The Role of ^{18}F-FDG Accumulation and Arterial Enhancement as Biomarkers in the Assessment of Typing, Grading and Staging of Hepatocellular Carcinoma Using ^{18}F-FDG-PET/CT with Integrated Dual-phase CT Angiography

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Abstract. *Aim: The purpose of the present study was to evaluate the possibility of detection, staging and differentiation assessment of hepatocellular carcinoma (HCC) using a combination of dual-phase computed tomography (CT)-angiography in the arterial and portal phase with positron emission tomography (PET) imaging using ^{18}F-fluorodeoxyglucose (^{18}FDG). Patients and Methods: From a set of 10,000 patients who underwent ^{18}FDG-PET/CT, we examined a total of 65 patients (52 males, 13 females; mean age=61.7 years, ranging from 35-82 years) with HCC. The imaging included CT data acquisition after intravenous application of iodinated contrast material in arterial and portal phases, allowed to obtain data in CT angiography quality. Histological diagnosis of the resection sample (21), biopsy (37) or necropsy (7), including the evaluation of the hepatocytary origin of the tumor and the grade of its differentiation, was determined in all patients. Results: The most sensitive sign in the detection of HCC was the alternative presence of hypervascularity or hyperaccumulation of ^{18}F FDG that reached 93.8%. The high level of ^{18}F-FDG accumulation showed sensitivity of 84.1% and specificity of 75.0% for distinguishing between well- and poorly differentiated HCC. Conclusion: The combination of the dual-phase CT angiography with ^{18}FDG PET helps in the assessment of staging and differentiation of HCC and has an important role in treatment decision-making.*

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Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide and the most common cause of death in patients with liver cirrhosis. Currently, the diagnosis of HCC is based on the laboratory finding of increased alpha-fetoprotein (AFP) and imaging methods. Hybrid imaging positron emission tomography/computed tomography (PET/CT) enables a concurrent evaluation of the morphological and metabolic changes of the organs affected by cancer using a combination of the multidetector computer tomography (MDCT) and PET (1). The purpose of the present work was to evaluate the possibility of detection, of staging and differentiation assessment of HCC by means of a combination of dual-phase imaging with multidetector CT-angiography (MDCTA) in the arterial and portal phase with the metabolic PET imaging using ^{18}F- fluorodeoxyglucose (^{18}-F-FDG), the most available PET radiopharmaceutical. This retrospective study was approved by the local Ethic committee.

Patients and Methods

In a set of 10,000 patients who underwent ^{18}FDG-PET/CT, we examined a total of 62 patients with HCC (53 males, 14 females; mean age=61.7 years, ranging from 35-82 years). The examinations were performed by means of the hybrid PET/CT scanner Biograph 16 (Siemens Healthcare, Knoxville/Erlangen, USA/Germany) that integrates the PET subsystem with the detector system made of luthecium-orthosilicate (LSO) and a fully diagnostically usable 16-row CT. Histological diagnosis of the resection sample (21), biopsy (37) or necropsy (7), including the evaluation of the hepatocytary origin of the tumor and the grade of its differentiation, was determined in all patients.

Table I. *Summary of findings in HCC.*

	CT enhancement	SUV_{max} <5	SUV_{max} 5 to 10	SUV_{max} >10
Well-differentiated	Hypovascular	4	0	0
	Hypervascular	17	7	0
	All	21	7	0
Poorly-differentiated	Hypovascular	0	1	4
	Hypervascular	0	20	9
	All	0	21	13
Mixed	Hypovascular	0	0	0
	Hypervascular	0	3	0
	All	0	3	0

Table II. *Sensitivity of hypervascularity or hypermetabolism in HCC detection.*

Sensitivity	Well-differentiated	Poorly differentiated	All tumors
Hypervascularity	0.857	0.828	0.836
High accumulation	0.250	1.000	0.677
Hypervascularity or high accumulation	0.857	1.000	0.938

Table III. *Differential diagnostic signs between well- and poorly differentiated HCC.*

Well- *versus* poorly differentiated	Sensitivity	Specificity
Hypervascularity	0.653	0.444
High accumulation	0.841	0.750

^{18}F-FDG at a dose of 4 MBq/kg of body weight was applied to patients through the antecubital vein after previous check of blood glucose level. The oral preparation with 1,000 ml of 2.5% aqueous solution of mannitol was performed during the 60-minute accumulation of the radiopharmaceutical at rest in bed. The data acquisition, initially MDCT and then PET, followed the accumulation and peroral preparation. The MDCT part of the examination was performed using the collimation of 16×0.75 mm, pitch factor of 1.5 and exposure values 120kV and 240 effective mAs. One hundred ml of iodine contrast substance was applied intravenously (Iomeron 350; Bracco, Milan, Italy) at a flow of 3 ml/s and flushing with 50 ml of saline solution by a double-piston pressurized injector (Stellant; Medrad, Millwaukee, Mi , USA). The examinations were performed both in the arterial and portal phase. The arterial phase of the examination was performed with a 20-second delay after the administration of the contrast agent from the cranial base to the proximal third of the thighs and the portal phase followed in the caudocranial direction with a pause of 5 seconds from the proximal third of the thighs to the level of the diaphragmatic cupola. T he reconstruction of the thin layers with the reconstruction increment of 0.7 mm achieved a sub-millimeter isotropic spatial differentiation for the evaluation of the MDCT (a cubic voxel with one side of 0.7 mm). The subsequent PET data acquisition was divided into 7 positions in total (beds) and the acquisition of one positron took 3 minutes. The spatial PET differentiation achieved 5 mm. The on-line images with a correction of attenuation were reconstructed also as the uncorrected images.

The corrected and uncorrected PET images, CT examination in the arterial and portal phase, pulmonary HRCT and a fusion of the PET/MDCT were used for the respective evaluation of the examination. The metabolic activity in the liver tumors was evaluated using the measurement of the highest ^{18}FDG uptake (maximum standardized uptake value-SUV_{max}) in the area of the liver tumor process. Based on the achieved value, we determined a grade of the glycolytic activity of the tumors in three various levels, comparable with the surrounding liver tissue (SUV_{max}<5), increased activity (maximum SUV_{max} values between 5 and 10) and finally the extreme level of the glycolytic metabolism (SUV_{max} above 10). We evaluated the presence of the metabolic active metastases in the lymphatic nodes, bones and lungs.

Apart from the metabolic activity and general morphological changes, we also evaluated the vascular system with a focus on blood perfusion of the liver and pathophysiological vascular changes related to the tumor using the multiplanar reconstructions (MPRs), as well as the reconstructions in layers using maximum intensity projection (MIP). We also evaluated the presence of the arterioportal shunts, tumor hypervascularization-of a nodular or diffuse character - and the invasion of the tumor into the portal vein.

Results

Out of 67 patients the diagnosis of hepatocellular character was confirmed in 66 cases; 28 cases of well-differentiated HCC, in 3 cases we found a tissue of well- and poorly-differentiated tumor and in 34 cases, a de-differentiated hepatocellular carcinoma. An increased level of glycolytic activity (accumulation of ^{18}F-FDG) above the surrounding liver tissue in 7 well-differentiated tumors and a comparable level of glycolytic activity with normal liver tissue in 21 tumors, respectively, were found. Liver tumors, with regions of well-differentiated and poorly-differentiated tumor (three cases), showed a differentiation-related distribution; the area where the tumor grew into the portal vein showed an increased accumulation and the major part of the tumor showed only an increased level of ^{18}F-FDG metabolism . In poorly-differentiated tumors, there was an increased and extremely increased level of glycolytic activity in 21 and 13 patients, respectively, while anaplastic malignant tumors showed an extreme level of ^{18}F-FDG metabolism. To note that to estimate differentiation, the level of accumulation of ^{18}F-FDG is highly important.

In case of vascular changes, some degree of hypervascularization in the arterial phase of the CT was observed in all 67 tumors. The diagnosis of HCC was also determined in this tumor type before PET/CT as a working diagnosis, which was confirmed by a marked invasion of the tumor into

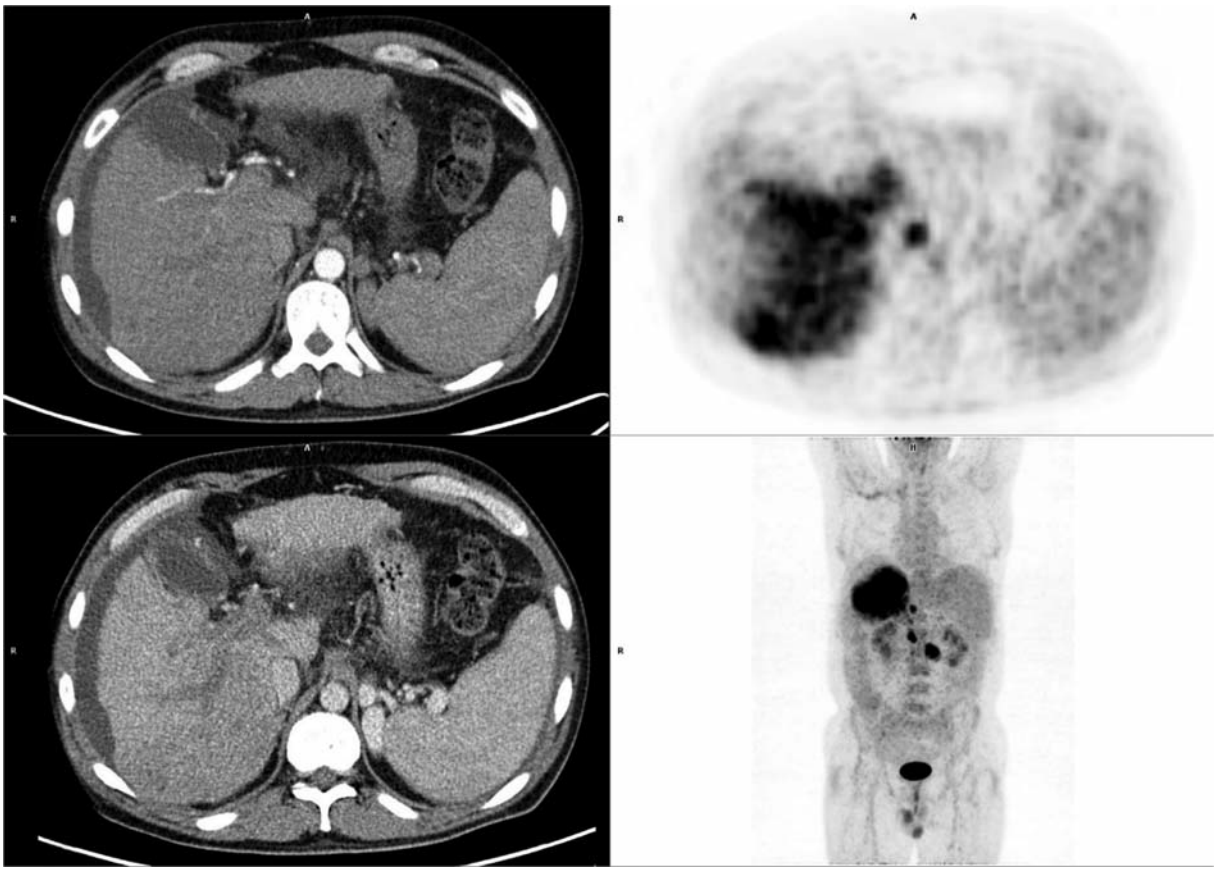

Figure 1. *^{18}F-FDG hypermetabolic, but hypovascular poorly-differentiated HCC with invasion into the portal vein, multiple hypermetabolic lymph node metastases and ascites. Axial CT image in the arterial phase (upper row left), axial CT image in the portal phase (lower row left), PET image (upper row right) and whole body PET image (lower row right).*

the portal vein with extremely expressed atrerioportal shunt. The arterioportal shunt, with a common filling of some of the portal veins, could be found in all tumors in the group. Table I is showing all findings.

According to the accumulation within the tumorous tissue and according to the hypervascularisation, an important improvement in detection of the HCC was found using as alternative the high accumulation or hypervascularity, which improved the sensitivity to 93.8 % from 83.6% (hypervascularity) and 67.7 (high accumulation), respectively, independently to the each sign. An important sensitive and specific sign for distinguishing well- and poorly differentiated HCC is the high accumulation of tissue (sensitivity, 84.1%; specificity, 75.0%). Thanks to the common sign of hypervascularity in well- or poorly differentiated HCC, the iodine contrast enhancement in the arterial phase has a minimal role for assessing the grade of the HCC (sensitivity, 65.3%; specificity, 44.4%). These findings are summarized in Tables II and III.

Invasion into the portal vein was reported in 24 tumors (36.9%) of which five tumors were clearly well-differentiated, in one tumor with regions of well- and poorly- differentiated HCC and in 19 poorly-differentiated tumors.

In eleven patients (16.9%), we found metastases-in three well-differentiated HCC we found multiple bone metastases (a bulky metastasis in the sternum was even the first symptom of the HCC in one patient). The metastases were present only in the pulmonary parenchyma in two poorly differentiated HCC and in one anaplastic tumor. The metastases were present only in the lymphatic nodes in 4 poorly differentiated HCC. In 2 tumors (one with the regions of well- and poorly differentiated HCC and in one poorly differentiated), the metastases were present in the lymphatic nodes together with metastases in bones. Ten of the metastatic tumors had a concurrent invasion into the portal vein and all the metastases had an increased turnover of ^{18}F-FDG (90.9%).

Discussion

As it stems from various studies, the sensitivity of ^{18}F-FDG PET in the detection of HCC ranges between 50 and 70% (1-3). The level of accumulation of FDG in the cells depends on several enzymatic mechanisms, such as the activity of the glucose transporter (Glut 1), phosphorylation using hexokinase (mammalian isoenzyme HK II) and de-phosphorylation of glucoso-6-phosphatase. Glucoso-6-phospatase prepares FDG for the re-transport by the glucose transporter into the extracellular space and it has a key contribution in displaying the hepatocellular elements by means of ^{18}F-FDG.

Extra-intracellular exchange of ^{18}F-FDG in the hepatocellular cells is different from the other tissues (4). Most of the malignant tumors have a high activity of the glucose transporter (from the primary liver tumors in cholangiocellular carcinoma). However, in the HCC the gene of the glucose transporter is expressed only minimally (5-7). In well- and poorly differentiated HCCs the gluconeogenesis has a comparable intensity as in the hepatocytes of the healthy tissue and it causes a comparable accumulation of ^{18}F-FDG in these types of HCCs and in the healthy liver tissue (3, 5). HCC is metabolically more dependent on glutamine than glucose and the fatty acids are the main source of energy in its tissue. High activity of glucoso-6-phosphatase in the liver cells prevents accumulation of ^{18}F-FDG in the cells of the normal liver tissue, as well as in well-differentiated HCCs. On the contrary, cancer cells of poorly differentiated HCC have a reduced activity of glucose-6-phosphatase, slower dephosphorylation of ^{18}F-FDG-6-phosphate; the intermediate product accumulates intracelullary and, as for the activity, the tissue markedly exceeds the surrounding parenchyma due to increased accumulation of the emitter.

Okazumi classifies three basic types according to the behavior of the HCC after administration of ^{18}F-FDG (3). In poorly-differentiated HCC, there is a higher activity of hexokinase (mammalian isoenzyme HKII) and, on the other hand, a reduced activity of glucoso-6-phospatase. this is the reason why these histological types of HCC highly accumulate ^{18}F-FDG (Okazumi type 1) (Figure 1). In the normal liver cell, there is a low activity of the glucose transporter and glucoso-6-phosphatase and, hence, the accumulation of glucose in the normal liver is intermediary. If the activity of the enzymes in the HCC is identical, it cannot be differentiated from the surrounding tissue (Okazumi type 2) (Figure 2). In relation to the normal liver tissue, the HCC appears to be less accumulating FDG in the case that the activity of glucoso-6-phosphatase in the liver tissue is higher compared to the surrounding normal hepatocytes (Okazumi type 3). Type 2 and 3 represent up to 45% of falsely-negative findings in PET out of the total amount of all HCCs and, therefore, they are responsible for a low sensitivity of ^{18}F-FDG PET in detection of HCC (1, 2, 5-7), despite the efforts to prolong the accumulation time (8, 9).

Apart from the marker of aerobic glycolysis (^{18}F-FDG), the substance involved in the lipid metabolism can be used as a carrier of the positron emitter. Due to the high turnover in HCC, ^{11}C-acetate can be used for imaging (10, 11). ^{11}C-acetate is involved in the Krebs cycle *via* the intermediary metabolite acetyl-coenzyme-A and further *via* esterification in fatty acid beta-oxidation, and also *via* synthesis of glycine for production of heme and as a precursor of citrate in the synthesis of cholesterol (10). The sensitivity of ^{11}C-acetate-PET in the detection of HCC is increased to 87% (11). On the one hand there is a negligible accumulation of ^{11}C-acetate in other liver tumors, both primary and secondary, but also, for example, in the focal nodular hyperplasia. A disadvantage of ^{11}C-acetate is a low accumulation in poorly differentiated HCCs. ^{11}C-acetate accumulates less compared to ^{18}F-FDG in the metastases of the HCC except for the brain and, therefore, it is more suitable to use ^{18}F-FDG for general detection. ^{11}C-acetate and ^{18}F-FDG are complementary radiopharmaceuticals for tracing HCC. ^{11}C-acetate accumulates approximately in one third of the tumors, both carriers in one third and ^{18}F-FDG in one third. While accumulation of acetate prevails in the differentiated tumors, ^{18}F-FDG accumulation dominates in poorly differentiated tumors. The reason for the increased sensitivity of ^{11}C-acetate PET in the detection of HCC of a smaller size below 3 cm is the higher number of well-differentiated HCCs of this size. However, if detection of liver cancer of unknown origin is concerned, the accumulation of ^{11}C-acetate becomes a considerable disadvantage. A complementarity of radiopharmaceuticals is used in the method of dual ^{18}F-FDG/^{11}C-acetate-PET that is, however, more complicated and costly. The impossibility to use a radiopharmaceutical outside the centers equipped with a cyclotrone is also a problem because the half-time of ^{11}C is 20 min compared to 110 min with ^{18}F.

Shortening the duplication time in readily growing HCC tumor cells and, hence, accelerating the development of the membrane phospholipids, enables the use of choline labeled with ^{11}C and ^{18}F in the imaging of HCC with the PET (12, 13). Choline is involved in the synthesis of one of the basic membrane facilitating factors of cell division-phosphatidylinositole and therefore its metabolism in dividing cancer elements is markedly increased. Apart from renal and prostatic cancers, choline has also been tested in the diagnosis of HCC. The limitation of using labeled choline is similar as in acetate.

Currently, in addition to PET, the increased level of the lipid metabolism is also used in MRI by means of hepatocyte-specific contrast agents. In these cases, gadolinium is bound in the molecule of a lipophilic character (EOB-GdDTPA) that is well accumulated in the hepatospecific phase in well-differentiated hepatocellular tissues, while there is no accumulation present in other tissues, including the poorly differentiated HCCs.

The general picture of HCC after CT examination shows three characteristic types: focal, multifocal and diffusionally infiltrating (14). In all types of HCC growth in the liver

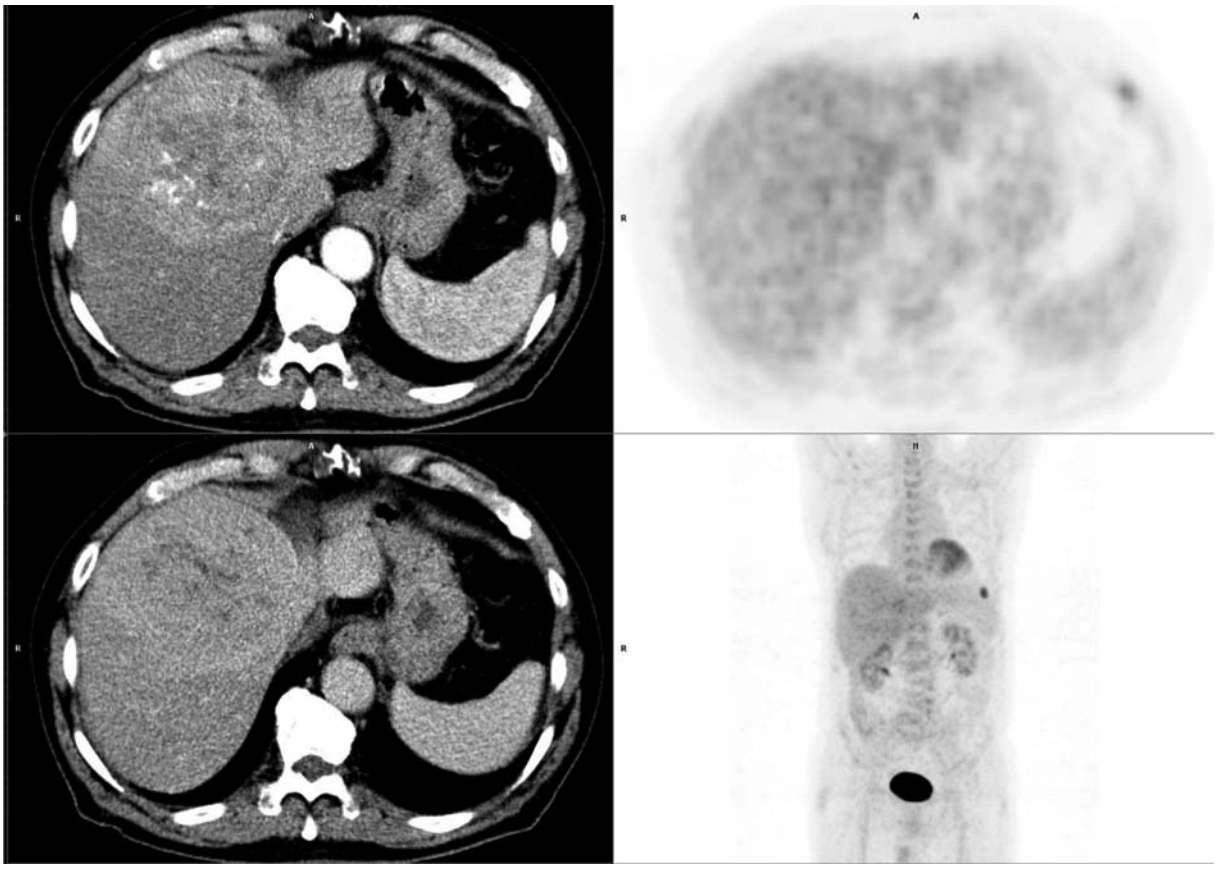

Figure 2. *^{18}F-FDG non-accumulating, but hypervascular well-differentiated HCC. Axial CT image in the arterial phase (upper row left), axial CT image in the portal phase (lower row left), PET image (upper row right) and whole body PET image (lower row right). The hypermetabolic focus on the left side is rib fracture.*

parenchyma, CT diagnostics is based on the evidence of hypervascularization in the arterial phase of the contrast agent (5, 6, 14). In some tumors, almost the whole tumorous mass is hypervascularized, while in the others, especially in difusionally infiltrative types, this basic symptom is sometimes not very well pronounced. If the examination is performed only in, portal phase, the tumor may be overlooked. Discretely hypervascularized tumors have often only minimal signs of presence in the liver. This is due to the fact that only a part of these tumors is poorly differentiated and the presence of high accumulation of ^{18}F-FDG in the liver tissue markedly facilitates their detection and differentiation of the extent of liver infiltration. In more advanced stages of HCC, an intravascular invasion is commonly present, which is more often in the portal vein than in the liver veins or vena cava inferior. Due to the fact that the development of HCC is often preceded by liver cirrhosis, it is an important diagnostic problem in detection of the development of HCC in the cirrhotic environment. In the terrain of cirrhotic liver parenchyma, the nodes saturated by the contrast agent in the arterial phase occur often (14). In addition to the regenerative nodes, which are benign, there are also dysplastic nodes with a higher possibility of growth and change into the aggressive HCC. Apart from their size, the dysplastic nodes are different from the regenerative nodes by their presence in the arterioportal shunt (14) that is differentiated in the arterial phase of the saturation of the liver parenchyma. Because of the concurrent occurrence of the regenerative and dysplastic nodes it is very difficult to detect small nodes of the HCC in the cirrhotic liver. If a fully diagnostically valuable double-phase CT is performed, which is included in the PET/CT protocol, we can use all advantages of the CT diagnostic in the hybrid PET/CT imaging as well.

Based on our results, a high turnover of ^{18}F-FDG, which indicates the differentiability of the tumor, a significant marker for the biological behavior of the tumor is very important for the estimation of the liver tumor. By performing a diagnostically full-quality double-phase CT imaging in the arterial and venous phase, we markedly increase the possibility to detect the minimal morphological changes in well-differentiated tumors in which the CT changes are the only ones that enable

to assume the presence of the HCC. At the same time, low or only increased level of accumulation of ^{18}F-FDG indicates a well-differentiated tumor. A significant advantage of ^{18}F-FDG-PET/CT also includes the possibility of detection of remote metastases or metastases in the lymphatic nodes. Their presence significantly limits resection surgery or liver transplantation. On the other hand, a quite strong association can be found in relation to prognosis and accumulation of ^{18}F-FDG. The high level of accumulation is associated with the higher response to anti-vascular endothelial growth factor treatment (15) and also with the rapid response to an embolisation therapy (even if it is chemoembolisation or radioembolisation) (16) or selective stereotactic radiotherapy (17). Tumor accumulation heterogeneity also predicts poorer response to therapy and rapid progression in highly dedifferentiated tumors. The use of ^{18}F-FDG with the combination of arterial enhancement as combined biomarker in hepatocellular carcinoma reflects the current needs to predict the response to therapy and helps to select the most effective way of treatment (18).

Conclusion

^{18}F-FDG-PET/CT is a simple and widely available method of imaging HCC. Imaging of the tumor tissue metabolism, which has an important role in the treatment decision in HCC patients, contributes to evaluating the grade of differentiation of the HCC and detecting metastases in the regional lymphatic nodes and remote metastases in the pulmonary parenchyma and bones

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