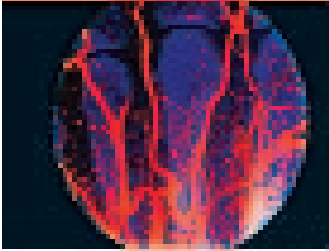


**Key words:** PET/CT; patient outcome; thorax, lung lesions; cost-effectiveness



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# Should integrated PET/CT be used for thoracic lesions?

## A critical appraisal

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### Abstract

Integrated positron emission tomography-computed tomography (PET/CT) is an innovative imaging test offering the potential for a higher degree of accuracy and sensitivity compared with plain radiographic investigations. It was shown that PET/CT might enable differentiation of benign from malignant lesions

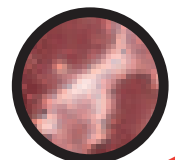
without histology in the majority of cases. From a conservative point of view, a new diagnostic tool that is expensive and exposes the patient to radiation should be used routinely only if this test was shown, by the highest level of evidence, to meet certain criteria. That is, the test must be cost-effective, spare other costly or potentially harming investigations, spare therapeutic strategies that are of no value to the patients, or contribute to better patient management resulting in improved outcome (i.e. survival) or quality of life. Unfortunately none of these claims can be answered completely with regard to the use of PET/CT in thoracic lesions. Therefore, PET/CT should be employed mainly in the setting of prospective trials and should not be used widely as standard procedure in the work-up of thoracic lesions.

### Introduction

In the work-up of patients with thoracic lesions, PET scans and PET/CT are highly sensitive methods that add information to the results of existing imaging methods and have the potential to differentiate benign from malignant nodules.<sup>1</sup> PET/CT has theoretical advantages over CT and PET scans performed separately, and these advantages have been shown to contribute to improvements in diagnostic certainty.<sup>2</sup> Before a decision is made to perform a new test in an individual patient, the treating physician should be aware of the consequences of the results that may be obtained. There are many different scenarios of a thoracic lesion in which one might consider including

PET/CT in the further work-up of the case. In this discussion article, we do not aim to critically compare the accuracy or technology of PET/CT with existing alternatives, but instead we aim to ask: in which clinical situations has a benefit of PET/CT for the individual patient already been proven?

For this aim, we would like to shed some light on the distinct indications that, unfortunately, are often not clearly mentioned in the articles concerning PET or PET/CT. We have chosen a conservative point of view and have tried to establish if there are any situations in which a PET/CT scan contributes to an improved outcome for the patient. This point of view assumes that an existing standard algorithm is not changed until the benefit of the new algorithm is shown to be greater. With this supposition, it is clear that we have to include the critical appraisal of a PET scan alone for the work-up of thoracic lesions, as this method is not the standard of care. PET and PET/CT are both costly investigations associated with a radiation exposure far above that of plain radiographs.<sup>3</sup> In many societies (e.g. in Germany and the UK), institutions that offer PET and PET/CT are not widespread and, for patients without private medical insurance, there is no realistic chance of receiving the scan within a medically acceptable time-frame, even if it is clearly indicated. These factors underline the need to identify the particular indications that demand PET/CT, and the need for well-conducted trials to better define these indications.



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### Different scenarios of a thoracic lesion for which PET/CT can be useful

#### **Screening in populations at high risk of lung cancer**

For decades, physicians have desired a screening test for populations at high risk for lung cancer (i.e. heavy smokers) since this disease is typically diagnosed at an advanced stage and the outcome for patients is poor.<sup>4</sup> Spiral CT is able to detect lung cancer at an early stage. However, with this technique, a high rate of small and potentially benign lesions are operated on or investigated repeatedly.<sup>4</sup> Recent results of a prospective trial with PET in the screening algorithm, suggest that PET improves the positive and negative predictive value for patients found to have non-calcified lesions >7 mm in size.<sup>4</sup> This study supports further research in this field because the prognosis is excellent for patients in whom lung cancer is detected by this approach. However, at present, a screening programme for lung cancer in high-risk populations – with or without PET or PET/CT and outside a trial – is not indicated since a decrease in mortality with screening has not yet been shown.

#### **Patient with thoracic lesion of unknown pathology**

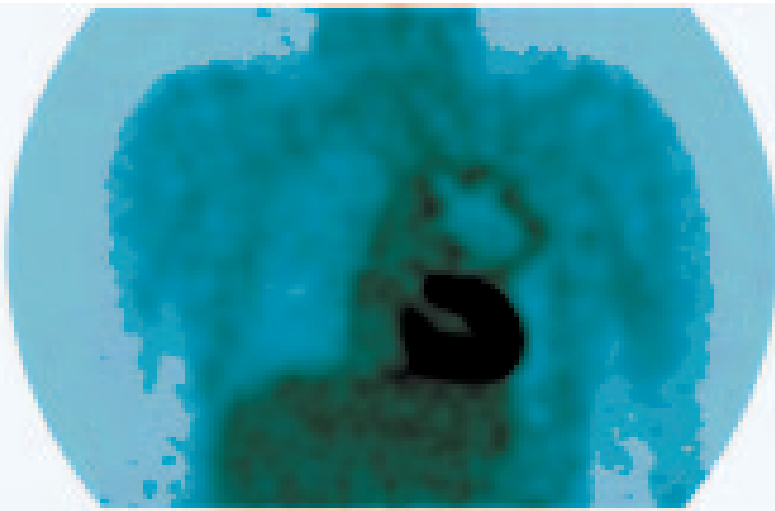
The next scenario is a patient with a thoracic lesion, which may or may not be malignant. What do we want to know in order to define the appropriate therapy for this patient? If the lesion is malignant, it may be the only manifestation or one of many. PET is a possible diagnostic test, although its benefit compared with classical staging procedures has not yet been shown.<sup>1</sup> If the lesion is a single focus, or multiple foci, confined to the thorax, the diagnosis could be lymphoma, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC) or the metastasis of an unknown primary tumour. Histology is mandatory in any of these diseases before a specific therapy can be planned, particularly if PET identifies the lesion to be malignant. Even if PET diagnoses 'non-malignancy', reliance on this data without a histological test is risky because, if the lesion

is later found to be malignant, it is difficult to convince the patient that earlier intervention would not have altered his or her prognosis.

#### **Patient with potentially curable NSCLC, confirmed by histological tests**

Many studies showing the merits of PET and PET/CT were conducted in patients with proven or highly suspected NSCLC, at a stage when surgical resection might be required. It seems accepted – although not proven in clinical trials – that detection of widespread disease is of value to the patient. In this case the curatively-intended treatment, such as potentially life-threatening surgery or combined chemo-radiation treatment, is no longer indicated and can be avoided.<sup>5</sup> We agree that whole body PET imaging is a useful diagnostic tool for disease staging and, compared with standard imaging procedures (i.e. bone scan, magnetic resonance imaging (MRI) of the brain, CT of the abdomen), it might disclose more stage VI cases and save time, money and radiation exposure.

One of the major problems in interpreting studies involving PET or PET/CT of potentially operable NSCLC is that management protocols for stage IIA, IIB, IIIA or IIIB disease are not clearly defined. The following strategies are currently used in and outside trials, and not always in a stage-specific manner: resection followed by adjuvant chemotherapy; pre-operative chemotherapy followed by chemo-radiation followed by operation; or definitive chemo-radiation alone or combined with chemotherapy. So the question is: in which situation would the prediction of lymph node involvement help us to decide the best treatment option? One trial has shown a significant improvement in the exact prediction of T- and N-stage lesions in operable NSCLC with PET/CT compared with separate PET and CT.<sup>2</sup> However, further analysis of outcomes is precluded by the small number of patients (n=50) in the trial.



A randomised study of 188 patients concluded that PET helps to avoid 'futile thoracotomies' compared with a conventional work-up.<sup>6</sup> However, the author's definition of a 'futile thoracotomy' (i.e. in IIIA N2 disease) is probably not widely accepted, and no patient-relevant endpoints like survival or quality of life were reported. Another group hypothesised that upstaging by PET would decrease the rate of all types of thoracotomies and therefore selected the rate of thoracotomies as the primary endpoint of their trial.<sup>7</sup> This study was adequately powered with 183 stage I and II patients, randomised into two groups for investigation with or without a PET scan. There was no significant difference between the groups for the rate of thoracotomies.<sup>7</sup> Recently, a larger trial was presented that was powered to detect differences in patient-focused endpoints.<sup>8</sup> Dutch investigators conducted a multicentre trial of 465 patients without overt disseminated disease, who were randomised to traditional work-up or PET imaging. For most of the outcomes, there were no significant differences between the groups, except the PET group, where a lower proportion of patients received an invasive test to determine N-stage lesions.<sup>8</sup>

In conclusion, PET/CT improves the diagnostic accuracy of potentially operable NSCLC, but further benefits of this approach remain to be determined.

***Evaluating the efficacy of treatment with PET in patients with lymphoma, testicular cancer, oesophageal cancer or lung cancer***

Repeated PET scanning as part of the treatment regimen for patients with lymphoma, testicular cancer, oesophageal cancer or lung cancer (which are generally chemo-sensitive diseases) is an evolving method. The prediction of a response to chemotherapy or radiation, or the interpretation of residual masses after potentially curative therapy of lymphoma were remarkably improved by the use of PET compared with

conventional imaging.<sup>9,10</sup>

However, the question remains: what are the consequences of increasing the diagnostic accuracy? Furthermore, has the time come to abandon invasive testing of residual disease, and change our existing strategy of using established regimens with a curative intent? A negative result from PET after therapy does not exclude a relapse in lymphoma, and alteration of the treatment strategy might harm the patient.<sup>11</sup> What is the value of the knowledge that regimen 'A' did not work as well as anticipated in my patient? Early prediction of response of a stable lesion using conventional imaging can help in deciding whether or not to change to an alternative regimen, where viable alternative therapies exist. However, in the case of stable disease, in which circumstances would one alter the regimen early? We think repeated PET or PET/CT are interesting and highly predictive investigations that should be evaluated in prospective trials for their use in improving patient outcomes, or avoiding the continuation of potentially harmful and insufficient therapies. As soon as a high level of evidence is obtained to prove their value, one should include these investigations in clinical practice.

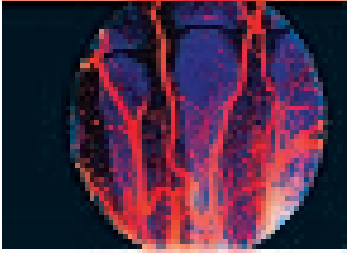
**Conclusion**

PET/CT provides a sensitive diagnostic tool that can be of value in imaging some thoracic lesions. However, the technique has some drawbacks – including cost, radiation exposure and accessibility of equipment – and improvement in patient outcome has not been established for all thoracic lesions. Therefore, PET/CT cannot be considered currently as a standard procedure to be demanded in the work-up of thoracic lesions. Further investigation of PET/CT in prospective trials will enable identification of the particular indications for which it could



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### Key Learning

- PET/CT is a highly sensitive diagnostic tool, although its drawbacks include:
  - expense
  - greater radiation exposure compared with plain radiographs, and
  - limited access to equipment for many patients
- It is important to identify clearly (from clinical trials) the indications where use of PET/CT offers improved outcomes for patients
- PET or PET/CT could be considered a useful technique for:
  - further work-up of pulmonary lesions detected by CT
  - evaluating patients with a thoracic lesion of unknown pathology
  - staging of histologically confirmed, potentially curable NSCLC, and
  - assessing efficacy of therapy in patients with lymphoma, testicular cancer, oesophageal cancer or lung cancer
- The use of PET/CT should be investigated further in prospective trials and, at present, cannot be considered standard procedure in the work-up of thoracic lesions

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