INVITED COMMENTARY

^{11}C-Acetate: A New Tracer for the Evaluation of Hepatocellular Carcinoma

Hepatocellular carcinomas (HCCs) arise from the malignant transformation of hepatocytes and are a common risk factor in the setting of chronic liver disease such as viral hepatitis or cirrhosis or in patients exposed to carcinogens. HCC has been a relatively uncommon malignancy in the United States but is being seen with increasing frequency associated with the marked increase in hepatitis C infection. HCC represents the predominant type of primary liver cancer and is associated with chronic liver disease and underlying cirrhosis in 70% of patients (*1*). HCC most frequently metastasizes to regional lymph nodes, lung, and bone. Because the majority of patients present with advanced-stage malignancy and associated cirrhosis, treatment options remain limited. Even in patients who are able to undergo successful curative resection, up to 50% will develop intrahepatic recurrence from second primaries or from intrahepatic spread.

The diagnostic issues of conventional imaging include early detection of these tumors, differentiation from regenerative nodules and other benign liver tumors, accurate tumor staging, and assessment of the response to therapy. Evaluation and screening for hepatic lesions is commonly performed with transabdominal ultrasonography, CT, or MRI. Ultrasonography can detect lesions as small as 1 cm in diameter but is operator dependent, is inherently 2-dimensional, and suffers from poor specificity. CT and MRI have been the conventional method for screening the liver at many institutions in the United States. Although tomographic imaging studies (CT and MRI) have been the mainstay for diagnosis and staging of HCC, attempts to improve staging and follow-up of patients with known HCC have led to the evaluation of molecular imaging in HCC.

LIMITATIONS OF ^{18}F-FDG FOR EVALUATION OF HCC

^{18}F-FDG, which allows the evaluation of glucose metabolism, is the most commonly used tracer in oncology because of the practical half-life of ^{18}F (110 min) compared with that of the other positron emitters. Most tumor cells have increased glucose metabolism because of increased levels of glucose transporter proteins and increased levels of intracellular enzymes that promote glycolysis, such as hexokinase and phosphofructokinase (*2–4*). In most malignant cells, the relatively low levels of glucose-6-phosphatase lead to accumulation and trapping of ^{18}F-FDG intracellularly, allowing the visualization of increased ^{18}F-FDG uptake compared with that of normal cells. PET imaging with ^{18}F-FDG has proven useful in differentiating malignant tumors from benign lesions on the basis of differences in their metabolic activity, in detecting malignant recurrence, evaluating tumor stage, and monitoring therapy for various malignant neoplasms (*5*).

Differentiated hepatocytes normally have a relatively high glucose-6-phosphatase activity, which allows dephosphorylation of intracellular FDG and its egress from the liver. Although experimental studies (*6,7*) have demonstrated that glycogenesis decreases and glycolysis increases during carcinogenesis in the liver, studies have shown that the accumulation of ^{18}F-FDG in HCCs is variable, owing to varying degrees of activity of the enzyme glucose-6-phosphatase (*8–10*). Approximately one third of HCCs do not accumulate ^{18}F-FDG and will provide false-negative ^{18}F-FDG PET imaging. Therefore, ^{18}F-FDG PET is not a screening tool to detect small HCC in patients at risk and in these patients ^{18}F-FDG PET provides no information regarding intrahepatic or distant disease (*11,12*). Therefore, efforts have been made to seek alternative tracers for screening patients at risk, staging, and monitoring regional therapy of patients with HCC.

^{11}C-ACETATE AND ^{18}F-FDG COMPLEMENTARITY

The study of Ho et al. (*13*) describes an interesting approach using a dual-isotope PET protocol using ^{18}F-FDG and ^{11}C-acetate as radiopharmaceuticals. ^{11}C-Acetate is a metabolic substrate of β-oxidation and precursors of amino acid and sterol and has proven to be useful in detecting various malignancies (*14*); although the sensitivity does not appear as high as with ^{18}F-FDG, it may play a complementary role for tumors that are not ^{18}F-FDG avid as it has been suggested for urologic tumors.

In the study of Ho et al. (*13*), the poorly differentiated HCCs were detected by ^{18}F-FDG and the well-differentiated types were detected by ^{11}C-acetate This finding supports previous data suggesting a correlation between the degree of ^{18}F-FDG uptake, including both the standardized uptake value and the phosphorylation constant (k_3), and the grade of malignancy (*9*). It is also interesting to observe that approximately 30% of the HCCs were both

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^{18}F-FDG and ^{11}C-acetate avid and actually demonstrated heterogeneity of metabolism in different parts of the same tumor.

Another interesting observation is the specificity of ^{11}C-acetate for HCC compared with that of other malignant tumors affecting the liver, including metastases from other primaries that were not ^{11}C-acetate avid. On the other hand, some focal nodular hyperplasia did accumulate ^{11}C-atetate to a mild degree. The authors conclude that the dual-isotope technique can be very useful to evaluate indeterminate hepatic lesions. When the lesion accumulates both tracers or accumulates only ^{11}C-acetate, HCC is high in the differential diagnosis; when it accumulates only ^{18}F-FDG, a non-HCC malignancy should be favored; and if it is negative for both tracers, a benign pathology is more likely.

Because poorly differentiated HCCs are more likely to metastasize and tend to be ^{18}F-FDG avid, metastases are more likely to be detected with ^{18}F-FDG, as found by Ho et al. (*13*). This finding supports data in our study of 91 patients with HCC who underwent ^{18}F-FDG PET for initial staging, where 64% of patients had increased uptake in the primary tumor and 10% of those had unsuspected extrahepatic metastases demonstrated by ^{18}F-FDG PET images (*15*).

Because the majority of patients with HCC have advanced-stage tumors or underlying cirrhosis with impaired hepatic reserve, surgical resection is often not possible. Therefore, other treatment strategies have been developed, including transarterial chemoembolization, tumor ablation (cryoablation, ethanol ablation, radiofrequency ablation), and, in highly selected cases, liver transplantation. In patients with ^{18}F-FDG-avid HCC treated with hepatic arterial chemoembolization, ^{18}F-FDG PET is more accurate than lipiodol retention on CT in predicting the presence of residual viable tumor. The presence of residual uptake is some lesions can help in guiding further regional therapy (*16–18*). In our study of 91 patients, ^{18}F-FDG PET had an impact on the management of 30% of patients either by guiding the biopsy at the metabolically active site, by identifying distant metastases, by monitoring the response to treatment with hepatic chemoembolization, by guiding additional regional therapy, or by detecting recurrence (*15*). ^{11}C-Acetate may be the alternative tracer for monitoring therapy of patients with non–^{18}F-FDG-avid HCC.

The usefulness of combined ^{18}F-FDG/^{11}C-acetate imaging also becomes apparent and clinically relevant in the subgroup of patients who have unresectable HCC, but who may be under consideration for liver transplantation. In this group the ability to more accurately screen for distant metastases is particularly helpful. Clearly, the implications of undetected metastatic cancer in this patient subgroup justify a thorough approach for accurate tumor staging. Recent estimates of costs for each year of life gained after liver transplantation for HCC range from $44,000 to $183,000 (*19*). In this setting the marginal costs associated with PET imaging become negligible.

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REFERENCES

1. Kaczynski J. Prevention of cirrhosis is the best measure against hepatocellular cancer [in Swedish]. *Lakartidningen*. 1999;96:338–341.
2. Flier JS, Mueckler MM, Usher P, Lodish HF. Elevated levels of glucose transport and transporter messenger RNA are induced by ras or src oncogenes. *Science*. 1987;235:1492–1495.
3. Monakhov NK, Neistadt El, Shavlovskii MM, Shvartsman Al, Neifakh SA. Physiochemical properties and isoenzyme composition of hexokinase from normal and malignant human tissues. *J Natl Cancer Inst*. 1978;61:27–34.
4. Knox WE, Jamdar SC, Davis PA. Hexokinase, differentiation, and growth rates of transplanted tumors. *Cancer Res*. 1970;30:2240–2244.
5. Delbeke D, Martin WH, Patton JA, Sandler MP, eds. *Practical FDG Imaging: A Teaching File*. New York, NY: Springer Verlag; 2002.
6. Weber G, Cantero A. Glucsose-6-phosphatase activity in normal, precancerous, and neoplastic tissues. *Cancer Res*. 1955;15:105–108.
7. Weber G, Morris HP. Comparative biochemistry of hepatomas. III. Carbohydrate enzymes in liver tumors of different growth rates. *Cancer Res*. 1963; 23:987–994.
8. Okazumi S, Isono K, Enomoto K, et al. Evaluation of liver tumors using fluorine-18-fluorodeoxyglucose PET: characterization of tumor and assessment of effect of treatment. *J Nucl Med*. 1992;33: 333–339.
9. Torizuka T, Tamaki N, Inokuma T, et al. In vivo assessment of glucose metabolism in hepatocellular carcinoma with FDG PET. *J Nucl Med*. 1995; 36:1811–1817.
10. Messa C, Choi Y, Hoh CK, et al. Quantification of glucose utilization in liver metastases: parametric imaging of FDG uptake with PET. *J Comput Assist Tomogr*. 1992;16:684–687.
11. Khan MA, Combs CS, Brunt EM, et al. Positron emission tomography scanning in the evaluation of hepatocellular carcinoma. *J Hepatol*. 2000;32:792–797.
12. Delbeke D, Martin WH, Sandler MP, Chapman WC, Wright JK Jr, Pinson CW. Evaluation of benign vs malignant hepatic lesions with positron emission tomography. *Arch Surg*. 1998;133:510–515.
13. Ho C-L, Yu SCH, Yeung DWC. ^{11}C-Acetate PET imaging in hepatocellular carcinoma and other liver masses. *J Nucl Med*. 2003;44:213–221.
14. Liu RS. Clinical applications of C-11-acetate in oncology [abstract]. *Clin Positron Imaging*. 2000; 3:185.
15. Wudel LJ, Delbeke D, Morris D, et al. The role of FDG-PET imaging in the evaluation of hepatocellular carcinoma. *Am Surg*. 2002. In press.
16. Vitola JV, Delbeke D, Meranze SG, Mazer MJ, Pinson CW. Positron emission tomography with [^{18}F]fluorodeoxyglucose to evaluate the results of hepatic chemoembolization. *Cancer*. 1996;78: 2216–2222.
17. Torizuka T, Tamaki N, Inokuma T, et al. Value of fluorine-18-FDG PET to monitor hepatocellular carcinoma after interventional therapy. *J Nucl Med*. 1994;35:1965–1969.
18. Akuta K, Nishimura T, Jo S, et al. Monitoring liver tumor therapy with [^{18}F]FDG positron emission tomography. *J Comput Assist Tomogr*. 1990;14: 370–374.
19. Sarasin F, Giostra E, Mentha G, Hadengue A. Partial hepatectomy or orthotopic liver transplantation for the treatment of respectable hepatocellular carcinoma? A cost-effectiveness perspective. *Hepatology*. 1998;28:436–442.