPN. It would probably be best to exclude the patients with abnormal findings in the mediastinum.

Answer
The solitary pulmonary nodule is traditionally defined as a relatively spherical opacity 3 cm or less in diameter surrounded by lung parenchyma. This definition is based predominantly on information obtained from the chest radiograph. The expanding role of computed tomography (CT) in medical imaging is leading to additional insights into this definition. We used the more possible generic term to describe a solitary pulmonary nodule and this study was designed to assess all types of nodules rather than one specific type as the first question posed by our study investigated how SPN is managed in daily practice. Our hypothesis was that nodule characteristics and mediastinal lymph node enlargement could influence clinician strategies to evaluate patients with solitary pulmonary nodule so we include the collected information about mediastinal involvement in our analysis.

4. In Table 4, it would be more informative to report the median and interquartile range for days to diagnosis.

Answer: The table 4 is modified median and interquartile were reported

**Discretionary Revisions**

1 The statement that 150,000 SPNs are investigated in the US each year is supported by a reference from a review article. Please cite an original source.

Answer: We apologize for this error. The reference 3 is modified.
Reviewer: Giuseppe Madeddu

Major Compulsory Revisions

1. The selection of pulmonary nodules made by the authors excluding those with a <1 cm size seems to too limited. The authors should better clarify this aspect.

Answer

The detection of focal rounded pulmonary opacities "nodules" as small as 1–2 mm in diameter has become usual since the introduction of helical CT in the early 1990s. In fact, the majority of smokers who undergo thin-section CT have been found to have small lung nodules, most of which are smaller than 1 cm diameter. However, the clinical importance of these small nodules differs from that of larger nodules. This issue has been highlighted in recent publications on CT screening for lung cancer, and the positive relationship of lesion size to likelihood of malignancy has been clearly demonstrated.

2. The authors should report whether the radiologists have used common evaluation criteria in reading Chest CT.

Answer

Detection of pulmonary nodules may become an important part of the daily tasks of many radiologists, both those who specialize in thoracic imaging and general radiologists. In clinical practice, radiologists are often used evidence based criteria to make an initial assessment for the presence or absence of SPN in reading Chest CT. As observational designed stud, radiologists were informed to participate but we did not insist on compulsory common criteria in daily practice for reading chest CT.
3. The authors should also specify whether there was a team of radiologists among the research assistants to review CT images, to better ensure homogeneous results and to obtain consensus by all the groups participating in the study.

Answer

Our study was conducted under conditions representing the daily practice management of SPN in a geographic area. The research assistants included each newly diagnosed SPN recorded in the radiology reports and a team of physician ensure homogeneous among research assistant.

4. The authors should give more information about nodule characteristics, either in the 112 patients included in the follow up or in the other 40 patients who were lost to follow up. These data should also be reported in the tables.

Answer

The characteristics of nodule at the moment of the first observation of SPN on chest CT were reported in the table 1. In this table we compared the characteristics of patients and the nodules for lost follow-up patients and patients with evidence diagnosis (malignant or benign) that made by a physician.

5. Among the 40 patients who lost follow up, excluding the 6 cases who died without evidence of definitive diagnosis, in how many cases was it possible to ascertain the diagnosis at the moment of the first observation? The latter sentence of this paragraph may due to a casual factor or do the authors retain that another explanation may be suggested?

Answer
For 34 patients, it was not possible to gather data about the process of diagnosis performed by the general practitioner or the primary managing hospital physician. It was not possible to ascertain diagnosis by the radiologists at the moment of the first detection of SPN on chest CT. So these patients with a newly diagnosis SPN reported by the radiologists were considered as lost follow-up.

Lost follow up patients were less likely to have a current or past history of smoking compared with patients with evidence of diagnosis. As likelihood of cancer is low in patients without history of smoking we could imply that physician have less attention to require another assessment (invasive or non invasive) for these patients. The attention bias is traditionally referred in observational study.

6. The authors should describe which definitive diagnosis they obtained in the 57 patients in whom no histological examination was performed.

Answer

If the physicians involved in the patient care recommend that invasive examination is not require, this suggests that diagnosis is an infectious process or a benign neoplasm, this nodules could be considered a benign SPN.

7. The authors should also explain why PET was performed in only two cases. Probably, some diagnostic procedures performed after Chest CT would have been avoided.

Answer
PET was not available in French hospitals at the time when this study was conducted. However some bordering patients could be referred by the generals practitioners, if need, to perform PET in a nearest foreign country (two patients in our study).

8. The authors should report histological type of lung cancer in the 30 patients in whom a definitive cancer diagnosis was made. The authors should also write how many patients with cancer have been diagnosed during the follow up of 2 years.

Answer

The table below describe the histological type of lung cancer in the 30 patients in whom a definitive cancer diagnosis was made.

<table>
<thead>
<tr>
<th>Histological type</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell carcinoma</td>
<td>13</td>
<td>43.3</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>10</td>
<td>33.3</td>
</tr>
<tr>
<td>Bronchioloalveolar carcinoma</td>
<td>2</td>
<td>6.7</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>2</td>
<td>6.7</td>
</tr>
<tr>
<td>Small cell lung carcinoma</td>
<td>1</td>
<td>3.3</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>1</td>
<td>3.3</td>
</tr>
<tr>
<td>Unspecified lung cancer</td>
<td>1</td>
<td>3.3</td>
</tr>
</tbody>
</table>

During the follow-up of 2 years cancer was not diagnosed in any follow-up patients.

9. Mediastinal involvement was reported in 31 patients: the authors should better clarify whether the involvement was always associated with cancer, since only in 30 patients cancer
was ascertained, or whether it was also present in patients in whom a definitive diagnosis was not made.

Answer

Among 31 patients with mediastinal involvement at the first observation of SPN 16 (51, 61\%) patients were diagnosed with cancer at the end of process of diagnosis. We analyse the association between mediastinal involvement and outcome (malignant or benign). The results of analysis showed that the mediastinal involvement was more likely to be associated with cancer (p= 0.005)

10. The authors should modify the percentage of cancer in the 112 selected patients: it is not exact.

Answer: We apologize for this mistyping, the percentage was modified in the text.

11. The histological classification in all 30 patients with cancer should be reported.

Answer: Please see answer for comment n 8.

12. Discussion is too long and should also be modified on the basis of the corrections of the text, as suggested. Moreover, the diagnostic pathway followed in the patients should be discussed more in detail.

Answer: Discussion is modified on the basis of the corrections.
Reviewer: egbert f smit

Major Compulsory Revisions

1. Diagnostic outcome is provided as cancer or no cancer. Preferably the latter category should be described more clearly, i.e. which alternative diagnosis other than cancer was established in the diagnostic process.

Answer

If the physicians involved in the patient care recommend that invasive examination is not require, this suggests that diagnosis is an infectious process or a benign neoplasm, this nodules could be considered a benign SPN.

2. 15 patients that were diagnosed with a T1 carcinoma were not operated upon. Could the authors give details of the stage of disease in which the cancer bearing patients were diagnosed?
The table below describes the stage of disease for patients with cancer.

<table>
<thead>
<tr>
<th>Stage of cancer</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td>IB</td>
<td>8</td>
<td>26.7</td>
</tr>
<tr>
<td>IIA</td>
<td>1</td>
<td>3.3</td>
</tr>
<tr>
<td>IIB</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>IIIA</td>
<td>2</td>
<td>6.7</td>
</tr>
<tr>
<td>IIIB</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>IV</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Non reported in medical report</td>
<td>4</td>
<td>13.3</td>
</tr>
</tbody>
</table>

3. The authors state that inconclusive tests were uncommon. A clear definition of an inconclusive test must be provided as I suspect that some of these tests were performed to stage presumed cancer rather than establishing a diagnosis.

Answer

An inconclusive test is a test(s) whose results are equivocal, technically non interpretable, or discordant with a patient's other clinical data so it could not establish the malignity or the benignity of SPN. In this study inconclusive tests were common.
4. Using Swenson's criteria, it is possible to define an a priori chance of malignancy. It would be of interest to know how these were distributed in the population that form the basis of this report (i.e. the 112 patients that are represented in figure 1)

Answer

Swensen criteria are derived from multivariate logistic regression in 629 patients. The equation is based on 3 clinical and 3 radiographic variables. It takes account of age, cancer, cigarette, diameter, speculation and location. As this study was designed to observe daily practice of SPN management many of these criteria were not available in the radiology report for all the cases of SPN.