Evaluation of Early Imaging Response After Chemoembolization of Hepatocellular Carcinoma by Phosphorus-31 Magnetic Resonance Spectroscopy—Initial Experience

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ABSTRACT

Purpose: To evaluate the value of phosphorus-31 (^{31}P) magnetic resonance (MR) spectroscopy in early monitoring and predicting the response of hepatocellular carcinoma (HCC) after chemoembolization.

Materials and Methods: The authors evaluated 17 HCC target tumors with ^{31}P MR spectroscopy before and after chemoembolization. Alterations of phosphorus metabolism were analyzed by the MR spectroscopy analysis package (SAGE 7.0; GE Medical Systems, Milwaukee, Wisconsin). Ratios of the peak areas of phosphomonoesters (PME), phosphodiesters (PDE), and inorganic phosphate (Pi) to the peak area of nucleoside triphosphates (NTP) or the total phosphorus content (TPC) were measured. The changes in these ratios after chemoembolization were calculated from baseline (before chemoembolization). The therapy effect was assessed by computed tomography (CT) or MR imaging 4 weeks after chemoembolization. The ability of phosphorus metabolism in monitoring therapy effect was evaluated by using receiver operating characteristic analysis.

Results: Decreases in the PDE/NTP ratio (Wilcoxon signed rank test, $P = .024$) and the PDE/TPC ratio (Wilcoxon signed rank test, $P = .011$) that occurred after treatment were the most remarkable changes secondary to chemoembolization. Of the 17 lesions evaluated quantitatively, at the follow-up examination done 4 weeks after chemoembolization, 12 lesions were responsive to chemoembolization, whereas 5 were not. In the responsive group, the PDE/TPC ratio (median 24.15% vs 13.15%; $P = .008$) was significantly decreased after chemoembolization, whereas the NTP/TPC ratio (median 37.35% vs 49.9%; $P = .024$) was significantly increased. In the nonresponsive group, phosphorus metabolism had no significant changes after treatment. Results from the receiver operating curve analysis showed that the threshold percentage change of the PDE/NTP (%PDE/NTP) value was −1.25% with 91.7% sensitivity and 100% specificity for identifying tumor response to chemoembolization, and the threshold percentage change of the NTP/TPC (%NTP/NTP) value was 15.3% with 75% sensitivity and 100% specificity.

Conclusions: Phosphorus-31 MR spectroscopy is a promising technique for the noninvasive assessment of HCC response to chemoembolization. Future studies are necessary to confirm these preliminary results.

ABBREVIATIONS

HCC = hepatocellular carcinoma, NTP = nucleoside triphosphates, ^{31}P = phosphorus-31, PCr = phosphocreatine, PDE = phosphodiesters, %NTP/TPC = percent change in NTP/TPC ratio, %PDE/NTP = percent change in PDE/NTP ratio, Pi = inorganic phosphate, PME = phosphomonoesters, TPC = total phosphorus content

Image-guided transcatheter tumor therapy is a well-accepted treatment with some survival benefits for unresectable hepatocellular carcinoma (HCC) (1). Early evaluation of tumor response to chemoembolization is crucial for subsequent therapeutic planning. Several methods are used at the present time to monitor the early response to chemo-

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embolization; however, each has its own drawbacks. With computed tomography (CT), for patients with oily chemoembolization, good iodized oil retention is associated with some prolongation of median survival rate (2,3), but it does not indicate complete tumor necrosis and cannot be correlated with the size of the necrotic area (4). In dynamic enhanced CT, iodized oil hyperattenuation impairs the assessment of the residual tumor enhancement. For patients with chemoembolization with drug-eluting particles and no oil, contrast-enhanced CT is fine. In gadolinium-enhanced magnetic resonance (MR) images, the embolization site enhancement shows the viable tumor and the posttreatment granulation tissue (5). MR diffusion-weighted imaging and apparent diffusion coefficient parametric maps can differentiate between viable tumor tissues and necrotic tumor tissues (6). These modalities have also been used to detect diffusion changes secondary to the alteration of microscopic capillary perfusion and tumor cell structures after therapy (7,8). However, diffusion-weighted imaging can assess the effectiveness of therapy only by monitoring secondary changes of intracellular and extracellular water after therapy.

MR spectroscopy is another promising noninvasive technology that can be used for in vivo examination of many cancers. It can be used to identify the early tumor response to chemotherapy and to specify tumor grade and stage (8,9). Phosphorus-31 (^{31}P) nuclear MR spectroscopy measures the relative levels of important cellular phosphate compounds in tissue metabolism and provides information on bioenergetic metabolites such as nucleoside triphosphates (NTP), phosphocreatine (PCr), inorganic phosphate (Pi), and phosphomonoesters (PME) and phosphodiesters (PDE), which are involved in lipid synthesis of biologic membranes. Localized ^{31}P MR spectroscopy can be performed on animals and humans in a noninvasive manner and has great potential in oncology for monitoring tumor response to radiotherapy, chemotherapy, or immunotherapy (10–14).

Phosphorus-31 MR spectroscopy of murine and human tumors after irradiation by ^{31}P MR spectroscopy has been previously investigated (10,11). These studies suggested that the tumor response was related to radiation-induced metabolic changes (11) and the pretreatment status of the phosphorus metabolism (12). In addition, previous attempts in the quantification of liver tumors with ^{31}P MR spectroscopy after chemotherapy or chemoembolization were reported (13,14). In malignant tumors, a significant decrease in NTP and an increase in Pi had been observed in the early phase of therapy (representing necrosis of tumor cells), followed by changes in PDE and PME levels (13,14). However, to our knowledge, the value of the level of phosphorus metabolites in predicting the chemoembolization response of HCC has not been ascertained. The purpose of this pilot study was to investigate HCC ^{31}P MR spectroscopy changes in patients undergoing chemoembolization, compare the changes with control spectra from each patient the day before therapy, and evaluate the value of the variation in predicting and early monitoring of tumor response to chemoembolization.

MATERIALS AND METHODS

Patients

The protocol in our study was approved by our institutional review board, and informed consent was obtained from all patients. The criteria for inclusion in this study were a confirmed diagnosis of HCC, receiving chemoembolization treatment, and performance of ^{31}P MR spectroscopy within 72 hours of chemoembolization. The study participants included patients with multifocal cancer and patients with cirrhosis who were deemed unsuitable for resection, transplantation, or ablation on review in a multidisciplinary hepatobiliary tumor conference. Treatment is contraindicated in main portal vein tumor thrombus but is permitted in branch portal vein disease. This prospective study included 15 consecutive patients diagnosed with HCC by fine-needle aspiration or core biopsy. Phosphorus-31 MR spectroscopy evaluated 17 HCC target tumors before and after chemoembolization. Patient demographic, clinical, and procedural data are summarized in **Table 1**.

Chemoembolization

Selective chemoembolization procedures were performed with microcatheters positioned at the hepatic artery branches supplying the tumors. The chemoembolic mixture contained cisplatin, 150–300 mg (Platinol; Bristol-Myers Squibb, Princeton, New Jersey); epirubicin, 40–50 mg (Pharmorubicin; Pharmacia & Upjohn, Milan, Italy); mitomycin, 6–10 mg (Mitomycin-C; Kyowa Hakko Kogyo, Tokyo, Japan); and nonionic contrast material, 6–30 mL (Ultravist; Schering, Berlin, Germany) in iodized oil (Lipiodol Ultra Fluide; Laboratoires Guerbet, Roissy CdG Cedex, France). The dose given depended on the size of the tumor, hepatic function, and health status of the patient. Gelatin sponge particles saturated with contrast medium were injected into the tumor to slow down blood flow to the tumor after the iodized oil injection. The amount of particulate embolization also varied with underlying factors, such as the presence of main branch portal or hepatic venous tumor invasions.

MR Spectroscopy Evaluation

The examinations were performed using a 1.5 T MR imager (GE Signa HD scanner; GE Medical Systems, Milwaukee, Wisconsin), and ^{31}P MR spectroscopy was performed using a circular surface coil. Data were collected using a one-dimensional chemical shift imaging technique with repetition time of 2 seconds, spectral line width of 5,000 Hz, 1,024 points and scanned 64 times over 3–5 minutes, and field of view of 3–4 cm. Phosphorus-31 MR spectroscopy was performed immediately before and within 72 hours after chemoembolization. Spectra were processed with an