

# Quantification of $^{18}\text{F}$ -FDG Uptake in Non-Small Cell Lung Cancer: A Feasible Prognostic Marker?

**N**on-small cell lung cancer (NSCLC) is a heterogeneous group of carcinomas with a similar cellular and molecular origin but different biologic behaviors and prognoses. Accurate staging is essential for estimating prognosis and choosing the best combination of treatment modalities such as surgery, radiation, or chemotherapy. Because of the considerable heterogeneity of tumors, determination of prognosis is difficult. NSCLC is associated with increased glucose consumption and can therefore be visualized with the glucose analog  $^{18}\text{F}$ -FDG and PET. Further evidence that  $^{18}\text{F}$ -FDG PET can be used for assessment of prognosis in patients with lung cancer is reported by Guo et al. on pages 1334–1339 of this issue of *The Journal of Nuclear Medicine* (1). In their preliminary study, a tumoral  $^{18}\text{F}$ -FDG uptake of standardized uptake value (SUV) > 5.0 was shown to be associated with a worse prognosis ( $P = 0.004$ ). Furthermore, a significant correlation between  $^{18}\text{F}$ -FDG uptake and cell differentiation was shown ( $P = 0.007$ ). In resected lung tumors, choline and lactate concentration were measured by proton magnetic resonance spectroscopy, and no correlation between lactate or choline concentration and prognosis or tumoral  $^{18}\text{F}$ -FDG uptake was found. The authors therefore concluded that tumoral  $^{18}\text{F}$ -FDG uptake as measured by SUV better indicates prognosis in NSCLC than does lactate or choline concentration.

Some limitations have to be considered when applying the findings of Guo et al. (1) to clinical practice and to cancer derived from other tissues. Despite accurate performance of proton MRI, the values for lactate and choline concentration may have been influenced by tissue heterogeneity and tissue-sampling error. Because the study of Guo et al. included a limited number of patients, the highly significant correlation between tumoral  $^{18}\text{F}$ -FDG uptake and prognosis may not hold up in a larger series comprising additional histologic subtypes such as squamous cell cancer or large cell cancer. Furthermore, SUV was used for quantification of  $^{18}\text{F}$ -FDG uptake. Determination of SUVs is subject to many sources of variability, which—in other populations or measurement protocols—could hide an actual correlation between SUV and prognosis (2). For example, SUV normalizes to body weight and therefore depends on the patient population. In addition, the fact that SUV is dependent on the uptake period and plasma glucose levels should be considered. The investigated tumor sizes were greater than 1.6 cm, which is about 3 times the reported full width at half maximum (FWHM) of 0.5 cm at the center. Although recovery and partial-volume effects should not have played an important role in the work of Guo et al., the significant correlation between SUV and the size of the primary tumor is interesting ( $P = 0.01$ ,  $r = 0.58$ ). An  $r^2$  of 0.33 suggests that one third of the change in the SUV can be explained simply by respective tumor size. The importance of recovery and partial-volume effects has also to be considered, especially if the tumor is not larger than about

$2.5 \times \text{FWHM}$  in every direction and if the tumor is not homogeneous (i.e., contains necrotic regions).

To date, more than 150 prognostic factors have been described for NSCLC (3), whereas the TNM staging system is the most powerful prognostic tool for predicting survival rates. At clinical stage IA, 3- and 5-y survivals are 71% and 61%, respectively. Stage IV is advanced or metastatic disease, no longer amenable to cure. At stage IV, survival rates decrease to 2% and 1%, respectively (4). The TNM staging system does not, however, always satisfactorily explain individual patient survival. Most patients with stage I disease can be cured, but some have an early relapse and die. Several factors, including proliferative activity, neoangiogenesis, apoptosis, and altered glucose metabolism, have been identified as corresponding to more aggressive behavior by NSCLC (5–9). All these findings may contribute to the relationship between  $^{18}\text{F}$ -FDG uptake, biologic aggressiveness, and prognosis in NSCLC. Recently, overexpression of glucose transporters Glut-1 and Glut-3 has been reported to be associated with a worse prognosis (10). A relationship between  $^{18}\text{F}$ -FDG uptake and prognosis may also be explained, at least in part, by a correlation between  $^{18}\text{F}$ -FDG uptake and the growth rate and respective proliferation capacity of NSCLC (11,12).

Several research groups (13–15) have reported that  $^{18}\text{F}$ -FDG PET assessment of glucose metabolism has an independent prognostic value, further confirming the results of Guo et al. (1). In a series of 125 patients with an initial diagnosis of NSCLC, Vansteenkiste et al. reported that an  $^{18}\text{F}$ -FDG

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SUV > 7 had an independent prognostic value apart from clinical stage and performance status (13). In patients with resected T1 tumors, the 2-y survival was 86% if SUV was below 7 and 60% if above 7. Similar findings, based on a cutoff SUV of 10, have been reported (14). It has also been demonstrated that the performance of  $^{18}\text{F}$ -FDG PET after treatment might be of prognostic relevance (16). Patients with persisting  $^{18}\text{F}$ -FDG uptake in the primary tumor after initial treatment had a median survival of 12 mo, whereas 85% with a PET scan negative for uptake were still alive after a median follow-up of 34 mo ( $P = 0.002$ ). In addition, the presence and extent of relapse on  $^{18}\text{F}$ -FDG PET has been reported to be of prognostic value (17). A significant correlation between increased  $^{18}\text{F}$ -FDG uptake and worse prognosis has also been described for other tumor entities, such as small-cell lung cancer (18), breast cancer (19), cervical cancer (20), and osteosarcoma (21).

For many years, increased glycolysis has been known to be a distinctive feature of malignant tumors (22).  $^{18}\text{F}$ -FDG uptake in the primary tumor can vary substantially, and specific tumor characteristics have been shown to determine the degree of glucose metabolism in NSCLC. In vitro studies have indicated that  $^{18}\text{F}$ -FDG uptake is determined in part by the fraction of viable tumor cells (23). Necrotic or fibrotic tissue may reduce tracer uptake, and the presence of inflammatory cells may increase  $^{18}\text{F}$ -FDG accumulation (24,25).  $^{18}\text{F}$ -FDG uptake in the primary tumor is also determined by the histologic subtype, and false-negative findings have been reported for bronchioloalveolar cell carcinoma and carcinoid tumors (26,27). Guo et al. (1) also found a significantly lower  $^{18}\text{F}$ -FDG uptake in bronchioloalveolar and well-differentiated adenocarcinoma than in moderately and poorly differentiated adenocarcinoma. Factors significantly influencing  $^{18}\text{F}$ -FDG uptake in NSCLC comprise expression of glucose transporters (Glut-1, Glut-3), hexokinase activity, microvessel density,

and proliferative activity (11,13,16,17). Hypoxia causes upregulation of the hypoxia-inducible factor 1 (HIF-1) transcription factor and was demonstrated to induce glycolysis, angiogenesis, and erythropoiesis (28). Recently, HIF-1 $\alpha$ - and HIF-1 $\beta$ -protein expression were shown to correlate significantly with patient survival in NSCLC (29). Tumoral uptake of  $^{18}\text{F}$ -FDG is probably related to HIF-1-induced upregulation of Glut-1. However, a correlation between  $^{18}\text{F}$ -FDG uptake and HIF-1 expression in NSCLC has not been investigated so far.

An interesting finding of Guo et al. (1) is the lack of correlation between  $^{18}\text{F}$ -FDG uptake and the lactate content of the resected tumor, as measured by proton magnetic resonance spectroscopy. This result may indicate that  $^{18}\text{F}$ -FDG does not necessarily reflect anaerobic glycolysis. For example, utilization of  $^{18}\text{F}$ -FDG by the pentose phosphate pathway has also to be considered. However, there is no reliable explanation for this finding, which therefore needs further evaluation.

$^{18}\text{F}$ -FDG is not specific for malignancy, and false-positive findings can occur in inflammatory lesions such as pneumonia, tuberculoma, or sarcoidosis (30,31). Besides increased levels of glucose metabolism, the genetic changes of lung cancer comprise increased tumor blood flow and vascular permeability, neoangiogenesis, amino acid transport, and protein synthesis; enhanced DNA synthesis and cell proliferation; and induction of apoptosis. All these processes have a potential for imaging NSCLC with PET, and a variety of novel tracers has been studied in vitro and in vivo. Tumor cells show an increased uptake of choline, one of the components of phosphatidylcholine, which is an essential element of phospholipids in the cellular membrane (32,33). High physiologic uptake of  $^{11}\text{C}$ -choline is seen in the liver, kidney, pancreas, and salivary glands. Pieterman et al. evaluated  $^{11}\text{C}$ -choline and  $^{18}\text{F}$ -FDG for TNM staging in 17 patients with lung cancer (34). With both tracers, all primary tumors have

been detected. However, the sensitivity of  $^{11}\text{C}$ -choline PET for detection of pulmonary or pleural metastases was 57%—significantly lower than for  $^{18}\text{F}$ -FDG (98%).  $^{18}\text{F}$ -FDG was also more sensitive in the detection of abdominal tumor manifestations and metastatic lymph nodes, at a sensitivity of 95% and 67%, respectively. This is in contrast to the study of Hara et al., who reported a sensitivity of 100% for  $^{11}\text{C}$ -choline and a sensitivity of only 75% for  $^{18}\text{F}$ -FDG (35). Because of the limited data available, no final conclusion on the clinical utility of  $^{11}\text{C}$ -choline or the concentration of choline for staging and estimating prognosis in NSCLC can yet be drawn.

Determination of tumor cell proliferation by means of Ki-67 immunohistochemistry is currently used to predict the clinical outcome in lung cancer (36). Precursors of DNA synthesis such as thymidine analogs have been introduced for imaging tumoral proliferation. In lung cancer, a close correlation between uptake of 3'-deoxy-3' [ $^{18}\text{F}$ ] fluorothymidine (FLT) and the proliferation fraction has been reported (37). However, it remains to be determined if radiotracers specifically reflecting proliferative activity are suitable biomarkers for assessment of prognosis in NSCLC.

In summary, besides the diagnostic relevance for staging and restaging lung cancer,  $^{18}\text{F}$ -FDG PET turns out to be a suitable tool for estimating the prognosis of patients with NSCLC. Uptake of  $^{18}\text{F}$ -FDG in the primary tumor reflects in part proliferative activity, the number of viable tumor cells, microvessel density, tumor grading, and histologic subtype and has been shown to be an independent prognostic marker in NSCLC. However, the prognostic potential of  $^{18}\text{F}$ -FDG PET seems to be determined mainly by exact nodal and metastatic staging and by its ability to detect recurrent disease and to determine response to therapy. Because  $^{18}\text{F}$ -FDG is not a specific tracer for malignancy, novel radiotracers, including  $^{11}\text{C}$ -choline as an indirect measure of phosphatidylcholine synthesis

or  $^{18}\text{F}$ -FLT as a measure of proliferative activity, may offer advantages over  $^{18}\text{F}$ -FDG for predicting prognosis in NSCLC and determining tumor response to therapy.

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