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EDITORIAL

Prognosis of Hepatocellular Carcinoma: Known to Be Poor: Yet Difficult to Predict

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors in the world today and approximately one million individuals develop this disease per year (*1*). Recent advances in early detection and treatment of HCC have improved the prognosis, and long-term survival has been reported particularly in those individuals who have small encapsulated subclinical HCC (*2–4*). In general, however, the prognosis of HCC is poor (*5,6*). Survival of patients with HCC is influenced by many complex factors such as the presence of hepatic cirrhosis, location of tumor, and extent of disease (*7*). Other important considerations in the response to therapy include the serum bilirubin and AFP levels (*8*) as well as the biologic behavior of the tumor with respect to its growth characteristics (*9*). Another important prognostic indicator is the histologic type and grade of the tumor at the time of diagnosis (*10,11*). There is a general need to develop reliable, sensitive, and specific techniques that will aid the clinician in assessing the prognosis of the disease at the time of clinical presentation.

In this issue of the *Journal*, Hasegawa et al. (*13*) have shown that late imaging of HCC by a technetium agent, namely, ^{99m}Tc(Sn)-N-pyridoxyl-5-methyltryptophan (^{99m}Tc-PMT) may be useful for predicting long-term survival of patients with HCC. The authors have demonstrated in a carefully performed study of 162 patients with HCC that increased uptake of ^{99m}Tc-PMT in the tumor was associated with a significantly longer survival (n = 82, median survival: 1013 days) as compared to those who did not show a similar increased uptake of the imaging agent (n = 80, median survival: 398.5 days). This finding is of considerable clinical interest since increased uptake of ^{99m}Tc-PMT into the tumor appears to be an independent marker different from most of the other parameters used to assess the prognosis of the disease. First, the two study groups that showed increased and decreased uptake of ^{99m}Tc-PMT had comparable clinical characteristics and it is important to note that no significant differences in age, sex, distribution, treatment received, serum level of albumin, tumor size, or degree of hepatic dysfunction as assessed by Child's classification were found. It is especially noteworthy that their finding of improved survival with increased uptake within the tumor was independent of the type of therapy, which included such approaches as hepatic resection and transarterial embolization. Thus, the prognosis of HCC patients was clearly correlated with the tumor concentration of ^{99m}Tc-PMT. However, these differences in survival between the two groups (Figs. 1 and 2) had a tendency to disappear and, indeed, the two groups merged with time following the initial diagnosis. Nevertheless, the availability of a reliable and simple test to predict early survival of patients with this disease may be an important prognostic indicator for the choice of various therapeutic interventions.

Recently, hepatobiliary imaging agents have been widely used in nuclear medicine in the diagnosis of liver diseases. Many investigators have taken advantage of the fact that some HCCs maintain a high degree of differentiated hepatic function since such tumors retain the capability to take up these agents. The previous observations have stimulated the development of hepatic scintigraphy as a diagnostic aid to determine the localization of HCC with the liver. Many other radionucleotide-conjugated hepatobiliary agents have also been reported to be useful in this regard as well (*14–18*).

Identification of HCC as measured by regions of increased uptake has been an attractive feature of this approach even though there has been a low detectability rate of HCC by this method (*15–18*). Calvet et al. have reported of a relationship between the uptake of hepatobiliary agents and tumor cell differentiation. Thus, the sensitivity of liver scintigraphy using ^{99m}Tc-labeled agents were related to this important biologic property of the tumor (*18*). For example, these investigators found that most of the well-differentiated HCCs that concentrate radiolabeled hepatobiliary agents are usually well visualized as "hot areas" by scintigraphic scanning images. In contrast, moderately or poorly differentiated HCCs are usually not visualized by this approach. This clinical pathologic correlation is especially important since

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the histologic type of the tumor is one of the most important prognostic factors in predicting survival of patients with HCC (*10–12*).

Another difficulty in the assessment of patients with HCC is the lack of suitable liver biopsy material for histologic examination. Also, there is heterogeneity within the tumor that complicates the evaluation of the cellular differentiation, since limited regions of the tumor are usable for study. It is not possible to appraise long-term survival by diagnostic liver biopsy unless the surgically resected HCC specimens are available for more complete inspection. Another advantage of the imaging technique described by Hasegawa et al. is the use of a noninvasive approach that correlates with the histologic grade of the tumor. It is highly likely that the histologic grade of the tumor is an important factor that will influence the response of the tumor to chemotherapeutic reagents or to other therapeutic modalities. The scintigraphic findings using ^{99m}Tc-PMT may be useful in the selection of treatments in the future.

However, there are geographical differences in the etiology and clinical behavior of HCC that may affect the ability of ^{99m}Tc-PMT to concentrate within the tumor (*19*). We will need additional data from North America, Europe, and Africa to determine if the procedure described by Hasegawa et al. is universally useful for the prediction of survival of HCC patients outside of Japan.

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