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Research article

Combined hyperpolarized ^{13}C-pyruvate MRS and ^{18}F-FDG PET (hyperPET) estimates of glycolysis in canine cancer patients

Adam E. Hansen[a,*], Henrik Gutte[a], Pernille Holst[b], Helle H. Johannesen[a], Sofie Rahbek[a], Andreas E. Clemmensen[a], Majbritt M.E. Larsen[b], Christina Schøier[b], Jan Ardenkjaer-Larsen[c], Thomas L. Klausen[a], Annemarie T. Kristensen[b], Andreas Kjaer[a]

[a] Department of Clinical Physiology, Nuclear Medicine & PET and Cluster for Molecular Imaging, Rigshospitalet and University of Copenhagen, Denmark
[b] Department of Veterinary Clinical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Frederiksberg C, Denmark
[c] Department of Electrical Engineering, Center for Hyperpolarization in Magnetic Resonance, Technical University of Denmark, Lyngby, Denmark

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ABSTRACT

^{13}C Magnetic Resonance Spectroscopy (MRS) using hyperpolarized ^{13}C-labeled pyruvate as a substrate offers a measure of pyruvate-lactate interconversion and is thereby a marker of the elevated aerobic glycolysis (Warburg effect) generally exhibited by cancer cells. Here, we aim to compare hyperpolarized [1-^{13}C]pyruvate MRS with simultaneous ^{18}F-2-fluoro-2-deoxy-D-glucose (FDG) PET in a cross-sectional study of canine cancer patients.

Methods: Canine cancer patients underwent integrated PET/MRI using a clinical whole-body system. Hyperpolarized [1-^{13}C]pyruvate was obtained using dissolution-DNP. ^{18}F-FDG PET, dynamic ^{13}C MRS, ^{13}C MRS Imaging (MRSI) and anatomical ^{1}H MRI was acquired from 17 patients. Apparent pyruvate-to-lactate rate constants were estimated from dynamic ^{13}C MRS. ^{18}F-FDG Standard Uptake Values and maximum [1-^{13}C]lactate-to-total-^{13}C ratios were obtained from tumor regions of interest. Following inspection of data, patients were grouped according to main cancer type and linear regression between measures of lactate generation and ^{18}F-FDG uptake were tested within groups. Between groups, the same measures were tested for group differences.

Results: The main cancer types of the 17 patients were sarcoma (n = 11), carcinoma (n = 5) and mastocytoma (n = 1). Significant correlations between pyruvate-to-lactate rate constants and ^{18}F-FDG uptake were found for sarcoma patients, whereas no significant correlations appeared for carcinoma patients. The sarcoma patients showed a non-significant trend towards lower ^{18}F-FDG uptake and higher lactate generation than carcinoma patients. However, the ratio of lactate generation to ^{18}F-FDG uptake was found to be significantly higher in sarcoma as compared to carcinoma. The results were found both when lactate generation was estimated as an apparent pyruvate-to-lactate rate constant from dynamic ^{13}C MRS and as an [1-^{13}C]lactate to total ^{13}C ratio from ^{13}C MRSI.

Conclusions: A comparison of hyperpolarized [1-^{13}C]pyruvate MRS with simultaneous ^{18}F-FDG PET indicate that lactate generation and ^{18}F-FDG uptake in cancers can be related and that their relation depend on cancer type. This finding could be important for the interpretation and eventual clinical implementation of hyperpolarized ^{13}C. In addition, the differences between the two modalities may allow for better metabolic phenotyping performing hybrid imaging in the form of hyperPET.

1. Introduction

Clinical imaging of cancer has during the last decades witnessed morphological imaging modalities such as CT and MRI being supplemented and augmented by molecular imaging of tumor function [1–3]. PET offers whole-body functional imaging and ^{18}F-2-fluoro-2-deoxy-D-glucose (^{18}F-FDG) PET often in combination with diagnostic CT, is a widely used clinical tool for detection of cancer, staging and assessment of response to therapy [4–6]. FDG is a glucose analog, which is transported into cells and trapped as FDG-6-phosphate. The ^{18}F FDG uptake is a measure of regional glucose uptake and thereby an indirect marker of the elevated aerobic glycolysis, Warburg effect, generally exhibited by cancer cells [7,8].

Magnetic Resonance Spectroscopy (MRS) can also characterize cancer metabolism [9] and enabled by the development of dissolution Dynamic Nuclear Polarization (d-DNP) [10,11], hyperpolarized ^{13}C

* Corresponding author at: Department of Clinical Physiology, Nuclear Medicine & PET, Rigshospitalet, 3992, Blegdamsvej 9, DK-2100 Copenhagen Ø, Denmark.
E-mail address: adam.espe.hansen@regionh.dk (A.E. Hansen).

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MRS has reached clinical accessibility. In particular, ^{13}C MRS Imaging (MRSI) of prostate cancer using hyperpolarized ^{13}C-labeled pyruvate as a substrate has been demonstrated in patients [12]. Here, the elevated aerobic glycolysis can be measured through the appearance of the ^{13}C-lactate signal, and dynamic ^{13}C MRS can provide an estimate of the apparent pyruvate-to-lactate rate constant. The measured rate constant is apparent since it is also affected by e.g. expression of monocarboxylic transporters in the cell membranes.

Accordingly, both ^{18}F FDG PET and hyperpolarized ^{13}C-pyruvate MRS are molecular imaging modalities sensitive to glycolysis. However, PET is well-established clinically while hyperpolarized MRS is still at its infancy [11,13–15]. The relation between ^{18}F FDG PET and hyperpolarized ^{13}C-pyruvate MRS in cancer has been explored in a limited number of preclinical studies using a sequential setup [13,16–18], focusing on feasibility [17] and treatment effects [13,16,18]. With the availability of integrated PET and MRI in a clinical, whole-body system [19], simultaneous PET and hyperpolarized ^{13}C MRS (hyperPET) [20,21] is possible. We have recently demonstrated, in a series of 10 canine cancer patients, an overall spatial concordance of ^{13}C-lactate and ^{18}F FDG uptake patterns [22], but have also observed canine cancer patients with a spatial mismatch [23]. Cancer cells utilize both glycolysis and oxidative phosphorylation for energy metabolism [8,24,25] and the degree of glycolysis might be heterogeneous across cancer cell types [24,26].

To further compare the two modalities of ^{18}F FDG PET and hyperpolarized ^{13}C-pyruvate MRS, we investigate in this study the relation between ^{18}F FDG uptake and apparent pyruvate-to-lactate rate constants in a larger series of canine cancer patients with different cancer types. This allows us to compare ^{18}F FDG PET and hyperpolarized ^{13}C-pyruvate MRS estimates of glycolysis in a cross-sectional study, with the very basic hypothesis that tumor ^{18}F FDG uptake and apparent pyruvate-to-lactate rate constants are correlated and may depend on cancer type.

2. Materials and methods

2.1. Study population

Seventeen canine cancer patients with solid tumors were consecutively enrolled in the study. All patients underwent physical examination as well as routine pre-anesthetic and diagnostic work up laboratory evaluation. Inclusion criteria were diagnosis of malignant tumor type and complete hyperPET data (^{18}F-FDG PET, dynamic ^{13}C MRS and ^{13}C MRSI). Exclusion criteria were clinical or laboratory work up precluding anesthesia. All canine cancer patients underwent PET/MRI with ^{18}F FDG PET as part of their diagnostic and staging work-up prior to therapy recommendation. Hyperpolarized ^{13}C MRSI was performed concomitantly. The owners gave informed consent and the study was approved by the Ethics and Administrative Committee, Department of Veterinary Clinical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen.

2.2. Experimental setup

PET/MRI was performed using an integrated system (Siemens Biograph mMR) with a 3 T MR imager. ^{13}C MRSI utilized a ^{1}H/^{13}C dual-tuned transmit/receive surface flex coil centered on the lesion, or (patient 16, Table 1), a ^{13}C transmit/receive birdcage head coil (RAPID Biomedical).

The canine patients were anesthetized using a bolus injection of Propofol and maintained by administration of air/oxygen enriched gas mixture with Sevoflurane. Heart rate, oxygenation, and blood pressure were monitored throughout the scanning procedure.

Hyperpolarized [1-^{13}C]pyruvate was obtained using dissolution-DNP (SpinLab, GE Healthcare) using the procedure as described by Gutte et al. [22]. The amount injected was 0.68 mL/kg body weight of 250 mM [1-^{13}C]pyruvate.

2.3. ^{1}H-MRI

Anatomical ^{1}H MRI included T2 turbo spin echo (tse) [repetition time (TR) 4000 ms, echo time (TE) 89 ms, pixel size 0.6 × 0.5 mm^2, 19 slices of 3 mm thickness] in 3 planes. A single slice T2-tse angulated and centered as the ^{13}C MRSI was obtained as a geometrical reference. In most patients, the exam included transverse fat saturated T1-tse [TR 550 ms, TE 6.5 ms, pixel size 0.7 × 0.6 mm^2, 27 slices of 3 mm thickness] following gadolinium injection (0.1 mL/kg Gadovist).

Table 1
Summary of patient characteristics.

patient	weight [kg]	PET p.i. time [min]	Tumor location	Tumor tissue type	Grade	Classif. based on
1	15	42	Subcutaneous, face	Soft tissue sarcoma (Fibrosarcoma)	inter-mediate	Histo-pathology
2	42	41	Posterior paw	Soft tissue sarcoma	1	Histo-pathology
3	46	48	Nasal cavity	Squamous cell carcinoma	÷	Histo-pathology
4	50	26	Maxilla	Soft tissue sarcoma (Fibrosarcoma)	low	Histo-pathology
5	29	30	Nasal cavity	Chondrosarcoma	1	Histo-pathology
6	22	32	Scapula	Osteosarcoma – telangiectatic	2	Histo-pathology
7	13	39	Spine and axilla	Soft tissue sarcoma (pro peripheral nerve sheath)	2	Histo-pathology
8	21	78	Femur	Osteosarcoma – medullary	low	Histo-pathology
9	32	58	Thyroid	Carcinoma, follicular	n.r.	Histo-pathology
10	39	65	Axilla	Unspecified Sarcoma	÷	Cytology*
11	27	55	Thyroid	Adenocarcinoma – producing	n.r.	Histo-pathology
12	24	55	Thyroid	Carcinoma – C-cell	n.r.	Histo-pathology
13	19	60	Thyroid	Carcinoma, follicular	n.r.	Histo-pathology
14	48	61	Knee	Mastocytoma	2	Histo-pathology
15	33	58	Subcutaneous, thoracic wall	Soft tissue sarcoma	1	Histo-pathology
16	31	57	Trigeminal nerve	Pro soft tissue sarcoma – peripheral nerve sheath	÷	Imaging findings†
17	8	59	Maxillla	Soft tissue sarcoma (Fibrosarcoma)	low	Histo-pathology

n.r.: no relevant.
÷: not available.
* : The histopathological sample contained muscle cells only. Cytology showed malignantmesenchymal tumor cells, identifying the tumor as an unspecified sarcoma.
† : Initial diagnosis based on MRI findings prior to referral indicated neoplasia of the right trigeminal/mandibular nerve – most likely peripheral nerve sheath tumor (sarcoma). FDG-PET is consistent with neoplasia.