Update in PET Imaging of Nonsmall Cell Lung Cancer

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NONSMALL CELL Lung cancer (NSCLC) is the leading cause of cancer death in both men and women in the United States. Despite continuing developments in diagnosis and treatment, the mortality from lung cancer remains high, with an overall 5-year survival rate of only 15%.[1] The primary treatment of lung cancer is surgery, and the best chance for a complete cure comes from total resection of localized disease. Once nodal or distant metastases have developed, the benefits of primary surgical intervention decline and patients may benefit from adjuvant chemotherapy or radiation therapy. Accurate delineation of disease extent is therefore critical in treatment planning of patients with lung cancer. Positron emission tomography (PET) with 2-[F-18]-2-deoxy-D-glucose, or fluorodeoxyglucose (FDG), has proven to be a valuable noninvasive imaging test for the evaluation of the patient with known or suspected lung cancer. This article will review the current status of PET imaging for the diagnosis, staging, and restaging of NSCLC and will also discuss potential future applications of the technique.

DIAGNOSIS/EVALUATION OF PULMONARY NODULES

The incidental identification of one or more pulmonary nodules is a common occurrence. In the United States, approximately 150,000 indeterminate pulmonary nodules are discovered each year, or 41 nodules per working hour. It is likely that lung cancer screening programs, if implemented, will result in far greater numbers of nodules identified.[2,3] Estimates of the likelihood of malignancy in these nodules vary widely, but whatever the precise value the incidence of cancer is not low enough for benign neglect, and not high enough for uniform resection.

Strategies must therefore be developed to estimate the likelihood of malignancy for each patient who presents with a pulmonary nodule. The simplest means of assessing nodules is with x-ray computed tomography (CT). Certain patterns of calcification or the presence of fat within the nodule are virtually diagnostic of a benign etiology,[4] obviating the necessity of further testing. Thin section imaging may be required to demonstrate these findings. CT also provides some assessment of the likelihood of malignancy based on morphology and the presence of secondary findings, such as hilar or mediastinal adenopathy. In some cases, CT alone can provide sufficient information and guide further management. In patients with a high likelihood of malignancy based on CT and who are at low risk for an interventional procedure, transthoracic needle aspiration or video assisted thoracoscopy with wedge resection may be the next step. In patients with a low likelihood of malignancy based on CT and who are at high risk of procedure-related morbidity or mortality, serial radiographic follow up might be the most prudent course.

In many patients, particularly in those whose pulmonary nodules are truly indeterminate on CT, additional information regarding the likelihood of malignancy is often desired before consideration of an invasive procedure. Two widely available imaging tests can provide this information: positron emission tomography with [18-F]-fluorodeoxyglucose (FDG–PET) and contrast-enhanced dynamic CT (dCT).

Using PET, uptake of fluorodeoxyglucose is used as a means to differentiate benign from malignant pulmonary nodules. Interpretation can be performed in two ways. First, FDG uptake in a nodule can be compared with background activity in the mediastinum. Nodules that are hyperintense to the mediastinum are considered malignant, whereas nodules that are hypointense to the mediastinum are considered benign. The second means of assessment is the use of the standardized uptake value (SUV), a semiquantitative measure of fluorodeoxyglucose uptake. The most widely used cutoff for the differentiation of benign and malignant pulmonary nodules is at an SUV of 2.5, with a value below this threshold indicating a benign etiology and a value above this threshold indicating a malignant etiology. With application of these two criteria, FDG-PET is approximately 95% sen-

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Table 1. Evaluation of Pulmonary Nodules Using FDG–PET

Author	Year of Publication	Number of Patients	Malignant/Benign Nodules	PET Criteria: SUV vs. Visual	Sensitivity of PET (%)	Specificity of PET (%)
Kubota et al[5]	1990	22	12/10	SUV ≥ 2.0	83	90
Duhaylongsod et al[6]	1995	87	59/28	SUV ≥ 2.5	97	82
Bury et al[7]	1996	50	33/17	Visual assessment	100	88
Knight, et al[8]	1996	48	32/16	SUV ≥ 2.5	100	63
Gupta et al[9]	1996	61	45/16	Visual assessment	93	88
Lowe et al[10]	1997	197	120/77	SUV ≥ 2.5	96	77
Lowe et al[11]	1998	89	60/29	SUV ≥ 2.5	92	90
Totals		554	361/193		95	81

sitive and 80% specific for malignancy, as shown in Table 1.[5-11] Examples of true positive and true negative FDG–PET scans are shown in Figs 1 and 2.

There do exist causes of false positive and false negative PET scans. Although most benign pulmonary nodules do not accumulate FDG, active granulomatous infection can be metabolically active on PET imaging, as shown in Fig 3. Tuberculosis, aspergillosis, and histoplasmosis can be intensely hypermetabolic, and indistinguishable from lung cancer on PET imaging.[12-14] Noninfectious granulomas may also be metabolically active, including sarcoidosis.[15] The reverse situation is similar, that whereas most lung cancers are hypermetabolic on PET imaging, some low-grade tumors, including bronchoalveolar cell carcinoma[16] and bronchial carcinoid,[17] can have low levels of FDG accumulation. Examples of nonmetabolic lung tumors are shown in Figs 4 and F5.

Dynamic CT measures nodule perfusion and uses this information to provide an estimate of the likelihood of malignancy. The study can be performed on a standard CT scanner using intravenous iodinated contrast material. Once the nodule is localized, thin-section (3 mm) images are obtained using a narrowed field of view and a precontrast density measurement in Hounsfield units (HU) is obtained. After bolus injection of contrast material, repeat thin-section images of the nodule are obtained at 1, 2, 3, and 4 min, with density measurements performed at each time point. A peak enhancement is then determined for the nodule, as defined by the difference in density measurement between the precontrast scan and peak enhancement. Enhancing nodules are presumed to be malignant (Fig 6), and nonenhancing nodules are presumed to be benign (Fig 7). Using a threshold of 15 HU, this technique has a sensitivity of 98%, a specificity of 58%, and an overall accuracy of 77%.[18] By further lowering the threshold to 10 HU, sensitivity is increased to 100%.

Compared with FDG–PET, the sensitivity of dCT is equal to slightly higher, but the specificity is significantly lower. The primary strength of dCT, though, is its negative predictive value. For nodules that are otherwise radiographically indeterminate, a negative dCT (at a threshold of 10 HU) virtually excludes malignancy. A positive study is less definitive, and, like FDG–PET, false-positive results can be seen with granulomatous infection or inflammation.

Both FDG uptake and enhancement on dCT are related to nodule vascularity.[19] FDG–PET is additionally dependent on the surface expression of glucose transporter molecules and the presence of intracellular phosphorylating enzymes.[20,21] The information provided by these studies is therefore complimentary rather than redundant. In one study, 36 patients with pulmonary nodules larger than 8 mm were evaluated with both FDG–PET and dCT.[22] The mean time between the two studies was 7 days. Using the criterion of SUV >2.5, PET was found to have a sensitivity of 81% and a specificity of 87%. When PET scans were interpreted qualitatively, with nodule activity subjectively compared with activity in the mediastinum, sensitivity increased to 95% and specificity decreased to 80%. Dynamic CT, at a cutoff of 15 HU, was again found to have a sensitivity of 100%. The specificity of dCT was lower than previously reported, however, with a value of 27%. Of 15 patients with benign disease, 9 had a false-positive dCT but a true negative FDG-PET. Of 21 patients with malignant disease, 4 had a false-negative PET but true-positive dCT. The higher incidence of false-positive studies for both modalities compared with previously published reports may be related to a high prevalence of histoplasmosis in the study

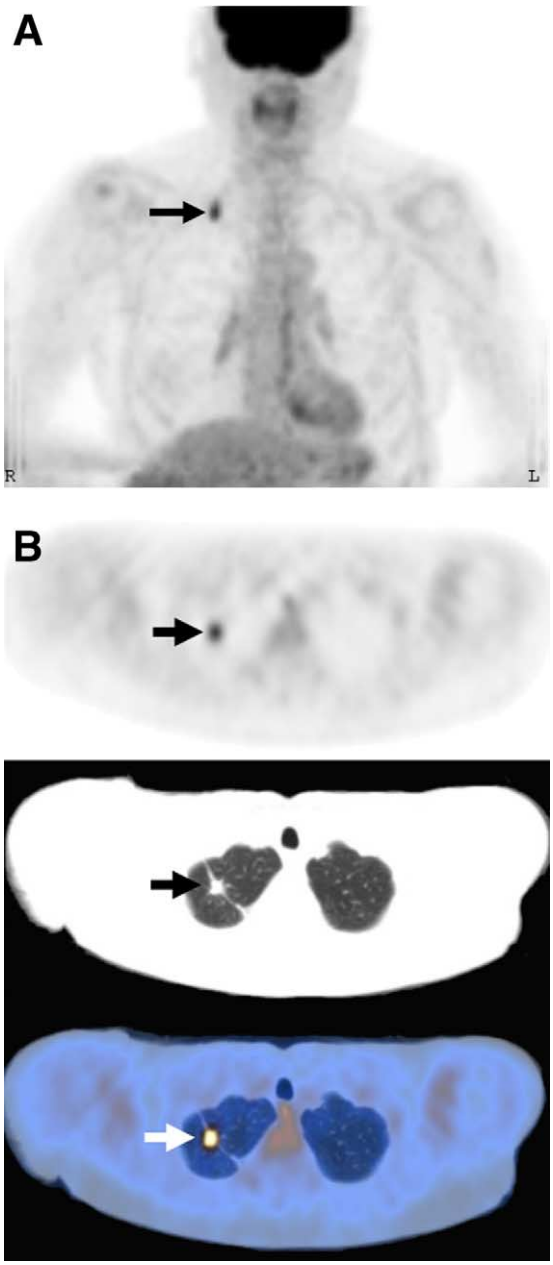

Fig 1. True-positive PET scan. A 76-year-old subject with a newly discovered right apical lung mass. (A) Frontal maximum intensity projection (MIP) image from the FDG–PET scan showing a hypermetabolic lesion at the right lung apex (arrow) with an average SUV of 6.5. There is no abnormal FDG uptake elsewhere in the chest. (B) Composite PET/CT fusion images showing the focal FDG uptake at the right lung apex localizes to a small spiculated pulmonary nodule on CT (arrows). This nodule was resected, and found to be a grade 3 pulmonary adenocarcinoma. All nodes sampled at the time of surgery were negative for tumor.

population, a phenomenon that has been reported previously.[12]

An effective approach to the diagnosis of lung cancer can employ both FDG–PET and dCT. One diagnostic algorithm is shown in Fig 8. In this approach, initial evaluation is performed with thin-section CT performed without intravenous contrast. Nodules that have typical benign characteristics do not require further workup. In day-to-day practice, many of the pulmonary nodules identified are simply too small to characterize by imaging, and must therefore be followed with serial radiographic studies until either growth or stability can be demonstrated. Nodules that are larger than 8 to 10 mm can be adequately assessed by FDG-PET or dCT.

Selection of a particular technique depends on the specific clinical setting. Patients who have a low pretest likelihood of malignancy, such as young age, nonsmokers, or a low-risk radiographic appearance of the nodule, are better evaluated with dCT. In these patients, a negative dCT scan can confidently exclude malignancy, avoiding the need for future follow up. A positive dCT study could be followed by biopsy if the patient is at low risk for procedural complication. However, the low specificity of dCT means that many positive studies will be falsely positive. FDG-PET may be a reasonable follow up examination after a positive dCT scan since over half of falsely positive dCT scans can be shown to be truly negative on PET imaging.[22]

Patients who have an intermediate or high likelihood of malignancy, including older patients, smokers, or those with worrisome radiographic features, are better evaluated with FDG–PET. In addition to primary assessment of the nodule, PET can also provide staging information in those patients who are subsequently proven to have lung cancer, as illustrated in Fig 9. The staging information thereby obtained can be used to plan subsequent diagnostic strategies, such as percutaneous needle aspiration or mediastinoscopy, and to guide appropriate therapy.

A controversial issue in PET imaging is the management of patients whose nodule is negative (defined as SUV < 2.5) by PET imaging. Unlike dCT, a negative study does not confidently exclude malignancy, and in most series the sensitivity of PET is approximately 90 to 95%.[5-11] At best, then, 1 in 10 to 1 in 20 pulmonary nodules that are negative by PET imaging may, in fact, be malig-

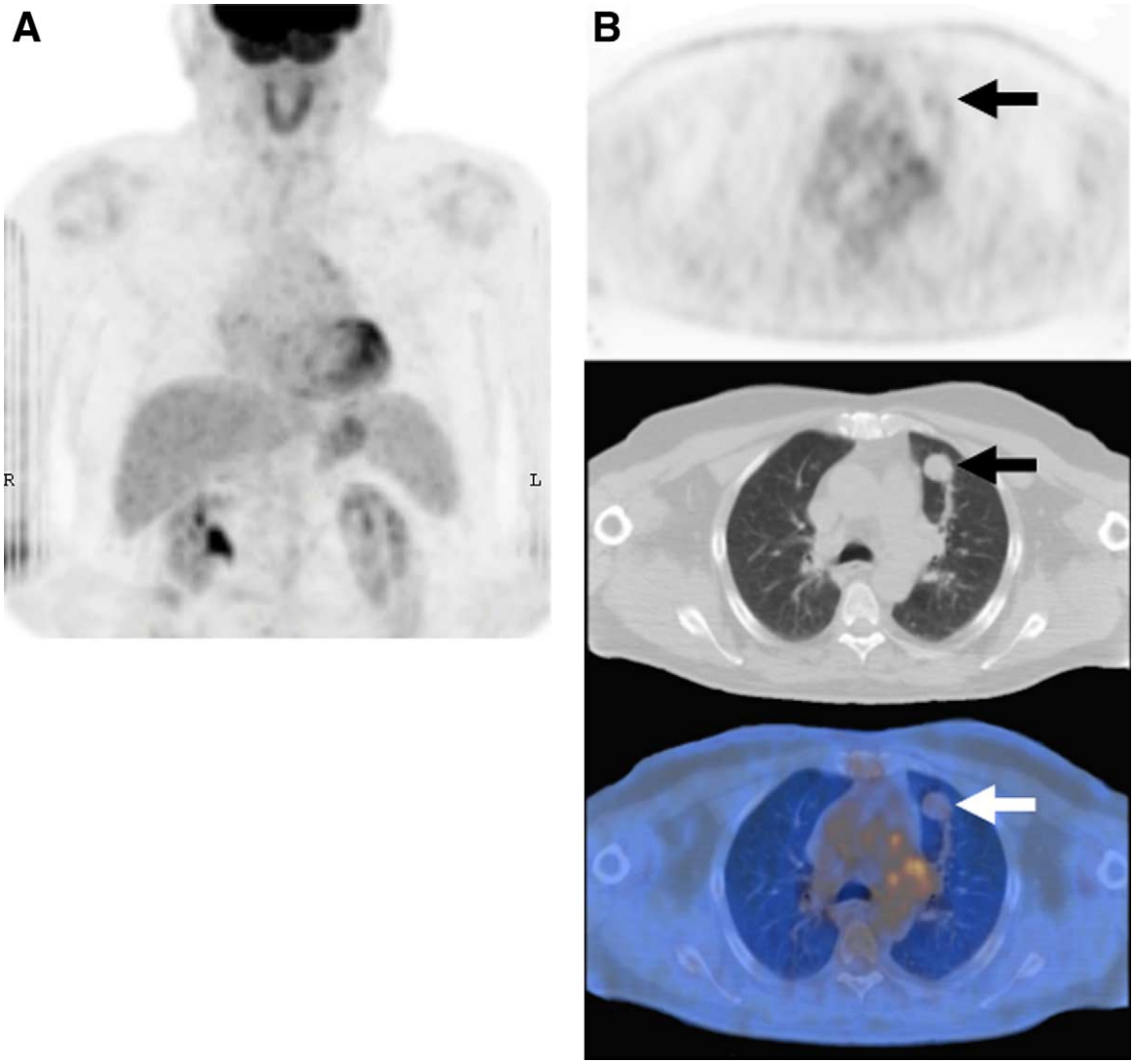

Fig 2. True-negative PET scan. A 75-year-old patient with a newly discovered pulmonary nodule in the left upper lobe. (A) Frontal MIP image from the FDG-PET scan showing no abnormal FDG uptake in the chest. (B) PET/CT fusion images showing that the nodule in the left upper lobe anteriorly has only minimal associated FDG uptake (arrows), with an average SUV of 1.2. As the nodule was new as compared with a previous CT from 3 years previous, the patient elected for resection of the nodule. Pathology revealed necrotizing granulomas, and tissue stains were positive for *Histoplasma capsulatum*.

nant. If one is willing to accept this false negative rate, then perhaps no further workup of these patients is necessary. If this is not an acceptable miss rate for cancer, one approach is to follow patients with a negative PET scan with serial CT examination. Since a negative PET scan virtually excludes high-grade lung carcinoma, there is a low risk to following patients over 1 to 2 years to assess for nodule growth. In one study, all the nodules that were falsely negative on initial PET and subsequently found to be malignant during radiographic follow-up were determined to be T1 N0 M0 cancers at the time of surgery.[23]

A second approach to patients with a negative PET scan is to obtain dual time-point PET imaging.[24,25] This appears particularly suited for patients whose nodules measure at or near the 2.5 SUV cutoff. In this approach, nodule SUV is measured 1 and 3 hours after injection of FDG. Relative FDG uptake in malignant nodules tends to increase between the scans, whereas the relative FDG uptake in benign nodules tends to remain

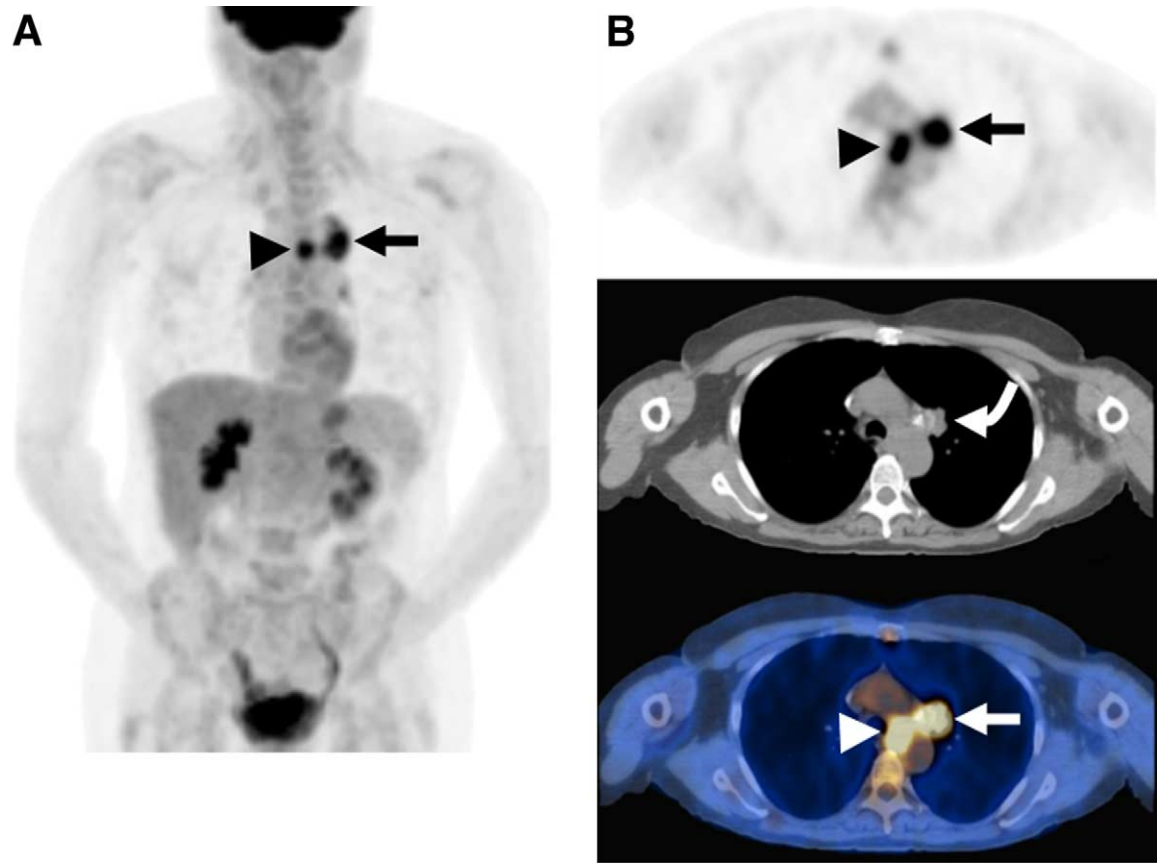

Fig 3. False-positive PET scan. A 54-year-old subject with a history of colorectal carcinoma. (A) Frontal MIP image from a PET scan obtained for restaging of colorectal cancer shows a hypermetabolic left upper lobe pulmonary nodule (arrow) with associated mediastinal adenopathy (arrowhead). (B) PET/CT fusion images confirming the hypermetabolic pulmonary (arrows) and mediastinal (arrowheads) disease. Note that on CT, the pulmonary nodule is partially calcified (curved arrow). Mediastinoscopy revealed necrotizing granulomas but no malignancy. Special stains and tissue cultures were negative.

stable or decrease slightly. In one study, using a threshold of a 10% increase in SUV between 1 and 3 hours led to an increase in sensitivity for FDG-PET from 80% to 100%. This came at a cost of specificity, however, which decreased from 94% to 89%. Early reports also indicate that dual time-point PET imaging may aid in the staging of disease in the mediastinum.[26]

DISEASE STAGING

Once the diagnosis of lung carcinoma has been established, the focus of imaging turns from diagnosis to staging. Multiple staging systems exist for NSCLC, the most standardized of which is the TNM system. T denotes features of the primary tumor mass, including size, location, and invasion; N denotes regional lymph node status; and M indicates the presence or absence of metastatic disease. Once the T, N, and M status of a particular patient's lung cancer is determined, the information is used to determine overall disease stage. The most widely used imaging tests for the determination of TNM staging are CT and FDG-PET. Magnetic resonance imaging (MRI), ultrasound, and other imaging modalities may have a role in specific clinical scenarios, but are not routinely used for disease staging.

Evaluation of the Primary Tumor

T staging is based on features of the primary tumor mass. T1 lesions are those that are confined to the pulmonary parenchyma, are less than 3 cm in maximum diameter, and do not involve a main bronchus. T2 lesions are those that are greater than 3 cm in size, invade the visceral pleura, are associated with distal atelectasis, or which involve

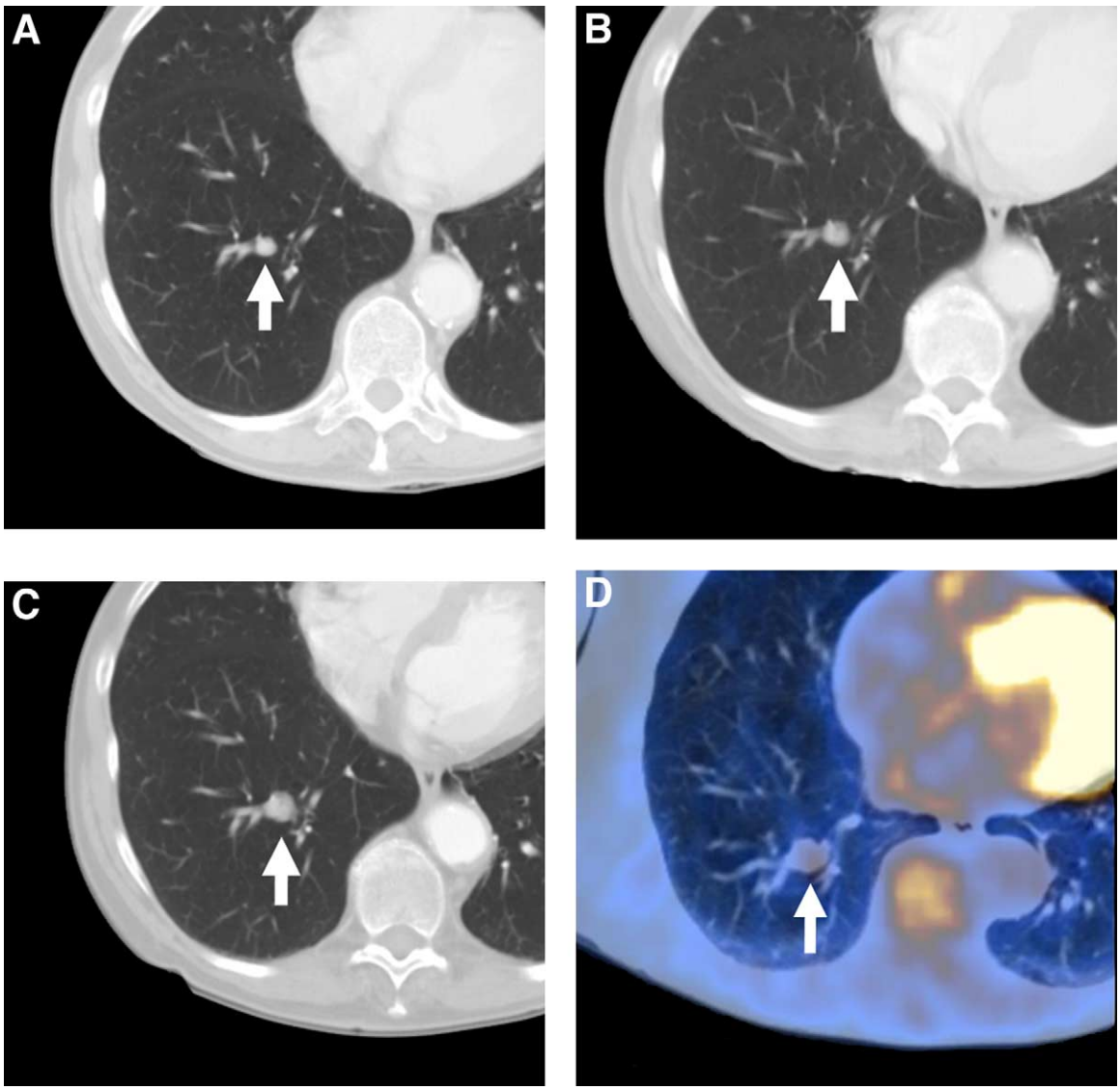

Fig 4. False-negative PET scan. A 68-year-old subject with a history of lymphoma. (A) CT scan obtained for restaging of lymphoma showing a small, noncalcified pulmonary nodule in the right lower lobe (arrow). (B) Follow-up CT obtained 6 months later showing this nodule to have increased slightly in size (arrow). (C) Follow-up CT obtained 1 year after the first showing this nodule to have further increased in size (arrow). (D) PET/CT fusion image from an FDG-PET scan obtained for evaluation of the pulmonary nodule. The nodule is hypometabolic, with activity less than that of the mediastinum. The average SUV of the nodule was 1.5. Because of the progressive growth documented by CT, this nodule was resected and found to be a grade 2 pulmonary adenocarcinoma. All nodes sampled at the time of surgery were negative for tumor.

a main bronchus at least 2 cm distal to the carina. T3 lesions are those that invade the parietal pleura, pericardium, chest wall, diaphragm, or mediastinum, are associated with complete pulmonary atelectasis, or involve the main bronchus within 2 cm of the carina but do not involve the carina. T4 tumors invade major structures such as the heart, a great vessel, the carina, the esophagus, or a vertebral body, have an associated malignant pleural effusion, or metastatic nodules in the same pulmonary lobe as the primary tumor. Most of the criteria which determine the T status of disease require precise anatomic detail that can best be demonstrated by CT. In cases where the nodule is small and clearly confined to the pulmonary parenchyma, PET can confidently determine T1 stage, as in Fig 1. However, PET scanning alone does not have the spatial resolution nor the definition of anatomic

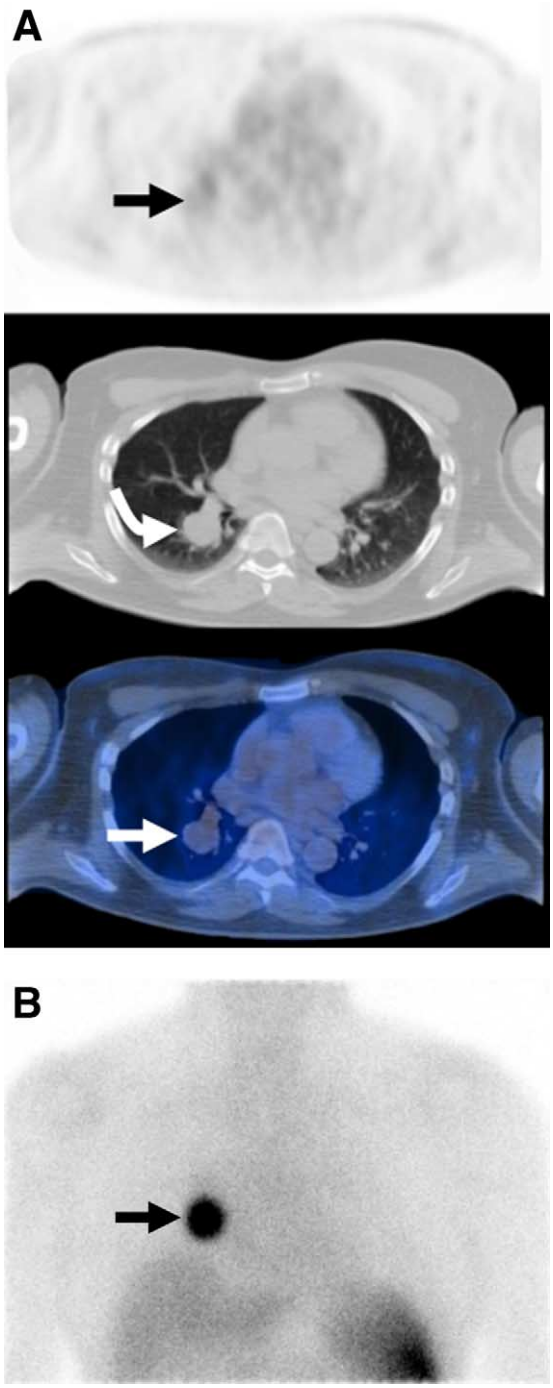

Fig 5. Carcinoid tumor. A 66-year-old subject with a pulmonary nodule discovered on chest radiograph. (A) PET/CT fusion images showing the nodule in the right lower lobe (curved arrow) to have only minimal associated FDG uptake (arrows). The average SUV of this nodule was 1.6. (B) Anterior planar image from an 111-In Octreoscan™ study, obtained 4 hours after injection of radiotracer. The nodule in the right lower lobe is intensely Octreoscan™ avid (arrow). On surgical resection, this was found to be a typical bronchial carcinoid tumor.

boundaries to provide sufficient information for higher levels of T staging. Combined PET/CT scanners would provide this information, but the relevance of this information is questionable since most patients will have had a standard chest CT for diagnosis before referral for PET imaging. Ultimately, the final determination of tumoral invasion is often not determined until the time of surgery.

There are two settings in which PET imaging may be helpful in assigning a T stage. The first is in the evaluation of additional pulmonary nodules in the same lobe as the known lung carcinoma. Like with the evaluation of the solitary pulmonary nodule, FDG-PET can be used to determine the likelihood of malignancy in these nodules, and to direct confirmatory biopsy as indicated. The second role of PET in the determination of T stage is for the identification of malignant pleural effusions. Pleural effusions in cancer patients may be reactive or malignant, and CT is rarely able to differentiate between the two types. The presence of FDG uptake in the pleural space is a worrisome sign of a malignant effusion.[27,28] Caution should be exercised, though, that the patient has not undergone talc pleurodesis or other procedure which might cause falsely positive FDG uptake in the pleural cavity.[29]

Evaluation of Nodes

Metastatic disease to regional lymph nodes is categorized by location in relationship to the tumor. N1 denotes metastatic disease to ipsilateral hilar, lobar, or interlobar lymph nodes. N2 indicates metastatic disease to ipsilateral mediastinal lymph nodes or subcarinal lymph nodes. The highest nodal stage, N3, includes metastatic disease to contralateral mediastinal or hilar lymph nodes, or disease in scalene or supraclavicular lymph nodes. Survival decreases with increasing N stage, from a 5-year survival of 60% for patients with N0 disease to 20% for patients with N2 disease. N3 disease has a poor prognosis, with few patients surviving for 5 years.

Nodes may either be assessed invasively, most typically with mediastinoscopy, or noninvasively using CT or FDG-PET. Outside of thoracotomy, mediastinoscopy is considered the gold standard for mediastinal lymph node staging. However, there are shortcomings to this procedure that must be understood.[30,31] First is sampling error. Al-

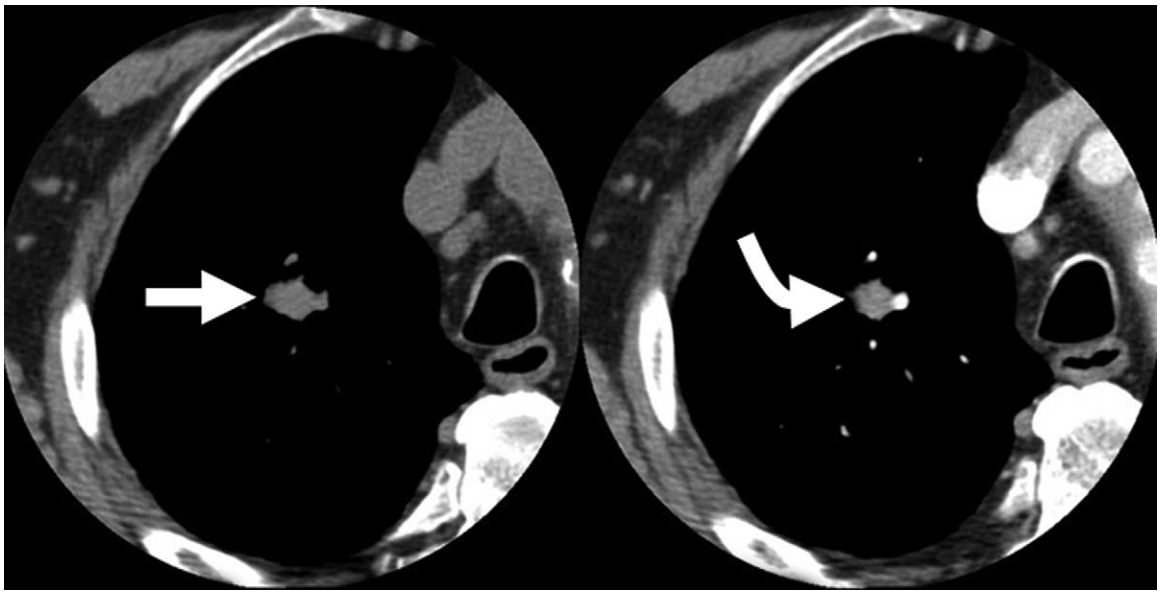

Fig 6. Dynamic contrast-enhanced CT: lung cancer. A 71-year-old subject with a suspicious pulmonary nodule. Thin-section CT images through the nodule before (arrow) and after (curved arrow) bolus administration of iodinated intravenous contrast material showing enhancement of the nodule. The difference in density between the precontrast image and the maximum enhancement image was 30 HU. The nodule was resected, and found to be grade 3 pulmonary adenocarcinoma.

though surveillance biopsies are obtained from various nodal stations, there is a chance that disease could be missed because the specific site of disease was not sampled. Second is coverage. Currently, mediastinoscopy cannot sample all nodal stations with a single entry port, and there are certain sites that present technical challenges, specifically the aortopulmonary window. Despite these limitations, the sensitivity of mediastinoscopy is high, approximately 90%, and this technique remains the standard to which noninvasive imaging tests are often compared.

Noninvasive assessment of lymph nodes can be accomplished using CT or PET. On CT, the presence of disease is determined by whether lymph nodes exceed 1 cm in short axis dimension. Nodes above this size are presumed to be malignant, and nodes below this size are presumed to be benign. The limitation of this approach is that nodes containing metastatic disease are often less than 1 cm in size, whereas nodes greater than 1 cm in size may be reactive rather than malignant. Higher or lower thresholds for differentiating benign versus malignant nodes may increase either sensitivity or specificity, but at the expense of decreasing the other.

FDG–PET, being a functional imaging technique, is not directly reliant on node size for determination of N status. Subcentimeter nodes containing tumor will be hypermetabolic due to the presence of tumor cells, and large reactive nodes will have little or no FDG accumulation. Numerous studies have compared the accuracy of PET and CT for determination of nodal metastases in patients with lung cancer.[32-40] A summary of selected studies is shown in Table 2. The articles selected represent single-institution, prospective comparisons using a histopathologic gold standard. In all these studies, PET was superior to CT for detection of lymph node metastases. The average sensitivity of PET for nodal disease from these studies was 88%, as compared with 63% for CT. The average specificity of PET was 91%, as compared with 76% for CT. Of note, the sensitivity of PET is equal to the reported sensitivity of mediastinoscopy. Unlike mediastinoscopy, PET has the advantage of complete hilar and mediastinal surveillance, and is not limited to evaluation of certain nodal groups.

The newest-generation PET scanners are coupled with state-of-the-art multislice CT scanners. The coacquisition of PET and CT scans allows for several advantages over separately acquired PET and CT scans. First, the density map provided by CT allows for more precise attenuation correction than do the conventional rotating positron sources

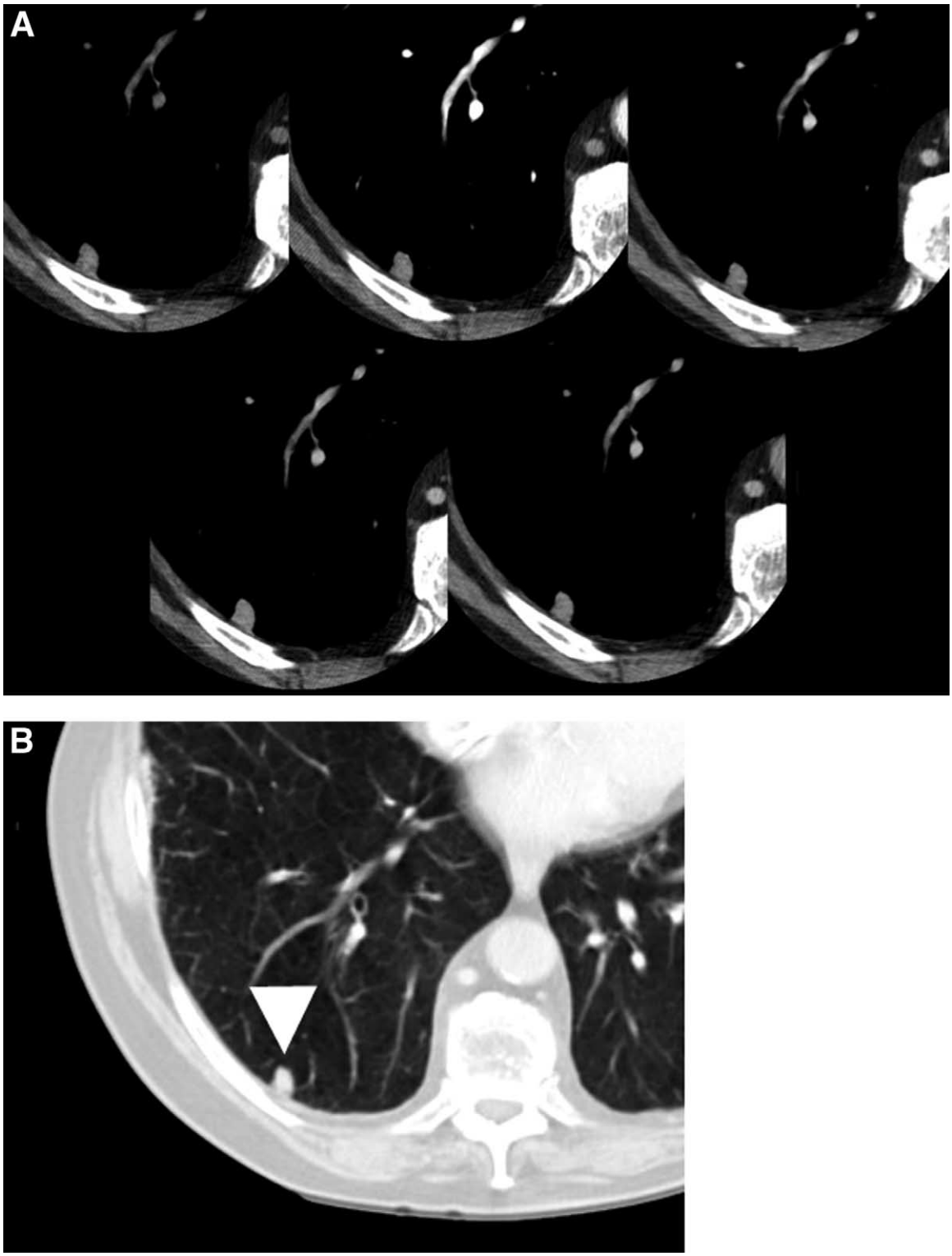

Fig 7. Dynamic contrast-enhanced CT: benign nodule. A 72-year-old subject with prostate carcinoma and an incidental pulmonary nodule discovered on abdominal CT examination. (A) Sequential images from a dynamic CT scan, with imaging performed precontrast, and at 1, 2, 3, and 4 min after contrast injection. The difference in density between precontrast image and the maximum enhancement image was 3 HU. (B) Axial image from a CT scan obtained 5 years later showing no change in the small right basilar pulmonary nodule (arrowhead).

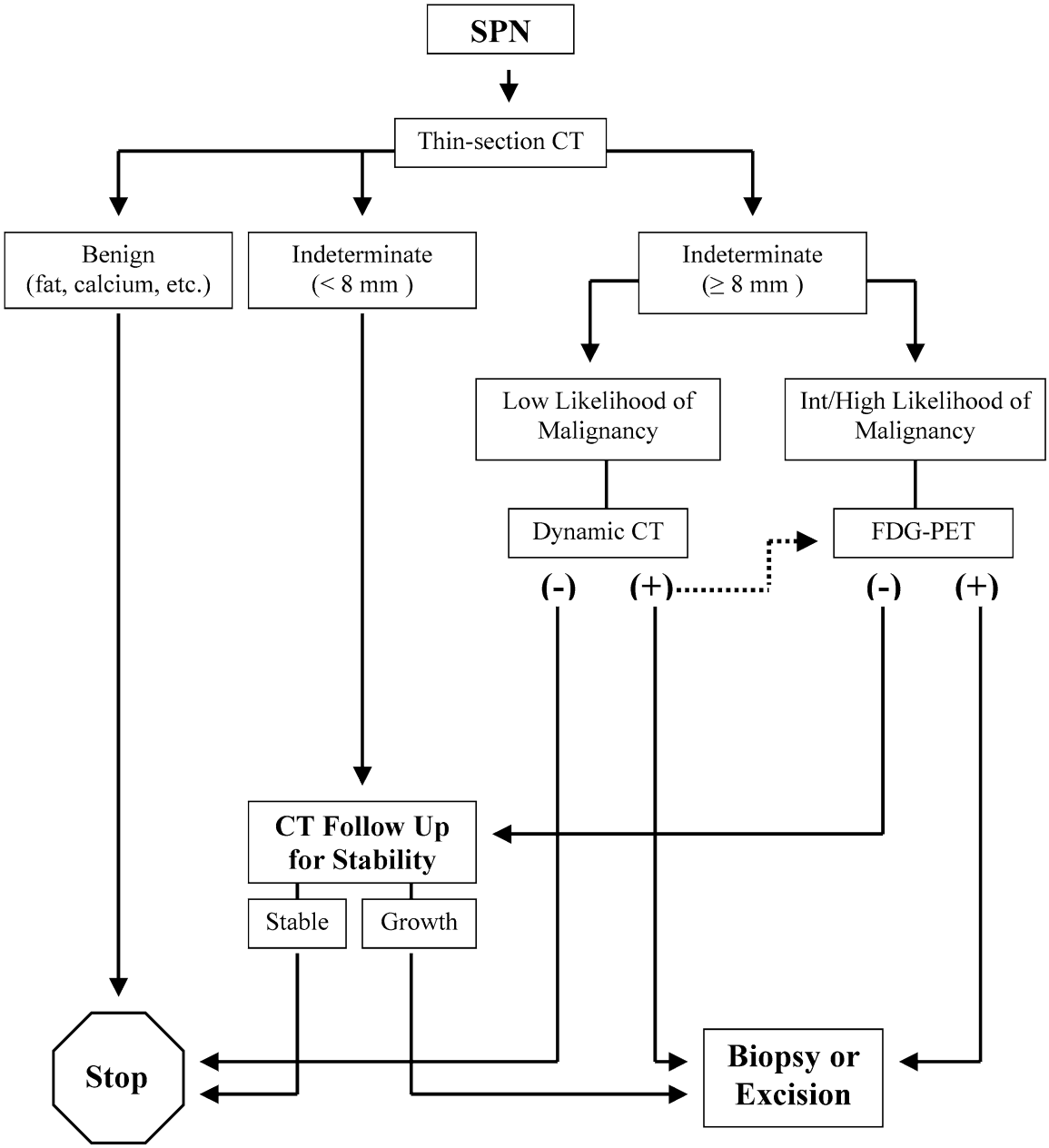

Fig 8. Algorithm for the use of conventional CT, dynamic contrast-enhanced CT, and FDG–PET for evaluation of pulmonary nodules

used on older PET scanners. Second, the attenuation-corrected PET images can be fused to the CT images, allowing better anatomic localization than is possible with PET alone. As a result, combined PET/CT scans may be superior to either PET or CT alone for evaluation of the cancer patient. In a recent article, 50 patients with known or suspected NSCLC were evaluated prospectively using CT alone, PET alone, visual correlation of separately acquired PET and CT scans, and integrated PET/CT fusion imaging.[41] For each patient, a TNM stage was assigned based on the interpretations of each of the modalities. Histopathologic evaluation and/or additional imaging comprised the reference standard. Of the imaging options, integrated PET/CT provided the highest diagnostic

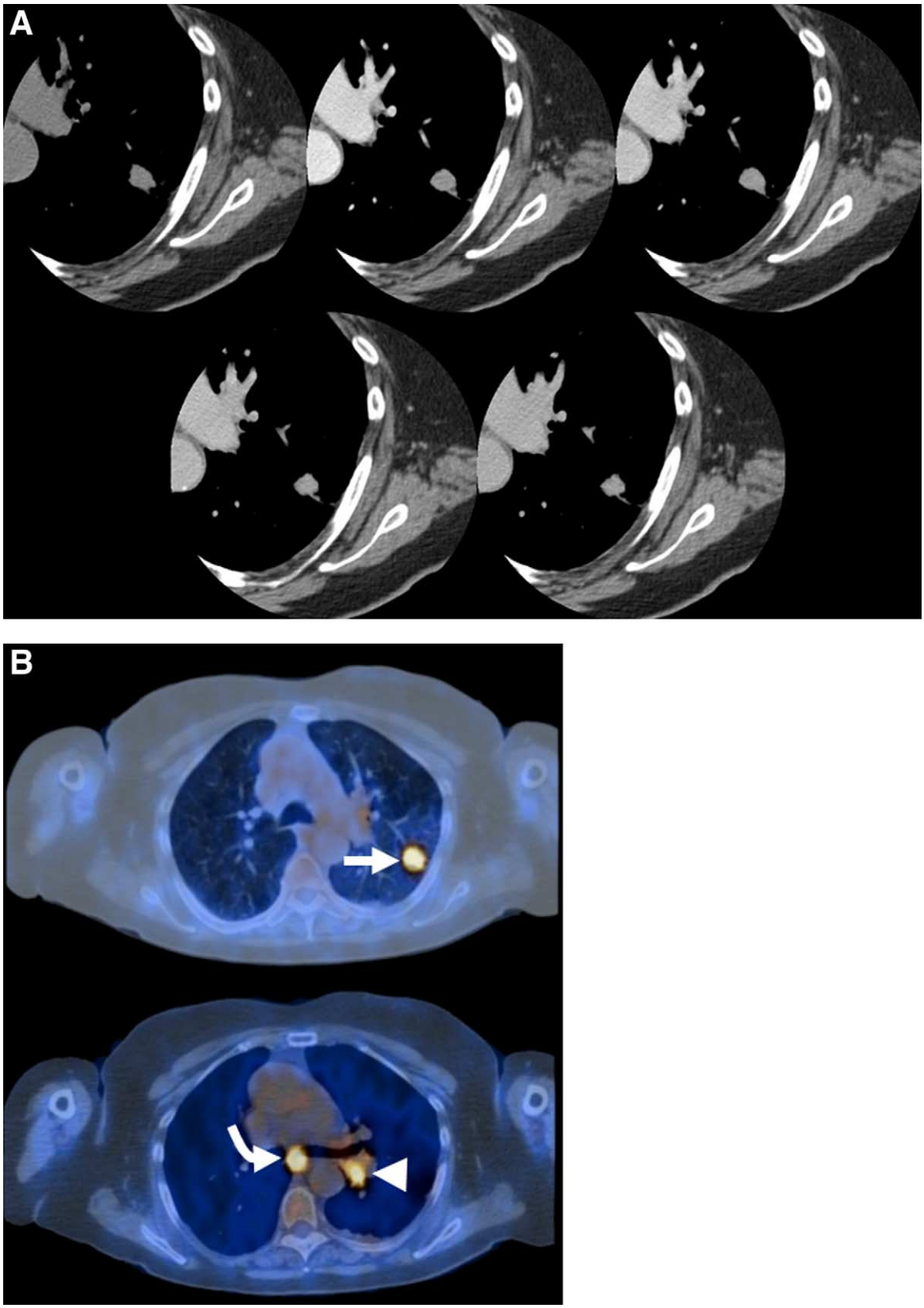

Fig 9. Added Value of FDG–PET and Dynamic CT. An 81-year-old patient with spiculated left upper lobe nodule. (A) Composite image of a dynamic contrast-enhanced CT showing the pulmonary nodule to be strongly enhancing. The difference in density between the precontrast image and the maximum enhancement image is 65 HU. (B) PET/CT fusion images from an FDG-PET scan showing intense FDG uptake in the left upper lobe nodule (arrow), an in left hilar (arrowhead) and subcarinal (curved arrow) lymph nodes. In addition to indicating a high likelihood of malignancy for the pulmonary nodule, PET is also able to determine the tumor stage, in this case IIIA.

Table 2. Evaluation of Nodal Disease Using FDG–PET

Author	Year of Publication	Number of Patients	Sensitivity PET (%)	Specificity PET (%)	Sensitivity CT (size criterion)	Specificity CT (%)	Significance PET vs. CT
Wahl et al[32]	1994	23	82	81	64% (1.0 cm)	44	$p < 0.05$
Scott et al[34]	1994	62	100	98	60% (1.0 cm)	93	$p = 0.031$
Patz et al[33]	1995	42	83	82	43% (1.0 cm)	85	$p < 0.01$
Valk et al[38]	1995	76	83	94	63% (1.0 cm)	73	$p < 0.01$
Sasaki et al[35]	1996	29	76	98	65% (1.0 cm)	87	$p < 0.05$
Sazon et al[37]	1996	32	100	100	81% (1.0 cm)	56	$p < 0.01$
Steinert et al[36]	1997	47	89	99	57% (0.7–1.1 cm)	94	$p = 0.013$
Vansteenkiste et al[39]	1999	105	89	99	79% (1.5 cm)	54	$p < 0.0003$
Pieterman et al[40]	2000	102	91	86	75% (1.0 cm)	66	$p < 0.001$
Totals		518	88	91	63 %	76	

accuracy in TNM staging. For determination of nodal disease, PET/CT was significantly better than PET alone. An example of nodal staging with PET/CT is shown in Fig 10.

Evaluation of Distant Metastases

In general, the presence of metastatic disease precludes a curative resection in patients with nonsmall cell lung carcinoma. Identification of metastatic disease is therefore critical for appropriate management. A standard "whole-body" PET scan does not, in fact, cover the whole body. While a true head-to-toe scan is feasible with PET, inclusion of the lower limbs is usually of low yield and increases the scan time significantly. A typical scan extends from the orbits or base of skull through the pelvis, covering the most common sites of metastatic disease. On the newest PET/CT scanners, a high-quality scan can be obtained with this coverage in approximately 20 minutes.

Common sites of metastases from lung carcinoma include lung, brain, adrenals, and bone.

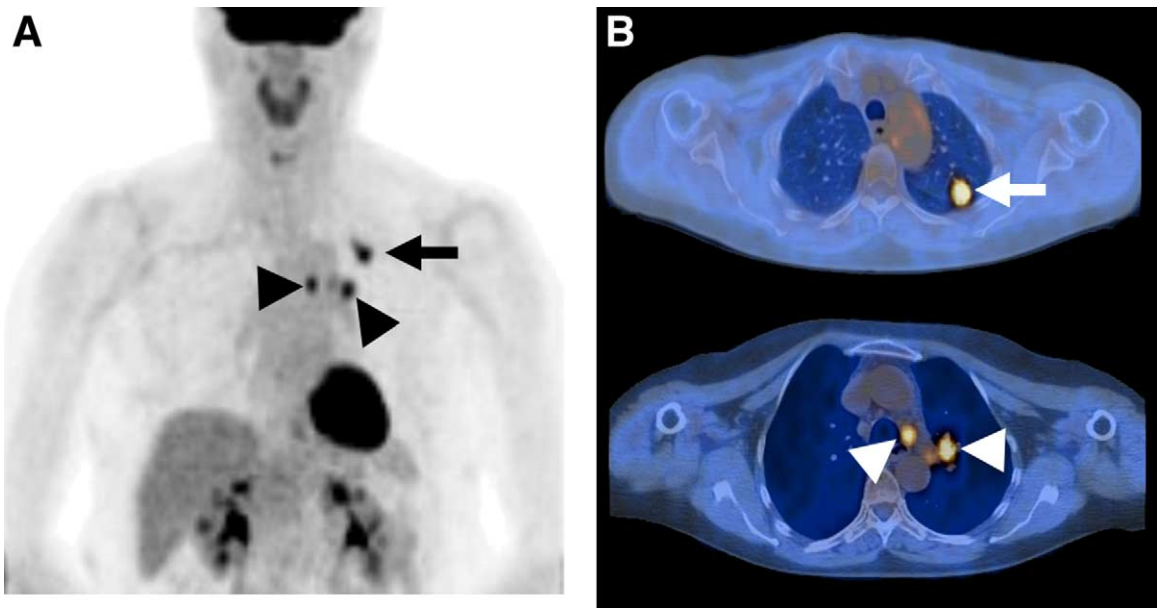

Fig 10. Nodal staging with FDG–PET. A 59-year-old subject with biopsy-proven NSCLC in the left upper lobe. (A) Frontal MIP image from an FDG–PET scan showing intense uptake in the left lung cancer (arrow), as well as in left hilar and left mediastinal lymph nodes (arrowheads). (B) PET/CT fusion images confirming uptake in the left upper lobe cancer (arrow), with a maximum SUV of 8.3. Coregistration with CT images demonstrate that the nodal disease is located in the left hilum and in the left paratracheal space (arrowheads). This information can be useful in planning confirmatory biopsy procedures such as mediastinoscopy or transbronchial needle aspiration.

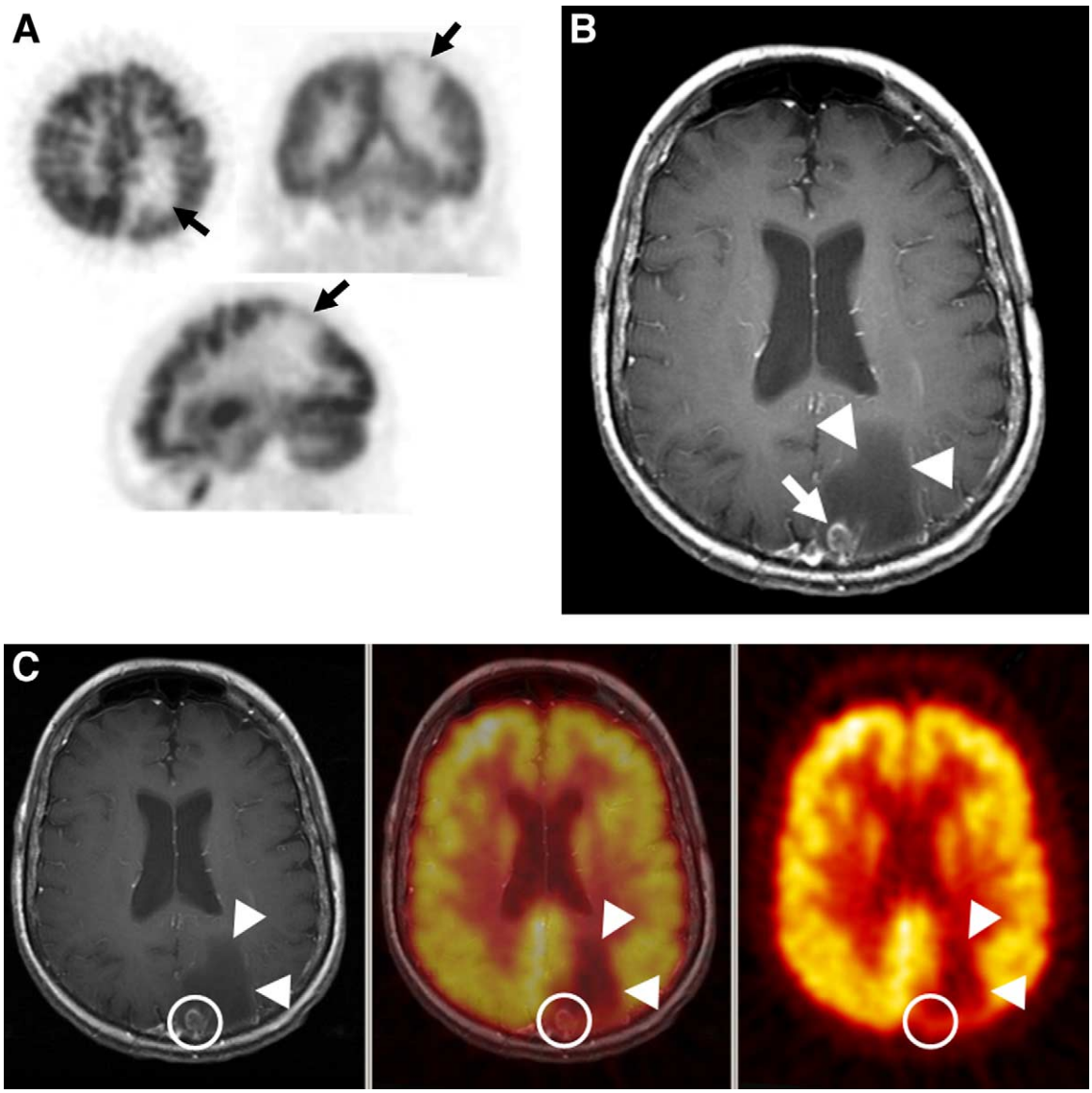

Fig 11. FDG–PET and cerebral metastases. A 68-year-old subject with newly diagnosed NSCLC. (A) Axial, coronal, and sagittal images of the brain from an FDG–PET scan showing a large region of photopenia involving the left parietal lobe (arrows). In a patient with malignancy, metastatic disease must be considered. However, stroke or other vascular disease could also cause this appearance. (B) Axial T1-weighted MR image obtained after intravenous administration of gadolinium, showing a small cortical metastasis in the medial parietal lobe on the left (arrow). There is extensive vasogenic edema (arrowheads) adjacent to the metastasis. (C) Surface-matched fusion images of the contrast-enhanced MR and FDG-PET studies. The location of the left parietal metastatic lesion is circled on each image. On the PET image, the metastatic lesion is hypometabolic compared with normal cerebral cortex, and is not visible as a discrete abnormality. The large region of hypometabolism seen on the initial brain images corresponds to the extent of vasogenic edema (arrowheads).

Metastases to other sites, including liver and soft tissue, are also seen but are less common. As discussed previously, PET is readily able to evaluate pulmonary nodules and masses in addition to the known primary tumor, and can therefore be used to identify metastatic disease to additional pulmonary lobes or to the contralateral lung. Occasionally, patients with lung cancer present with synchronous primary tumors, for which PET may also be useful for evaluation.

Radiographic screening for cerebral metastases

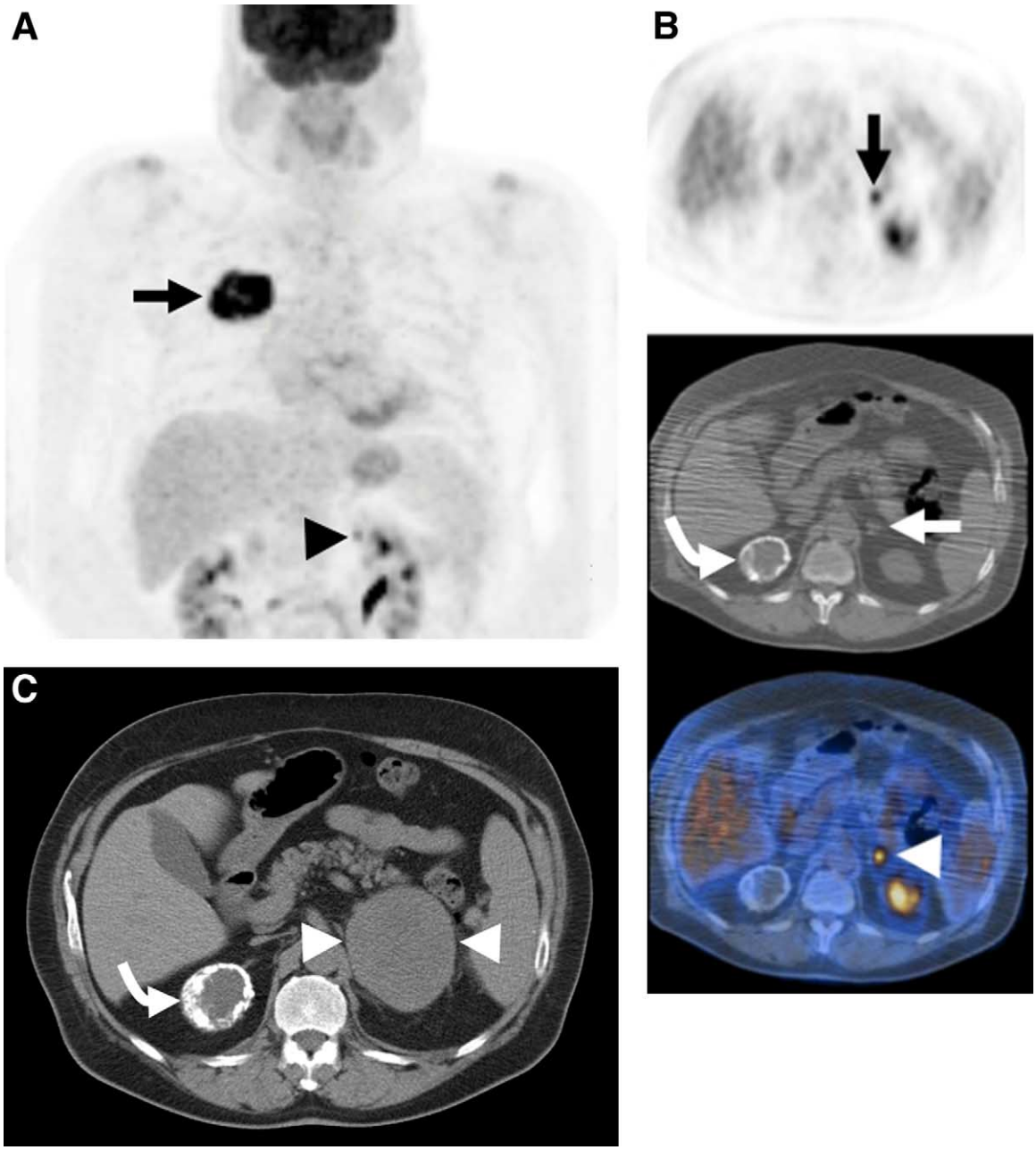

Fig 12. FDG–PET and adrenal metastases. A 72-year-old subject with biopsy-proven NSCLC. (A) Frontal MIP image from an FDG–PET scan showing a large, intensely hypermetabolic mass in the right upper lobe (arrow) corresponding to the patient's known cancer. A tiny focus of FDG uptake is also seen superior and medial to the left kidney, in the region of the left adrenal gland (arrowhead). (B) PET/CT images showing intense FDG uptake localizing to the left adrenal gland (arrows). A rim-calcified mass in the left adrenal gland (curved arrow) is not metabolically active, consistent with previous hemorrhage. (C) Axial image from a CT scan of the abdomen obtained approximately 8 months later showing development of a large left adrenal mass (arrowheads) consistent with metastatic disease. The benign rim-calcified mass in the right adrenal gland (curved arrow) is unchanged.

in patients with NSCLC is a controversial issue. Certainly in patients with neurologic signs and symptoms it may be prudent to obtain CT or MR imaging to evaluate for metastatic disease. Screening may also be performed in patients with a high clinical likelihood of disease. Current evidence indicates little role, however, for screening in asymptomatic individuals. Unfortunately, FDG-

PET has little to offer in the routine evaluation of the brain in cancer patients. Unlike most other organs, the brain utilizes high levels of glucose at basal state and as a result the cerebral cortex is routinely intensely hypermetabolic on PET imaging. Lesions which appear hyperintense on the background of normal lung parenchyma or other hypometabolic substrate can easily be masked when set in the background of normal cerebral activity, as shown in Fig 11. Several studies have demonstrated PET to have a low sensitivity and specificity when used to screen for cerebral metastases,[42,43] and in one report it was estimated that brain metastases had to be greater than 1.5 cm in size to reach a 90% detection level using PET.[44] In many instances of cerebral metastases, it is the secondary effects of the metastatic lesion such as vasogenic edema, with resulting cortical hypometabolism, that is visualized rather than the metastatic focus itself.

For other metastatic sites, PET is highly accurate for the detection of disease. In patients with NSCLC, PET has been shown to be superior to CT for detection of adrenal metastases,[45,46] and superior to technetium bone scanning for detection of osseous metastases.[47,48] Examples are shown in Figs 12 and 13. Overall, PET is able to detect sites of disease which may not be apparent by standard imaging strategies (Fig 14), and therefore change management in many patients. The frequency of a change in treatment planning based on PET varies by report, with some reports indicating a change in as few as 10% of patients, and other reports indicating a change in as many as 40%.[49,50]

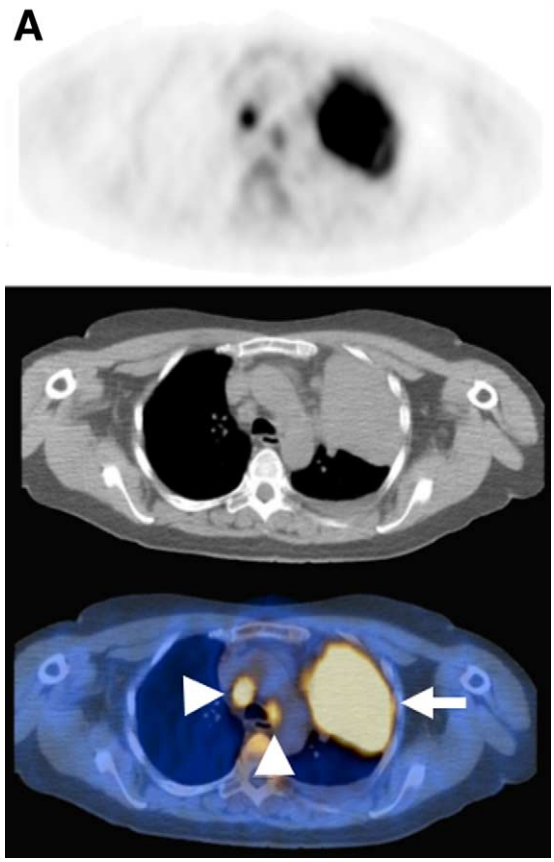

Fig 13. FDG–PET and osseous metastases. A 67-year-old subject with a large left upper lobe NSCLC. (A) Axial PET/CT fusion images showing the large hypermetabolic cancer in the left upper lobe (arrow) with metastatic disease to pretracheal and left paratracheal lymph nodes (arrowheads). (B) Selected axial PET/CT fusion images showing extensive osseous metastases, including rib (arrow), sacrum (arrowheads), and proximal femur (curved arrow). The inferior lesion in the sacrum (lower left image) was biopsied percutaneously, confirming the diagnosis of stage IV lung cancer.

MONITORING THERAPY AND DETECTION OF RECURRENCE

Treatment of NSCLC often involves multiple modalities, with varying roles for surgery, chemotherapy, and radiation therapy. The best chance at cure is through complete resection of a stage I cancer. Unfortunately, a significant number of lung cancer patients present with advanced disease, and the overall 5-year survival of this group is only 15%.

Imaging plays an important role in following patients who are undergoing therapy, and is used to determine the success or failure of a particular therapeutic regimen. By radiographic techniques, including chest radiography and CT, response to therapy is determined by a decrease in tumor size. It is often unclear, until subsequent serial studies are obtained, whether this decrease in size represents a complete or a partial response to therapy. FDG-PET, by providing metabolic rather than anatomic information, allows for functional assessment of lung tumors during or shortly after therapy. A decrease in FDG uptake after therapy may be a positive sign that the tumor is responding to a particular therapy. Patients with a complete resolution of FDG uptake in their tumor following therapy have been shown to have a good prognosis, as compared with patients with residual FDG uptake in their tumor. Residual FDG uptake despite therapy, on the other hand, implies residual

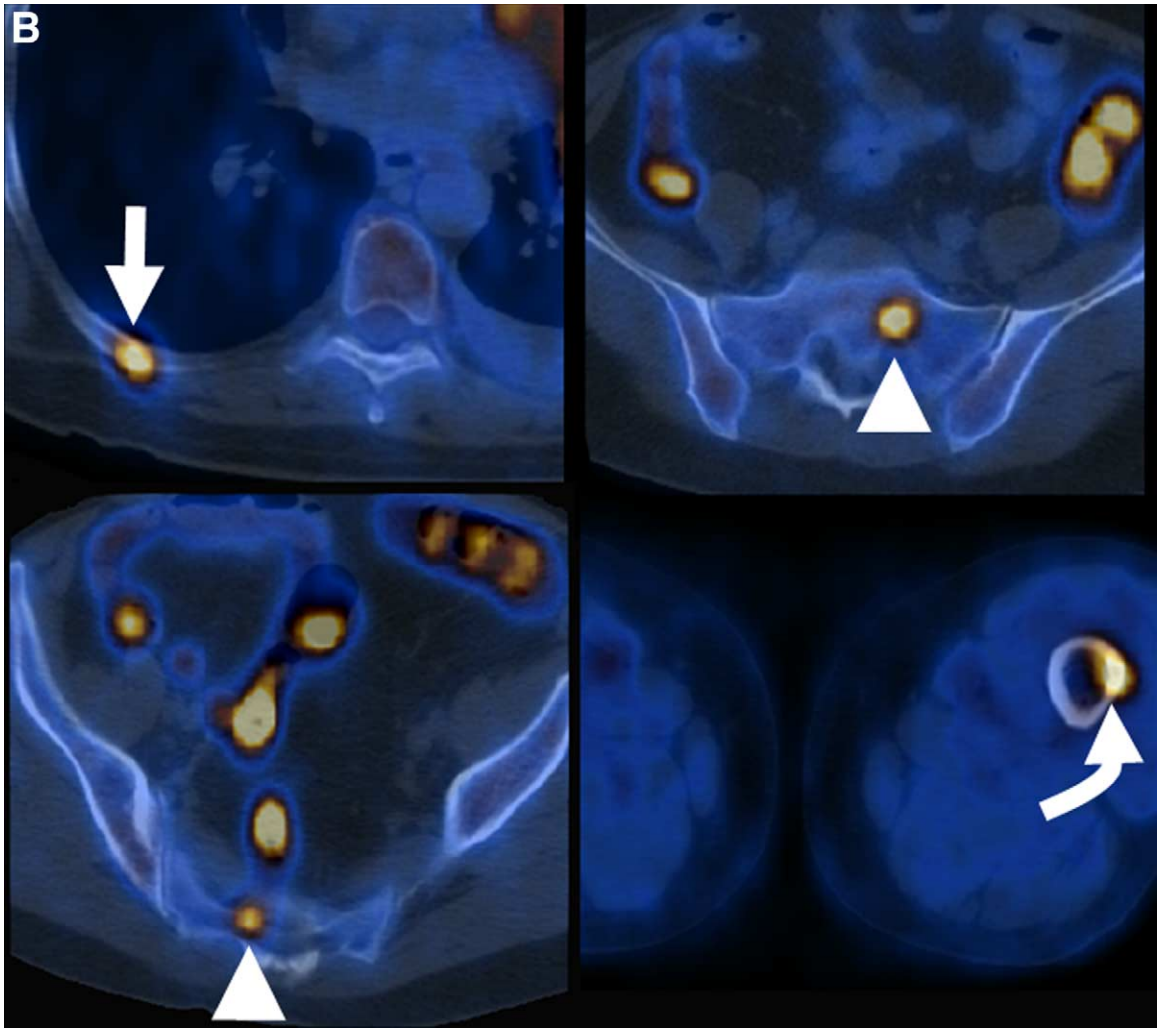

Fig 13 (cont'd).

viable tumor, and has been used in some reports to guide additional therapy, even when patients are otherwise asymptomatic.[51]

Care must be taken when interpreting scans obtained during or shortly after therapy. Some treatment modalities, particularly radiation therapy, can incite tissue necrosis and macrophage-mediated inflammation which may be metabolically-active on PET imaging.[51] As with the radiographic findings of radiation pneumonitis, these changes take some time to develop, and usually peak within 6 to 12 weeks following completion of therapy. Afterward, FDG uptake in radiation necrosis diminishes in intensity over time[52] and usually resolves by 6 months. Occasionally, however, FDG uptake in regions of necrosis can persist for longer periods of time. When possible, follow up scanning in patients treated with radiation should be delayed for at least 3 to 6 months after completion of therapy. The typical appearance of radiation pneumonitis on PET imaging is diffuse low-grade or intermediate-grade FDG activity confined to a geographic field corresponding to the radiation port. The presence of new or progressive focal hypermetabolism (SUV $\geq$2.5) within a region of radiation change should raise concern for residual or recurrent tumor.

FUTURE TRENDS IN PET IMAGING OF LUNG CANCER

FDG–PET imaging is becoming an established imaging modality for evaluation of patients with a

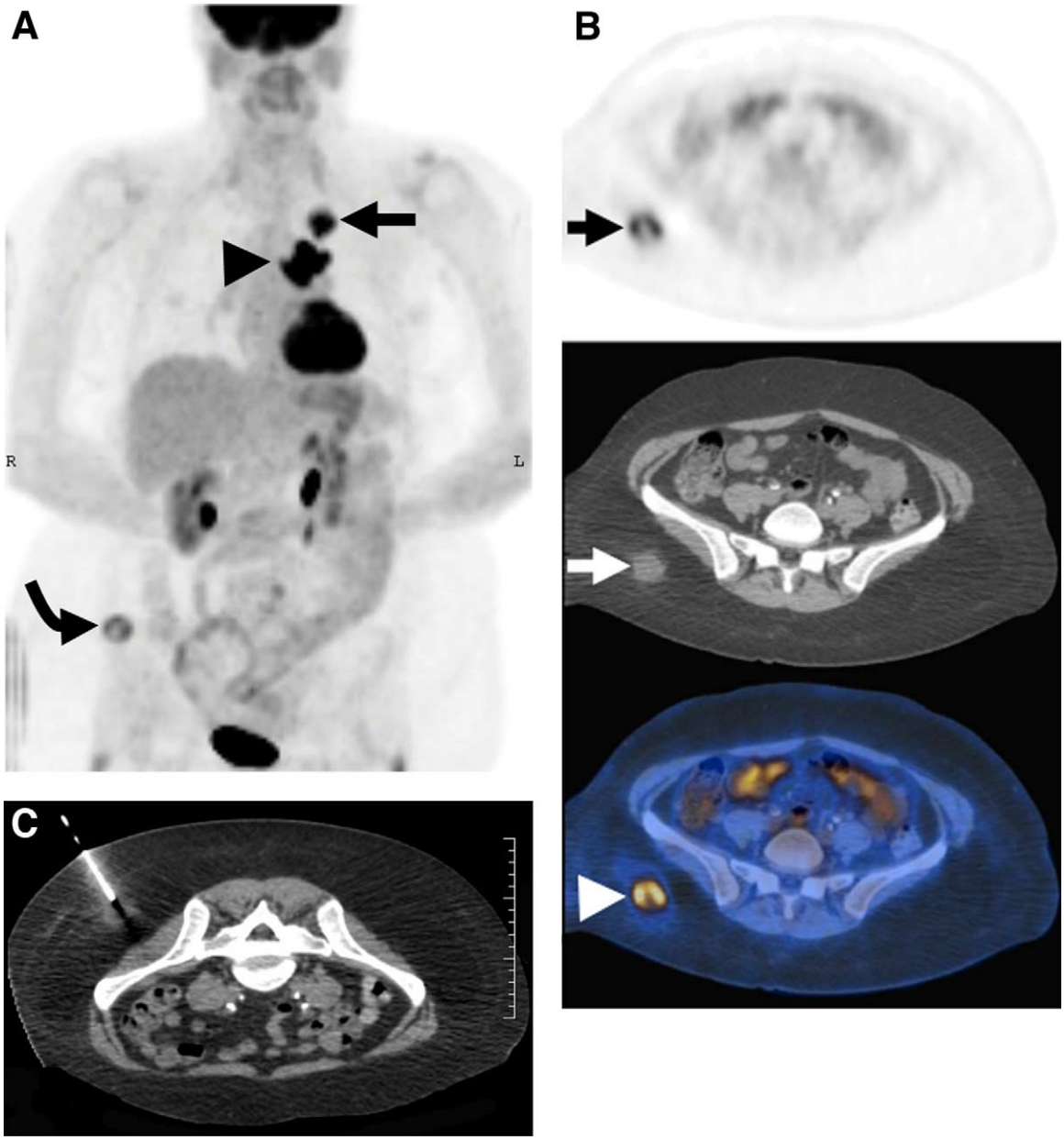

Fig 14. Unusual site of metastatic NSCLC. A 50-year-old subject with newly diagnosed lung carcinoma. (A) Frontal MIP image from an FDG-PET scan, showing that in addition to the left upper lobe lung cancer (arrow) with left mediastinal adenopathy (arrowhead), there is a hypermetabolic mass in the right flank (curved arrow). (B) PET/CT fusion images showing that the hypermetabolic flank lesion (black arrow) corresponds to a soft tissue nodule located deep in the subcutaneous fat of the right gluteal region (white arrow and arrowhead). (C) Representative axial image obtained during CT-guided percutaneous biopsy of the flank mass. Pathology revealed metastatic grade 4 nonsmall cell lung carcinoma, confirming stage IV disease.

variety of tumors. Studies have repeatedly shown PET to be superior to CT for diagnosis, staging, and restaging patients with NSCLC. For all this, PET imaging is still a developing field, with new avenues of evaluation constantly being explored. While PET may fail to prove clinically useful in some applications, there will continue to be new applications of the science that will improve patient care.

One application that is gaining acceptance is the

role of FDG-PET in the planning of radiotherapy. PET can provide metabolic information, which can then be used to determine planning target volumes (PTV), target coverage, and critical organ dose. Combined PET/CT scanners are particularly suited to this task, providing simultaneously acquired functional and anatomic datasets. In one study, PTV was determined using CT alone, and using a fused set of separately-acquired PET and CT scans.[53] Inclusion of the PET scan resulted in a change in PTV in approximately 30% of cases because of more accurate delineation of metabolically active tumor. In addition, 23% of patients were changed from a radical to a palliative radiotherapy protocol based on the additional information provided by PET. In a second study, PTV was changed in all patients after inclusion of PET scanning into preprocedural evaluation.[54] In some cases, PTV was increased to include additional sites of metabolically-active tumor. In other cases, PTV was decreased to exclude nonmetabolic atelectasis or to avoid unnecessary irradiation of heart or spinal cord. Future studies will continue to define the role of PET in the field of radiation therapy.

A second newer use of PET imaging is in determination of prognosis based on metabolic activity of the primary tumor. FDG uptake in NSCLC correlates with tumor grade, which accounts for the high rate of false negative PET scans in low-grade tumors such as bronchoalveolar cell carcinoma. Most high-grade lung cancers, on the other hand, are intensely hypermetabolic, with standardized uptake values well above the 2.5 cutoff. Studies have shown that as the intensity of FDG uptake in the tumor increases, survival decreases. In one such study, the maximum SUV of lung tumors was analyzed for prognostic value, in association with traditional prognostic features such as disease stage and cell type.[55] It was determined that tumors with an SUV_{max} of ≥ 7 had a relative risk of 6.3 as compared with those with an SUV_{max} of <7. This increase in relative risk was found to be independent of other prognostic features, particularly for the subgroup of patients with adenocarcinomas. In two additional studies, median survival of patients with NSCLC was shown to decrease as the SUV of the tumor increased.[56,57] In the first of these studies, mean survival fell from 24.6 months in patients with tumor SUV <10, to 11.4 months in patients with tumor SUV >10, to 5.7 months in patients with tumor SUV >10 and tumor size >3 cm. In the second study, one year survival of patients with tumor SUV_{max} <10 was 75%. Survival fell progressively as tumor SUV increased above 10, and in the small subgroup of patients with tumor SUVmax >20, the 1-year survival was only 17%. The prognostic value of the SUV in these patients was again found to be independent of other traditional staging criteria.

Finally, the future of PET imaging will certainly involve the development and clinical application of new radiotracers. The term PET imaging, like planar scintigraphy and SPECT imaging, simply refers to the hardware used in image acquisition. In the future, there will likely be a wide array of PET imaging agents that bear no more resemblance to each other than medronate does to metaiodobenzylguinidine. Already, numerous imaging agents are under investigation, each targeted at a particular physiologic process. Radiolabeled thymidine, for example, serves as a marker of DNA synthesis and cellular proliferation, and correlates well with histopathologic proliferative indices.[58] Other systems include choline agents for evaluation of membrane synthesis and turnover and radiolabeled amino acids for evaluation of protein catabolism. Many of these agents are under investigation for potential utility in patients with NSCLC.[59,60]

CONCLUSION

Optimized management of patients with known or suspected lung cancer requires accurate delineation of the extent of disease. PET has proven to be valuable in the evaluation of radiographically indeterminate pulmonary lesions, as well as in the staging and restaging of disease in patients with known lung carcinoma. Studies also suggest that PET may be helpful in planning radiation treatment volumes and monitoring the response to various therapeutic regimens. Because of its proven advantages over conventional CT staging, PET is becoming a widely accepted modality for the evaluation of the patient with lung cancer. Ongoing technologic improvements, including the optimization of integrated PET/CT cameras and the introduction and validation of new imaging agents, will keep PET at the forefront of tumor imaging for the foreseeable future.

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