Development of an Intrabiliary MR Imaging-monitored Local Agent Delivery Technique: A Feasibility Study in Pigs¹

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Purpose:

To investigate the feasibility of using magnetic resonance (MR) imaging to monitor intrabiliary delivery of motexafin gadolinium (MGd) into pig common bile duct (CBD) walls.

Materials and Methods:

Animal studies were approved by the Institutional Animal Care and Use Committee. Initially, human cholangiocarcinoma cells were treated with various concentrations of MGd, a compound serving as a T1-weighted MR imaging contrast agent, chemotherapy drug, and cell marker. These cells were then examined by means of confocal microscopy to confirm the intracellular uptake of MGd. In addition, an MGd/trypan blue mixture was locally infused into CBD walls of six cadaveric pigs using a microporous balloon catheter. CBDs of six pigs were infused with saline to serve as controls. Ex vivo T1-weighted MR imaging of these CBDs was performed. For in vivo technical validation, the microporous balloon catheter was placed in the CBD by means of a transcholecystic access to deliver MGd/trypan blue into CBD walls of six living pigs. T1-weighted images were obtained with both a surface coil and an intrabiliary MR imaging guidewire, and contrast-to-noise ratios of CBD walls before and after MGd/trypan blue infusions were compared in the two groups by means of paired *t* test, with subsequent histologic analysis to confirm the penetration and distribution of the MGd/trypan blue agent into CBD walls.

Results:

In vitro experiments confirmed uptake of MGd by human cholangiocarcinoma cells. The ex vivo experiments demonstrated the penetration of MGd/trypan blue into the CBD walls. The in vivo experiment confirmed the uptake of MGd/trypan blue, showing an increased contrast-to-noise ratio for the CBD after administration of the mixture, compared with images obtained prior to MGd/trypan blue administration (11.6 ± 4.2 [standard deviation] vs 5.7 ± 2.8 ; $P = .04$). Histologic results depicted the blue dye stains and red fluorescence of MGd in CBD walls, confirming the imaging findings.

Conclusion:

It is feasible to use MR imaging to monitor the penetration of locally delivered MGd into pig CBD walls.

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Pancreatobiliary malignancy with biliary obstruction has a very poor prognosis. Obstructive pancreatobiliary malignancies are often unresectable at the time of presentation and unresponsive to chemotherapy and radiation therapy. For the minority of patients with resectable tumors, surgical treatment is often associated with substantial morbidity and mortality (1). In most cases, palliative treatment with intrabiliary stent placement is the primary available option for treatment of obstruction. However, intrabiliary stent placement has a 30-day mortality rate of more than 10% and very limited long-term patency (1,2). Systemic chemotherapy is a poor option for palliative treatment of pancreatobiliary malignancies, as it does not permit delivery of sufficient drug doses for effective disease control and can cause substantial undesired toxicities to other vital organs. Recent studies have further confirmed that inefficient drug delivery is an important contributor to chemoresistance in pancreatobiliary cancers (3).

A recent advance in medical imaging is the establishment of intraluminal magnetic resonance (MR) imaging and interventions, and the development of a U.S. Food and Drug Administration–approved MR imaging guidewire (4). The guidewire has a “three-in-one” function that allows simultaneous imaging, catheter guidance, and local tissue heating (5–7). The advantages of an intraluminal MR imaging guidewire and associated interventions may benefit the management of obstructive pancreatobiliary disease.

Advance in Knowledge

- MR imaging can be used to monitor the penetration and distribution of locally delivered motexafin gadolinium (MGd) into pig common bile duct (CBD) walls and shows a significantly higher contrast-to-noise ratio (11.6 ± 4.2 vs 5.7 ± 2.8 , $P < .05$) in the MGd-infused CBD walls than that in the saline-infused CBD walls.

Motexafin gadolinium (MGd) is a porphyrin-like molecule that is taken up preferentially by malignant cells and has a multiplicity of functions as (a) a chemotherapeutic agent (8), (b) a T1-weighted MR imaging contrast agent (9), (c) an emitter of red-colored fluorescence for histologic/laboratory correlation (10), and (d) a sensitizer to both radiation and chemotherapy (11,12). Combining the use of MGd with intrabiliary MR imaging might improve the management of malignant pancreatobiliary obstruction by assuring that the agent is delivered to all of the diseased area. The aim of this study was to investigate the feasibility of using MR imaging to monitor intrabiliary local delivery of MGd into pig common bile duct (CBD) walls.

Materials and Methods

Study Design

This study was divided into three phases, as follows: (a) *in vitro* experiments to confirm the intracellular uptake of MGd by human cholangiocarcinoma cells, (b) *ex vivo* experiments to establish the initial protocol for intrabiliary MR imaging–monitored MGd delivery, and (c) an *in vivo* experiment to validate the feasibility of using intrabiliary MR imaging to monitor the local delivery of MGd into CBD walls of pigs.

In Vitro Experiments

Cell culture and MGd treatment.—We used a human cholangiocarcinoma cell line (MZ-ChA-1; originated from the laboratory of Dr. J. Gregory Fitz, University of Texas Southwestern Medical School, Dallas, Tex). A total of 1×10^5 cells were seeded and grown in a four-chamber cell culture plate (Nalge

Nunc International, Rochester, NY). Cells were then treated by adding MGd (Pharmacyclics, Sunnyvale, Calif) at concentrations of 0, 25, 50, 75, 100, and 125 $\mu\text{g/mL}$ for 48 hours. The cell cultures were then washed twice with phosphate-buffered saline (PBS) to remove free MGd and fixed in 4% paraformaldehyde. The cell plates were counterstained with 4',6-diamidino-2-phenylindole (DAPI; Vector Laboratories, Burlingame, Calif), and then imaged with a laser confocal microscope (A1R; Nikon, Tokyo, Japan) to compare the intensities of MGd-emitted red fluorescence in the plasma of MZ-ChA-1 cells.

MR imaging.—To determine the optimal dose range for MGd, the same human cholangiocarcinoma cells were cultured and grown on a 24-well plate (BD Falcon, Franklin Lakes, NJ). The subsequent confluent cell cultures were treated with MGd at 0, 25, 50, 75, 100, 125 and 150 $\mu\text{g/mL}$ for 48 hours. The cells were washed with culture medium. The 1×10^6 cells were transferred to 0.6-mL Eppendorf tubes and dispersed in 1% agarose. MR imaging of these cell tubes was performed with

Published online

10.1148/radiol.11110723 Content codes:

Radiology 2012; 262:846–852

Abbreviations:

CBD = common bile duct
CNR = contrast-to-noise ratio
MGd = motexafin gadolinium
PBS = phosphate-buffered saline
SI = signal intensity

Author contributions:

Guarantors of integrity of entire study, F.Z., H.G.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, F.Z., X.Y.; experimental studies, F.Z., J.L., Y.M., J.S., S.S.S., P.W., H.G., X.Y.; statistical analysis, F.Z., X.Y.; and manuscript editing, F.Z., S.S.S., P.W., D.G., X.Y.

Funding:

This research was supported by the National Institutes of Health (grant R01EB012467).

Potential conflicts of interest are listed at the end of this article.

Implication for Patient Care

- The technique of MR imaging–monitored intrabiliary local delivery of therapeutic agents into bile duct walls may open alternative avenues to effectively manage obstructive pancreatobiliary malignancies.

a 3.0-T MR system with a wrist coil (SENSE wrist four-element coil; Philips Healthcare, Best, the Netherlands). T1-weighted images were acquired in the sagittal and transverse planes by using a spin-echo sequence: repetition time msec/echo time msec, 550/12; 90° flip angle; 100-mm field of view; 1-mm section thickness; 500 × 498 matrix; and eight signals acquired.

Imaging analysis.—MR images of cholangiocarcinoma cells with various concentrations of MGd were analyzed by measuring the signal intensities (SIs) of cell-containing tubes. The SI of each tube was measured by using a Digital Imaging and Communications in Medicine viewer (DICOM Viewer R2.5, version 1 level 1; Philips Healthcare). The region of interest at 3 mm² size was placed at the center of the tube by one radiologist (F.Z., 10 years of experience with MR imaging).

Ex Vivo Experiments

Preparation and MR imaging.—Twelve cadaveric pig livers with intact bile ducts and a portion of the duodenum were obtained. Access was obtained via the gallbladder, and a custom agent delivery balloon catheter that had multiple micropores on the balloon was advanced, via the cystic duct, into the CBD. Since the average diameters of the CBD lumens of 40–50-kg pigs were approximately 4 mm, we used a balloon with a diameter of 5.0–5.5 mm. Five milliliters MGd (75 µg/mL) mixed with trypan blue dye was locally infused into the walls of six CBDs at 0.5 mL/sec, while the CBDs in the control group of six pigs were infused with 5 mL PBS. The optimal concentration of MGd in the mixture was determined by the results of the *in vitro* study. The entire CBD with its surrounding connective tissue was then harvested and placed into the PBS solution in a 45-mL centrifuge tube. Each tube with either MGd-infused or PBS-infused CBD was then imaged with the 3.0-T MR system by using a custom-made spiral coil dedicated for imaging rats. Fat-suppressed transverse T1-weighted images were acquired using a spin-echo sequence (550/12, 90° flip angle, 100-mm field

of view, 1-mm section thickness, 168 × 168 matrix, and eight signals acquired). Immediately after MR imaging, the CBD specimens were cryosectioned at 8-µm and examined by using confocal microscopy to detect MGd red fluorescence and light microscopy to detect trypan blue within the CBD walls.

Imaging analysis.—We measured SIs of the CBD walls, SI_{CBD}, and the peri-CBD tissues, SI_{peri-CBD}, by using four regions of interest along the CBDs at 0, 3, 6, and 9 o'clock positions, and then calculated the average contrast-to-noise ratio (CNR) by using the following equation: $(SI_{CBD} - SI_{peri-CBD})/SD_{noise}$, where SD_{noise} is the standard deviation of the background noise. The 1-mm² region of interest was placed by one radiologist (F.Z.).

In Vivo Experiment

Animals.—The animal protocol was approved by the Institutional Animal Care and Use Committee and was in compliance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Six domestic pigs, 40–50 kg in weight, were first sedated by intramuscular injection of telazol at 4.4 mg per kilogram of body weight and xylazine at 1 mg per kilogram of body weight and were then mechanically ventilated with 1%–3% isoflurane.

Catheterization of CBDs.—Through a subcostal laparotomy, the gallbladder was mobilized and lifted out of the peritoneal cavity. With use of fluoroscopic guidance, a 6-F introducer was advanced, through the gallbladder and the cystic duct, into the CBD over a 0.035-inch hydrophilic guidewire (Terumo Corporation, Tokyo, Japan). Through the introducer, we placed a 6 mm × 20 cm balloon catheter (Ultra-Thin SDS; Boston Scientific, Natick, Mass) into the CBD. This saline-inflated “imaging balloon” functioned to reshape the CBD axial profile, which enabled the wall of the CBD to be clearly delineated as a bright ring, as the saline-inflated balloon was hypointense on T1-weighted images. Through the balloon catheter, we then inserted a custom-made 0.032-inch MR imaging guidewire into the CBD. The guidewire was made of a

nitinol coaxial cable with a 3-cm extension of its inner conductor. We placed the guidewire so the junction of the inner and outer conductors was centered in the middle of the balloon (Fig 1). The abdominal incision was then closed with sutures and the introducer was secured to the skin.

MR imaging.—Each animal was placed supine on the 3.0-T MR imager table. After inflating the imaging balloon, we acquired two sets of fat-suppressed and respiration-gated T1-weighted images using a torso phased-array surface coil and the MR imaging guidewire prior to intrabiliary MGd delivery. MR imaging was performed with a turbo field echo sequence with the following parameters: 10/1, 300-mm field of view, 15° flip angle, 5-mm section thickness, 320 × 320 matrix, and five signals acquired. Then, the imaging balloon was exchanged for the microporous balloon. Through the microporous balloon, 5 mL MGd (75 µg/mL) diluted with trypan blue dye was infused into the CBD wall at 0.5 mL/sec. Immediately after the MGd administration, the microporous balloon was replaced by the imaging balloon to obtain two sets of post-MGd infusion MR images of the CBD wall with either the torso phased-array surface coil or the intrabiliary MR imaging guidewire using the same parameters as described for pre-MGd infusion MR imaging. The 3.0-T MR machine was unable to obtain images with the simultaneous use of both the surface coil and the MR imaging guidewire.

Imaging analysis.—We measured SIs of the CBD walls and the peri-CBD tissues using four regions of interest along the CBDs at 0, 3, 6, and 9 o'clock positions and then calculated the average using the same formula as for the *ex vivo* experiments. The 1-mm² region of interest was placed by one radiologist (F.Z.).

Histologic Evaluation

Immediately after MR imaging, each animal was sacrificed. The MGd/trypan blue-infused CBD segment or uninflated CBD segment (as a control) was harvested for histologic correlation to

Figure 1

Figure 1: Surgery and cholangiography of the intrabiliary interventional procedure. **(a)** By means of laparotomy, the gallbladder (*Gb*) is exposed and raised by two forceps. **(b)** Transcholecystic insertion of a 6-F introducer (open arrow) into the CBD. Solid arrow = gallbladder. **(c)** Cholangiogram shows saline-inflated balloon (long solid arrow) as a filling defect, with contrast agent outlining the left hepatic duct (open arrow). Short solid arrows = metal markers of the balloon, *Du* = duodenum. **(d)** MR imaging guidewire (long solid arrow) is advanced via the introducer (open arrow) into the inflated balloon catheter. Short solid arrows = metal markers of the balloon, *Du* = duodenum.

Figure 2

Figure 2: **(a–f)** Confocal microscopic images of human cholangiocarcinoma cells treated with MGd at different concentrations show increased intracellular uptake of MGd (pink dots) as MGd concentration increases. (Original magnification, $\times 20$.) **(g)** In vitro T1-weighted MR images of human cholangiocarcinoma cells treated with MGd at different concentrations show increasingly high SI as MGd concentration increases. **(h)** Measurements of MR SIs further confirm the findings in **g**, demonstrating a linear increase in SI from 25 to 75 $\mu\text{g/mL}$ MGd, followed by a plateau pattern of SI from 75 to 150 $\mu\text{g/mL}$ MGd.

confirm the successful penetration of MGd/trypan blue into the CBD wall. We cryosectioned the CBDs at 8 μm and then examined the histologic slides by using laser confocal microscopy to detect red-fluorescent MGd and light microscopy to detect blue dye staining of the CBD walls.

Statistical Analysis

Software (SPSS, version 17.0; SPSS, Chicago, Ill) was used to perform the statistical analyses. We used a paired Student *t* test to compare the average CNRs between the MGd- and PBS-infused groups. For the in vivo experiment, we compared the average CNRs

of CBDs between **(a)** the images obtained before and after infusion of the MGd/blue mixture and **(b)** images obtained using the surface coil and the intrabiliary MR imaging guidewire. A *P* value less than .05 was considered to denote a statistically significant difference.

Figure 3: Ex vivo MR imaging of intrabiliary delivery of (a–d) MGd/trypan blue dye mixture and (e–h) PBS. Surgical images show (a) a blue-stained CBD with MGd/trypan blue infusion (arrow), which is not seen in (e) the control CBD with saline infusion. MR images of CBDs show (b) high SI of the CBD wall and peri-CBD tissue with MGd/blue dye infusion (arrow), which is not seen with (f) PBS infusion. (c, d) Histologic images confirm the successful delivery of blue dye (arrowheads on c) and MGd as red fluorescence (d) within the CBD wall, which are not seen in (g, h) the control CBD wall. Autofluorescence of the CBD wall is seen in h. (Original magnification, $\times 20$.)

Results

In the in vitro experiments, confocal microscopy confirmed the intracellular uptake of MGd by human cholangiocarcinoma cells, and the uptake increased as the MGd concentrations increased (Fig 2). In vitro MR imaging further confirmed these cytologic findings, demonstrating a linear increase of SIs from 25 to 75 $\mu\text{g/mL}$ and then a plateau pattern of SIs from 75 to 150 $\mu\text{g/mL}$ of MGd.

The ex vivo experiments successfully demonstrated MGd/blue dye penetration into the pig CBD walls, confirmed by (a) ex vivo MR imaging, which demonstrated a significantly higher average CNR in the MGd/trypan blue-infused CBD walls than that in the controlled CBD walls (144.5 ± 17.3 [standard deviation] vs 23 ± 5.3 , $P = .0008$); and (b) histologic evaluation, which demonstrated trypan blue-stained CBD walls and red fluorescence emission from the MGd-deposited CBD walls and peri-CBD tissues. These findings were not present in the PBS-infused control CBDs (Fig 3).

During the in vivo validation study, all pigs survived until sacrifice. Figure

4 summarizes the average CNRs obtained from both pre- and post-MGd/trypan blue infusion MR images using either a surface coil or an intrabiliary MR imaging guidewire. Postinfusion MR images demonstrated a higher average CNR than preinfusion MR images when using either the surface coil (11.6 ± 4.2 vs 5.7 ± 2.8 , $P = .025$) or the intrabiliary MR imaging guidewire (41.5 ± 9.7 vs 29.6 ± 6.3 , $P = .046$). Intrabiliary MR imaging generated a higher average CNR than surface coil-based MR imaging on both preinfusion and postinfusion images ($P = .003$ and $.005$). Histologic examination confirmed these MR imaging findings, demonstrated as blue dye infiltration and MGd-emitting fluorescence within the CBDs (Fig 5).

Discussion

The results of our study demonstrated that human cholangiocarcinoma cells could take up MGd in a concentration-dependent manner and MR imaging is a valuable modality to monitor the penetration and distribution of MGd into pig CBD walls after intrabiliary administration. This interventional technique

may be of value for managing pancreatic adenocarcinoma and cholangiocarcinoma, the two most common intractable malignancies causing obstruction of the CBDs. These malignancies tend to be hypovascular, making systemic chemotherapy less effective. Rapid delivery of high-dose therapeutic agents into the targeted CBD walls and peri-CBD tissues may enhance the chemotherapeutic effect on pancreatobiliary malignancies as well as minimize toxicities to other organs compared with systemic chemotherapy (6). The important role of MR imaging in monitoring the distribution of the locally delivered therapeutics within the CBDs and peri-CBD tissues should enable the operators to assess the immediate technical success of the intrabiliary local agent delivery.

Because of the small caliber and deep location of the CBDs, as well as complex anatomy of the porta hepatis, the in vivo assessment of CBD walls is a difficult task and drug delivery specifically to the CBD walls has been very challenging. The need to visualize the CBD walls and accurately identify tumor extension from the CBD walls motivated the development of intrabiliary diagnostic MR

Figure 5

Figure 5: A–D, MR imaging—monitored local MGD/trypan blue delivery into the CBD wall with surface coil and intrabiliary MR imaging guidewire demonstrate MGD-enhanced CBD region (arrow on B and D) after intrabiliary MGD/trypan blue infusion. Insets images = magnifications of the CBD regions. E, Image obtained at surgery shows blue-stained CBD (open arrow), which is confirmed by F, histologic correlation as blue-penetrated CBD wall (arrows). (Original magnification, $\times 20$.) Solid arrow in E = control CBD segment with no MGD/trypan blue infusion. G, Confocal microscopic image shows MGD-created red fluorescent emission in the CBD wall, compared with H, the control CBD segment with no MGD/trypan blue infusion, in which only autofluorescence is seen. (Original magnification, $\times 20$.)

Figure 4

Figure 4: Average CNRs in CBDs of living pigs. CNRs are higher after MGD/trypan blue infusion than before infusion and are higher for intrabiliary MR imaging than for surface coil-based MR imaging.

imaging for biliary tumor staging (13). In our study, we extended the application of intrabiliary MR imaging from a purely diagnostic tool to intrabiliary interventional MR imaging, with emphasis on MR imaging-monitored intrabiliary local delivery of MGD into the CBD walls.

There were limitations in our study. At the preliminary stage, the focus of our study was on the “proof of principle”

of the concept “MR imaging—monitored intrabiliary local agent delivery.” We didn’t perform real-time MR imaging to guide the interventional procedure and instantly visualize the MGD distribution within the CBD walls, which depends on a suitable fast MR imaging sequence with the 3-T MR system. Dynamic contrast-enhanced MR imaging may be the optimal technique which can be used to

instantly monitor the delivery of MGD into pig CBD walls within 10 seconds of breath hold in pigs by turning off the mechanical ventilation. The SI detected at intrabiliary MR imaging contains combined components of near field effect of the intrabiliary coil and high SI generated from MGD. Further improving the performance of the intrabiliary coil may be expected to reduce the near field effect to a minimum level.

In conclusion, it is feasible to use MR imaging to monitor the penetration of locally delivered MGD into pig CBD walls, which demonstrates the potential application in managing obstructive pancreatobiliary malignancies.

Acknowledgment: The authors thank Bensheng Qiu, PhD, for his technical assistance with MR imaging.

Disclosures of Potential Conflicts of Interest: E.Z. No potential conflicts of interest to disclose. J.L. No potential conflicts of interest to disclose. Y.M. No potential conflicts of interest to disclose. J.S. No potential conflicts of interest to disclose. S.S.S. No potential conflicts of interest to disclose. P.W. No potential conflicts of interest to disclose. H.G. No potential conflicts of interest to disclose. D.G. No potential conflicts of interest to disclose. X.Y. No potential conflicts of interest to disclose.

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