Review Article

The application of ^{18}F-FDG PET/CT imaging for human hepatocellular carcinoma: a narrative review

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Background and Objective: Primary hepatocellular carcinoma (HCC) poses a significant threat to human health. The mean overall survival (OS) of HCC is approximately 15.8 months whereas the 6-month and 1-year OS rates are only 71.6% and 49.7%, respectively. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) has been widely used for the management of several solid cancers; however, HCC frequently displays low ^{18}F-FDG uptake; approximately 50% of HCC cases do not take up ^{18}F-FDG. Therefore, ^{18}F-FDG PET is not considered very useful for the visualization of HCC and is not currently a recommended standard imaging modality for HCC. Conversely, ^{18}F-FDG PET/CT has been reported to be clinically important in the management, staging, and prognosis of HCC patients. Currently, reports relating to ^{18}F-FDG uptake in HCC are unclear and controversial. There is an urgent need to clarify the efficacy of ^{18}F-FDG PET for the management of HCC.

Methods: The PubMed database was searched for all articles on the application of ^{18}F-FDG PET/CT imaging for human HCC up to December 2021. The following search terms were used: 'Hepatocellular carcinoma', '[18F]FDG PET/CT', 'Hypoxia', '[^{11}C]Choline'.

Key Content and Findings: In this review, we re-evaluate the potential hypoxia-dependent uptake mechanism of ^{18}F-FDG in HCC and review the usefulness of ^{18}F-FDG PET/CT for identifying, managing, and investigating the biological properties of HCC.

Conclusions: ^{18}F-FDG PET/CT is very useful for HCC visualization, management, and the evaluation of biological properties. A negative test for ^{18}F-FDG uptake is not meaningless and may reflect a relatively better outcome. ^{18}F-FDG-positive lesions indicate a significantly less favorable prognosis.

Keywords: Hepatocellular carcinoma (HCC); ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT); hypoxia; prognosis; management

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver and the fourth leading cause of cancer-related death globally (1). The mean overall survival (OS) for HCC is 15.8 months whereas the 6-month and 1-year OS rates are 71.6% and 49.7%, respectively (2). The etiology of HCC is closely related to viral hepatitis, non-alcoholic fatty liver disease, and subsequent cirrhosis (3). Due to its morbidity and high mortality, HCC poses a significant threat to human health. The current treatment options for HCC patients mainly include radiofrequency ablation/percutaneous ethanol injection, partial liver resection, and transarterial chemoembolization (4).

Early diagnosis of HCC is particularly important when considering treatment options and the prognosis of patients. In clinical practice, liver biopsy is not routinely performed due to the risk of tumor spread and bleeding. At present, the diagnosis of HCC is mainly based on imaging examinations such as ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI), and related laboratory tests. However, morphological characteristics, based on the number and size of tumors, do not incorporate the biological behavior of the tumor, and thus would not accurately predict aggressiveness, prognosis, and the risk of recurrence of the tumor.

^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) imaging is widely used for the management of several solid cancers and is also used to monitor recurrence, metastatic spread, and the response to therapy, thus providing valuable prognostic information (5,6). PET is valuable for reflecting the biological status of tumor aggressiveness which is highly associated with the tumor pathology (7). However, HCC cases frequently exhibit low ^{18}F-FDG uptake. The so called "false-negative" rate of ^{18}F-FDG PET/CT is almost 50% when imaging HCC (8). Therefore, ^{18}F-FDG PET is not generally considered very useful for HCC visualization and is not currently a recommended standard imaging modality for the diagnosis of HCC. Subsequently, ^{11}C-choline and other PET tracers have been used for HCC visualization; the detection rate and sensitivity of these methods for lesions has been reported to be higher than that of ^{18}F-FDG (9). However, a growing body of evidence indicates that ^{18}F-FDG PET/CT has important clinical significance for therapeutic strategy, staging, prognosis, and recurrence in HCC patients (10-12). Although multiple PET tracers have been developed and attempted for HCC visualization, none have been shown to be superior to ^{18}F-FDG in clinical practice. Patients with ^{18}F-FDG-positive lesions have a higher risk of recurrence; survival time and survival rates are significantly less favorable than those with ^{18}F-FDG-negative lesions (13-15). ^{18}F-FDG non-avidity HCC may reflect a relatively more favorable outcome.

Studies of patients with lung cancer, colorectal cancer, and microscopic peritoneal tumors have revealed that ^{18}F-FDG uptake may not be intrinsic to solid cancer, and that hypoxia may be one of the most fundamental driving forces, thus resulting in altered energy metabolism by virtue of increased anaerobic glycolysis (16-21). Hypoxia-induced glucose transporter expression may lead to increased FDG uptake, leading to the transformation of HCC into a more aggressive disease phenotype, such as a larger tumor size, recurrence, and poor survival (22). The relationship between ^{18}F-FDG uptake and hypoxia may help to explain the relationship between ^{18}F-FDG uptake and prognosis, thereby providing more effective clinical treatment decisions for HCC patients.

Articles relating to the application of ^{18}F-FDG PET/CT in HCC are controversial. Some believe that the role of ^{18}F-FDG PET in the diagnosis of HCC is minimal (8,9), yet many others have shown that it is of great significance to the prognosis of HCC (10-12). Research has shown that the uptake of FDG in well-differentiated tumor cells is low and that the prognosis of patients is good. In this article, we revisit and review the usefulness of ^{18}F-FDG PET/CT for visualizing, managing, and investigating the biological properties of HCC. In addition, we discuss the potential mechanisms underlying ^{18}F-FDG uptake in HCC. We present this article in accordance with the Narrative Review reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-22-1420/rc).

Methods

A search was conducted in the database of PubMed for articles on the application of ^{18}F-FDG PET/CT imaging for human HCC up to December 2021. The search terms used included the following: 'Hepatocellular carcinoma', '[^{18}F]FDG PET/CT', 'Hypoxia', '[^{11}C]Choline'. The detailed search strategy is displayed in *Table 1*.

Non-^{18}F-FDG PET imaging agents for HCC

^{18}F-FDG PET is less sensitive for the diagnosis of HCC and is not routinely used as a diagnostic modality for HCC. This has led to studies of other non-^{18}F-FDG PET imaging

Table 1 The search strategy of PubMed

Items	Specification
Date of search	2021.12.31
Databases	PubMed
Search terms used	'Hepatocellular carcinoma'[MeSH] OR 'HCC' [MeSH]
	'[^{18}F]FDG uptake'[MeSH] AND 'Tumor' [MeSH]
	'[^{18}F]FDG PET/CT' [MeSH]
	'Hepatocellular carcinoma'[MeSH] AND '[^{18}F]FDG PET/CT' [MeSH]
	'Hypoxia' [MeSH] AND 'Tumor' [MeSH]
	'[^{11}C]Choline' [MeSH] AND 'Hepatocellular carcinoma' [MeSH]
	'[^{18}F]FDG PET/CT' [MeSH] AND 'Tumor' [MeSH]
Timeframe	1990–2021
Inclusion and exclusion criteria	Articles about PET/CT and human hepatocellular carcinoma was mainly included. It excluded articles that have no [^{18}F]FDG
Selection process	It was conducted independently by Yong Yao and Xiao-Feng Li; data selection is the intersection of the search of two authors

^{18}F-FDG PET/CT, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography.

agents, such as ^{11}C-choline, ^{11}C-acetate, and its ^{18}F-labeled derivatives. The advent of new radiotracers makes it possible to visualize other metabolic processes besides glucose metabolism.

Due to heterogeneity within a tumor, the differential uptake patterns detected by different tracers can be exploited. ^{11}C-acetate is used to evaluate the synthesis of fatty acids; these are related to the growth and invasion of tumor cells. Park *et al.* studied the combination of ^{18}F-FDG and ^{11}C-acetate in HCC patients and found that the sensitivity of the combined use of tracers was 83%, whereas that of the single tracers was 75% and 60%, respectively (13). Ho *et al.* also evaluated the use of ^{18}F-FDG in combination with ^{11}C-acetate for HCC patients. These authors found that the sensitivity of ^{11}C-acetate alone in well-differentiated tumors was good, whereas that of ^{18}F-FDG in poorly differentiated tumors was better (23). More choline, especially phosphatidylcholine, is needed as substrate for phospholipid synthesis during malignant tumor transformation; this promotes the development of nuclide-labeled choline compounds as imaging biomarkers for cell membrane synthesis. ^{11}C-choline is a potential tracer that could supplement ^{18}F-FDG to detect HCC lesions. Yamamoto *et al.* have shown that ^{11}C-choline PET has a higher detection rate for moderately differentiated HCC lesions but not for poorly differentiated HCC lesions; ^{18}F-FDG PET produced the opposite result (9). Furthermore, the development of ^{18}F-fluoroacetate and ^{18}F-fluorocholine overcame the problem created by the short half-life of ^{11}C radionuclides. The alternative or complementary functions of these imaging agents in HCC characterization and the clinical impact of dual-trace PET with FDG and choline/acetate require further research and dosimetry considerations. Our previous clinical results showed that perfusion combined with metabolic ^{18}F-FDG PET/CT could provide information relating to the blood perfusion and glucose metabolism of HCC and could be performed routinely for outcome prediction and anti-cancer management. In our opinion, ^{11}C-choline PET provides little additional information beyond perfusion dynamic ^{18}F-FDG PET.

Application of ^{18}F-FDG PET in HCC

As a functional imaging method, ^{18}F-FDG PET can reflect metabolic changes within the body and could be used for whole body imaging. Combined with the precise positioning of CT, ^{18}F-FDG PET has important clinical significance for treatment strategies, staging, and the prognostic and efficacy evaluation of HCC patients, especially with regards to the detection of metastatic lesions and the monitoring of recurrence (*Table 2*). According to

Table 2 ^{18}F-FDG PET has important clinical significance for HCC patients

Clinical significance	Author	Principal comments
Diagnostic	Yamamoto Y (9)	The detection rate and sensitivity of ^{11}C-choline for lesions higher than that of ^{18}F-FDG
	Ho CL (23)	The sensitivity of ^{11}C-acetate alone in well-differentiated tumors was good, whereas that of ^{18}F-FDG in poorly differentiated tumors was better
	Khan MA (8)	The so called "false-negative" rate of ^{18}F-FDG PET/CT is almost 50% when imaging HCC
Treatment strategies	Lee SM (10)	With a high FDG uptake, a variety of treatments may be more effective for tumor control
	Kitamura (24)	The level of FDG uptake before rescue liver transplantation was able to identify which patients could benefit from hepatectomy
Staging	Ferda J (25)	Poorly differentiated HCCs are more often FDG-positive than well-differentiated HCCs
	Lee JD (26)	the pattern of ^{18}F-FDG uptake could reflect the possibility of tumor progression and metastasis
Prognostic	Haug AR (15)	The prognosis of FDG-positive HCC is significantly worse than that of FDG-negative HCC
	Ma W (27)	Patients with a low FDG uptake have longer progression-free survival and longer overall survival
Recurrence	Han JH (28)	FDG uptake was significantly associated with tumor recurrence
	Takada (29)	The 5-year recurrence rate of PET-negative patients was significantly lower
	Ling (30)	The 3-year cumulative recurrence rate with a high FDG uptake was significantly higher

^{18}F-FDG PET/CT, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; HCC, hepatocellular carcinoma.

^{18}F-FDG PET results, we can accurately assess the benefits and risks of HCC patients, especially in the prediction of the aggressiveness of advanced HCC. We are also able to detect hidden malignancies and extrahepatic metastases that can be missed by other imaging methods (7). ^{18}F-FDG PET allows for the characterization of cancer biology. Poorly differentiated HCCs are more often FDG-positive than well-differentiated HCCs (25). Furthermore, the pattern of ^{18}F-FDG uptake could reflect the possibility of tumor progression and metastasis (26).

The accurate staging of HCC is not only critical to therapeutic options; it is also critical to prognosis. ^{18}F-FDG PET has shown promising results with regards to the detection of extrahepatic metastases. HCCs with a high FDG uptake are more aggressive than those with a low FDG uptake. The uptake of ^{18}F-FDG by HCC is significantly and positively correlated with the tendency for extrahepatic metastasis, and metastatic HCC lesions would also increase the uptake of ^{18}F-FDG (23). HCCs with high FDG uptake also have a high risk of early recurrence and distant metastasis (31). Trojan *et al.* showed that in patients with moderately or poorly differentiated HCC, ^{18}F-FDG PET facilitated the effective non-invasive staging of patients with tumors >5 cm (32). Takeuchi *et al.* retrospectively analyzed the records of HCC patients who received FDG PET/CT prior to initial treatment and concluded that FDG PET/CT imaging biomarkers should be considered in the HCC staging system (33). Lin *et al.* further showed that the combined estimates of sensitivity, specificity, positive likelihood ratio (PLR), and negative likelihood ratio (NLR) of FDG PET for detecting metastatic HCC were 76.6%, 98.0%, 14.68, and 0.28, respectively (34). By evaluating the gene expression profiles of HCC, Lee *et al.* found that the pathological tumor grade was closely related to the ^{18}F-FDG uptake pattern, and that HCCs with high ^{18}F-FDG uptake had more aggressive biological characteristics than those with low uptake (35).

In addition to detecting unexpected extra-hepatic metastases, PET also increases the prognostic value of predicting survival. Previous studies have shown that among HCC patients receiving treatment, patients with a low FDG uptake have longer progression-free survival (PFS) and longer OS, thus indicating that the FDG avidity of HCC was significantly correlated with clinical outcomes (27,36). It has been reported that tumor doubling time has a positive association with FDG uptake of HCCs (37). Furthermore, Haug *et al.* have found that in terms of recurrence time, PFS, and survival, the prognosis of FDG-positive HCC is significantly less favorable than that of FDG-negative HCC (15).

^{18}F-FDG PET may be used not only to predict the prognosis, but also to adjust the surgical strategies according to the level of FDG uptake (38). Considering

the differences in FDG uptake, HCC will exhibit different tumor characteristics; therefore, different treatment strategies are required according to the performance of FDG PET in HCC patients. A previous study showed that when liver transplantation was performed under neoadjuvant conditions, the level of FDG uptake before rescue liver transplantation could be used to identify which patients could benefit from hepatectomy (24). For HCC patients with a high FDG uptake, a variety of treatments may be more effective in tumor therapy, whereas patients with a low ^{18}F-FDG uptake seem to be less affected by treatment modality (10). In addition, for HCC patients with a high FDG uptake, major hepatectomy should be chosen to minimize the possibility of residual tumors in order to obtain survival benefits (39). Kang *et al.* studied patients receiving living-donor transplantation and confirmed that combining FDG PET findings with clinical factors could effectively select HCC patients who are candidates for liver transplantation (40).

^{18}F-FDG PET also plays a promising role in monitoring the recurrence of HCC (41). Han *et al.* found that ^{18}F-FDG uptake was significantly associated with tumor recurrence in HCC patients undergoing curative surgical resection; patients with a high FDG uptake had worse survival (28). The overall risk of recurrence in PET-positive HCC patients is higher than that of negative patients. Takada *et al.* collected data from 182 HCC patients who received liver transplantation and found that the 5-year recurrence rate of PET-negative patients was significantly lower than that of other patients; furthermore, PET-positive status was a significant and independent risk factor for recurrence (29). A retrospective analysis of 67 HCC patients who underwent curative hepatic resection showed that a tumor-to-normal liver standardized uptake value ratio (TNR) ≥1.53 was an independent predictor of distant metastasis recurrence; the specificity, sensitivity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of distant metastasis recurrence for HCC were 76.4%, 91.7%, 45.8%, 97.7%, and 79.1%, respectively (42). Ling *et al.* found that the 3-year cumulative recurrence rate with a high FDG uptake was 70.8%, which was significantly higher than that for HCC patients with a low FDG uptake (30).

^{18}F-FDG PET imaging for HCC and hypoxia

The false-negative rate of ^{18}F-FDG PET/CT is almost 50% when imaging patients with HCC. This leaves the question as to why some HCCs take up ^{18}F-FDG yet others do not. It has been reported that ^{18}F-FDG PET/CT has a low sensitivity in the diagnosis of HCC and that this is mainly related to the specificity of glucose uptake in HCC tumor cells. It is believed that in well-differentiated HCC tumor cells, the higher concentration of glucose-6-phosphatase can accelerate the rapid clearance of ^{18}F-FDG, thus resulting in lower ^{18}F-FDG content in tumor cells. The concentration of glucose-6-phosphatase in poorly differentiated HCC cells is relatively lower, the retention of ^{18}F-FDG is higher, and the lesions show high concentrations of radioactivity (43,44).

^{18}F-FDG uptake may be not intrinsic to cancer, although hypoxia may be one of the fundamental driving forces. The common feature of solid tumors is hypoxia; this is closely related to chemotherapy resistance and tumor prognosis (45,46). Hypoxia is caused by the oxygen consumption ratio of tumors exceeding the oxygen supply rate from the vasculature. Due to the unlimited proliferation of tumor cells exceeding the existing vasculature, the oxygen demand is increased (47).

The anoxic microenvironment plays a crucial role in inducing the high uptake of ^{18}F-FDG, thus resulting in the transformation of glucose metabolism to anaerobic glycolysis (48-50). As an energy generation pathway, anaerobic glycolysis has relatively low utilization efficiency and requires more glucose substrate to produce equivalent adenosine triphosphate (ATP). The uptake of ^{18}F-FDG is lower in tumor areas with good blood perfusion; therefore, oxygenated tumor cells cannot be mapped. In HCC, highly differentiated tumor cells with slow proliferation have less ^{18}F-FDG uptake because the rate of angiogenesis remains high. In poorly differentiated liver cancer tissues, due to the excessive proliferation of tumor cells, the rate of angiogenesis cannot keep up, thus resulting in hypoxia; the rate of ^{18}F-FDG uptake remains high. This also indirectly reflects the high ^{18}F-FDG uptake in undifferentiated and poorly differentiated HCC.

Our previous studies demonstrated that ^{18}F-FDG uptake was significantly higher in hypoxic portions of larger tumors and severe hypoxic ascites carcinomas (16,20). Hypoxia-specific probe pimonidazole showed that the spatial distribution of ^{18}F-FDG in the peritoneal tumor model perfectly matched that in the tumor (*Figure 1*). In addition, our lung cancer clinical data provides indirect evidence that ^{18}F-FDG PET reports tumor hypoxia (*Figure 2*) (20). Early ^{18}F-FDG dynamic imaging is mainly defined by blood delivery or supply, which can be used to assess tumor perfusion. Over 60-min of ^{18}F-FDG metabolic imaging, the

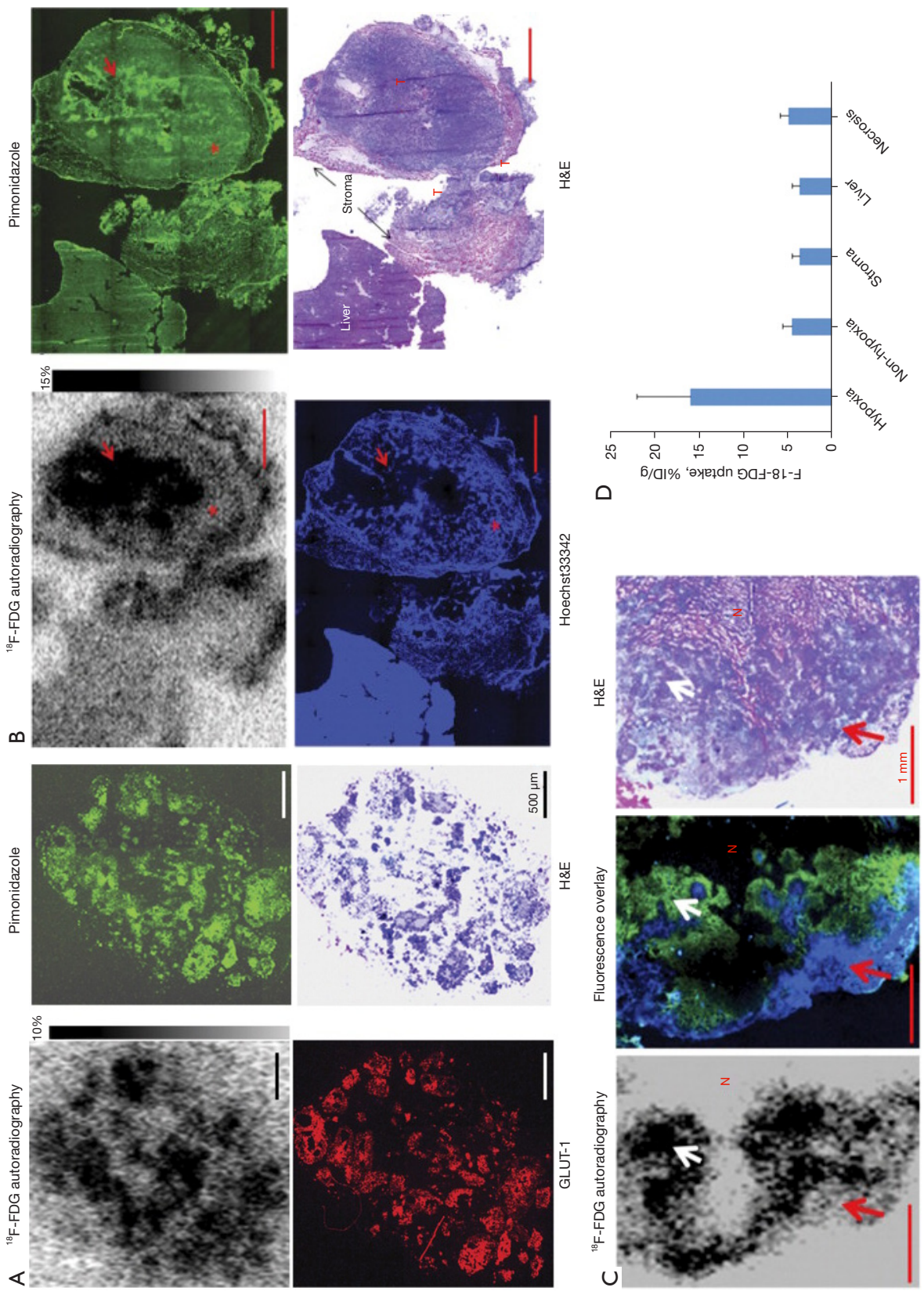

Figure 1 The relationship between ^{18}F-FDG uptake and tumor hypoxia (arrow). (A) A549 ascites tumors have high ^{18}F-FDG uptake and high pimonidazole binding and GLUT-1 expression. (B) ^{18}F-FDG uptake was coincident with high pimonidazole binding in A549 serosa tumors. Scale bar, 2 mm. (C) High ^{18}F-FDG uptake is coincident with high pimonidazole in HT29 subcutaneous xenograft (hypoxia, as indicated by arrows). (D) ^{18}F-FDG uptake was significantly higher in hypoxia regions than normoxic tumor tissue. Pimonidazole is a hypoxia marker, and pimonidazole-stained positive regions suggest hypoxia. Hypoxia is defined as PO_2 less than 10 mmHg or 1.3% O_2. ^{18}F-FDG, ^{18}F-fluorodeoxyglucose. GLUT, glucose transporter. [This figure was originally published in *Transl Oncol*, Li *et al.*, reused with permission from (16)].

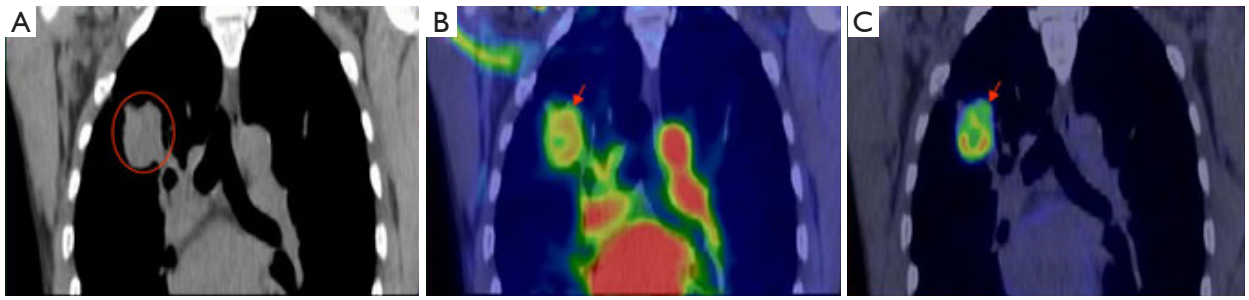

Figure 2 A 52-year-old man with pathologically confirmed right lung adenocarcinoma underwent ^{18}F-FDG PET early perfusion imaging and 60 min metabolic imaging (right lung lesion, as indicated by a circle and arrow). (A) CT image shows a mass in the upper lobe of the right lung (circle); (B) early perfusion imaging; (C) metabolic imaging. There was a significant mismatch between perfusion and metabolism. ^{18}F-FDG PET, ^{18}F-fluorodeoxyglucose positron emission tomography; CT, computed tomography. [This figure was originally published in Oncotarget, Shen *et al*., reused with permission from (20)].

activity accumulated in cells via the GLUT-1/hexokinase pathway, thus indicating that the uptake concentration of ^{18}F-FDG was highest in the tumor volume associated with low blood perfusion (20).

Similar results have been reported in other studies. Hwang *et al.* retrospectively analyzed the results of multi-detector CT and PET/CT of 66 HCC patients who underwent surgical treatment and confirmed that on the multi-detector CT, the increase of ^{18}F-FDG uptake was associated with a reduction in arterial and portal perfusion. Furthermore, higher ^{18}F-FDG uptake and lower perfusion patterns were significantly associated with shorter OS (51). Xia *et al.* reported that hypoxia-induced glucose transporter expression may lead to changes in ^{18}F-FDG PET-CT imaging (22). Yamamoto *et al.* have developed new hyper-polarized MRI and electron paramagnetic resonance imaging procedures that can quantitatively evaluate the glycolysis and oxygenation status of tumors more directly (52). These authors demonstrated that PO_2 was negatively correlated with ^{18}F-FDG uptake. Kaira *et al.* have also found a significant correlation between hypoxia and ^{18}F-FDG uptake (53). These findings demonstrated that viable and well-perfused cancer regions have low ^{18}F-FDG uptake whereas areas with low to absent blood perfusion have high ^{18}F-FDG uptake.

Possible mechanism underlying hypoxia-induced ^{18}F-FDG uptake in HCC

In tumor PET imaging, the degree of hypoxia is highly correlated with ^{18}F-FDG uptake. The specific mechanism of hypoxia-induced ^{18}F-FDG uptake remains unclear. Yao *et al.* have shown that this may be related to the activation of macrophages, metabolic changes, and glycolysis-related enzyme activity changes induced by hypoxia (54). The lack of hypoxia-related basic research, such as immunohistochemistry and autoradiography, will need to be addressed in the future. Other studies have shown that age and the blood glucose level are also influential factors of liver standardized uptake value (SUV) (55,56).

Hypoxia will cause cells to activate the angiogenesis process to increase oxygen delivery; furthermore, cell fuel metabolism is adjusted from mitochondrial respiration to glycolysis (57,58). Another consequence of hypoxia is the activation of hypoxia inducible factor (HIF) which enhances glycolysis and glucose uptake by directly inducing the transcription of GLUT1 and glycolytic genes (59,60). In order to meet their bioenergetic demands, cells must then rely on glycolysis. Since anaerobic glycolysis is inefficient in energy production, hypoxic tissue cells require more ^{18}F-FDG uptake. In order for tumor cells to meet their rapid growth needs, GLUT1 is overexpressed on the surface of tumor cells, which will facilitate more glucose transport to tumor cells (17). Xia *et al.* used quantitative reverse transcription polymerase chain reaction (qRT-PCR) to detect the expression of GLUT1 and GLUT3 in different HCC cells under hypoxic and normoxic conditions. These authors showed that hypoxia can significantly induce the expression of GLUT1 and GLUT3 and that this is related to the high rates of glycolysis and ^{18}F-FDG uptake (22).

Hypoxia causes upregulation of hexokinase protein, which promotes glucose uptake and metabolism (61). The diagnostic accuracy of ^{18}F-FDG PET in HCC is limited by the difference in enzyme expression between

different tumor gradings. In contrast, the enzyme activity in moderately/poorly differentiated HCC compared with non-involved liver regions resulted in an increase in SUV, thus allowing tumor detection (11). Lee *et al.* found that HCC with a high tumor-to-liver SUV ratio (TLR) expressed higher levels of glucose transporter isoform 1 than HCC with a low TLR; furthermore, the proliferation and migration of HCC cells with high ^{18}F-FDG uptake reduced after treatment with glucose uptake inhibitors (62). Chen *et al.* showed that the maximum standardized uptake in HCC patients was inversely correlated with the expression of fructose 1,6-bisphosphatase 1 (FBP1) and that FBP1 may inhibit ^{18}F-FDG uptake through the HIF1A pathway (63).

In HCC, the infiltration of pro-inflammatory macrophages into the tumor microenvironment can promote tumor growth and is associated with invasion and metastasis (64). Active inflammatory processes are common in many tumors, which also predict aggressive behavior. In patients with non-small cell lung cancer, ^{18}F-FDG uptake has been found to be highly correlated with tumor-associated macrophages (TAM) which can significantly enhance tumor hypoxia (65). Reinfeld *et al.* used PET tracers to measure the acquisition and uptake of glucose and glutamine by specific cell subgroups in the tumor microenvironment and found that the factor responsible for a tumor's high-speed consumption of glucose is not the cancer cells but macrophages in tumor tissues and other immune cells (66). Different types of cells in the tumor environment consume different nutrients according to their metabolic activities. For example, immune cells and cancer cells preferentially obtain glucose and glutamine, respectively.

Understand the meaning of ^{18}F-FDG uptake in HCC

Since 95% of solid malignant tumors have a certain degree of hypoxia, ^{18}F-FDG PET can be used successfully for cancer surveillance. ^{18}F-FDG accumulates heavily in hypoxic tumor cells with poor proliferation and low perfusion, but undergoes low uptake in oxygen-rich tumor cells with good proliferation and high perfusion (16). Therefore, the correct interpretation of ^{18}F-FDG uptake is of great clinical significance for the formulation of clinical treatment programs, and the evaluation of curative effect and prognosis.

Since ^{18}F-FDG uptake is not obvious in well-differentiated HCC, ^{18}F-FDG PET is not currently a recommended standard imaging modality for the diagnosis of HCC. However, this procedure has important clinical significance in the therapeutic strategy, staging, prognosis, and recurrence of liver cancer patients. Jo *et al.* found that HCC cells with low proliferation potential under hypoxic conditions have a high possibility of inducing the epithelial-mesenchymal transition process and promoting cell invasion (67). Jo *et al.* speculated that HCC with a high FDG uptake had a better response to radiotherapy than HCC with low uptake (68). Well-differentiated HCC tumor cells grow slowly; therefore, the blood supply can keep up, hypoxia is not serious, and ^{18}F-FDG uptake is low. However, poorly differentiated HCC tumor cells proliferate faster than angiogenesis; therefore, the blood supply cannot keep up, hypoxia is severe, and ^{18}F-FDG uptake is high. In other words, a high FDG uptake indicates that tumor cells may be seriously hypoxic. The reason for this is that the proliferation rate of tumor cells exceeds the rate of angiogenesis. This also indirectly reflects the poorly differentiated state of tumor cells, thus indicating that the patient has a poor prognosis and a short lifespan. If FDG is not taken up, it means that the tumor cells are not severely hypoxic. The reason for this is that the tumor cells proliferate slowly and the blood supply can keep up. This also indirectly reflects the highly differentiated state of tumor cells.

Poorly differentiated HCCs are more often FDG-positive than well-differentiated HCC. Patients with ^{18}F-FDG-positive lesions have a higher risk of recurrence; furthermore, survival times and survival rates are significantly worse than those with ^{18}F-FDG-negative lesions; therefore, conservative treatment and clinical care should be given priority. A negative result for ^{18}F-FDG uptake is not meaningless; rather, it indicates that the patient has a good prognosis and that active treatment is necessary.

Conclusions

^{18}F-FDG PET/CT is very useful for HCC visualization, management, and the evaluation of biological properties. A negative test for ^{18}F-FDG uptake is not meaningless and may reflect a relatively better outcome. ^{18}F-FDG-positive lesions indicate a significantly less favorable prognosis. Hypoxia may be one of the possible mechanisms underlying ^{18}F-FDG uptake in HCC.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-22-1420/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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