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Review Article

Clinical Application of ^{18}F-fluoro-2-deoxy-D-glucose Positron Emission Tomography-Computed Tomography for Cancer Cells in Lung Cancer

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Abstract

Purpose: One of the most important tools used in the diagnosis and treatment of lung cancer in patients with or suspected of having lung cancer is positron emission tomography-computed tomography (PET-CT). The popularity of this method is rapidly increasing. **Material and Review Method:** We searched papers on the topic of the recognition of cancer cells in lung cancer using ^{18}F-fluoro-2-deoxy-D-glucose (FDG) PET-CT using keywords such as ^{18}F-FDG PET-CT and lung cancer, ^{18}F-FDG PET-CT imaging in oncology, cancer and nuclear medicine, diagnosis of lung cancer and imaging, molecular imaging in cancer, false-positive ^{18}F-FDG PET-CT scans and oncology, application of ^{18}F-FDG PET-CT in staging and metabolic activity assessment of cancer, and PET-CT imaging method. **Results:** In this review, we found the following results: 1.Due to the high diagnostic sensitivity of PET-CT scans, it is possible to reject malignancy in pulmonary cells using this method 2. PET-CT scans decrease the number of unnecessary procedures. 3. According to the findings of this review study, high sensitivity in PET-CT is the major advantage compared to other methods used to rule out the possibility of malignancy of lung cells; it is necessary but not sufficient. **Conclusions:** Regarding the imaging of abnormal pulmonary cells using PET-CT, except for a few exceptions, if the result of a PET-CT scan is negative, these abnormalities can confidently be considered to be benign. These exceptions include nonsolid and small (<1 cm) pulmonary nodules. Until all metastases in the pulmonary cells are imaged and detected by PET-CT, no drug regimen should be started. Finally, lymph node tumor metastasis cannot be ruled out solely based on a negative result of PET-CT imaging with these abnormalities, and to confirm it, aggressive staging should be performed in most patients before mediastinal metastasis is confirmed or rejected.

Keywords: ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography-computed tomography, imaging, lung cancer, positron emission tomography-computed tomography, pulmonary cell

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Introduction

Since the introduction of positron emission tomography (PET) between 1970 and 1980 and the clinical laboratory introduction of PET-computed tomography (PET-CT), the use of molecular imaging with PET scans has significantly increased.[1] No sign of a plateau has been observed in the use of PET-CT, and its use continues to rise. Therefore, it seems that a review of the initial detection of cancer cells using PET-CT may be interesting for clinicians dealing with PET-CT scans.[2,3] Many international organizations and health care, thoracic and medical oncology societies have issued instructions regarding the application of ^{18}F-fluoro-2-deoxy-D-glucose (FDG) PET-CT in lung cancer.[4-13] The growing use of PET-CT, given its increasing costs, is a challenge for health-care systems. While international health-care systems encounter financial difficulties, the occurrence of lung cancer has not decreased, and the demand on health-care services continue to increase due to the provision of safe and effective services for all patients.[14] In recent years, a large number of articles have been published regarding the application of PET-CT scan in lung cancer. Most of these articles have discussed the precision of PET-CT scan detection, and only a few have discussed the potential clinical application of PET-CT in lung cancer. Therefore, as shown in Figure 1, such work does not offer a clinically relevant assessment in the diagnosis of lung cancer. If a diagnostic method can support the process from A to B to C, it seems that its use is clinically legitimate if there are no other contradictions. If this method fails to support the process from A to B to C, then the clinical application is not acceptable or is very limited. To illustrate this, three examples are given below:

1. An evidence-based study has shown that the sensitivity of a PET-CT scan to diagnose a specific disease, such as lung cancer, is about 75%–50% compared to a CT scan. Although these results are scientifically interesting, they are not clinically important, because, as the results of this study show, neither a PET-CT scan nor CT scan can definitely exclude the possibility of a disease
2. If a PET-CT scan can prevent unnecessary thoracotomy, then it has a very high clinical significance. However, if PET-CT only changes the current condition of a patient with no immediate difference in treatment (such as the diagnosis of N1 disease in a patient who is believed to have NO disease) it is clinically nonsignificant, even though it is considered to be scientifically important
3. If six metastatic lesions identified by CT or eight metastatic lesions identified by PET-CT are detected in the liver of a patient, it is not important for workup studies (an intensive diagnostic study), and even though in this example, PET-CT is more sensitive than CT in distinguishing liver metastases, there will be no therapeutic consequences.

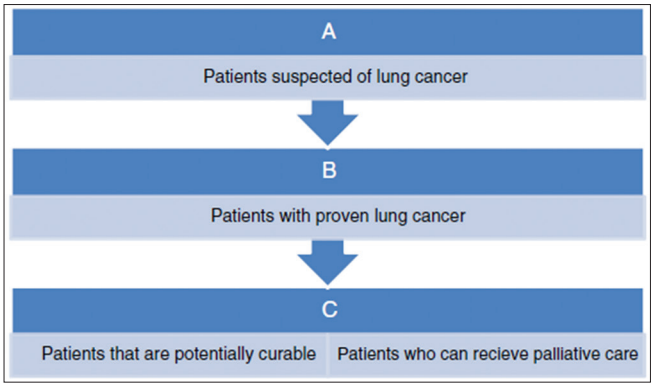

Figure 1: The process of diagnosing lung cancer

This paper differs from most other articles about PET-CT because it emphasizes the clinical application of PET-CT in the evaluation of lung cancer. This study aims to collect, classify, and depict the evidence and proof associated with the clinical application of ^{18}F-FDG PET-CT in the early diagnosis of lung cancer. For this reason, a number of questions are raised and will be answered in the following sections.

1. Is PET-CT capable of reliably and practically detecting a malignant pulmonary tumor from a benign tumor on CT, thus preventing the potential risk of a lung biopsy?
2. Is PET-CT capable of preventing unnecessary treatment trials (e.g., by detecting hidden metastases)?
3. Is PET-CT capable of reliably diagnosing or ruling out mediastinal lymph node metastases, and as a result prevent surgery or endoscopy?

Material and Review Method

An overall research methodology was developed to answer the three questions raised in the introduction. We then searched for relevant papers on the topic of evaluating cancer cells in lung cancer through ^{18}F-FDG PET-CT using keywords including ^{18}F-FDG PET-CT and lung cancer, ^{18}F-FDG PET-CT imaging in oncology, cancer and nuclear medicine, diagnosis of lung cancer and imaging, molecular imaging in cancer, false-positive ^{18}F-FDG PET-CT scans and oncology, application of ^{18}F-FDG PET-CT in staging and metabolic activity assessment of cancer and PET-CT imaging. A number of databases, including the Web of Science, PubMed, Scopus, and Embase from 2003 to 2018, were used; however, attempts were made to access the most up-to-date literature in this field. The papers were then fully read, and their findings summarized. The results are summarized in Table 1. This study was conducted using the rapid evidence assessment (REA) method, which is used when a general, clear, and up-to-date input is required to inform health policy decision-makers.[15] Regardless of the lack of coordination and stability in the REA method, it is broadly used by Health Technology Assessment manufacturers around the world to communicate the latest data required by health-care determination-creators.[16] By shortening the conventional systematic review process (normally an 8–12 months' process), the REA method allows for the quick collection of evidence regarding a specific topic. The REA method allows for the equivalent evaluation of clinical hardness using a systematic review method for the search, classification, and valuation of documents in a defined topic. This method limits the comprehensiveness of any process, for example, focusing on a few or only a single research topic,

Table 1: The primary results of this research

Subject of articles/first author and year [ref.]	No. of articles/ modality	Total no. of patients	Study design	Important findings and results	Evidence level
PET(−CT) in SPN (pooled results)	14	1847	3 controle 11 CASE-CONTROL	PET-CT can rule out malignancy in a solid SPN due to high sensitivity, and reduces need for biopsy if negative because of higher specificity than CT (recommendation level A)	
Fletcher *et al*., 2008[15]	PET	532	Controle	Sensitivity PET vs. CT 92% vs. 96% Specificity PET vs. CT 82% vs. 41%	1b
Christensen *et al*., 2006[16]	PET	41	CASE-CONTROL	Sensitivity PET vs. CT 96% vs. 100% Specificity PET vs. CT 76% vs. 29%	2b
Harders 2012[17]	PET-CT	168	Controle	Sensitivity PET-CT vs. CT 97% vs. 93–96% Specificity PET-CT vs. CT 47% vs. 34–53%	1b
Kagna *et al*., 2009[18]	PET-CT	307	CASE-CONTROL	Sensitivity PET-CT vs. CT 94% vs. 97% Specificity PET-CT vs. CT 70% vs. 48%	2b
Jeong *et al*., 2008[19]	PET-CT	100	CASE-CONTROL	Sensitivity PET-CT vs. CT 88% vs. 82% Specificity PET-CT vs. CT 77% vs. 66%	2b
Kim *et al*., 2007[20]	PET-CT	42	CASE-CONTROL	Sensitivity PET-CT vs. CT 97% vs. 93% Specificity PET-CT vs. CT 85% vs. 31%	2b
Yi *et al*., 2006[21]	PET-CT	119	CASE-CONTROL	Sensitivity PET-CT vs. CT 96% vs. 81% Specificity PET-CT vs. CT 88% vs. 93%	2b
Bar-Shalom *et al*., 2008[22]	PET-CT	56	CASE-CONTROL	Sensitivity PET-CT 96% Specificity PET-CT 83%	2b
Nomori *et al*., 2004[23]	PET	131	Controle	Sensitivity PET solid SPN >1 cm 90% Specificity PET solid SPN >1 cm 71% Sensitivity PET GGO >1 cm 10% Specificity PET GGO >1 cm 20% Sensitivity PET SPN <1 cm 0%	1b
Herder *et al*., 2004[24]	PET	35	CASE-CONTROL	Sensitivity SPN PET ≤1 cm93% Specificity SPN PET ≤1 cm77%	2b
Dewan *et al*., 1995[25]	PET	33	CASE-CONTROL	Sensitivity PET 100% Specificity PET 78%	2b
Heynemann *et al*., 2002[26]	PET	15	CASE-CONTROL	Sensitivity PET 38%	2b
Yap *et al*., 2002[27]	PET	41	CASE-CONTROL	Sensitivity of PET depends on BAC-component In pure BAC, sensitivity of PET was 33%	. 2b
Daniels *et al*., 2007[28]	PET	16	CASE-CONTROL	Sensitivity PET 75%	2b
PET-CT before curative-intent treatment (pooled results)	9	1866	8 controle 1 CASE-CONTROL	PET-CT reduces the number of futile treatment trials and invasive staging (recommendation level A)	
Herder *et al*., 2006[29]	PET	465	Controle	Reduction in invasive tests requiring general Anaesthesia (*P*=0.0074). No reduction in futile thoracotomies (P=0.43)	1b
Kozower *et al*., 2008[30]	PET	122	Controle	PET prevents 7.4% non-therapeutic thoracotomies in stage IA lung cancer	1b
Viney *et al*., 2004[31]	PET	184	Controle	PET altered clinical stage in 20% No reduction in futile thoracotomies	1b
Maziak *et al*., 2009[32]	PET-CT	337	Controle	PET-CT correctly upstaged 13.8% vs. 6.8% in control group (*P*=0.046).	1b
Fischer *et al*., 2009[33]	PET-CT	189	Controle	Significant reduction in futile thoracotomies in PET-CT group vs. control group 35% vs. 52% (*P*=0.05).	1b
MacManus *et al*., 2001[34]	PET	167	Controle	PET detected unknown distant metastasis in 7.5% (stage I), 18% (stage II) and 24% (stage III)	1b
Reed *et al*., 2003[35]	PET	303	Controle	PET potentially avoided unnecessary thoracotomy in 1 of 5 patients	1b
Lardinois *et al*., 2003[36]	PET-CT	49	Controle	PET revealed unknown metastasis in 16%	1b
De Wever *et al*., 2007[37]	PET-CT	50	CASE-CONTROL	Correct M-stage by PET-CT 98% vs. 88% By CT (non-significant).	2b

Contd...

Table 1: Contd...

Subject of articles/first author and year [ref.]	No. of articles/ modality	Total no. of patients	Study design	Important findings and results	Evidence level
PET-CT to rule out mediastinal dissemination (Pooled results)	9	1678	6 controle 3 CASE-CONTROL	PET-CT in general cannot rule out mediastinal lymph node 3 metastasis (recommendation level A)	
GonzalezStawinski *et al*., 2003[38]	PET	202	CASE-CONTROL	PET sensitivity 64.4% PET specificity 77.1%	2b
Darling 2011[39]	PET-CT	149	Controle	PET-CT sensitivity 70% PET-CT specificity 94%	1b
Herth *et al*., 2008[40]	PET	97	Controle	8% had false-negative lymph nodes at PET	1b
Lee *et al*., 2007[41]	PET	224	CASE-CONTROL	Central tumour more often false-negative at PET in N2 nodes than peripheral tumour, (P<0.001) Large tumour more often false-negative at PET in N2 nodes than small tumour (P<0.001) All false-negative PET at N2 nodes (16 patients) were adenocarcinoma	2c
Harders 2012[17]	PET-CT	114	Controle	PET-CT sensitivity 50% PET-CT specificity 74%	1b
Fischer *et al*., 2011[42]	PET-CT	189	Controle	15% had false-negative mediastinal lymph nodes at PET-CT	1b
Al-Sarraf *et al*., 2008[43]	PET-CT	153	CASE-CONTROL	16% had N2 disease despite negative PET-CT. Predictors of false-negative PET-CT were: Central tumour (P=0.049) Right upper lobe tumour (P=0.04) >1 cm lymph nodes (P=0.048)	2b
Bryant *et al*., 2006[44]	PET-CT	397	Controle	PET-CT sensitivity 91% PET-CT specificity 88% Study design primarily to test optimal SUVmax	1b
Cerfolio *et al*., 2006[45]	PET-CT	153	Controle	2.9% and 3.7% had N2 disease by mediastinoscopy and EUS, respectively, despite negative PET-CT if clinically N0. If clinically N1, 17.6% and 23.5%, respectively, had N2 disease	1b

BAC: Bronchoalveolar carcinoma, PET: Positron emission tomography, CT: Computed tomography, SPN: Solitary pulmonary nodule, GGO: Groundglass opacity, EUS: Endoscopic ultrasound

evaluating literature in a limited period, or only providing information from summaries of available evidence and review articles rather than from original studies. Therefore, the whole process, depending on the limit, takes about 2–6 months.[17,18] The REA method suggests that review articles should be categorized by their titles and summaries based on pre- and post-planned criteria. It also sets the level of qualification from 1 to 5, where 1 denotes "the highest quality of evidence."[19] Finally, the summary of results was provided in evidence tables comprising the purpose of the review, review design, review course, study crowd, number of patients studied, the results, comments, and evidence level. Using these evidence tables, suggestions were made for the use of PET-CT in lung cancer. These recommendations were based on a grading scale of A to D, where A represents the best state, and D represents the weakest state.[19]

Results

By searching the databases with the relevant keywords, 4208 articles were obtained, of which 981 were review papers and 41 were original papers. However, of the 981 review articles, only 139 were reviewed, and the remaining (842) were excluded from the study for the following reasons:

- Articles irrelevant to the title and main purpose of the article (n = 71)
- Non-English text (n = 2)
- Articles on cancer but not about lung cancer (n = 66)
- Articles about PET-CT other than our work (not clinical assessment) (n = 102)
- Papers on PET-CT discussing its diagnostic properties (n = 232)
- Articles irrelevant to the population, intervention, comparison, and outcome (PICO) question that did not answer the study questions (e.g., basic research, technical issues, and animal experiments) (n = 369).

As mentioned and shown in Table 1 and Figure 2, to prepare this article, 41 original articles were also used. These original articles were categorized as follows:

- Fourteen original articles on PET/PET-CT which emphasized the evaluation of solitary pulmonary nodules (SPNs)
- Nine original papers on PET/PET-CT which focused on curative-intent treatment trials

- Eighteen original articles on PET/PET-CT that specifically addressed the planning of invasive procedures.

The important clinical findings of these papers are summarized in Table 1 and within the content of this paper.

Can positron emission tomography-computed tomography differentiate malignant tumors from benign tumors using computed tomography and thus avoid the need and risk of a lung biopsy?

To answer this question, PICO questions were first raised:

If using invasive tests, what effects do these tests have? Why in the evaluation of SPNs using PET-CT (I) is there a possibility of malignancy being ignored, while other imaging techniques (evaluations without PET-CT [C]) increase the suspicion of lung cancer (P)?

As mentioned, we identified 14 main articles about this issue, of which three were articles with level 1b evidence,[20-22] and 11 had level 2b evidence[23-33] for different SPNs. These types of material cannot be compared directly; however, some studies offered a wider view of the application of PET and PET-CT in different SPNs (e.g., different sizes, risk profiles, and densities), so PET-CT could detect malignant tumors from benign tumors using CT. In this study, we excluded cases with small or nonsolid SPNs. The articles examined in this study showed that PET and PET-CT had a sensitivity of 88%–100%. Jeong *et al*.[32] reported a sensitivity of 88% for PET-CT in the diagnosis of malignancies. However, additional examinations showed that false negatives (which led to a sensitivity of 88%) were often due to nonsolid SPNs or bronchoalveolar carcinoma (BAC). Yi *et al*.[23] analyzed 119 patients who underwent PET-CT imaging for classifying an unknown SPN. In their paper, the sensitivity was 96%, which is compatible with most studies. This sensitivity is higher than 81%, which they reported for CT. Heynemann *et al*.[24] and Yap *et al*.[25] conducted separate case-control epidemiologic studies on the PET scans of 56 patients with BAC, and found that PET scans for BAC and ground-glass opacities (GGOs) had a low sensitivity (38% and 33%, respectively). On the other hand, Nomori *et al*.[22] reported a very low sensitivity of PET in detecting malignancy of about 20% for GGOs in a controlled study of 131 patients. In a similar study in 2007, Daniels *et al*.[28] conducted a case-control epidemiologic study of 16 patients with pulmonary carcinoid tumors, and reported that the sensitivity of PET for malignancy was 75%. Numerous differences existed regarding the findings for small SPNs (commonly referred to as <1 cm). Nomori *et al*.[22] reported 0% sensitivity using PET, while Herder *et al*., in a case-control epidemiological study performed on 35 patients with small tumors (<1 cm), showed a sensitivity of 93% using PET.[29] These two studies were different; so that SPN was defined as PET positive, which may elucidate the reason behind the diverse findings. Madsen *et al*. compared SPN uptake with mediastinal blood pool.[34] Madsen *et al*. calculated the contrast ratio between highly active SPN (T = tumor) and the contralateral lung (N = normal).[34] They defined the SPN as being FDG-positive when $(T - N)/(T + N) \geq 0,4$. In other words, if the FDG uptake of the SPN exceeded ~ 2.3 times the contralateral lung, it was considered to be FDG positive.

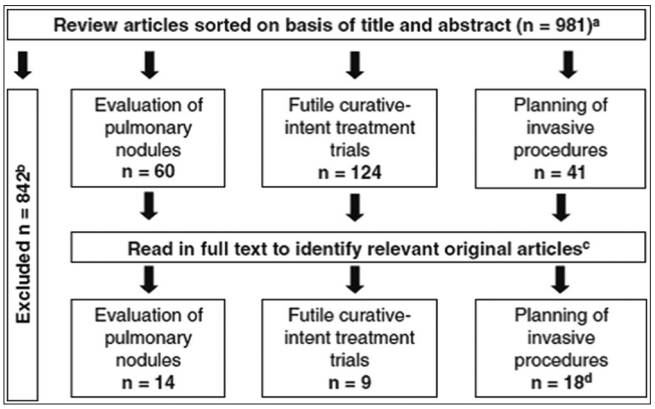

Figure 2: Method of selecting articles: [a]Among the 981 articles categorized by the accessed databases as review articles, 842 of them were omitted. The other 139 articles were arranged based on which population, intervention, comparison, and outcome question they answered. The arrangement is as follows: 60 articles addressed population, intervention, comparison and outcome 1 (assessing pulmonary nodules), 124 articles dealt with population, intervention, comparison and outcome 2 (futile curative-intent treatment), and 41 articles examined population, intervention, comparison and outcome 3 (planning of invasive procedures). Considering a significant number of articles addressed more than one of the population, intervention, comparison, and outcome questions, the sum is not 139. Considering the distribution of articles, not all of them can be categorized as review articles. [b]This exclusion of articles from the total ($n = 842$) could be explained as follows: non-relevant type of paper (e.g., editorial) ($n = 71$), non-English language ($n = 2$), non-lung cancer ($n = 66$), positron emission tomography-computed tomography topic but primarily not on diagnosis ($n = 102$), articles on positron emission tomography-computed tomography in treatment decisions (e.g., treatment response evaluation following radiotherapy) ($n = 232$), and articles unrelated to the population, intervention, comparison and outcome-question (e.g., "basic research, technical issues, and animal experiments") ($n = 369$). [c]Overall, 139 review articles were considered. Considering a significant number of review articles addressed more than one of the population, intervention, comparison and outcome questions, the sum of review articles for each population, intervention, comparison, and outcome question (60 + 124 + 41) does not equal 139. [d]Among 18 original articles, nine of them assessed mediastinal staging

Can positron emission tomography-computed tomography avoid unnecessary therapeutic trials by revealing hidden metastasis?

To answer this question, the following PICO questions were asked:

How does routine PET-CT affect patients with lung cancer (I)? How is routine PET-CT used in patients with curative-intent treatment (P)? How does routine PET-CT use affect the number of curative-intent treatment trials (O)? How is routine PET-CT compared to the evaluation of non-PET-CT (C)?

In our review, nine original articles were found about this subject (eight of which were certified with level 1b evidence[35–42]

and one with level 2b evidence[43]). These articles usually assessed the cumulative value of adding PET-CT to standard research prior to treatment, even though no definite metastases were identified. Nevertheless, the research plans were varied, and they emphasized using PET-CT before surgery and before to curative-intent oncological treatment. Studies using diverse control arms included dissimilar "standard research." F studies showed few useless or nondrug thoracotomies, such as Kozower *et al*.[36] who showed this in 122 control patients. In comparison to standard tests with chest and upper abdomen CT, bone scintigraphy and brain imaging, PET avoided the need for more nontherapeutic thoracotomies in Stage IA. Reed *et al*.[41] and Fischer *et al*.[39] reported an even larger reduction. They assessed 492 patients and compared PET and PET-CT with typical investigations (chest and upper abdomen CT, bone scintigraphy, and brain imaging),[41] and chest and abdomen CT and bronchoscopy[39] prior to surgery. They identified a significant proportion of useless thoracotomies in the PET-CT group and concluded that one of five thoracotomies could have been avoided. MacManus *et al*.[40] conducted a controlled study of 167 patients, in whom the treatment plan was curative-intent chemotherapy and radiotherapy. In 32 of these patients, PET identified metastasis left undetected by CT of the chest and abdomen or by scintigraphy of the bone. Herder *et al*.[35] carried out a major prospective study in 2006, which did not indicate any decline in useless thoracotomies. In the study group, 465 patients were examined, of whom half were randomly assigned to receive PET and were assessed for suspected lung cancer. The primary objective of the test was to examine whether PET could reduce the number of tests and methods used to adjust and define the operation. No significant decline was observed in the number of diagnostic tests using PET; however, a considerable reduction was seen in the need for surgery and general anesthesia. Lardinois *et al*.[42] conducted a control and randomized study of 184 patients with lung cancer (Stage I and II) who did not receive routine invasive mediastinal staging prior to treatment, and the results showed no significant reductions in futile thoracotomy; however, PET changed the presumed clinical stage in 20% of the cases, so PET-CT did prevent unnecessary therapeutic trial testing by revealing hidden metastasis.

Can positron emission tomography-computed tomography distinguish or reject mediastinal and hilar lymph node metastases, and thus prevent mediastinal surgery or endoscopy?

To be able to answer this question, a third PICO question was raised:

What is the effect of adding PET-CT (I) as compared to CT alone (C) on the number of inappropriate/unnecessary invasive tests (O) in patients with suspected or confirmed lung cancer who are undergoing invasive examinations for diagnosis or staging (P)?

A review of this topic resulted in the identification of 18 original articles (nine with level 1b evidence,[21,35,44–50] eight with level 2b evidence,[51-58] and one with level 2c evidence[59]). These articles were mainly divided into two categories: PET and PET-CT articles on mediastinum evaluation (nine papers), to classify changes in the adrenal glands (five articles). Further, in this article, as shown in Table 1, we initially examined the articles about mediastinal staging. Consistent results were obtained from these studies, all of which showed insufficient sensitivity for PET and PET-CT in detecting mediastinal dissemination with regards to ruling this out. Darling *et al*.[45] conducted a controlled study that analyzed 149 patients with non-small cell lung cancer that seemed to be practicable. However, with mediastinoscopy and/or surgery as a reference, they obtained 70% sensitivity for PET-CT in detecting N2/N3 disease. Conversely, in a literature review, while PET-CT was apparently insufficient regarding the ruling out of mediastinal dissemination,[34] some articles suggested that small tumors lacking evidence of lymph node dissemination on CT or PET-CT could, in fact, undergo noninvasive surgery. For example, Lee *et al*.[59] reported their findings regarding a case–control study of 224 patients undergoing CT of the chest and abdomen and PET. With mediastinoscopy and surgery as a reference, they found "only 3 of 103 N2 cases (2.9%) patients with small, peripherally located tumors as opposed to 5 of 20 (25%) patients with large, centrally located tumors." Therefore, PET-CT could distinguish or reject mediastinal and hilar lymph node metastases, and thus prevent mediastinal surgery or endoscopy.

Discussion

Lung cancer is one of the most common cancers in industrial countries, with a survival rate of only 17% within 5 years after initial treatment. When diagnosed in early stages, surgical or oncological curative-intent treatment can increase survival rates to >50%, provided the diagnosis is made at an early stage of the disease.[14] It is likely that a prolonged evaluation time is critical, especially in low-stage disease.[60]

Solitary pulmonary nodule

The current review supports the widespread use of PET-CT; as a result, a significant quantity of subcutaneous biopsies could be prevented in the event of PET-CT-negative SPNs. This offers three main clinical implications. First, a subcutaneous lung biopsy is associated with many complications, and the risk of pneumothorax is 20%;[61,62] however, not all of these patients require a chest tube. Therefore, special emphasis is placed on other tests prior to a percutaneous biopsy. Second, biopsy and other diagnostic methods performed prior to malignant SPN have been ruled out due to the excessive risks and recurring costs that could be eliminated with a negative PET-CT result. Third, if PET-CT rules out malignancy, a significant part of the patient's anxiety can be resolved. Nonetheless, small SPNs remain a diagnostic challenge because of the current physical features of PET-CT scanners. Both of the studies[22,29] on small SPNs were published in 2004, and the PET scanners lacked CT attenuation correction and had a spatial resolution of 7 mm, making the detection of small lesions somewhat

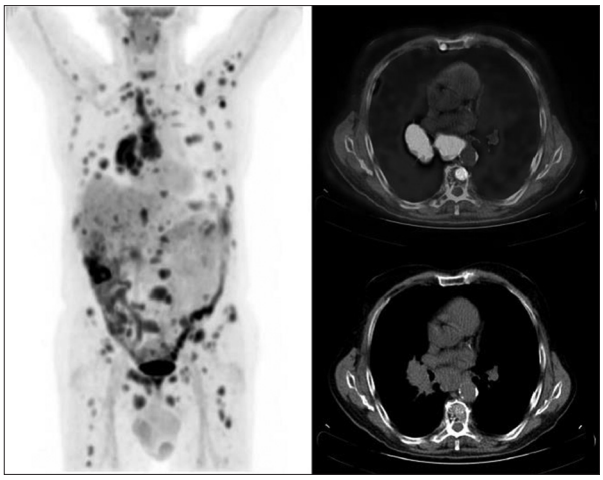

Figure 3: A patient shown in this image was diagnosed by bronchoscopy and endobronchial ultrasound with non-small cell lung cancer. "No signs of distant metastases were observed on computed tomography of the chest and abdomen, or in the biochemical analysis." Nevertheless, positron emission tomography-computed tomography identified numerous bone metastases. This required the treatment method to be modified from curative-intent to palliative

difficult. While recent methods have lowered the complications of a partial volume effect and respiratory motion,[63-65] these problems are yet to be eradicated. Hence, these patients must be identified through reliable follow-up programs, such as that proposed by the Fleischner Society.[66,67]

Unnecessary thoracotomy and other curative-intent treatment trials

Several studies have reported that a substantial number of patients with lung cancer undergoing surgery have from occult disseminated disease. These patients suffer from the complications and side effects of drug therapy trials, and since there is no benefit, a number of cases of unnecessary treatment could be eliminated. Studies in this area have not shown benefits on mortality with the use of PET-CT. However, since the hospital mortality rate following pneumonectomy is >5% (lower for lobectomy and segmentectomy), reducing instances of surgery should be helpful in decreasing mortality rates.[68] In addition, the patients who are safe from the risk of death due to thoracotomy are also protected from the harmful effects of long-term chemotherapy and radiotherapy, which are considered to be the result of inappropriate surgery. An example of this is shown in Figure 3.

Mediastinal staging

The result of a reduction in invasive mediastinal staging methods was measured based on the hypothesis that reducing the number of invasive procedures such as endoscopic ultrasound (EUS), endobronchial ultrasound (EBUS), and mediastinoscopy would reduce the associated diagnosis time and the morbidity linked to invasive testing methods and general anesthesia. A majority of the reviewed studies concluded that PET-CT was unsuitable for most patients in

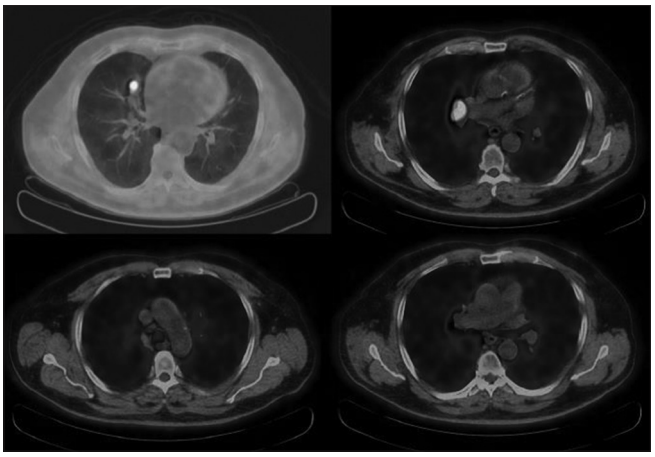

Figure 4: Refractory hyponatremia was observed in a patient; computed tomography and positron emission tomography-computed tomography revealed a metabolic active tumor of 2.8 cm in the middle lobe, while enlarged lymph nodes at stations 11R and 4R were found on computed tomography. Positron emission tomography-computed tomography was confirmed at station 11R alongside the tumor. "No fluoro-2-deoxy-D-glucose-accumulation was found in stations 4R and 7, but endobronchial ultrasound and endoscopic ultrasound were positive for malignancy in stations 11R, 4R, and 7." The tumor, node, and metastasis classification based on computed tomography and positron emission tomography-computed tomography was T1bN1M0; thus, it was modified to T1bN2M0 following endobronchial ultrasound and endoscopic ultrasound. Considering the treatment was changed from primary surgery to curative-intent chemotherapy and radiotherapy, the clinical implications herein are profound

verifying or excluding mediastinal dissemination, although this result "was seldom observed in patients with small peripheral primary tumors without enlarged lymph nodes on CT or metabolic active glands on PET-CT." In contrast to the proven applications of PET-CT, such a modality may not be adequate for ruling out lymph node dissemination, with the exception of small peripheral tumors. An example of this situation is shown in Figure 4. Although this issue was not the main focus of our research, it is important to note that a PET-CT image alone is insufficient for detecting malignancy. Thus, all of the positive findings of PET-CT should be generally documented by cytology or histology. A practical exception is patients with extensive dissemination in their imaging. "No patient should be considered without treatment if only one or a few PET-CT-positive foci are present, as many nonmalignant conditions (such as infection, sarcoidosis, and tuberculosis) are known to be PET-CT positive."[34] Furthermore, PET-CT must be conducted prior to any interventions such as a biopsy, EBUS, and surgery, because these methods could lead to false-positive PET-CT results.[69]

Conclusions

This study may form the basis for standardizing the application of PET-CT in lung cancer in areas where PET-CT is not commonly used. It would be logical to test the use of

initial PET-CT in evaluating lung cancer for these areas. Early study results should be assessed on the number of (1) avoided invasive testing and related complications, (2) avoided unnecessary treatment trials, and (3) missed malignant diagnoses. One of the problems posed by PET-CT is the number of false-positive results with at least four negative implications. Another problem is patient anxiety in anticipating ruling out of malignancy. Another problem is that a false positive could at times remove the focus on the actual illness, for example, when PET-CT causes doubt about second cancer. The best approach toward treating this dilemma remains unsolved; however, in our study, we examined all random findings that were not clearly physiologic. ^{18}F-FDG PET-CT is an appropriate imaging technique for suspected or proven lung cancer and should be used as a standard procedure. This study may form the basis for the following statements:

1. SPNs can safely be considered to be benign provided the PET-CT result is negative, with the exception of SPNs <1 cm and nonsolid SPNs (Recommendation A)
2. No curative-intent treatment such as surgery should be initiated until PET-CT has ruled out occult distant metastasis (Recommendation A)
3. In general, lymph node metastasis in the mediastinum cannot be ruled out based only on a negative PET-CT result (Recommendation A).

Consequently, regardless of mediastinal PET-CT results, invasive staging using EBUS, EUS, or mediastinoscopy should be conducted in most patients prior to curative-intent treatment trials.

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Conflicts of interest

There are no conflicts of interest.

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