Imaging of Lung Cancer Staging

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Abstract

Lung cancer is a leading cause of cancer-related mortality worldwide. Imaging is integral in accurate clinical staging to stratify patients into groups to predict survival and determine treatment. The eighth edition of the tumor, node, and metastasis (TNM-8) staging system proposed by the International Association for the Study of Lung Cancer in 2016, accepted by both the Union for International Cancer Control and the American Joint Committee on Cancer, is the current standard method of staging lung cancer. This single TNM staging is used for all histologic subtypes of lung cancer, including nonsmall cell lung cancer, small cell lung cancer, and bronchopulmonary carcinoid tumor, and it addresses both clinical and pathologic staging. Familiarity with the strengths and limitations of imaging modalities used in staging, the nuances of TNM-8, its correct nomenclature, and potential pitfalls are important to optimize patient care. In this article, we discuss the role of computed tomography (CT) and positron emission tomography/CT in lung cancer staging, as well as current imaging recommendations pertaining to TNM-8.

Keywords
- lung cancer
- staging
- metastasis
- TNM-8

Despite improvements in diagnosis and treatment, lung cancer is a leading cause of cancer-related mortality worldwide, accounting for 1.80 million deaths in 2020.[1] Computed tomography (CT) and 18-fluoro (F)-2-deoxy-D-glucose (FDG) positron emission tomography (PET)/CT in combination are commonly used in the initial staging of lung cancer. The eighth edition of the tumor, node, and metastasis (TNM-8) staging system proposed by the International Association for the Study of Lung Cancer (IASLC) in 2016, accepted by both the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC), is the current standard method of staging lung cancer. This single TNM staging is used for all histologic subtypes of lung cancer, including nonsmall cell lung cancer (NSCLC), small cell lung cancer (SCLC) and bronchopulmonary carcinoid tumor, and addresses both clinical and pathologic staging.[2] Lung cancer staging classification stratifies patients into groups to predict survival and is based solely on the anatomical extent of the malignant tumor in terms of three components: primary tumor (T), nodal status for metastasis (N), and metastasis to the distant organs (M; ►**Tables 1** and **2**). In regard to the staging of SCLC, analysis of the IASLC database (which included more than 5,000 patients with SCLC) confirmed the prognostic value of TNM staging in patients with SCLC supporting its continued usage.[3] In regard to the staging of bronchopulmonary carcinoid tumors, Yoon et al demonstrated worsening disease-specific survival with increasing TNM stage (such as stage I vs. Stage II) for typical and atypical carcinoid tumors; however, there was significant overlap in disease-specific survival between subcategory stages (such as IA1 vs. IA2).[4] Further studies are needed to evaluate if modifications to the TNM system are needed to accurately address the staging of bronchopulmonary carcinoid tumors.

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Table 1 IASLC lung cancer staging project T, N, and M descriptors for the TNM-8 classification of lung cancer (adapted from Goldstraw et al[2])

T–primary tumor		
Category	**Subcategory**	**Descriptors**
TX		Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0		No evidence of primary tumor
Tis		Carcinoma in situ: Tis(AIS): adenocarcinoma Tis(SCIS): squamous cell carcinoma
T1		Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus). The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a
	T1mi	Minimally invasive adenocarcinoma
	T1a	Tumor 1 cm or less in greatest dimension
	T1b	Tumor more than 1 cm but not more than 2 cm in greatest dimension
	T1c	Tumor more than 2 cm but not more than 3 cm in greatest dimension
T2		Tumor more than 3 cm but not more than 5 cm; or tumor with *any* of the following features. T2 tumors with these features are classified T2a if 4 cm or less, or if size cannot be determined; and T2b if greater than 4 cm but not larger than 5 cm • Involves main bronchus regardless of distance to the carina, but without involving the carina • Invades visceral pleura • Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, either involving part of the lung or the entire lung
	T2a	Tumor more than 3 cm but not more than 4 cm in greatest dimension
	T2b	Tumor more than 4 cm but not more than 5 cm in greatest dimension
T3		Tumor more than 5 cm but not more than 7 cm in greatest dimension or one that directly invades any of the following: parietal pleura (PL3), chest wall (including superior sulcus tumors), phrenic nerve, parietal pericardium; or associated separate tumor nodule(s) in the same lobe as the primary
T4		Tumors more than 7 cm or one that invades any of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; separate tumor nodule(s) in a different ipsilateral lobe to that of the primary
N–regional lymph nodes		
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2		Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3		Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
M–distant metastasis		
M0		No distant metastasis
M1		Distant metastasis
	M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural or pericardial effusion. Most pleural (pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is non-bloody and is not an exudate Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor
	M1b	Single extrathoracic metastasis in a single organ and involvement of a single distant (nonregional) node
	M1c	Multiple extrathoracic metastases in one or several organs

Abbreviations: IASLC, International Association for the Study of Lung Cancer; TNM, tumor–node–metastasis.

Table 2 Stage groupings for NSCLC

T or M stage		N0	N1	N2	N3
T1	T1a	IA1	IIB	IIIA	IIIB
	T1b	IA2	IIB	IIIA	IIIB
	T1c	IA3	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIIA	IIIB
	T2b	IIA	IIB	IIIA	IIIB
T3	T3	IIB	IIIA	IIIB	IIIC
T4	T4	IIIA	IIIA	IIIB	IIIC
M1	M1a	IVA	IVA	IVA	IVA
	M1b	IVA	IVA	IVA	IVA
	M1c	IVB	IVB	IVB	IVB

Abbreviations: NSCLC, non–small cell lung cancer; TNM, tumor–node–metastasis.

Clinical staging includes all tests and imaging studies done for initial evaluation of the extent of disease and information obtained from endobronchial ultrasound-guided nodal biopsy and mediastinoscopy but not from thoracotomy. Pathologic staging is the staging obtained at the time of surgical resection. Most of the clinical staging that assesses the extent of disease relies on imaging. Accurate clinical staging allows one to tailor treatment to patients' needs and determines prognosis. Thus, familiarity with the current TNM staging, its correct nomenclature, potential pitfalls, and limitations are important to optimize patient care. In this article, we discuss the role of CT and PET/CT in lung cancer staging, as well as current imaging recommendations for lung cancer staging (TNM-8).

Tumor Classification

The tumor classification characterizes the size, degree of local tumor invasion, and the existence and location of separate tumor nodules. IASLC recommends measurement of the primary tumor rounded to the nearest millimeter on contiguous 1-mm sections with lung window setting on any plane that shows the greatest diameter. For solid lung cancers, the longest diameter of the tumor should be reported.[5] For part-solid lung cancers, the long axis diameter of the solid component should also be reported, as this is thought to represent the invasive component on pathology.[5]

The TNM-8 database validated the 3-cm cut-off to separate T1 from T2 tumors, as well as a degradation of survival associated with each 1-cm increment.[6] Therefore T1 tumors were divided into three subgroups with T1a measuring 1 cm or less, T1b measuring more than 1 cm but equal to or less than 2 cm, and T1c measuring more than 2 cm but equal to or less than 3 cm.[7] Likewise, T2 tumors were divided into two subgroups with T2a tumors measuring more than 3 cm and less than or equal to 4 cm, and T2b lesions measuring more than 4 cm and less than or equal to 5 cm.[7] T3 lesions are defined as measuring more than 5 cm and less than or equal to 7 cm, and T4 lesions include tumors measuring more than 7 cm.

In addition to size criteria, relationship to main and lobar bronchi is also considered in TNM staging. To be classified as a T1 tumor, there can be no evidence of invasion into the lobar or more proximal bronchi.[7] Tumors less than or equal to 5 cm that invade a main bronchus regardless of the distance from the carina are considered T2.[7] Additionally, tumors less than or equal to 5 cm with associated partial or complete lung atelectasis, pneumonitis, or invasion of the visceral pleura are considered T2.[7] Tumors measuring less than or equal to 7 cm that directly invade the parietal pleura, chest wall, phrenic nerve, or parietal pericardium are considered T3. Tumors of any size that invade the mediastinum, diaphragm, heart, great vessels, recurrent laryngeal nerve, vertebrae, or carina are considered T4.[7] Separate tumor nodules in the same lobe as the dominant tumor are considered T3, while separate tumor nodules in a different lobe of the same lung are considered T4.[7] Of note, separate nodules in the contralateral lung to the primary tumor are considered intrathoracic metastatic disease M1a (►**Fig. 1**).

Additional advantages of FDG PET/CT include the ability to delineate central obstructing primary tumors from adjacent atelectasis and postobstructive change providing important information for biopsy target selection and radiation treatment planning[8,9] (►**Fig. 2**). Furthermore, FDG PET/CT is helpful in the detection of recurrent laryngeal nerve involvement (T4) manifesting as vocal cord paralysis (►**Fig. 3**).

It is important to be aware of the various pitfalls in FDG PET/CT in lung cancer staging. False-positive FDG PET results may be due to nonneoplastic processes such as infections/pneumonias, hamartomas, granulomatous disease, sarcoidosis, amyloidosis, lung parenchymal or pleural fibrosis, and rounded atelectasis.[10] Although uncommon, false-negative results can be seen with typical carcinoid tumors and early-stage disease (preinvasive and minimally invasive lung adenocarcinoma[10]; ►**Fig. 4**). Although many preinvasive and minimally invasive adenocarcinomas may be below the size threshold for PET characterization, focal FDG uptake has been shown to correlate with invasive tumor in both pure ground-glass lesions and part-solid lesions.[11]

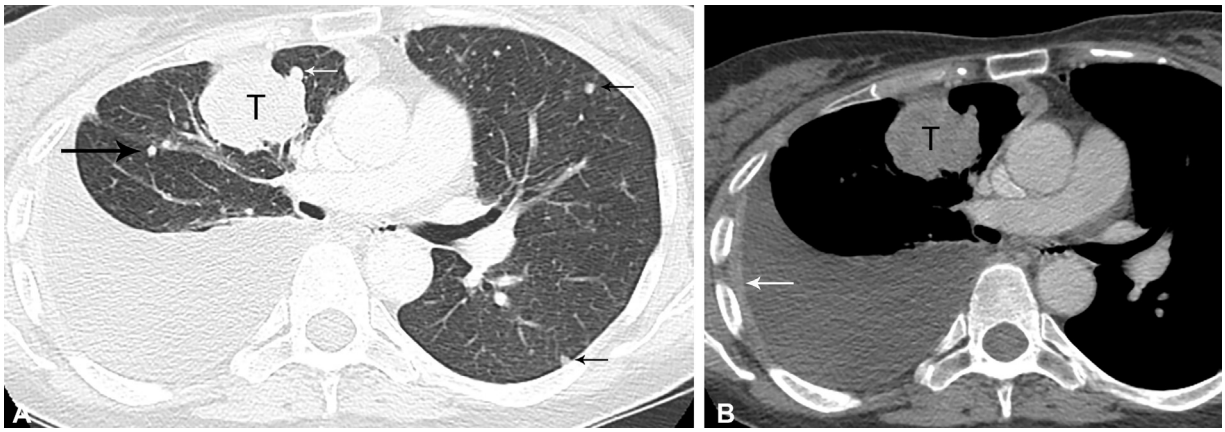

Fig. 1 A 60-year-old woman with M1a disease. (**A**) Contrast-enhanced CT shows 4-cm primary tumor (T) in the right upper lobe. Separate nodule in the same lobe (white arrow) as the primary tumor is T3 disease. Separate nodule (long black arrow) in the right lower lobe, different lobe, same lung as the primary tumor is T4 disease. Separate nodules in the contralateral lung (small black arrows) constitute M1a disease, intrathoracic metastatic disease. (**B**) Contrast-enhanced CT shows the primary tumor in the right upper lobe and a moderate right pleural effusion with right pleural thickening (white arrow). Thoracentesis showed malignant pleural effusion, also M1a disease. Staging is determined by the highest descriptor and thus the final stage is stage IVA. CT, computed tomography.

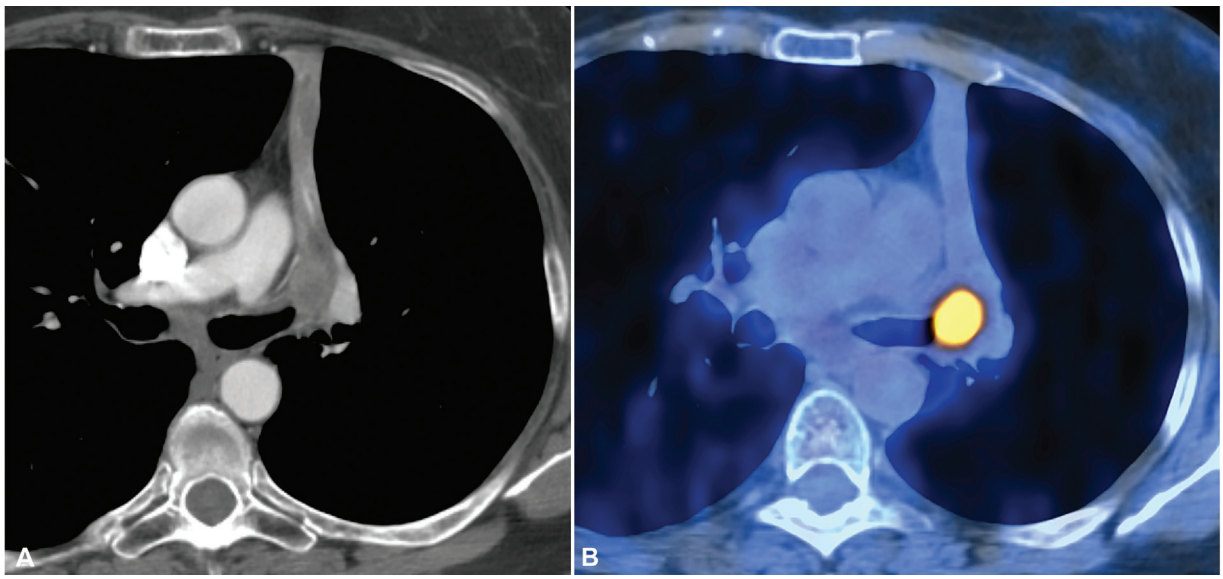

Fig. 2 A 64-year-old woman with T2 disease. (**A**) Contrast-enhanced CT shows 2-cm primary tumor in the left upper lobe centrally associated with lobar collapse. (**B**) Axial PET/CT shows FDG avidity of the primary tumor and is useful in radiation treatment planning. Tumor size of 2 cm is T1b; however, lobar/lung atelectasis is T2 disease. As there is no nodal and no distant metastasis, the final stage is stage IB. CT, computed tomography; FDG, fluoro-2-deoxy-D-glucose; PET, positron emission tomography.

Nodal Classification

The nodal classification describes the regional extent of disease with the presence or absence of intrathoracic lymph node metastases. The nodal status is one of the most reliable indicators of prognosis.[12] For lung cancer staging, nodal status is dependent on anatomical location of metastatic lymph nodes.[12] However, future revision of TNM staging may take into consideration the tumor burden or number of lymph nodes involved. The IASLC defines nodal status as N0 (no regional lymph node involvement), N1 (ipsilateral peribronchial, interlobar, or hilar lymph node involvement), N2 (ipsilateral mediastinal lymph node involvement), or N3 (contralateral mediastinal, contralateral hilar, or supraclavicular node involvement[12,13]; ►**Fig. 5**). Other lymph nodes including the internal mammary, anterior diaphragmatic, middle diaphragmatic and intercostal lymph nodes, not addressed in the IASLC lymph node map represent distant (M) metastatic disease (►**Fig. 6**).

The IASLC staging project is global, and thus does not dictate the use of advanced imaging for clinical staging, as the availability of imaging modalities varies around the world. The ability of imaging to predict the N-status depends on the modality used. Thus, it is important to understand the strengths and limitations of various imaging modalities in detecting nodal metastasis in clinical staging. The American Society of Clinical Oncology (ASCO) recommends at minimum to perform a chest CT,[14] and if no distant metastases

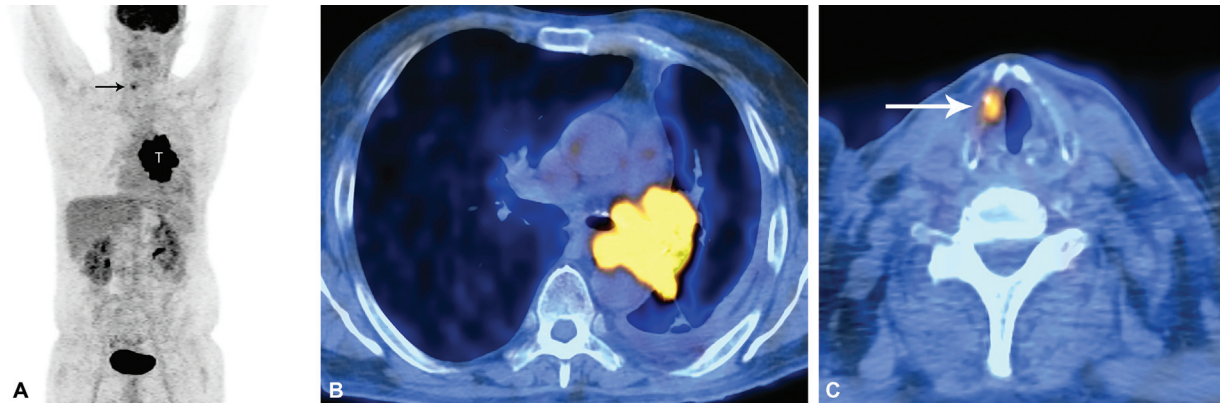

Fig. 3 A 58-year-old man presents with hoarseness and dysphagia for 2 months. (**A**) Whole body PET shows the FDG avid left upper lobe primary tumor (T) invading the mediastinum and physiologic uptake of FDG in the right vocal cord (arrow). (**B**) Axial PET/CT shows the bulky primary tumor invading the mediastinum in the aortopulmonic window. Involvement of the left recurrent laryngeal nerve resulted in left vocal cord paralysis. (**C**) PET/CT at the level of the vocal cords shows asymmetric FDG uptake in the normal right vocal cord (arrow) and no FDG uptake in the paralyzed left vocal cord. Involvement of the recurrent laryngeal nerve is T4 disease. CT, computed tomography; FDG, fluoro-2-deoxy-D-glucose; PET, positron emission tomography.

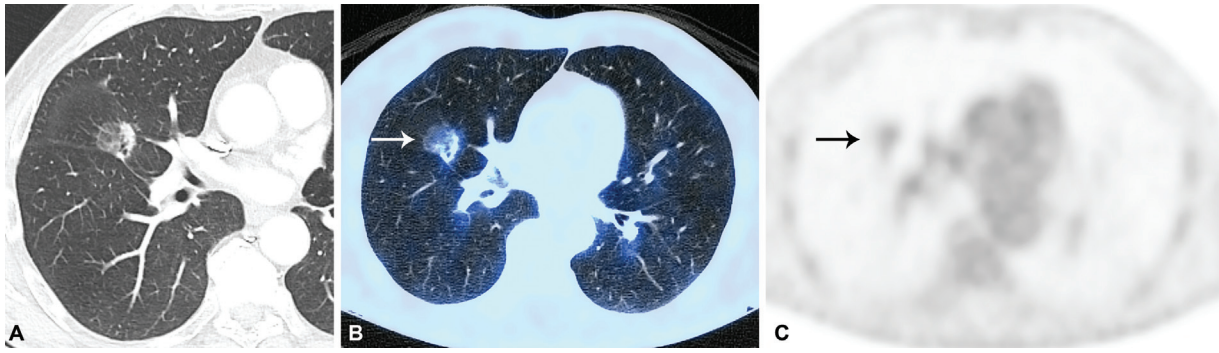

Fig. 4 A 69-year-old man with lung adenocarcinoma. (**A**) CT shows right middle lobe 2 cm part-solid nodule abutting the major and minor fissures. The lesion shows focal "bubbly" internal lucencies and a solid component along the anteromedial aspect. (**B**) PET/CT and (**C**) PET show the nodule is not FDG-avid (arrow) with SUV max of 1.6. Biopsy revealed well-differentiated adenocarcinoma. Part solid lung adenocarcinomas may not be FDG avid on PET scan due to slow cell proliferation or poor cellularity. CT, computed tomography; FDG, fluoro-2-deoxy-D-glucose; PET, positron emission tomography.

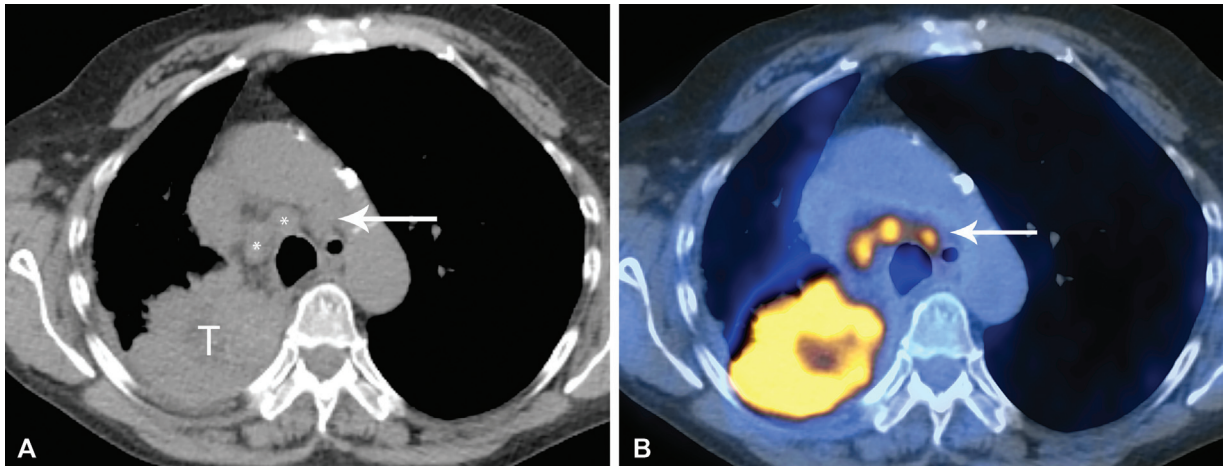

Fig. 5 A 57-year-old woman with N3 node metastasis. (**A**) CT shows the 6-cm tumor (T) in the right lung (T3) with two 1.1-cm right paratracheal lymph nodes (asterisks) and an 0.8-cm left paratracheal lymph node (arrow). The size criterion for nodal involvement on CT is greater than 1 cm in short axis diameter. (**B**) Axial PET/CT shows FDG uptake in the primary tumor in the right lung, as well as in the bilateral paratracheal lymph nodes. Biopsy confirmed nodal metastases in N2 (right paratracheal) and N3 (left paratracheal) nodal stations. PET/CT is superior to CT in the detection of nodal metastasis. Staging is determined by the highest descriptor and thus the final stage is stage IIIC. CT, computed tomography; FDG, fluoro-2-deoxy-D-glucose; PET, positron emission tomography.

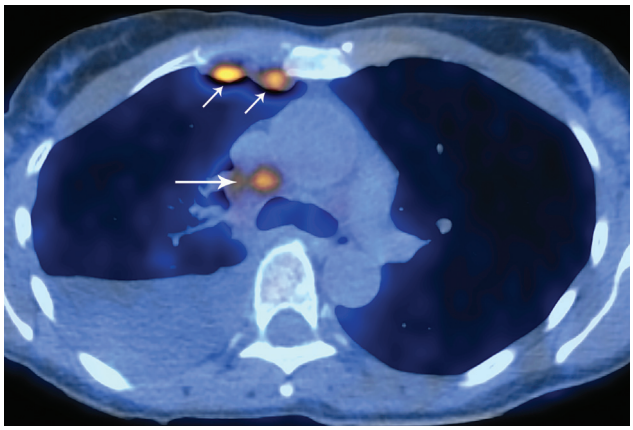

Fig. 6 A 49-year-old woman with right upper lobe lung cancer and internal mammary nodal metastases. Axial FDG PET/CT shows FDG avid lymph nodes in the right paratracheal region (long arrow) denoting N2 disease and in the right internal mammary region (short arrows). The N status represents regional spread of disease. Lymph nodes which appear on chest imaging but not considered regional are the internal mammary, anterior diaphragmatic, middle diaphragmatic, intercostal, and axillary lymph nodes, and represent metastatic disease. CT, computed tomography; FDG, fluoro-2-deoxy-D-glucose; PET, positron emission tomography.

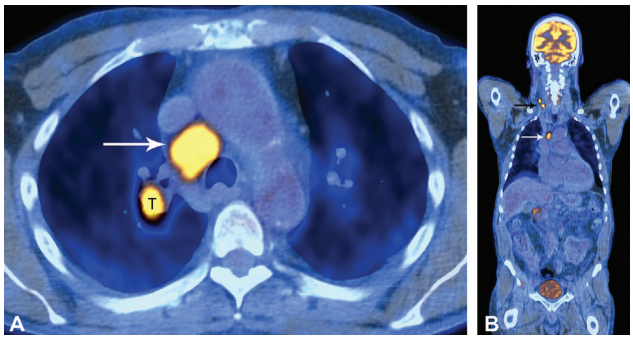

Fig. 7 A 62-year-old man with false positive N3 disease. (**A**) Axial PET/CT shows the FDG avid right upper lobe neuroendocrine cancer (T) and right paratracheal adenopathy (arrow). (**B**) Coronal PET/CT shows FDG avid lymph nodes in the right paratracheal (white arrow) and right supraclavicular (black arrow) regions suspicious for N2 and N3 disease respectively. Biopsy of the right paratracheal node confirmed nodal metastasis from neuroendocrine carcinoma. However, biopsy of the right supraclavicular node showed noncaseating granulomatous inflammation and no malignant cells. Increased FDG uptake in infectious and inflammatory conditions has been reported to be due to increased glycolysis in leukocytes, lymphocytes, and macrophages. CT, computed tomography; FDG, fluoro-2-deoxy-D-glucose; PET, positron emission tomography.

identified, to be followed by FDG PET/CT. Due to the limited sensitivity and specificity of CT for identifying mediastinal nodal metastasis,[15] the current National Comprehensive Cancer Network (NCCN) guidelines recommend FDG PET/CT for initial assessment of the hilar and mediastinal lymph nodes.[15] Widely used for noninvasive staging of the lymph nodes, CT uses the sole criterion of size to differentiate benign from malignant lymph nodes. The most widely used criterion for identifying a malignant lymph node is a short-axis diameter of greater than 1 cm.[16] This criterion was chosen as a fine balance between sensitivity and specificity to minimize false-negative results. Numerous studies have looked at the performance of CT in distinguishing benign and malignant lymph nodes in patients with NSCLC. Two meta-analyses showed sensitivities of 61 to 64% and specificities of 74 to 79%.[17,18] The accuracies of CT and magnetic resonance imaging (MRI) in detecting nodal metastases are similar: the accuracy of CT ranges from 56 to 82% and that of MRI from 50 to 82%.[19–24] Limitations in the use of CT and MRI in nodal staging is due to the fact that normal-sized lymph nodes may harbor tumor and nodal enlargement may reflect a benign reactive process[25,26] (►**Figs. 5** and **7**). Attempts to seek alternatives to the size criterion for nodal metastasis including MRI nodal characteristics, such as the presence of high signal intensity, eccentric cortical thickening, or obliterated fatty hilum, have shown similar limitations, with accuracies of 70 to 73%.[27,28] Recent studies evaluating diffusion-weighted imaging (DWI) by MRI are promising. Two meta-analyses show that the pooled sensitivity for N-status using DWI is 0.65 to 0.68 and 0.92 to 0.97.[29,30] However, due to limitations with small sample size and lack of standardization of this imaging technique, more studies are needed to determine the role of diffusion-weighted MRI in N staging of lung cancer. Currently, DWI is not widely used in clinical practice.

The accuracy of PET is superior to that of CT in nodal staging, but the results should be interpreted with caution and in conjunction with CT scans. Nonneoplastic inflammatory processes can show increased FDG activity (►**Fig. 7**). For example, lymph nodes in the lymphatic drainage pathway for the parietal pleura can demonstrate FDG uptake for years following talc pleurodesis, and physicians must exercise caution in the interpretation of these findings to avoid misdiagnosis of nodal metastases[31] (►**Fig. 8**).

As with the limitation of PET resolution in the evaluation of the pulmonary nodule, PET is less accurate in the evaluation of lymph nodes smaller than 10 mm. In patients whose mediastinal lymph nodes are smaller than 1 cm, approximately 20% show a falsely negative PET scan.[18] In a pooled analysis of multiple studies in which a total of 2,865 patients were evaluated, the sensitivity and specificity of PET for identifying metastatic lymph nodes were 74 and 85%, respectively.[32] In a meta-analysis of 17 studies comprising 833 patients, the overall sensitivity of PET for detecting nodal metastases was 83% and specificity 92%, while the sensitivity and specificity of chest CT were 59 and 78%, respectively.[33] Integrated PET/CT improves nodal staging as compared with PET alone.[34,35] In the presence of enlarged lymph nodes, PET and PET/CT become less specific and less accurate but more sensitive in detecting nodal metastatic spread. In one meta-analysis, the median sensitivity and specificity of PET scans were 100 and 78%, respectively, in patients with enlarged lymph nodes.[18] The reduced specificity in the presence of enlarged lymph nodes is due to FDG avid reactive or inflammatory lymphadenopathy. Even with the use of FDG PET/CT, because of the low specificity in diagnosing lymph node metastases in enlarged lymph nodes, and low sensitivity in diagnosing metastatic disease in small lymph nodes, when curative intent treatment is planned, ASCO recommends mediastinal lymph node biopsy for confirming nodal

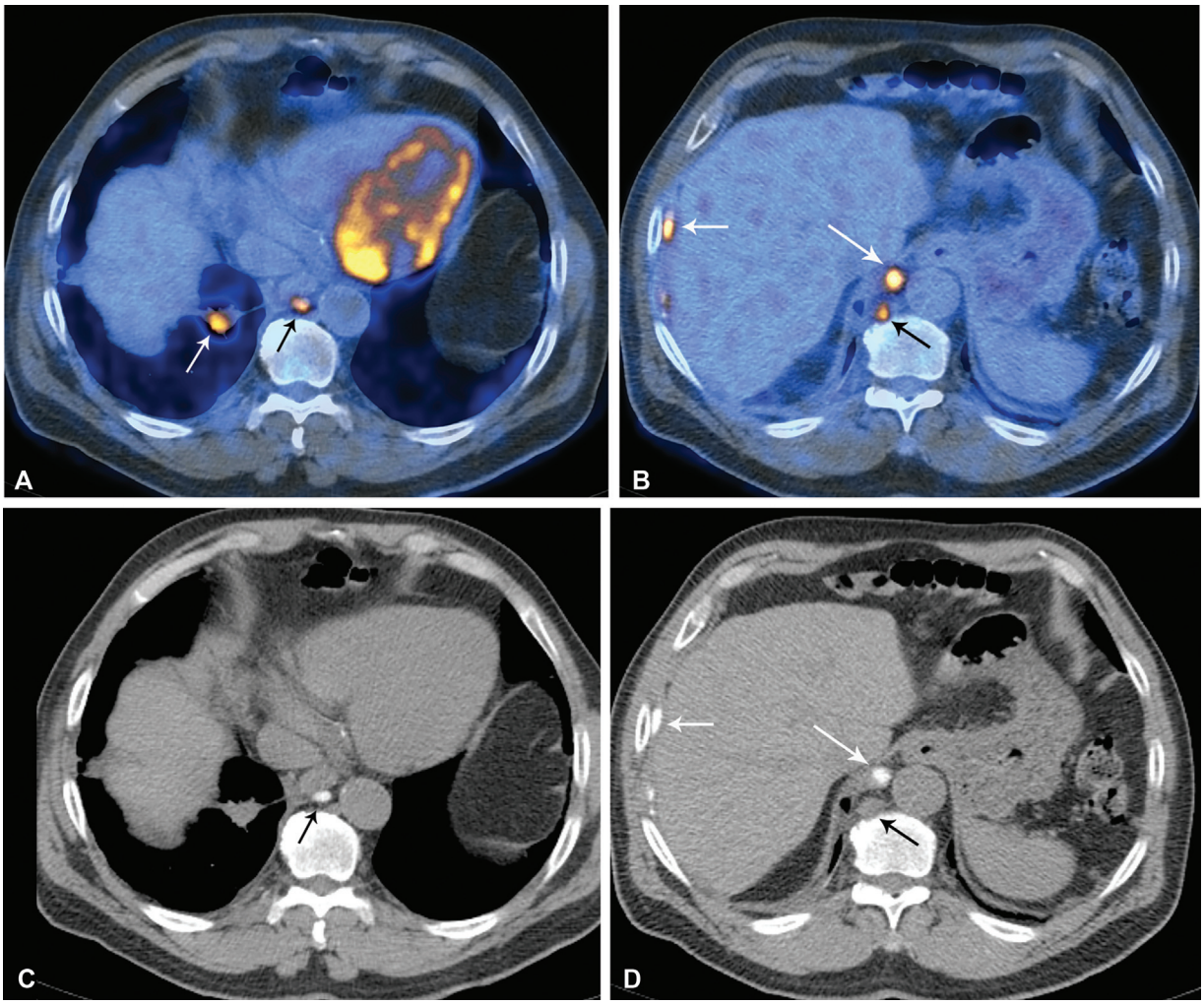

Fig. 8 A 71-year-old man with lung cancer and talc pleurodesis. (**A, B**) FDG-PET/CT shows increased FDG uptake in the right lower lobe primary tumor (white arrow), paraesophageal lymph node (black arrow), and at a lower level (**B**), the diaphragmatic pleura medially and laterally (white arrows) and a right retrocrural lymph node (black arrow). (**C, D**) CT at these two levels show the para-esophageal lymph node has high attenuation (black arrow) and at the lower level (**D**) the FDG avid foci localize to high attenuation material in the right diaphragmatic pleura (white arrows) consistent with talc pleurodesis. Note lymph nodes in the lymphatic drainage pathway for the parietal pleura can show FDG uptake for years following pleurodesis. Both the right retrocrural and high attenuation paraesophageal lymph node (black arrows) are FDG avid. CT, computed tomography; FDG, fluoro-2-deoxy-D-glucose; PET, positron emission tomography.

involvement. The importance of imaging is then, in selecting the biopsy site, to confirm the highest possible disease stage and to maximize tissue yield.[14]

One of the criticisms to the current location-based pN classification is that it does not reflect tumor burden at all. For example, a microscopic single hilar lymph node metastasis and gross involvement of numerous greater than 1.5 cm hilar lymph nodes are categorized into the same category of N1. It has been shown in studies that instead of using the anatomy based pN (pathology) classification, simply counting the number of involved nodes, using an nN (nN refers to counting the number (n) of nodes for nodal staging (N)) system may have better prognostication.[36,37] Statistical work on the IASLC database used for the TNM-8 staging showed that indeed patients with pN2 metastasis at a single N2 station without hilar lymph node involvement had a better survival that those patients with pN1 metastases in multiple N1 stations, supporting the notion that the number of lymph nodes is important for prognostication.[12] However, the database used for the eighth-edition staging had insufficient data of the number of lymph nodes involved in each station, and it was not possible to assess the value nN as a replacement of the location based pN staging. There was also insufficient data to assess nN for clinical staging (cN). In addition, use of nN staging may be problematic to implement. It is difficult by imaging, whether using the poor spatial resolution of PET imaging or even CT to count the number of involved lymph nodes when there is a conglomeration of lymph nodes. Practical issues arise when trying to count the number of lymph nodes involved when fragments of lymph nodes are collected from mediastinoscopy or endobronchial ultrasound-guided biopsies and sent to the pathologist. Even when lymph nodes are harvested at the time of surgical resection, they are sent to the pathologist en bloc. The number of lymph nodes involved is determined by how meticulous the gross pathology specimen is handled, as

lymph nodes may either be missed or one may be cut into two and counted as two involved lymph nodes. As this issue needs further analysis for future TNM revisions, it is recommended that when interpreting a staging study, the number of lymph nodes involved should be recorded and not just the location.

Metastasis Classification

The metastasis classification designates the presence or absence of distant metastasis. The absence of distant metastasis is considered M0. The IASLC considers pleural/pericardial effusion or nodules, contralateral/bilateral tumor nodules, or a combination of these findings as intrathoracic metastases (M1a).[38] For TNM-8, M1b was reclassified as a single extrathoracic metastatic site such as a single metastatic lesion in the brain, liver, bone, peritoneum, skin, adrenal gland, or a distant lymph node[38] (►**Figs. 9** and **10**). TNM-8 initiated M1c as a new classification for patients with multiple metastatic lesions in a single organ or lesions in multiple organs[38] (►**Fig. 10**). The decision to separate M1b and M1c was based on the definitions of oligometastatic disease and the associated prognostic disparities between patients with a single metastasis and those with multiple metastases.[7]

The strength of PET/CT imaging in lung cancer staging is the detection of occult metastatic disease (with common sites including the adrenal glands, liver, and bones), thereby sparing the patient from futile aggressive local therapy.[15] A meta-analysis of 56 studies including 8,699 patients showed improved detection of occult metastasis with the use of integrated FDG PET/CT scan compared with clinical staging without PET scan.[39] Distant metastases have been reported in 21% of patients with newly diagnosed NSCLC.[40] Of patients with clinical stage-III lung cancer, 17 to 24% had unexpected stage-IV disease detected by FDG-PET.[41]

In terms of detection of adrenal metastases, the use of FDG PET/CT has been established. PET/CT, using metabolic activity on FDG PET and attenuation values of <10 Hounsfield's units on CT to diagnose an adenoma, showed sensitivity, specificity, positive-predictive value, and negative-predictive value of 100, 98, 97, and 100%, respectively.[42] Blake et al assessed the accuracy of PET/CT for characterization of adrenal lesions in patients with proven or suspected malignancy and found that all malignant lesions had FDG metabolic activity greater than that of the liver with a mean adrenal lesion-to-liver ratio of 4.04 (range: 1.53–17.08), compared with the benign adrenal lesions, with a mean adrenal lesion-to-liver activity ratio of 0.66.[43] The meta-analysis by Boland et al concluded that adrenal masses can be characterized by FDG PET/CT, and subsequent imaging is usually not necessary.[44]

FDG PET/CT is effective for detecting bone metastasis in patients with NSCLC. In a retrospective single-center study, Ak et al demonstrated that FDG PET/CT detected bone metastases in 20% of NSCLC patients with a normal technetium 99m methylene diphosphonate (Tc-99m MDP) bone

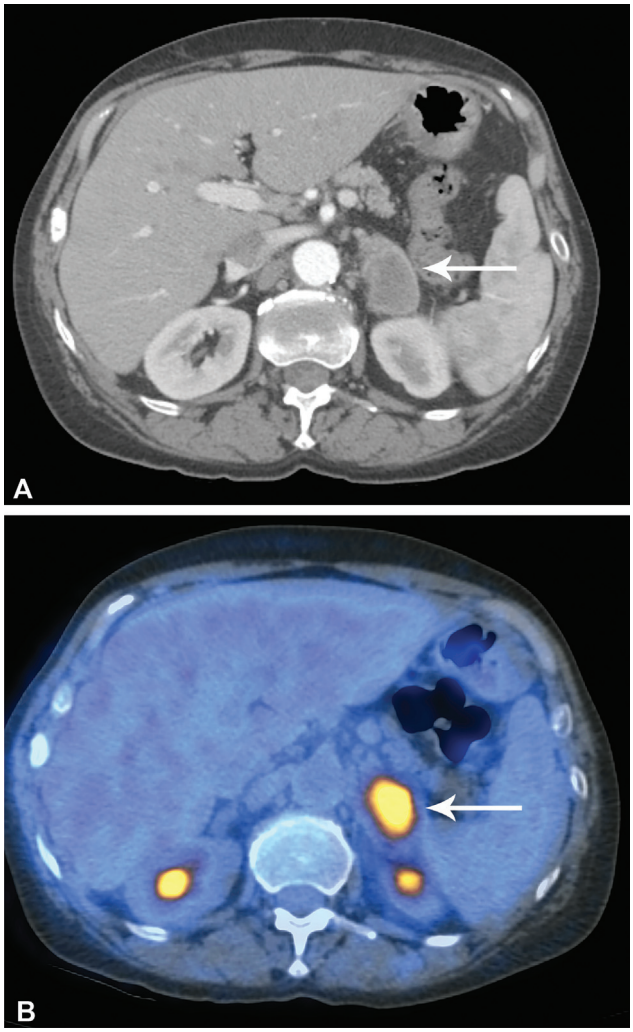

Fig. 9 A 57-year-old woman with adrenal metastasis. (**A**) Contrast-enhanced CT shows a left adrenal 4-cm mass (arrow). (**B**) PET/CT shows intense FDG uptake in the left adrenal mass (arrow) and biopsy confirmed metastasis. A single focus of extrathoracic metastasis is M1b disease, which constitutes stage IVA. CT, computed tomography; FDG, fluoro-2-deoxy-D-glucose; PET, positron emission tomography.

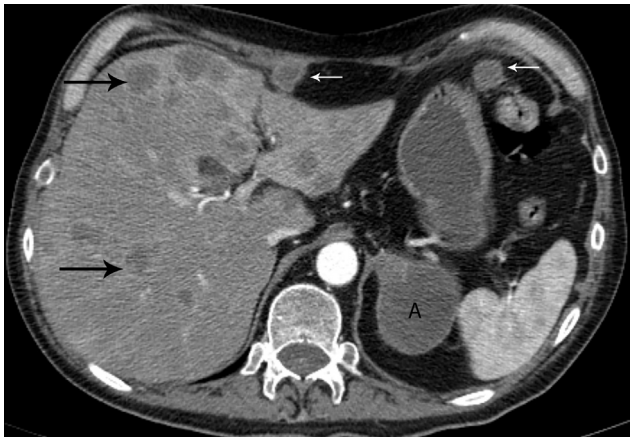

Fig. 10 A 58-year-old man with M1c disease. Contrast-enhanced CT shows multiple metastases in the liver (black arrows), peritoneum (white arrows) and left adrenal (A). M1c disease, multiple extrathoracic metastases, constitutes stage IVB. CT, computed tomography.

scintigraphy.[45] In a retrospective single-center study, Song et al found that FDG PET/CT was significantly more sensitive (94.3 vs. 78.1%) and more specific (98.8 vs. 97.4%) than ^{99m}Tc-DPD (3,3-diphosphono-1,2-propane-dicarbon acid) bone scintigraphy for detecting NSCLC bone metastases.[46]

A limitation of FDG PET/CT, however, is the detection of central nervous system (CNS) metastases, due to the increased uptake of glucose by the brain. In asymptomatic patients with stage-III lung cancer, studies demonstrated up to 21% of patients with clinically occult CNS metastases.[47–49] Consequently, brain imaging with contrast-enhanced MRI scan (a contrast-enhanced head CT scan may be substituted if MRI is contraindicated) is recommended to exclude clinically silent CNS metastases in patients with clinical stage-III lung cancer.[14]

A potential pitfall of FDG PET/CT in lung cancer staging involves the detection of FDG-avid lesions unrelated to the lung cancer mimicking distant metastases (►**Fig. 11**). Lardinois et al demonstrated that 9% of solitary FDG-avid extrathoracic lesions detected on staging PET for lung cancer were benign and 37% were unrelated to the lung cancer.[50]

A mimic of pleural metastasis is talc pleurodesis, a treatment for persistent or recurrent pleural effusion or pneumothorax. Talc incites an inflammatory reaction that adheres the parietal and visceral pleura together obliterating the pleural space and reducing the possibility that fluid or air can reaccumulate.[51] Talc pleurodesis manifests as areas of pleural thickening and high attenuation nodularity or thickening on CT.[51] The talc pleural deposits demonstrate intense FDG avidity on PET which can persist for years following the procedure[10] (►**Fig. 8**).

ASCO recommends that for suspected stage-III (T4, N0, or T3, N1–3, or T1–4, N2–3) NSCLC patients, any suspected metastatic site identified on CT or PET/CT should be confirmed pathologically with a biopsy. In general, biopsy sites should be selected to confirm highest possible disease stage and to maximize tissue yield.[14]

Resectability

In terms of the T, N, and M descriptors, staging evaluation is usually aimed at distinguishing resectable from unresectable disease (some T4 lesions or N3 or M1). The differentiation of T1 to T3 from T4 lung cancer and the detection of contralateral nodal (N3) and/or metastases (M1) are important, as these descriptors typically preclude surgical resection and are treated with chemotherapy and/or radiotherapy.

Positron Emission Tomography/Computed Tomography for Lung Cancer

The use of FDG PET/CT in lung cancer staging is established. The strength of FDG PET/CT lies in the detection of nodal and extrathoracic metastases. In a multicenter randomized controlled trial, Maziak et al found that FDG PET/CT upstaged 13.8% of patients, compared with 6.8% of patients who underwent staging with CT and whole-body bone scan.[52] In a randomized controlled trial, Fischer et al found that preoperative staging with FDG PET/CT for NSCLC reduced the total number of thoracotomies and futile thoracotomies (defined as any of the following results: benign lung lesion, stage IIIA or higher, inoperable T3 or T4 disease, or recurrent disease or death from any cause within 1 year after randomization).[53]

In terms of future direction, new pharmaceutical agents are being studied with PET/CT. While typical bronchial carcinoid tumors can have no or minimal FDG uptake, gallium 68 (^{68}Ga) 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)–octreotate (DOTATATE, GaTate) PET/CT has been demonstrated to show higher and more selective uptake in these tumors[54] (►**Fig. 12**). In cases where there is a high degree of suspicion for typical carcinoid tumor based on clinical and imaging findings, ^{68}Ga-DOTATATE may confirm the diagnosis and avoid the need for invasive procedures.

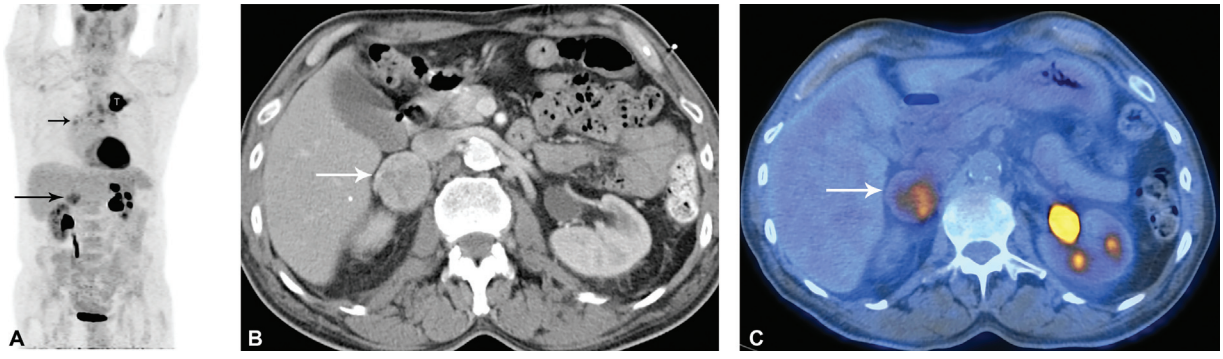

Fig. 11 A 73-year-old man with pheochromocytoma mimicking metastasis. (**A**) Whole body FDG PET shows the left upper lobe primary tumor (T) and FDG avid lymph nodes in the ipsilateral and contralateral mediastinal and right hilar (short arrow) regions suspicious for N2 (ipsilateral mediastinal) and N3 (contralateral mediastinal and contralateral hilar) disease respectively. The FDG avid right adrenal lesion (long arrow) is suspicious for M1b disease, single focus of extrathoracic metastasis. (**B**) Contrast-enhanced chest CT and (**C**) PET/CT show a 4-cm heterogeneously enhancing right adrenal mass (arrow) with increased FDG uptake and SUV max of 4.6 suspicious for metastasis. Biopsy revealed pheochromocytoma, and the patient was considered for surgical resection. Nodal staging with endobronchial ultrasound guided biopsy of multiple mediastinal and hilar lymph nodes showed no malignant cells. The patient proceeded to left upper lobectomy. FDG-avid lesions suspicious for metastases in NSCLC patients being considered for surgical resection should be biopsied to obtain a histopathologic diagnosis. Note PET/CT is useful in the detection of extrathoracic metastases as well as second primaries. CT, computed tomography; FDG, fluoro-2-deoxy-D-glucose; NSCLS, non-small cell lung cancer; PET, positron emission tomography.

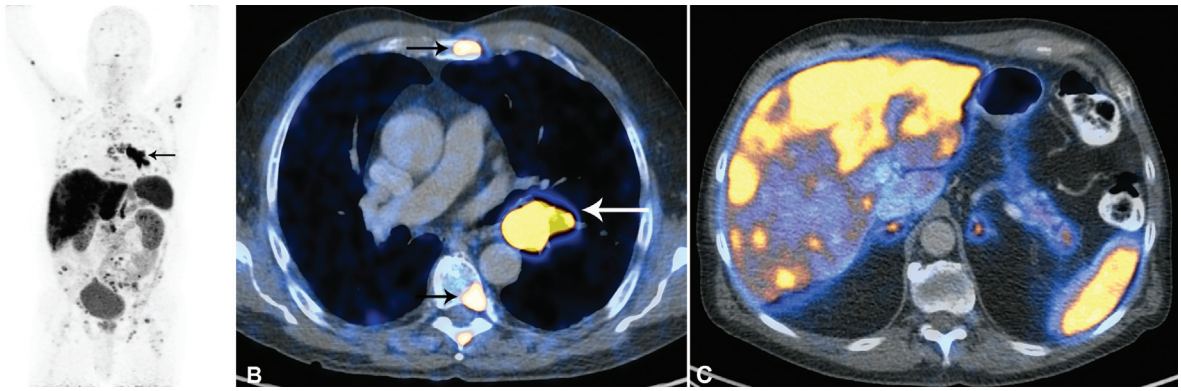

Fig. 12 A 71-year-old man with neuroendocrine cancer of the lung with metastases in the liver and bones. (**A**) Whole body gallium 68 (68Ga) 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)–octreotate (DOTATATE, GaTate) PET shows the left hilar primary tumor (arrow) and extensive metastases. (**B**) Axial DOTATATE PET/CT shows the somatostatin avid left hilar primary tumor (white arrow) and sternal and spine metastases (black arrows). (**C**) Axial DOTATATE PET/CT shows bilobar hepatic metastases. Note physiologic uptake in the spleen and bilateral adrenals. CT, computed tomography; PET, positron emission tomography.

Conclusion

Accurate clinical staging is essential to the treatment planning for patients with lung cancer. TNM-8 is the standard classification system for NSCLC, SCLC, and bronchopulmonary carcinoid tumors. CT remains the preeminent modality for thoracic imaging including lung cancer diagnosis and staging. FDG PET/CT plays an important role in lung cancer staging and has established benefits over CT, including the detection of lymph node, distant solid organ, and bone metastases. Potential pitfalls in the use of PET/CT in staging include false negative lung cancers (carcinoid and indolent adenocarcinoma), false-positive lymph nodes due to infectious and inflammatory conditions, and extrathoracic FDG avid foci unrelated to lung cancer. Knowledge of the strengths and limitations of various imaging modalities is essential for accurate clinical staging of lung cancer.

Conflict of Interest
None declared.

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