PET/CT AND ITS ROLE IN STAGING AND FOLLOW UP OF LUNG CANCER

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Abstract:
Lung cancer is a fairly common malignancy. An early diagnosis and a reliable staging and re-staging with the aim to detect both local and distant relapse are of utmost importance in planning the therapeutic management. The imaging diagnostic work-up of patients with lung cancer usually includes conventional imaging (chest X-ray, contrast-enhanced CT, bone scan) and more recently ^{18}F-FDG PET/CT. Great advances in the management of lung cancer are based on the information provided by ^{18}F-FDG PET/CT, as it supplies both metabolic and anatomic information (better localisation). There is vast evidence in the literature demonstrating its utility in (a) characterising benign versus. malignant solitary nodules, (b) staging and re-staging lung cancer, (c) guiding the type of therapy, (d) monitoring treatment response and (e) predicting outcome. In particular, given its specificity in differentiating ^{18}F-FDG-avid relapse from post-surgical changes or post-radiation fibrosis (which do nott take up ^{18}F-FDG), PET/CT can detect recurrent disease after initial treatment and (being a whole-body technique) and has demonstrated high accuracy in the detection of distant metastases or secondary tumours. In conclusion, ^{18}F-FDG PET/CT can be considered a highly accurate and reliable method for staging and re-staging lung cancer, and is highly effective in guiding personalised therapies.

Keywords: PET/CT, staging, lung cancer.

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Introduction:

Bronchogenic carcinoma staging is crucial for treatment strategy, planning, and prognosis prediction with radiological imaging play a cornerstone role in staging. Patients with stage I are suitable for lobectomy or pneumonectomy while stage II patients are treated surgically followed by adjuvant chemotherapy. Patients with stage IIIA receive chemotherapy and radiotherapy followed by surgery if downstaging occurred while for patients with stage IIIB or IV, the surgery has no role in their treatment **(1)**.

CT is the most commonly used radiological modality for tumoral staging due to its availability and rapid scanning with high-resolution images, but it has some limitations in identifying the actual tumoral boundaries separating it from the nearby adjacent non-malignant pulmonary changes such as collapse, atelectasis, or consolidation. Also, the assessment of pleural, pericardial, and mediastinal invasions is difficult to be accurately assessed by CT **(1)**.

Radiological follow-up of bronchogenic carcinoma to assess therapy response using CT established by using Response Evaluation Criteria In Solid Tumor (RECIST criteria) depending on size change and reduction of the tumoral mass. However, structural changes may occur late after positive biological response, giving a false impression of stationary course. Also, central necrosis or hemorrhage secondary to treatment may cause an increase in the tumor mass size, giving a pseudo-progression result in CT **(2)**.

PET/CT is a radiological modality that can assess the tumoral malignant activity depending on fluorodeoxyglucose (FDG) uptake by the malignant tissue. Hence, it can accurately delineate the tumoral mass separating it from the surrounding non-malignant reaction and detect early biological changes in response to therapy even before the structural changes. Also, PET/CT can detect the activity of pulmonary nodules detected during the interpretation of the CT chest differentiating the benign from malignant one as well as the metastatic changes. The follow-up of bronchogenic carcinoma using PET/CT is done using PET/CT Response Criteria In Solid Tumor (PERCIST criteria) depending on standardized uptake value (SUV uptake) changes by the tumoral mass **(3)**.

PET/CT offers both structural and functional information about the tumoral mass and malignant activity overall the body and hence can accurately assess the tumor staging and tumor response to therapy **(4)**.

Protocol for 18F-FDG PET/CT

Each patient is scanned using the PET/CT scanner. Shanghai Sinovac Pharmaceutical Co., Ltd. produce and distribute 18F-FDG. Before receiving an injection of 18F-FDG (0.1 mCi/kg), all patients are required to fast for at least 4 h before the assessment and to maintain their blood glucose levels below 10 millimoles per liter. One hour after the injection, PET/CT scans are taken from the base of the head to the middle of the femur. CT scans (scan parameters: slice thickness, 3.75 mm; pitch, 0.984; tube voltage, 120 kV; noise value (NI), 12.82; tube current, 70–180 mA) are performed after the examination range had been determined; scanning time, 20–30s **(5)**.

After that, PET images of the patient's whole body are obtained using 8–10 beds in three-dimensional mode, a rate of 1.5 min per bed position. The inspection is completed in 1.5 h, and the measurement is carried out in 1.5 h. The CT scans are used to calculate the attenuation correction for the PET images. To produce fusion pictures in three planes (transverse, sagittal, and coronal), PET/CT scans are reconstructed using an iterative technique **(5)**.

Role of PET in the diagnosis, staging and response assessment of non-small cell lung cancer

Patients suspected or diagnosed with lung cancer are managed by a multidisciplinary team whose role is to accurately diagnose, stage and then treat patients. Traditional radiological imaging techniques such as chest radiography, ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI), play an essential role in staging, which ultimately determines the management options available to a patient. However, the development of positron emission tomography (PET) with 18F-fluorodeoxyglucose (FDG), a radiolabelled glucose analogue, has significantly impacted on the contribution of radiology to the management of this disease **(6)**.

This is routinely performed as a hybrid technique with PET-CT, which combines anatomical localisation and morphological information from CT with functional data provided by PET. Malignant tumours are often highly metabolically active, with increased glucose metabolism and consequently FDG uptake, and can be detected as 'hot spots' with higher standardised uptake values (SUV). This is not always the case and often small tumours or those of the 'bronchoalveolar' type have lower SUV. A meta-analysis concluded that FDG-PET can diagnose malignant pulmonary

lesions with an estimated sensitivity of 94.2% and specificity of 83.3% **(7)**.

Combining the FDG-PET scan with simultaneous CT scan further increases its accuracy by avoiding the technical challenges of interpreting the two scans independently. Subsequently PET-CT has become a standard of care **(Figure** 11**)**. The success of PET-CT has resulted in a search for similar radiolabelled ligands to be utilised in conjunction with other radiological modalities such as MRI, and this is an important area of research **(8)**.

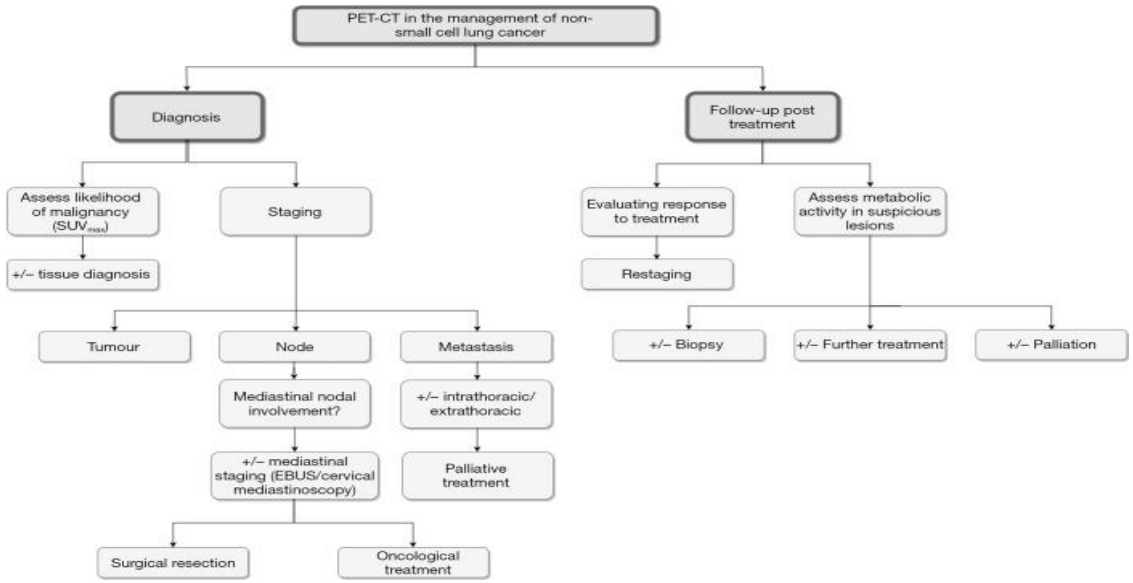

Figure 11: The roles of PET-CT in the management of non-small cell lung carcinoma. PET-CT, positron emission tomography-computed tomography (6)

Role of PET-CT in the diagnosis and evaluation of lung lesions

Small pulmonary nodules are frequently identified as an incidental finding on imaging performed for other reasons. It has been reported that they are identified on up to 0.2% of chest radiographs and around 1% of thoracic CT scans. Although the majority of solitary pulmonary nodules are benign lesions such as a granuloma or hamartoma, in up to 20% of cases they represent a malignant tumour, especially in older patients and smokers. The incidence of malignancy in these higher risk groups can approach 70% **(9)**.

After a nodule has been identified, patients are referred and managed by a multidisciplinary team to investigate the nature of the nodule. For suspicious lesions, PET-CT has an important role in aiding differentiation between benign and malignant lesions, with metabolically active lesions more likely to represent malignancy. PET-CT is relied upon to guide decision making in regard to proceeding to obtain a tissue diagnosis. A large recent retrospective analysis reported PET-CT to have a diagnostic accuracy of 93.5% in diagnosing malignant pulmonary nodules, and a false positive rate of 6.5% **(10)**.

Interestingly, there is some data suggesting that the degree of FDG uptake on PET-CT can differentiate between different tumour histology. Data has been presented, for example, that demonstrated that squamous cell carcinomas tend to have significantly higher FDG uptake than bronchioloalveolar carcinoma, adenocarcinoma in situ and carcinoid tumours. In these tumour types false-negative PET-CT studies can occur. This is also the case for sub-centimeter pulmonary nodules. On the other hand, false-positive results can be observed in metabolically active, often inflammatory, benign lesions such as bacterial pneumonia, pyogenic abscesses, tuberculosis, sarcoidosis, infective granulomas and fibrosing mediastinitis **(10)**.

Subsequently, if suggestive of malignancy on PET-CT, a tissue diagnosis is sought in order to appropriately manage the patient. A tissue diagnosis can be obtained through multiple routes depending on the location of the tumour. Peripheral lesions are routinely sampled with CT-guided biopsy which is now well established as a diagnostic technique for pulmonary nodules, with a diagnostic accuracy of up to 98%, although occasionally can be complicated by pneumothorax. Central lesions may be more amenable to bronchoscopic techniques including endobronchial ultrasound (EBUS) guided biopsy **(11)**.

The detection of metastases, mediastinal or more distally, on the PET-CT can direct an alternative route to obtaining tissue for pathological diagnosis.

For example, an accessible mediastinal or supraclavicular lymph node may be deemed a more appropriate biopsy target, with lower risk, than CT-guided biopsy of the main lesion—particularly for patients with more advanced tumours in which a tissue diagnosis is required to determine the appropriate oncological therapy **(12)**.

Role of PET-CT in the staging of lung carcinoma

Following diagnosis of a lung cancer, the disease must be staged which is an assessment of tumour size, tumour location, involvement of mediastinal lymph nodes and the presence of metastases. Since the patients prognosis and therefore management is determined by disease staging, it is essential that this can be performed reliably and accurately. Staging requires the combination of imaging modalities to identify the extent of tumour progression and the ability to obtain biopsies of suspicious pulmonary nodules, lymph nodes and/or potential metastases **(13)**.

The TNM staging system is the standard staging system used worldwide for lung carcinoma. Recently the 8th edition was published. The system assesses the tumour (T), lymph nodes (N) and metastases (M). The tumour is assessed based for its size, location and spread beyond the visceral pleura; the presence of enlarged or abnormal lymph nodes within the lung, hilum and mediastinum is quantified; and the presence of intrathoracic or extrathoracic metastatic involvement is assessed. The stage of disease determines the optimum management **(13)**.

For early, stage I, disease surgical resection by lobectomy or pneumonectomy with curative intent is the gold standard currently. Patients with stage II disease with a good performance status will usually be offered surgical resection, followed by adjuvant chemotherapy to reduce the risk of tumour recurrence **(14, 15)**.

Stage IIIA disease can be treated with tri-modality therapy: combined chemotherapy and radiotherapy, followed by surgical resection for patients who are 'down-staged' following the oncological therapy and have a good performance status **(16)**.

Patients with stage IIIB disease, are usually treated with a combination of chemotherapy and radiotherapy, with surgery having little role. Patients with more advanced, stage IV disease, will be offered a combination of systemic chemotherapy and/or radiotherapy depending on their performance status, and palliative radiotherapy for symptom relief. PET-CT is now a standard staging investigation in patients with lung carcinoma and can aid detection of nodal and distant metastases **(17)**.

- **T staging**

Primary lung tumor extent is mostly evaluated using thoracic CT, which, in cases of superior sulcus extension, thoracic wall invasion, or heart or large vessel involvement, is supplemented by magnetic resonance imaging (MRI). The major contribution of 18F-FDG PET/CT is accurate tumor delineation from surrounding post-obstructive atelectasis **(Figure** 22**)**, which is important for therapy planning; 18F-FDG PET/CT can also be useful for detecting chest wall invasion **(18)**.

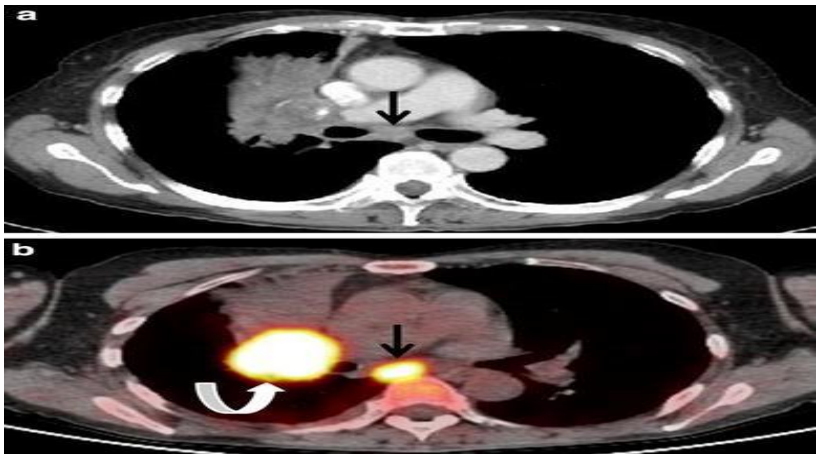

Figure 22: A 68-year-old man with non-small-cell lung cancer with post-obstructive atelectasis and multiple lymph node metastases at initial staging. a Contrast-enhanced computed tomography (CT) shows a mass and atelectatic lung extending from the superior right hilum, without a clear distinction between the soft-tissue mass and the consolidated lung, as well as a 12 × 13 mm swollen subcarinal lymph node (#7) (*arrow*), suggesting the presence of spreading nodal cancer. b Positron emission tomography/CT using 2-[18F]fluoro-2-deoxy-D-glucose (18F-FDG) shows intense 18F-FDG uptake in the primary tumor (*curved arrow*), with no

uptake in obstructive atelectasis of the right upper lobe. The swollen subcarinal lymph node shows intense FDG uptake (*arrow*), confirming nodal metastasis (18)

- **Nodal staging**

Lymph node staging is an important step in determining whether the patient is offered surgical resection and therefore, considerable effort is made to evaluate mediastinal lymph nodes. PET-CT has a significantly greater accuracy than conventional CT imaging which relies on lymph node size alone **(19)**.

PET-CT has been reported to have an accuracy of 90% for correctly diagnosing the presence or absence of mediastinal lymph node involvement, with a sensitivity of 79–85% and specificity of 87–92%. This compares very favourably to the values reported for CT alone—an accuracy of 75%, sensitivity of 57–68% and a specificity of 76–82% **(Figure** 3**3) (20)**.

However, it is important to be aware that there is reduced accuracy of PET-CT detecting malignancy in small nodes <10–15 mm diameter. As such, occult nodal metastases are often detected by post-operative histopathology. This is termed stage migration. One study reported a 25.9% rate of occult nodal metastases. Researchers identified that combining tumour size with SUV_{max} offered some predictive ability—for tumours >2.5 cm with SUV_{max} >4.35, there was an 88.9% chance of detecting occult lymph node metastases **(20)**.

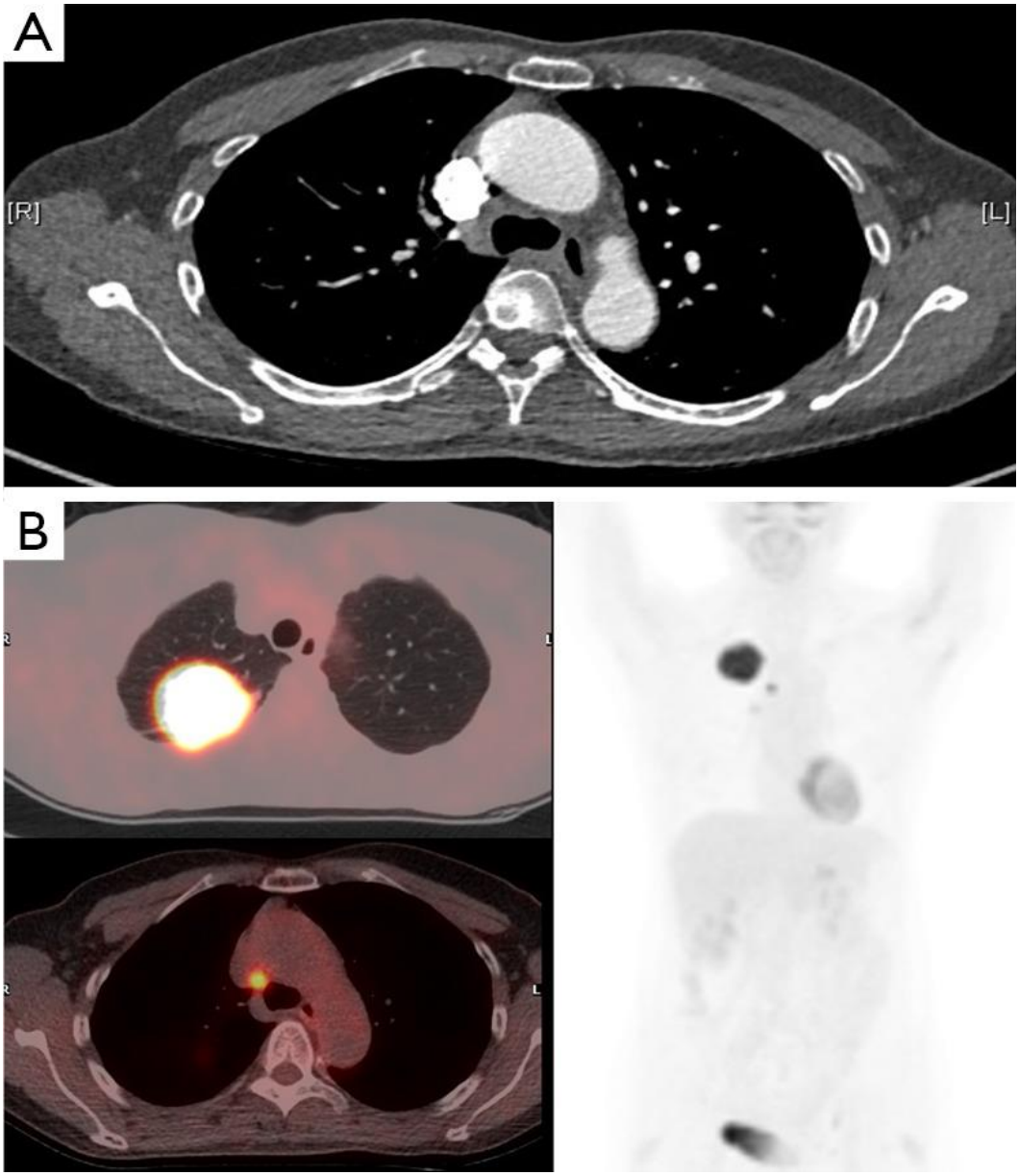

Figure 33: The value of PET-CT to staging. Patient with non-small cell lung carcinoma. The tumour in the right upper lobe shows avid tracer uptake (SUV_{max} =19.4). There is a 5 mm station 4R node adjacent to the azygos vein and superior vena cava on the staging CT scan. This shows tracer uptake on the PET-CT (SUV_{max} =9.7) and was shown to contain tumour cells on endo-bronchial ultrasound guided sampling. If

PET-CT had not been performed this N2 node would have been missed. PET-CT, positron emission tomography-computed tomography (6)

In view of the diagnostic accuracy recorded with PET-CT, when there is suggestion of malignant involvement of mediastinal lymph nodes, further assessment is necessary. If the PET-CT scan is positive for mediastinal or hilar nodes, the lymph node status needs histological confirmation in order to accurately stage the patient, whereas patients with negative mediastinal nodes on PET-CT examination can generally proceed to surgical resection without the need for invasive mediastinal staging **(6)**.

Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and EBUS-guided transbronchial needle aspiration (EBUS-TBNA) are becoming the investigations of choice for obtaining tissue for mediastinal staging and have been demonstrated to be both clinically and cost effective when compared to surgical staging. It is becoming increasingly appreciated that combining PET-CT and EBUS-TBNA can significantly increase the diagnostic accuracy of nodal staging **(21)**.

For mediastinal lymph nodes that are suspicious based on size-criteria on the CT, but negative on PET-CT, further staging with histological examination should be sought by the multidisciplinary team to ensure surgical resection is appropriate. Conversely, patients with mediastinal nodes positive on PET should not be denied potentially curative surgery without histological confirmation, with knowledge that positivity can be due to other factors such as infection or inflammation **(21)**.

- **Distant metastases (M staging)**

Forty percent of patients with NSCLC are reported to present with metastatic disease. The commonest sites of NSCLC metastasis include the adrenal glands, bones, liver, or brain. PET-CT is more accurate than conventional CT at diagnosing the presence of metastases. It has been reported that up to 10% of patients are found to have metastases on PET-CT that were not detected on prior CT, and therefore offers an important additional benefit to patient staging **(22)**.

In up to 20% of patients with NSCLC, adrenal tumours are identified on CT. Incidental adrenal adenomas are not uncommon in the population though. The ability of PET-CT to differentiate metabolically active, potentially metastatic, lesions from metabolically quiescent lesions can be very useful, although caution should be exercised when interpreting PET-CT for small adrenal nodules, as the false-positive and false-negative rates will be higher. One study reported accuracy of 95% in diagnosing adrenal metastasis with PET-CT. They reported a positive predictive value of 95% and a negative predictive value of 94% **(22)**.

FDG-PET can also aid the diagnosis of bone metastases which are seen as ‘hot spots’ within the bone **(23)**.

The more traditional approach was with bone scintigraphy. Reports describe sensitivity in the range 90%, but specificity as low as 60%. This is due to uptake of the radio-nucleotide tracer in areas of inflammation and degeneration that may be associated with arthritic changes or post-trauma. PET-CT is found to be superior to bone scintigraphy for detection of bone metastases with accuracy quoted to be as high as 96%, with sensitivity (90%) and a specificity (98%) **(24)**.

FDG-PET offers superiority in the diagnosis of liver metastases when compared with conventional imaging modalities. Uptake of FGD is highly suspicious of malignancy. In contrast, FDG-PET detects brain metastases with a sensitivity of lower than 46% due to the high levels of glucose uptake within normal brain tissue. Conventional CT or MRI is considered the investigation of choice for accurately diagnosing the presence of brain metastases **(25, 26)**.

The added benefit of FDG-PET can be appreciated by comparing the staging pre and post PET-CT. It has been observed that in up to 62% of cases the TNM stage is modified following a PET-CT scan. This is obviously of crucial importance as management decisions are determined by the final stage of disease and as such, a PET-CT can prevent patients from being subjected to unnecessary further investigations and surgical procedures that will offer them no prognostic benefit **(27)**.

The value of PET-CT in the staging of lung cancer has been reinforced in international guidelines—all of which emphasise the importance of having rapid access to PET-CT due to its ability to facilitate accurate disease staging which is important to guide management decisions and allow prognosis to be predicted **(28)**.

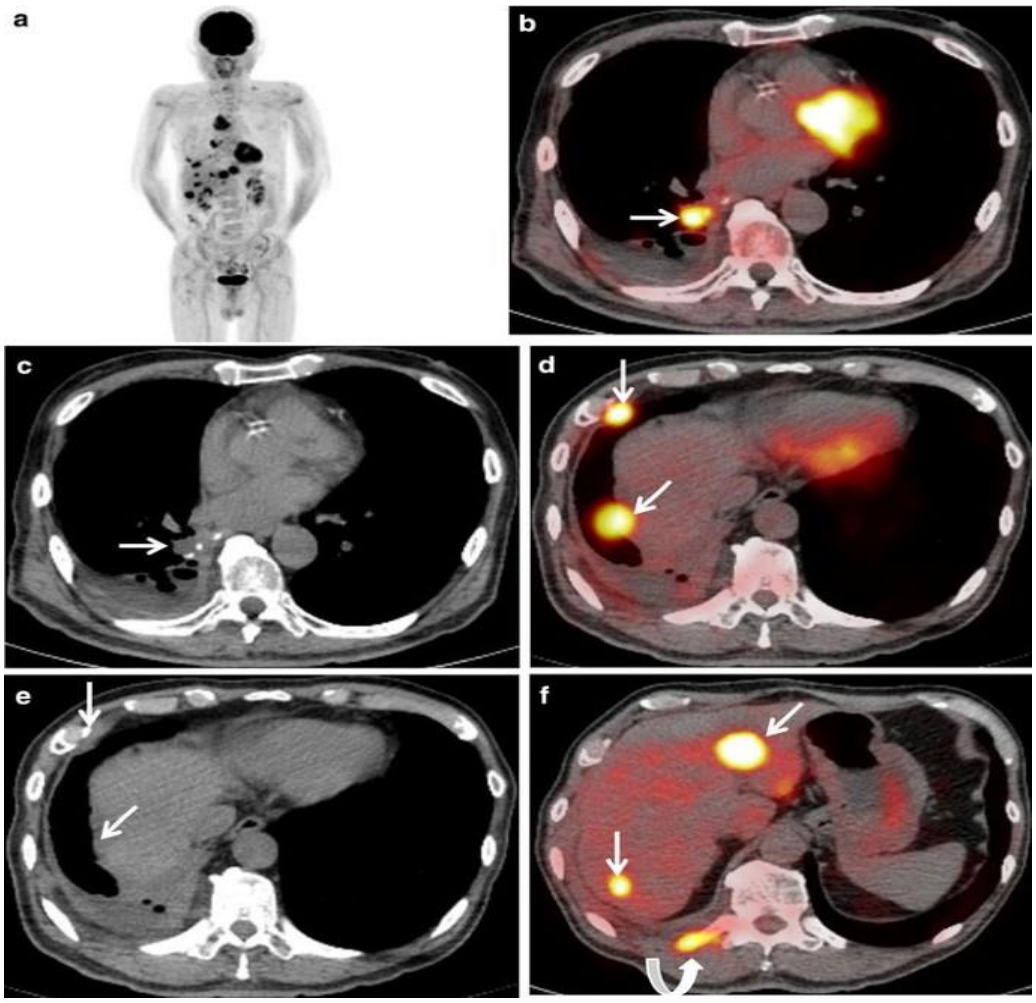

Figure 4: A 76-year-old woman who underwent right lower lobe resection due to non-small cell lung cancer 6 months prior showing multiple recurrent lesions consisting of local recurrence, mediastinal nodal metastasis, pleural dissemination, liver metastases, and bone metastases at restaging. a Maximum intensity projection of an image acquired by positron emission tomography (PET) using 2-[18F]fluoro-2-deoxy-D-glucose (18F-FDG) shows multiple abnormal intense uptakes in the right lung, mediastinum, right pleura, liver, and spine. b 18F-FDG PET/computed tomography (CT) and c CT alone show abnormal FDG uptake corresponding to local recurrence at the postoperative stump (*arrow*). It is difficult to diagnose this local recurrence by CT alone. d 18F-FDG PET/CT and e CT show abnormal FDG uptakes corresponding to the right pleural dissemination (*arrows*). It is difficult to diagnose pleural dissemination by CT alone. f 18F-FDG PET/CT shows abnormal FDG uptakes corresponding to liver metastases (*arrows*) and pedicle bony metastasis (*curved arrow*). It is difficult to diagnose this bone metastasis based on CT alone (18)

Role of PET-CT in evaluating response to treatment

PET-CT scans are not necessarily just performed as a one-off test and can be used to track disease over time—particularly to assess the impact of oncological therapies—i.e., chemotherapy and radiotherapy. FDG-PET offers benefit over conventional CT where although tumour shrinkage may be observed, radiation-induced inflammation and fibrosis after neoadjuvant chemotherapy or radiation therapy can make assessment difficult **(29)**.

On conventional CT imaging identifying a response to treatment is simply based on a reduction in size and volume of the tumour—however, this does not necessarily correlate with clinical outcomes. PET-CT offers the opportunity to assess the level of FDG uptake and therefore tumour activity which may be a better marker. Decreased FDG uptake as detected on PET-CT is found to correlate with improved outcomes and is a marker of effective responsiveness to the chemotherapy **(30)**.

Conversely therefore, if there is no change in activity level, this could direct a change in chemotherapeutic approach. It has been reported that evidence of high FDG uptake following the first chemotherapy cycle correlates with a poorer prognosis than patients with low FDG uptake, with median survival of 12 months compared with 34 months **(31)**.

Role of PET-CT in disease surveillance

In addition to measuring the impact of therapy, PET-CT can also play an important role in the diagnosis of disease recurrence following an abnormality being detected on conventional imaging. The role of PET-CT in long-term follow up is not well described, and there are many studies which do not recommend PET-CT for the routine surveillance of patients following treatment for NSCLC. However, on conventional imaging, pathology such as atelectasis, consolidation and radiation fibrosis can easily be confused with disease recurrence, whilst different FDG uptake on PET-CT can facilitate this differentiation **(32)**.

Consequently, a PET-CT scan can be useful for identifying disease recurrence in patients with suspicious lesions on conventional imaging with a sensitivity reported to be 98%, specificity of 82% and overall accuracy of 93%. Moreover, a negative PET-CT at follow up is highly predictive of improved survival, even after adjustment for the therapy given, whereas conventional staging offers only modest prognostic stratification **(33)**.

While these benefits are recognised, PET-CT is not utilised as a routine first-line follow-up surveillance investigation, in current guidelines, but can be utilised if there is suspicion of tumour recurrence or metastatic disease detected on standard CT. The high cost is likely an important factor in this decision. There is some evidence correlating pre-operative tumour SUV_{max} with risk of recurrence and death in patients with NSCLC and it may be that with greater understanding, PET-CT will play a greater role in follow-up of higher risk patients following curative therapy **(34)**.

Impact of 18F-FDG PET/CT in staging patients with small cell lung cancer

SCLC is an aggressive high-grade neuroendocrine tumor characterized by rapid growth and early development of metastatic spread. Most SCLC patients have metastatic disease at the initial diagnosis, and about one-third of them has limited disease confined to the chest, whereas two-thirds of them has hematogenous metastases. Even if SCLC is usually highly sensitive to chemotherapy and radiation therapy, however, most patients develop recurrent disease **(35)**.

Computed tomography (CT) of chest and abdomen and brain magnetic resonance imaging (MRI) are the most used imaging methods for staging SCLC. However, if LD-SCLC is suspected, molecular imaging using fluorine-18 fluorodeoxyglucose positron emission tomography (18F-FDG PET) can be performed to assess for distant metastases. In particular, hybrid imaging using 18F-FDG PET/CT, providing both functional and morphological data, has been demonstrated to be superior to 18F-FDG PET alone, and it is the current state of art for molecular imaging of lung cancer **(35)**.

As SCLC is an aggressive neuroendocrine tumor with increased metabolism and 18F-FDG is a radiolabeled glucose analog, an increased uptake of this radiopharmaceutical is expected by SCLC lesions. Compared to non-small cell lung cancer, less data are available about the impact of molecular imaging using 18F-FDG PET/CT in staging patients with SCLC **(35)**.

Impact of 18F-FDG PET/CT staging on outcome of SCLC patients

About the impact of 18F-FDG PET/CT staging on outcome of SCLC patients, the survival outcomes were similar in patients staged with or without 18F-FDG PET/CT, according to the recently published analysis of the CONVERT randomized controlled trial; however, this analysis cannot support the omission of 18F-FDG PET/CT for SCLC staging due to some study limitations **(36)**.

Xanthopoulos et al. found that LD-SCLC patients staged with 18F-FDG PET/CT exhibited improved disease control and survival when compared with LD-SCLC patients staged without 18F-FDG PET/CT. The median overall survival from diagnosis in patients staged with 18F-FDG PET/CT was 32 vs. 17 months in patients staged without PET/CT ($p = 0.03$), and 3-year survival was 47 vs. 19%, respectively. Median time-to-distant failure was 29 vs. 12 months, respectively ($p = 0.04$); median time-to-local failure was not reached vs. 16 months, respectively ($p = 0.04$). On multivariable analysis, 18F-FDG PET/CT staging was associated with survival (odds ratio = 0.24; $p = 0.04$) **(37)**.

PET-CT in lung cancer

- **Adenocarcinoma**

Adenocarcinoma mainly located in the peripheral segment and shows higher FDG uptake **(Figure 5) (38)**.

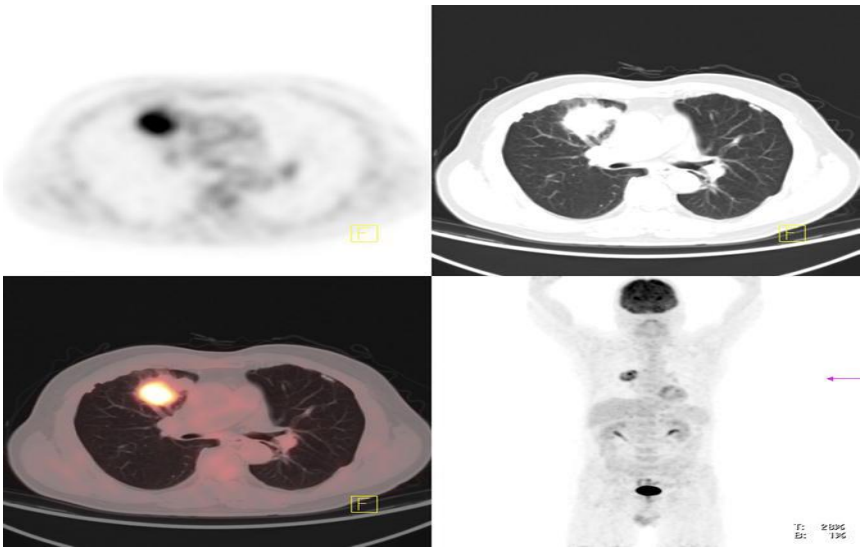

Figure 5: Axial PET, CT, PET-CT, and MIP images in a patient of adenocarcinoma. An irregular mass showing higher FDG uptake in the lesion was discovered in the anterior segment of the right upper lobar (38)

- **SCC**

segment and shows moderate FDG uptake **(Figure 6) (38)**.

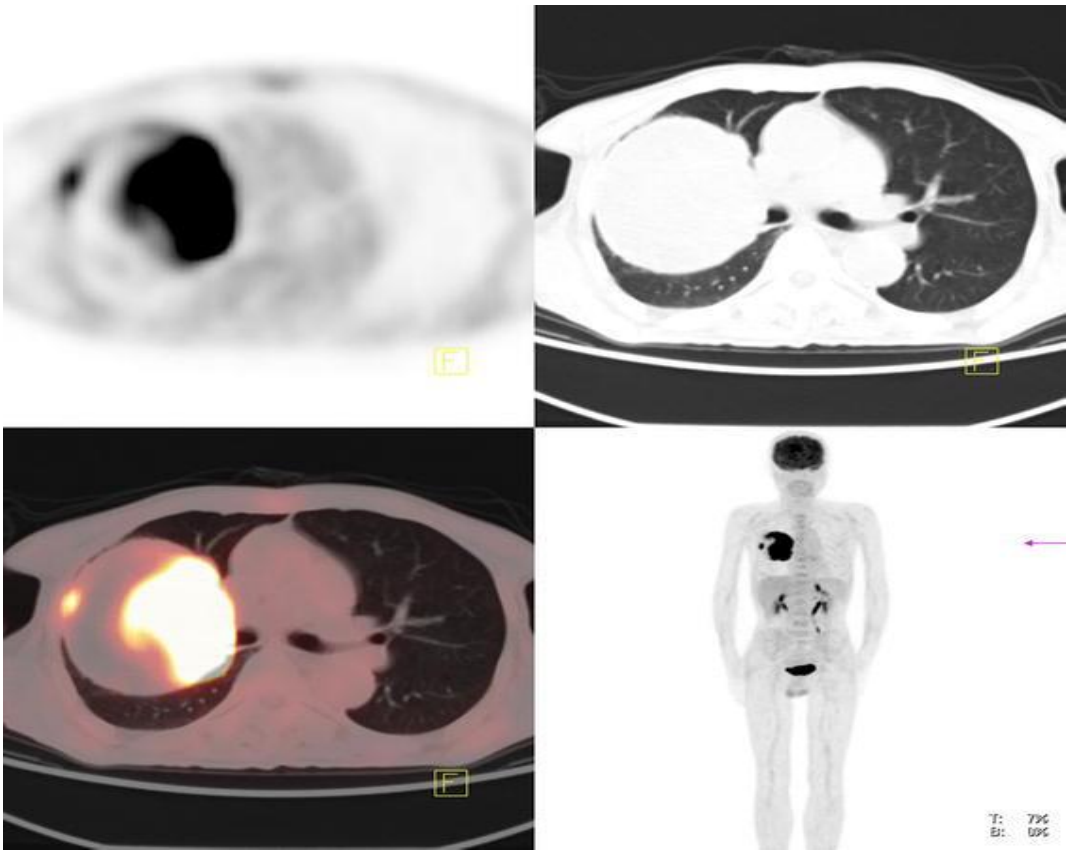

Figure 6: Axial PET, CT, PET-CT, and MIP images in a patient of squamous cell carcinoma. An irregular mass showing moderate FDG uptake in the lesion was discovered in the central segment of the right lung, with inflammation around the malignant lung lesion (38)

- **Large cell lung cancer**

Large cell lung cancer always shows moderate FDG uptake and diffused distribution **(Figure 7) (38)**.

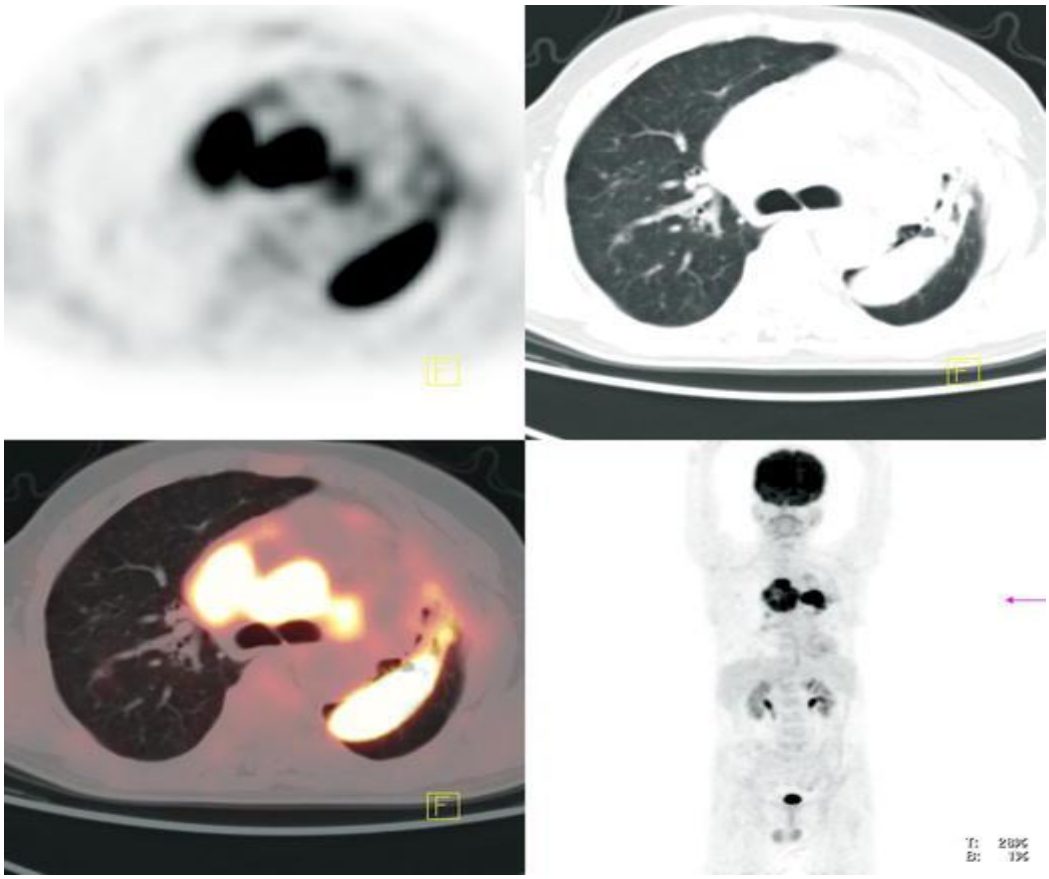

Figure 7: Axial PET, CT, PET-CT, and MIP images in a patient of large cell cancer. Multisite masses showing higher FDG uptake in the lesion were discovered in the left and right lung field, with inflammation and enlarged lymph node in the mediastinum (38)

- **Small cell lung cancer**

Small cell lung cancer shows a small mass with moderate FDG uptake **(Figure 8) (38)**.

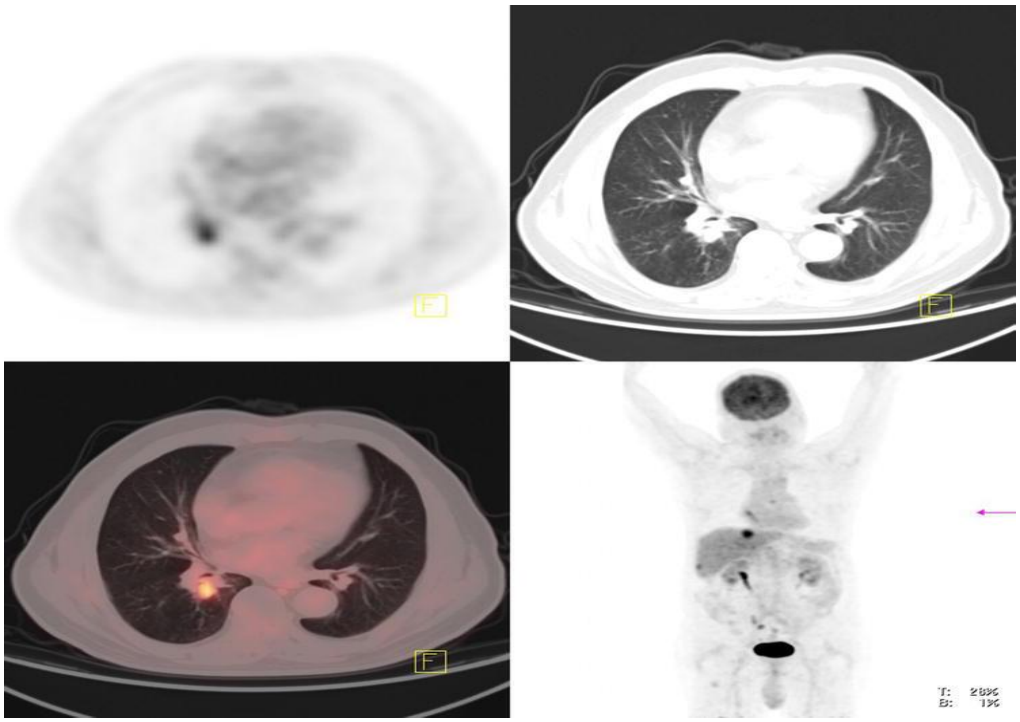

Figure 8: Axial PET, CT, PET-CT, and MIP images in a patient of small cell lung cancer. Small mass located in the right hilar with slight FDG uptake in the lesion was discovered in the right lung field (38)

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