PURPOSES: Pancreatobiliary cancers have limited response to systemic chemotherapy due to inefficient drug delivery into tumor tissues and the high resistance of cancer cells to chemotherapeutics. The aim of this study was to validate the feasibility of using 14 Tesla MRI to monitor RFH-enhance chemotherapeutic effect on mice cholangiocarcinomas.

METHODS: For in vitro evaluation, green fluorescent protein (GFP)-labeled human cholangiocarcinoma cells (Mz-ChA-1) were cultured in four-chamber slides and treated by using (a) 20-min RFH at approximately 42 °C plus 500-mM gemcitabine; (b) 20-min RFH-only; (c) 500-mM gemcitabine-only; and (d) no treatment to serve as a control. Cell viabilities were assayed using trypan blue exclusion. For in vivo evaluation, cells were subcutaneously implanted into the backs of 24 nu/nu nude mice to create cholangiocarcinoma mice models. Six mice in each group were treated by (a) intratumor injection of gemcitabine and 5-fluouracil (5-FU) at 25mg/kg, followed by RFH at approximately 42°C for 20 min; (b) 20-min RFH alone; (c) intratumor injection of 25mg/kg gemcitabine and 5-FU; and (d) phosphate buffer solution (PBS) injection to serve as controls. 14Tesla MRI, including T2 weighted imaging and diffusion-weighted imaging (DWI) was used to image the tumors at day 1 before treatment and day 1, 7, and 14 after treatment. Tumor size and apparent diffusion coefficient (ADC) were measured. HE staining, apoptosis assay and confocal microscopy were performed to establish image/histology correlation.

RESULTS: The in vitro experiments demonstrated that RFH-enhanced chemotherapy can significantly inhibit tumor cells growth, as compared to chemotherapy alone and the RFH alone group (0.58±0.10 vs 0.72±0.8 and 0.58±0.10 vs 0.65±0.11, p<0.05) (Figure 1). The in vivo experiments show a significant decrease in relative tumor growth in the group with RFH-enhanced chemotherapy, compared with chemotherapy and RFH only group (1.6±0.2mm vs 3.7mm±0.41mm and 1.6±0.2mm vs 2.9mm±0.33mm) (Figure 2). ADCs in RFH-enhanced chemotherapy group increased at day 1 and day 7 after treatment and return to the same level as that of the pre-treatment. For the chemotherapy and RFH group, there is no significant change in ADCs between and pre-and post-treatment(Figure 3E). Histology confirmed that RFH can enhance the chemotherapeutic effect on tumors (Figure 3A-D).

CONCLUSIONS: This study demonstrates the feasibility of using DW MRI to monitor RFH-enhanced chemotherapeutic effect of gemcitabine and 5-fu on mice cholangiocarcinomas and shows that ADC is a useful biomarker for evaluating the therapeutic effect, which may open new avenues to effectively manage pancreatobiliary malignancies.