

## Current state of imaging for lung cancer staging

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Lung cancer remains the leading cause of cancer death among men and women in the United States. In 2002 169,400 patients were diagnosed with lung cancer and 155,000 deaths resulted from the disease [1]. In part, this poor survival reflects the fact that the majority of patients who have lung cancer present with locally advanced or metastatic disease. Forty-nine percent of patients who were diagnosed lung cancer in 2002 were found to have distant metastases at the time of presentation, and 26% of patients had mediastinal lymph node involvement [1]. Therefore, less than 25% of patients are candidates for surgery as the sole method of treatment.

From the perspective of the thoracic surgeon, the primary issue in the care of patients who have non-small-cell lung cancer is a determination of the stage of their disease. Stage determines the treatment patients will receive and their prognosis. Inaccurate staging might deny patients access to potentially curative treatment and expose them to unnecessary therapy. In effect, accurate staging is as critical to the care of patients who have lung cancer as their ultimate treatment.

The critical issue in staging is to identify patients who have extrathoracic disease, who are not candidates for surgery, and to identify patients who have N2 disease, whose survival might be improved by induction chemotherapy followed by surgery. Several imaging techniques are available to help inform the determination of a patient's stage, including CT, positron emission tomography (PET), bone scintigra-

phy (BS), and MRI. Each of these studies carries a financial cost and measurable false-positive and false-negative rates. The injudicious use of imaging leads to excessive costs and unnecessary invasive procedures. Worse, a false-positive study might deny a patient potentially curative surgery. This article reviews these imaging techniques and their indications for use based on current guidelines of clinical practice.

### Staging the primary tumor

When a pulmonary nodule is found to be malignant, the initial step in defining the clinical stage of the tumor is to determine the tumor (T) stage. Outside the context of clinical trials, the distinction between T1 and T2 disease does not usually impact on the recommendation for treatment; however, the distinction between invasion of the chest wall or other resectable structures (T3) versus mediastinal structures such as the trachea or heart (T4) has significant surgical implications.

#### CT

Tumors that invade the chest wall are considered to be T3 disease. The finding of chest wall invasion at the time of surgery does not preclude curative resection; however, the preoperative diagnosis of chest wall invasion does allow the surgeon and patient to anticipate en-bloc resection of the chest wall with the primary tumor and the need for subsequent reconstruction. Several findings on CT such as extensive contact with the parietal pleura, extrapleural soft tissue, and obliteration of the extrapleural fat plane suggest chest wall invasion but are relatively

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nonspecific [2,3] (Fig. 1). The only findings on CT that have been found to be highly predictive of chest wall invasion are destruction of adjacent ribs and clear extension of tumor beyond the chest wall [4], and even these signs have a sensitivity of only 20% [5]. The most accurate predictor of T3 disease is dynamic CT, which can document fixation of the tumor to the chest wall through the respiratory cycle [6]. This specialized study is not widely available, however.

The distinction between resectable tumors, which invade the mediastinal pleura (T3), and unresectable tumors, which invade structures such as the heart or trachea (T4), is difficult to make on the basis of CT imaging alone. Frequently, tumors abut the mediastinum and obliterate the normal fat plane on CT but are deemed to be resectable at the time of thoracotomy (Fig. 2). For example, in a retrospective study of 180 patients who had lung cancer staged by conventional CT, only 62% of patients staged T4 by

CT were found to have T4 disease at the time of surgery [7]. Findings on CT that increase the likelihood of unresectability include involvement of the carina or encasement of more than half the circumference of the aorta, esophagus, or proximal left and right pulmonary arteries [8]; however, even when these signs are strictly applied, the predictive value of CT in determining T4 disease is quite low [9,10]. Tumors that have equivocal signs of invasion—even with obliteration of the normal mediastinal fat planes—should not be considered to be unresectable on the basis of CT imaging alone [11].

### MRI

MRI has found limited applicability in the imaging of lung cancer, although it might be more useful than CT scanning in specific circumstances. In 1991 the Radiologic Diagnostic Oncology Group (RDOG)

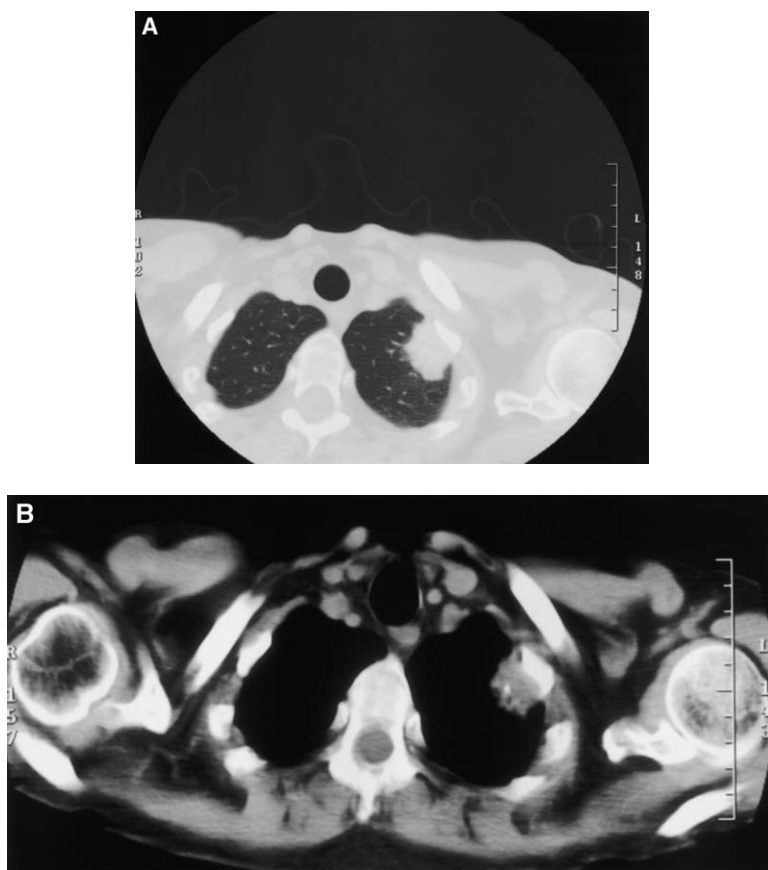


Fig. 1. False-positive CT scan suggesting chest wall invasion. (A) Lung window, (B) mediastinal window.



Fig. 2. False-positive CT scan of mediastinal invasion. The tumor (*arrow*) was completely resectable at the time of thoracotomy and the mediastinal pleura was not invaded.

directly compared the accuracy of MRI and CT in 170 patients who had operable non-small cell lung cancer. The sensitivity and specificity of CT in distinguishing T0–2 from T3–4 tumors were 63% and 84%, respectively. No significant difference was noted between CT and MRI, which had a sensitivity and specificity of 56% and 80%, respectively [12]. Although no differences were noted in the determination of chest wall or airway invasion, MRI was significantly more accurate in determining invasion of the mediastinum.

Since the RDOG report, MRI technology has improved, and its utility in evaluating patients who have lung cancer has expanded. For example, the development of MR angiography has allowed for much improved resolution of hilar and mediastinal vessels. In a pilot study of 50 patients imaged with MR angiography, the overall accuracy in predicting hilar or mediastinal invasion was 88%, which was superior to contrast-enhanced CT or conventional T1-weighted MRI [13]. However, because of the low imaging signal of air, MRI is inferior to conventional CT in documenting endobronchial invasion [14].

One area in which MRI is clearly superior to CT is in the evaluation of tumors of the superior sulcus. The structures adjacent to the apex of the lung (eg, the brachial plexus and subclavian vessels) are not well visualized in the axial plane. MRI, unlike CT, can image these structures in the coronal and sagittal plane, and consequently is the imaging study of choice for Pancoast tumors [15]. MRI can also

determine invasion of the vertebral body and extension of disease into the neural foramina, which is critical information for preoperative planning [16] (Fig. 3). Overall, MRI has been found to have a 94% correlation with surgical findings for Pancoast tumors, compared with 63% accuracy for CT [17].

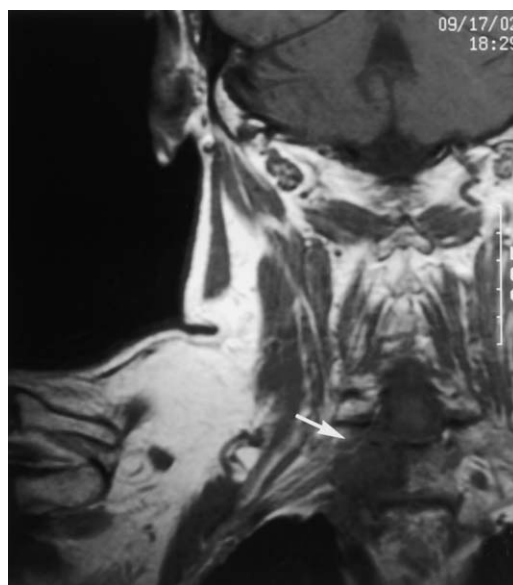


Fig. 3. T1-weighted MRI showing vertebral invasion (*arrow*) by a Pancoast tumor.

### *Thoracoscopy*

Although a detailed discussion is outside the scope of this article, it should be mentioned that minimally invasive techniques can be used to determine resectability when imaging is equivocal. Thoracoscopy allows for the cytologic evaluation of pleural effusions and can determine invasion of the chest wall and mediastinal structures by direct visualization [18,19]. Thoracoscopy can also be used to directly explore the pericardial cavity. In a small study of 27 patients who had clinical T4 tumors, the pericardial sac was explored using the same equipment and port sites as for standard thoracoscopy. This technique identified, with no complications, six patients who were unresectable on the basis of invasion of the heart or main pulmonary artery [20].

### **Staging the mediastinum**

The involvement of mediastinal lymph nodes has a significant impact on the treatment and prognosis of patients who have lung cancer. Mediastinoscopy remains the gold standard to detect N2 nodal metastases before thoracotomy. The procedure can be performed with a complication rate well below 1% and has a negative predictive value (NPV) of 93% [21]. Although noninvasive modalities such as PET have emerged to stage the mediastinum, none of these techniques has a specificity high enough to exclude patients from resection without confirmation by tissue biopsy.

### *CT*

The detection of nodal metastases on CT is based on nodal size. By convention, a mediastinal node larger than 1 cm in the short axis is considered to be enlarged [22]; however, this convention suffers from many limitations. First, the normal size of mediastinal lymph nodes varies by nodal station. Hilar nodes can measure up to 7 mm, and benign subcarinal nodes can be as large as 15 mm [23]. In addition, surrounding mediastinal structures and volume averaging effects might make precise determination of nodal size difficult. Consequently, interobserver variability in the measurement of nodal size is relatively high. Most importantly, normal-sized nodes might harbor micrometastatic disease and enlarged nodes might be reactive because of infection or inflammatory processes rather than malignancy. The accuracy of CT scanning, therefore, is relatively low. In a meta-analysis of more than 20 studies with

3438 evaluable patients, the pooled sensitivity and specificity of CT was 57% and 82%, respectively [24]. There was marked heterogeneity between studies, however, which was in part attributable to variability between study populations. For instance, the incidence of micrometastases to mediastinal lymph nodes is higher in adenocarcinomas compared with squamous cell cancers. As a consequence, the false-negative rate of CT scans is significantly higher in this group of patients [25]. Furthermore, the specificity of CT varies with the location where the study is performed. For example, the false-positive rate will be higher in areas where sarcoidosis or other granulomatous diseases are endemic [26].

### *MRI*

MR signal characteristics and relaxation times are unable to discriminate benign from malignant nodes; therefore, the only criterion used to determine nodal involvement in standard MR imaging is that of size [27]. Consequently, the overall accuracy of MRI in detecting nodal metastases is no better than that of CT [9,12]. Other limitations in the imaging of thoracic lymph nodes are unique to MRI. For example, MRI is unable to visualize calcification within a lymph node, a finding that would suggest a benign etiology for nodal enlargement on CT. Because of the poor spatial resolution of MRI, a group of normal-sized nodes might be interpreted as a single node, which would falsely raise the suspicion of metastatic disease [28].

Refinements in MRI might make this modality more useful for determining nodal stage in the future. It has been shown in a small pilot study that the pattern of enhancement of malignant nodes with gadolinium is significantly different than for benign nodes [29]. Although larger, confirmatory studies are needed, this technique might prove to be a relatively simple way to discriminate patients who have nodal disease. Another emerging technology is that of MR lymphography, in which superparamagnetic iron oxide particles are used as the contrast agent. Iron oxide particles are readily phagocytosed by macrophages in normal nodal tissue and lower the signal intensity of the node on T2-weighted sequences. Nodes that harbor metastatic disease do not accumulate the contrast agent as readily and therefore have greater signal intensity on T2 images [30]. Early studies of MR lymphography have demonstrated high sensitivity and specificity in patients who have urologic malignancies [31]; however, only small studies on patients who have bronchogenic carcinoma have been reported so far [32].

### Positron emission tomography

Without question, PET scanning using fluorodeoxy glucose (FDG) has shown the greatest promise in staging the mediastinum noninvasively (Fig. 4). In some centers PET scanning has become an almost routine component of the preoperative evaluation of patients who have lung cancer. This practice is justified by several meta-analyses that have demonstrated the superiority of PET over CT in staging the mediastinum [20,33,34]. In a representative meta-analysis [20] that included 1045 patients enrolled in 18 studies, the pooled sensitivity and specificity of PET scanning were 84% and 89%, respectively. A

direct comparison of PET and CT by receiver operating characteristic analysis demonstrated PET scanning to be significantly more accurate. Perhaps the most relevant measure of a staging study is the negative predictive value (NPV) of the test, which defines the likelihood that a patient who has a negative test result does not have the disease. The NPV of PET scanning to stage the mediastinum in this study was 93%, compared with only 83% for CT scanning.

Several studies have documented the high impact and cost-effectiveness of PET scanning on clinical decision-making [35,36]. In addition to these retrospective series, the utility of PET scanning has been evaluated in a prospective, randomized trial. The

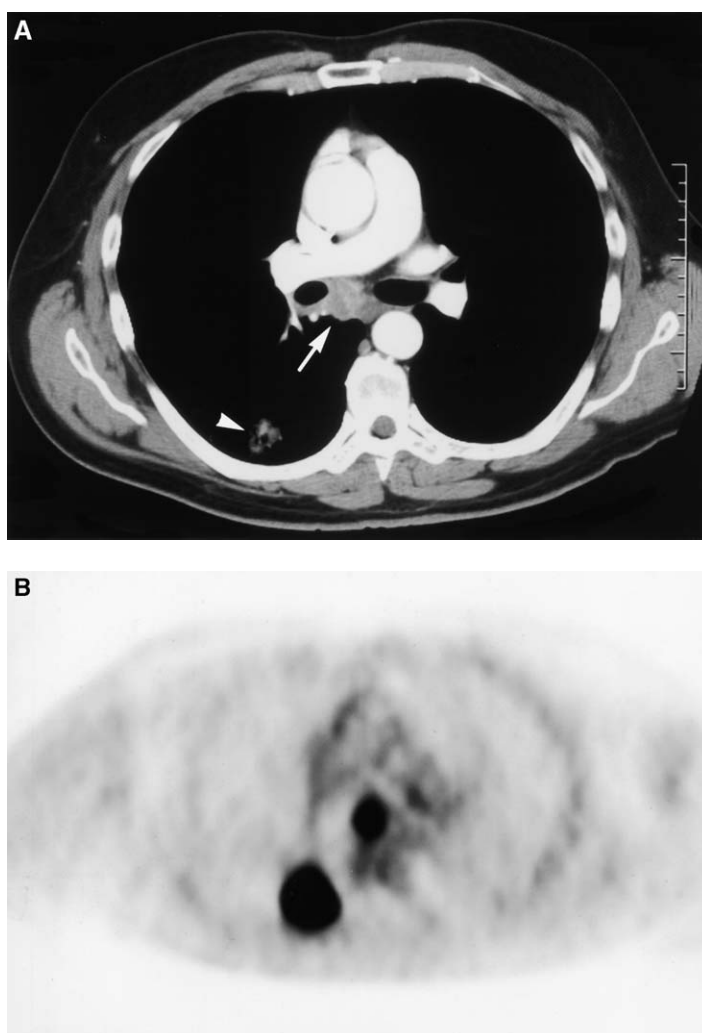


Fig. 4. Mediastinal spread of a right lower lobe lung cancer. (A) Subcarinal lymphadenopathy (arrow) on chest CT. The primary tumor is also visible (arrowhead). (B) An axial FDG-PET scan demonstrating increased glucose uptake in the primary tumor and the subcarinal space.

results of this trial, known as the PET in Lung Cancer Staging Study (PLUS) were reported in 2002 [37]. In this trial 188 patients who had suspected or proven non-small cell lung cancer were assigned to a conventional workup (as determined by local practice) or a conventional workup plus a PET scan. The end-point of the study was a reduction in the number of futile thoracotomies, which was defined as thoracotomy for benign disease, thoracotomy without resection, unsuspected N2 or T4 disease, or relapse within 12 months of surgery. In the conventional workup group 41% of patients had a futile thoracotomy compared with 21% in the PET group, which represents a relative reduction of 51%, which is highly significant. One criticism of this study is that the extent of the conventional workup was not specified in the protocol. For example, it is not clear whether or not the percentage of patients in whom the suspicion of lung cancer was confirmed by a needle biopsy was similar in both groups. Such a difference might explain the observation that the number of thoracotomies for benign disease was three times higher in the conventional group than the PET scan group. In centers in which needle biopsy is practiced routinely, the impact of PET scans would be less than that reported by the PLUS trialists.

There are other limitations of PET scanning. The test carries considerable cost and limited availability. In the United States the cost of a PET scan is approximately \$2000. Furthermore, given a half-life of 110 minutes, the radioisotope must be produced by an onsite cyclotron or be manufactured within 200 km

of the imaging center. Clinicians must also be cautioned that not all PET scan centers use the same technology. The published literature demonstrating the superiority of PET to stage the mediastinum is based on the use of dedicated PET scanners. Competing systems using gamma cameras have been introduced in an effort to lower the cost of the study. It is estimated that there are nearly twice as many camera-based scanners than dedicated PET scanners currently in use [38]; however, imaging based on gamma cameras is clearly less sensitive than that of a dedicated PET system, and the overall accuracy might not be much higher than standard CT alone [39].

Even with the use of dedicated systems, the accuracy of PET scans should not be assumed in all clinical situations. The spatial resolution of PET scans is clearly inferior to that of CT, and PET is particularly poor at documenting N1 disease [31]. In addition, the utility of PET in restaging patients after induction chemotherapy has not been well established. To date, two studies reporting on a total of 90 patients have been published with contradictory findings [40,41]. In the authors' experience PET did not predict nodal status accurately in more than half of patients restaged after induction chemotherapy, with an equal proportion over- and understaged [42].

#### *CT/positron emission tomography fusion*

Interpretation of a PET scan in the presence of CT images clearly improves the sensitivity and spec-

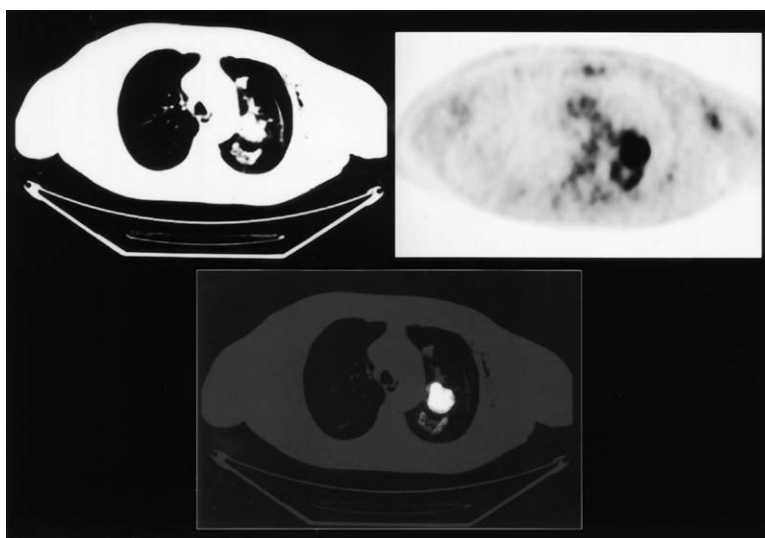


Fig. 5. A CT/PET fusion of a left lower lobe lung cancer.



ificity of the study [43]. The development of hybrid PET/CT scanners is a natural outgrowth of this observation (Fig. 5). The first prototype, which used a single-detector CT scanner combined with a partial-ring rotating PET scanner, was introduced recently [44]. The benefits of this new technology have not yet been clarified. Experience with a more advanced scanner using multidetector CT combined with a full-ring detector PET scanner was reported in 2002. In this study of 53 patients who had a variety of malignancies including lung cancer, PET/CT fusion was felt to significantly improve diagnostic accuracy over PET alone [45]. Another variation of this technology is the combination of CT with a camera-based PET scanner. A small study of 21 patients who had thoracic malignancies showed that the accuracy of this system was equal to that of a dedicated PET scanner [46]. If replicated in larger studies, this finding might obviate the need for dedicated PET scanners, which are more expensive and limited in availability.

### *Endoscopic ultrasound*

While mediastinoscopy is a proven tool for staging patients who have non-small cell lung cancer, the technique has recognized limitations. Although mediastinoscopy is an outpatient procedure, the procedure requires general anesthesia, is difficult to perform more than once, and has a small but defined complication rate. Certain nodal stations such as levels VIII and IX are also difficult to access by standard mediastinoscopy. Endoscopic ultrasound (EUS) has been proposed as an alternative to mediastinoscopy in specific circumstances. The technique is no different than EUS used for staging esophageal cancer and involves the use of an ultrasound probe placed at the tip of a modified endoscope. EUS provides excellent visualization of the subcarinal space and nodes in the inferior mediastinum. Suspicious nodes are identified on the basis of size and by disruption of the normal architecture, and they can be sampled by fine-needle aspiration (FNA). In a pooled analysis of five studies, the reported sensitivity for this technique was 78% and the specificity was 71% [20]; however, a recent study in which all nodes were sampled regardless of appearance showed that the stage of 42% of patients was changed by EUS/FNA [47]. A significant drawback of this technique is its inability to visualize right-sided paratracheal nodes. Given this limitation, it is likely that EUS will at best complement, rather than replace, staging by CT, PET, or mediastinoscopy.

### **The search for extrathoracic disease**

The central questions in the search for extrathoracic disease are when such an investigation is worthwhile and to what extent it should be pursued. Patients who have clinical signs or symptoms of distant disease should undergo a full metastatic workup; however, in the absence of clinical findings the yield of such a workup is quite low. For example, the incidence of silent metastases in patients who have clinical stage I lung cancer is as low as 1% [48]. A uniform policy of imaging for extrathoracic disease in this group of patients would therefore incur considerable expense, unnecessary invasive procedures, and perhaps a significant delay in definitive treatment [49].

The ability of a thorough clinical evaluation to exclude metastatic disease has been well studied. Seventeen studies have been published in which clinical evaluation was compared with the gold standard of CT imaging of the brain. The pooled NPV among 1784 patients studied was 94% [20]. In the same meta-analysis of studies evaluating the presence of abdominal or bony metastases by the clinical examination (including routine serum chemistry), the NPV was 95% and 90%, respectively [20].

If the search for silent metastases is restricted to patients who have more advanced-stage disease, the yield will be substantially higher. Approximately 25% of patients who have clinical N2 disease will harbor metastatic disease [50], and patients who have tumors greater than 3 cm are more likely to have brain metastases when screened by MRI. Tumor histology alone is not an independent risk factor for metastatic disease [42]. Consequently, there is no indication that patients who have adenocarcinoma require a more thorough evaluation than patients who have squamous cell cancer in the absence of clinical findings.

The single randomized study to address the issue of screening for metastases in patients who have non-small-cell lung cancer was reported by the Canadian Lung Oncology Group in 2001 [51]. In this study all patients were evaluated with a CT of the chest and mediastinoscopy. Patients were then randomized to immediate thoracotomy or additional evaluation by bone scintigraphy and dedicated CT scans of the abdomen and brain. The hypothesis of the study was that additional evaluation would lead to a lower rate of thoracotomies without cure, defined as an incomplete resection or thoracotomy with subsequent recurrence. Among the 634 patients who were randomized, thoracotomy without cure occurred in 73 patients in the limited investigation group and in 58 patients in the full investigation

group. This trend was not statistically significant ( $P = 0.20$ ) and no difference in survival was observed between the two groups. An economic analysis calculated less cost in the full investigation group because of the avoidance of additional surgical procedures; however, it is not clear whether or not this would hold true in the United States' health care system.

Should a metastatic workup be deemed necessary, some organ-specific considerations are discussed herein, followed by the authors' current imaging recommendations.

### Brain

Central nervous system (CNS) metastases occur in less than 3% of all asymptomatic lung cancer patients [52]. Furthermore, in one study routine CNS scanning led to a false-positive rate of 11% [53]. While asymptomatic patients need not be screened for brain metastases, the definition of what constitutes symptoms differs widely among physicians. Often, patients who have mild symptoms such as headache or dizziness are classified as asymptomatic, although these patients are clearly documented to have a higher rate of brain metastases [54].

CT and MRI are both suitable imaging studies for evaluating for brain metastases. Gadolinium-enhanced MRI can detect smaller lesions and has a higher sensitivity than a CT with contrast. Although MRI can detect more lesions in a *single patient*, it has not been shown to upstage a greater *number of*

*patients* compared with CT [55]. Consequently, the detection of smaller metastases by MRI is rarely of clinical significance. Prolonged survival in patients whose lesions were detected by MRI over CT is likely caused by lead-time bias rather than a true survival benefit [56].

### Adrenal

Adrenal lesions are common in the general population and most often represent adrenal adenomas [57]. The assumption that an adrenal mass in a cancer patient represents a metastasis is not always valid. Although an adrenal mass is more likely to be malignant in patients who have advanced-stage disease [58], adenomas predominate in patients who have clinical stage IA cancer [59]. It is therefore critical that these lesions be characterized precisely. A patient can be denied potentially curative surgery if an adenoma is mistakenly presumed to represent metastatic disease. On the other hand, select patients might be candidates for synchronous adrenalectomy and pulmonary resection if a definitive diagnosis is made.

Typically, an adrenal mass is diagnosed on the lower cuts of a contrast-enhanced chest CT performed to evaluate the primary tumor (Fig. 6). Characteristics of an adenoma include a low attenuation lesion of less than 5 cm with a smooth, high attenuation rim. A definitive diagnosis based on these criteria is not always possible, however, and further assessment becomes necessary [60]. One option is to acquire delayed images to observe the pattern of



Fig. 6. CT scan with contrast demonstrating bilateral adrenal metastases (arrows).



contrast washout. Adenomas typically display moderate contrast enhancement with substantial washout after 15 minutes. Adrenal metastases show the opposite pattern: intense enhancement and little washout. This technique has a reported sensitivity and specificity of 96% [61].

Another option is to repeat the CT without contrast. Adenomas are characterized by their high fat content and consequently have a low attenuation value on nonenhanced CT. The specificity of the method will vary with the threshold used to define malignancy. In a meta-analysis of 10 studies, the specificity varied from 100% at a cutoff of 2 Hounsfield units (HU) to 87% at 20 HU. This study recommended that a threshold of 10 HU be used [62].

MRI has also been used to differentiate adenomas from malignant disease on the basis of fat content. Initial experience with MRI has suggested that adenomas can be identified by their low signal on T2-weighted images [63]. Further evaluation has shown that this finding is relatively nonspecific, and newer techniques using MR spectroscopy have supplanted routine MR imaging. Using chemical shift imaging and dynamic gadolinium enhancement, MRI was shown to have a specificity of 100% and specificity of 81% [64]. Unfortunately, this specialized examination is not widely available.

Finally, PET scanning can also be used to characterize adrenal masses. In three studies evaluating 88 patients who had a variety of malignancies, PET scanning was shown to have a sensitivity of 100% and a specificity between 80% and 100% [65–67]. Thus, an adrenal mass seen on CT that is negative on PET is unlikely to be malignant. However, because of a small but defined false-positive rate, patients should undergo a confirmatory percutaneous needle biopsy if the PET scan suggests an adrenal metastasis.

### Bone

Routine BS in asymptomatic patients leads to positive results in up to 40% of cases [68], however bone scans are relatively nonspecific and have a false-positive rate as high as 40% because of the prevalence of preexisting traumatic or degenerative skeletal disease [69]. MRI is also plagued by a high number of false-positive scans, and it does not seem that the overall accuracy of MRI surpasses that of standard BS [70]. Although there are fewer studies of PET scanning in this setting, they suggest that its sensitivity and specificity are at least equal to, if not superior to, bone scans [71,72]. In one study PET was shown to have an equivalent sensitivity but a superior specificity (98% versus 61%) to bone scans, but

direct comparison between these techniques is difficult because of a flawed study design. In the majority of reports a suspicious lesion was not definitively diagnosed by a fine needle biopsy, so the true false-positive rate could not be established.

### Extrathoracic staging with positron emission tomography

The hope that whole-body PET might replace the standard metastatic workup for patients who have lung cancer deserves special mention (Fig. 7). The accuracy of PET in imaging metastases to the bone or solid organs excluding the brain equals or surpasses that of standard imaging. PET has been shown to detect extrathoracic metastases in 11% to 14% of patients who were thought to have localized disease by conventional imaging [61,73]. Furthermore, negative PET scans can exclude metastatic disease suggested by CT scans with a reported 1% false-negative rate [61,63].

PET has some limitations in whole-body staging, however. PET cannot replace standard imaging of the brain. Because of the high metabolic rate of nor-

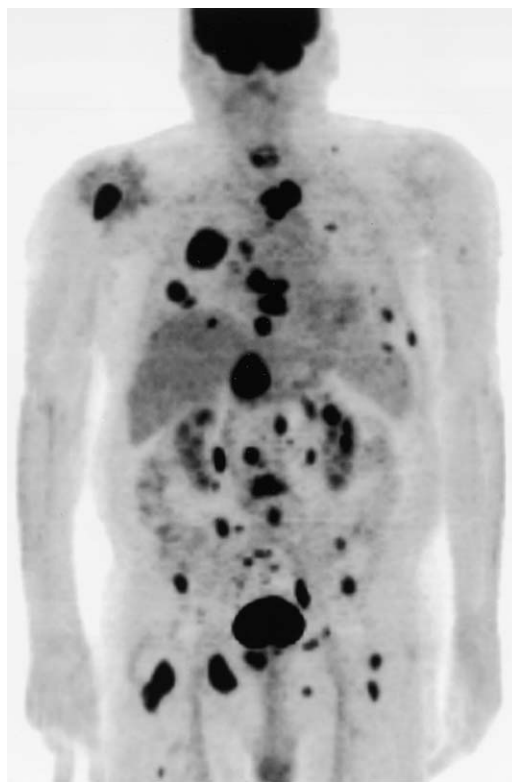


Fig. 7. FDG-PET demonstrating multiple sites of metastatic disease.

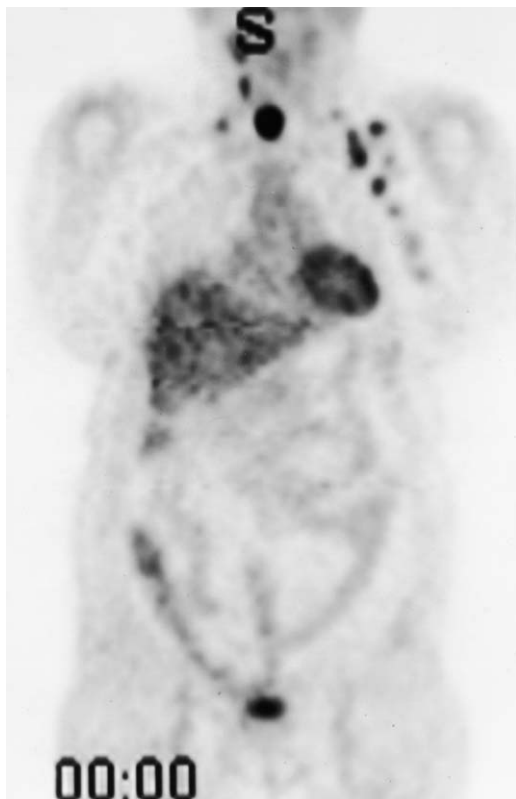


Fig. 8. False-positive FDG-PET of an early-stage lung cancer. Supraclavicular lymph node biopsy revealed sclerosing lymphadenitis.

mal brain tissue, PET is extremely poor at detecting cerebral metastases, with a sensitivity of only 60% [61]. There is also a concern regarding the widespread application of whole-body imaging in an asymptomatic population. As more patients who have early-stage lung cancer are staged by PET, the issue of false-positive studies becomes more relevant (Fig. 8). If every asymptomatic patient was screened with PET, which has a specificity between 80% and 100% for bone and adrenal lesions, a significant number of invasive and perhaps unnecessary diagnostic procedures would result.

## Summary

Proper selection and interpretation of imaging studies is essential to provide optimal treatment to patients who have lung cancer. The following combines the recommendations of the American College

of Chest Physicians [74] and the authors' current clinical practice guidelines:

- All patients who have known or suspected lung cancer should undergo a CT of the chest and upper abdomen.
- An FDG-PET study should be performed, if available.
- Mediastinoscopy should be performed in all patients except those who have peripheral small (<2 cm) tumors and no evidence of N2 disease on CT or PET imaging.
- MRI should be performed for tumors of the superior sulcus to define the relationship of the tumor to adjacent neurovascular structures.
- Patients who have neurologic signs or symptoms should undergo a brain imaging study (CT or MRI).
- Screening for extrathoracic disease is not necessary in asymptomatic patients who have clinical stage I or II disease.

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