^{18}F-FLT and ^{18}F-FDG PET-CT imaging in the evaluation of early therapeutic effects of chemotherapy on Walker 256 tumor-bearing rats

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Abstract. The present study aimed to evaluate the early therapeutic effects of chemotherapy on Walker 256 tumor-bearing Wistar rats via F-18-fluoro-3'-deoxy-3'-L-fluorothymidine (^{18}F-FLT) and F-18-fluoro-deoxyglucose (^{18}F-FDG) positron emission tomography-computed tomography (PET-CT) imaging. Walker 256 tumor-bearing Wistar rats were subjected to ^{18}F-FLT and ^{18}F-FDG PET-CT imaging prior to and 24 and 48 h after epirubicin chemotherapy. ^{18}F-FLT and ^{18}F-FDG uptake [tumor/muscle (T/M)], the percentage of injected dose per gram (% ID/g), and the Ki-67 labeling index (LI-Ki-67) were quantitatively determined for each rat prior to and following epirubicin chemotherapy. The correlation between % ID/g and tumor LI-Ki-67 was analyzed. Both ^{18}F-FLT and ^{18}F-FDG tumor uptake decreased significantly at 24 and 48 h after chemotherapy ($P<0.01$ and $P<0.05$, respectively). LI-Ki-67 also significantly reduced 24 and 48 h after chemotherapy ($P<0.001$). Furthermore, ^{18}F-FLT and ^{18}F-FDG T/M tumor uptake correlated positively with LI-Ki-67 before and after chemotherapy ($r=0.842$ and 0.813, respectively). During the early post-chemotherapy stage, ^{18}F-FLT and ^{18}F-FDG uptake in Walker 256 tumors reduced significantly, which correlated positively with the tumor cell proliferative activity.

Introduction

Traditionally, the therapeutic effects of anti-tumor therapies are determined by detecting reductions in tumor size via ultrasonography, computed tomography (CT), and magnetic resonance imaging. However, this process requires a lengthy time interval of several months on average. For some intractable tumors, early treatment response evaluation can help to adjust the therapeutic schedule prior to changes in tumor size, which may avoid unnecessary toxic reactions and economic waste. Tumor cell proliferative activity is an important biological characteristic of malignant tumors that has been used to evaluate the responses of tumors to various treatments (1). However, not all tumors can be evaluated clinically via biopsy to detect alterations in the tumor cell proliferative activity during treatment. Therefore, a noninvasive, simple, and accurate *in vivo* method to detect tumor cell proliferative activity is required. Given the development of clinical applications for positron emission tomography (PET)-CT imaging, it is possible to use positron imaging agents to evaluate the effects of treatments on tumors, particularly with respect to early curative effects. Currently, F-18-fluoro-deoxyglucose (^{18}F-FDG) is the most widely applied clinical positron imaging agent. This agent reflects glucose metabolism in organs and tissues and thereby is widely used in tumor diagnosis, staging, curative effect determination, and recurrence monitoring (2). However, some metabolically active tissues or lesions, including the myocardium, brain tissue, inflammatory areas, and certain benign tumors, may also exhibit increased uptake of imaging agents, leading to poor ^{18}F-FDG imaging specificity (2). Previous preclinical and clinical studies have shown that F-18-fluoro-3'-deoxy-3'-L-fluorothymidine (^{18}F-FLT), which is a pyrimidine analogue, reflects changes in the tumor cell proliferative activity and its uptake in tumor tissues is associated with this activity (3-13). Therefore, ^{18}F-FLT may be used as a positron imaging agent for early evaluation of the curative effects of therapies on tumors. However, some studies have indicated that there may not be an association between ^{18}F-FLT uptake and tumor cell proliferative activity (14,15).

Although ^{18}F-FLT shares some biochemical characteristics with thymidine, it serves as a terminator of DNA strand synthesis and is not incorporated into the DNA strand. In addition, the dynamic differences between ^{18}F-FLT and thymidine have not yet been clearly defined (16). The underlying mechanism of ^{18}F-FLT, as well as its significance with respect to tumor diagnosis, also remains unclear. However, ^{18}F-FLT is expected to be of value in terms of tumor diagnosis and curative effect evaluations. In the present study, ^{18}F-FLT and

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^{18}F-FDG uptake were used to evaluate the early therapeutic effects of chemotherapy in Walker 256 tumor-bearing Wistar rats, and the correlations between uptake and tumor cell proliferative activity were analyzed.

Materials and methods

Establishment of the rat model. A total of 3 walker 256 ascites tumor-bearing Wistar rats (mean age, 6 weeks; mean weight, 135 g) were obtained from the Institute of Oncology, Chinese Academy of Medical Science (Beijing, China). All rats were pathogen-free and were housed in a specific pathogen-free room at a constant temperature of 25˚C and humidity of 45%, with a 12 h light/dark cycle and *ad libitum* access to food and water. When the rats exhibited abdominal bulging, 5-6 ml of flaxen-colored ascites were collected and diluted with physiological saline to a $4x10^7$ cells/ml suspension. A total of 30 additional healthy female Wistar rats (age, 5 weeks; weight, 120±20 g) were obtained from the Laboratory Animal Center of China Medical University (Shenyang, China). The prepared Walker 256 cell suspension was subcutaneously inoculated into the right axilla of healthy rats (0.2 ml/rat). Tumors grew within 7-10 days. Rats were used in the following experiments once the maximum tumor diameters at the inoculation sites grew to 1.5-2.0 cm. The present study was conducted in strict accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health. The animal use protocol was reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) of China Medical University.

Animal grouping and treatment. Walker 256 tumor model rats were randomly divided into two groups, a control group (n=10) and a chemotherapy group (n=20). Chemotherapy was performed via tail intravenous injection of epirubicin (Zhejiang Hisun Pharmaceutical Co., Ltd., Shanghai, China). Epirubicin was diluted to a concentration of 1 mg/ml, and each rat was administered a volume of 0.5-0.7 ml at a dose of 5 mg/kg body weight. At 24 h after chemotherapy, five rats each underwent ^{18}F-FLT PET-CT or ^{18}F-FDG PET-CT imaging. At 48 h after chemotherapy, five each of the remaining 10 rats underwent ^{18}F-FLT PET-CT and ^{18}F-FDG PET-CT imaging. Rats in the control group received tail intravenous injections of equivalent volumes of physiological saline and subsequently underwent ^{18}F-FLT or ^{18}F-FDG PET-CT imaging (n=5 for each treatment).

^{18}F-FLT and ^{18}F-FDG PET-CT imaging. ^{18}F-FLT and ^{18}F-FDG were synthesized at the PET-CT Center of the Affiliated Shengjing Hospital of China Medical University with a Minitrace drug synthesis system (GE Healthcare Bio-Sciences, Pittsburgh, PA, USA). The FLT precursor was produced by Jiangsu Huayi Chemical Co., Ltd., (Changshu, China). A 0.2-ml volume of ^{18}F-FLT or ^{18}F-FDG (0.5 mCi) was administered to each rat via caudal vein injection. The radioactive intensity of the syringe was detected prior to and following injection. Following a period of 40 min, the rats were anesthetized via intraperitoneal injection of chloral hydrate (Chinese Medicine Group Chemical Reagent Co., Ltd., Shanghai, China) at a dose of 3 ml/kg body weight. Each rat was subjected to PET-CT imaging 1 h after imaging agent injection. Each rat was fixed on a foam plate and placed in a PET-CT imaging system (Discovery ST16 PET-CT; GE Healthcare Bio-Sciences). CT acquisition conditions were set to 120 kV, 60 mA, and 5-mm layer thickness. A 3-dimensional acquisition model was used for PET. Each bed was scanned for 3 min from head to tail. Images were subsequently processed on a Xeleris workstation (GE Healthcare Bio-Sciences). The ratio of ROI radioactivity counts in the tumor tissue to those in the same area of the contralateral soft tissue (T/M) was quantitatively determined.

Tumor tissue processing. Following imaging, the rats were immediately sacrificed by cervical dislocation and weighed. Tumor tissues were removed, flushed with physiological saline, and wiped dry to determine the radioactive intensities and weights. The percentage intake of radioactivity per gram of tumor tissue (% ID/g) was calculated. Tumor tissues were subsequently fixed in 10% neutral formaldehyde and processed into paraffin-embedding blocks within 24 h. Embedded tissues were sectioned into slides and stained with hematoxylin and eosin. Immunohistochemical Ki-67 staining of the tumor tissues was performed using an Envision kit (cat. no. D-C1-08C22C; Wuhan Boster Biological Technology Ltd., Wuhan, China) according to the manufacturer's instructions. Ki-67 expression was determined via light microscopy by an experienced pathologist. Samples were considered to be Ki-67-positive if the tumor cell nuclei and occasional cytoplasm were stained brown. If only the cytoplasm but no nuclei were stained, the sample was considered negative. The positive percentage of Ki-67, which was termed as the labeling index (LI-Ki-67), was identified by scanning 10 random high-powered (magnification, x400) fields per tumor section.

Statistical analysis. Data processing was performed using SPSS 17.0 statistical software (SPSS, Inc., Chicago, IL, USA). Measurement data are shown as the mean ± standard deviation. Mann-Whitney tests were used to compare the data collected before and after chemotherapy, and Pearson correlation analysis was implemented. $P<0.05$ was considered to indicate a statistically significant difference.

Results

^{18}F-FLT and ^{18}F-FDG radioactivity distribution. PET-CT imaging demonstrated significant reductions in the distribution of ^{18}F-FLT radioactivity in tumor-bearing mice at 24 and 48 h after chemotherapy, as compared with the control group (Fig. 1A-C). The T/M ratios were also significantly reduced ($P<0.01$, Table I). Similarly, the distribution of ^{18}F-FDG radioactivity and T/M ratio significantly reduced at 24 and 48 h after chemotherapy (Fig. 1D-F; $P<0.05$; Table I).

Ki-67 labeling index. Tumor cells with brown-stained nuclei were considered to be proliferating cells. Compared with the LI-Ki-67 of the control group, the LI-Ki-67 values at 24 and 48 h after chemotherapy were significantly reduced in the tumor-bearing mice (58.92±4.85% vs. 41.00±5.70% and 58.92±4.85% vs. 25.96±3.42%, respectively; $P<0.001$; Fig. 2A-C; Table I).

Table I. ^{18}F-FLT and ^{18}F-FDG uptake and LI-Ki-67 in tumor tissues.

	^{18}F-FLT uptake		^{18}F-FDG uptake		
Groups	T/M	% ID/g	T/M	% ID/g	LI-Ki-67
Before chemotherapy	2.128±0.145	0.334±0.034	6.374±0.649	4.100±0.573	58.92±4.85
24 h after chemotherapy	1.572±0.181	0.244±0.032	5.482±0.459	3.232±0.441	41.00±5.70
48 h after chemotherapy	1.156±0.221	0.168, 0.030	4.744±0.309	2.636±0.364	25.96±3.42
P-value[a]	0.001	0.003	0.036	0.028	0.001
F[b]	8.221	8.198	5.704	4.819	12.419
P-value[b]	<0.001	<0.001	0.001	0.001	<0.001

Data are presented as the mean ± standard deviation. [a]24 h after chemotherapy was compared with the control group; [b]48 after chemotherapy was compared with the control group.

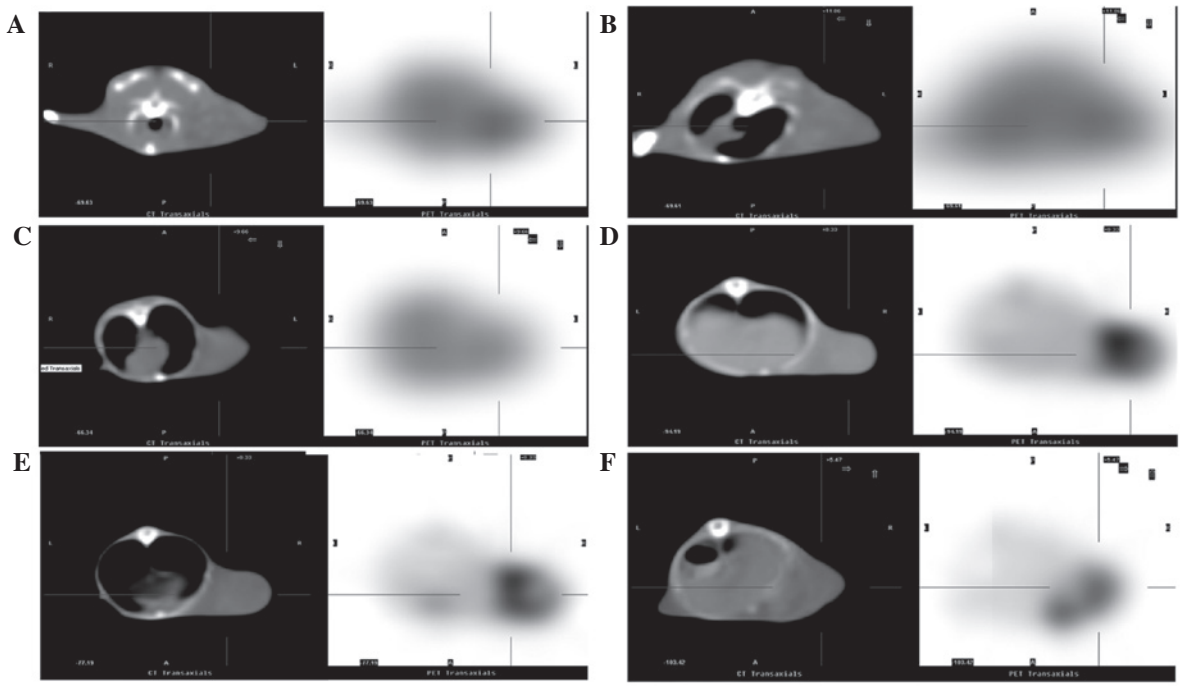

Figure 1. ^{18}F-FLT and ^{18}F-FDG radioactive distribution in tumor tissues. (A) ^{18}F-FLT radioactive distribution in tumor tissue was markedly higher than the surrounding background in the control group. (B) At 24 h after chemotherapy, ^{18}F-FLT radioactive distribution in tumor tissue was markedly reduced, as compared with the control group. (C) At 48 h after chemotherapy, ^{18}F-FLT radioactive distribution in tumor tissue was further decreased. (D) ^{18}F-FDG radioactive distribution in tumor tissue was markedly higher than the surrounding background in the control group. (E and F) At 24 h and 48 after chemotherapy, ^{18}F-FDG radioactive distribution in tumor tissue was markedly decreased, as compared with the control group. Quantitative analysis is presented in Table I.

Correlation analysis. ^{18}F-FLT uptakes (T/M) at both 24 and 48 h after chemotherapy correlated positively with the LI-Ki-67 (r=0.899). Meanwhile, the ^{18}F-FDG uptake (T/M) after chemotherapy also correlated positively with the LI-Ki-67 (r=0.813). In both the ^{18}F-FLT and ^{18}F-FDG groups, the T/M correlated positively with the % ID/g (r=0.898 and 0.843, respectively).

Discussion

The present study primarily investigated whether changes in the ^{18}F-FLT and ^{18}F-FDG uptake in Walker 256 tumors during the early post-chemotherapy stage may reflect alterations in the tumor cell proliferative activity. The applicability of ^{18}F-FLT for evaluating the early efficacy of tumor treatment was also assessed. The results demonstrated that alterations in the uptake of ^{18}F-FLT and ^{18}F-FDG after chemotherapy correlated positively with changes in tumor cell proliferation.

The present findings showed that the uptake of ^{18}F-FLT by Walker 256 tumors was reduced during the early stage after epirubicin chemotherapy (24 h) and that ^{18}F-FLT uptake exhibited an additional significant reduction 48 h after chemotherapy. Immunohistochemistry also demonstrated downregulated Ki-67 expression in the tumor tissues, suggesting that epirubicin may inhibit tumor proliferative activity, a process that could also be detected via ^{18}F-FLT PET-CT imaging.

An alteration in the hydroxyl group of 4'-epirubicin from a cis- to a trans-form renders epirubicin a cell cycle-nonspecific drug, and its main mechanism of action is mediated

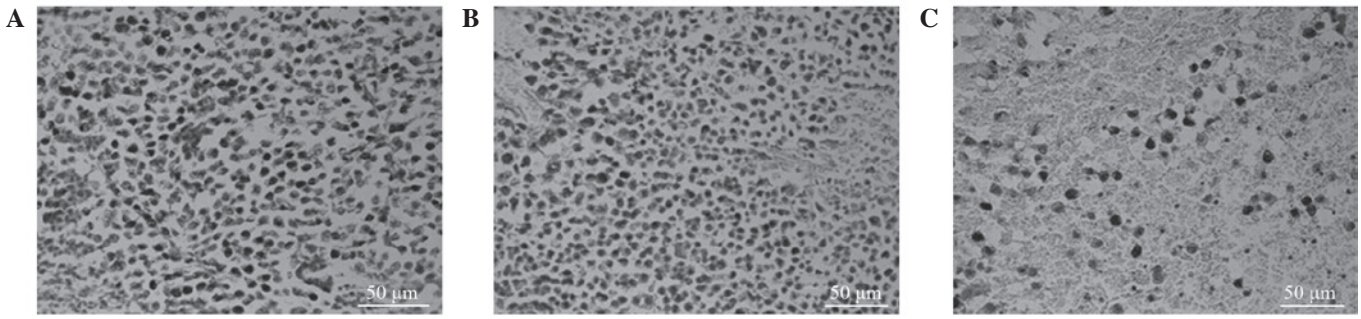

Figure 2. Ki-67-positive cells in tumor tissues. (A) A large number of Ki-67-positive cells were detected in the tumor tissues of the control group. (B) The percentage of Ki-67-positive cells in the tumor tissue markedly decreased at 24 h after chemotherapy. (C) A further reduction in the percentage of Ki-67-positive cells in the tumor tissue was noted at 48 h after chemotherapy. Quantitative analysis is presented in Table I.

through DNA binding (17,18). A previous *in vitro* experiment demonstrated that epirubicin was able to rapidly enter cells and bind to DNA, thereby inhibiting the nucleic acid synthesis and mitosis (19). From its mechanism of function, we concluded that since epirubicin inhibits cellular DNA synthesis, tumor cells use less thymidine and thus take up smaller amounts of the ^{18}F-FLT thymidine analogue. The pyrimidine analogue ^{18}F-FLT is involved in DNA synthesis, but not RNA synthesis, during the process of cell proliferation (20). ^{18}F-FLT is transported into cells via passive diffusion and facilitated by Na^+-dependent carrier transport. It is subsequently phosphorylated by thymidine kinase 1 (TK1) to yield ^{18}F-FLT-monophosphate and is retained in the cell. TK1 is among the key enzymes necessary for the DNA salvage pathway, which is inactive in resting cells but exerts maximal activity in the late G1 and S phases of proliferating cells (21). Therefore, TK1 catalytic phosphorylation is the basis for the use of ^{18}F-FLT as a tracer. It has previously been reported that TK1 activity is markedly increased in malignant tumor cells, when compared with benign cells (22). Furthermore, in tumor cells, mutations occur at the carboxy terminus of TK1, which inhibits the normal degradation of TK1 during the M phase; as a result, the activity of TK1 increases abnormally in tumor cells (23). Therefore, actively proliferating tumors are able to take up ^{18}F-FLT and exhibit focally concentrated radioactivity on PET-CT. Accordingly, the reduced uptake of ^{18}F-FLT by Walker 256 tumors following epirubicin chemotherapy may have been associated with inhibited cell proliferative activity. The amount of ^{18}F-FLT uptake may be used to reflect tumor cell proliferation during the early stage after chemotherapy.

Although the study demonstrated an association between ^{18}F-FLT uptake and cell proliferation, in contrast to the opposing results achieved by other scholars (14,15), it is important to note that there are two tumor DNA synthesis pathways, *de novo* synthesis and salvage synthesis. Different tumors may employ different DNA synthesis pathways. Some tumors predominantly use salvage synthesis, whereas others typically use *de novo* synthesis (24). TK1 is an enzyme that only acts within DNA salvage synthesis, and thus it can only reflect DNA salvage synthesis activity in tumors. Chemotherapy drugs can induce a transformation between the two synthetic routes. Certain chemotherapy drugs are able to activate the DNA salvage synthesis pathway by inhibiting the *de novo* synthesis pathway, thus increasing TK1 activity and ^{18}F-FLT uptake. For instance, the chemotherapy drug 5-fluorouracil (5-FU) can transform into its derivatives fluorodeoxyuridine monophosphate and fluorouridine triphosphate *in vivo* and thus block the synthesis of dTMP (25). Accordingly, 5-FU can affect DNA biosynthesis, induce S phase stasis, and subsequently activate the DNA salvage synthesis route. Eventually, 5-FU therapy can result in increased TK1 activity. This increased TK1 activity promotes ^{18}F-FLT uptake but downregulates DNA synthesis and subsequently reduces the cell proliferation rate (26). In such situations, ^{18}F-FLT uptake does not reflect tumor cell proliferation. Despite this finding, the role of ^{18}F-FLT in tumor research cannot currently be denied. Its association with tumor cell proliferation requires more in-depth and detailed studies.

Different drugs inhibit tumor growth via various mechanisms at different cell cycle phases. ^{18}F-FLT is only involved in the DNA salvage synthesis pathway, and thus, it does not reflect the proliferation of tumors that predominantly employ the *de novo* synthesis pathway. Therefore, when determining the effects of ^{18}F-FLT uptake on tumor cell proliferation, the anti-tumor drugs and their mechanisms of action should be considered to ensure that ^{18}F-FLT uptake provides a true reflection of tumor cell proliferation. Clinically, combination chemotherapy is used to treat patients with tumors, which leads to complicated changes in tumor DNA synthesis. In this situation, ^{18}F-FLT uptake can hardly reflect tumor cell proliferation. Accordingly, additional preclinical and clinical research is required to eludicate the roles of ^{18}F-FLT in different tumors treated via different methods (27).

^{18}F-FDG uptake by tumors also decreased during the early stage after chemotherapy in the present study, a phenomenon that may have been associated with the mechanism of ^{18}F-FDG uptake. In cells, ^{18}F-FDG uptake predominantly depends on glucose transporter expression and hexose phospho-kinase activity on the cell membrane (2). Potential explanations for the decreased ^{18}F-FDG uptake observed in tumors after epirubicin chemotherapy may include the following: Epirubicin may reduce the activity of hexose phospho-kinase and thus reduce ^{18}F-FDG uptake by the tumor, and epirubicin may inhibit tumor cell division and thus lead to a lower energy requirement in these cells. Glucose is the main source of energy for tumor growth. Therefore, ^{18}F-FDG uptake decreases if glucose utilization decreases. A decrease in ^{18}F-FDG uptake is an indirect result of reduced tumor cell proliferation, whereas a decrease in ^{18}F-FLT uptake by tumor cells is directly associated with

reduced tumor cell proliferation. Therefore, ^{18}F-FDG metabolism may also indirectly reflect tumor cell proliferation to some extent, although this metabolism may be influenced by various factors. For instance, blood sugar levels, the functional status of the brain tissue, and other factors may induce changes in the ^{18}F-FDG uptake of tumor tissues. Conversely, cell proliferative activity may be among the factors influencing ^{18}F-FDG uptake.

In conclusion, the results of the present study showed that ^{18}F-FLT and ^{18}F-FDG uptake by tumors correlated positively with the tumor cell proliferative activity during the early stage after chemotherapy. In other words, ^{18}F-FLT and ^{18}F-FDG uptake by tumors may reflect changes in the tumor cell proliferative activity during the early stage after treatment and may be an effective index for evaluating the early therapeutic effects of chemotherapy. In the present study, small animals were subjected to clinical PET-CT, resulting in poor image resolution. However, the correlation between the tumor uptake (T/M) as determined via PET-CT imaging and the actual tumor uptake (% ID/g) was also analyzed and the findings showed a good positive correlation between these factors, suggesting that PET-CT-determined T/M may reflect the actual uptake in small animal tumor tissues.

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