Imaging of cancer metabolism
: Metabolic radiotracers in the evaluation of HCCs

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A glycolytic phenotype even in the presence of available oxygen, the so-called Warburg effect, is considered to be a result of the low respiration rate in cancer cells. F-18 FDG, a glucose analog, is the most commonly used radiotracer in combination with PET for the detection of various malignancies based on this phenomenon. Unlike tumors showing Warburg effect, primary hepatocellular carcinomas (HCCs) exhibit a wide spectrum of F-18 FDG uptake, considerably reducing its sensitivity for tumor detection. The low sensitivity of FDG PET is attributed to low FDG uptake in low grade, well differentiated HCCs which is similar to that in the hepatic parenchyma. The false-negative rate of 18F-FDG PET in HCCs is known quite high up to about 40% to 50%. Other than HCCs, some other solid tumors such as prostate cancers, renal cell carcinomas, low-grade sarcomas, low-grade lymphomas, or some tumors with well differentiated histology also display low F-18 FDG uptake. Consequently, new radiotracers were developed to increase the accuracy of diagnosis in tumors that do not show increased F-18 FDG uptake on PET.

C-11 acetate was originally used in imaging cardiac oxidative metabolism. In the myocardium, C-11 acetate is rapidly converted into acetyl coenzyme A (CoA) after cellular uptake and dominantly enters the tricarboxylic acid cycle for CO2 generation. Shreve et al. reported a reduced rate of clearance of C-11 acetate in renal cell carcinoma, allowing differentiation of cancerous cells from normal and diseased non-neoplastic renal tissue. Since then, C-11 acetate has been proposed as an alternative radiotracer for detecting tumors not seen on F-18 FDG studies. The metabolic fate of C-11 acetate is not well understood in tumor cells. In a study using C-14 acetate, tumor cells incorporated C-14 activity into the lipid-soluble fraction rather than the water soluble or CO2 fraction. Considering the positive correlation between accumulation of the lipid-soluble fraction of C-14 and growth activity, the increased C-14 acetate uptake in tumor cells was attributed mainly to the increased lipid synthesis caused by the high level of proliferative activity in the tumors. With C-11 acetate, the sensitivity of PET for detecting primary HCCs was reported to be a little higher than 80%. Nonetheless, for the detection of small primary HCCs less than 2 cm, liver MRI is clearly superior to PET, especially with liver-specific contrast material. Other than detecting non-FDG avid HCCs, the potential of C-11 acetate needs to be further evaluated in the future.

What is important with F-18 FDG PET in evaluating HCCs is that the degree of F-18 FDG uptake correlates well with the aggressiveness of biologic behavior of tumors. Thus, F-18 FDG uptake is predictive of patient survival, with an inverse relation between SUV and survival. There are only a

few reports in the evaluation of LN metastasis of HCCs using PET. Given the fact that poorly differentiated HCCs tend to have more LN metastasis than well differentiated HCCs, PET with F-18 FDG have a potential in detecting LN metastasis from F-18 FDG avid high grade HCCs. F-18 FDG PET/CT has proven useful for the detection of extra-hepatic metastasis including lung and bone metastasis. It is also valuable for the detection of recurrent tumors after liver transplantation and interventional therapy, with an overall sensitivity, specificity, and accuracy of 90%, 83%, and 88%, respectively. Pretreatment tumor F-18 FDG uptake normalized to the liver uptake on PET/CT is an independent prognostic factor for OS in patients with BCLC stages 0 and A HCC undergoing curative treatment. In contrast, underlying liver function but not biological tumor factor such as TLR seems important in predicting the prognosis of patients undergoing TACE. In patients with intermediate-to-advanced stage HCCs, F-18 FDG uptake seems to be an independent prognostic factor for progression free survival and overall survival in HCC patients treated with TACE or CCRT. Especially, in HCCs with high F-18 FDG uptake, patients treated with CCRT showed better survival than those treated with TACE. F-18 FDG PET/CT may help determine the treatment modality for intermediate-to-advanced stage HCCs. The roles of FDG uptake in the primary tumors should be further evaluated as a new biological tumor factor associated with prognosis independent of tumor size in patients with HCC.