Evaluation of Benign vs Malignant Hepatic Lesions With Positron Emission Tomography

Dominique Delbeke, MD, PhD; William H. Martin, MD; Martin P. Sandler, MD; William C. Chapman, MD; J. Kelly Wright, Jr, MD; C. Wright Pinson, MD, MBA

**Background:** In most malignant cells, the relatively low level of glucose-6-phosphatase leads to accumulation and trapping of [18F]fluorodeoxyglucose (FDG) intracellularly, allowing the visualization of increased uptake compared with normal cells.

**Objectives:** To assess the value of FDG positron emission tomography (PET) to differentiate benign from malignant hepatic lesions and to determine in which types of hepatic tumors PET can help evaluate stage, monitor response to therapy, and detect recurrence.

**Design:** Prospective blinded-comparison clinical cohort study.

**Setting:** Tertiary care university hospital and clinic.

**Patients:** One hundred ten consecutive referred patients with hepatic lesions 1 cm or larger on screening computed tomographic (CT) images who were seen for evaluation and potential resection underwent PET imaging. There were 60 men and 50 women with a mean (±SD) age of 59 ± 14 years. Follow-up was 100%.

**Interventions:** A PET scan using static imaging was performed on all patients. The PET scan imaging and biopsy, surgery, or both were performed, providing pathological samples within 2 months of PET imaging. All PET images were correlated with CT scan to localize the lesion. However, PET investigators were unaware of any previous interpretation of the CT scan.

**Main Outcome Measures:** Visual interpretation, lesion-to-normal liver background (L/B) ratio of radioactivity, and standard uptake value (SUV) were correlated with pathological diagnosis.

**Results:** All (100%) liver metastases from adenocarcinoma and sarcoma primaries in 66 patients and all cholangiocarcinomas in 8 patients had increased uptake values, L/B ratios greater than 2, and an SUV greater than 3.5. Hepatocellular carcinoma had increased FDG uptake in 16 of 23 patients and poor uptake in 7 patients. All benign hepatic lesions (n = 23), including adenoma and fibronodular hyperplasia, had poor uptake, an L/B ratio of less than 2, and an SUV less than 3.5, except for 1 of 3 abscesses that had definite uptake.

**Conclusions:** The PET technique using FDG static imaging was useful to differentiate malignant from benign lesions in the liver. Limitations include false-positive results in a minority of abscesses and false-negative results in a minority of hepatocellular carcinoma. The PET technique was useful in tumor staging and detection of recurrence, as well as monitoring response to therapy for all adenocarcinomas and sarcomas and most hepatocellular carcinomas. Therefore, pretherapy PET imaging is recommended to help assess new hepatic lesions.

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and monitor the therapy for various malignant neoplasms. The liver is known to have increased activity of glucose-6-phosphatase. Although experimental studies have demonstrated that glycolysis decreases and glycogenosis increases during carcinogenesis in the liver, some studies have shown that the accumulation of FDG in hepatocellular carcinomas is variable, owing to varying degrees of activity of the enzyme glucose-6-phosphatase. Therefore, it has been predicted that evaluation of liver tumors, especially hepatocellular carcinomas, with FDG PET would require dynamic imaging and kinetic analysis, which is difficult to perform and not practical clinically compared with standard static imaging.

The purpose of this study was to assess the value of FDG PET, using static imaging to differentiate benign from malignant liver lesions, and to determine in which types of liver tumors PET is potentially helpful in detecting recurrence, evaluating stage, and monitoring response to therapy.

The types of lesions are listed in Table 1. There were 97 patients with malignant lesions (6 of these 97 patients also had a total of 8 benign lesions) and 13 patients with 15 benign lesions. The malignant lesions included metastases of various primaries including colon carcinoma (n = 53), pancreatic carcinoma (n = 3), esophageal carcinoma (n = 1), carcinoma of unknown origin (n = 6), sarcoma (n = 2), and adenoid cystic carcinoma of the parotid (n = 1) in 66 patients, cholangiocarcinoma in 8 patients, and hepatocellular carcinoma in 23 patients. The benign lesions were 2 adenomas, 3 fibro-nodular hyperplasia, 1 cavernous hemangioma, 1 biliary cyst, 1 simple cyst, 1 hamartoma, 1 hematoma, 6 regenerating nodules, 4 benign postoperative sites, and 3 granulomatous abscesses.

Malignant tumors in 97 patients had increased FDG uptake except for 7 of the 23 patients with hepatocellular carcinomas (Table 1). Benign lesions in all patients had poor FDG uptake except for 3 abscesses, 2 of which had equivocal uptake and 1 of which had a rim with marked FDG uptake (Table 1 and Figure 1).

Table 2 lists the average L/B ratios and SUVs for different types of lesions. The SUV for malignant lesions was 7.8 ± 4.5, significantly higher than that obtained for benign lesions (2.0 ± 1.7; P < .001). The difference between the L/B ratio for malignant (4.0 ± 2.0) and benign (1.2 ± 1.2) lesions is also statistically significant (P < .001).

Figure 2 shows the distribution of values for L/B ratio in different groups of lesions. The horizontal line represents the L/B ratio of 2, which has been previously shown to be the best cutoff level to differentiate benign.
Table 1. Visual Assessment of FDG Uptake in Liver Lesions

<table>
<thead>
<tr>
<th>Pathologic Diagnosis</th>
<th>Total No.</th>
<th>Definite FDG Uptake, L/B Ratio &gt;2, No.</th>
<th>Equivocal FDG Uptake, 1 &lt; L/B Ratio &lt;2, No.</th>
<th>Poor FDG Uptake, L/B Ratio &lt;1, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant</td>
<td>97</td>
<td>87</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Metastases†</td>
<td>66</td>
<td>66</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>8</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hepatocellular carcinoma‡</td>
<td>23</td>
<td>13 (57%)</td>
<td>3 (13%)</td>
<td>7 (30%)</td>
</tr>
<tr>
<td>Benign</td>
<td>23</td>
<td>1</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>Miscellaneous§</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Abscess</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

*FDG indicates [18F]fluorodeoxyglucose; L/B, lesion-to-normal liver background.
†The 97 malignant lesions were classified as follows: colon carcinoma (n = 53), pancreatic carcinoma (n = 3), esophageal carcinoma (n = 1), carcinoma of unknown origin (n = 6), sarcoma (n = 2), and adenoid cystic carcinoma of the parotid (n = 1).
‡Of the 23 hepatocellular carcinomas, 57% had L/B ratios of more than 2, 13% had L/B ratios between 1 and 2, and 30% had L/B ratios less than 1.
§The 20 miscellaneous benign lesions were diagnosed as follows: adenoma (n = 2), fibronodular hyperplasia (n = 3), cavernous hemangioma (n = 1), biliary cyst (n = 1), simple cyst (n = 1), hamartoma (n = 1), hemangoma (n = 1), regenerating nodules (n = 8), and benign postoperative site (n = 4).

Table 2. Semiquantitative Assessment of FDG Uptake in Liver Lesions

<table>
<thead>
<tr>
<th>Pathologic Diagnosis</th>
<th>Total No.</th>
<th>L/B Ratio</th>
<th>SUV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant</td>
<td>97</td>
<td>4.0 ± 2.0†</td>
<td>7.8 ± 4.5†</td>
</tr>
<tr>
<td>Metastases†</td>
<td>66</td>
<td>4.4 ± 2.0</td>
<td>8.6 ± 4.5</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>8</td>
<td>3.7 ± 1.8</td>
<td>7.2 ± 3.2</td>
</tr>
<tr>
<td>Hepatocellular carcinoma‡</td>
<td>23</td>
<td>3.0 ± 2.0</td>
<td>5.5 ± 3.9</td>
</tr>
<tr>
<td>Benign</td>
<td>23</td>
<td>1.2 ± 1.2</td>
<td>2.0 ± 1.7†</td>
</tr>
<tr>
<td>Miscellaneous§</td>
<td>20</td>
<td>0.9 ± 0.2</td>
<td>1.6 ± 0.5</td>
</tr>
<tr>
<td>Granulomatous</td>
<td>3</td>
<td>3.1 ± 2.9</td>
<td>5.0 ± 4.0</td>
</tr>
</tbody>
</table>

*FDG indicates [18F]fluorodeoxyglucose; L/B ratio, lesion-to-normal liver background ratio; and SUV, standard uptake value. Data are given as mean ± SD. See the footnotes to Table 1 for the breakdown of malignant metastases and benign miscellaneous lesions.
†P < .001.

Figure 1. A 74-year-old man with right upper quadrant pain at initial evaluation. A, The computed tomographic (CT) scan demonstrates a large necrotic mass in the right lobe of the liver (arrow) and a smaller lesion in the left (not shown). B, The positron emission tomographic image (slice corresponding to the CT slice) shows that the lesion in the right lobe had a large photopenic center with a rim of marked uptake (lesion-to-normal liver background ratio, 6.5; standard uptake value, 9.6) (arrow). The patient was explored surgically and found to have a yeast abscess.

have varying amounts of Kupffer cells and appear cold, isointense, or warm,19 and focal fatty infiltration, which is isointense.19 Single photon emitters that are used to detect and evaluate malignant lesions have known major limitations. Gallium and thallium are poor imaging agents for hepatic lesions because of intrinsic high liver background activity. In addition, gallium is accumulated in inflammatory lesions.20,21 Despite these limitations, 70% to 90% of hepatocellular carcinomas have gallium uptake greater than the liver, and gallium scintigraphy in conjunction with sulfur colloid imaging can be helpful in differentiating hepatocellular carcinoma from regenerating nodules in patients with cirrhosis.22 Radioimmunoscinintigraphy is limited by difficulty in antigen modulation and variable depiction of tumor and nontumor cells, as well as by physiological hepatic excretion.23,24 Although FDG shares some of these limitations, the high ratio of uptake between tumor and liver background in most malignant tumors improves their visual detection.

As previously reported by multiple investigators,6-10,14,16 the data from this larger series of patients confirm that definite accumulation of FDG greater than liver background was seen in 100% (66 of 66 patients) of liver metastases, 100% (8 of 8 patients) of cholangiocarcinomas, and 55% (13 of 23 patients) of hepatocellular carcinomas. These percentages are similar to those reported by other investigators25-28 who have performed kinetic analy-
sis in smaller series of patients. They found that the phosphorylation kinetic constant \( k_3 \) is elevated in malignant tumors, including hepatocellular carcinomas, compared with normal liver tissue. The dephosphorylation kinetic constant \( k_4 \) was low in metastatic liver lesions\(^{16} \) and in cholangiocarcinomas,\(^{14} \) but \( k_4 \) was similar to \( k_3 \) for the 45% of the hepatocellular carcinomas that did not trap FDG above liver background.\(^{14,15} \) To our knowledge, there are very few benign liver neoplasms of which images have been taken using FDG PET. The benign liver lesions in this series did not accumulate FDG more than liver background. Among the 3 abscesses, however, 1 demonstrated marked FDG accumulation. This was a yeast abscess with granulomatous inflammation, and it is well known that some inflammatory lesions (mainly granulomatous) can have FDG uptake. This presumably is due to the presence of activated macrophages, and these inflammatory lesions may be mistaken for malignant neoplasms by radiological examination.\(^{25} \)

It is now well demonstrated in the literature\(^{10,26-31} \) that FDG PET is helpful in the evaluation of patients with recurrent colorectal carcinoma to identify metastases when the carcinoembryonic antigen level is elevated and the CT is normal, to clarify the benign or malignant nature of lesions equivocal on CT (eg, postsurgical sites), and to evaluate cancer stage in patients considered for curative resection of recurrent disease, because FDG PET is a whole-body imaging technique. To our knowledge, there are now 7 studies (including ours)\(^{10,26-31} \) with a total of 378 patients that have shown the greater accuracy of FDG PET compared with CT to stage recurrent colorectal carcinoma, leading to detection of unsuspected metastases in 27% of the patients and to a change in management in 37% of the patients. These indications for FDG PET can be extended to all malignant tumors that demonstrate FDG uptake.

Data from this series of patients confirm that about 30% (7 of 23 carcinomas) of hepatocellular carcinomas do not accumulate FDG, and this is a limitation of FDG PET to evaluate liver lesions. However, in the 70% of hepatocellular carcinomas that do accumulate FDG, PET is potentially helpful for lesion staging (as demonstrated in Figure 4) and monitoring of therapy.\(^9 \) In some patients from this study, the whole-body PET scan showed unsuspected extrahepatic metastases (Figure 4), as was the case for many patients with colon carcinoma.\(^{10} \) Regional therapy such as transcatheter arterial chemoem-
bolization has been shown to be beneficial in the treatment of malignant nonresectable liver tumors, especially hepatocellular carcinomas. Our group and others have shown the potential for FDG PET to evaluate the results of such treatments. In 1 patient with hepatocellular carcinoma in this study, FDG PET was the only imaging modality allowing good visualization of the tumor and allowing monitoring of therapy. A pretherapy scan, however, is necessary to assess the degree of FDG uptake, especially for hepatocellular carcinomas, if FDG PET is to be considered for monitoring therapy.

Patients with lesions smaller than 1 cm have not been included in this study to minimize the problem related to partial volume averaging that may prevent visualization of small lesions and result in inaccurate semiquantitation of FDG uptake.32

Cost analysis of including FDG PET in the evaluation of patients with various body tumors has been performed. The greater accuracy of FDG PET compared with CT saves cost by avoiding unnecessary invasive and expensive procedures.

For example, the cost-effectiveness of including PET in evaluating patient stage with non–small cell lung carcinoma has been demonstrated using decision-tree sensitivity analysis. The CT and PET strategy in the conservative decision tree showed a savings of $1154 per patient without a loss of life, compared with the alternative strategy of CT alone.33

Including FDG PET in the evaluation of patients with recurrent colorectal carcinoma was shown to be cost-effective in preliminary studies using both a retrospective review of costs and a decision-tree sensitivity analysis. The report of a retrospective review of costs demonstrates a net savings-to-cost ratio of 4:1, with savings of approximately $4300 per patient. The approach using the decision-tree sensitivity analysis shows that the
PET strategy (carinoembryonic antigen measurement, CT scan, and PET imaging) showed an incremental cost savings of $220 per patient with recurrence without a loss of life as compared with the conventional strategy (carinoembryonic antigen measurement and CT scan).

In summary, because the liver is known to have increased activity of glucose-6-phosphatase that may prevent trapping of FDG in malignant neoplasms, dynamic imaging with kinetic analysis has been recommended to evaluate these lesions. However, it is not clinically practical to perform dynamic imaging, which would delay and compromise whole-body static imaging for tumor staging. These data show that conventional static FDG PET imaging can differentiate malignant from benign lesions in the liver with the limitations of false-positive granulomatous inflammation and false-negative hepatocellular carcinoma. The value of FDG PET in patients with suspected hepatic oncological disease includes differentiation of benign from malignant lesions, tumor staging, detection of recurrence, as well as monitoring response to therapy.

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DISCUSSION

Philip E. Donahue, MD, Chicago, Ill: This ambitious paper attempted a prospective differentiation of benign from malignant lesions, with the secondary goal of determining which tumors could be staged effectively or which tumors could have their response to therapy evaluated. The authors have achieved these goals in the sense that 90 of 97 malignant cases were properly identified and all of the benign lesions had very low uptake. They have concluded that pretreatment FDG PET scanning should be included in the evaluation of new hepatic lesions. In addition, the paper as well as the presentation described some unique attributes of this technology, the most important of which was the identification of unsuspected distant metastases. There

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are other cases in which the FDG PET scan was the only imaging modality that identified the tumor.

Clearly, FDG PET imaging has great potential use in some cases. The question that all of us have is, “Is this yet another technology which is useful in some cases, or is it something which we should all be striving to obtain, regardless of cost considerations (which will come up as my second question).” If this modality can simplify or streamline the evaluation of patients, and it can only do that if it eliminates other tests, leading to either an earlier definitive tissue diagnosis or an indication that operation is unnecessary, then it can achieve cost savings.

The first question is, have you been able to develop an algorithm for evaluation of new hepatic lesions that allows you to eliminate tests such as MRI or some of the other fancy radionuclide imaging tests? Secondly, please tell us about cost considerations. What is the cost of an FDG PET scan compared with magnetic resonance cholangiography, gadolinium scanning, or other techniques?

Jack R. Pickelman, MD, Maywood, Ill: I noticed your sensitivity in detecting hepatic colorectal metastases was 100%. Are you utilizing this test at this point for those patients who have had colon carcinoma and then subsequently have an elevated CEA level? Do you think this FDG PET scan might be an appropriate screening test for that subgroup of patients?

Theodore X. O’Connell, MD, Los Angeles, Calif: I have a question about the practical clinical application of this test. In theory, it seems to work fine, but how can we take it back to our hospitals and offices? What is the value added to the CAT scan? First of all, with metastatic disease, there is little problem figuring what it is. The patient has a history of the carcinoma of the colon and has the elevated CEA; they get a CAT scan, and you see a lesion; and it is probably metastatic carcinoma of the colon. The only value here would be if it precludes you from doing surgery. So, in those cases, I am not so interested in what is showing in the liver, but what is outside the liver. Does the FDG PET scan show disease elsewhere in the abdomen or elsewhere in the body that would stop one from doing a hepatic resection?

Regarding hepatocellular carcinoma, my problem is different from that with the metastatic disease. Here the patient comes in without a prior history and has a single lesion in the liver picked up because of pain, incidentally, etc. The problem is to decide whether it is benign or malignant. However, 30% of the FDG PET scans were false-negative with hepatocellular carcinoma, with another 17% or so being equivocal. So with almost 50% being false-negative, can you rely on a negative FDG-PET scan result to determine that patient does not need an operation and has benign disease?

Don M. Morris, MD, Albuquerque, NM: We need to realize that when one explores the usefulness of new techniques, many questions are not answered with early studies. If I am correct, there were no patients in the study with breast cancer, and I wonder if you have had a chance to image those patients? I would also like to know what the baseline status of the liver was? Did the patients have cirrhosis; were they diabetic with fatty infiltration? There are many different conditions that involve the entire liver that might change the metabolism of the compound, and I would specifically like to know if you have treated any diabetics and if they were different from patients who do not have diabetes? What is the smallest lesion that you detected with this technique?

Roger E. Alberty, MD, Portland, Ore: In its wisdom, HCFA is just now approving reimbursement for the FDG PET scan in lung cancer. I wonder where you are as far as imaging livers. Did you get reimbursed for this study?

Dr Pinson: I want to emphasize that the main purpose of this research effort was to report on the differentiation between benign and malignant lesions. There have been several previous reports on the value of FDG PET imaging to stage colorectal carcinoma. However, there is very little in the literature looking at what we find with benign lesions.

Regarding the algorithm that Dr Donahue asked about, we have found that FDG PET has similar sensitivity, but much greater specificity than CT scan. We have gained enough confidence clinically in this study that we now use an FDG PET scan as our first staging scan. There have been other articles from investigators with experience with PET scanning who state that as well. This then replaces chest CT, abdominal CT, bone scan, and MRI in those patients where you find extrapancreatic disease, such as aortocaval lymph nodes or thoracic metastases. With regard to cost, the charge for an FDG PET scan at our institution is $1500, and that is not much different from an MRI scan. The combination of a chest, abdominal, and pelvic CT scan is slightly more, about $2000. So, if those other imaging procedures are avoided in the patients where an initial screening PET scan is positive, there are some savings. The greater savings in my mind has to do with avoiding unnecessary operations. Correlation of PET scan with other anatomic scans provides very accurate staging preoperatively, almost always. We avoid nontherapeutic laparotomies in all but less than 3% of our cases, compared with other reports in the literature in the range of 20%. There is a lot of discussion about using laparoscopy to stage hepatic malignancy. All of that is avoided if you have confidence in your constellation of radiographic studies, which includes FDG PET.

Dr Pickelman, we have gained confidence that FDG PET is a very good test for screening patients with recurrent carcinoma. You are right that, because we are hepatobiliary surgeons, most of the patients who come in our direction are patients in whom recurrence is suspected on the basis of elevated CEA or a mass that was found on CT scan sometime subsequent to their colon resection. But FDG PET would be suitable for this follow-up screening. We find that FDG PET scan is a very good way to follow up patients who have already had a liver resection as well; we have used it in some patients for our follow-up after liver resection for malignancy.

There was a question about the practical application of FDG PET. The discussant, Dr O’Connell, was correct when he said the real value for FDG PET in hepatic malignancy is in looking at what is going on outside of the liver. The greatest clinical value to me has been finding disease in the chest or in the retroperitoneum that was otherwise unknown. He also brings up a very good question about the uncertain hepatic lesion. That is what we were trying to address with this particular work: can FDG PET be useful to evaluate a benign vs malignant lesion? He is correct that the false-negative results with the hepatocellular carcinomas are a problem. However, the clinical circumstance, such as whether the patient does or does not have cirrhosis, coupled with the findings on CT images and FDG PET scans can answer the question usually. Occasionally, we do run into trouble and a biopsy is required, but rarely.

Dr Morris, we have not studied breast cancer in this work, but there are other works that demonstrate definite uptake for breast metastases. Our experience has been that fatty liver is isointense on FDG PET scans.

Dr Alberty, currently, we are having some trouble with government reimbursement, but that is being reviewed by HCFA and, at this time, approval is expected within the next few months.