

The Utility of Metabolic Imaging by 18F-FDG PET/CT in Lung Cancer: Impact on Diagnosis and Staging

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INTRODUCTION

Lung cancer is the leading cause of cancer deaths in both men and women in the USA. The incidence of lung cancer is higher in men than in women, but at present the incidence is increasing in women.

Lung cancer is expected to account for 26% of all female cancer deaths in 2011 and has been the leading cause of cancer death in women since 1987 (1).

Smoking tobacco is the primary risk factor for lung cancer (2-4). Heavy smoking is associated with a 20 to 30-fold increase in lung cancer risk compared to nonsmokers. Cigarette smoking is the cause of lung cancer in 90% of cases (2).

Squamous cell carcinomas, small cell lung carcinoma, large cell carcinoma, and to a lesser extent adenocarcinoma have an increased incidence with increased number of cigarettes smoked per day.

Radon, a radioactive gas, is the second cause of lung cancer in general population (5), and is the main cause of lung cancer in nonsmokers. Second-hand smoke is the third leading cause of lung cancer (6, 7).

The WHO divided lung cancer into 2 major classes: Non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Non-small cell lung cancer accounts for more than 85% of lung cancer cases and has 2 major

subtypes: Squamous cell carcinoma and non squamous cell carcinoma.

In general, 30% of lung cancer cases are squamous cell carcinoma which is strongly associated with smoking. Cavitation is more common in this type than the other types of lung cancer. About two third of squamous cell carcinomas arise within the main bronchus and lead to atelectasis and consolidation. In one third of cases, SCC can be seen in the periphery as a lung nodule or mass.

Adenocarcinoma is the most common type of lung cancer and accounts for 35% of cases. It is most commonly seen in women and nonsmokers. The periphery of the lung especially the upper lobe is the dominant area of localization. The margins of tumor are speculated and irregular.

Large cell carcinoma accounts for 10% of lung cancers and typically presents as a large peripheral mass with early metastasis and poor prognosis.

In total, 15% of lung cancer cases are small cell lung cancer (SCLC). When compared, SCLC has a more rapid doubling time in comparison to NSCLC and earlier development of metastases. Most patients with SCLC have hematogenous metastases, and limited disease confined to the chest is seen in only one third of cases. Other types present small percentage of all lung carcinomas.

IMAGING IN LUNG CANCER

The primary role of imaging is initial staging (8). Accurate staging is very important for management strategies and evaluation of prognosis. The management strategies for NSCLC and SCLC are significantly different. In the early stages of NSCLC, surgery provides the best chance of cure either alone or in combination with chemotherapy or radiotherapy. But most patients have metastatic disease at the time of diagnosis. Small cell lung cancer initially responds well to chemotherapy and radiation and surgery should be considered only for stage I (T1-T2 N0) (9).

Computed tomography (CT) and magnetic resonance imaging have been used for NSCLC staging. CT provides morphologic information about the tumor size and the extent of disease (10) but has limited ability to differentiate between benign and malignant lesions.

PET, Positron Emission Tomography, also called PET imaging or a PET scan, is a type of nuclear medicine imaging. Nuclear medicine is a branch of medical imaging that uses small amounts of radioactive material to diagnose or treat a variety of diseases, including many types of cancers. Radionuclide imaging procedures are noninvasive and with the exception of intravenous injections, are usually painless medical tests. These imaging scans use radioactive materials called radiopharmaceuticals or radionuclide.

The radionuclide positron emitter is injected into a vein and accumulates in the target organ. After a positron is emitted, it travels a short distance in tissue and losing almost all kinetic energy, it annihilates with an electron. Annihilation produces a pair of photon in opposite directions, each with energy of 511keV (Figure 1).

These photons are detected by a device called a PET scanner. A PET scan measures important body functions, such as blood flow, oxygen use, and glucose metabolism, to evaluate function of organs and tissues.

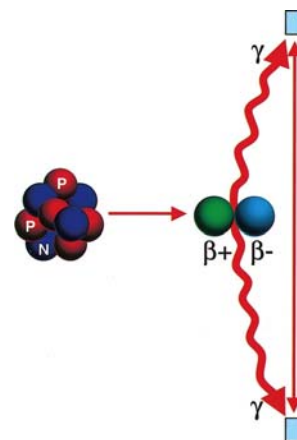


Figure 1. Annihilation reaction (Kapoor V et al. Radiographics 2004;24:523-543)

Now, manufacturers are making positron emission tomography/computed tomography (PET/CT) units that are able to perform both imaging studies at the same time.

In these new systems, the PET and CT images are fused and provide combined physiologic information as well as exact anatomic localization in a single examination. FDG-PET uses 18 F-fluorodeoxyglucose, which is a short-lived radioactive compound that localizes in tumor cells. Tumoral cells have a high metabolic activity and use more glucose; 18 F-fluorodeoxyglucose is a glucose analog that after entering the cell, has the similar metabolism pathway as glucose. After phosphorylation, FDG-6-Po₄ is not further metabolized and does not diffuse out of the cell, thus remain trapped which is ideal for imaging.

Following IV injection, F-18 FDG rapidly distributes into the body and kidneys are the main route of excretion.

The half life of F-18 is 109.7 minutes and the optimal time for imaging is 60 minutes after injection.

Serum glucose level competes with FDG and decreases its uptake by tumoral cells; thus fasting for 4 hours is strongly recommended prior to PET-scan. For this reason special preparation is needed for diabetic patients to control glucose.

STAGING OF NON-SMALL CELL LUNG CANCER

Tumor staging by the TNM system provides information about the extent of disease and determines the best therapy and prognosis (11). Resectability is the most important decision made by using TNM system.

T status describes the extent of the primary tumor by its size and its invasion to the pleura, bronchovascular structures, diaphragm, and mediastinum. Presence of mediastinal fat planes or lung between the tumor and the mediastinum means no direct extension into the mediastinum.

Lymph node (N) status is an important factor for determining the resectability; N describes the presence or absence and localization of regional lymph node metastasis. The location of the primary tumor determines the lymphatic pathway and localization of regional lymph node involvement (12). A tumor in the right lung metastasizes to the right hilar lymph node and then to the right paratracheal lymph nodes. Only in 4% of cases, contralateral mediastinal lymph nodes are involved by metastasis. Primary tumor in the left upper lobe metastasizes to the aortopulmonary window and left paratracheal nodes. T Lung cancer in the both lower lobes and right middle lobe may send early metastasis to subcarinal nodes. Initial involvement of left hilar lymph nodes may be seen in left upper and lower lobe tumors.

N1 means metastasis to lymph nodes in the ipsilateral peribronchial or hilar region.

N2 is defined as a metastasis to ipsilateral mediastinal or subcarinal lymph nodes and represents at least IIIA.

N3 is defined as a metastasis to contralateral hilar, contralateral mediastinal, ipsilateral or contralateral scalene, or supraclavicular lymph nodes and represents at least IIIB.

The CT evaluation of mediastinal lymph nodes has extremely variable sensitivity and specificity: %60 and 77%, respectively (13). CT criteria for abnormal size of lymph node is more than 1cm in the short axis (14). Micrometastases may be seen in normal-size lymph nodes in %15 of patients with stage I, thus size alone is not a reliable criteria (15,16). Fatty hilum in lymph node is another morphologic sign that emphasizes its benignity (17).

Distant metastasis (M status) is a critical factor for the resectability of a tumor. M defines tumoral involvement of

distant lymph node or organs. Common sites of metastases are brain, bone, liver, adrenal glands (M1b) and contralateral lung (M1a) (18).

The frequency of occult metastasis at the time of presentation is 30% in patients with adenocarcinoma or large cell carcinoma and 15% in squamous cell carcinoma of the lung (19). The most common sites of distant occult metastases are adrenal gland and liver. The frequency of incidental nonfunctioning cortical adenomas is 5% in general population and in 10% of patients with lung cancer adrenal mass is seen on CT (20,21). If the HU of adrenal mass is less than 10 on unenhanced CT, it is considered benign. F-FDG PET is sensitive for detection of adrenal metastases. Adrenal may be the only site for metastasis but liver is never the only site except in adenocarcinoma.

ROLE OF F-18 FDG-PET IN STAGING

Integrated PET-CT is a useful method for the determination of invasion of lung cancer to the chest wall (Figure 2). Because of the exact F-18 FDG uptake correlation to anatomic finding in PET-CT images, the primary lung cancer precisely delineated which leads better determination of chest wall infiltration (potentially resectable T3a) and mediastinal invasion. F-18 FDG-PET can differentiate tumor from peritumoral atelectasis. This is especially important in radiotherapy planning to reduce the field of radiation.

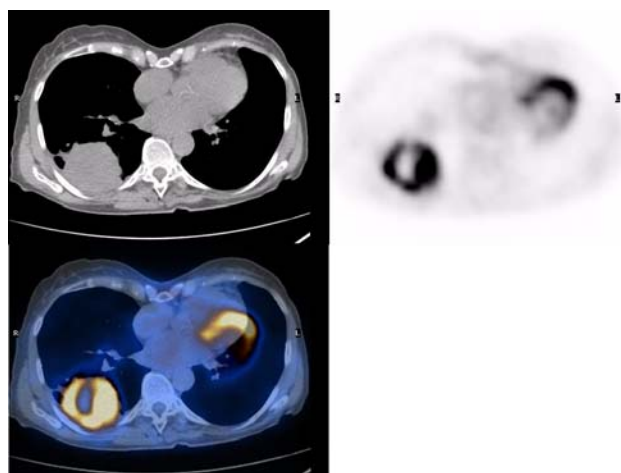


Figure 2. Non small cell Lung cancer.

Hypermetabolic cavitary lung mass is seen in right lower lobe. Abnormal mass in RLL is seen in CT that cannot be characterized. The PET study shows increased glucose uptake in the periphery of the mass indicating viable tumor tissue without chest wall infiltration and no uptake in the center means central necrosis; thus, exact localization of biopsy site is easy with PET/CT fusion image.

The value of addition of 18F-FDGPET to conventional radiology in NSCLC staging was the prevention of unnecessary surgery in 1 of 5 patients (22). In non-central tumors, PET has high negative predictive value for mediastinal lymph node involvement; thus, preventing unnecessary mediastinoscopy. The sensitivity and specificity of PET were 91 % and 86%, respectively for detection of mediastinal lymph node metastasis (23).

Some medical centers accept negative results because of high negative predictive value of PET without pathologic confirmation and resection of tumor by surgery. However, controversy exists about the role of PET in mediastinal staging (24).

Size of the metastasis is very important. Takamochi et al. found false-negative PET results in lesions with 1 to 7.5mm in diameter (25). Misregistration from respiratory, cardiac, and body motions leads to mediastinal activity as another source of error.

If the disease is stage I (T1ab, N0 lesions) according to clinical examination with negative CT and PET result, because of the low prior probability of lymph node involvement, routine mediastinoscopy in these patients is excluded (26).

If the PET/CT scan is positive in the mediastinum, the lymph node status needs pathologic confirmation. EBUS-TNBA can be used to determine the situation(27,28). However, in case of negative EBUS-TNBA findings, mediastinoscopy can be done to confirm the results (28,29).

In patients with peripheral T2a, central T1ab, or T2-T3 lesions with negative PET/CT scans, there is high risk for

mediastinal lymph node involvement and mediastinoscopy is recommended (30).

Gonzalez-Stawinski et al. showed the false-negative rates of mediastinoscopy and PET to be 3% and 11.7%, respectively in stage II and III diseases (31). Thus, for stage II and III diseases, mediastinoscopy will remain part of the standard protocol for staging.

Differentiation of stage IIIA from IIIB (suspected N3) diseases is a very important factor for using mediastinoscopy and to determine which patient needs curative resection (32,33).

N status is not relevant in stage IV disease; thus, PET for mediastinal staging is less of an issue.

F-FDG shows metabolic activity and increased glucose uptake by activated macrophages and inflammatory cells leading to increased uptake of 18F-FDG in sites of inflammation. Thus, FDG-PET cannot distinguish malignancy from inflammation or infection (34).

FDG-PET has positive predictive value of 75% -95% for evaluation of the mediastinum (35,36). The high rate of false-positive results revealed that we need mediastinoscopy for better staging of PET-positive mediastinal lymph nodes (37,38).

The benefit of PET in this situation is localization of mediastinal lymph node for biopsy and selecting another invasive method for inaccessible lymph nodes by mediastinoscopy (VATS and thoracotomy).

FALSE-NEGATIVE AND FALSE-POSITIVE FINDINGS IN FDG-PET SCAN

F-18 FDG-PET results can be false negative in pulmonary carcinoid tumors that are highly differentiated and in BAC (39,40). Lymph node metastasis smaller than 4–6 mm is another false negative result. Imaging modalities cannot detect micro-metastasis.

Tuberculosis, eosinophilic lung disease, histoplasmosis, aspergillosis, lung emphysema and occult lung infarction may have abnormal increased uptake of F-18 FDG leading

to false positive findings (41). Chronic inflammatory lesions usually do not increase the uptake of FDG.

DISTANT METASTASIS

There is no need for curative surgical resection in Stage IV because of distant metastasis. An important advantage of PET-CT is the use of whole-body scanning to detect distant metastasis (Figure 3).

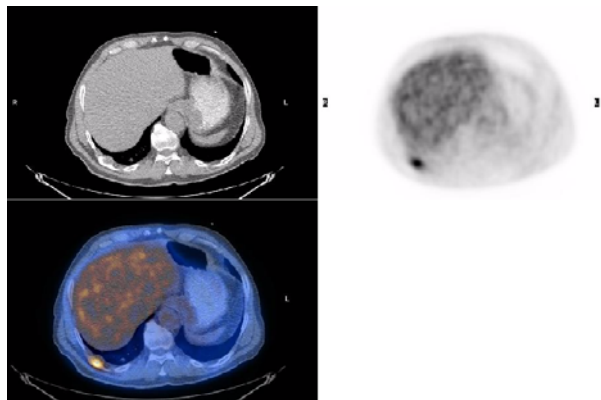


Figure 3. The PET study shows unsuspected abnormal increased FDG uptake in posterior aspect of right chest, which is best localized in right dorsal rib in PET/CT fusion image.

Distant metastases commonly involve the adrenal glands, bones, liver, and brain (42). The mean frequency of extra-thoracic metastases by PET studies was 13%. The frequency of distant metastases was 7.5% in stage I, 18% in stage II, and 24% in stage III (43). The adrenal glands and liver are the most common sites of extra-thoracic metastases in lung cancer. At the time of presentation, up to 10% of patients have adrenal mass and two thirds of them are not malignant (44, 45). Sensitivity, specificity and accuracy of PET for detecting adrenal metastasis were 100%, 94%, and 96%; respectively (46).

Also, 18F-FDG PET has a sensitivity similar to that of bone scan but its specificity is more than bone scintigraphy. Fogelman et al. (47) in their study of breast cancer in patients with bone metastases showed that 18F-FDG PET has the advantage of detecting osteolytic lesions; whereas, bone scintigraphy can detect osteoblastic lesions (48). PET is less effective than CT or MRI for the detection

of brain metastasis because of high FDG uptake by normal brain (49).

The routine use of magnetic resonance imaging (MRI) (to rule out asymptomatic brain metastases) and bone scans (to exclude bone metastases) is not recommended. Brain MRI is recommended for patients with stage II, III, and IV disease to rule out metastatic disease if aggressive combined-modality therapy is being considered (50).

The increased sensitivity of PET/CT scans, compared with other imaging methods, may identify additional metastases and, thus, spare some patients from unnecessary surgery. However, positive PET/CT scan findings need pathologic or other radiologic confirmation.

RESTAGING

Morphologic response usually occurs over several weeks to months after therapy. During the interim phase, approximately one-third of non-responder patients in the first line of chemotherapy are treated without any benefit from therapy bearing unacceptable side effects from several weeks of toxic and costly treatment. Morphologic evaluation may be incorrect because of edema and peritumoral scar tissue formation, which may mask tumor regression (51). Considering the above mentioned reasons, the morphologic response is not ideal.

Decreased metabolic activity, standardized uptake value (SUV) after one cycle of chemotherapy is closely correlated with effective chemotherapy (52). The treatment regimen may be changed to second-line therapy if there is no metabolic response; thereby, reducing the costs and morbidity from ineffective therapy. Patients with positive FDG PET results after first-line treatment, have a significantly worse prognosis than those with negative FDG PET results, with median survival of 12 months versus 34 months, respectively (53). PET is highly specific for the characterization of viable tumor and scar tissue after therapy (54).

Mass or symptoms suggestive of relapse after curative therapy are common and characterization of them is difficult.

Hicks et al. demonstrated early detection of relapse by PET that changed the management in 63% of patients from curative to palliative, from palliative to curative or active management in PET negative patients (55).

STAGING OF SMALL CELL LUNG CANCER (SCLC)

SCLC represents approximately 15% of all cases of lung cancer (56, 57). Nearly all cases are related to cigarette smoking. Two third of patients with SCLC present with hematogenous metastases, while the remainder of patients have limited disease confined to the chest.

SCLCs are typically located centrally with a large hilar mass and bulky mediastinal lymphadenopathy (57, 58) often with encasement of mediastinal structures and tracheobronchial compression (59, 60) that cause coughing and dyspnea. Frequently, patients present symptoms of metastatic disease, such as weight loss, bone pain, and neurologic problems. Solitary peripheral nodule without central adenopathy is an uncommon finding. Unlike the NSCLC, there is a 2-stage classification according to the growth pattern for SCLC:

- 1) Limited-stage disease is confined to the ipsilateral hemithorax, which can be safely included in a radiation field. Contralateral mediastinal and ipsilateral supraclavicular lymphadenopathies are classified as limited-stage disease, while contralateral hilar and supraclavicular lymphadenopathy is controversial.

- 2) Extensive-stage disease is beyond the ipsilateral hemithorax, including the malignant pleural or pericardial effusion or hematogenous metastases (61).

Patients with limited disease are given chemoradiation; whereas, patients with extensive disease are given chemotherapy alone.

In the new TNM staging system, any T, any N and M0 is limited-stage SCLC. Extensive-stage is any T, any N, M1a/b, and T3-4 with multiple lung nodules (not fit in tolerable radiation field).

If limited-stage is suspected, PET-CT should assess distant metastases. PET scans can increase staging accuracy in patients with SCLC (62).

By PET, 15% of patients are up-staged from limited to extensive stage, and pathologic confirmation is required for PET/CT-detected lesions; while, only 5% are down-staged from extensive to limited stage.

PET/CT is superior to standard imaging for metastasis; however, PET/CT is inferior to MRI or CT for brain metastases (63).

Surgery is considered for 5% of patients with stage I (T1-2 N0) SCLC in whom biopsy and pathologic staging of mediastinum is required to confirm PET/CT findings and also in patients with clinical stage T1-2, N0 disease (64). In stage I disease, 5-year survival rate is 40%-60% (65, 66).

PET staging changed management in 16%-38% of patients mainly due to change of radiation field because of more accurate detection of intrathoracic sites (67, 68).

In brief, PET-CT scan can identify distant metastatic disease and may be applied to guide mediastinal evaluation, if not previously done.

CONCLUSION

One of the most important applications of FDG-PET is staging and restaging of lung cancer. PET is superior to conventional imaging modalities for detection of unsuspected mediastinal lymph node and distant metastasis. FDG-PET by accurate staging can guide the most appropriate therapy and by evaluation of therapy, reduce the morbidity and costs of ineffective treatment. Adequate information about the limitations of FDG-PET will also provide the most accurate interpretation of PET-scan.

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