Chapter

PET-CT Principles and Applications in Lung Cancer Management

Long Chen, Hua Sun and Yunchao Huang

Abstract

Lung cancer is the most common malignant cancer throughout the world; the positron emission tomography/computed tomography (PET-CT) combines both the metabolism information from PET and anatomy details from CT, which is the state of the art. This manuscript introduced the PET-CT and applications in lung cancer diagnosing, staging, and treatment. Several aspects including clinical features, classification, grading and pathology of the lung cancer, principles of PET-CT, and evaluation of diagnosing and treatment had been covered. Detailed demonstration of each cancer subtype, staging criteria, and classification was described. The content will benefit the clinical doctors as well as radiologists.

Keywords: lung cancer, PET-CT

1. Lung cancer: an overview

1.1 Clinical features

Totally lung cancer remains the first leading cause of cancer incidence and mortality, with about 2.1 million incidence and 1.8 million deaths in 2018 among 185 countries [1]. In 2018, an estimated 234,030 new cases of lung and bronchial cancer will be diagnosed, and 154,050 deaths are estimated to occur because of the disease [2]. The 5-year over survival rate is <20% once diagnosed [3]. Lung cancer is a unique disease for its etiologic agent is an addictive product cigarette, made and produced by an industry. Voluntary or involuntary (secondhand) cigarette smoking leads to nearly 90% cases, suggesting that effective public health policies to prevent initiation of smoking, oversight of tobacco products, and other tobacco control measures will play crucial roles in reducing lung cancer mortality [4]. Increased exposure to smoke from the burning of charcoal for heating and cooking is believed to contribute to the high lung cancer incidence, rather than smoking that is thought to be the leading cause of high lung cancer incidence in western countries [5].

1.2 Classification

1.2.1 Non-small cell lung cancer (NSCLC)

There are four major cell types of lung cancer according to the World Health Organization (WHO) classification: adenocarcinoma (ADC), squamous cell

carcinoma (SCC), large cell carcinoma, and small cell carcinoma [6]. The first three types are also called non-small cell lung cancer, consisting of the most majority of all lung cancers. This molecular-based classification is important for therapeutic decision-making for several reasons: (i) overall survival was statistically superior for cisplatin/pemetrexed versus cisplatin/gemcitabine in patients with ADC (12.6 versus 10.9 months, respectively). In contrast, in SCC patients, there was a significant improvement in survival with cisplatin/gemcitabine versus cisplatin/pemetrexed (10.8 versus 9.4 months, respectively) [7]. (ii) SCC patients receiving treatment with carboplatin and paclitaxel plus bevacizumab (15 mg/kg) are prone to suffering from life-threatening major hemoptysis [8]. (iii) ADC patients are likely to harbor epidermal growth factor receptor (EGFR) mutations which are predictive of responsiveness to tyrosine kinase inhibitors (TKI).

Age, smoking history, previous cancer history, family history, occupational exposures, other lung diseases (chronic obstructive pulmonary disease [COPD], pulmonary fibrosis), exposure to infectious agents (e.g., endemic areas of fungal infections, tuberculosis) or risk factors, or history suggestive of infection are all potential or obvious risk factors.

1.2.2 Small cell lung cancer

Neuroendocrine tumors account for about 20% of lung cancers, and most are small cell lung cancer (SCLC) [9]. SCLC is sometimes called oat cell cancer, accounting for approximately 10–15% of lung cancers, and is considered as a separate entity from NSCLC due to its early metastases and relative response to chemotherapy and radiation. Unfortunately, although small cell lung cancer usually responds very well initially to treatment, long-term survival remains low. To be specific, the 5-year survival rate is 31% for stage I, 19% for stage II, 8% for stage IV, and only 2% for stage IV disease. There is no significant difference in the AJCC TNM staging system between NSCLC and SCLC. In fact, in addition to the TNM staging, SCLC can also be defined as "limited stage" when the tumor is encompassed within a tolerable radiation field or defined as "extensive stage" when the tumor is too large or too widespread to be encompassed within tolerable radiation field, according to the older Veterans Administration (VA) [10]. Then the NCCN Panel adopted a combined approach for staging SCLC using both the AJCC TNM staging system and the VA scheme for SCLC. In applying the TNM classifications to the VA system, the so-called limited-stage SCLC is defined as stage I to III (any T, any N, M0) which can be effectively treated with definitive radiation therapy, while extensive-stage SCLC is defined as stage IV (any T, any N, M1a/b) or T3-T4 harboring multiple lung nodules or having tumor volume that is too large to be encompassed in a tolerable radiation plan. Positron emission tomography-computed tomography (PET-CT) scan will be useful to assess for distant metastases when limited-stage disease is suspected, and a bone scan can be performed if PET-CT is ambiguous or not available; bone biopsy can be applied if the bone scan is equivocal. Although PET-CT is superior to PET or CT alone in detecting most metastatic sites, it is inferior to MR for the detection of brain metastases [11].

1.2.3 Rare carcinoma of the lung

Adenosquamous carcinoma (ASC) is a rare subtype of lung cancer, making up 0.4–4% of all lung cancer cases, and it is made up of two of the main tumor types: adenocarcinoma and squamous [12]. People suffering from ASC are prone to survive within a shorter time than those with pure lung adenocarcinomas or squamous cell carcinomas of the lung, no matter whether it is diagnosed earlier or later. In addition, the proportion of the adenocarcinoma/squamous cell component

has no effect on the outcome. Cisplatin (a chemotherapy drug used in the squamous cancer cell) rather than the pemetrexed (commonly used in adenocarcinomas) tends to be more effective in the treatment of ASC. Some studies have shown that ASC has its own clinical characteristics: patients are mainly males, the average age is 68.7 years old, most patients with ASC have smoking history, and most of the diseases are located in the peripheral rather than the central segment [12].

Carcinoid tumors are a type of tumor that relates to the neuroendocrine system, accounting for about 1–6% of all lung tumors, and approximately a quarter of patients suffering from carcinoid have no symptoms at the time of discovery. Although a common X-ray or chest CT scan can detect this disease, ^{18}F-FDG PET-CT scans are not sensitive enough to discover it or see if they have spread distantly because no obvious uptake can be discovered. Consequently, octreotide rather than FDG will be given if some are suspected of having a carcinoid tumor [13].

Granular cell lung tumors are extremely rare, accounting for approximately 0.2% of all lung tumors. Narrowed airways, which are caused by small, firm, and solitary nodules, can always be found. However, in most situations, this kind of disease is benign. Malignant or cancerous granular cell lung is even rarer [14].

Sarcomatoid carcinomas are another rare lung carcinoma, making up 0.3–3% of all NSCLC. Some studies have shown that heavy smoking and exposure to asbestos possibly, at least partially, are responsible for this disease [15].

1.3 Molecular pathology of lung cancer

Traditionally, according to histological features, NSCLC has been classified into small cell and non-small cell lung cancers and further was subdivided into squamous cell carcinoma, adenocarcinoma, and large cell carcinoma. Historically, little attention was given to the differentiation of the specific subtypes because there are no therapeutic implications, especially prior to the 2004 WHO classification. Various driver mutations have been associated with these cancers over time [16]; the genetic alterations and specific protein expression level have attracted much attention (**Figure 1**).

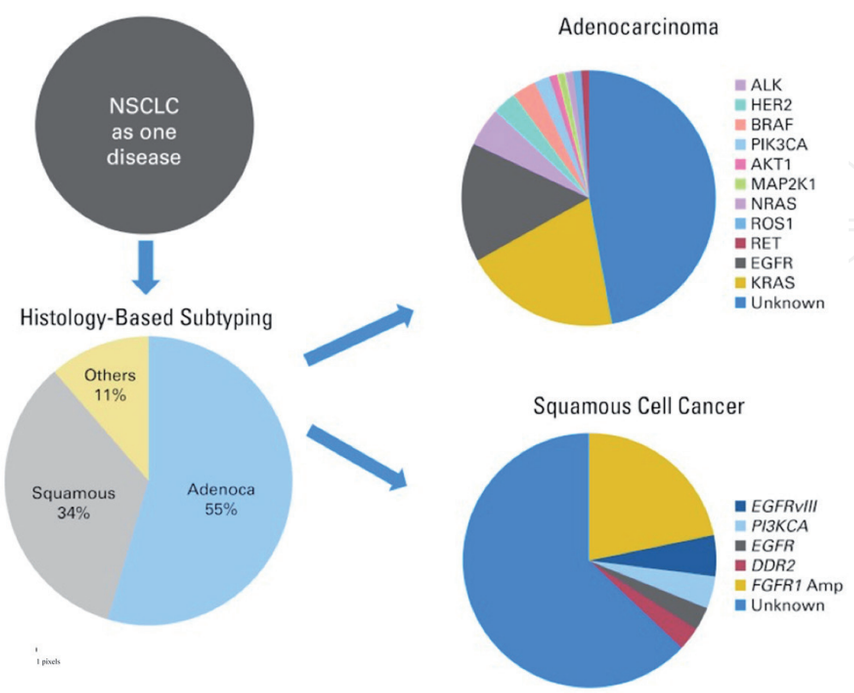

Figure 1.
Classifications of lung cancer: from histology to molecular based [16] (Reprinted with permission. © 2013 by the American Society of Clinical Oncology. All rights reserved).

1.4 TNM staging

The primary tumor (T), regional lymph node involvement (N), and distant metastasis (M) are the bases of staging for lung cancer. The International Association Society of Lung Cancer (IASLC) recommends the TNM classification of malignant tumors published by the Union Internationale Contre Le Cancer (UICC) and the American Joint Committee on Cancer (AJCC), and the latest eighth edition was published in 2016 [17]. Based on the different T, N, and M combinations, patients are grouped into different stages, which will determine the clinical treatments and can also predict various prognoses. The staging system is described in **Table 1**, and the stage groupings based on the TNM are listed in **Table 2**.

T—Primary tumor	
T category	T criteria
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
	Squamous cell carcinoma in situ (SCIS)
	Adenocarcinoma in situ (AIS): adenocarcinoma with pure lepidic pattern, ≤3 cm in greatest dimension
T1	Tumor ≤3 cm 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)
T1mi	Minimally invasive adenocarcinoma: adenocarcinoma (≤3 cm in greatest dimension) with a predominantly lepidic pattern and ≤ 5 mm invasion in greatest dimension
T1a	Tumor ≤1 cm in greatest dimension. A superficial, spreading tumor of any size whose invasive component is limited to the bronchial wall and may extend proximal to the main bronchus; also is classified as T1a, but these tumors are uncommon
T1b	Tumor >1 cm but ≤2 cm in greatest dimension
T1c	Tumor >2 cm but ≤3 cm in greatest dimension
T2	Tumor >3 cm but ≤5 cm or having any of the following features: • Involves the main bronchus regardless of distance to the carina, but without involvement of the carina • Invades visceral pleura (PL1 or PL2) • Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung T2 tumors with these features are classified as T2a if ≤4 cm or if the size cannot be determined and T2b if >4 cm but ≤5 cm in greatest dimension
T2a	Tumor >3 cm but ≤4 cm in greatest dimension
T2b	Tumor >4 cm but ≤5 cm in greatest dimension
T3	Tumor >5 cm but ≤7 cm in greatest dimension or directly invading any of the following: parietal pleura (PL3), chest wall (including superior sulcus tumors), phrenic nerve, parietal pericardium; or separate tumor nodule (s) in the same lobe as the primary
T4	Tumor >7 cm or tumor of any size invading one or more of the following: the diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina; separate tumor nodule(s) in an ipsilateral lobe different from that of the primary
N—Regional lymph	
N category	N criteria

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 category	M criteria
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodules or malignant pleural or pericardial effusion. Most pleural (pericardial) effusions with lung cancer are a result of the tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and not an exudate. If 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 (including involvement of a single nonregional node)
M1c	Multiple extrathoracic metastases in a single organ or in multiple organs

Table 1.
The eighth edition of TNM for lung cancer.

Stage group	T	N	M
Stage IA	T1	N0	M0
Stage IA1	T1mi, T1a	N0	M0
Stage IA2	T1b	N0	M0
Stage IA3	T1c	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
Stage IIB	T1a-c, T2a, b	N1	M0
	T3	N0	M0
Stage IIIA	T1a-c, T2a, b	N2	M0
	T3	N1	M0
	T4	N0, N1	M0
Stage IIIB	T1a-c, T2a, b	N3	M0
	T3, T4	N2	M0
Stage IIIC	T3, T4	N3	M0
Stage IVA	Any T	Any N	M1a, b
Stage IVB	Any T	Any N	M1c

Table 2.
Stage groupings in the eighth edition of TNM staging system for lung cancer.

1.5 Synoptic reporting of lung cancer

Synoptic reporting for lung cancer aimed to standardize diagnostic reports, including recommended clinical and histopathologic variables. This includes the

Terms
Clinical details
Clinical information provided on request Nature of the resection Additional extrapulmonary tissue Site and laterality of tumor Results of previous cytological investigations or biopsies Details of any previous treatment of the current tumor Details of previous cancer diagnosis Risk factors for lung cancer (e.g., smoking history, ethnicity, and asbestos exposure) Clinical tumor stage New primary cancer or recurrence Pathology accession number Principal clinician caring for the patient Other clinical information received
Macroscopic Operative procedure Specimen laterality Attached anatomical structures Accompanying specimens Block identification key Tumor site Tumor location Separate tumor nodules *Number of tumors* *Site* Maximum tumor dimension Macroscopic appearance of pleura overlying tumor Extent of direct spread of tumor to other tissues Distance of tumor to closest resection margin Tumor involves main bronchus within 20 mm of carina Lymph nodes *Site(s) and number of lymph nodes* Atelectasis/obstructive pneumonitis *Extent* Nonneoplastic lung Other relevant information and comments
Microscopic Histological tumor type *Adenocarcinoma classification* Histological grade Visceral pleural invasion *Extent of pleural involvement* Lymphovascular invasion *Vessel(s) involved* *Type of involvement* Perineural invasion
Pathological staging (AJCC seventh edition) Suffixes Primary tumor (T) Regional lymph nodes (N) Distant metastasis (M) Residual tumor status Completeness of surgical resection Diagnostic summary

Table 3.
Synoptic reporting of lung cancer.

clinical details and macroscopic, microscopic, and pathological staging as essential requirements. In addition, there should be an assessment of lymphovascular invasion and neurotropism and the presence of absence of satellite lesions; all these are shown in **Table 3**.

2. Management of lung cancer

2.1 Surgical management of primary lung cancer

Generally speaking, surgery is the best chance for stage I or II lung cancer patients [18]. Surgical oncology consultation is necessary for any patient being considered for local therapy. The general treatment plan, the essential imaging studies, and laboratory results should be determined before any nonemergency treatment is started. If patients cannot tolerate surgery or are inoperable, minimally invasive techniques, such as sublobar resection, can be a better choice [19]. Selected patients, including those who are not eligible for lobectomy and those with a peripheral nodule 2 cm or less with very low-risk features, are recommended to go through sublobar resection, either segmentectomy (preferred) or wedge resection. On the other hand, segmentectomy (preferred) or wedge resection should achieve parenchymal resection margins that are (1) 2 cm or more or (2) the size of the nodule or more.

2.2 Radiotherapy

The principles of radiation therapy in the NSCLC algorithm has been described thoroughly, including the following: general principles for early-stage, locally advanced, and advanced NSCLC; target volumes, prescription doses, and normal tissue dose constraints for early-stage, locally advanced, and advanced NSCLC; and RT simulation, planning, and delivery [20]. Treatment recommendations should be made by a multidisciplinary team. Because of the potential role of radiotherapy in all stages of NSCLC, whether it is a definitive treatment or palliative treatment is not known. Radiotherapy uses for NSCLC include, but are not limited to, (1) definitive treatment of locally advanced NSCLC, usually combined with chemotherapy; (2) definitive treatment of early NSCLC in patients with surgical contraindications; (3) partial preoperative or postoperative treatment of surgical patients; (4) treatment of limited recurrence and metastasis; and/or (5) palliative treatment of incurable NSCLC patients [21–23].

2.3 Immunotherapy and targeted therapy

Specific targeted therapies can be used to treat advanced NSCLC. Bevacizumab is a monoclonal antibody, targeting vascular endothelial growth factor, while ramucirumab is a recombinant monoclonal antibody that targets VEGF receptors. Cetuximab is a monoclonal antibody that targets EGFR. Erlotinib, gefitinib, and afatinib inhibit EGFR-sensitizing mutations; osimertinib inhibits both EGFR-sensitizing mutations and T790 M. ALK rearrangement, ROS1 rearrangement, and MET were all inhibited by crizotinib. Patients with ALK rearrangement are recommended to ceritinib which inhibits the IGF-1 receptor. Alectinib inhibits ALK and RET rearrangement. Brigatinib inhibits various ALK rearrangements and other targets. Dabrafenib/trametinib inhibits the BRAF V600E mutation; trametinib also inhibits MEK; both drugs inhibit different kinases in the RAS/RAF/MEK/ERK pathway [24, 25].

3. Role of PET-CT in lung cancer

3.1 Principles of PET-CT

PET-CT is a nuclear medicine technique that combines a positron emission tomography (PET) scanner with an X-ray computed tomography (CT) scanner. The anatomical imaging obtained by CT scan and the functional imaging obtained by PET (which depicts the spatial distribution of metabolic or biochemical activity in vivo) can achieve the same machine fusion more accurately, and the generated fusion image can be based on general software and control system to obtain 2D and 3D image reconstruction. Previously pure PET imaging cannot provide accurate anatomical positioning, and thus its value was limited, while PET-CT revolutionized medical diagnosis in many areas by increasing the accuracy of anatomical positioning in functional imaging. For example, the diagnosis and classification of benign and malignant tumors, the development of surgical plans, and the delineation of radiotherapy target areas have rapidly changed under the influence of PET-CT availability [26]. PET-CT-based grading staging has significantly changed clinical decisions; so many hospitals' nuclear medicine departments have gradually reduced the usage of traditional PET devices and replaced them with PET-CT. One of the barriers to the wider use of PET-CT is its relatively expensive price. Another obstacle is the difficulty and cost of producing and transporting of radiopharmaceuticals for PET imaging, which usually have a short half-life (e.g., radioactive fluorine-18). The half-life of (^{18}F) is used to track glucose metabolism (using fluorodeoxyglucose (FDG)) for only 106 minutes, and its production requires very expensive cyclotrons and radiopharmaceutical production lines [27].

3.2 Preoperative staging

Identifying the stage of lung cancer not only helps determine the appropriate treatment but also is essential for prognosis. Incorrect staging of lung cancer can lead to mistaken resections of benign nodules and early local or distant relapse after surgery with curative intent. Barbara randomly assigned patients referred for preoperative staging of NSCLC to either conventional staging plus PET-CT or conventional staging alone followed until death or for at least 12 months. They defined ineffective thoracotomy as any of the following: thoracotomy, pathologically confirmed mediastinal lymph node involvement (stage IIIA [N2]), stage IIIB or IV disease, or benign lung disease; exploratory thoracic incision; or thoracotomy in patients who have relapsed or died for any reason within 1 year after randomization. Ninety-eight patients were assigned to the PET-CT group and 91 to the conventional staging group. Sixty patients in the PET-CT group and 73 in the conventional staging group underwent thoracotomy ($P = 0.004$). Among these thoracotomies, 21 in the PET-CT group and 38 in the conventional staging group were futile ($P = 0.05$). Both groups had a reasonable thoracotomy and had similar survival. The use of PET-CT in the preoperative staging of NSCLC reduced the total number of thoracotomy and the number of ineffective thoracotomy, but did not affect overall mortality [28] (**Figure 2**).

3.3 Evaluation of treatment effect

Franco et al. conducted research aiming to evaluate the utility between PET-CT and the contrast-enhanced (CE) CT. The low-dose CT scans were performed for attenuation correction of the PET images, and the PET scanner was fully cross-calibrated, allowing accurate standard uptake value measurements. The protocols

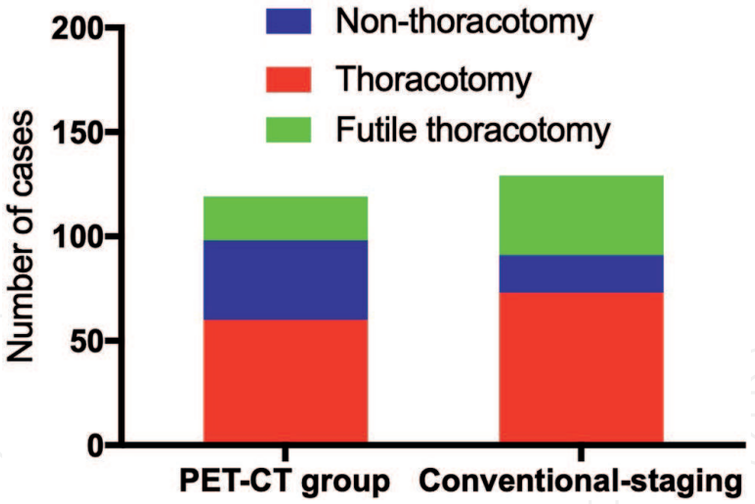

Figure 2.
Preoperative staging of NSCLC between PET-CT group and conventional staging group.

for CE-CT are the following: (1) all chest CT scans were performed according to the conventional low-dose chest multi-detection CT protocol, including head-to-tail orientation, arms raised on the head, single breath, and the amount of scan from the diaphragm level to the level directly above the chest entrance; and (2) the injected volume of contrast medium was tailored to the individual body weight: 60 mL at 2 mL/s for <50 kg or 80 mL at 2.5 mL/s at 50 kg or heavier with a fixed contrast delay of 35 seconds. The study enrolled 96 patients who received curative-intent treatment, and the results showed that the sensitivity, specificity, and positive predictive value for detecting cancer recurrence (95% confidence interval) were 0.88, 0.62, and 0.56 for PET-CT and 0.93, 0.72, and 0.64 for CE-CT, respectively, indicating that PET-CT is not superior to CE-CT in detecting cancer recurrence during 2 years after curative-intent treatment of non-small cell lung cancer [29].

3.4 Surveillance

Using systematic review and meta-analysis, Nie et al. evaluated the prognostic value of metabolic tumor volume (MTV) and total lesion glycolysis (TLG) for small cell lung cancer and used the pooled hazard ratio (HR) to measure the influence of MTV and TLG on survival. They found that patients with high MTV are associated with a significantly poorer prognosis OS and PFS, while high TLG is associated with a significantly poorer prognosis regarding OS for SCLC [30].

3.5 Guiding biopsy

When lung cancer is discovered, accurate staging at baseline is necessary to maximize patient benefit and cost-effective use of healthcare resources. Although CT remains a powerful tool for the staging of lung cancer, advances in combined imaging modalities, specifically PET-CT, have improved the baseline staging accuracy over that of CT alone [31]. FDG PET-CT has been considered a "metabolic biopsy" tool in the evaluation of nonlung lesions with indeterminate biopsy results [32]. PET-CT data coregistered with intraprocedural CT images could guide needle placement in the viable portion of the lesion and thus increase the chances of achieving a definitive diagnosis and CT-guided, fine-needle aspiration (FNA) biopsies performed with FDG PET scans of pulmonary lesions contributing substantially to the management and treatment of pulmonary disease [33].

4. PET-CT in lung cancer: teaching cases

4.1 Adenocarcinoma

Teaching point: adenocarcinoma mainly located in the peripheral segment and shows higher FDG uptake (**Figure 3**).

4.2 SCC

Teaching point: adenocarcinoma is mainly located in the central segment and shows moderate FDG uptake (**Figure 4**).

4.3 Large cell lung cancer

Teaching point: large cell lung cancer always shows moderate FDG uptake and diffused distribution (**Figure 5**).

4.4 Small cell lung cancer

Teaching point: small cell lung cancer shows a small mass with moderate FDG uptake (**Figure 6**).

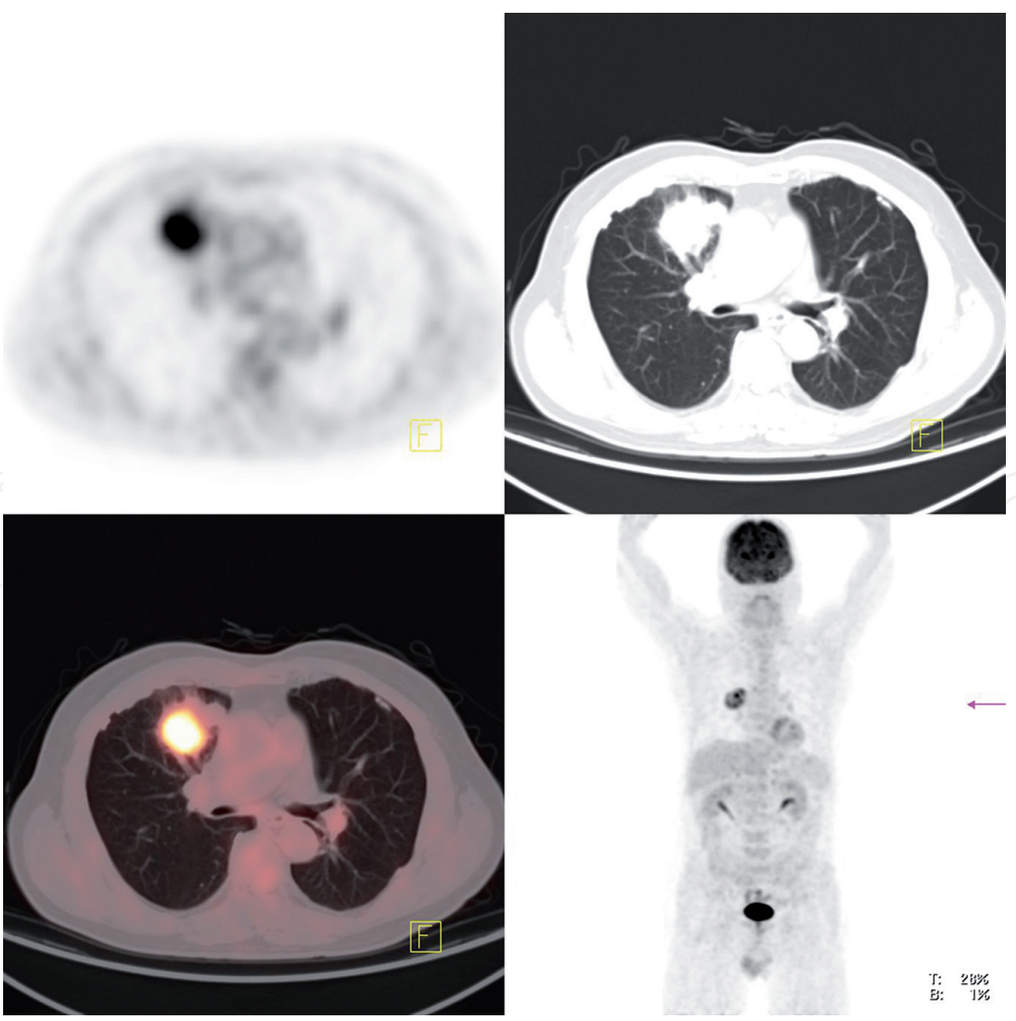

Figure 3.
Axial PET, CT, PET-CT, and MIP images in a patient of adenocarcinoma. An irregular mass showing higher FDG uptake in the lesion was discovered in the anterior segment of the right upper lobar.

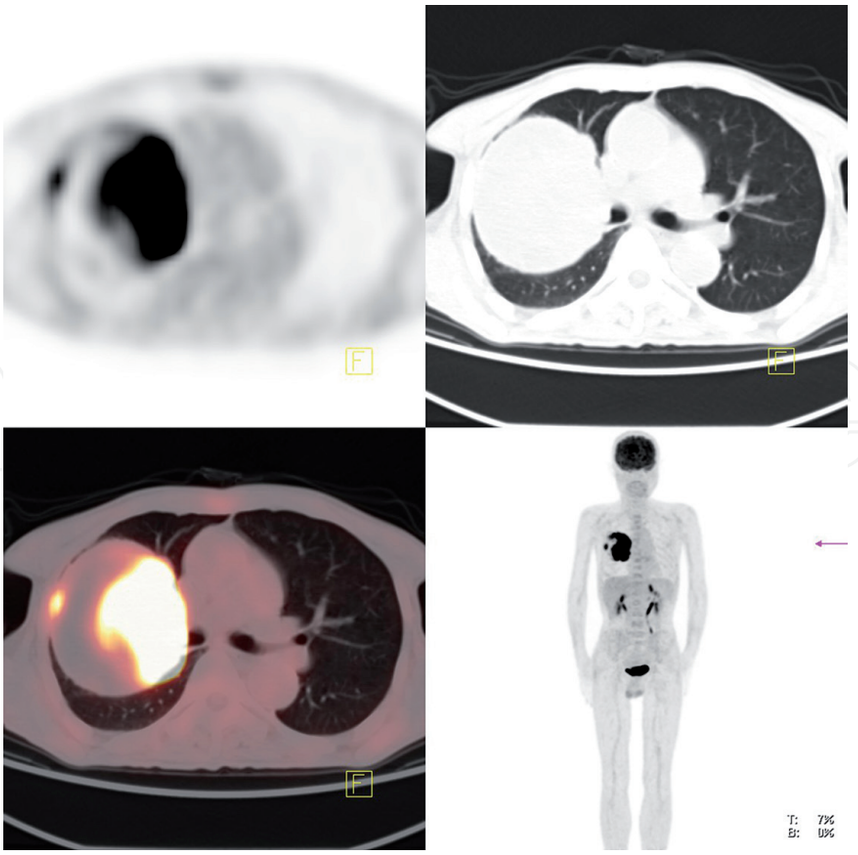

Figure 4.
Axial PET, CT, PET-CT, and MIP images in a patient of squamous cell carcinoma. An irregular mass showing moderate FDG uptake in the lesion was discovered in the central segment of the right lung, with inflammation around the malignant lung lesion.

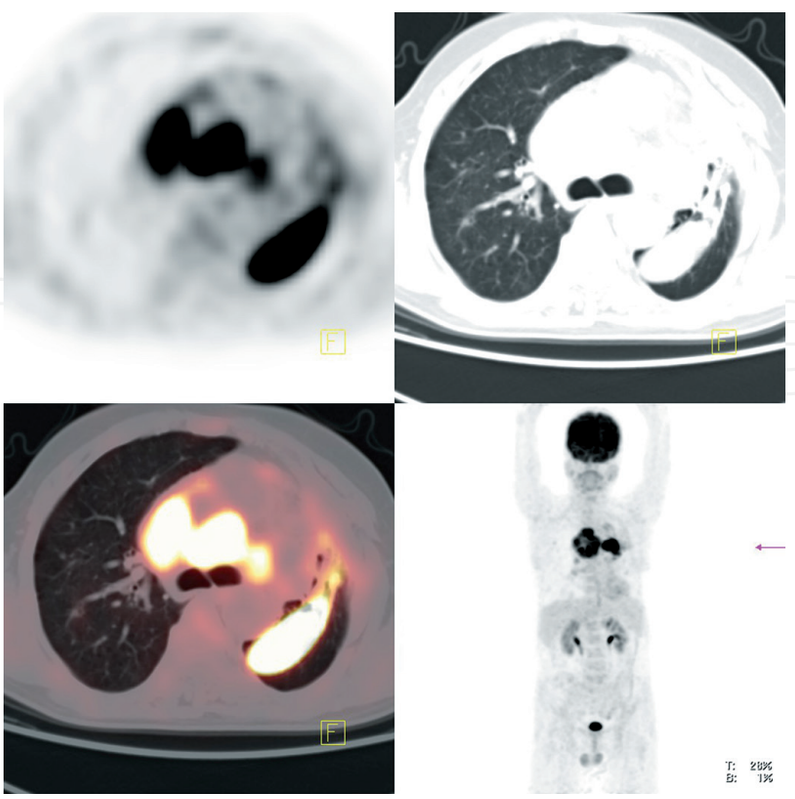

Figure 5.
Axial PET, CT, PET-CT, and MIP images in a patient of large cell cancer. Multisite masses showing higher FDG uptake in the lesion were discovered in the left and right lung field, with inflammation and enlarged lymph node in the mediastinum.

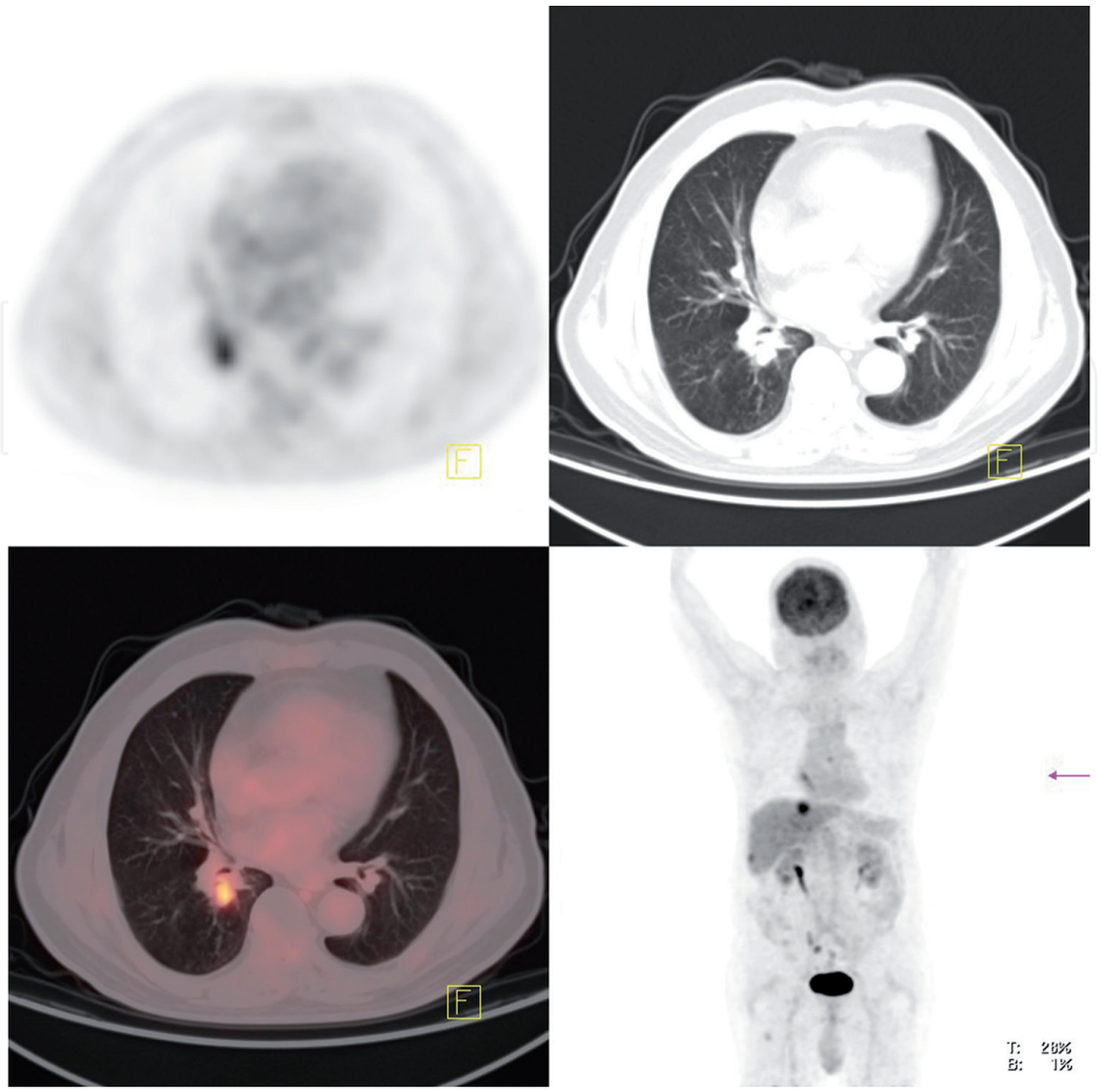

Figure 6.
Axial PET, CT, PET-CT, and MIP images in a patient of small cell lung cancer. Small mass located in the right hilar with slight FDG uptake in the lesion was discovered in the right lung field.

5. Conclusions

The current chapter focused on the PET-CT utility in lung cancer diagnosis and summarized the basic clinic utilities, including guiding to select the biopsy site, improving target delineation accuracy, evaluating disease progression on first-line therapy, and detecting hilar, mediastinal nodes and metastatic disease. PET-CT scans have been widely used to help evaluate the extent of disease and to provide more accurate staging and has been recommended by the NCCN. Patients with suspected malignant lung nodules should be scanned by PET-CT for accurate diagnosis of local or distant metastasis.

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