



## Pilot Study Experiences With Hyperpolarized [1-13C]pyruvate MRI in Pancreatic Cancer Patients

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Pancreatic cancer is one of the most lethal cancers with a five-year survival of less than ten percent (1) and incidence rate of less than 13 in 100,000 people (2). Most patients present with locally advanced or systemic disease, but even patients with resectable tumors have a poor prognosis as the cancer recurs in more than 80% of the cases (3).

Adjuvant chemotherapy (4) and preoperative chemotherapy or combined chemoradiotherapy have the potential to improve survival (5). However reliable methods to predict the treatment efficacy of both chemotherapy and radiotherapy at an early stage are desirable. It might be possible to use functional imaging of microenvironmental factors to improved patient stratification (2,6,7).

Hyperpolarized  $^{13}\text{C}$  MRI (8) has proven feasible in experimental models, differentiating exocrine pancreas, pancreatitis and pancreatic cancer tissue by the enzymatic conversion of pyruvate-to-lactate and pyruvate-to-alanine (represented by the alanine-to-lactate ratio or alanine transferase/lactate dehydrogenase ratio) and furthermore demonstrated that this relationship correlates with disease progression and treatment response (9). We hereby present our experiences with hyperpolarized MR using  $[1-^{13}\text{C}]$ pyruvate for characterization of heterogenous and hypoxic pancreatic tumors in humans.

## **MATERIALS AND METHODS**

Two patients with stage IV pancreatic cancer with liver metastases were studied. Both patients had received more than 8 cycles of FOLFIRINOX (5-FU/leucovorin, irinotecan, and oxaliplatin), and had a partial response according to Response Evaluation Criteria in Solid Tumours (RECIST) guidelines (10). The patients were included after having provided written informed consent. The scientific ethical committee of the Central Denmark Region and the Danish Medicines agency approved the study. Both patients were still on treatment with the last chemotherapy treatment administrated 1 week before the study. Patient no 1 was a 57-year old male, active smoker, performance status 1 with diabetes but no other comorbidity. He was treated with daily insulatard subcutaneously. Patient no 2 was a 58-year old female, non-smoker, performance status 0, who was diagnosed with a pulmonary embolism at the same time as the pancreatic cancer and was treated with daily dalteparin subcutaneously. Hyperpolarized  $[1-^{13}\text{C}]$ pyruvate for intravenous injection was prepared less than 24 hours prior to injection and polarized in a 5T SPINlab™ polarizer (GE healthcare, Brøndby, DK)

according to the manufacture instructions (8). Prior to administration, a quality control (QC) system ensured safety and technical parameters (See table 1). A standard non-contrast enhanced  $^1\text{H}$  MRI protocol of the pancreas and liver region was performed using a GE 3T MRI 750 system (GE healthcare, Brøndby, DK). The  $^1\text{H}$  MRI protocol included a diffusion weighted imaging (DWI) sequence consisting of a Spin Echo EPI with two b-values of  $50 \text{ s/mm}^2$  (NEX=1) and  $700 \text{ s/mm}^2$  (NEX=2) (TR/TE/FOV/matrix/slice thickness  $3663\text{ms}/49,8\text{ms}/420\times420 \text{ mm}^2/80\times128/7\text{mm}$ ). Immediately following injection of hyperpolarized  $[1-^{13}\text{C}]$ pyruvate, a  $^{13}\text{C}$  MR spectroscopy (MRSI), consisting of 1D dynamic  $^{13}\text{C}$  spatially localized MRSI with 2048 number of points and a spectral width of 5000 Hz was performed in patient no 1. In patient no 2, a 2D single-time point chemical shift imaging (CSI) for spatial determination with 256 number of points and a spectral width of 5000 Hz (FOV/matrix/TR/flip angle/slice thickness/  $240\times240\text{mm}^2/16\times16/75\text{ms}/10^\circ/20\text{mm}$ ) was performed 35 seconds after start of the injection. A volume of  $0.43\text{ml/kg}$  pyruvate was used in both patients. Patients were observed and vital signs including blood pressure, heart rate, peripheral oxygenation, temperature and glasgow coma scale were registered at 0 min, 1 min, 15 min, 30 min, and 60 min after injection of hyperpolarized  $[1-^{13}\text{C}]$ -pyruvate. Blood and urinary test were performed before and after the injection and any toxicity according to CTCAE 4.1 were registered.

## RESULTS

In patient no 1, a dynamic 1D MR spectrum was acquired, demonstrating a late hemodynamic and metabolic response in the pancreatic region (Figure 1). This information was used to determine the optimal time point for the chemical shift imaging (CSI) acquisition performed in patient no 2. In this patient, the acquired metabolic images showed a heterogeneous signal of  $[1-^{13}\text{C}]$ lactate (Lactate-to-Pyruvate ratio of 0.36) and  $[1-^{13}\text{C}]$ alanine (Alanine-to-Pyruvate ratio of 0.12) largely originating from the pancreatic tumor, with an intra-tumor alanine-to-lactate ratio of 0.33 (Figure 2). Alanine signal was mostly localized to the tumor, whereas the lactate signal was more diffusely distributed in the tumor and in the surrounding tissue. A less intense signal was observed in the non-cancerous part of the exocrine pancreas for both lactate and alanine as well as a lower alanine-to-lactate ratio of 0.23 (Figure 2, purple arrow). No adverse events were reported in relation to the hyperpolarized MR examination. A low intra-tumoral water apparent diffusion coefficient (ADC) of  $794.4 \text{ mm}^2/\text{s}$  was observed (Figure 2).

## DISCUSSION

Hyperpolarized  $[1-^{13}\text{C}]$ pyruvate MRI, successfully differentiated pancreatic tumor tissue from surrounding tissue  $>30$  s after the injection via  $[1-^{13}\text{C}]$ lactate and  $[1-^{13}\text{C}]$ alanine production. No adverse events were observed or reported.

Metabolic cross-talk in the local microenvironment between pancreatic ductal adenocarcinoma (PDAC) cells and exocrine pancreatic cells results in altered secretion and consumption patterns of lactate and alanine (7). This is likely the origin of the distinct alanine/lactate ratio seen in pancreatic cancer experimental models, where similar pool sizes are correlated with disease progression (9). We observed a high intra-tumor signal of both alanine and lactate in the pancreatic tumor compared to other tissues in the abdomen. The tumor alanine-to-lactate ratio was similar to prior work (9) and higher than exocrine pancreas tissue. Thus, indicating that the alanine/lactate ratio could be a potential marker used to differentiate suspected malignant pancreatic lesions from nonmalignant lesions or detect local recurrences at an early stage in the near future. Also, the  $[1-^{13}\text{C}]$ pyruvate MRI was performed in patients responding to chemotherapy, which might influence the uptake and subsequent metabolism. The diffuse lactate signal could be due to a high lactate signal bleeding to adjacent tissue.

These results support further investigations in pancreatic patients, and calls for further improvement of MRI scanner equipment and imaging strategies.

Figure legends:

Figure 1 A. Axial slice showing the pancreas, liver and kidneys in the slice of the 1D spectroscopic acquisition. B. A spectrum of the targeted metabolic pathways using  $[1-^{13}\text{C}]$ pyruvate, showing downstream metabolites  $[1-^{13}\text{C}]$ lactate,  $[1-^{13}\text{C}]$ alanine and  $^{13}\text{C}$ -bicarbonate and C. the timely evolution of the injected tracer  $[1-^{13}\text{C}]$ pyruvate and the metabolic  $[1-^{13}\text{C}]$ lactate production in patient no 1.

Figure 2 Top row: Anatomical axial slice showing the pancreatic tumor in patient no 2 with a white arrow and the exocrine pancreas with a purple arrow (green ROI outlines pancreas and pancreatic cancer). The apparent diffusion coefficient (ADC) is greatly reduced in the tumor tissue. Bottom row: A heterogeneous distribution of  $^{13}\text{C}$  signal was observed in the abdomen, with a general high signal observed for  $[1-^{13}\text{C}]$ pyruvate,  $[1-^{13}\text{C}]$ lactate and  $[1-^{13}\text{C}]$ alanine in the pancreatic tumor ( $> 30$  s after injection of  $[1-^{13}\text{C}]$ pyruvate).

Table 1 Quality control (QC) results prior to injection.

	Patient 1	Patient 2
Pyruvate Concentration (mM)	226	227
pH	7.7	7,6
EPA concentration (uM)	1.4	1.8
Temperature (C)	35.7	35.3
Volume (mL)	>40 mL	>40 mL
Hyperpolarization (%)	28	27

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Figure 1:

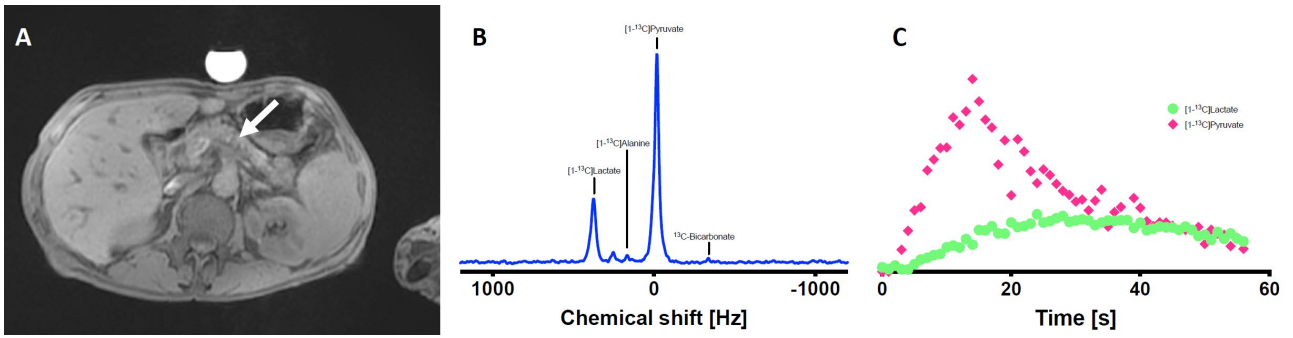


Figure 2:

