Abstract #182 | Oral or Poster presentation

Gemcitabine/Abraxane treatment monitoring by 3D bSSFP imaging with hyperpolarized [1-^{13}C]pyruvate in a murine endogenous model of PDAC

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a highly heterogeneous disease with poor prognosis and a high mortality rate[1]. Due to early metastatic spread, most PDAC patients are not eligible for surgery and instead receive palliative chemotherapy-based treatment. Here, we aim to examine changes in tumor metabolism caused by Gemcitabine/Abraxane, a standard of care, using a complex endogenous murine PDAC model[2] and a 3D balanced steady-state free precession (bSSFP)[3] MR imaging of hyperpolarized (HP) [1-^{13}C]pyruvate and its metabolite [1-^{13}C]lactate.

Methods

Tumor model: 6 *Ptf1a$^{wt/cre}$;KRAS$^{wt/G12D}$;p53$^{fl/fl}$* mice with 28 distinct tumor nodules identified based on T2-weighted anatomical imaging.

MR system: 7T preclinical MRI system, dual-tuned ^{1}H/^{13}C volume coil (31mm ID)

Imaging: 3D bSSFP with HP-[1-^{13}C]pyruvate (80 mM). TR 6.63 ms, TE = TR/2, matrix 32x16x12, FOV 56x28x21 mm^3, with 900 Hz FWHM pulses applied offset by 234/735 Hz for pyruvate/lactate, imaging on day 0 and on day 3 post-therapy

Treatment: 100µg/g Gemcitabine and 30µg/g Abraxane were injected intraperitoneally/intravenously into 3 animals after the first imaging on day 0 and consecutively on day 2.

Analysis: Data was reconstructed and analyzed in MATLAB using in-house developed bSSFP software and GraphPad Prism 7.0. Area under the curve ratios of lactate and pyruvate were calculated.

Results/Discussion

We observed high intra- and inter-tumoral heterogeneity between individual PDAC nodules reflected by their corresponding metabolite ratios (area under the curves of lactate to pyruvate spectral peak time-courses, AUC_l/AUC_p) (Fig. 1). Tumors were divided into two groups AUC_l/AUC_p^{low} (0.95±0.26) and AUC_l/AUC_p^{high} (1.67±0.19) based on the populations mean AUC_l/AUC_p of 1.35 (Fig. 2). AUC_l/AUC_p^{low} tumors

showed a significant increase in AUC_l/AUC_p following treatment ($p<0.05$, Fig. 2A), whereas AUC_l/AUC_p^{high} tumors revealed a heterogeneous response pattern with a trend towards a decrease in values (Figure 2B). Vehicle treated tumors and reference tissues revealed no change in values in response pattern to treatment (Fig. 2 C-F).

These findings may indicate different tumor compositions[2] or molecular subtypes[4] and will be further investigated by a detailed correlation of corresponding *in vivo* values and histopathology, including H&E, Movat and monocarboxylate transporter 4 (MCT4) stainings[4].

Conclusions

We established a metabolic imaging protocol for treatment response monitoring in an endogenous PDAC model using a modified 3D bSSFP sequence and detected significantly increased lactate to pyruvate signal ratios in a subset of tumors. Considering the metabolic heterogeneity in PDAC and its association with molecular subtypes, further analysis of individual tumor responses will help understand the link between tumor subtype and treatment response.

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Disclosure

I or one of my co-authors have no financial interest or relationship to disclose regarding the subject matter of this presentation.

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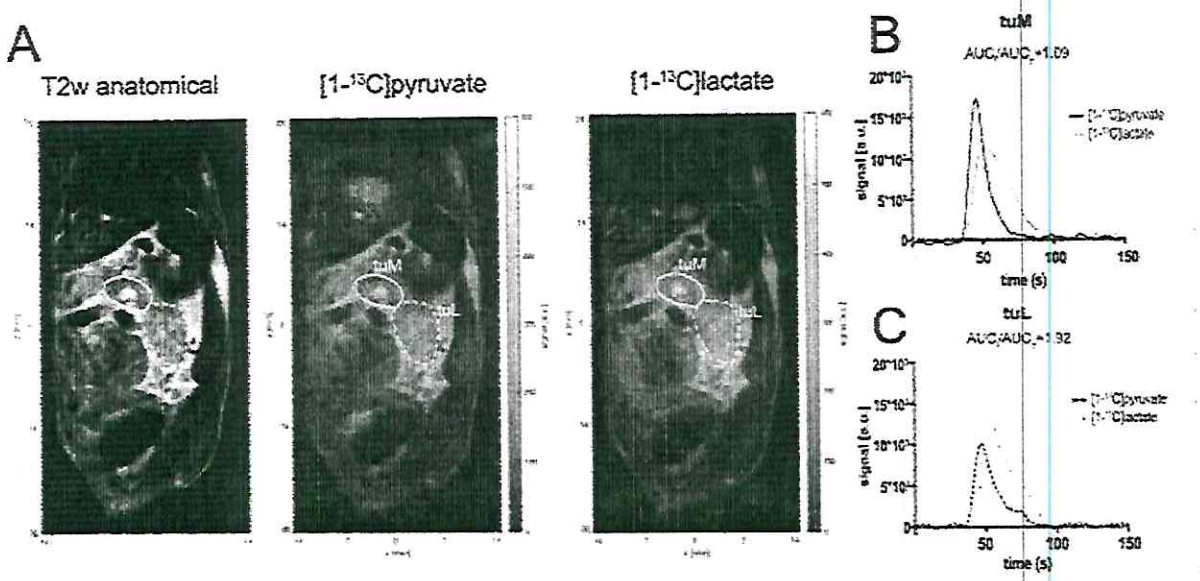

Figure 1: 3D metabolic imaging with modified bSSFP sequence of pancreatic tumors.
A) A representative example of a mouse scan. From left to right: T2w anatomy image, [1-^{13}C]pyruvate and [1-^{13}C]lactate image (all time points) showing two tumors (tuM and tuL) with different signal. **B-C)** Smoothened and plotted metabolite time courses of tuM **(B)** and tuL **(C).**

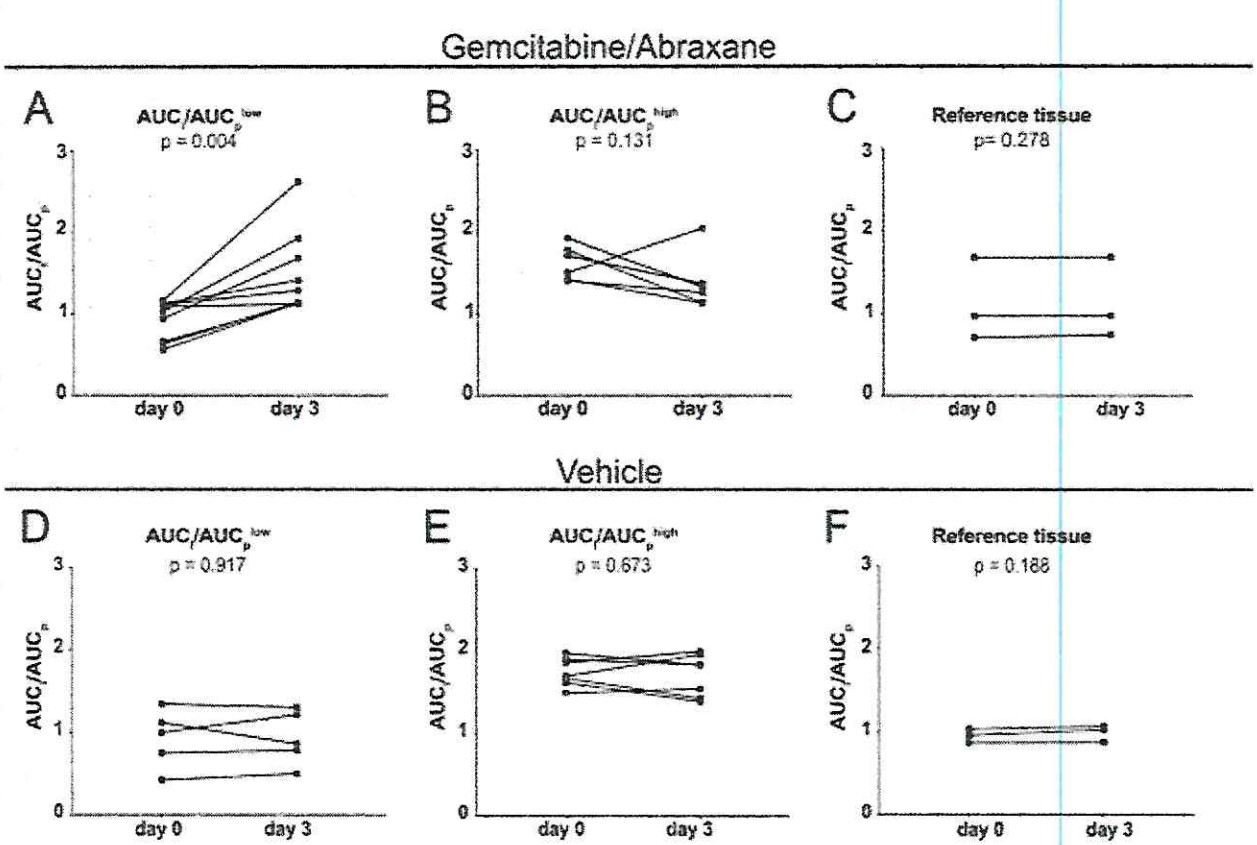

Figure 2: Therapy response monitoring in AUCl/AUCplow and AUCl/AUCphigh tumors.
A) Significant increase in AUC values in AUC_l/AUC_p^{low} tumors of mice injected with Gemcitabine/Abraxane **B)** No significant change but a trend towards a decrease in AUC values of AUC_l/AUC_p^{high} tumors of mice injected with Gemcitabine/Abraxane **C)** Reference tissue: right kidney of mice injected with Gemcitabine/Abraxane **D)** AUC values in AUC_l/AUC_p^{low} tumors in control cohort, injected with NaCl **E)** AUC_l/AUC_p^{high} tumors in control cohort **F)** Reference tissue: right kidney of mice in control cohort