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CONTINUING EDUCATION

^{18}F-FDG Uptake in Lung, Breast, and Colon Cancers: Molecular Biology Correlates and Disease Characterization*

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It is hoped that in the not too distant future, noninvasive imaging–based molecular interrogation and characterization of tumors can improve our fundamental understanding of the dynamic biologic behavior of cancer. For example, the new dimension of diagnostic information that is provided by ^{18}F-FDG PET has led to improved clinical decision making and management changes in a substantial number of patients with cancer. In this context, the aim of this review is to bring together and summarize the current data on the correlation between the underlying molecular biology and the clinical observations of tumor ^{18}F-FDG accumulation in 3 major human cancers: lung, breast, and colon.

Key Words: molecular biology; molecular imaging; oncology; PET; PET/CT; breast cancer; colon cancer; ^{18}F-FDG; lung cancer

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The emergence of the central role of PET with ^{18}F-FDG for the imaging evaluation of patients with cancer is undeniable. The development of hybrid PET/CT systems, regional distribution centers for ^{18}F-FDG, rapidly accumulating clinical experience, and improved reimbursement have all contributed to this phenomenal success. ^{18}F-FDG PET has been used for diagnosis, initial staging, restaging, prediction, and monitoring of treatment response, surveillance, and prognostication in a variety of cancers. The new dimension of diagnostic information that is provided by ^{18}F-FDG PET has also led to improved clinical decision making and management changes in a substantial number of patients (*1–3*).

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^{18}F-FDG PET is a molecular imaging technique that monitors tissue glucose metabolism. It has long been known that most tumors are hypermetabolic, with increased glucose metabolism (Warburg effect). The underlying mechanism and reason for elevated glucose metabolism in cancers is multifactorial and more complex than it may appear at first glance (*4*). These factors include but are not limited to tumor-related components (e.g., type and histologic differentiation), biochemical and molecular alterations (e.g., glucose metabolic pathway, hypoxia), and nontumor-related constituents (e.g., inflammation) (*5–8*). The 2 recent excellent reviews by Gillies et al. and Plathow et al. summarized the current understanding of the phenotype of elevated glucose metabolism in cancers (*9,10*). In simple terms, it was postulated that the relationship between tumor growth and glucose metabolism may be explained in terms of adaptation to hypoxia through upregulation of glucose transporters (GLUTs) and translocation and increased enzymatic activity of hexokinase. However, energy production by glycolysis is relatively inefficient (2 adenosine triphosphates produced per glucose with glycolysis rather than 30 ATPs produced with complete oxidation) and produces a toxic acidic microenvironment (*9,10*). It has been proposed that the increased extracellular acid production may be the underlying basis for promoting tumor survival and spread in the context of the 6 hallmarks of cancer—self-sufficiency in growth signals, insensitivity to antigrowth signals, evasion of apoptosis, limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis (*11*). It has been suggested that 2 additional hallmarks of cancer include evasion of tumors from the immune system and increased glucose metabolism (*12*). The toxic tumor microenvironment results in the death of normal cells while the tumor cell survives by evading apoptosis and maintaining normal intracellular pH that consequently gives the tumor a Darwinian competitive advantage for local growth, leading ultimately to local basement membrane invasion and spread of metastatic envoys to distant sites (*13*). Further

research is still needed to better understand if these are the key reasons for a switch to inefficient glycolysis by tumor cells.

In the context of this brief introduction on tumor glucose metabolism, the aim of this review was to bring together and summarize the current data on the correlation between the underlying molecular biology and the clinical phenotypic observations of tumor ^{18}F-FDG accumulation in 3 major human cancers (lung, breast, colon) after a brief background note on GLUT and hexokinase proteins, which are the 2 major constituents of enhanced glucose metabolism (*14*). It is hoped that in the not too distant future, noninvasive imaging–based molecular interrogation and characterization of tumors can improve our fundamental understanding of the dynamic biologic behavior of cancer. Moreover, the recent development of software tools for the combined assessment of quantitative PET, microarray–based gene expression profiling, and proteomic data can facilitate clinical decision making, management, and outcome prediction in individual patients (*15*). However, unfortunately, higher gene expression does not always translate to higher protein levels, and it is the protein levels, location, and activity that really dictate cellular metabolism and function.

GLUT AND HEXOKINASE PROTEINS

Glucose is transported into and out of the cell via a family of 14 facilitative GLUTs that are cell-specific and affected by hormonal and environmental controls (*16*). A list of these facilitative GLUTs can be found at http://www.genenames.org/cgi-bin/hgnc_search.pl. Although the currently approved gene symbol is designated as SLC2Ax, for the sake of familiarity we will use the symbol GLUTx. The upregulation of GLUT proteins is common in most cancers and is negatively associated with patient prognosis (*16,17*). The GLUT is the first rate-limiting step for glucose metabolism that allows energy-independent glucose transport across the cell membrane down the concentration gradient (*18*). The enhanced tumor glucose metabolism is associated with the deregulated overexpression of GLUTs (primarily hypoxia-responsive GLUT1 or GLUT3 proteins) (*19*). The complex tumor-mediated interactions with the GLUT1 promoter or enhancer elements are the likely mechanism for GLUT1 gene overexpression (*9,18*), which is also tightly linked with increased coexpression of cellular invasiveness markers such as matrix metalloproteinase-2 (MMP-2) (*20*). More recently, trafficking of intracellular GLUT12 to the plasma membrane has also been implicated in the enhanced glucose accumulation in some cancers including breast cancer (*21*). Additional studies are needed to assess the type, level, and extent of GLUT family expression in various cancers.

Increased hexokinase enzymatic level and activity (primarily hexokinase type II [HK-II] of the 4 types in mammalian tissue) has also been implicated in many cancers (*22–26*). HK-II binds to the mitochondrial membrane at the voltage-dependent anion channel (porin) and efficiently phosphorylates glucose to glucose-6-phosphate using the energy produced by the mitochondrion (*27,28*). Similarly, ^{18}F-FDG is phosphorylated to FDG-6-phosphate, but contrary to glucose-6-phosphate, it cannot be metabolized further in the glycolytic pathway and becomes trapped in the cell because of its negative charge. The low activity of the reverse enzyme, glucose-6-phophatase, in the tumor cells (except some cancers such as well-differentiated hepatocellular carcinoma) leads to the tumor cell accumulation of FDG-6-phosphate (*29*).

^{18}F-FDG is not specific for cancer and can accumulate in inflammatory processes. However, it has been demonstrated that the temporal profile of ^{18}F-FDG accumulation in malignancy may be different from that for benign lesions and inflammatory processes. These observed temporal profile differences are likely due to the different level and extent of GLUT and hexokinase expressions in normal tissue, inflammatory lesions, and cancer. Dual- or multiple-time-point imaging strategies have been devised to take advantage of this observation, with some encouraging results, although some overlap still remains between the accumulation levels of ^{18}F-FDG in cancer and benign conditions (*30–33*).

LUNG CANCER

Lung cancer is a leading cause of cancer mortality and morbidity. One of the cancers that was initially investigated with ^{18}F-FDG PET was lung cancer. The diagnostic and prognostic utility of ^{18}F-FDG PET in lung cancer has been studied relatively extensively. ^{18}F-FDG PET not only has been useful in characterizing solitary pulmonary nodules but also has improved the staging accuracy in identifying potentially curative resectable disease, guiding therapy, monitoring treatment response, and predicting outcome (*34–37*).

Many studies have concentrated on the correlation and relationship of lung tumor ^{18}F-FDG accumulation to the underlying biologic factors. Such understanding can potentially improve the biologic interpretation and stratification of ^{18}F-FDG PET.

It has been observed that the GLUT1 gene expression is significantly higher in primary lung tumors than in normal lung tissue (*38*). Interestingly, although GLUT1 overexpression may be similar between the primary and metastatic lung tumors, the GLUT3 and GLUT5 gene expression levels are significantly higher in the liver metastases of lung cancer than in the primary lung tumor, suggesting that the energy transporters in metastatic lung lesions may be different from those in the primary lung tumors (*38*).

A group of Dutch investigators examined the correlation of ^{18}F-FDG accumulation in non–small cell lung cancer (NSCLC) with histology and expression of GLUTs and hexokinase (*39*). Poorly differentiated tumors showed

higher GLUT1 expression and ^{18}F-FDG accumulation than moderately differentiated tumors. There was a moderate correlation between tumor ^{18}F-FDG accumulation, as depicted by maximum standardized uptake value (SUV), and GLUT1 and GLUT3 expression ($r = 0.37$ and 0.35, respectively). A similar finding of significant correlation ($r = 0.52$–0.66) between tumor SUV and GLUT1 overexpression has been reported by other studies (*40–42*); however, this has not been observed by some investigators (*43*) or has been shown to also be the case with benign conditions (e.g., lymphoid follicular hyperplasia) (*44*). At least to some extent, the differences in methodology, tumor type (e.g., higher ^{18}F-FDG accumulation and GLUT1 expression in squamous cell carcinomas than in adenocarcinomas), tumor differentiation grade, study population, and intratumoral heterogeneity of ^{18}F-FDG distribution may account for the discrepant findings (*14,45–47*). A statistically significant positive relationship was also seen between percentage of necrotic tumor compounds and the immunoreactive level of hexokinase isoforms and tumor cell differentiation. It was presumed that the reason for the latter finding is related to the localization of the hexokinase protein expression (mainly HK-II) near hypovascular areas of tumor in correlation with the expression of the hypoxia-inducible factor-1α (HIF-1α) protein expression in response to chronic hypoxia (*48*).

A recent South Korean study correlated the expression of GLUT1 and ^{18}F-FDG in primary and locoregional metastatic lymph nodes of NSCLC (*49*). Statistically significant correlations were found between malignant lymph nodes and the primary tumors with respect to maximum SUV ($r = 0.65$), percentage GLUT1 expression ($r = 0.83$), and GLUT1-staining intensity ($r = 0.83$). The authors concluded that the high correlation between the primary tumors and metastatic lymph nodes with respect to the GLUT1-mediated ^{18}F-FDG accumulation may be useful for improved mediastinal lymph node staging. More recently, a high correlation between primary lung lesions and metastases was observed when a dual-time-point (60 and 180 min) SUV retention index (RI) was used as the parameter for image analysis. Moreover, the RI SUV of the metastatic lesions was approximately 0.5–2 times the RI SUV of primary tumors. The accuracy of ^{18}F-FDG PET was improved when RI SUV was used for detecting lymph node and distant metastases, primarily due to the significant improvement in specificity, although some overlap between malignant and benign lesions remained (*50*).

In another study, it was found that although there was a wide range of ^{18}F-FDG accumulation in neuroendocrine lung tumors (maximum SUV, 0.6–29.5), the level of ^{18}F-FDG accumulation was significantly and positively correlated with tumor GLUT1 protein expression ($r = 0.65$) (*51*). A similar study for bronchioloalveolar carcinomas has shown that the relatively lower sensitivity of ^{18}F-FDG PET in this clinical setting may be due to the varying level and extent of tumor GLUT1 expression (*52*). An additional modulatory factor for ^{18}F-FDG accumulation may be related to P-glycoprotein (Pgp) overexpression in tumors, although the exact underlying mechanism and relationship to glucose metabolism remains unclear (*53*). It has been observed that the lower ^{18}F-FDG accumulation in bronchioloalveolar lung cancer was associated with an overexpression of Pgp as an in vivo marker of multidrug resistance (*54*).

Prior studies have shown associations among hypoxia-induced genes, GLUTs, and angiogenic factors (*55*). Pedersen et al. from Denmark examined the relationship between ^{18}F-FDG accumulation and GLUT and vascular endothelial growth factor (VEGF) expression in 2 human small cell lung cancer (SCLC) cell lines during varying periods of hypoxia (*56*). Higher SCLC tumor ^{18}F-FDG accumulation was associated with higher levels of GLUT1. Hypoxia resulted in significant upregulation of GLUT1 and VEGF messenger RNA but not the HIF-1α in these SCLC cell lines. In an Australian study, the glucose metabolic rate of surgical specimens of NSCLC was correlated with the markers of hypoxia and angiogenesis depicted, respectively, by tissue uptake of ^{18}F-fluoromisonidazole (FMISO) and microvessel density (*57*). Although a weakly positive correlation was found between FMISO uptake, ^{18}F-FDG uptake, and Ki-67 proliferation index, the correlation between tumor uptakes of FMISO and ^{18}F-FDG with the markers of hypoxia and angiogenesis was poor. Interestingly, 1 study has suggested that tumor maximum SUV is more valuable than GLUT1 or Ki-67 expression in terms of predicting prognosis in patients with resected NSCLC (*58*). However, a group of investigators from The Netherlands observed that the higher the metabolic activity of the NSCLC tumors, the higher the proportion of tumors expressing HIF-1α and GLUT1, without a significant correlation to the Ki-67 proliferation index (*59*). Therefore, this study concluded that hypoxia is associated with GLUT1-mediated enhanced tumor ^{18}F-FDG accumulation in NSCLC. The hypoxia-induced increase in tumor ^{18}F-FDG accumulation, and conversely the decline in uptake level with improved tumor oxygenation, has been observed in other cancers (*7,60*).

A group from Japan studied the relationship between ^{18}F-FDG accumulation and alterations in tumor suppressor genes (Rb, p16, p27, p53) in surgical specimens that were obtained from 28 patients with primary lung cancer (adenocarcinoma, 17; squamous carcinoma, 10; large cell carcinoma, 1) (*61*). The mean SUV in tumors with any suppressor gene alteration was significantly higher than that in those tumors without alterations in any suppressor genes (6.83 vs. 1.95, respectively; $P < 0.0001$). The study concluded that the presence of any tumor suppressor gene abnormality is associated with an expected augmentation of ^{18}F-FDG accumulation in lung cancer.

The level of ^{18}F-FDG accumulation in lung cancer is modulated by many histologic and molecular factors. Higher ^{18}F-FDG accumulation is generally noted in squamous cell carcinomas than in adenocarcinomas and in

poorly differentiated carcinomas than in other tumor grades. These phenotypic observations are generally due to GLUT1 overexpression and to some extent GLUT3 and GLUT5 overexpression in metastatic lung tumors. In turn, the GLUT1-mediated increased ^{18}F-FDG accumulation in lung tumors is modulated by hypoxia-induced factors (including HIF-1α and mitochondrial HK-II), alterations in tumor suppresser genes, and Pgp activity.

BREAST CANCER

Breast cancer is the most common cancer in women in the United States. The histopathologic types of breast cancer include ductal adenocarcinoma, lobular carcinoma, lymphoma, sarcoma, and Paget disease of the nipple. ^{18}F-FDG PET has been evaluated for diagnosis, staging, restaging, monitoring therapy response, and prognostication in patients with breast cancer (*62*). Although the current data suggest that ^{18}F-FDG PET may have limited diagnostic utility in detecting small primary tumors, staging for the involvement of the axilla, and detecting blastic osseous metastatic lesions, PET has superiority over conventional imaging in detecting distant metastases and recurrent disease and in monitoring therapy response (*63–65*).

An in vitro study of human breast cancer cell lines MCF-7, MDA-MB-435, and MDA-MB-231 has shown that cell surface GLUT1 expression was positively and GLUT2 and GLUT5 were inversely associated with cellular invasiveness (*66*). Brown et al. studied the expression of GLUT1 and HK-II in animal tumor models of breast cancer and in women with untreated primary breast cancer (*67–69*). In the human studies, immunohistochemical staining showed that 61% of tumors were positive for GLUT1 and 79% of tumors were positive for HK-II (*67*). The HK-II staining was cytoplasmic, suggesting mitochondrial localization. Cells that expressed HK-II did not always express GLUT1 and vise versa. However, interestingly, ^{18}F-FDG accumulation appeared to be associated with increased GLUT1 expression ($P = 0.02$) but not with HK-II expression ($P = 0.6$) (*67*). Other studies reported no such clear relationship between tumor ^{18}F-FDG accumulation and GLUT1 expression (*70*). Other recent studies suggest involvement of a novel GLUT protein, GLUT12, located intracellularly and at the cell surface (*21*). Trafficking of intracellular GLUT12 to the plasma membrane may contribute to the enhanced glucose accumulation in breast cancer. It has also been observed that estradiol and epidermal growth factor increase GLUT12 protein levels in cultured breast cancer cells (*18*). Therefore, targeting GLUT12 may provide a novel opportunity for the detection and treatment of breast cancer.

Buck et al. studied the biologic correlates of ^{18}F-FDG accumulation in primary breast cancer (*71*). ^{18}F-FDG localization was significantly higher in ductal carcinoma than in lobular carcinoma (mean tumor-to-background ratio, 17.3 vs. 6.5, respectively). Of all the parameters examined in this study (c-erb B2, tumor grade, estrogen receptor status, progesterone receptor status, tumor size, axillary lymph node status, proliferation index Ki-67), only Ki-67 showed a statistically significant positive correlation to ^{18}F-FDG accumulation in ductal breast cancer. Other groups have reported a similar positive correlation between ^{18}F-FDG uptake and Ki-67 (*72*).

Crippa et al. also showed that the tumor median SUV was significantly higher in the infiltrating ductal carcinomas than in the lobular carcinomas (5.6 vs. 3.8, respectively) and in grade 3 carcinomas than in grades 1–2 carcinomas (6.2 vs. 4.9, respectively) (*73*). Moreover, the SUV was significantly higher in carcinomas with a high level of p53 expression, whereas other studies have shown a similar correlation with diminished p53 function (*74*). Another study has shown that ^{18}F-FDG accumulation in the breast tumor is a function of microvasculature density for delivering nutrients ($P = 0.005$), GLUT1 for transportation of the tracer into the cell ($P < 0.001$), hexokinase for entering the tracer into glycolysis ($P = 0.02$), number of viable cancerous cells per volume ($P = 0.009$), the proliferation rate ($P = 0.001$), the number of lymphocytes ($P = 0.03$), and the HIF-1α upregulation of GLUT1 (*75*). A related investigation has demonstrated that a hypoxia-induced increase in ^{18}F-FDG accumulation in MCF-7 breast cancer cells is in part related to an increase in GLUT activity resulting from modification of the glucose transport proteins, whereas the modulation of hexokinase activity is probably not involved (*76*).

Several studies have failed to demonstrate a statistically significant correlation between tumor ^{18}F-FDG accumulation and other important clinical and biologic factors such as the size of the primary breast tumor, axillary lymph node status, and expressions of estrogen receptor (ER) and progesterone receptor (PR), *HER2*/neu, and the protooncogene c-erbB2 and VEGF (*70,72,77*). Similarly, in 1 related investigation, multivariate regression analysis of the factors that are associated with false-negative ^{18}F-FDG PET in breast cancer showed that only tumor size (≤10 mm) and low tumor grade were independently associated with false-negative results, whereas no statistically significant relationship was found with age, menopausal status, tumor type, c-erbB-2, ER and PR, sentinel lymph node or distant metastasis, parenchymal density, and multifocality of primary breast tumor (*78*).

However, a recent report has found that the level of ^{18}F-FDG uptake in the primary breast tumor can be a good surrogate marker for the amount of expected disease burden both locally in the axilla and in distant sites (*79*). The study included 174 patients with newly diagnosed breast cancer who were divided into 3 groups: 64 patients with primary and metastatic axillary lymphadenopathy (group I), 18 patients with both axillary and distant metastases (group II), and 92 patients with neither axillary nor distant metastatic disease (group III). The average maximum SUV (obtained at a mean of 63 min after tracer administration) of the

primary lesions in group II (7.7 ± 6.2) was significantly higher than that in group I (4.8 ± 3.9) followed by those in group III (2.9 ± 2.7). Therefore, this study suggested that higher metabolic activity of the primary breast tumors as depicted by higher ^{18}F-FDG accumulation can effectively reflect the metastatic propensity of the tumor. Higher breast tumor ^{18}F-FDG accumulation has also been shown to be predictive of poor response to neoadjuvant chemotherapy (*80*).

The ability of ^{18}F-FDG PET to characterize breast cancer was examined in another recent report that compared ER-negative (ER−)/PR-negative (PR−)/*HER2*-negative tumors with ER-positive/PR-positive/*HER2*-negative tumors (*81*). The study included women with newly diagnosed breast carcinoma (18 patients with triple-negative tumors and 59 patients with ER-positive (ER+)/PR-positive (PR+)/*HER2*-negative tumors) who underwent dual-time-point (mean, 63 and 101 min after tracer administration) ^{18}F-FDG PET before any therapeutic interventions. The maximum SUV of the tumor at each imaging time was correlated to surgical histopathology reports. The average maximum SUV for the triple-negative lesions at imaging times 1 and 2 were 7.27 ± 5.6 and 8.29 ± 6.4, respectively. The average maximum SUV for the ER+/PR+/*HER2*-negative tumors at imaging times 1 and 2 were 2.68 ± 1.9 and 2.84 ± 2.2, respectively, which were significantly lower than the triple-negative tumor values. Stage for stage, the triple-negative tumors showed higher average maximum SUVs at imaging time 1 (63 min) than did the non–triple-negative tumors. The authors concluded that the triple-negative breast tumors were associated with enhanced ^{18}F-FDG uptake that is reflective of their aggressive biology. The same group of investigators also examined the effects of ER, PR, and c-erb B2 receptor on ^{18}F-FDG accumulation in primary breast cancer (*82*). The average maximum SUVs for ER+ and ER− lesions were 3.03 ± 0.26 and 5.64 ± 0.75, for PR+ and PR− lesions were 3.24 ± 0.29 and 4.89 ± 0.67, and for c-erb-B2R+ and c-erb-B2R− were 4.64 ± 0.70 and 3.70 ± 0.35, respectively. Tests for interactions between these biologic parameters showed that if either ER or PR is positive, the other tends to be positive as well. If ER was positive, then c-erb B2R tended to be negative. No interaction was noted between PR and c-erb B2R states. It was also determined that although the PR state alone and c-erb B2R state alone had no effect on ^{18}F-FDG uptake in the tumor, the ER state alone had an independent and significant effect on the uptake level. A similar correlation of enhanced tumor ^{18}F-FDG uptake with ER negativity has recently been reported by a group of Japanese investigators (*83*). The latter studies suggest that the ^{18}F-FDG signature of breast cancer can provide important information about the underlying tumor biology that may have implications on individualized treatment planning and outcome prediction.

The current available data support the notion that ^{18}F-FDG accumulation in breast cancer is primarily GLUT1-mediated and that ductal carcinomas are more metabolically active than lobular carcinomas. Moreover, many studies suggest that ER negativity and triple-negative tumors are more metabolically active than tumors without these molecular features, probably reflecting the underlying aggressive biologic behavior of the tumor. It was also suggested that the higher the ^{18}F-FDG accumulation in primary breast cancer, the poorer the overall prognosis and the higher the probability of metastatic disease involving the local axillary nodes and the distant sites, again likely reflecting the underlying degree of tumor invasiveness.

COLON CANCER

Colon cancer is the third most common malignancy in the United States. Most colon cancers are adenocarcinomas. The utility of ^{18}F-FDG PET in colon carcinoma has been studied relatively extensively (*84*). For preoperative diagnosis, both CT and ^{18}F-FDG PET may miss the involvement of the local lymph nodes. However, ^{18}F-FDG PET is superior to CT for detecting liver metastases. The detection of the primary tumor depends on the size of the tumor and the background activity. Colon may occasionally demonstrate high ^{18}F-FDG localization. However, focal intense hypermetabolism is highly suggestive of neoplasm that may include carcinoma (*85*). False-negatives may also result in subcentimeter and mucinous tumors. ^{18}F-FDG PET is particularly useful in the detection of recurrence and metastatic disease in patients with elevated or increasing serum carcinoembryonic antigen (CEA) level for differentiating posttreatment changes from residual or recurrent cancer and in monitoring treatment response (*86–88*). More recently, PET/CT colonography has also been found to be useful in the evaluation of colon cancer (*89,90*). The inclusion of ^{18}F-FDG PET in the imaging evaluation of patients with recurrent colon cancer can significantly affect the clinical management of these patients in a cost-effective manner (*91*).

The biologic correlates of ^{18}F-FDG accumulation in colon cancer are less well studied than those in lung and breast cancers. A recent study found that colon tumor GLUT1 expression had a significantly positive correlation with the SUV ($\rho = 0.619$, $P = 0.003$) (*92*). This positive correlation is despite an observation that GLUT1 may be expressed in only about 18% of colorectal tumors (*93*). Another recent investigation reported on the correlation between ^{18}F-FDG accumulation in colon tumor and expression of GLUT1, GLUT3, Ki-67, p53, p27, and BCL-2 (a marker for apoptosis) in the surgically harvested tumors (*94*). Tumor maximum SUV showed a statistically significant correlation with GLUT1 ($P = 0.03$), Ki-67 ($P = 0.03$), and p53 ($P = 0.02$) but not with GLUT3, p27, and BCL-2. Interestingly, such correlation of colon tumor glucose metabolism to p53 activity was not observed in another study that compared the levels of ^{18}F-FDG uptake in wild-type p53-expressing tumor xenografts to p53 gene–silenced xenografts (*95*).

The ^{18}F-FDG kinetics in colorectal cancer may also be modulated by angiogenesis-related genes. Strauss et al. correlated the 2-compartment-model–derived ^{18}F-FDG kinetic parameters to the level of angiogenesis-related gene expression in surgical specimens of tumor and normal tissue (*96*). The ^{18}F-FDG transport parameter k_1 was significantly correlated with VEGF-A ($r = 0.51$), whereas the intracellular phosphorylation parameter k_3 was negatively correlated with VEGF-B ($r = -0.46$) and positively correlated with angiopoietinlike 4 gene ($r = 0.42$), which inhibits vascular permeability and tumor motility. This diverging effect of the correlations of k_1 and k_3 to gene expression was presumed to explain the observed lack of a significant correlation between the angiogenesis-related gene expression and the SUV as a global measure of ^{18}F-FDG uptake in the tumor. Nevertheless, angiogenesis-related genes were noted to affect about 57% of the total variance of ^{18}F-FDG kinetic data. In another related study by the same group of investigators, it was noted that analysis of the dynamic PET data of the primary colon tumor may also be predictive of the presence of hepatic metastatic lesions (*97*).

Another study examined the significance of GLUT1 expression at the deepest invasive site of advanced colorectal cancer (*98*). GLUT1 expression was detected in 37% of resected lesions at the deepest invasive site, which also correlated significantly with histologic grade, depth of invasion, lymphatic invasion, lymph node metastasis, Duke stage, and Ki-67 expression. A multivariate logistic regression analysis for 5-y survival showed that lymph node metastasis and GLUT1 expression were significant risk factors. Therefore, the study concluded that GLUT1 expression at the deepest site of tumor invasion can be a useful predictor of prognosis in patients with advanced colorectal cancer. Similar results were reported by another group from Japan in a study that also showed a significant correlation between GLUT1 positivity (≥10% of cellular immunostaining) and depth of invasion (45% T1 vs. 74% T2, $P < 0.01$), histologic differentiation (49% well vs. 74% moderately to poorly, $P < 0.05$), and morphologic type (42% polypoid vs. 73% depressed, $P < 0.05$) (*99*). Combining the results of these studies suggests that GLUT1-mediated ^{18}F-FDG accumulation in colon cancer can predict the underlying tumor biology in terms of malignancy potential and prognosis. Similar tumor behavior prediction with ^{18}F-FDG PET in relation to activity of hexokinase enzyme has also been reported in experimental colon cancer (*100*). However, other animal studies with implanted human colon cancer cell lines suggest that, compared with hexokinase activity, GLUT1 is the more essential factor for ^{18}F-FDG accumulation in the colon tumor (*101*). However, cells in culture can genetically drift and one must be careful about the applicability of results from cell culture or xenograft models to patient tumors.

A group of Taiwanese investigators reported on the relationship between the level and extent of ^{18}F-FDG localization in colon tumors and the various serum CEA levels above 5 ng/mL in patients with negative or equivocal conventional imaging studies (*87*). ^{18}F-FDG PET could help in the triage of patients for the appropriate management (resectable vs. nonresectable) with unexplained CEA elevation less than 25 ng/mL. For patients with unexplained CEA elevation greater than 25 ng/mL, ^{18}F-FDG PET was essentially useful for the confirmation of advanced disease and for the identification of resectable lesions on rare occasion.

Despite relatively limited studies, it appears that ^{18}F-FDG accumulation in colon cancer is partly influenced by the level and extent of GLUT1 expression. The GLUT1-mediated ^{18}F-FDG accumulation by the colon tumor is also dependent on and predictive of tumor differentiation, tumor invasiveness, and overall prognosis. Moreover, analysis of the ^{18}F-FDG kinetics parameters in colorectal cancer suggests that ^{18}F-FDG accumulation is also correlated with intracellular phosphorylation (hexokinase activity) and may be modulated by angiogenesis-related genes.

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