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Value of whole-body FDG PET in management of lung cancer

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^{18}F-fluorodeoxyglucose (FDG) PET imaging provides physiologic and metabolic information that characterizes lesions that are indeterminate by CT. FDG PET imaging is sensitive to the detection of lung cancer in patients who have indeterminate lesions on CT, whereas low grade malignancy such as bronchioloalveolar carcinoma and carcinoid may be negative on FDG PET. The specificity of PET imaging is less than its sensitivity because some inflammatory processes, such as active granulomatous infections, avidly accumulate FDG. This possibility should be kept in mind in the analysis of PET studies of glucose metabolism aimed at differentiating malignant from benign solitary pulmonary nodules. FDG uptake is considered to be a good marker of cell differentiation, proliferative potential, aggressiveness, and the grade of malignancy in patients with lung cancer. FDG PET accurately stages the distribution of lung cancer. Several studies have documented the increased accuracy of PET compared with CT in the evaluation of the hilar and mediastinal lymph-node status in patients with lung cancer. Whole-body PET studies detect metastatic disease that is unsuspected by conventional imaging. Management changes have been reported in up to 41% of patients on the basis of the results of whole-body studies. Whole-body FDG PET is also useful for the detection of recurrence. Several studies have indicated that the degree of FDG uptake in primary lung cancer can be used as an independent prognostic factor. Thus, whole-body FDG PET is clinically very useful in the management of lung cancer.

Key words: ^{18}F-fluorodeoxyglucose, positron emission tomography, lung cancer

INTRODUCTION

THE POTENTIAL VALUE of positron emission tomography with ^{18}F-fluorodeoxyglucose (FDG PET) for diagnosing and staging cancer has been investigated over the past 10 years. The initial studies were done in patients with suspected or proven lung cancer. In Japan, lung cancer claimed approximately 55,000 lives in 2001. Health insurance began coverage of FDG PET for the diagnosis, staging, and restaging of non-small cell lung cancer in April, 2002. By then, many large studies had shown the diagnostic accuracy of FDG PET in the investigation of pulmonary nodules, in staging mediastinal lymphnode involvement and distal metastatic disease, in the detection of persistent or recurrent disease, and to assess its value in determining prognosis and its cost effectiveness in lung cancer.[1–3] This review will briefly survey the value of whole-body FDG PET scanning in the management of lung cancer.

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Factors Affecting FDG Uptake in Lung Cancer

Glut-1 is a major glucose transporter expressed in non-small cell lung cancer, and the contribution of the other transporters to the overall glucose metabolism in non-small cell lung cancers appears to be minor.[4] The abundance and cellular localization of Glut-1, as compared to other glucose transporters, suggest that Glut-1 may be the chief transporter for the movement of sugars into cancer

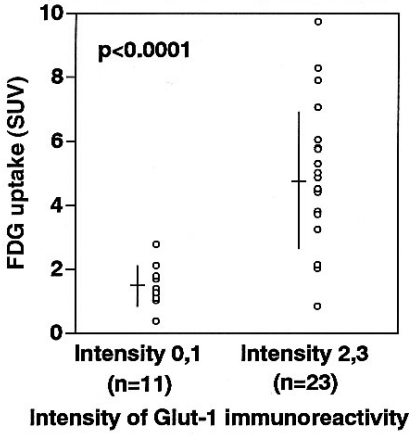


Fig. 1 Correlations between intensity of Glut-1 immunoreactivity and FDG uptake (SUVs). FDG uptake was significantly different between the groups intensities 0, 1 and intensities 2, 3 ($p < 0.0001$).

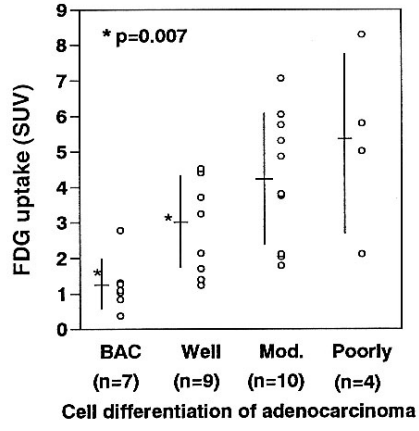


Fig. 2 Relationship between degree of cell differentiation and FDG uptake (SUVs) in lung adenocarcinoma. The mean SUV of bronchioloalveolar carcinomas was significantly lower than that of poorly differentiated adenocarcinomas. BAC: bronchioloalveolar carcinoma, Well: well differentiated adenocarcinoma, Mod: moderately differentiated adenocarcinoma, Poorly: poorly differentiated adenocarcinoma.

cells.[4] Glut-1 expression correlated with FDG uptake in lung cancer (Fig. 1).[5] The rate of glucose uptake via glucose transporter can be regulated under conditions related to cell proliferation, differentiation, and transformation.[6] Changes in the rates of glucose uptake and overexpression of glucose transporters are also associated with adaptation to hypoxia partly due to increased dependency on glycolysis as an energy source,[7–9] a condition that may arise in rapidly growing tumors.[10] So the state of Glut expression can reflect the biologic behavior of cancer cells. For example, according to Younes et al.[11] Glut-1 expression increased in breast carcinoma showing higher histologic grade and proliferative activity, as detected by Ki-67 immunostaining. Ogawa et al.[12] reported that Glut-1 amplification correlated with proliferative cell nuclear antigen staining in lung cancer, and the survival period of patients whose tumors showed Glut-1 amplification was significantly shorter than that of patients whose tumors did not. Younes et al.[13] also reported that the appearance of Glut-1 positive clones is associated with aggressive tumor behavior, and Glut-1 is a significant poor prognosis indicator in cases of non-small cell lung cancer. Enhanced FDG uptake via overexpression of Glut-1 could be related to the clinicopathologic manifestation connecting abnormal biologic behaviors of cancer cells.

The influence of hypoxia on FDG accumulation in cultured human cancer cells was reported by Clavo et al.[7] FDG accumulation is increased in hypoxic cancer cells, in part due to increased membrane expression of the Glut-1 glucose transporter[7,14] Kubota et al. reported that FDG uptake was increased in prenecrotic (hypoxic) cells at the peripheral rim of necrosis.[14] The finding of Clavo et al. was consistent with that of Waki et al.[15] with Glut activity, and not hexokinase activity, being rate-limiting for FDG uptake in cancer cells.

Hexokinase I and II, hexokinase II in particular, are indeed glucose metabolism regulators in cancer cells.[16] An *in vitro* and an *in vivo* study[15,17] have both suggested that Gluts, especially Glut-1, are responsible for [^{3}H]-2-deoxyglucose and FDG uptake rather than the total amount of cellular hexokinase activity. However, some controversy surrounds this finding. In an *in vivo* macroautoradiographic study, Yutani et al.[9] reported that [^{14}C]deoxyglucose uptake may not be determined only by the amount of Glut-1 expression. In their study, some necrotic cancer cells in necrotic areas were strongly stained by anti-Glut-1 antibody, whereas deoxyglucose uptake was almost absect in necrotic areas. In an *in vitro* study, Aloj et al.[18] reported that FDG uptake correlates more closely with the FDG phosphorylating activity of mitochondrial preparations rather than the level of expression of the Glut-1 or hexokinase I and II genes. They emphasized that phosphorylating activity in the mitochondria plays a more important role in determining how much FDG is retained by cells and perhaps glucose metabolic rates. However, Torizuka et al.[19] have shown, by kinetic modeling of clinical FDG PET studies, that the phosphorylation step appears to be rate determining in the uptake of FDG in primary breast cancers but not so in primary lung cancers, suggesting that there may be differences among cancers derived from different tissues in terms of how FDG uptake and perhaps glucose metabolism are controlled by the cells.

Some studies also suggest that the lack of glucose-6-phosphatase activity in tumors plays a role in determining [^{3}H]-2-deoxyglucose retention by preventing dephosphorylation of [^{3}H]-2-deoxyglucose-6-P to [^{3}H]-2-deoxyglucose.[20] A variety of factors besides Glut-1 expression could be related to FDG uptake in lung cancer. For example, phosphorylating activity in the mitochon-

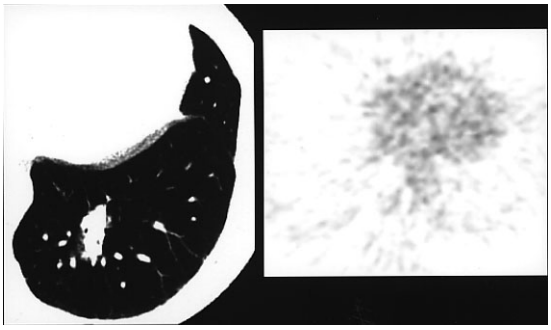


Fig. 3 Bronchioloalveolar carcinoma. 2.2 cm. CT image shows nodule in left lung, mimicking organized pneumonia. FDG PET shows no significant accumulation in the tumor (SUV 0.84).

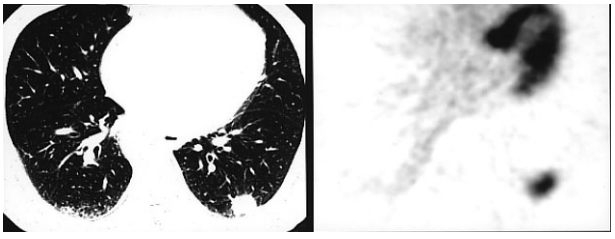


Fig. 4 Adenocarcinoma, poorly differentiated. 2.5 cm. CT image shows nodule in left lung. FDG PET shows hot accumulation in the tumor (SUV 6.13).

dria and the diminished rate of dephosphorylation could be related to FDG uptake. The question of the relative importance of transport versus phosphorylating activity in the mitochondria and the diminished rate of dephosphorylation is still unanswered.

Tissue Characterization of Lung Cancer

FDG uptake is considered to be a good marker of cell differentiation, proliferative potential, aggressiveness, and the grade of malignancy in patients with lung cancer. A negative correlation was observed between FDG uptake and the degree of cell differentiation in adenocarcinoma of the lung (Fig. 2).[21,22] The mean SUV of well differentiated adenocarcinomas was significantly lower than that of poorly differentiated adenocarcinomas (Figs. 3, 4). Bronchioloalveolar carcinoma is a form of lung cancer exhibiting many features that distinguish it from all other forms of lung cancer, including non-bronchioloalveolar adenocarcinoma. Bronchioloalveolar carcinoma, which is a well differentiated tumor, had a significantly lower SUV than that of non-bronchioloalveolar carcinoma.[21] Recent evidence suggests that the number of cases of adenocarcinoma of the lung has increased dramatically in the last decade and that this overall increase is largely due to an increase in bronchioloalveolar carcinoma.[23,24] It is known that the mean doubling time for bronchioloalveolar carcinoma is longer than that for non-bronchioloalveolar

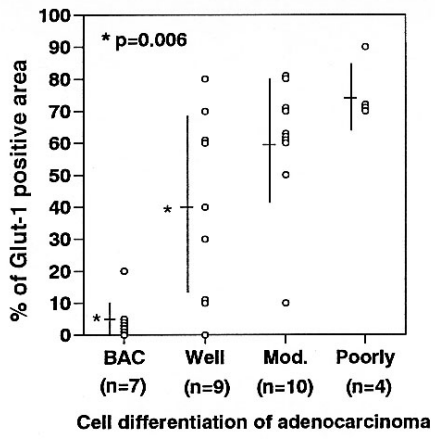


Fig. 5 Relationship between degree of cell differentiation and the percentage of Glut-1-positive area in lung adenocarcinoma. The mean Glut-1 expression of bronchioloalveolar carcinomas was significantly lower than that of poorly differentiated adenocarcinomas. BAC: bronchioloalveolar carcinoma, Well: well differentiated adenocarcinoma, Mod: moderately differentiated adenocarcinoma, Poorly: poorly differentiated adenocarcinoma.

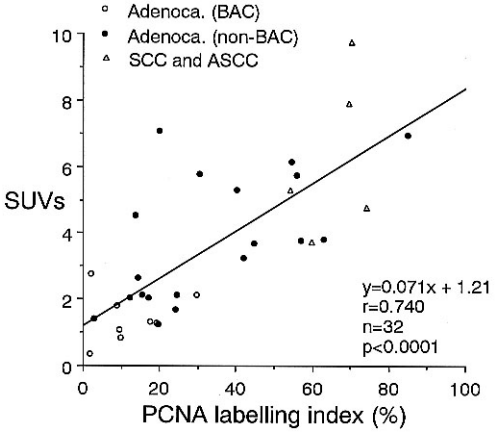


Fig. 6 FDG uptake (SUVs) correlated significantly with PCNA labeling index ($r = 0.740$, $p < 0.0001$). Adenoca.: adenocarcinoma, BAC: bronchioloalveolar carcinomas, SCC: squamous cell carcinoma, ASCC: adenosquamous cell carcinoma.

adenocarcinoma.[25] The proliferative potential for bronchioloalveolar carcinoma is lower than that for non-bronchioloalveolar carcinoma.[26] Bronchioloalveolar carcinoma also differs from non-bronchioloalveolar adenocarcinoma in that metastases are more frequent.[24] Noguchi et al.[27] reported that localized bronchioloalveolar carcinoma without foci of active fibroblastic proliferation showed no lymph node metastases and promises the most favorable prognosis of all adenocarcinomas. We found that Glut-1 expression was negative in 6 of 7 bronchioloalveolar carcinomas, and both FDG uptake and Glut-1 expression were significantly lower in bronchioloalveolar carcinomas than in non-bronchioloalveolar carcinomas.[5]

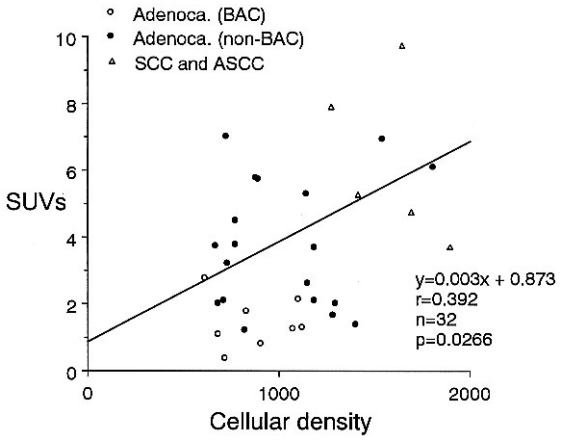


Fig. 7 FDG uptake (SUVs) correlated only weekly with cellular density (r = 0.392, p = 0.0266). Adenoca.: adenocarcinoma, BAC: bronchioloalveolar carcinomas, SCC: squamous cell carcinoma, ASCC: adenosquamous cell carcinoma.

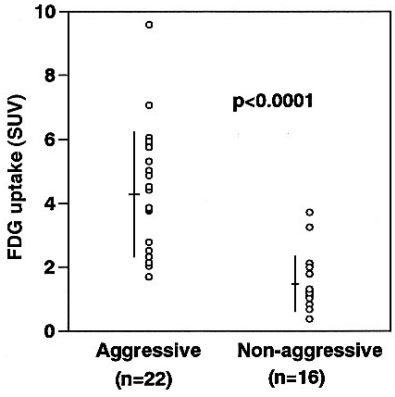


Fig. 8 Comparison of FDG uptake (SUVs) between aggressive and non-aggressive adenocarcinomas. The mean SUV of aggressive adenocarcinomas was higher than that of non-aggressive ones.

Our study also suggested that the degree of cell differentiation may correlate with Glut-1 expression and FDG uptake in adenocarcinoma of the lung (Figs. 2, 5),[25] and the increased expression of Glut-1 correlated with the lesser differentiation of adenocarcinoma.[5,28,29]

In a microautoradiographic study, Kubota et al. showed that FDG uptake is higher in faster-growing than in slow-growing tumors.[30] In a clinical study, lung tumor growth estimated by doubling time correlations with glucose metabolism measured by FDG PET.[31] FDG uptake also correlated with proliferative potential as assayed by PCNA and Ki-67 labeling index (Fig. 6).[22,32] FDG uptake was related to cell proliferation rather than to the cellular density of non-small cell lung cancer (Fig. 7),[32] while FDG uptake was also related to cellular density.[33]

The distribution of FDG uptake in aggressive adenocarcinomas of the lung, as revealed by PET, was significantly higher than that in the non-aggressive ones (Fig. 8).[34] The degree of FDG uptake in the primary lung lesion was significantly associated with the presence of aggressiveness (pleural involvement, vascular invasion or lymphatic permeation) as determined by pathology and prognosis in pulmonary adenocarcinoma. Adenocarcinomas with a high SUV value have a significantly higher likelihood of aggressiveness than those with a low SUV value, and FDG PET may be used as a non-invasive diagnostic technique to aid in measuring aggressiveness and prognosis in patients with adenocarcinoma of the lung. Younes et al.[13] also reported that the appearance of Glut 1-positive clones in stage I non-small cell lung cancer is associated with aggressive biological behavior. These results are in agreement with Kubota's report[35] of differentiation between invasive and non-invasive thymoma by using FDG PET. This study demonstrated that invasive thymomas showed a higher SUV value than the non-invasive ones.

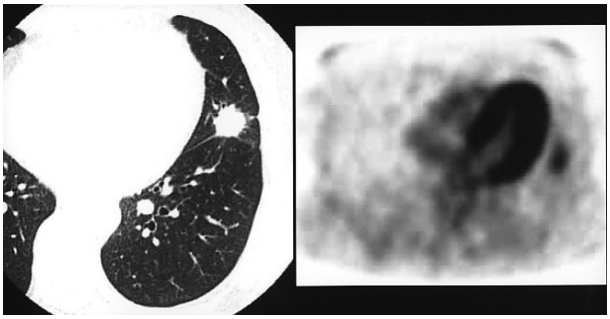


Fig. 9 Inflammatory nodule. CT image shows nodule in left lung, mimicking lung cancer. FDG PET shows intense accumulation in the nodule. The nodule disappeared 3 months later.

Solitary Pulmonary Nodules

Differential diagnosis of lung tumors has been studied extensively with both computed tomography (CT) and FDG PET. It has been established that FDG PET is clinically very useful and that its diagnostic accuracy is higher than that of CT. FDG PET has reached widespread application in the assessment of pulmonary nodules. Forty studies that included 1,474 focal pulmonary lesions met the inclusion criteria for a meta-analysis on the accuracy of FDG PET for the diagnosis of pulmonary nodules and mass lesions.[36] The maximum joint sensitivity and specificity, at which sensitivity and specificity were equal, was 91.2%. Physicians interpreting FDG PET scans generally operate at a point on the summary receiver-operating-characteristics (ROC) curve that corresponds to a sensitivity of 96.8% and a specificity of 77.8%. Most of the data were on nodules 1 cm or greater, and the diagnostic accuracy was the same irrespective of the size of the lesion and method of image analysis (i.e., semiquantitative or qualitative).

Patients with small tumors,[37] as well as those with slow growing tumors such as bronchioloalveolar carcinomas

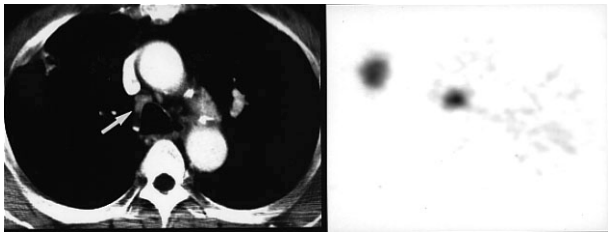


Fig. 10 Adenosquamous cell carcinoma. pT2N2M0. CT image shows normal-sized lymph node (*arrow*) in the mediastinum. FDG PET shows intense FDG uptake by the lymph node. Metastatic cancer was proven in the right mediastinal nodes of this patients.

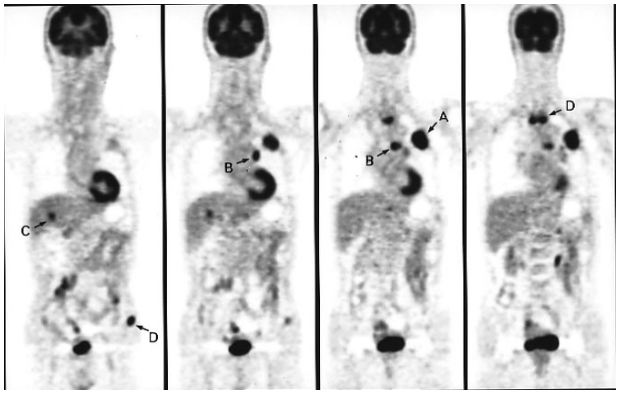


Fig. 11 Adenocarcinoma. CT2N2M1. Whole-body FDG PET shows intense FDG uptake by primary tumor (A), lymph node metastases (B), liver metastasis (C), and bone metastases (D).

(Fig. 3),[21,37–39] and carcinoid tumors,[37,40] were more likely to have a negative PET scan. Also FDG uptake is not specific for cancer. High FDG accumulation is seen in macrophages and granulation tissues by microautography,[41,42] Some active infectious or inflammatory lesions may have significant uptake of FDG.[43] Sarcoidosis,[44] bacterial pneumonia,[45] tuberculous pneumonia, tuberculoma,[46] cryptococcosis, histoplasmosis, aspergillosis[47] and other active infections[48] may have substantial FDG accumulation and SUV values in the abnormal range (Fig. 9). This possibility should be kept in mind in the analysis of PET studies of glucose metabolism aimed at differentiating malignant from benign solitary pulmonary nodules.

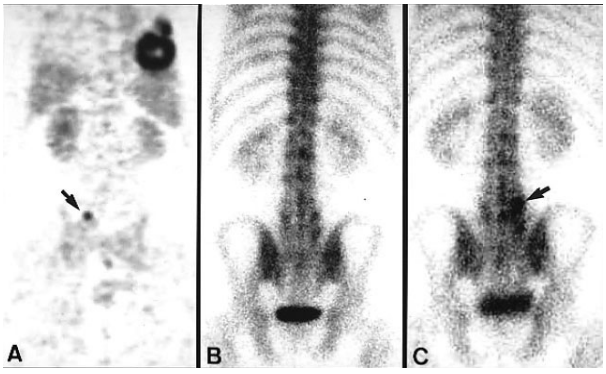
Dual Time Point Scanning

Kubota et al.[49] compared whole-body FDG PET at 1 and 2 hr after injection, in patients with lung cancer. They found that all malignant tumors exhibited a higher FDG uptake at 2 hr than at 1 hr, and the sensitivity was improved. Ukena et al.[50] also recommended a longer delay between injection of FDG and PET scanning, which yields a higher sensitivity than in the cited studies which started at 45 min, and 19/22 cases with a localized form of bronchioloalveolar carcinoma were correctly identified at 90 min. Similar results have been reported by Salman et al.[51] Matthies et al.[52] also compared the diagnostic accuracy of standard FDG PET scanning with those of dual time point FDG PET scanning. Dual time point scanning with a threshold value of 10% increase between scan 1 at 70 min and scan 2 at 123 min reached a sensitivity of 100%. They concluded that dual time point FDG PET results in a very high sensitivity for detection of malignant lung tumors. Zhuang et al.[53] investigated dual time point FDG PET imaging for differentiating malignant from inflammatory processes. The SUVs of delayed images from the known malignant lesions compared with those of earlier scans increased over time (19.2 ± 9.6%). By contrast, the SUVs of benign lung nodules decreased slightly over time (–6.3 ± 8.1%). Dual time imaging may be useful in distinguishing malignant from benign lesions. Higashi et al.[54] evaluated the relationship between temporal changes in FDG uptake and expression of hexokinase or glucose transporter. Retention index obtained from dual-phase FDG PET can predict hexokinase II and demonstrate that the SUV (at 1 h) has a positive correlation with Glut-1 expression but not with hexokinase II expression.

Staging

Detection of lymph node or distant metastases in known cancer patients using a whole-body imaging technique with FDG-PET has become a good indication for PET (Figs. 10, 11). A meta-analysis has also been done to compare the ability of PET with that of computed tomography (CT) to stage the mediastinum.[55] This study analyzed the staging performance of PET in 14 studies that included 514 patients and of CT in 29 studies that included 2,226 patients. From summary ROC curves and pooled point estimates of diagnostic performance, FDG PET was found to be significantly more accurate than CT for identifying nodal metastases. The mean sensitivity and specificity were 79% and 91%, respectively, for PET and 60% and 77%, respectively, for CT. However, in healthy subjects, fifty of 179 (28%) subjects had visually increased FDG uptake in the hilar regions with total 84 hilar lymph nodes.[56] This possibility should be kept in mind in the analysis of PET studies aimed at detecting nodal metastases.

Several studies have shown that FDG PET is more accurate than CT and radionuclide bone scans for staging lung cancer (Fig. 12). Bury et al.[57] evaluated the utility of FDG PET for the detection of bone metastasis in 110 patients with non-small cell lung cancer. Radionuclide bone scanning correctly identified 54 of 89 cases without osseous involvement and 19 of 21 osseous involvements. On the other hand, FDG PET correctly identified the absence of osseous involvement in 87 of 89 patients and



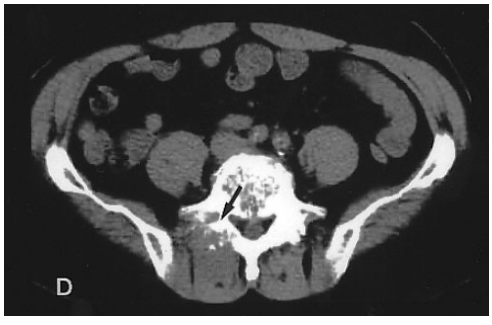


Fig. 12 Squamous cell carcinoma, poorly differentiated. Osseous involvement. Whole-body FDG PET shows a hot spot (*arrow*) in lumbar vertebra (A). However, bone scintigraphy (posterior view) shows no significant accumulation (B). Two months later, bone scintigraphy (posterior view) shows significant accumulation (*arrow*) in the lumbar vertebra (C). CT image shows bone destruction of the lumbar vertebra (*arrow*) (D).

the presence of bone metastasis in 19 of 21 patients. PET and bone scanning had, respectively, an accuracy of 96% and 66% in the evaluation of osseous involvement. Hsia et al.[58] also concluded that FDG PET had the same sensitivity and a better accuracy than those of Tc-99m MDP bone scan to detect metastatic bone lesions in patients with non-small cell lung cancer and suspected to have stage IV disease.[58]

Elasmus et al.[59] assessed the usefulness of FDG PET when differentiating benign from metastatic adrenal masses in patients with lung cancer and adrenal mass. The sensitivity for detecting metastatic disease to the adrenal gland was 100%, and the specificity was 80%.

In a study of 100 patients with newly diagnosed non-small cell lung cancer, FDG PET was accurate in 83% of patients and conventional imaging was accurate in 65%.[60] Nine patients had metastases detected by PET but not by conventional imaging. Vesselle et al.[61] evaluated the accuracy and anatomic information provided by FDG PET and its impact on improving the accuracy of surgical staging. A total of 142 patients with potentially resectable non-small cell lung cancer were imaged with PET. PET revealed unsuspected distal metastases in 24 of 142 patients (16.9%) and unsuspected pleural implants in 6 others. PET correctly differentiated resectable stages IA through IIIA (N1) from stages IIIA (N2) through IV in 88.7% of cases. Similar results have been reported by other studies.[62–66] MacManus et al.[63] prospectively studied 153 patients with unresectable non-small cell lung cancer who were candidates for radical radiotherapy after conventional staging and had PET scans. After PET, 107 patients actually received radical therapies, 46 patients received palliative treatment because of PET-detected distant metastasis or extensive locoregional disease. For radically treated patients, post-PET stage but not pre-PET stage was strongly associated with survival. Staging that incorporated PET provided a more accurate prognostic stratification than did staging based on conventional investigations. Eschmann et al.[64] also evaluated FDG PET for staging of advanced non-small cell lung cancer before combined neoadjuvant radio-chemotherapy. One hundred and one patients with stage IIIA or B according to conventional staging were studied. The PET findings led to a change in treatment in 29 patients (29%). Twenty-five patients were excluded from radio-chemotherapy due to the presence of previously unknown distant metastases. FDG PET is the most accurate non-invasive diagnostic procedure for the staging of advanced non-small cell lung cancer. Tinteren et al.[66] conducted a randomized controlled trial in patients with suspected non-small cell lung cancer, who were scheduled for surgery after conventional work-up, to test whether PET with FDG reduces the number of futile thoracotomies. In this study, in which the 188 patients were randomly allocated to either conventional work-up or conventional work-up plus PET, there was a 51% relative reduction (20 patients) in futile thoracotomies among the latter group. The addition of FDG PET to conventional work-up prevented unnecessary surgery in 20% of patients with suspected non-small cell lung cancer. Justified surgery was not decreased by the PET scan results because PET improved identification of patients who would benefit from thoracotomy.

In staging not only non-small cell lung cancer but also small cell lung cancer, FDG PET is a substantial tool for the discrimination of limited and extensive disease.[67–69] Schumacher et al.[67] estimated the role of FDG PET in staging small cell lung cancer, its efficacy in the discrimination of limited disease and extensive disease. In contrast to the results of conventional staging, FDG PET indicated extensive disease resulting in an upstaging in 7 of 24 patients.

Seltzer et al.[70] determined referring physicians' perspectives on the impact of FDG PET on staging and management of 274 patients with lung cancer. The primary reasons for PET referral were staging of lung cancer in 61% of patients, diagnosis in 20%, and monitoring of therapy in 6%. Physicians reported that PET caused them to change their decision on clinical stage in 44% of all patients: The disease was upstaged in 29% and downstaged in 15%. PET resulted in intermodality management change

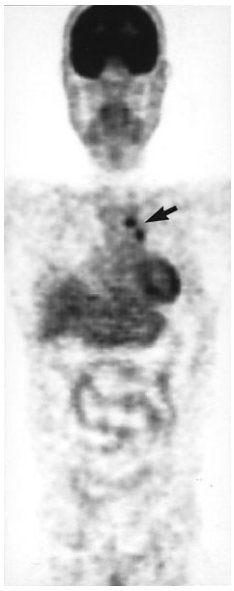


Fig. 13 Whole-body FDG PET for the detection of lung cancer recurrence. Adenocarcinomas in the bilateral lungs was resected. Three years later, elevation of CEA to 97 suggested recurrence. Whole-body FDG PET shows intense accumulations (*arrow*) in mediastinal lymph nodes.

(e.g., surgery to medical, surgery to radiation, and medical to no treatment) in 39% of patients. Similar results have been reported by other studies.[71]

Persistent or Recurrent Disease

After potentially curative therapy of non-small cell lung cancer, masses or symptoms suggestive of relapse are common but may be difficult to characterize. Early detection of recurrent lung cancer is important because salvage therapies are available for localized recurrence. Whole-body FDG PET is also useful for the detection of recurrence (Fig. 13). Patz et al.[72] studied 43 patients undergoing FDG PET scanning between 4 and 182 months after initial diagnosis and treatment of bronchogenic carcinoma. Thirty-five patients had recurrent or persistent cancer, documented by pathologic analysis in 25 patients or clinical and radiographic progression in 10 patients. The median SUV in the 35 patients who had recurrent or persistent cancer was 7.6, whereas the median SUV in the patients who had fibrosis after therapy was 1.6. Using an SUV value of 2.5 to indicate malignancy, FDG PET had a sensitivity of 97% and specificity of 100% for detection of persistent or recurrent disease. In another study of 39 lesions in 38 patients studied by FDG PET imaging after therapy for cancer, a sensitivity of 100% and a specificity of 62% were found.[73] FDG PET shows high diagnostic accuracy in detecting recurrent lung cancer in patients with prior curative tumor treatment, but cannot substitute for pathological diagnosis.[74] Hicks et al.[75] also evaluated whether FDG PET is useful and predictive of outcome in patients with recurrent non-small cell lung cancer. PET induced a major management change in 40 of 63 patients (63%) with suspected relapse. Both the presence and the extent of relapse on PET were highly significant prognostic factors. Akhurst et al.[76] compared FDG PET imaging with surgical staging of non-small cell lung cancer after induction therapy. Fifty-six patients with non-small cell lung cancer underwent chemotherapy (40 patients), chemoradiotherapy (11 patients), or radiation alone (5 patients) followed by PET and operations. PET after induction therapy accurately detected residual viable primary tumor, but not the involvement of mediastinal lymph nodes.

FDG PET better assesses the status of disease and stratifies prognosis than does conventional staging, affects patient management, and should be incorporated into paradigms for suspected recurrence of non-small cell lung cancer.

Monitoring Radio/chemotherapy

FDG PET is useful for monitoring the therapeutic response of tumor tissues in lung cancer. Radiotherapy results in injury to DNA, RNA, protein and membranes of cancer cells, so that altered metabolism and cell death are reflected in a reduction in methionine and thymidine uptake, which procedes the autolysis of cells observed as necrosis.[2] In monitoring radiotherapy, changes in FDG uptake correlate with the number of viable cancer cells,[2] and the reduction of viable tumor tissue is reflected by decreased FDG uptake.[2] No visible reduction of tumor volume is evident until a large part of the necrotic tissue has been removed.[2] FDG PET enables functional evaluation of tumor viability to assess the therapeutic effects on tumor tissue, earlier than morphologic evaluation of tumor volume reduction by CT scan.[2] The decrease in the uptake after therapy tended to be more prominent in the PR group than in the NC group.[77] Kubota et al.[78–81] compared tumor volume, amount of viable tumor tissue, and tracer uptake, after experimental radiotherapy in a rat tumor model. Thymidine and methionine uptake exhibited a rapid and sensitive response to irradiation, preceding both volumetric shrinkage and necrotic extension. Changes in FDG uptake correlate with the number of viable cancer cells. Reduction of FDG uptake is a sensitive marker of viable tissue. However, to detect and differentiate viable cancer cells in a residual tumor mass after radiotherapy, PET using ^{11}C-methionine or ^{11}C-thymidine may have some advantages over FDG, especially if the residual tumor includes larger areas of necrosis.[82]

In *in vitro* studies, FDG uptake per cancer cell increased at 24 and 48 hr after irradiation,[83,84] while the *in vitro* system differs from *in vivo* systems due to the absence of a blood supply *in vitro*, a lack of infiltrating

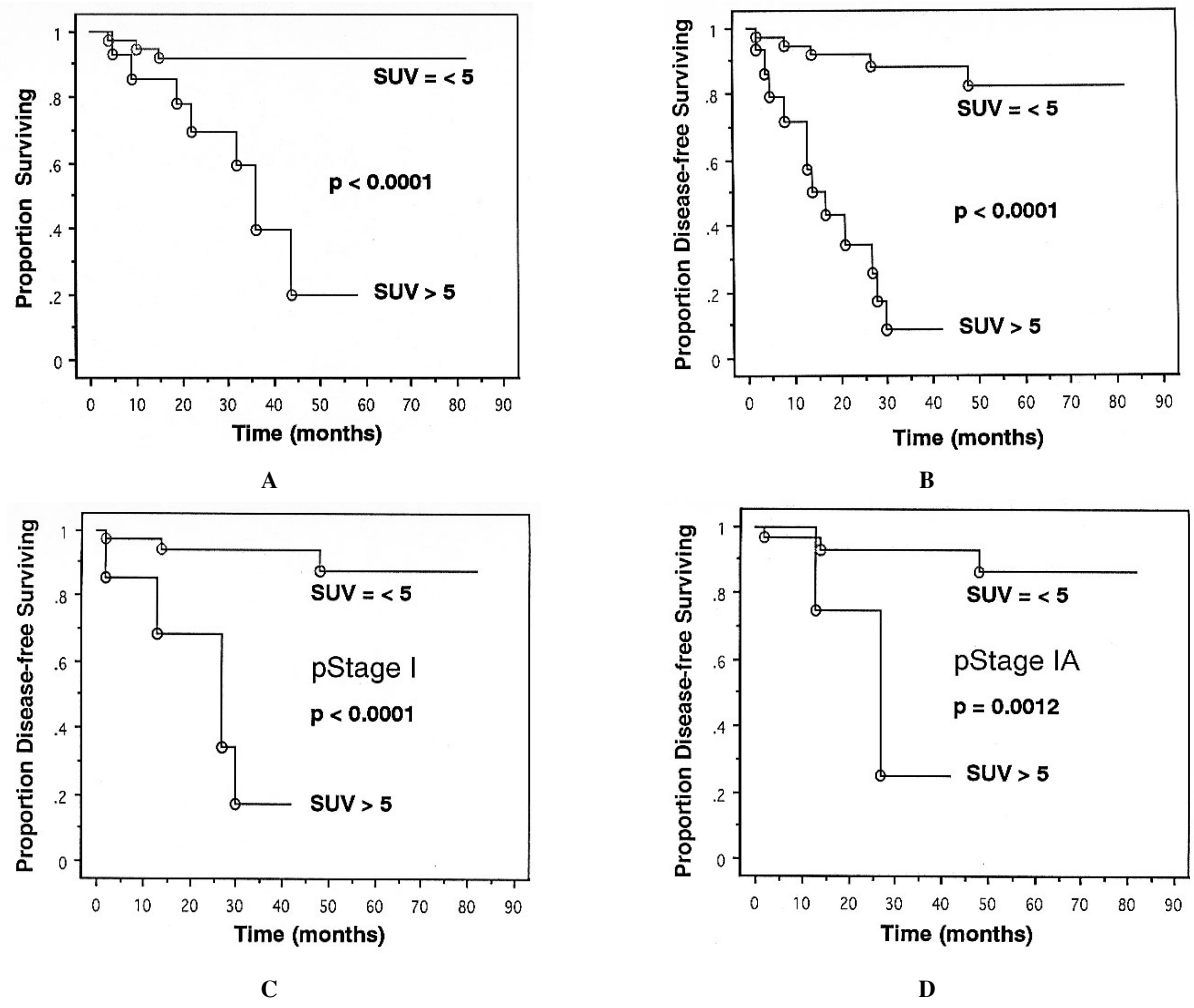


Fig. 14 (A) Kaplan-Meier survival curves of 57 patients with surgically resected non-small cell lung cancer (NSCLC). (B) Kaplan-Meier disease-free survival curves of all 57 patients. (C) Kaplan-Meier disease-free survival curves of 46 patients with pathologic stage I NSCLC. (D) Kaplan-Meier disease-free survival curves of 38 patients with pathologic stage IA NSCLC. Curves reveal clear demarcation, with poor survival or disease-free survival of subjects in high-SUV group.

leukocytes and other factors. Early assessment of the response to radiotherapy by PET with FDG may be complicated by this increase in tracer uptake postirradiation.[83] The activity determined within a certain tumor volume is a balance between the increased FDG uptake by surviving cells after therapy and the lack of FDG uptake by dead cells, which still contribute to the tumor volume.[84] The increase in FDG accumulation occurred only in radiosensitive tumors but not in tumors with low radiosensitivity, as early as 2 hr following irradiation.[85] This suggests that the increase was independent of recovery phenomena following radiation damage.[85] Maruyama et al.[86] reported a FDG PET study of brain tumor patients before and 4 hr after a 24–32 Gy single dose of stereotactic radiotherapy. FDG uptake (influx constant) in irradiated tumors exhibited a 30 ± 14% increase after radiotherapy. This increase was significantly correlated with decreased size of the irradiated tumors, as revealed by follow-up with CT and MRI.[86] Serial FDG PET could be a potential tool for predicting the outcome of radiotherapy by detecting hyperacute changes in tumor glucose metabolism.[86]

Choi et al.[87] estimated the dose-response relationship between the probability of tumor control on the basis of pathologic tumor response and residual metabolic rate glucose in response to preoperative chemoradiotherapy in locally advanced non-small cell lung cancer. The correlation between the gradient of residual metabolic rate of glucose after chemoradiotherapy and pathologic tumor response is an inverse dose-response relationship. Ryu et al.[88] also investigated the utility of FDG PET for restaging of the primary and mediastinal nodal lesions 2 weeks after the completion of preoperative chemoradiotherapy in patients with stage III non-small cell lung cancer. For the primary lesions, SUV based analysis has high sensitivity but limited specificity for detecting residual tumor. In contrast, for restaging of mediastinal lymph nodes, FDG

PET is highly specific, but has limited sensitivity.

Radiation Planning

Three-dimensional conformal radiation therapy commonly uses CT to accurately delineate the target lesion and normal tissues. Imaging with FDG PET in conjunction with CT can improve the accuracy of lesion definition. Erdi et al.[89] investigated the potential benefits of incorporating PET data into the conventional treatment planning of non-small cell lung cancer. The incorporation of PET data improves definition of the primary lesion by including positive lymph nodes into the planning target volume. Thus, the PET data reduces the likelihood of geographic misses and hopefully improves the chance of achieving local control. Mac et al.[90] prospectively studied the impact of coregistering FDG PET imagings with CT images on the planning target volume, target coverage, and critical organ dose in radiation therapy planning of non-small cell lung carcinoma. Thirty patients with poorly defined tumors on CT, referred for radical radiation therapy, underwent both FDG PET and CT. The coregistration of planning CT and FDG PET imagings led to significant alterations to patient management and to the planning target volume. Ultimately, changes to the planning target volume resulted in changes to the radiation treatment plans for the majority of cases. Similar results have been reported in an other study.[79]

Prognosis

The clinical or pathologic TNM staging does not always provide a satisfactory explanation for differences in relapse and survival. Thus, it is of major importance to be able to predict these relapses and prevent them with an active chemotherapy and/or radiotherapy program. Several studies have indicated that the degree of FDG uptake in primary lung cancer can be used as a prognostic indicator.[4,59,92–96] Tumor aggressiveness (vascular invasion, pleural involvement, and lymphatic permeation) is a useful parameter for determining the prognosis of lung cancers.[97] Lung adenocarcinomas with increased FDG uptake are more metabolically active and more biologically aggressive.[34] The more metabolically active the tumor, the worse the outcome. We estimated whether the level of metabolic activity observed with FDG uptake correlates with the probability of postoperative recurrence in patients with non-small cell lung cancer (Fig. 14).[92] Patients with pathologic stage I disease had an expected 5-year disease-free survival rate of 88% if the SUV was <5, and 5-year disease-free survival rate of <17% if the SUV was >5. FDG uptake was superior to pathologic stage in predicting relapse of patients with non-small cell lung cancer. The prognostic significance of FDG uptake in lung cancer was assessed in a study of 155 patients who presented with a new diagnosis of non-small cell lung cancer.[93] The semiquantitative standardized uptake value (SUV) was used to stratify the cancers. The 118 patients with SUVs of less than 10 had a median survival of 24.6 months, whereas the 37 patients with SUVs of more than 10 had a median survival of 11.9 months ($p = 0.0049$). Multivariate analysis showed that the SUV provided prognostic information independent of the clinical stage and size of lesion.

FDG uptake in primary non-small cell lung cancer on PET has an important prognostic value and could be complementary to other well-known factors in deciding on adjuvant treatment protocols.

Cost-effectiveness

FDG PET has also been found in cost-effectiveness studies to lead to cost-savings when used for the diagnosis and staging of cancer. The savings have been derived primarily from the avoidance of surgery that would not benefit the patient.[98,99]

In Japan, Kubota, et al.[100] analyzed the potential effect of whole-body FDG PET on the medical cost for the management of patients suspected of having lung cancer. In the differential diagnosis, chest CT plus FDG PET protocol reduced the number of bronchofiberscopies and biopsies by one fourth of that in the conventional protocol using CT alone. However, it increased the total cost of examinations by 25% due to the higher cost of PET than that of bronchofiberscopy and biopsy in Japan. In the staging of lung cancer, whole-body PET reduced unnecessary surgery by 67%, and showed a saving of the cost of examination of 5%, and of the total medical cost of 2.5% compared to that in the conventional protocol using CT, brain MRI, and bone scan. Kosuda et al.[101] also assessed the cost-effectiveness of the chest CT plus chest FDG PET strategy, and concluded that the chest CT plus chest FDG PET strategy in patients with non-small cell lung cancer is unlikely to be cost-effective in Japan.

Comparison with Other Tracers

PET with FDG is used for detection and staging of lung cancer; however, more specific PET radiopharmaceuticals would be welcome.

Kubota et al.[102] performed a prospective study of 46 cases with ^{11}C-methionine and FDG using PET to predict the nature of non-calcifying lung tumor. ^{11}C-methionine study showed a sensitivity of 93%, a specificity of 60%, and an accuracy of 79% in differentiation between lung cancers and benign nodules. No significant differences were observed between the two tracers. The FDG study showed 83%, 90%, 86%, respectively. Similar results have been reported by other studies.[103,104]

^{11}C-choline is a new radiopharmaceutical potentially useful for tumor imaging, since it is incorporated into cell membranes as phosphatidylcholine. Hara et al.[105] com-

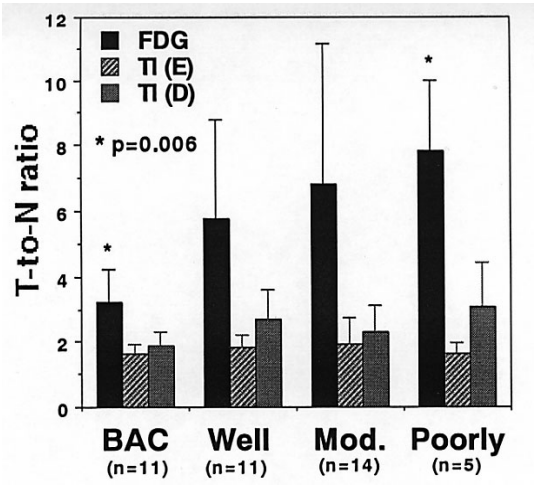


Fig. 15 Correlation was seen between FDG T/N and degree of cell differentiation in adenocarcinoma of lung. However, in Tl ER and DR, no significant difference was found between bronchioloalveolar carcinomas and poorly differentiated adenocarcinomas. In lung adenocarcinoma, FDG uptake, but not Tl uptake, reflects degree of cell differentiation. BAC: bronchioloalveolar carcinoma, Well: well differentiated adenocarcinoma, Mod: moderately differentiated adenocarcinoma, Poorly: poorly differentiated adenocarcinoma.

pared the capability of ^{11}C-choline with that of FDG in detecting mediastinal lymph node metastasis originating from non-small cell lung cancer. Twenty-nine patients were studied. The sensitivities of ^{11}C-choline PET and FDG PET in detecting mediastinal lymph node metastasis were 100% and 75%, respectively. Pieterman et al.[106] also investigated whether ^{11}C-choline PET has advantages over FDG PET in 17 patients with thoracic cancer. All primary thoracic tumors were detected with ^{11}C-choline PET and FDG PET. Both ^{11}C-choline PET and FDG PET also correctly identified all 16 patients with lymph node involvement. However, in a lesion-to-lesion analysis, ^{11}C-choline PET detected only 29 of 43 metastatic lymph nodes, whereas FDG PET detected 41 of 43. ^{11}C-choline PET detected fewer intrapulmonary and pleural metastases than FDG PET (27/47 vs. 46/47). More brain metastases were detected with ^{11}C-choline PET (23/23) than with FDG PET (3/23). For primary tumor, the median standardized uptake values of ^{11}C-choline and FDG were 1.68 and 4.22, respectively. ^{11}C-choline PET can be used to visualize thoracic cancers. Although detection of lymph node metastases with ^{11}C-choline PET was inferior compared with FDG PET, the detection of brain metastases was superior.

We compared the diagnostic value of FDG PET and ^{201}Tl SPECT in the evaluation of pulmonary nodules.[47,107] Sixty-three patients with 66 pulmonary nodules suspected to be lung cancer based on chest CT were examined by both FDG PET and ^{201}Tl SPECT (early and delayed scans). In the detection of lung cancer of less than 2 cm in size, FDG PET provided higher sensitivity than did ^{201}Tl SPECT.[107] However, bronchioloalveolar carcinoma and well differentiated adenocarcinoma may be visualized only on ^{201}Tl SPECT but not on FDG PET, because FDG uptake but not ^{201}Tl uptake reflects the degree of cell differentiation in lung adenocarcinoma (Fig. 15).[47] There was no significant difference in specificity between FDG PET and ^{201}Tl SPECT for differentiating between malignant and benign pulmonary nodules.[47] The results from this study suggest that the combination of FDG PET and ^{201}Tl SPECT may provide additional information regarding the tissue characterization of pulmonary nodules.

CONCLUSION

FDG uptake is considered to be a good marker of cell differentiation, proliferative potential, aggressiveness, and the grade of malignancy in patients with lung cancer. FDG PET accurately stages the distribution of lung cancer. Several studies have documented the increased accuracy of PET compared with CT in the evaluation of the hilar and mediastinal lymph-node status in patients with lung cancer. Whole-body PET studies detect metastatic disease that is unsuspected by conventional imaging. Management changes have been reported in up to 41% of patients on the basis of the results of whole-body studies. Whole-body FDG PET is also useful for the detection of recurrence. Several studies have indicated that the degree of FDG uptake in primary lung cancer can be used as an independent prognostic factor. Thus, FDG PET is clinically very useful in the management of lung cancer.

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