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FUNCTIONAL IMAGING IN THE MANAGEMENT OF LUNG CANCER

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ABSTRACT

Despite the remarkable reduction in the incidence of lung cancer among men in many developed countries, there has been a fourfold increase in lung cancer in women over the past 30 years associated with a rising trend in female lung cancer related mortality. Early diagnosis and appropriate treatment of lung cancer are two important determinants of prognosis and overall disease outcome. Functional imaging has recently gained a prominent role in the management of numerous pulmonary malignancies. The successful introduction of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) along with PET/CT image fusion has revolutionized diagnostic imaging in lung cancer. Currently, ^{18}F-FDG PET/CT is considered the most precise diagnostic test for a wide range of pulmonary malignancies. This is primarily attributed to its unique ability to assess the global metabolic state of each individual tumor. In fact, the high sensitivity and the whole body mode of data acquisition are two critical advantages that favor ^{18}F-FDG PET/CT over other cross sectional imaging modalities like CT and MRI. Noteworthy, however, is the complementary role of dynamic contrast enhanced CT in characterizing indeterminate pulmonary nodules and adrenal lesions. Besides its distinguished diagnostic potentials, especially in unmasking occult tumor foci, ^{18}F-FDG PET/CT can precisely delineate the locoregional tumor burden for an accurate radiotherapy treatment planning. Furthermore, PET can offer reliable prognostic information since the avidity of both de novo and previously treated cancerous lesions to ^{18}F-FDG has been shown to correlate with the overall disease outcome and patient survival. In the near future, further brilliant horizons are expected since the development trials of other radiotracers that target tumor proliferation, apoptosis, and hypoxia are emerging.

INTRODUCTION

Lung cancer is the leading cause of cancer mortality around the world. In the United States, the disease now accounts for 29 percent of deaths from cancer (1). Several case control studies have argued that women are more susceptible to the carcinogenic effect of cigarette smoke than men with a significantly higher risk for developing lung cancer (2). For instance, the lower DNA repair capacity along with the tobacco-related p53 mutations are more common in female lung cancer patients than in their male counterparts, suggesting that women may be more vulnerable to the carcinogenic effect of tobacco smoke than men (2,3). Another potential contributing factor is the role of female steroid sex hormones in inducing lung carcinogenesis.

Lung cancer histologies include squamous cell carcinoma, adenocarcinoma, large cell carcinoma and small cell carcinoma. The former 3 histological subtypes, which accounts for

approximately 85 percent of lung cancer, constitute non-small cell lung cancer (NSCLC). Cigarette smoking is linked to all 4 histological subtypes of lung cancer especially squamous-cell and small-cell carcinomas, whereas, the proportion of non-smokers is highest in those who present with adenocarcinoma (2,4). Despite uniform staging and treatment, the 5-year survival rate of women with stage I-III NSCLC is better than men overall and at each stage. Women are more likely to have adenocarcinoma, to present with earlier stage disease, and to show better response to neoadjuvant chemotherapy (5).

Many diagnostics modalities have been developed for early diagnosis of lung cancer including high resolution CT, MRI, and PET scanners. The recent introduction of PET/CT hybrid system has dramatically improved the proper staging, assessment of treatment response, detection of recurrence, and metastatic spread, as well as, treatment planning using intensity modulated radiation therapy.

This review will shade light on different aspects of using Fl-FDG PET/CT in diagnosis and follow up of lung cancer.

The Solitary Pulmonary Nodule:

Continuous efforts have been devoted to detect lung cancer at an early stage. However, since both chest radiography and cytologic analysis of sputum, which were the mainstay of most screening programs, were not proven to significantly reduce mortality from lung cancer, high-resolution CT screening has emerged as an efficient tool for early detection of lung cancer (6). Preliminary outcome data has revealed a significant reduction in mortality of patients with lung cancer detected by CT screening with an overall five-year survival rate of 84 percent in comparison with 49 percent for those who have been screened by chest radiography (6). Despite the high sensitivity of high-resolution CT, 25 to 39 percent of malignant nodules are misclassified as benign after radiologic assessment of morphologic characteristics and about half of the biopsied indeterminate pulmonary nodules turn out to be benign lesions (7-9). Accordingly, improving the specificity of CT in characterizing indeterminate pulmonary nodules would be of great clinical value.

Recently published guidelines for the management of small pulmonary nodules have recommended no CT follow-up for nodules ≤4 mm, whereas, for nodules >4-6 mm and >6-8 mm, follow-up at 12 months, and 6-12 months must be considered, respectively(10).

Another proposed strategy is to use 18F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) for further evaluation of suspicious nodules of high-risk persons. For now, the largest meta-analysis for the performance of ^{18}F-FDG PET in characterizing indeterminate pulmonary nodules larger than 1 cm and pulmonary mass lesions has yielded a sensitivity of 96 percent and specificity of 78 percent (11). The high sensitivity figure is attributed to the fact that the vast majority of lung cancers are ^{18}F-FDG avid. This tracer competes with glucose for uptake into cells, where it accumulates after being phosphorylated by hexokinase (12). The amount of ^{18}F-FDG accumulation over a fixed period is thus an indicator of the rate of cellular glucose metabolism and appears to correlate well with the malignant potential of most cancerous lesions. Noteworthy, however, is that the focal form of bronchioloalveolar carcinoma and typical carcinoid are two common sources of false negative PET findings (13, 14), owing to their unremarkable ^{18}F-FDG uptake. In contrast, the relatively lower specificity of ^{18}F-FDG PET in characterizing indeterminate lung

nodule and pulmonary mass lesions is due to the invariable ^{18}F-FDG accumulation in active inflammatory or infectious lesions (15). Several reports have previously highlighted pathological ^{18}F-FDG uptake in pulmonary granulomas ,histoplasmosis, tuberculosis, sarcoidosis, and Aspergillus infection (16). Furthermore, any injurious lesion that results in activation of granulocytes or macrophages within the lung parenchyma, like needle biopsy, recent radiotherapy and lung infarction, may equally induce pathologic ^{18}F-FDG accumulation and consequently false positive PET interpretation (17,18).

The recent introduction of PET/CT hybrid systems has dramatically improved lesions' characterization since the concomitantly acquired CT data has provided direct morphological correlation for each ^{18}F-FDG signal (19,20). Furthermore, the worthful role of dynamic contrast enhanced CT in characterizing indeterminate pulmonary nodules and pulmonary mass lesions is very promising. In this approach, dynamic acquisition centered over the questionable lesion is performed. It usually consists of a single native acquisition followed by multiple dynamic frames up to 15 minutes after I.V injection of iodinated contrast medium (21,22). Quantitative image analysis is established by creating a time density curve to study the kinetics of the contrast medium in the pulmonary lesion under investigation (Figure 1). Currently, there is unanimous agreement that quantifying the wash-in and washout of a given pulmonary nodule is associated with a remarkable improvement in the overall specificity of CT analysis (22,23). In a study involved 107 patients with a solitary pulmonary nodule, when diagnostic criteria for malignancy of both wash-in of 25 Hounsfield Unit (HU) or greater and washout of 5-31 HU were applied, sensitivity, specificity, and accuracy for malignancy were, 94 percent, 90 percent, and 92 percent, respectively (22). Accordingly, we may conclude that for indeterminate pulmonary lesions smaller than 8 mm, CT volumetric follow-up seems to be the examination of choice, which when reveals a significant volume increase, a reasonable second-step must be fine needle biopsy or surgical resection. For indeterminate lesions larger than 8 mm, the integration of dynamic contrast enhanced CT with ^{18}F-FDG PET may optimize the overall specificity of lesion characterization. It has to be recognized, however, that surgical biopsy must always be considered whenever there is a high clinical or radiological suspicion of lung cancer or metastatic pulmonary lesion(s).

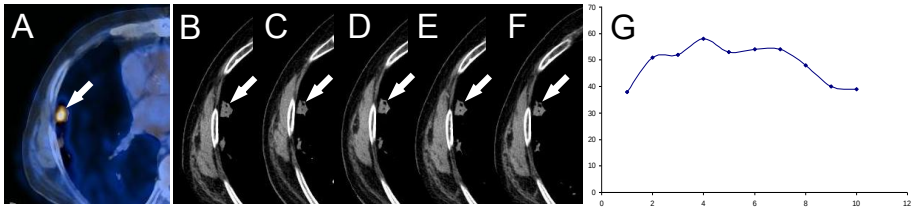

Figure 1 (A) False positive 18F-FDG PET/CT of a 15mm non necrotizing gigantocellular inflammatory granuloma (arrow) in a 76-year-old patient. (B-F) Dynamic CT scans and (G) time-density curve of nodule hemodynamics show a benign enhancement pattern (<25 HU wash-in with almost complete washout).

Non Small-Cell Lung Cancer:

According to the international TNM staging system ,patients who present with early NSCLC (i.e., stage I-II) and selected patients with stage IIIA can be considered for curative surgical resection, whereas chemoradiotherapy and palliative care are reserved for those who present with stage IIIB and IV, respectively (24). Since mediastinal lymph node involvement and extrathoracic metastases are found in 26 percent and 49 percent of patients with lung cancer at the time of diagnosis (25), accurate staging is crucial for selecting the most suitable therapeutic approach and for determining prognosis. With the successful introduction of PET/CT, a significant improvement in the diagnostic accuracy of lung cancer has been achieved, principally because of the more accurate topographic resolution provided by the concomitantly acquired CT (26-29). Precise identification of mediastinal and distant metastases by ^{18}F-FDG PET/CT has the potential to limit the number of tests and invasive procedures required for the metastatic workup of patients with lung cancer.

Tumor (T) status:

The T status resumes the extent of the primary tumor by size and invasiveness to neighboring structures like the pleura, bronchovascular tree, and mediastinum. While T1-T3 tumors are generally considered as resectable primary lesions, T4 status, in contrast, preclude surgical resection with curative intent (9,30). A notable exception for inoperability in T4 disease is the existence of metastatic nodule(s) in the same lobe as the main lesion (31). Therefore, accurate T stage in NSCLC is an integral step for determining tumors' resectability and preoperative planning especially before en bloc resection of chest wall infiltrating tumors. Both CT and MRI are of equal diagnostic value for distinguishing T3-T4 tumors from T1-T2 tumors with sensitivity and specificity of 63 percent and 84 percent for the former and 56 percent and 80 percent for the later (32). They have, however, some well recognized limitations: For instance, distinguishing neoplastic contiguity with the pleura, mediastinum or chest wall from definite invasion is quite challenging (Fig. 2) (33, 34). Furthermore, variability in image interpretation may take place even among expert observers. Accordingly, both CT and MRI may not be conclusive in some settings.

Studies that favor ^{18}F-FDG PET/CT for the assessment of T stage in lung cancer are emerging. In a prospective study of 50 patients, integrated PET/CT was correct for T staging in 88 percent of patients, corresponding values for PET alone and CT alone were 40 percent and 58 percent, respectively (26). Additional investigations by other research groups

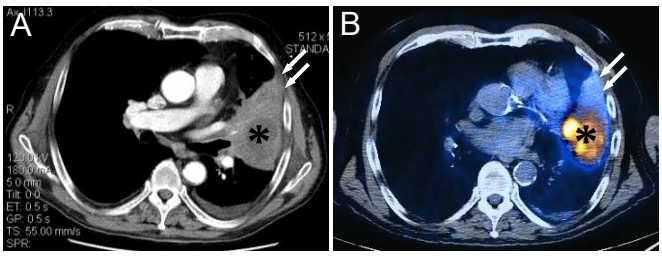

Figure 2, Adenocarcinoma of the left upper lobe in a 67-year-old patient. (A) Contrast enhanced CT shows that the mass (*) has a wide contact with the pleural surface with a questionable chest wall invasion (arrows). (B) 18F-FDG PET/CT reveals the true tumor extension, no chest wall invasion has been found and the contacting soft tissue density was confidently interpreted as post-stenotic atelectasis (arrows).

have reached similar conclusions (27,28). The added benefits of PET/CT in this setting are obvious since precise delineation of tumor boundaries for any potential chest wall infiltration or mediastinal invasion can be easily achieved by virtue of anatometabolic image fusion (Fig. 2). Despite the better performance of PET/CT over that of cross sectional imaging modalities, further comparative studies for T staging of special tumor entities like superior sulcus tumor or those that are at close proximity to the diaphragm are needed before standardizing PET/CT for T stage of lung cancer.

Nodal (N) status:

Nodal status besides being a strong prognostic factor for resectable NSCLC, has also a remarkable impact on patient management and disease outcome. While surgical intervention with curative intent is the standard therapeutic approach for patients with resectable primary tumors and N1 nodal status, those who harbor N2 disease are potential candidates for neoadjuvant therapy protocols before applying any curative surgical intervention. In contrast, N3 nodal status is considered unresectable (35). Accordingly, accurate nodal staging has become of critical importance for patients with NSCLC. Computed tomography of the chest has been considered for a long time as the workhorse for noninvasive evaluation of the mediastinum in patients with NSCLC. However, the CT criteria for tumor involvement, that rely on the size or shape of the lymph nodes, have been shown to be far from ideal with a sensitivity and specificity in the range of 61 - 64 percent and 62 - 79 percent, respectively (36,37). These figures are related to the fact that normal sized lymph nodes (less than 1 cm in short-axis diameter) may harbor metastasis on histological examination, and nodal enlargement may be due to reactive hyperplasia or other benign condition like silicoanthracosis (38). Several groups have investigated the role of ^{18}F-FDG PET and PET/CT in evaluating the mediastinum of patients with NSCLC. With a range of sensitivity between 82 and 91 percent and specificity between 82 and 86 percent (38, 39), ^{18}F-FDG PET has been shown to perform better than CT for mediastinal nodal staging. These encouraging results have been optimized after the successful introduction of PET/CT. In fact, the diagnostic accuracy of ^{18}F-FDG PET/CT in mediastinal nodal staging was significantly better than that of PET alone and CT alone (26-28). This is not surprising since the morphologic data obtained from the CT part of PET/CT represents a cornerstone for the identification of the true origin of each ^{18}F-FDG signal. Multiple studies have demonstrated positive predictive values for PET of 74 to 93 percent in mediastinal evaluation (38, 40), whereas, others revealed negative predictive values of 88 to 95 percent (39, 41). These figures are explained by the lack of specificity of ^{18}F-FDG, which accumulates in inflammatory and reactive lymph nodes, and by the limited spatial resolution of the currently available PET scanners that could miss lesions smaller than 8 mm (42). Accordingly, for PET-positive mediastinal lymph nodes, both mediastinoscopy and endoscopic ultrasound guided biopsies must be considered as two complementary diagnostic approaches for an accurate staging of the mediastinum. However, in patients with clinical stage I tumors and negative mediastinal lymph nodes shown by PET/CT, mediastinoscopy can be omitted or better replaced by sentinel lymph node mapping and intraoperative frozen sections owing to the low (5.6 percent) likelihood of mediastinal involvement in this patient group (39, 43,44). It has to be recognized, however, that omitting mediastinoscopy in patients with central lung tumors and negative PET results in the mediastinum is still a

debating subject since the tumor's activity may easily mask lower levels of abnormal activity in adjacent mediastinal lymph nodes, and consequently, may lead to false negative PET results (38).

Detection of distant metastasis (M status):

The evaluation of distant metastases is also of paramount importance for determining the resectability of the tumor under investigation. In NSCLC, the brain, bone, liver and adrenal glands are common sites for distant metastases, and such extension is considered incompatible with curative surgical resection (i.e., M1 disease). Metastases to a different lung lobe, other than that where the primary tumor locates, are considered distant metastases as well (45, 46). The frequency of occult metastasis at the time of presentation has been shown to be as high as 30 percent in patients with adenocarcinoma or large cell carcinoma (47), whereas, squamous cell carcinoma has a relatively lower frequency (15 percent) of occult metastasis at presentation (48). Before the era of PET and PET/CT, a battery of noninvasive imaging modalities like CT, MRI, bone scan, and ultrasonography was required for the metastatic workup of NSCLC. Besides the considerable costs of these diagnostic tests combined, a dedicated diagnostic session is mandatory for each of them which may not always suit severely ill patients or those who are referred from remote areas. With regard to the thus far published data, ^{18}F-FDG PET/CT has been proven superior to either PET alone or CT alone for the detection of distant metastases from NSCLC (26-28). In fact, the integration of ^{18}F-FDG PET/CT into the screening for extrathoracic metastases has resulted in a change of therapeutic management in about 20 percent of patients (49). This can be reasoned by the distinguished ability of ^{18}F-FDG PET to unmask occult metastatic sites and to avert futile surgery in patients with unresectable disease (Figs. 3). However, because of the physiologic high uptake of ^{18}F-FDG in the brain, MRI has been shown to be much more sensitive than ^{18}F-FDG PET for detecting brain metastases and should be considered in patients with neurologic signs/symptoms or in asymptomatic patients with stage III disease (50, 51). Furthermore, some conflicting results have been published regarding the performance of PET in detecting osseous metastases compared with bone scan, with some authors reporting better sensitivity and others reporting lower sensitivity than with osteoblastic bone scan (52-54). However, it is generally agreed that PET has a better global accuracy (90 to 96 percent) than that of bone scan (66 to 78 percent) (52, 53). Future applications of complementary PET tracers like ^{18}F-fluoride may optimize the screening process for bone metastases in lung cancer patients (55).

Being occasionally the only extrathoracic site of metastasis, the assessment of the adrenal glands for any potential metastatic involvement has gained special importance in patients with NSCLC. Given that up to 10 percent of patients with bronchogenic cancer have an adrenal mass on CT and that 2 to 8 percent of the general population has benign nonfunctioning cortical adenomas (56, 57), characterizing adrenal lesions in patients with lung cancer may be challenging since some adrenal lesions like adenomas and benign pheochromocytoma are ^{18}F-FDG avid (Fig. 4) (58). Both nonenhanced CT and MRI are complementary to PET in differentiating metastases from benign adrenal adenomas that accumulate ^{18}F-FDG. This is primarily based on the augmented intracytoplasmic lipid contents of most adrenal adenomas that provoke a characteristic diagnostic signal upon nonenhanced CT or MRI examination (59, 60).

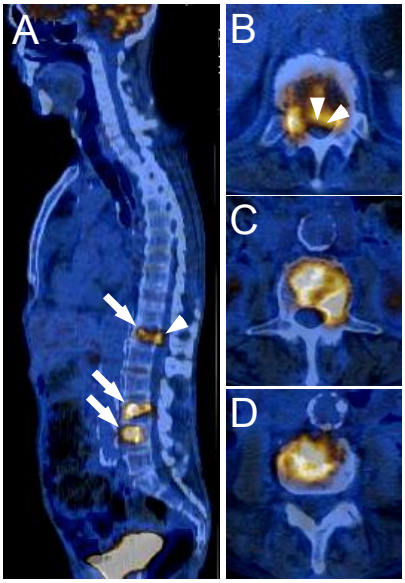

Figure 3 Bone metastases in a 63-year-old patient with large cell carcinoma. (A-D) 18F-FDG-avid soft-tissue mass in the lower dorsal and middle lumbar vertebrae (arrows) with an obvious encroachment on the spinal cord (arrow heads).

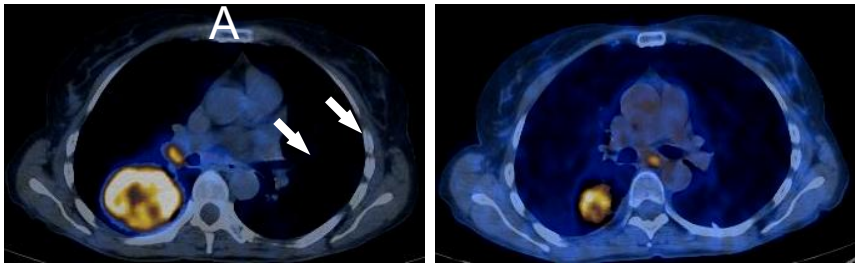

Figure 4 Large cell carcinoma in a 66-year-old patient. (A) A baseline 18F-FDG PET/CT image reveals hypermetabolic tumor mass in the right lower lobe associated with ipsi-lateral mediastinal lymph node metastasis (arrows). (B) Post-chemotherapy PET/CT displays significant reduction in both the 18F-FDG uptake as well as the size of the tumoral mass (arrow) along with a complete disappearence of the metastatic lymph node. Please note that the newly appearing focal hot spot (arrow head) was correctly identified by PET/CT to be the expression of a reflux oesophagitis and not of a cancer spread to the subcarinal nodal station.

MRI has been shown to be more sensitive than CT for the diagnosis of adrenal adenoma with sensitivity and specificity range from 81 to 100 percent and 94 to 100 percent, respectively (60). However, histopathologic verification of adrenal positive lesions on ^{18}F-FDG PET must be considered to avoid omitting surgical intervention in an otherwise operable patient. However, histopathologic verification by fine needle biopsy is an invasive manoeuvre that should be avoided whenever possible.

Therapy Monitoring:

While patients with stage I-II NSCLC are suitable candidates for curative surgical resection, those who present with stage IIIA are considered for more aggressive therapeutic alternative like neoadjuvant chemotherapy and/or radiotherapy aiming at reducing their advanced locoregional tumor burden in order to reach an operable stage (24). Complete pathological response to neoadjuvant treatment is an important prognostic indicator of favorable

outcome and prolonged disease free survival. Given the potential toxicity of these regimens along with their considerable costs, a reliable response predictor in an early phase of neoadjuvant treatment that might allow using alternative regimen for non-responders or those who develop fulminating disease course would be of great clinical benefit.

The vital role of ^{18}F-FDG PET in therapy monitoring is obvious, since responding tumors have been shown to display a significant reduction in their initial ^{18}F-FDG uptake even after the first cycle of induction chemotherapy (61). This distinguished diagnostic criterion of PET is believed to be able to predict the subsequent histopathological tumor response and consequently disease outcome.

Since CT has been considered for a long time as the backbone of assessing the treatment response of NSCLC, numerous studies have compared the performance of CT with that of ^{18}F-FDG PET in this regard. As expected, the accuracy of ^{18}F-FDG PET has surpassed that of CT for predicting the complete pathologic response after neoadjuvant therapy with a sensitivity, specificity, and accuracy of 100 percent, 95 percent, and 96 percent for ^{18}F-FDG PET and 63 percent, 54 percent, and 57 percent for CT provided that a cutoff of ≥60 percent is used for the decrease in initial tumoral ^{18}F-FDG uptake as measured by PET as well as for the reduction in tumor size as estimated by CT (Fig. 4) (62). This can be reasoned by the fact that resistant viable cell clones may exist in a shrinking tumor mass, whereas on the other hand, residual masses can be completely necrotic or fibrotic, thus morphological criteria do not always provide reliable diagnostic information for therapy monitoring of locally advanced NSCLC.

In contrast to the primary tumor response, mediastinal restaging after induction chemotherapy or chemoradiotherapy for NSCLC remains a challenging task despite the tremendous improvement provided by ^{18}F-FDG PET. Previously published reports have revealed sensitivity, specificity and accuracy of ^{18}F-FDG PET for the detection of residual mediastinal nodal disease in the range of 58-64 percent, 93-96 percent, and 85-91 percent, respectively (63, 64). Recently, these figures could be globally improved by using PET/CT which yielded sensitivity, specificity and accuracy of 77 percent, 92 percent, and 83 percent, respectively (65). The rather low sensitivity is due to either residual microscopic cell nests within the lymph nodes that are beyond the spatial resolution capacity (~6mm) of the currently available PET scanners or a process of chemotherapy induced metabolic stunning for the ^{18}F-FDG–avid tumor cells in these false negative lymph nodes. Furthermore, some false positive results have been reported owing to early reactive inflammatory changes after induction therapy. Accordingly, it has been recommended that at least 4 weeks must be elapsed after completion of chemotherapy to establish accurate ^{18}F-FDG PET results (61). However, it has to be recognized that despite these inherent limitations in ^{18}F-FDG PET/CT imaging, the results obtained so far are better than those derived from mediastinal restaging using remediastinoscopy. In fact, postinduction remediastinoscopy has been previously shown to be inaccurate in up to 40 percent of patients owing to mediastinal fibrosis and adhesions from initial extensive mediastinoscopy (65). Future comparative studies between ^{18}F-FDG PET/CT and endoscopic ultrasound needle aspiration may come up with optimal results through integrating these

2 diagnostic procedures in postinduction mediastinal staging of NSCLC.

Detection of recurrence:

After attempted curative treatment, patients with NSCLC have a risk of relapse and death exceeds 40% at five years (66). Surgical re-treatment with curative intent offers the best chance for long term survival, with a 3-year survival rate of 38% (67), whereas, chemoradiotherapy is reserved for those with extensive tumor manifestations. Detection of recurrent disease using cross sectional imaging modalities like CT and MRI may be hindered by the often extensive anatomic abnormalities induced by previous surgical treatment like parenchymal scarring, pleural thickening, pleural effusion, and mediastinal fibrosis. Furthermore, radiotherapy may induce slowly evolving parenchymal abnormalities in the lungs that may mimic local treatment failure owing to their nodular or masslike appearance (68). The development of ^{18}F-FDG PET has taken the evaluation of locoregional structural abnormalities beyond morphologic analysis to functional and metabolic analysis of disease. Studies that favor ^{18}F-FDG PET and PET/CT for the diagnostic workup of patients with suspected relapse of NSCLC after curative treatment with surgery, chemotherapy, or radiotherapy are emerging. Recently, two clinical trials have yielded quite convincing results in this regard with sensitivities of 93 to 98 percent, specificities of 82 to 89 percent, and accuracies of 86 to 92 percent (67-69). Another property of ^{18}F-FDG PET is the ability to simultaneously detect unsuspected tumor foci in order to avoid futile re-surgery in patients with extensive locoregional tumor burden or those with distant metastases. Integrating ^{18}F-FDG PET in the diagnostic workup of patients with suspected recurrence of lung cancer has been shown to impact patient management in more than 50 percent of cases (69-70).

Small-Cell Lung Cancer:

Small cell lung cancer (SCLC) is the most aggressive form of lung cancer. At presentation, 30 to 40 percent of patients with SCLC present with limited disease (LD), whereas, 60 to 70 percent present with extensive disease (ED) (71). According to the Veterans Administration Lung Cancer Study Group, LD is defined as disease confined to one hemithorax, mediastinum, and regional lymph nodes, which can be encompassed within a single tolerable radiation port. Disease extension outside the thorax or the existence of malignant pleural effusion is categorized as ED (72). Currently, most patients with LD SCLC are treated with a combination of chemotherapy and chest irradiation. This dual-modality therapy has been shown to increase complete response rate and to decrease local treatment failure (73, 74). In selected patients with very limited-stage disease (T1–T2, N0), surgical resection may be feasible. In extensive stage SCLC, chemotherapy remains the standard therapeutic approach (75). For patients who achieved complete response, prophylactic cranial irradiation is believed to improve the overall disease-free survival through reducing the risk of brain metastasis (76).

Initial Staging:

Accurate tumor staging is a pre-requisite for choosing the appropriate therapeutic approach in SCLC. The primary role of diagnostic imaging is to separate patients with LD from those with ED. On the basis of the widespread dissemination of SCLC, a battery of imaging tests is performed, such as CT of the chest and abdomen, CT or MRI of the

brain, and bone scan (77). Despite the high sensitivity of morphological cross-sectional imaging modalities to structural changes, identification of tumor tissue can be challenging in some settings (e.g., in normal-sized lymph nodes). Furthermore, morphologic imaging modalities are mostly used to evaluate a given anatomical region rather than the entire body. Metastases outside the imaging field are thus missed. The potential of ^{18}F-FDG PET in initial staging of SCLC has been investigated by many authors (78-79). In fact, ^{18}F-FDG PET has been proven superior to conventional staging procedures with an accuracy of 100, 99, and 96 percent for the detection of the primary lesions, regional lymph node metastases, and extracranial distant metastases, respectively. Corresponding values for conventional staging procedures are 100, 83, and 81 percent (79). Of note, is the remarkable impact of ^{18}F-FDG PET on patient management that reached 29 percent in some series (78). The better performance of ^{18}F-FDG PET can be explained by the known high avidity of SCLC to ^{18}F-FDG owing to its high proliferation potential and short doubling time. This allows PET to detect occult tumor nests in normal sized lymph nodes, in bone/bone marrow and in visceral organs (Fig. 5). Furthermore, PET has the potential to exclude malignancy in many indeterminate lesions that may be detected by morphologic cross-sectional imaging modalities. This effect can certainly alleviate the need for a further diagnostic workup to prove or disprove such indeterminate radiologic findings. However, it has to be recognized that because of the high physiologic accumulation of ^{18}F-FDG in the brain, PET scans is not sensitive enough for the detection of brain metastases (78, 79). This suggests that, in patients who are found to have LD with PET, if brain metastases need to be excluded, a gadolinium-enhanced MRI scan of the brain remains necessary. Despite the limited number of published studies on the utility of ^{18}F-FDG PET/CT in SCLC, it is obvious that combining functional and anatomical data would maximize the specificity and consequently the overall diagnostic accuracy by virtue of referring each individual ^{18}F-FDG signal to its true origin. Recently, this hypothesis has been confirmed in a prospective study composed of 34 patients in which ^{18}F-FDG PET/CT yielded a specificity of 100 percent in comparison with 83 percent for ^{18}F-FDG PET alone (80).

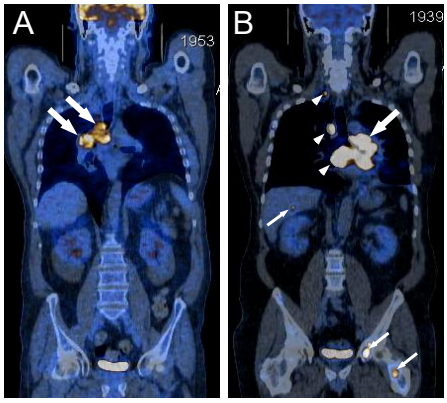

Figure 5 (A) Limited disease SCLC in a 53-year-old patient, PET/CT shows pathological 18F-FDG uptake in a right hilar mass, as well as in mediastinal lymph node metastases (arrows). (B) Extensive disease SCLC in a 67 -year- old patient, PET/CT shows pathological 18F-FDG uptake in a left hilar mass (arrow), with mediastinal and right supraclavicular lymph node metastases (arrow heads), and hepatic and osseous metastases (small arrows).

Therapy monitoring:

Being one of the most chemo-sensitive malignancies, tumor shrinkage under chemotherapy can easily be established in patients with SCLC using CT or MRI. Confirming complete remission of SCLC may allow prophylactic cranial irradiation to be performed, this has been shown to offer complete responders a significant improvement in both overall and disease free survival through reducing the potential occurrence of brain metastases (76). After treatment completion, however, the nature of any residual mass or lymph nodes can not be confidently determined by CT or MRI since post-therapy consolidation or fibrosis may structurally resemble viable tumor residue. In contrast, the metabolic characters of lesion detection by ^{18}F-FDG PET can be used to predict the true nature of any residual mass in SCLC (78). Consequently, early salvage therapy can be given to patients with persisting tumors, whereas, the administration of unnecessary toxic therapy to patients with a nonviable mass can be confidently withheld. In a recent study, ^{18}F-FDG PET could identify 5/5 (100 percent) patients with complete remission, 11/12 (91 percent) patients with residual disease and 3/3 (100 percent) patients with fulminating disease course under chemotherapy and was able to change therapeutic management in 15 percent of the studied population (78). Similar encouraging results were reported in another prospective study composed of 20 patients (81).

Detection of recurrence:

Despite a remarkable initial response rate to chemotherapy (45 to 75 percent in patients with LD and 20 to 30 percent in patients with ED), SCLC has a progression-free survival time of 12 months for patients with LD and approximately 4 months for those with ED (82). Recurrent SCLC after initial therapy has an extremely poor prognosis. Patients who have a relapse more than 4 months after the initial treatment have a 20 to 30 percent response to additional chemotherapy, whereas those with relapse less than 4 months after therapy have only 10 to 15 percent response rate. In patients with a relapse occurring later than 8 months after initial therapy, long term survival may be possible after second-line therapy (83). Therefore, a close follow-up schedule for patients with SCLC during the first 3 years after therapy has been recommended (83). Recurrent SCLC can be revealed by clinical symptoms, physical examination, laboratory tests, chest radiography, and computed tomography. The role of ^{18}F-FDG PET and PET/CT is certainly promising but, unfortunately, has not been well studied in recurrent SCLC. However, since ^{18}F-FDG PET is known by its very high sensitivity for the detection of primary SCLC, its integration in the follow-up schedule of this patient group may allow early identification of tumor recurrence in order to apply the appropriate therapeutic intervention before further disease progression. Whether the integration of PET results will ameliorate the overall outcome of recurrent SCLC, needs to be established.

Radiation Therapy Planning:

An essential parameter for careful planning of radiotherapy is to know whether the primary tumor and the nodal metastases will be included within a suitable radiation port in such a manner that critical organ doses are not exceeded. For that purpose, cross sectional imaging modalities like CT and MRI have widely been applied. However, CT and MRI are not always able to delineate the limits between malignant tumor and adjacent normal tissue and the same hold true for determining regional lymph node involvement. Radiation treatment planning based only on^{2} CT or MRI

findings is likely to miss regions of macroscopic tumor in some patients and may lead to the irradiation of unnecessarily large volumes in others (84). Incomplete irradiation may cause poor local control and high rate of relapse, whereas, irradiating adjacent normal tissue (i.e., collapsed lung) may result in a considerable morbidity besides the non ignorable risk of developing a second radiation induced primary tumor that may adversely affect long-term outcome. The innovation of 3-dimentional radiotherapy and intensity-modulated radiation therapy (IMRT) has enabled the delivery of radiation doses with high degree of accuracy. The implementation of these 2 modalities, however, requires an adequate selection and delineation of target volumes on the basis of a reliable imaging procedure (85). One imaging modality with the potential to distinguish accurately between benign and malignant lesions and to precisely define the extent of disease is whole-body PET with ^{18}F-FDG. In a recent study of 101 patients, the incorporation of ^{18}F-FDG PET results into radiotherapy planning and the use of radiotherapy simulation using PET/CT image fusion has been shown to modify the size of the gross tumor volume in up to 49 percent of cases (84). These results can be reasoned by the unique ability of ^{18}F-FDG PET/CT to discriminate between tumor tissue and atelectasis or necrotic areas and by its high sensitivity and negative predictive value for the detection or exclusion of disease spread to mediastinal lymph nodes regardless the size of these nodes (85). Another study went further to conclude that contrast enhanced PET/CT was superior to low dose unenhanced PET/CT in the assessment of lesion delineation especially in case of mediastinal and chest wall invasion. Furthermore, many groups have reported a significant reduction in both inter- as well as intra-observer variability when ^{18}F-FDG PET data was available for tumor volume delineation (86). Despite these encouraging results, the impact on treatment outcome and the cost-effectiveness of PET/CT remain to be established.

Risk Stratification/Outcome Prediction:

The overall outcome of NSCLC is strongly related to the international TNM staging system. However, some patients with relatively earlier TNM stage infrequently develop post operative disease relapse and die ahead of their illness. Understanding the biological behavior of lung cancer may help to identify high-risk patient groups who could benefit from alternative or aggressive therapeutic pathways aiming at an optimal disease free survival. Since ^{18}F-FDG PET has the potential to gauge the global metabolic state of each individual tumor, it is obvious that it could play a pivotal role in predicting the outcome of patients with lung cancer as it has been previously shown for other tumors types like breast, head and neck, and pancreatic cancers in addition to lymphoma and sarcoma (87-89). Using different cutoff points ranged from 5 to 10, the standardized uptake value (SUV), which is a semiquantitative measure of ^{18}F-FDG uptake, has been proven an independent prognostic factor in NSCLC whatever had been the applied therapeutic approach (89). In fact, patients who harbored tumors that are characterized by a relatively low SUV, such as focal form of bronchioloalveolar carcinoma and well differentiated adenocarcinoma, had a significantly better disease free survival rate than those who had tumors that display higher values. In a study involved 498 patients with lung cancer, gradual increase in SUV was associated with a remarkable decrease in patients' survival that reached 37 percent at 24 months for those with tumors that displayed SUV between 17

and 48 (90). Recently, other investigators have confirmed the same observations for SCLC as well as for any residual tumor tissue of pulmonary origin after concluding chemo- or radio-therapy (91).

Future Perspectives:

The development trials of alternative radiotracers and diagnostic tools for lung cancer are of great clinical importance. For instance, the proliferation potential of lung cancer can be assessed in vivo by using tracers that target the process of DNA synthesis like 3'-^{18}F-fluoro-3'-deoxy-L-thymidine (^{18}F-FLT). Although the sensitivity of ^{18}F-FDG has far surpassed that of ^{18}F-FLT in initial staging of lung cancer (92), the tumoral uptake of ^{18}F-FLT has been shown to correlate with Ki-67 labeling index, a distinguished criterion that may permit ^{18}F-FLT PET to monitor treatment of lung cancer with cytostatic drugs (93). Another radiopharmaceutical of potential prognostic benefit is ^{18}F-fluoromisonidazole (^{18}F-FMISO). This tracer has been shown to be a true hypoxia marker both in vitro and in vivo (93). Identifying the regional distribution of tumor hypoxia is mandatory for careful radiotherapy planning. Preliminary results have revealed that a steady tumoral accumulation of ^{18}F-FMISO over the time is a predictor of unsuccessful radiotherapy and high recurrence rate that exceeds 90 percent (95). Identifying this high risk group before radiotherapy planning may allow them to benefit from intensified treatment protocols to obtain long term disease remission.

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