Biopsy of Suspicious Liver Nodules: Does it Change Management?

In an early scene from the movie Dirty Harry, Clint Eastwood, in the title role of Harry Callahan, breaks up a bank robbery and eventually corners one of the thieves in a gun-barrel-to-gun-barrel version of “chicken.” After a memorable description of the power of his handgun and as to whether he had fired 5 or 6 shots and still had a round in the firing chamber, Harry queries, “you’ve got to ask yourself the question: Do I feel lucky?” After dropping his weapon, the thief replies “I gots to know.” Thus the dilemma faced by those involved in the practice of medicine. Frequently a diagnosis may not be apparent and clinical decision making is based on the need to know because the diagnosis may affect the future health of the patient. In some cases, the decision is relatively easy because benefits are high and risks are relatively low. However, other clinical situations are not as clear cut. Liver nodules and masses frequently raise concerns, for very good reasons. With or without a history of cirrhosis, a liver nodule or mass immediately raises the possibility of malignancy, either primary or metastatic, with the potential for surgery as a therapeutic option. The prospect of liver surgery, whether a resection or transplant, even with the highly successful techniques and advancements made over the past 2 decades, usually leaves patients and physicians with an uneasy feeling in the epigastric region.

In this issue of Clinical Gastroenterology and Hepatology, Bialecki et al1 review a single center’s experience with the biopsy examination of suspicious liver nodules and masses. In their study, 118 percutaneous liver biopsy specimens obtained for the purpose of determining whether a patient had hepatocellular carcinoma (HCC) because of a suspicious lesion seen on an imaging study were studied with regard to patient demographics, radiographic and histologic characteristics of the lesion, and patient follow-up evaluation through a retrospective review of the medical records. Subsequent tissue from later samplings was examined, whether from the biopsy procedure, autopsy, or the liver explant, to determine whether HCC was present. The biopsy specimen findings then were compared with established criteria of the European Association for the Study of Liver Disease (EASL)2 and the United Network for Organ Sharing (UNOS).3 The latter criteria initially were established to allow a higher priority on the transplant waiting list for patients with suspicious hepatic lesions, eliminating the need for a biopsy examination in all patients because of concerns regarding biopsy examination-related complications. In the current report, 63% of the biopsy specimens were consistent with HCC on the initial tissue sample, whereas another 10 specimens were confirmed as HCC with follow-up evaluation, leaving a total of 71% with biopsy examination–proven HCC. Of these latter 10 cases, 5 were less than 3 cm in greatest diameter, although additional details are not given with regard to the number of nodules greater than 2 cm. All but 1 of 22 patients with an α-fetoprotein (AFP) level greater than 200 ng/mL had biopsy examination–proven HCC. Finally, the sensitivity of the biopsy examination, as compared with the noninvasive criteria proposed by EASL and UNOS, was 87.2%, 68.6%, and 79.2%, respectively, when 6 patients with a previous history of HCC with new nodules were not included in this aspect of the analysis. The authors concluded that there should be a greater role for image-guided biopsy examination of hepatic lesions “clinically suspicious for HCC where confirming the diagnosis would alter the treatment plan.”

In the United States, the current UNOS guidelines for liver transplantation for HCC are based on the Milan criteria, recommendations derived from a study from a single transplant center.4 Patients currently are eligible for the liver transplant waiting list and receive a higher priority if they have HCC meeting the modified TNM staging classification stage 2 criteria: 1 tumor nodule no bigger than 5 cm in greatest diameter or no more than 3 tumor nodules, none of which may be larger than 3 cm in diameter, in the absence of extrahepatic malignancy. As outlined in the article by Bialecki et al,5 patients need not have biopsy examination–proven HCC. Criteria were established for the diagnosis of HCC, in the absence of histologic confirmation. These criteria included a vascular blush on imaging studies, an AFP level greater than 200 ng/mL, arteriographic findings consistent with tumor, or treatment of a nodule with ablative or chemoembolization techniques. Any one of these findings allow the diagnosis of HCC to be made. Initially, patients with a tumor of stage 1 or 2 or received extra Model for End-Stage Liver Disease (MELD) points, not because of the risk for death, the usual goal of the MELD prioritization system, but because of the risk for disease progression beyond stage 2 disease. When introduced in the United States in 2002, there was a marked increase in the number of transplants performed with HCC as the primary indication. Review of the explants from these cases revealed that not all patients with the diagnosis of HCC had detectable tumor, although whether this was related to an inaccurate diagnosis or complete eradication of the tumor as a result of adjunctive treatments has not been clarified. Thus, patients without tumor theoretically could receive a donor liver at a higher priority because of the presence of a suspicious lesion meeting the UNOS noninvasive criteria for HCC, sooner than the MELD system normally would allow in the absence of the...
lesion. This potentially could prevent another patient from receiving a transplant owing to the incorrect awarding of extra MELD points to the patient with the suspicious lesion who, in fact, does not have HCC. From a review of a single center’s data, patients transplanted for HCC, either by pretransplant histologic or noninvasive criteria, had no histologic evidence of tumor in the liver explant 33% of the time based on the analysis of patients receiving extra MELD points for stage 1 and 2 tumors. Whether this has improved since the number of extra points awarded was changed 2 years ago, allowing higher priority only to patients with stage 2 disease, is unclear. The other issue is whether biopsy examination findings influence the decision to proceed with a liver resection, a therapeutic option in patients with well-compensated cirrhosis or liver disease without cirrhosis. This is a frequently debated topic, often eliciting impasioned oration, depending on the interest of a surgeon (ie, transplant vs liver resection).

Does this study prove that liver biopsy examination of a nodule suspicious for HCC is indicated? Bialecki et al state in the introduction, “it is our practice to obtain biopsies of all hepatic lesions suspicious for HCC.” This is certainly not the case at most institutions with a focused interest in management of HCC. Thus, is their approach justified? Answering this question is difficult because of the lack of breakdown of the data. First, the study only examines lesions that underwent a biopsy examination. How many other lesions did not undergo a biopsy examination and for what reasons? Second, what radiographic criteria were used to call a lesion suspicious and how many radiologists were involved? If strict criteria were not used and a number of different radiologists interpreted the imaging studies, the validity of the data and the conclusions certainly can be called into question. Furthermore, one of the descriptors used was “evidence of vascular invasion or metastasis,” another interesting indication for biopsy examination of a lesion in the absence of additional data regarding the severity of the underlying liver disease and the potential therapeutic options available for individual patients with metastatic disease. Third, although the number of patients with different size lesions is given, detail regarding the Child-Pugh classification or MELD score is not. In this regard, it is impossible to determine whether having a histologically proven diagnosis would have added MELD points to a transplant candidate on the waiting list, thus resulting in a change in management. Fourth, 32 of the patients had suspicious nodules greater than 5 cm in diameter, effectively eliminating them from consideration for the extra MELD points awarded patients with HCC because of the presence of disease beyond stage 2. However, one certainly can imagine that a patient with a large benign liver mass and hepatic synthetic dysfunction easily justifies transplantation. Therefore, biopsy examination would appear to be indicated in these patients to definitively rule out HCC. However, 25 of these 32 patients (78%) had biopsy examination–proven HCCs. Thus, no change in management occurred for these 25 patients with a lesion suspicious for HCC, but beyond the current eligibility criteria for a transplant, other than satisfying the “I want to know” question. The outcome of the 7 patients without HCC on biopsy examination is unclear. Was their management changed? Was a liver transplant performed successfully? The lack of follow-up evaluation makes it difficult to justify a biopsy examination in this group.

The key group in this article was the group with suspicious nodules between 2 and 5 cm in diameter. These patients, if otherwise candidates for transplantation, potentially would benefit from the diagnosis of HCC based on a biopsy examination or noninvasive criteria because of the possibility of additional MELD points. Forty-five of these 60 (75%) patients had HCC verified histologically, whereas UNOS noninvasive criteria diagnosed HCC in only 70% of patients. Thus, the fear that UNOS criteria overdiagnose HCC is not true in this group of patients. Ultimately, biopsy examination of the lesion did lead to the diagnosis of HCC in more patients than the noninvasive criteria; however, 8 of the patients were diagnosed during follow-up evaluation. Whether additional patients would have been diagnosed using noninvasive criteria with follow-up evaluation is not clear. Furthermore, it is not clear whether all of the patients meeting noninvasive criteria for HCC had positive biopsy examination results or if those with positive biopsy examination results met noninvasive criteria, once again making it difficult to tell if the biopsy examination findings changed management.

In the group of patients with nodules less than 2 cm in diameter, 6 of 17 (35.3%) were biopsy examination–positive for HCC, although none of the lesions fulfilled either EASL or UNOS criteria. However, radiographic follow-up evaluation of these lesions, along with the serum AFP level, a common practice at many transplant centers, may have led to noninvasive criteria being met and extra MELD points awarded without a biopsy procedure. Because details regarding follow-up evaluation of this specific group of patients was not given, conclusions cannot be made. At most liver transplant centers, nodules less than 2.0 cm in patients with cirrhosis are carefully followed-up radiographically without biopsy examination and only if they grow to more than 2.0 cm is intervention considered (ie, chemoembolization, radiofrequency ablation, or transplantation). False-negative biopsy examination results may be common in this group as a result of sampling error. In any event, these patients are not candidates for UNOS listing exception points even with biopsy examination–proven HCC until their tumors reach stage 2.

The final group for consideration was the group of 11 patients with underlying liver disease but without cir-
rhosis. This may be the easiest group for whom biopsy examination of a suspicious liver nodule is justified because surgical resection or liver transplantation and their timing may be crucial to long-term survival. However, do all of these nodules require a biopsy examination? For example, what was the underlying liver disease in each case? Patients with chronic hepatitis B have an increased risk for HCC and are screened frequently for new hepatic lesions. If such a patient had a new nodule with an AFP level greater than 400 ng/mL, is a biopsy examination really needed? Ten patients from the entire study group had hepatitis B. How many were in the noncirrhotic group is unclear. In addition, EASL criteria did not apply to this subgroup because of the absence of cirrhosis, the only absolute requirement of their criteria. Thus, including these patients in the calculation of the sensitivity of the different methods is inappropriate.

The other topic at issue is the safety of biopsy examinations of suspicious liver lesions, a topic addressed in great detail by Bialecki et al. 1 This represents another topic of great debate, with arguments based on the most recent experience, either good or bad. Based on a number of articles in the published literature and individual center experience, the majority of centers accept the risk of biopsy examination–related complications, regardless of whether it relates to hemorrhage or tumor seeding. Some lesions require biopsy examination because of their suspicious nature, the lack of other factors identifying a diagnosis, and the need for a therapeutic plan. These decisions can be made only with the input of all involved: hepatologist, surgeon, radiologist, oncologist, and, most importantly, the patient.

Based on the findings of this article, what can we conclude? It would appear that nodules deemed suspicious for HCC are just that, with 65% of initial biopsy examinations confirming the diagnosis and a total of 71% proven with follow-up evaluation. Does this justify the approach taken by Bialecki et al.,1 who stated that “it is our practice to obtain biopsies of all hepatic lesions suspicious for HCC.” Hardly. The key in the “I gots to know” school is stated appropriately near the end: “...where confirming the diagnosis would alter the treatment plan.” Until additional follow-up evaluation of liver explant data are available, UNOS noninvasive criteria are reasonable for the diagnosis of HCC and the additional MELD points awarded to patients with surgically unresectable disease who meet criteria for liver transplantation. In this same population, 3 to 6 months of radiographic follow-up evaluation of suspicious lesions less than 2 cm in diameter, with additional intervention based on lesion growth, is appropriate. For noncirrhotic patients, the underlying liver disease, patient comorbidities, individual and serial AFP levels, and the risk for therapeutic intervention all should be considered carefully before a decision regarding biopsy examination is made. If this approach is used in the evaluation of patients with liver nodules suspicious for HCC, appropriate diagnoses and therapies will be provided for this complex group of patients.

Jeffrey S. Crippin, MD
Washington University School of Medicine
St. Louis, Missouri

References