

Monitoring response to drug-loaded PLGA nanoparticles in a Mia PaCa-2 pancreatic tumor model with T2 and diffusion-weighted MRI

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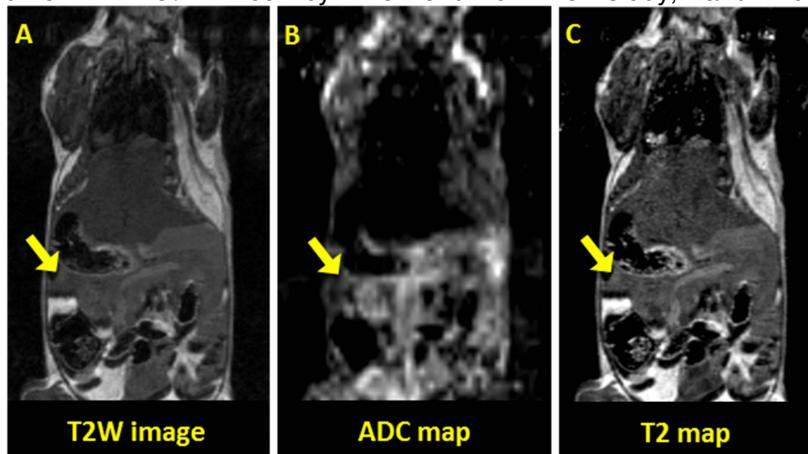
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Introduction: PHT-427 is a promising AKT-inhibitory chemotherapeutic against pancreatic cancer, but the hydrophobicity of PHT-427 limits pharmacokinetic delivery.¹ Poly(lactic-co-glycolic) acid nanoparticles (PLGA-NP) can improve delivery of hydrophobic drugs.² To assess the improved therapeutic effect of PLGA-NP-loaded with PHT-427 (PLGA-PHT-427), a method is needed to identify orthotopic pancreatic tumors in a mouse model, and to longitudinally monitor the tumor response to chemotherapy. This study employed parametric maps of the Apparent Diffusion Coefficient (ADC) and T2 relaxation time to identify orthotopic pancreatic tumors, and employed ADC measurements to track tumor response to therapy, following treatment of a MiaPaCa-2 pancreatic tumor model with PHT-427 or PLGA-PHT-427.

Methods: PLGA-PHT-427 was developed using an oil-water emulsion protocol to entrap the hydrophobic PHT-427 in the PLGA-NP.³ The MiaPaCa-2 tumor model was developed by implanting one tumor plug from a donor mouse into the pancreas tail of a SCID mouse. After 7-10 days, all groups of mice were scanned with MRI to identify the tumor and measure the baseline ADC value of the tumor. One group of 8 mice were treated with 75 mg/kg of PHT-427 in DMSO, and one group of mice was treated with PLGA-PHT-427 in water (at 20 mg/kg PHT-427 concentration), injected i.p. every 7 days for 4 weeks. A MRI scan was performed 24 hours after each injection. Respiration gated, T2 weighted MSME images were acquired using a Bruker 7T MRI scanner, with 1010.9 ms TR, 10.6 - 66.8 ms TE, 6x4 cm FOV, 234x312 μ m in-plane resolution, 0.5 mm SL, 14 slices, and 1 average. Respiration gated, diffusion weighted images were acquired with 3 orthogonal gradient directions, 1001 ms TR, 27 ms TE, 6x4 cm FOV, 938x625 μ m in-plane resolution, 0.5 mm SL, 4 slices, 1 average, and b values of 100, 300, and 700 s/mm. T2 and ADC parametric maps were calculated using Paravision Software Version 5.1.

Results: Pancreatic tumors were difficult to visualize in T2-weighted images (Fig. A). However, the T2 parametric maps (Fig. B) and ADC parametric maps (Fig. C) easily showed the location of the pancreatic tumor. The tumor ADC remained constant during treatment with PHT-427 (data not shown), but increased in response to PLGA-PHT-427 during the first three weeks of treatment, and then decreased at the fourth week (Fig. D). These results suggested that the bare drug had no therapeutic effect, while the drug-loaded nanoparticles caused reduced tumor cellularity for three weeks, and possibly followed by necrosis during the fourth week. Furthermore, mice treated with PHT-427 showed no change in tumor size and metastasis to liver, while PLGA-PHT-427 showed reduced primary tumor size with no evidence of primary tumor in 75% mice by the end of the study, and no evidence of liver metastasis in 84% mice.



Discussion: ADC and T2 parametric maps greatly improve localization of orthotopic pancreatic tumors and quantification of volume. The ADC values are sensitive to early therapeutic response in the pancreatic tumor model, which aided the comparison of the therapeutic effect of PLGA-PHT-427 relative to bare drug.

References: 1. Meuillet, et al., Mol Cancer Ther 2010;9:706-717. 2. Kim, et al., (2008). Cancer Res 68(20): 8369-8376. 3. Zhou, et al., (2013). Proc Natl Acad Sci U S A 110(29): 11751-11756.