Comparison Between Intravenous and Intraarterial Contrast Injections for Dynamic 3D MRI of Liver Tumors in the VX2 Rabbit Model

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Purpose: To test the hypothesis that catheter-directed intraarterial (IA) contrast agent injection increases tumor enhancement and conspicuity compared to intravenous (IV) injection.

Materials and Methods: Eight VX2 liver tumors were grown in five rabbits. After positioning a catheter in the hepatic artery, we performed 3D inversion recovery GRE MRI after IA and IV gadopentetate dimeglumine contrast injections at doses of 0.04 and 0.1 mmol/kg, respectively. Peak enhancement (signal-to-noise ratio (SNR)) and conspicuity (contrast-to-noise ratio (CNR)) were measured for each acquisition.

Results: The peak SNR and CNR were 21.7 ± 5.8 and 17.0 ± 4.8 (mean ± SD) after IA injection, and 16.9 ± 10.2 and 6.2 ± 2.6 after IV injection. The IA CNR was significantly greater than the IV CNR (P < 0.05), with a >60% increase in CNR for each tumor. For six of the eight tumors the IA SNR was greater than the IV SNR, but statistical significance was not achieved due to the small sample size of the study (P = 0.07).

Conclusion: We demonstrated the feasibility of using IA injection techniques to improve tumor conspicuity. This strategy could be employed to enhance the detection of small liver tumors or to conserve contrast agent in future MRI-guided transcatheter liver therapies.

Key Words: MRI; intraarterial; contrast injection; VX2; tumor; liver


EARLY DETECTION OF HEPATOCELLULAR CARCINOMA (HCC) (1–3) (i.e., small or isolated lesions) while the patient is asymptomatic and has adequate liver function can improve the chances for successful surgical (4) or palliative radiofrequency ablation (RFA) (5) therapy. Contrast-enhanced (CE) helical computed tomography (CT) with intravenous (IV) administration of iodinated contrast agent is the most commonly used radiologic imaging modality for the detection of HCC. However, CE CT exposes patients to ionizing radiation and potentially nephrotoxic contrast agents. CE magnetic resonance imaging (MRI) with IV injection of T1-shortening gadolinium chelate (Gd) contrast agent is the most commonly used MRI method to detect HCC. The sensitivity of CE-MRI for detecting HCC is 62–77% (6–8). In 50 cirrhotic patients, Burrel et al (9) showed that CE-MRI provided superior sensitivity compared to dynamic helical CT for detecting HCC (76% vs. 61%). Overall, MRI appears to be superior for detecting HCC (7–10).

The detection of small HCC lesions (<2 cm), however, remains a challenge. Reported sensitivity values for CT range from 70–80% (11–13), and MRI sensitivity of 84% was observed in a study with IV administered contrast agents (9). Thus, the traditional IV method of contrast agent delivery is inadequate for reliably detecting small HCC lesions.

One possible way to detect small HCC lesions is to increase the dose of contrast agent injected during a radiologic imaging examination. Runge (14) previously demonstrated a significant increase in tumor-to-liver tissue conspicuity (as assessed by the contrast-to-noise ratio (CNR) when the IV-injected Gd dose was increased from 0.1 to 0.3 mmol/kg in a rabbit model of liver cancer. However, increasing the contrast agent dose is not feasible or practical for iodinated contrast agents in CT because of their inherent nephrotoxicity. Furthermore, though small increases in the Gd contrast agent dose for CE-MRI may be better tolerated, ultimately the Gd dose levels must also be limited. A potentially viable alternative is to concentrate the con-
Contrast agent dose selectively to a specific hepatic region using an intraarterial (IA) delivery method.

Catheter-directed injections of Gd may be one approach to improve MRI detection of HCC tumors. Hepatic arterial catheter placement is currently widely used for therapeutic HCC interventions with bland or chemoembolization as well as radioembolization. Since 90–100% of the HCC tumor blood supply originates from the hepatic artery, these interventions focus and concentrate delivery of therapeutic agents predominantly to the tumor (15). Thus, IA contrast agent injection would also concentrate the dose predominantly in the tumor. A comparison of IV with IA administration of contrast agents for MRI of liver tumors is warranted.

Given the widespread use of hepatic arterial catheter placement for palliative or noncurative HCC therapies, the use of hepatic arterial catheters for diagnostic purposes is reasonable, especially if early detection of HCC can lead to the possibility of curative therapy. Previous studies using a hybrid CT-angiography unit in the setting of catheter-directed angiography demonstrated that the addition of cross-sectional CT imaging during catheter-directed angiography improved sensitivity for detection of small HCC lesions (92%) compared to catheter-directed superselective digital subtraction angiography (DSA) alone (65%) (16). In addition, CT imaging during catheter-directed angiography led to repositioning the catheter (15,16), and ultimately altered therapy in a subset of patients (16,17). Thus, the use of a hybrid X-ray MR angiography (MRA) unit in the setting of catheter-directed angiography may offer the same advantages provided by hybrid CT-angiography units. However, catheter-directed contrast agent injection techniques have yet to be evaluated for MRI of HCC.

We tested the hypothesis that selective IA Gd administration to liver tumor via hepatic artery injection would increase tumor enhancement and conspicuity as compared to traditional IV Gd administration in a rabbit VX2 liver tumor model.

MATERIALS AND METHODS

Animal Model

Our institutional animal care and use committee approved all of the animal experiments. Although the eastern woodchuck HCC animal model may be a better representative of human hepatocarcinogenesis (17), we used the rabbit VX2 tumor model because 1) it is an accepted liver tumor model in large animals (18); 2) its blood supply is almost entirely from the hepatic artery, and thus is similar to that of human HCC (19); 3) tumors can be detected by multiple imaging modalities (18); and 4) the rabbit vascular anatomy is well documented and rabbit hepatic arteries are large enough to permit hepatic artery catheterization (18).

We performed all experiments using live New Zealand white rabbits weighing approximately 5 kg. VX2 cells were initially grown in the hindlimb of an additional donor rabbit (four-week incubation period). Harvested hindlimb tumor tissues were minced and placed in sterile Hanks solution. For surgical VX2 liver implantation, we anesthetized each rabbit with intramuscular (IM) ketamine 44 mg/kg and xylazine 3–5 mg/kg and administered inhaled isoflurane 2–3% as needed during the procedure. After sterile preparation of the subxiphoid area, we performed a mini-laparotomy (6–8 cm), exposing the liver. We implanted minced pieces of harvested VX2 tumor with injections into the left and right liver lobes using an 18-gauge angiocatheter outer cannula (Fig. 1). The abdomen was closed using a three-layer technique. Liver tumors were incubated for approximately 30 days prior to imaging. X-Ray DSA

X-ray DSA was performed using a Siemens C-arm PowerMobil unit (Siemens Medical Solutions, Erlangen, Germany). Each rabbit was initially sedated using a mixture of IM ketamine (80 mg/kg) and xylazine (5 mg/kg). The animals were intubated using a 3-F endotracheal tube. We administered inhalational isoflurane (2–3.5%) for anesthesia through the endotracheal tube using a small-animal ventilator (Harvard Apparatus, Holliston, MA, USA), with additional IM ketamine as needed. The common femoral artery was accessed through a cut-down, and catheterized with a 3-F vascular sheath (Cook, Bloomington, IN, USA). A 2-F catheter (Cook JB-1) was advanced over a 0.014-inch diameter guidewire and the celiac artery was selectively catheterized.
We performed X-ray DSA of the celiac, common hepatic, or left hepatic arteries using hand injections of full-strength Omnipaque 350 (Amersham Health, Princeton, NJ, USA). When the catheter was positioned in the common hepatic artery, we secured it in place using a 2-0 silk suture in the rabbits’ groin. The animals were then transferred to the MRI scanner located in an adjacent room.

MRI

MRI was performed using a 1.5T Magnetom Sonata clinical MR scanner (Siemens Medical Solutions, Erlangen, Germany). The rabbits were imaged in the supine position using a flexible surface coil that conformed to the shape of the abdomen. The rabbits remained intubated for isoflurane administration throughout the MRI procedure.

We acquired T2-weighted (T2W) TSE images prior to contrast injection with the following parameters: TR/TE = 3000/80 msec, 256 × matrix size = 128, turbo factor = 7, 20 slices, slice thickness = 4 mm, bandwidth (BW) = 390 Hz/pixel, four signal averages, and voxel size = 2.3 × 2.3 × 4.0 mm³. The T2W images were used to optimize imaging positions for subsequent CE scans. We performed dynamic 3D inversion recovery (IR) GRE MRI following IA and IV gadopentetate dimeglumine (Magnevist; Berlex Laboratories, Wayne, NJ, USA) contrast injections. Dynamic CE (DCE) scans were performed after IA injection of 2 mL 20% gadopentetate dimeglumine solution (0.04 mmol/kg dose) and IV injection of 1 mL 100% gadopentetate dimeglumine solution (0.1 mmol/kg dose). Both IA and IV contrast agent injections were performed using a power injector (Spectris MR power injector; Medrad, Inc., Pittsburgh, PA, USA) at 0.3 mL/second. IA injections were administered through the catheter that was previously placed during DSA, whereas the IV injections were administered through a catheter in the rabbits’ ear vein.

Identical parameters were used for each four-minute DCE scan, during which the selected 3D image series was repeatedly sampled: acquisition time for each 3D volume = 2.1 seconds, TR/TE = 3.7/1.6 msec, inversion time (TI) = 50 msec, flip angle = 25°, FOV = 200 × 100 mm², 43 views/segment, matrix = 256 × 129, BW = 490 Hz/pixel, 6/8 partial Fourier, and five slices interpolated to 10 (5-mm thickness). The TI was defined as the time interval between the application of the global inversion preparation pulse and the sampling of the first phase-encode line of the centrically ordered acquisition. The TI and sequence flip angle were optimized to null signals from background tissues over a wide range of TI relaxation times in order to maximize the conspicuity of those tissues with TI significantly shortened by the presence of Gd contrast agent (TI shortened to <100 msec) (20,21). The TI and flip angle were optimized to ideally suppress all tissues that did not contain Gd contrast agent. Tissue signal intensities were allowed to return to baseline values between injections. To assess the return to baseline intensity values, the 3D image series was sampled at 10-minute intervals following each DCE study. From the axial image slice with the largest tumor area, the mean signal intensity within an enhancing region was measured, and a return to within 10% of the original mean signal intensity value was considered adequate to begin subsequent contrast injection and comparison DCE scans. In four rabbits IA injections were performed prior to IV injections, and for one rabbit IV injection was performed prior to IA injection. In order to maintain anatomic location and avoid registration complications, the animals were kept anesthetized within the scanner bore throughout the entire procedure. After imaging, we euthanized each animal to harvest and section the liver for tumor confirmation at gross necropsy.

Data Analysis

At each slice position containing tumor tissue, identical regions of interest (ROIs) were drawn in the IA and IV DCE image series to measure the mean tumor tissue signal (MTS) and mean liver tissue signal (MLS), as well as the relative noise (RN). The RN was estimated by measuring the standard deviation (SD) of the signal within peripheral image regions void of tissue. For each image collected during the four-minute interval following an injection, we calculated the relative tumor tissue signal-to-noise ratio (SNR) = MTS/RN, and the tumor-to-liver contrast-to-noise ratio (CNR) = (MTS-MLS)/RN. The SNR and CNR provided quantitative metrics for tumor enhancement and conspicuity, respectively. The peak SNR and CNR values for each corresponding IA and IV image series were compared using a Wilcoxon signed-rank test with α = 0.05. The time interval between contrast injection and peak CNR was also measured for each corresponding IA and IV image series and compared using a Wilcoxon signed-rank test with α = 0.05.

RESULTS

Animal Model and DSA

Each rabbit was successfully catheterized under DSA. VX2 liver tumors were present in each rabbit. Tumor diameter ranged from 1.1 to 3.0 cm. Three rabbits each produced two tumors, and two rabbits produced only a single tumor (eight tumors in total). A representative gross necropsy image for confirmation of VX2 tumor position is shown in Fig. 1. A DSA image following iodinated contrast injection into the common hepatic artery is shown in Fig. 2.

MRI

Dynamic CE-MRI successfully depicted tumor positions in each of the five rabbits. ROI tumor tissue enhancement measurements were performed in each of the eight tumors for both IA and IV injection protocols. No respiratory motion artifacts were observed in either IA or IV injection CE images series. The peak CNR following IA injection (17.0 ± 4.8 [mean ± SD]) was significantly greater than the peak CNR following IV injection (6.2 ± 2.62; P < 0.05). The IA technique produced a >60% increase in peak CNR at each measured position. The peak SNR following IA injection was
21.7 ± 5.8 (mean ± SD), whereas the peak SNR following IV injection was 16.9 ± 10.2. However, although in six of the eight tumors IA SNR was greater than IV SNR, overall these differences did not meet the criteria for statistical significance (P < 0.07). As expected, the time interval between contrast injection and peak CNR was significantly shorter for the IA technique (34.2 ± 6.3 seconds, compared to 61.9 ± 12.7 seconds (P < 0.05) for the IV technique). Representative time courses of VX2 tumor CNR following IA and IV injections are shown in Fig. 3. Return to baseline tissue signal intensities required time intervals of roughly one hour following IA contrast injection and three hours following IV contrast injection.

Representative liver tumor enhancement images at peak CNR following IA and IV contrast injections for two rabbits (Fig. 4) demonstrate improved contrast between liver tumor and normal liver parenchyma in the IA images compared to the IV images. In one of the rabbits no tumor enhancement was observed following IV injection, whereas clearly conspicuous enhancement of the tumor was observed following IA injection (Fig. 5).

**DISCUSSION**

These studies clearly demonstrate the feasibility of using IA injections for dynamic CE imaging of liver tumors. While using 60% less overall contrast agent dose, IA injections significantly improved tumor conspicuity over conventional IV injection techniques for dynamic 3D GRE MRI. Furthermore, a single tumor (Fig. 5) demonstrated significant enhancement following IA injection with no apparent enhancement following IV injection. While these promising results suggest the potential to improve HCC detection, further studies with a larger sample size are necessary to determine whether IA injection strategies actually increase the sensitivity of CE-MRI.

Hepatic artery cather placement strictly for diagnostic purposes of tumor detection may not be warranted. However, particularly for liver tumors, interventional oncology procedures increasingly require hepatic artery catheterization for targeted delivery of therapeutic agents (e.g., bland embolization, chemoembolization, and radioembolization). Within this setting, previous studies using hybrid CT-angiography systems demonstrated significantly improved detection of small HCC compared to conventional X-ray DSA techniques (16). CT imaging during catheter-directed angiography permitted adjustments in catheter position (15,16) to be made to optimize therapy (16,17). Catheter-directed CT-angiography is now routinely used to delineate the hepatic blood supply and the relative volume of targeted liver segments, permitting optimum dose calculation for superselective radioembolization (22). The recent development of hybrid X-ray MRI units has significantly reduced the complications of performing catheter-directed injections for CE-MRI of liver tumors. Not only may these developments lead to preprocedural detection of previously undetected lesions, IA catheter-directed CE-MRI may permit improved quantitative liver tumor perfusion measurements and lead to improved methods for preprocedural pharmacoangiography for embolic material dose estimations.

We were able to demonstrate that even though 60% less contrast agent was used for the IA injections, most tumors demonstrated increased enhancement and all tumors demonstrated significantly improved CNR compared to IV injections. While future studies are necessary to optimize the contrast agent dose relative to tumor SNR and CNR, these studies clearly demonstrate the potential to conserve contrast agent dose by using...
IA injections. Contrast agent dose conservation may become critical in the interventional setting because 1) iterative injections may be necessary to assess perfusion changes, and 2) the presence of contrast agent within tissues could confound alternative functional MRI (fMRI) measurements (22) or the tracking of Gd-labeled therapeutic agents. The relatively long washout times necessary for conventional IV injection would be incompatible with iterative measurements during most interventional procedures.

For these studies we used a dynamic CE IR-prepared 3D GRE MRI acquisition strategy rather than the more conventional multiphase CE breath-hold 2D GRE acquisition strategy. Conventional liver CE-MRI acquires images at only a few time points following injection (early and late arterial phases, and venous phase). For the IA studies we had no prospective knowledge about when to expect maximal tumor enhancement following contrast injection. For this reason we opted to use a dynamic acquisition strategy (i.e., repeated image acquisition at 2.1-second intervals) to avoid missing peak enhancement phases. For consistency, the dynamic acquisition strategy was used for both IA and IV injections. This study demonstrated that maximal IA tumor CNR occurred at roughly 30 seconds post-injection for each rabbit. Further studies are necessary to determine whether a conventional single- or multiphase 2D GRE imaging strategy could be utilized for breath-held acquisition following an appropriate delay (~30 seconds) after IA contrast injection. The time interval between IV injection and peak CNR correlated well with previous CE studies in the VX2 rabbit tumor model, which demonstrated peak enhancement at roughly one minute post-injection (14,23).

The pulse sequence used in this work was designed to maximize contrast between non-enhancing and enhancing tissues and thus improve the conspicuity of hypervascular lesions. We chose to use an IR preparation to achieve even greater T1 weighting than is possible with conventional 2D GRE liver imaging techniques.
However, the increased T1 weighting provided by IR preparation was gained at the expense of a nearly complete suppression of background tissues. The sequence used in this work may not be suitable for simultaneous interrogation of non-enhancing anatomy or the acquisition of a time series of images for perfusion measurements. For these alternative applications, an interleaved multislice 2D GRE sequence may be more optimal because it would provide improved SNR and a quantifiable relationship between contrast agent tissue concentration and enhancing tissue signal. The T1-shunting properties of Gd for CE-MRI are generally proportional to tissue concentrations of the contrast agent. Therefore, provided that tissue Gd concentrations remain within ranges dominated by T1 effects, the IA injection technique should offer similar tumor enhancement improvements over the IV injection technique independently of the chosen T1W imaging protocol.

There are several limitations to this study. First, for only one of the rabbits did we reverse the order of contrast injection strategies (i.e., IV prior to IA). The three-hour interval required for tumor signal to return to baseline after the larger 0.1 mmol/kg IV injection motivated us to perform IA injections prior to IV injections in the remaining five rabbits. While a return to baseline intensity values was monitored in an attempt to avoid experimental bias, a more optimal protocol would involve conditional randomization of injection order during each study. Second, the IA contrast agent dose used in this study may not be optimal. We chose to compare a single IA dose of 0.04 mmol/kg with the conventional IV dose of 0.1 mmol/kg. While this study establishes the feasibility of using IA injection to increase tumor conspicuity over IV injection, further studies are necessary to optimize IA dose levels to maximize tumor enhancement while minimizing contrast agent dose. Third, the limited sample size of this study established only the feasibility of performing IA contrast injection to improve tumor enhancement. A larger sample size may demonstrate significantly increased enhancement as well as conspicuity with IA contrast injections. Further studies are necessary to reproduce these results in a larger sample, and ultimately to determine whether the IA technique actually improves tumor detection sensitivity.

In conclusion, we demonstrated the feasibility of using catheter-directed IA contrast agent injection techniques to improve tumor conspicuity compared to IV injection techniques in a VX2 rabbit model of HCC. This strategy could be employed to enhance the detection of small liver tumors or to conserve contrast agent in future MRI-guided transcatheter liver therapies, especially in the setting of clinical hybrid MR X-ray angiography units.

REFERENCES


