Intrabiliary MR-Guided Local Agent Delivery

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Pancreatobiliary Malignancy with Biliary Obstruction

- Very poor prognosis
- Unresectable at the time of presentation
- Unresponsive to chemotherapy and radiation therapy
- No effective approaches to deliver high dose chemodrugs to tumors
- Current clinical management: Biliary stenting

Poor Long-Term Patency of Biliary Stenting

Tumor overgrowth by stent

Tumor ingrowth of stent

Need to find alternatives for pancreatobiliary malignancies

Intraluminal MRI
Why intraluminal MRI?

Intraluminal MRI

- Conventional MRI
  - Iliac A.
  - Intraluminal MR antenna

- Intraluminal MRI
  - Fibrotic cap
  - Lipid core
Clinical-sized intraluminal MR antenna

0.032 inch
The MR antenna has two functions:

1. An intraluminal MR receiver for:
   - high-resolution imaging of luminal walls

2. A conventional guidewire for:
   - guiding interventional procedures

Called an MR imaging-guidewire (MRIG)

Intravascular MR/RF-Enhanced Vascular Gene Therapy

A gene delivery balloon catheter

Gene delivery channel

Guidewire channel

0.014” MRIG

Angioplasty balloon channel

Tuning box
Intravascular MR/RF-enhanced VEGF expression in atherosclerotic arteries

Quantitative VEGF gene expression

Quantitative Western blot analysis

Intravascular MR/RF-enhanced VEGF gene therapy of atherosclerotic in-stent neointimal hyperplasia

Cholesterol diet

Pathology correlation

2 months

Stent placement

VEGF only

VEGF+heat

In-stent stenosis
Intravascular MR/RF-enhanced VEGF gene therapy of in-stent neointimal hyperplasia

Intraluminal MRI and Interventions

*Form vasculature to non-vasculatures*

Development of an Intrabiliary MR/RF-Enhanced Chemotherpay of Pancreatobiliary Malignancies
Phase I: Developing an intrabiliary MRI-guided local agent delivery technique

Three Components:

- In-vitro confirming agent uptake by cholangiocarcinoma cells
- Ex-vivo evaluating intrabiliary local agent delivery
- In-vivo validating the feasibility of this new technique
In-Vitro Confirmation

- To confirm the capability of cholangiocarcinoma cells in uptake of an imaging/therapeutic agent
Cells & Agent

• **Human cholangiocarcinoma cells**

• **Motexafin gadolinium** (MGd, Pharmacyclics Inc):
  - an intracellular T1 contrast agent for MRI
  - a chemotherapy drug for treating cancers
  - a red-fluorescent marker for MRI-histology correlation
    (Excitation=470nm; emission=758nm)
In-Vitro Experimental Protocol:
To confirm intracellular MGd uptake by cholangiocarcinoma cells
Confocal microscopy: MGd uptake by cholangiocarcinoma cells
75 µg MGd/mL is the optimal concentration of MGd.
Ex-Vivo Evaluation

- To establish a protocol for surgery-based transcystic intrabiliary placement of an agent delivery balloon catheter

- To prove the possibility of intrabiliary MRI-monitored delivery of MGd/blue dye mixture into the common bile duct walls (MGd / blue = 6 / 94%)
Ex-Vivo Experiment Protocol:
Introbiliary MRI-monitored MGd/blue delivery

MRI

Confocal microscopy

Philips

Nikon
Surgery-based transcystic intrabiliary balloon placement

Intrabiliary delivery of 2-mL MGd/blue (MGd=75-ug/mL) into CBD wall

CBD = common bile duct
Ex-vivo MRI of intrabiliary MGd/blue dye delivery
In-Vivo Validation

• To validate the feasibility of intrabiliary MRI-guided local delivery of MGd/blue mixture into common bile duct (CBD) walls of living pigs
In-Vivo Experimental Protocol:
Intrabiliary MRI-monitored local MGd delivery into CBD Walls

Pre- and post-infusion MRI:
- Surface coil-based MR, T1WI
- Intrabiliary MR, T1WI
Transcystic intrabiliary balloon placement

Surgery

- Gallbladder
- Sheath

DSA-intervention

- L. hepatic duct
- Balloon
- Duodenum
- Sheath
- MRIG
Surgery - intervention

Surgery

DSA
Intrabiliary MRI-Guided MGd Delivery into CBD Walls

Surface coil-MRI | Intrabiliary MRI | Contrast-to-noise ratio (CNR)

Pre-infusion

Post-infusion

![Images of MRI scans showing pre- and post-infusion contrast to noise ratio (CNR) comparisons](image-url)
Surgery – histological findings

Surgery

Microscopy

Confocal Microscopy

Control

Delivered MGd
CONCLUSION

It is feasible to use intrabiliary MRI to monitor local agent delivery into CBD walls, which establishes the groundwork for developing intrabiliary MR/RF-enhanced local chemotherapy of pancreatobiliary malignancies.

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