Role of FDG PET/CT in the Eighth Edition of TNM Staging of Non–Small Cell Lung Cancer

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Abbreviations: FDG = fluorine 18 fluorodeoxyglucose, IASLC = International Association for the Study of Lung Cancer, NCCN = National Comprehensive Cancer Network, NSCLC = non–small cell lung carcinoma

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SA-CME LEARNING OBJECTIVES

After completing this journal-based SA-CME activity, participants will be able to:

- Describe the eighth edition of the TNM staging system for lung cancer and the changes between the seventh and eighth editions.
- Explain how to apply the eighth edition of the TNM staging system of NSCLC to staging with FDG PET/CT, and describe the site-specific strengths and limitations of FDG PET/CT for staging.
- Identify the types of lung malignancies that may have low FDG uptake, leading to false-negative findings at PET/CT.

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Lung cancer is the leading cause of cancer-related mortality in the United States, and accurate staging plays a vital role in determining prognosis and treatment. The recently revised eighth edition of the TNM staging system for lung cancer defines new T and M descriptors and updates stage groupings on the basis of substantial differences in survival. There are new T descriptors that are based on the findings at histopathologic examination, and T descriptors are reassigned on the basis of tumor size and extent. No changes were made to the N descriptors in the eighth edition of the TNM staging of lung cancer, because the four N categories that are based on the location of the diseased nodes can be used to consistently predict prognosis. The eighth edition includes a new M1b descriptor for patients with a single extrathoracic metastatic lesion in a single organ (M1b), because they have better survival and different treatment options, compared with those with multiple extrathoracic lesions (M1c). Examination with fluorine 18 fluorodeoxyglucose (FDG) PET/CT is the standard of care and is an integral part of the clinical staging of patients with lung cancer. To provide the treating physicians with accurate staging information, radiologists and nuclear medicine physicians should be aware of the updated classification system and should be cognizant of the site-specific strengths and limitations of FDG PET/CT. In this article, the eighth edition of the TNM staging system is reviewed, as well as the role of FDG PET/CT in the staging of non–small cell lung carcinoma.

Introduction

Lung cancer is the leading cause of cancer-related death, with an estimated 234 030 new cases of lung cancer and 154 050 deaths from lung cancer in the United States in 2018 (1). Non–small cell lung carcinoma (NSCLC) is the most common type of lung cancer, with subtypes including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma (2). Optimal management of NSCLC is dependent on the histopathologic subtype, the molecular characteristics, and the stage of the tumor (3). The guidelines of the National Comprehensive Cancer Network (NCCN) recommend PET/CT with fluorine 18 fluorodeoxyglucose (FDG) for evaluation of patients with stage I to stage IV NSCLC (4). The American College of Radiology Appropriateness Criteria, the guidelines of the Society of Nuclear Medicine and Molecular Imaging, and the guidelines of the American College of Chest Physicians also recommend use of FDG PET/CT for staging in patients with NSCLC (5,6). Radiologists and nuclear medicine physicians need to be aware of the application of FDG PET/CT in the updated classification system, to provide accurate staging information to the treating physicians.

TEACHING POINTS

- On the basis of differences in the 5-year survival and prognosis, the eighth edition includes a few new T descriptors, new size cutoffs, and reassignment of previous categories. In the eighth edition of TNM staging, the 3-cm cutoff point still separates T1 from T2 tumors, and the 5-cm cutoff point separates T2 and T3 tumors, with every centimeter in size separating T1 and T2 tumors with markedly different prognoses. Invasion of the diaphragm, which was a T3 descriptor in the seventh edition, had a worse prognosis than other T3 descriptors and is designated as T4 in the eighth edition of the TNM staging system. Mediastinal pleural involvement is no longer considered a T descriptor, because it is difficult to determine at clinical staging and is usually associated with invasion into mediastinal tissues at pathologic staging.
- In eighth edition TNM staging, there are three categories of M descriptors, which is a change from the seventh edition of TNM staging, which had only two categories. Extrathoracic metastases, which were an M1b descriptor in the seventh edition of the TNM staging system, are now divided into M1b and M1c descriptors in the eighth edition of the TNM staging system. Patients with a single extrathoracic metastatic lesion in a single organ (M1b) have better survival rates than those with multiple extrathoracic lesions (M1c) and may be candidates for surgical resection or local ablative therapy.
- The NCCN imaging appropriateness criteria recommend FDG PET/CT performed from the skull base to the knees or whole-body FDG PET/CT for evaluation of patients with stage I to stage IV NSCLC. According to the NCCN guidelines, PET/CT findings that are positive for distant disease need histopathologic or other radiologic confirmation, and FDG uptake in mediastinal nodes needs histopathologic confirmation. The NCCN guidelines also recommend FDG PET/CT for evaluation of an incidentally detected lung nodule measuring more than 8 mm. A positive PET result is defined as a standardized uptake value greater than that of the baseline mediastinal blood pool.
- False-negative results of PET can be seen in small nodules, generally less than 8–10 mm in diameter (T1a), mucinous adenocarcinomas with a relatively small amount of cells, and low-grade malignancies such as carcinoma in situ (Tis) and minimally invasive adenocarcinoma [T1a(mi)].
- In patients with locally advanced NSCLC that is suitable for treatments with curative intent, FDG PET/CT may be used to identify unsuspected metastases, reducing the frequency of futile thoracotomies. The rates of progression-free survival and overall survival are significantly worse in upstaged disease with PET/CT. The NCCN guidelines do not recommend routine bone scintigraphy for staging NSCLC.

This review article aims to describe the eighth edition of the TNM staging system for lung cancer, highlighting changes between the seventh and eighth editions (7). The role of FDG PET/CT in lung cancer staging is illustrated, and the stage- and site-specific strengths and limitations of PET/CT are addressed.

Staging

The TNM staging system, which categorizes tumors on the basis of the primary tumor characteristics (T), regional lymph node involvement (N), and local or distant metastases (M), is presently the standard tool for determining the anatomic extent of tumor in patients with lung cancer (8). Stage groups are determined by the combination of T, N, and M descriptors. The TNM staging system can be applied to preoperative clinical staging, pathologic staging, restaging after therapy, or staging of a recurrence. The TNM stage provides a framework for optimal management and evaluation of treatment results, facilitates information exchange among multiple medical centers, and can be used to predict patient survival.

The staging system is periodically reviewed and refined by the Union for International Cancer Control (Union Internationale Contre le Cancer) and the American Joint Committee on Cancer. First proposed by Denoix et al in the 1940s, the TNM staging system has undergone multiple revisions, with the seventh edition of the TNM staging system in use from 2009 to 2017 in the United States (9). The seventh edition was based on a retrospective analysis of an international database derived between 1990 and 2000 from 81 495 lung cancer patients by the International Association for the Study of Lung Cancer (IASLC) (10).

Because all of the descriptors in the seventh edition of the TNM staging system could not be validated, a new database of 77 156 patients worldwide in whom lung cancer was diagnosed from 1999 to 2010 was constructed and used by the IASLC to inform the eighth edition of the TNM staging system. Changes in the eighth edition of TNM staging of NSCLC were based on substantial differences in survival measured from the date of diagnosis for clinically staged patients and the date of surgery for pathologically staged patients with different T and M descriptors (11). The eighth edition of the TNM staging system has been implemented as the standard of care for staging NSCLC since 2017.

Contrast material–enhanced CT and FDG PET/CT are routinely used in the clinical staging of NSCLC, and pathologic staging is based on the histopathologic findings. Since 2000, considerable advancement has occurred in the diagnostic and therapeutic options available to patients with NSCLC, including routine use of FDG PET/CT, minimally invasive endoscopic biopsy, precision radiation therapy techniques, minimally invasive surgery, molecular targeted therapy, and immunotherapy (12). In 2011, the IASLC, the American Thoracic Society, and the European Respiratory Society reclassified lung adenocarcinoma into *(a)* adenocarcinoma in situ, *(b)* minimally invasive adenocarcinoma, and *(c)* invasive adenocarcinoma, to reflect invasiveness and growth characteristics (13). The eighth edition of the TNM staging system attempts to reflect these advances and to validate all of the descriptors of the seventh

Table 1: Eighth Edition of TNM Staging of Lung Cancer

Category or Stage	Descriptor	5-year Survival Rate (%)
T category		
TX	Tumor in sputum and/or bronchial washings, not assessed at imaging or bronchoscopy	
T0	No evidence of primary tumor	
Tis	Carcinoma in situ	...
T1	≤3 cm in longest axis	...
T1a(mi)	Minimally invasive adenocarcinoma	...
T1a	≤1 cm in longest axis	92
T1b	>1 cm to ≤2 cm in longest axis	83
T1c	>2 cm to ≤3 cm in longest axis	76
T2	>3 cm to ≤5 cm in longest axis; involves main bronchus, visceral pleura, or atelectasis or obstructive pneumonitis extending to the hilum	67
T2a	>3 cm to ≤4 cm in longest axis	67
T2b	>4 cm to ≤5 cm in longest axis	60
T3	>5 cm to ≤7 cm in longest axis; invades chest wall, phrenic nerve, or parietal pericardium; or nodule in same lobe as the primary tumor	52
T4	>7 cm in longest axis; invades diaphragm, mediastinum, carina, trachea, heart, great vessels, recurrent laryngeal nerve, esophagus, or vertebral body; nodule in different ipsilateral lobe	38
N category		
N0	No regional nodal metastases	75
N1	Metastasis in ipsilateral peribronchial or hilar nodes or intrapulmonary nodes	49
N2	Metastasis in ipsilateral mediastinal nodes or subcarinal nodes	36
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular nodes	20
M category		
M0	No distant metastasis	
M1a	Tumor nodule in contralateral lung; tumor with pleural or pericardial nodules or malignant pleural or pericardial effusion	11.4
M1b	Solitary single-organ extrathoracic metastasis	11.4
M1c	Multiple extrathoracic metastases in one or multiple organs	6.3
Stage group		
Stage IA1	T1a(mi)N0M0, T1aN0M0	92
Stage IA2	T1bN0M0	83
Stage IA3	T1cN0M0	77
Stage IB	T2aN0M0	68
Stage IIA	T2bN0M0	60
Stage IIB	T1aN1M0, T1bN1M0, T1cN1M0, T2aN1M0, T2bN1M0, T3N0M0	53
Stage IIIA	T1aN2M0, T1bN2M0, T1cN2M0, T2aN2M0, T2bN2M0, T3N1M0, T4N0M0, T4N1M0	36
Stage IIIB	T1aN3M0, T1bN3M0, T1cN3M0, T2aN3M0, T2bN3M0, T3N2M0, T4N2M0	26
Stage IIIC	T3N3M0, T4N3M0	13
Stage IVA	Any T, any N, M1a; any T, any N, M1b	10
Stage IVB	Any T, any N, M1c	0

Sources.—References 11 and 14–16.

edition of the TNM staging system. The T, N, and M descriptors and the stage groupings of the eighth edition of the TNM staging system for lung cancer are defined in Table 1 (11,14–16).

T Descriptors

The T categories are defined by various descriptors, including the primary tumor size, invasion of main bronchi, atelectasis or pneumonitis, invasion into adjacent mediastinal or peripheral structures, and the location of an additional tumor nodule relative to the primary tumor. If a tumor exhibits multiple T descriptors, the one that confers the highest T stage determines the category. The long-axis measurement in centimeters (with millimeter increments), regardless of the plane, is used for staging purposes.

On the basis of differences in the 5-year survival and prognosis, the eighth edition includes a few new T descriptors, new size cutoffs, and reassignment of previous categories. In the eighth edition of TNM staging, the 3-cm cutoff point still separates T1 from T2 tumors, and the 5-cm cutoff point separates T2 and T3 tumors, with every centimeter in size separating T1 and T2 tumors with markedly different prognoses. Invasion of the diaphragm, which was a T3 descriptor in the seventh edition, had a worse prognosis than other T3 descriptors and is designated as T4 in the eighth edition of the TNM staging system. Mediastinal pleural involvement is no longer considered a T descriptor, because it is difficult to determine at clinical staging and is usually associated with invasion into mediastinal tissues at pathologic staging (14).

Tis: Carcinoma in Situ.—The tumor measures 3 cm or less, with no invasive component at histopathologic examination.

T1a(mi): Minimally Invasive Adenocarcinoma.—The tumor measures 3 cm or less, with an invasive component measuring 5 mm or less at histopathologic examination.

T1 Descriptors.—T1a tumors measure 1 cm or less. T1b tumors measure more than 1 cm and less than or equal to 2 cm. T1c tumors measure more than 2 cm and less than or equal to 3 cm. A superficial spreading tumor in the central airways is classified as T1a, regardless of the location (Fig 1).

T2 Descriptors.—T2 tumors measure more than 3 cm and less than or equal to 5 cm, with T2a tumors measuring more than 3 cm and less than or equal to 4 cm and with T2b tumors measuring more than 4 cm and less than or equal to 5 cm. Tumors that involve the main bronchus without involving the carina or invade the visceral pleura or cause atelectasis or postobstructive pneumonitis extending to the hilum are also classified as T2a tumors. Unlike the seventh edition of the TNM staging system, the new eighth edition classification does not distinguish between complete and partial atelectasis or use the distance from the carina for staging (Fig 2).

T3 Descriptors.—T3 tumors measure more than 5 cm and less than or equal to 7 cm. The presence of an additional tumor nodule in the same lobe, chest wall invasion, and involvement of the parietal pericardium or phrenic nerve are also T3 descriptors. A Pancoast tumor involving only the T1 or T2 nerve roots is classified as T3 (Fig 3).

T4 Descriptors.—T4 tumors measure more than 7 cm or may have an additional tumor nodule or nodules in an ipsilateral separate lobe. There may be invasion of the diaphragm, trachea, mediastinum, heart, great vessels, recurrent laryngeal nerve, esophagus, vertebral body, or carina. A Pancoast tumor involving the C8 or higher nerve roots, cords of the brachial plexus, subclavian vessels, vertebral bodies, or the spinal canal is classified as T4 (Fig 4).

The differences in T staging between the seventh and eighth editions of the TNM staging system are defined in Table 2.

N Descriptors

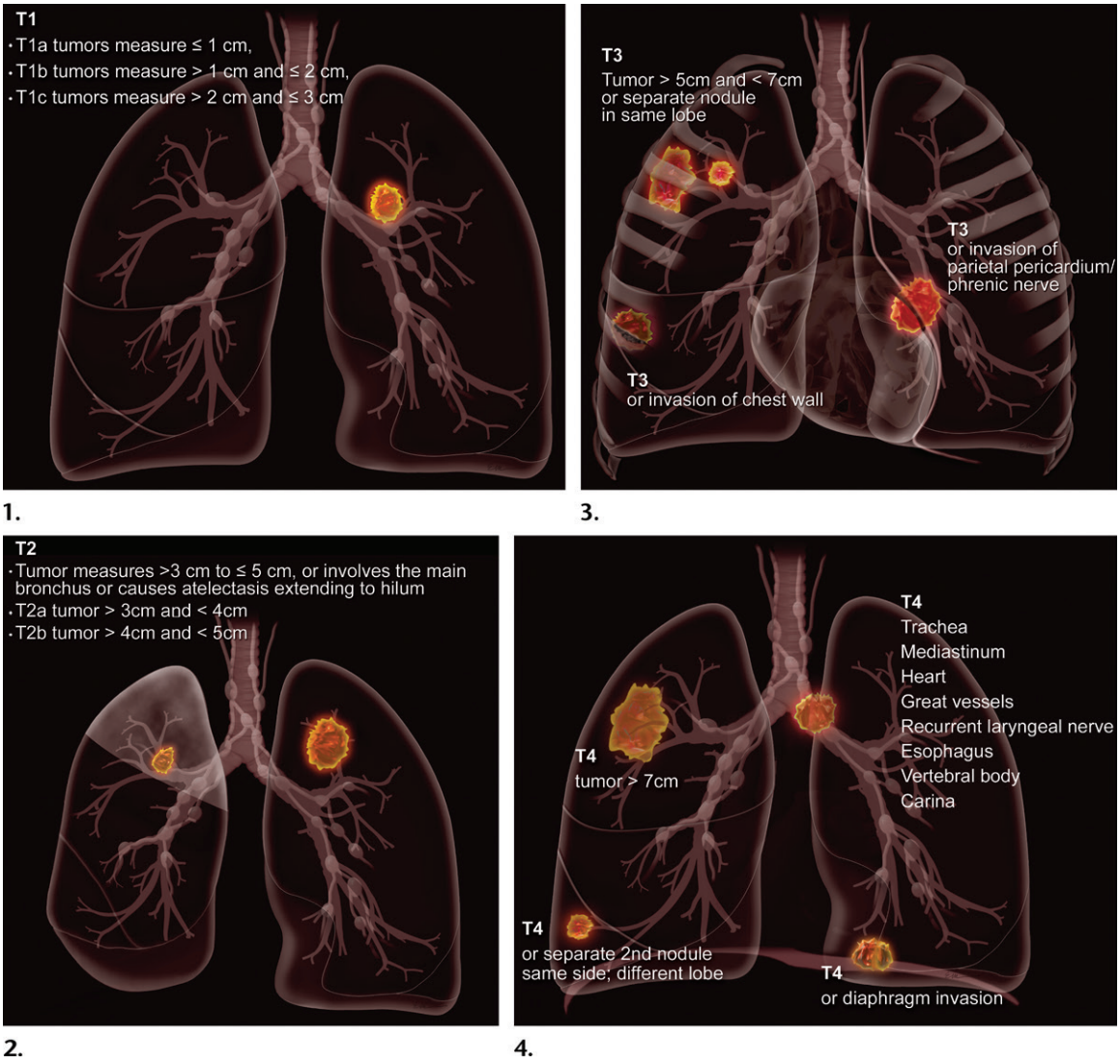
No changes were made to the N descriptors in the eighth edition of the TNM staging of lung cancer, compared with the seventh edition, because nodal categorization into N0, N1, N2, and N3 was again shown to consistently separate prognostically distinct groups (15). Lymph node staging is done according to the IASLC lymph node map (17).

N1 nodes include ipsilateral intrapulmonary, peribronchial, and hilar lymph nodes. N2 nodes include ipsilateral mediastinal or subcarinal lymph nodes. N3 nodes include contralateral hilar or mediastinal lymph nodes, ipsilateral or contralateral scalene nodes, and supraclavicular lymph nodes. The N stage does not consider less common intrathoracic nodal sites of metastasis, such as the internal thoracic and cardiophrenic chains (Fig 5).

Investigators have shown that the number of involved nodes in N1 and N2 locations, along with the presence or absence of skip metastases, is a better prognostic determinant than the location-based classification. Because this analysis was only performed on the histopathologic dataset that informed the eighth edition of the TNM staging system and could not be performed on the clinical dataset, the IASLC recommends clinical and histopathologic documentation of these additional parameters in the eighth edition of the TNM staging system for further testing (8,15). Nodal categories have been proposed that are based on the number of involved node stations and the presence of skip metastases (Table 3).

M Descriptors

In eighth edition TNM staging, there are three categories of M descriptors, which is a change from the seventh edition of TNM staging, which had only two categories (16). Extrathoracic metastases, which were an M1b descriptor in the seventh edition of the TNM staging system, are now divided into M1b and M1c descriptors



Figures 1–4. **(1)** Anatomic drawing illustrating the T1 descriptors. **(2)** Anatomic drawing illustrating the T2 descriptors. **(3)** Anatomic drawing illustrating the T3 descriptors. **(4)** Anatomic drawing illustrating the T4 descriptors.

in the eighth edition of the TNM staging system. Patients with a single extrathoracic metastatic lesion in a single organ (M1b) have better survival rates than those with multiple extrathoracic lesions (M1c) and may be candidates for surgical resection or local ablative therapy (18).

The M1a category is used to describe an additional tumor nodule or nodules in a contralateral lobe, or a tumor with malignant pleural or pericardial nodules or malignant pleural or pericardial effusion (Fig 6).

The M1b category is used to describe a solitary extrathoracic metastasis in a single organ—brain, liver, bone, distant lymph node, skin, peritoneum, or adrenal gland. Histopathologic confirmation is necessary in surgical candidates with a single atypical lesion (Fig 7).

The M1c category is used to indicate multiple extrathoracic metastatic lesions in a single organ or multiple extrathoracic metastatic lesions in multiple organs. Preferential sites of involvement include *(a)* bone, 34.3%; *(b)* lung, 32.1%; *(c)* brain, 28.4%; *(d)* adrenal glands, 16.7%; and *(e)* liver, 13.4% (19) (Fig 8).

The M stage does not take into account site-specific disease or the metastatic burden. The site of the metastasis is not prognostic for single or multiple lesions within a single organ.

Stage Groups

New stage groups are included in the eighth edition of the TNM staging system owing to changes in the T and M descriptors and modification of old stage groups to reflect substantial differences in patient survival. Stage I is divided into IA1, IA2, and IA3 on the basis of 1-cm cutoff points of T1 tumors without nodal or distant metastases. A new stage IIIC includes locally advanced T3 and T4 lesions with N3 disease but no distant metastases. Stage

Table 2: Differences in T Staging between the Seventh and Eighth Editions of the TNM Staging System for Lung Cancer

Descriptor	Seventh Edition	Eighth Edition
Carcinoma in situ	—	Tis (new category)
Minimally invasive adenocarcinoma	—	T1a(mi) (new category)
>1 cm to ≤2 cm in longest axis	T1a	T1b
>2 cm to ≤3 cm in longest axis	T1b	T1c
>4 cm to ≤5 cm in longest axis	T2a	T2b
>5 cm to ≤7 cm	T2b	T3
>7 cm	T3	T4
Bronchus <2 cm from the carina	T3	T2
Atelectasis of entire lung	T3	T2
Diaphragmatic invasion	T3	T4
Mediastinal pleural invasion	T3	—

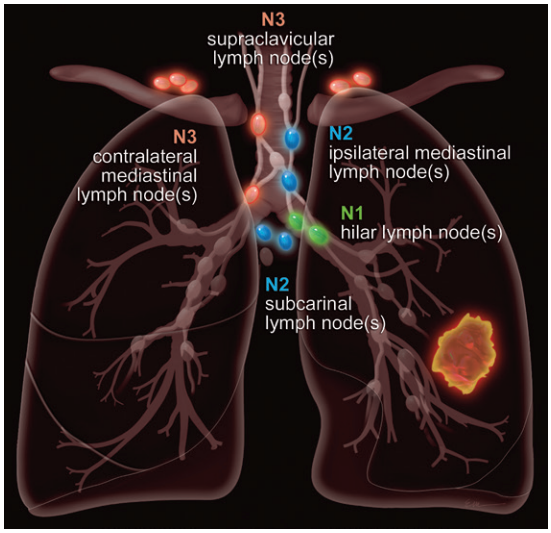


Figure 5. Anatomic drawing illustrating the N descriptors.

IVA includes M1a and M1b tumors, and stage IVB includes M1c tumors (20).

Strengths and Limitations of FDG PET/CT in Lung Cancer Staging

Evidence for Lung Cancer Staging with FDG PET/CT

FDG PET/CT combines anatomic data with functional and metabolic information. The anatomic detail provided by CT, such as tumor size and local aggressiveness, is complemented by the metabolic information of PET. Although conventional CT is still widely used for staging NSCLC, assessment of nodal metastases is limited with this modality (21).

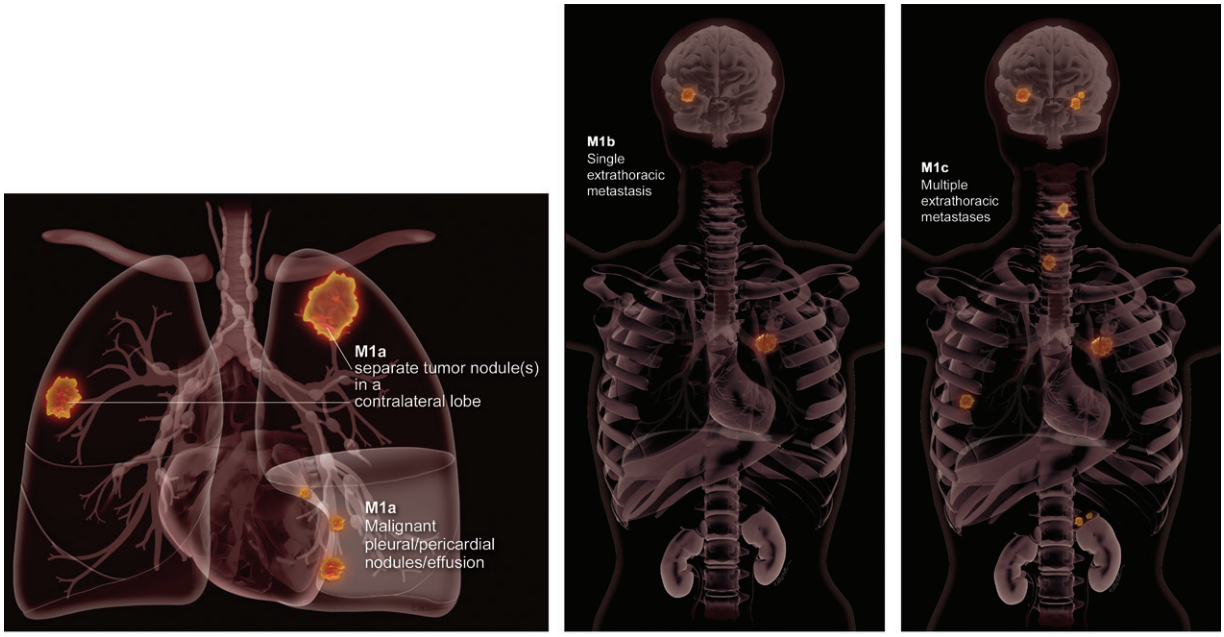
In the results of a prospective multicenter randomized trial, investigators showed that combining FDG PET with a conventional workup led to a 51% relative reduction in futile thoracotomy, with an overall one in five reduction in unnecessary surgery (ie, if patients had benign disease, pathologic stage IIIA-N2/IIIB, or postoperative relapse or death within 12 months, and exploratory thoracotomies), compared with conventional workup only (22).

In the findings of a prospective multicenter trial by Kubota et al (23), management strategies changed in approximately 72% of cases of lung cancer when FDG PET/CT examinations were used. In the results of a 2013 meta-analysis of 56 studies to evaluate the diagnostic value of FDG PET/CT in patients with NSCLC, pooled sensitivities and specificities of FDG PET/CT were 72% and 91% in determining mediastinal nodal staging. The pooled sensitivities and specificities of FDG PET/CT for detection of all extrathoracic metastases were 77% and 95% (24).

The NCCN imaging appropriateness criteria recommend FDG PET/CT performed from the skull base to the knees or whole-body FDG PET/CT for evaluation of patients with stage I to stage IV NSCLC (4, 25). According to the NCCN guidelines, PET/CT findings that are positive for distant disease need histopathologic or other radiologic confirmation, and FDG uptake in mediastinal nodes needs histopathologic confirmation. The NCCN guidelines also recommend FDG PET/CT for evaluation of an incidentally detected lung nodule measuring more than 8 mm. A positive PET result is defined as a standardized uptake value greater than that of the baseline mediastinal blood pool (25,26).

Role of FDG PET/CT in Evaluating the T Category

NSCLC includes a heterogeneous group of carcinomas with varying tumor biology and prognosis (12). Several investigators have noted a



6. 7. 8.

Figures 6–8. **(6)** Anatomic drawing illustrating the M1a descriptor. **(7)** Anatomic drawing illustrating the M1b descriptor. **(8)** Anatomic drawing illustrating the M1c descriptor.

relationship between the FDG uptake, measured semiquantitatively as the standardized uptake value, and the tumor size, histologic subtype, biologic aggressiveness, and prognosis (27,28) (Fig 9).

False-negative results of PET can be seen in small nodules, generally less than 8–10 mm in diameter (T1a), mucinous adenocarcinomas with a relatively small amount of cells, and low-grade malignancies such as carcinoma in situ (Tis) and minimally invasive adenocarcinoma [T1a(mi)] (29).

Carcinoma in situ (Tis) and minimally invasive adenocarcinoma [T1a(mi)] can manifest as ground-glass or part-solid ground-glass nodules on CT images (Figs 10, 11). Invasive adenocarcinomas with a predominant lepidic pattern can also appear as mixed solid and ground-glass nodules (30). In subsolid tumors, the recommendation of the Union for International Cancer Control is to measure the solid invasive component of the tumor to define its T category (31). FDG PET/CT is indicated for evaluation of subsolid ground-glass nodules only if the solid component measures more than 8 mm (32). Solid-type lung cancer lesions that measure less than 8–10 mm, lepidic carcinoma, and well-differentiated adenocarcinoma have been associated with false-negative PET/CT results (33).

Chest CT, with or without administration of contrast material, is the modality of choice for the evaluation of tumor size and invasiveness (25). In current clinical practice, CT performed during PET/CT utilizes a low-dose free-breathing technique with thick reconstruction intervals and may be suboptimal for the analysis of the morphologic structure of a nodule.

Table 3: Proposed N Descriptors That Are Based on the Number of Involved Node Stations and the Presence of Skip Metastases

Descriptor	Number of Involved Node Stations
N1a	Single N1 group involvement
N1b	Multiple N1 group involvement
N2a1	Single N2 group without N1 involvement (skip)
N2a2	Single N2 group with N1 involvement
N2b	Multiple N2 group involvement

FDG PET/CT is superior to CT in differentiating between tumor and postobstructive atelectasis, a distinction that is important for local disease staging, percutaneous biopsy, radiation therapy planning, and assessment of treatment response. Investigators have demonstrated higher FDG uptake in areas of atelectasis than in normal lung, as well as lower FDG uptake in areas of atelectasis than in tumor tissue (34) (Fig 12). PET definition of the gross tumor volume has been noted to be smaller than CT-measured tumor volume in 13%–17% of patients (35). FDG PET/CT is suboptimal to assess chest wall invasion owing to blooming artifact. Contrast material–enhanced CT and MRI are more accurate in depicting invasion of the chest wall or diaphragm (36,37) (Fig 13).

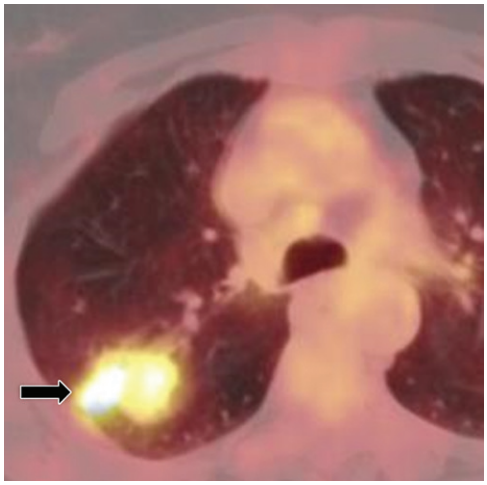
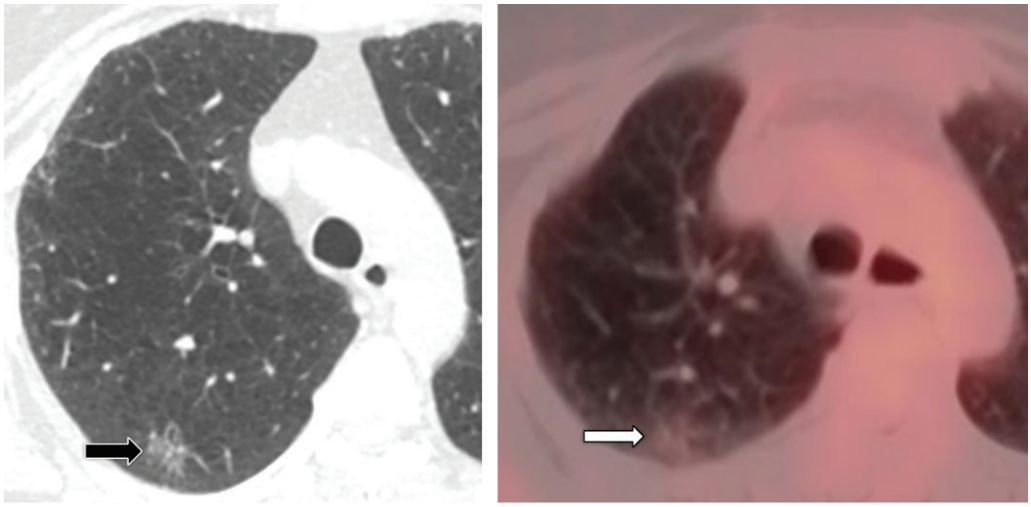
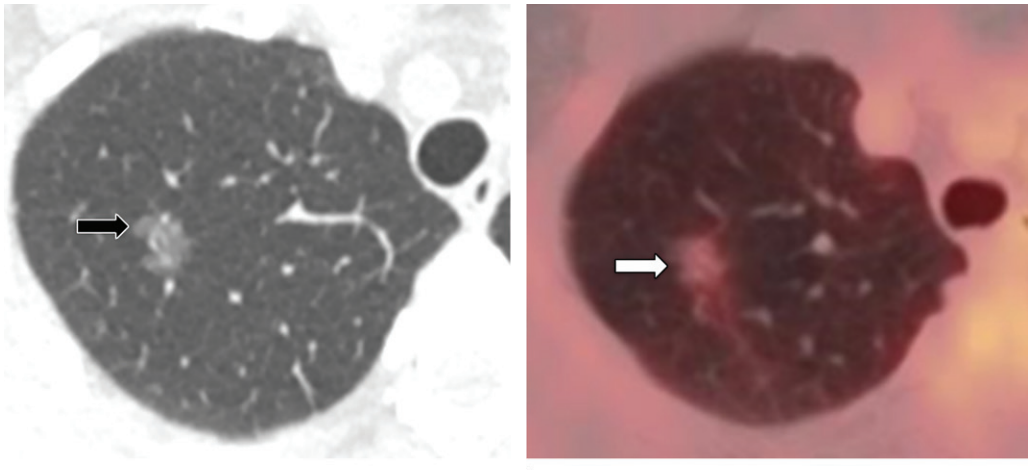


Figure 9. Moderately differentiated adenocarcinoma (T2a) of the lung in a 78-year-old woman. Axial fused FDG PET/CT image shows increased FDG uptake (arrow) in the right upper lobe mass.



a. **b.**

Figure 10. Adenocarcinoma in situ (Tis) in a 66-year-old woman. **(a)** Axial CT image shows a 7-mm ground-glass nodule (arrow) in the right upper lobe, which proved to be adenocarcinoma in situ at histopathologic examination. **(b)** Axial FDG PET/CT fused image shows no increased FDG uptake in the lesion (arrow).



a. **b.**

Figure 11. Minimally invasive adenocarcinoma [T1a(mi)] in the right upper lobe of a 69-year-old woman. **(a)** Axial CT image shows a 12-mm ground-glass opacity (arrow). **(b)** Axial FDG PET/CT fused image shows no FDG accumulation in this lesion (arrow), which measured less than 3.0 cm and had less than 5 mm of invasion at histopathologic examination.

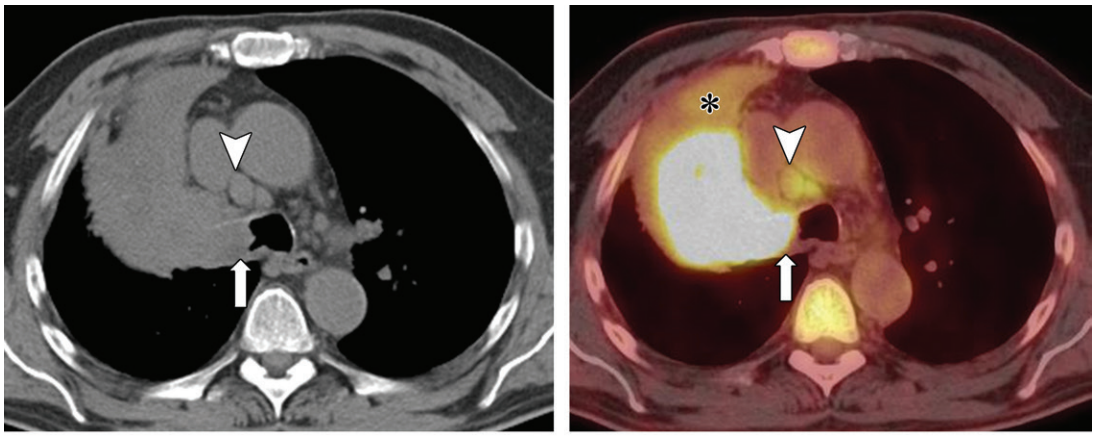


Figure 12. Poorly differentiated squamous cell carcinoma (T2) in a 65-year-old man. **(a)** Axial CT image shows right upper lobe atelectasis and an occluding mass in the right main bronchus (arrow) with no clear demarcation, as well as enlarged right paratracheal lymph nodes (arrowhead). **(b)** Axial fused FDG PET/CT image shows FDG uptake in the mass occluding the right bronchus (arrow), with relatively less FDG uptake anteriorly in the atelectatic lung (*). FDG uptake is also depicted in the enlarged right paratracheal nodes (arrowhead).

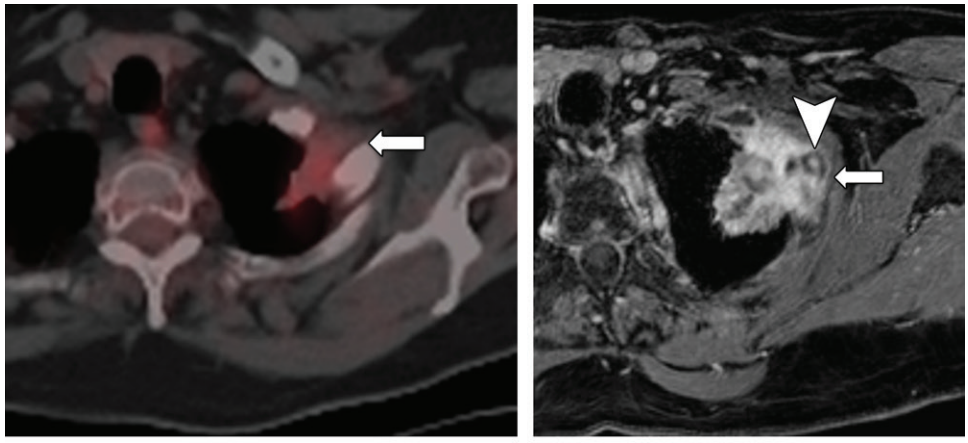


Figure 13. Primary lung adenocarcinoma (T3) in a 61-year-old woman. **(a)** Axial FDG PET/CT image shows an FDG-avid left upper lobe mass (arrow) abutting the adjacent chest wall. **(b)** Axial contrast-enhanced T1-weighted MR image clearly shows infiltration of the chest wall musculature (arrow) and rib (arrowhead) by the left upper lobe mass.

Lymphangitic carcinomatosis, a poor prognostic indicator, has not been added as a T descriptor. FDG PET/CT may add specificity to CT findings of lymphangitic carcinomatosis by showing increased metabolism in nodular interlobular septal thickening. The sensitivity and specificity of PET/CT for lymphangitic carcinomatosis are 86% and 100%, respectively (38).

Role of FDG PET/CT in Evaluating the N Category

In patients with NSCLC, lymph nodes measuring more than 1 cm in the short axis on CT or MR images are considered to be involved with metastatic disease. The reported ranges for the sensitivity and specificity of CT for the detection of diseased nodes are 51%–64% and 74%–86%, respectively (39).

FDG PET/CT has been shown to have a sensitivity of 58%–94% and a specificity of 76–96% for the detection of mediastinal lymph node metastasis (40) (Fig 14). The low sensitivity indicates a high chance of false-negative results, which may be due to low FDG uptake in a low-volume malignancy or in a malignancy with a low metabolic rate (41) (Fig 15). Nodal involvement with granulomatous infections such as tuberculosis and with inflammatory lesions such as sarcoidosis can result in false-positive PET findings. In the result of a meta-analysis of 10 studies using either integrated PET/CT or a visual combination of PET and CT, Wang et al (42) found that the negative predictive value for mediastinal metastases was 94% in T1 disease and 89% in T2 disease. FDG PET/CT may demonstrate FDG uptake in diseased nodes

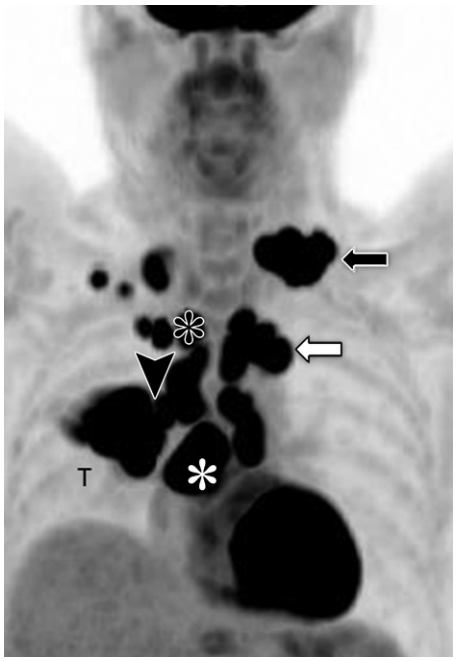
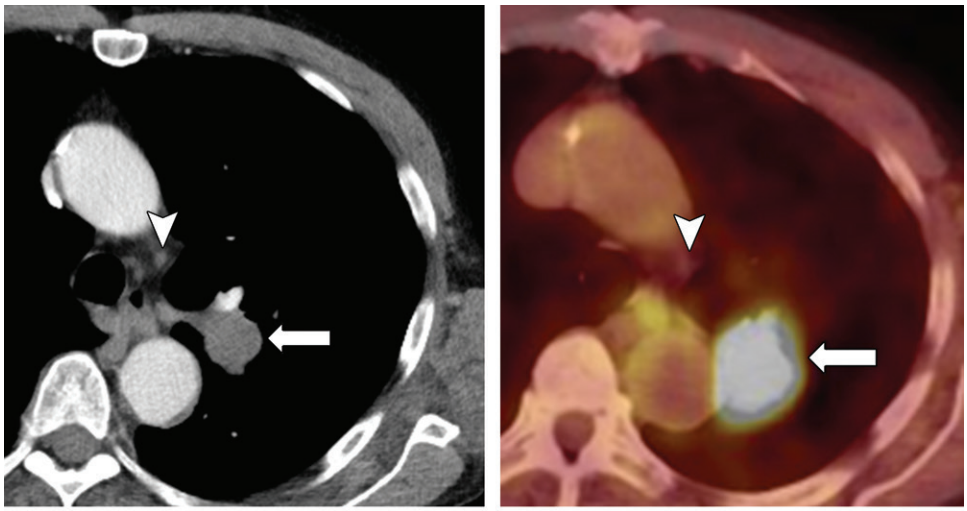


Figure 14. N descriptors in moderately differentiated squamous cell carcinoma in a 60-year-old man. FDG PET/CT maximum intensity projection image shows an FDG-avid right upper lobe mass *(T)* and enlarged FDG-avid right hilar lymph nodes (N1) (arrowhead), right mediastinal lymph nodes (N2) (black ∗), subcarinal lymph nodes (N2) (white ∗), contralateral mediastinal lymph nodes (N3) (white arrow), and supraclavicular lymph nodes (N3) (black arrow).



a. **b.**

Figure 15. False-negative FDG PET/CT findings in normal-sized lymph nodes in a 58-year-old man with large cell carcinoma. **(a)** Axial CT image shows a left upper lobe tumor (arrow) and nonenlarged station 5 lymph nodes (arrowhead). **(b)** Axial fused FDG PET/CT image shows FDG uptake (arrow) in the large cell carcinoma in the left upper lobe and no FDG uptake in the normal-sized station 5 lymph nodes (arrowhead). These lymph nodes demonstrated metastatic disease at histopathologic examination of the specimen from surgical biopsy.

measuring less than 10 mm or may show false-negative results in diseased nodes measuring more than 10 mm. High FDG uptake in the primary lesion is associated with a greater risk of occult nodal metastases (42). NCCN guidelines recommend histopathologic mediastinal lymph node evaluation before resection for all stage II tumors and optional histopathologic mediastinal lymph node evaluation before resection for solid tumors measuring less than 1 cm or purely nonsolid tumors measuring less than 3 cm with no diseased nodes identified at CT and PET (4,43).

Role of FDG PET/CT in Evaluating the M Category

FDG PET/CT is the modality of choice for evaluation of extraencephalic metastases in patients with NSCLC. Distant metastases (M1) occur in 11%–36% of patients with NSCLC, with common sites including the adrenal glands, liver, brain, bones, and abdominal lymph nodes (44). In the results of a 2013 meta-analysis of nine studies, FDG PET/CT had a sensitivity of 93%, a specificity of 96%, a positive likelihood ratio of 28.4%, and a negative likelihood ratio of 0.08% for detection of

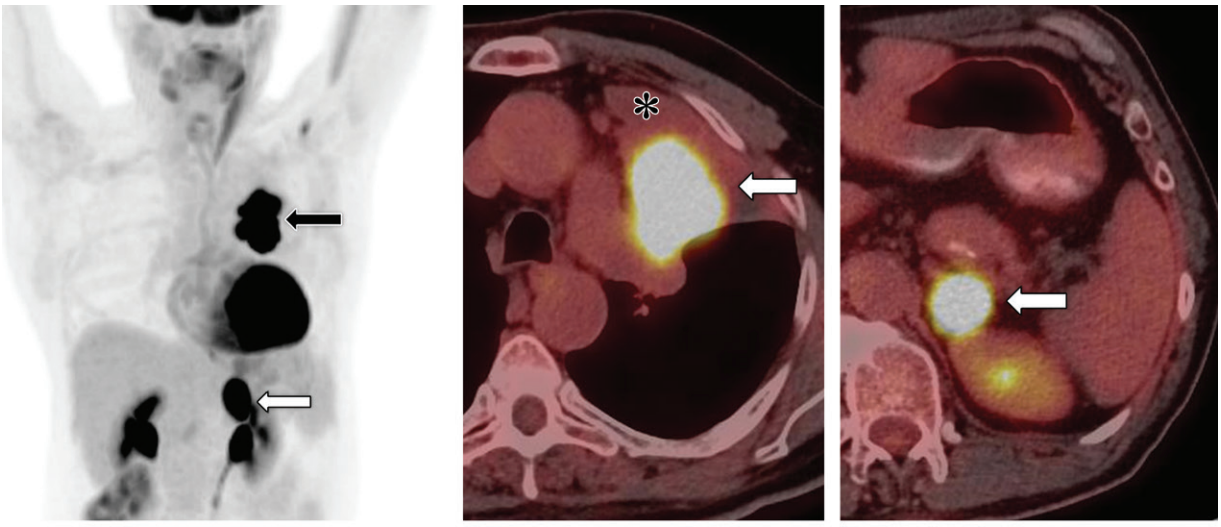


Figure 16. Poorly differentiated squamous cell carcinoma (M1b) in a 57-year-old man. **(a)** Coronal FDG PET/CT maximum intensity projection image shows the right upper lobe mass (black arrow) and a solitary adrenal metastasis (white arrow). **(b)** Axial fused FDG PET/CT image of the chest shows a 6.5-cm mass (arrow) in the left upper lobe. Note adjacent atelectatic lung (*) with no FDG uptake. **(c)** Axial fused FDG PET/CT image of the abdomen shows an FDG-avid 2.6-cm metastatic nodule (arrow) in the left adrenal gland.

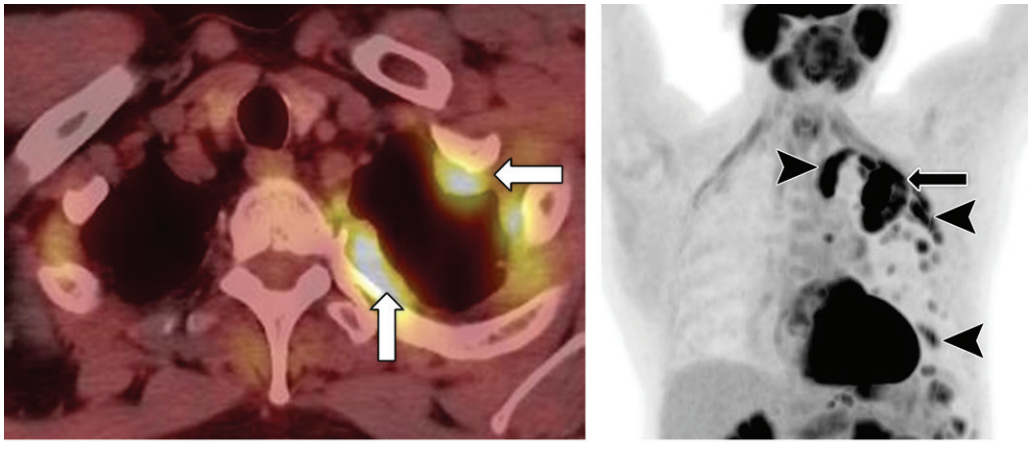
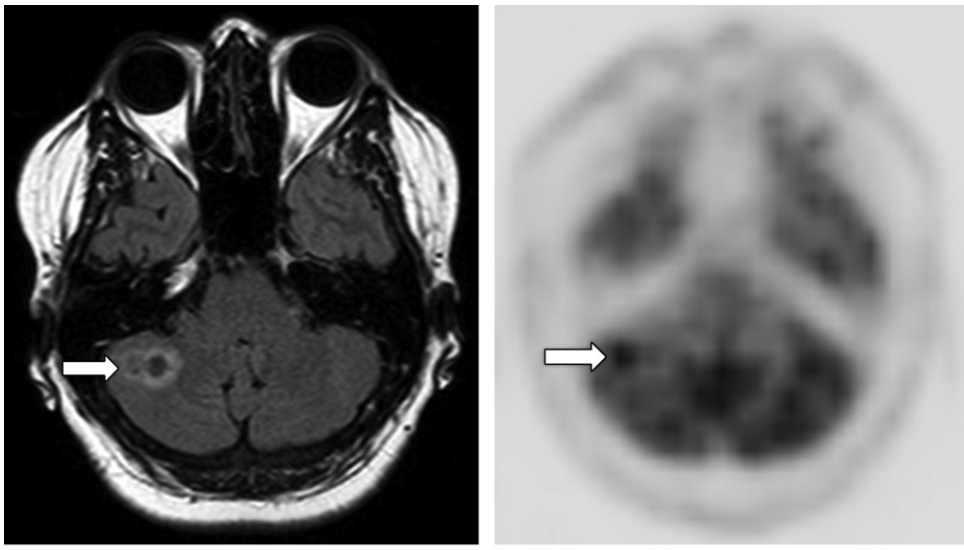


Figure 17. Pleural metastases in a 53-year-old woman with poorly differentiated adenocarcinoma. **(a)** Axial fused FDG PET/CT image shows multiple FDG-avid pleural nodules (arrows). **(b)** FDG PET/CT maximum intensity projection image shows the left upper lobe tumor (arrow) and multiple FDG-avid left pleural nodules (arrowheads).

distant metastases (45). According to the NCCN guidelines, any lesion with an increased FDG uptake suspicious for metastasis needs confirmation with biopsy or additional cross-sectional imaging to identify its highest stage. In clinically aggressive advanced-stage tumors, the NCCN guidelines recommend performance of PET imaging before diagnostic biopsy to select areas of abnormality that would confer the highest stage. Patients with a single extrathoracic metastatic lesion in a single organ—brain, liver, bone, distant lymph node, skin, peritoneum, or adrenal gland—have a better survival rate than those with multiple extrathoracic lesions and may be candidates for surgical resection or local ablative therapy. Histopathologic confirmation is necessary in surgical candidates with a single atypical lesion (46) (Fig 16).

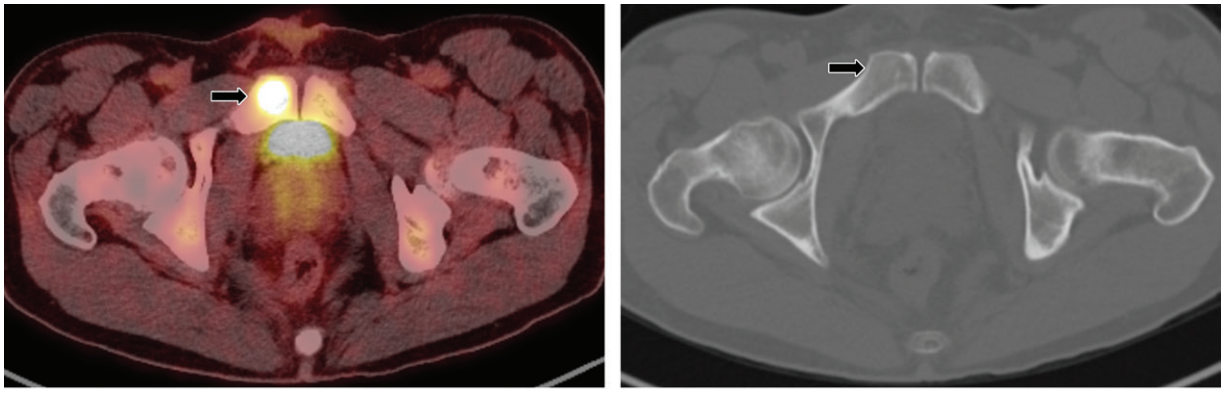
In patients with locally advanced NSCLC that is suitable for treatments with curative intent, FDG PET/CT may be used to identify unsuspected metastases, reducing the frequency of futile thoracotomies. The rates of progression-free survival and overall survival are significantly worse ($P < .001$) in upstaged disease with PET/CT (47). The NCCN guidelines do not recommend routine bone scintigraphy for staging NSCLC.

Pleural Metastases.—FDG accumulates in malignant pleural effusions, possibly in malignant cells. Several groups of investigators have



a. b.

Figure 18. Brain metastases in a 56-year-old woman with metastatic lung adenocarcinoma. **(a)** Axial T2-weighted fluid-attenuated inversion-recovery (FLAIR) MR image shows a necrotic metastasis (arrow) in the right cerebellum. **(b)** Axial FDG PET image shows subtle FDG uptake (arrow) in the right cerebellar lesion.



a. b.

Figure 19. Bone metastases in a 49-year-old man with moderately differentiated lung adenocarcinoma. **(a)** Axial fused FDG PET/CT image shows an area of FDG uptake (arrow) in the right pubic bone near the symphysis, a finding confirmed to be a metastasis at histopathologic examination of the specimen obtained at biopsy. **(b)** Axial CT image through the same location (arrow) does not show an anatomic correlate.

reported high accuracy of FDG PET/CT in the diagnosis of malignant pleural effusion (48). Multiple small pleural nodules in the absence of pleural effusion may not be FDG avid but should remain suspicious for dry pleural dissemination in patients with NSCLC (49) (Fig 17).

Brain Metastases.—Patients with NSCLC have a high incidence of metastases to the brain. Contrast-enhanced MRI has a higher sensitivity than FDG PET/CT for assessing brain metastases in patients with lung cancer. The results of a meta-analysis of prospective studies showed pooled sensitivities of 21% and 77% for PET and MRI, respectively, and specificities of 100% and 99% (50). Owing to the possibility of intrinsic intense FDG uptake by brain parenchyma obscuring FDG-avid lesions, NCCN guidelines recommend MRI to rule out brain metastases in patients with stage II to stage IV NSCLC (Fig 18).

Bone Metastases.—FDG PET/CT has greater sensitivity and specificity than bone scintigraphy for imaging metastases to the bone marrow, with a positive predictive value of 98% if the findings from PET and CT are concordant (51,52). In the results of a meta-analysis of patients with lung cancer, investigators found that FDG PET/CT and FDG PET were more accurate methods for the diagnosis of bone metastases than MRI or bone scintigraphy, and FDG PET/CT has a higher diagnostic value than any other method (53) (Fig 19).

Metastases in Extrathoracic Lymph Nodes.—FDG PET/CT may be used to identify unsuspected metastases. PET/CT may be used to identify metastases in normal-sized lymph nodes (<1 cm at CT), as well as in those with a fatty hilum. Nodal uptake of FDG that is higher than the FDG uptake in the blood pool is suspicious for nodal metastases, and nodal uptake of FDG

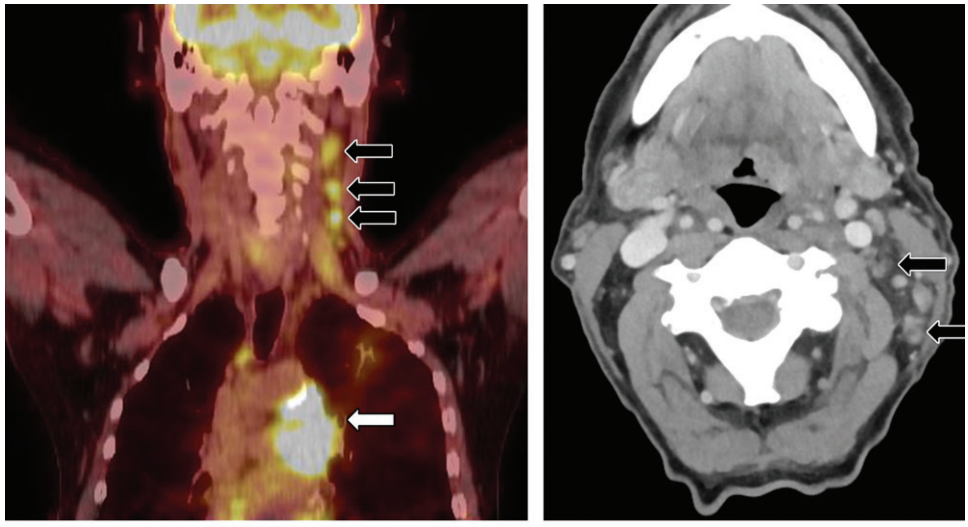


Figure 20. Extrathoracic nodal metastases in a 58-year-old man with lung adenocarcinoma. **(a)** Coronal fused FDG PET/CT image shows an FDG-avid left lung cancer (white arrow). Note the FDG-avid left cervical nodes (black arrows), which demonstrated metastatic disease at histopathologic examination of the specimen from biopsy. **(b)** Axial contrast-enhanced CT image of the neck shows that these nodes (arrows) measure less than 1 cm.

that is higher than the liver uptake of FDG is highly concerning for nodal metastases. Biopsy of an FDG-avid node is necessary to confirm its highest pathologic stage, which guides therapeutic decision making (Fig 20).

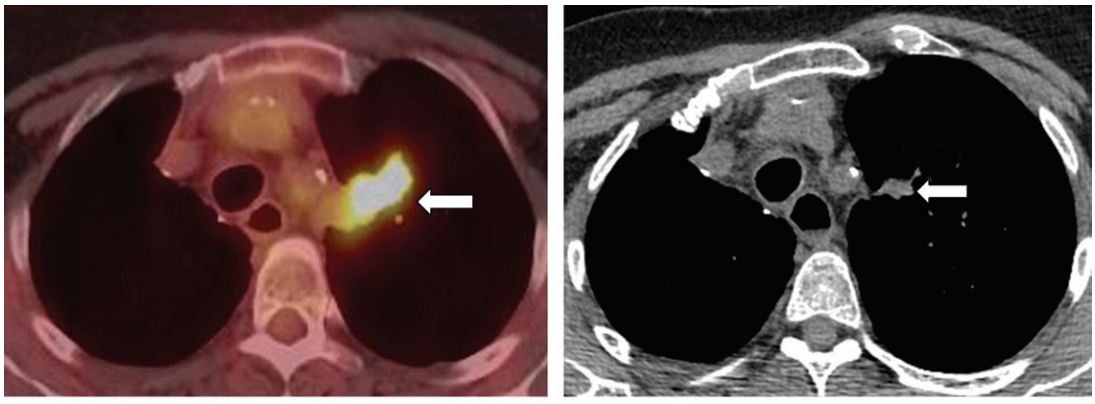
Adrenal Metastases.—Incidental adrenal nodules are found in 20% of patients with NSCLC; most nodules are benign adrenal adenomas. In a study of patients known to have or suspected of having lung cancer, the combination of a mean CT attenuation greater than 10 HU and a maximum standardized uptake value greater than 3.1 had a sensitivity and specificity of 97% and 86% for identifying metastatic disease. A cutoff ratio of the adrenal nodule's maximum standardized uptake value to the liver's average standardized uptake value of 2.5 had a 100% negative predictive value for malignancy (54). In the results of a recent meta-analysis of nine studies to evaluate the diagnostic accuracy of FDG PET/CT for the detection of adrenal metastasis in patients with lung cancer, the pooled sensitivity was 89%, the specificity was 90%, the positive likelihood ratio was 8.5, and the negative likelihood ratio was 0.09 (55). False-negative PET/CT results can occur in metastases with hemorrhage or necrosis and in lesions measuring less than 1 cm. Adrenal hyperplasia, adrenal adenoma, and infections such as tuberculosis can result in false-positive results. Histologic diagnosis is recommended if the adrenal gland is the only site of metastatic disease.

Detection of a Second Primary Malignancy

Whole-body FDG PET/CT may detect incidental areas of FDG activity that are suspicious for secondary primary tumors in about 4% of the patients with NSCLC, with approximately 25% of these findings corresponding to a second malignancy. The most common sites of uptake are the colon, thyroid, proximal aerodigestive tract, and ovaries. The risk of malignancy is based on the location, with the greatest risk if there is focal FDG uptake in the breast, colon, thyroid, or prostate. Approximately 30% of focal FDG uptake can be indicative of malignancy, whereas a diffuse pattern of FDG uptake usually indicates a benign cause. In the findings of one study, FDG PET/CT identified a second primary malignancy or premalignant lesion in 3% of patients with NSCLC, a finding that changed management from a curative intent to palliation in 27% of patients (56).

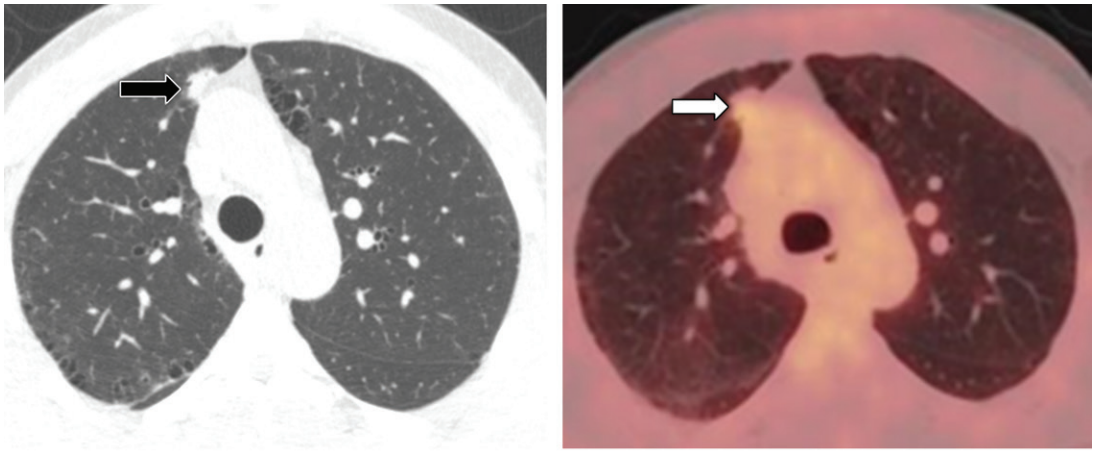
Limitations of PET/CT in the TNM Staging of NSCLC

False-Positive Lesions.—Inflammatory disease is a known confounder in FDG PET/CT studies, and a positive PET finding can be caused by infection or inflammation (25). The results of a retrospective study of patients with lung cancer revealed a false-positive rate of 7% with PET/CT. Causes of false-positive results included inflammatory pseudotumor (43%), tuberculoma (37%), and organizing pneumonia (6%). At multivariate analysis, the false-positive rate was related to higher levels of interleukin-6, positive findings on an interferon gamma release assay for tuberculosis (T-SPOT.TB; Oxford Immunotec, Abingdon, UK), age less than 50 years, and nondiabetic status (57). Nonadenocarcinoma histology and age older than 65 years are independent factors related to false-positive hilar and mediastinal lymph nodes in NSCLC staging with PET/CT (58). False-positive



a. b.

Figure 21. False-positive FDG PET/CT findings in a 78-year-old woman after right upper lobectomy for adenocarcinoma. **(a)** Axial fused FDG PET/CT image shows increased FDG uptake in a left upper lobe mass (arrow). Histopathologic examination of the specimen obtained at biopsy revealed pneumonia, and culture was positive for *Cladophialophora* species. **(b)** Axial CT image obtained after administration of a course of antibiotic therapy shows a decrease in the size of the left upper lobe mass (arrow).



a. b.

Figure 22. False-negative FDG PET/CT findings in a 68-year-old man with mucinous adenocarcinoma. **(a)** Axial CT image shows a 1.6-cm right upper lobe mass (arrow). **(b)** Axial fused FDG PET/CT image shows no increased FDG uptake in the 1.6-cm right upper lobe mucinous tumor (arrow).

lymph nodes may also be related to the presence of interstitial pneumonitis, previous tuberculosis, silicosis, and emphysema (59,60) (Fig 21).

False-Negative Lesions.—False-negative findings at PET can be the result of a small nodule, low cellular density in lesions such as carcinoma in situ, or low tumor avidity for FDG. The most important radiologic factor for risk assessment is change or stability compared with the findings from a previous imaging study (25). In solitary pulmonary nodules that demonstrate negative findings at PET, serial CT follow-up imaging may be performed in a patient with a low pretest likelihood of malignancy. In a patient with a high pretest likelihood of malignancy, tissue sampling or resection should be considered (61) (Fig 22).

Conclusion

The eighth edition of the TNM classification of lung cancer defines new T and M descriptors and creates new stage groupings that better determine prognosis. The new T descriptors are based on the primary tumor size and histopathologic findings. The M category has three descriptors that are based on the extent of metastatic disease. The NCCN guidelines recommend FDG PET/CT from the skull base to the knees or whole-body FDG PET/CT for the evaluation of patients with stage I to stage IV NSCLC (4). High FDG uptake that is suspicious for nodal metastases needs histopathologic confirmation, and high FDG uptake that is suspicious for metastatic disease needs histopathologic or other radiologic confirmation to confer the highest TNM stage. It is vital for radiologists

and nuclear medicine physicians to know the strengths and limitations of FDG PET/CT as applied to the current staging system.

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