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Hyperpolarized 1-[^{13}C]-Pyruvate Magnetic Resonance Imaging Detects an Early Metabolic Response to Immune Checkpoint Inhibitor Therapy in Prostate Cancer

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Increased aerobic glycolysis and pyruvate-to-lactate conversion are hallmarks of cancer. Hyperpolarized (HP) ^{13}C magnetic resonance imaging (MRI) is an emerging imaging technique that allows real-time assessment of metabolic pathways in vivo. We previously reported on the use of HP ^{13}C MRI to measure the intratumoral conversion rate of 1-[^{13}C]-pyruvate to 1-[^{13}C]-lactate (k_{PL}) in patients with prostate cancer (PC) [1] and observed higher rates of glycolytic metabolism in osseous metastases (mean k_{PL} 0.020 ± 0.006 s^{-1}) [2]. Furthermore, we observed that early decreases in intratumoral k_{PL} could predict treatment responses in PC patients treated with cytotoxic chemotherapy and androgen deprivation therapy [2,3].

Here we describe the first results indicating a metabolic response in a patient with metastatic castration-resistant PC (mCRPC) treated with the PD-1 inhibitor pembrolizumab. The patient had a history of mCRPC with prior progression according to Prostate Cancer Clinical Trials Working Group 3 criteria on two lines of androgen receptor–targeted therapy. He was started on pembrolizumab after findings of an elevated tumor mutation burden and microsatellite instability high status on a circulating tumor DNA analysis. Prostate-specific membrane antigen (PSMA) positron emission tomography (PET) and paired multiparametric MRI at the start of therapy demonstrated numerous new and enlarging PSMA-avid osseous metastases throughout the thoracolumbar spine, pelvis, and ribs (representative lesions shown in Fig. 1A); the patient's baseline prostate-specific antigen (PSA) at initiation of pembrolizumab was 82.182 ng/dl.

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The patient experienced a rapid decrease in serum PSA on pembrolizumab that reached undetectable levels after 9 wk of therapy. Multiparametric pelvic MRI at 8 wk showed stable osseous disease, with the exception of a decrease in left acetabular lesion size. Consistent with prior observations in mCRPC [2], paired HP 1-[^{13}C]-pyruvate MRI at this time point showed elevated intratumoral k_{PL} values relative to background in two representative left and right posterior iliac lesions. The patient's left acetabular lesion, however, exhibited an undetectable k_{PL} level consistent with a complete metabolic response (Fig. 1B). Repeat MRI/HP-MRI performed after 19 wk of pembrolizumab demonstrated a further decrease in the left acetabular lesion size with persistent undetectable k_{PL}, as well as decreases in size for the left and right iliac lesions, now associated with a complete (undetectable k_{PL}) and near-complete (k_{PL} 0.0006 s^{-1}) metabolic response, respectively (Fig. 1C).

The development of quantitative imaging biomarkers is an area of unmet need for patients with mCRPC with osseous metastases. Computed tomography and bone scintigraphy are neither sensitive nor specific for monitoring treatment response and are susceptible to treatment flare phenomena. Osseous lesions without soft tissue components are not considered measurable disease according to Response Evaluation Criteria in Solid Tumors [4] and as a result patients with mCRPC with bone-only metastases are frequently excluded from clinical trials. While newer radionuclide imaging modalities such as PSMA PET have shown superior diagnostic accuracy, they may also be prone to treatment flare effects [5] and their role in monitoring treatment response is not established. Our current findings highlight the feasibility of serial k_{PL} measurements via HP [^{13}C]-pyruvate MRI to quantify metabolic responses–independent of anatomic changes–and demonstrate a potential role for the use of k_{PL} as a novel treatment biomarker in PC.

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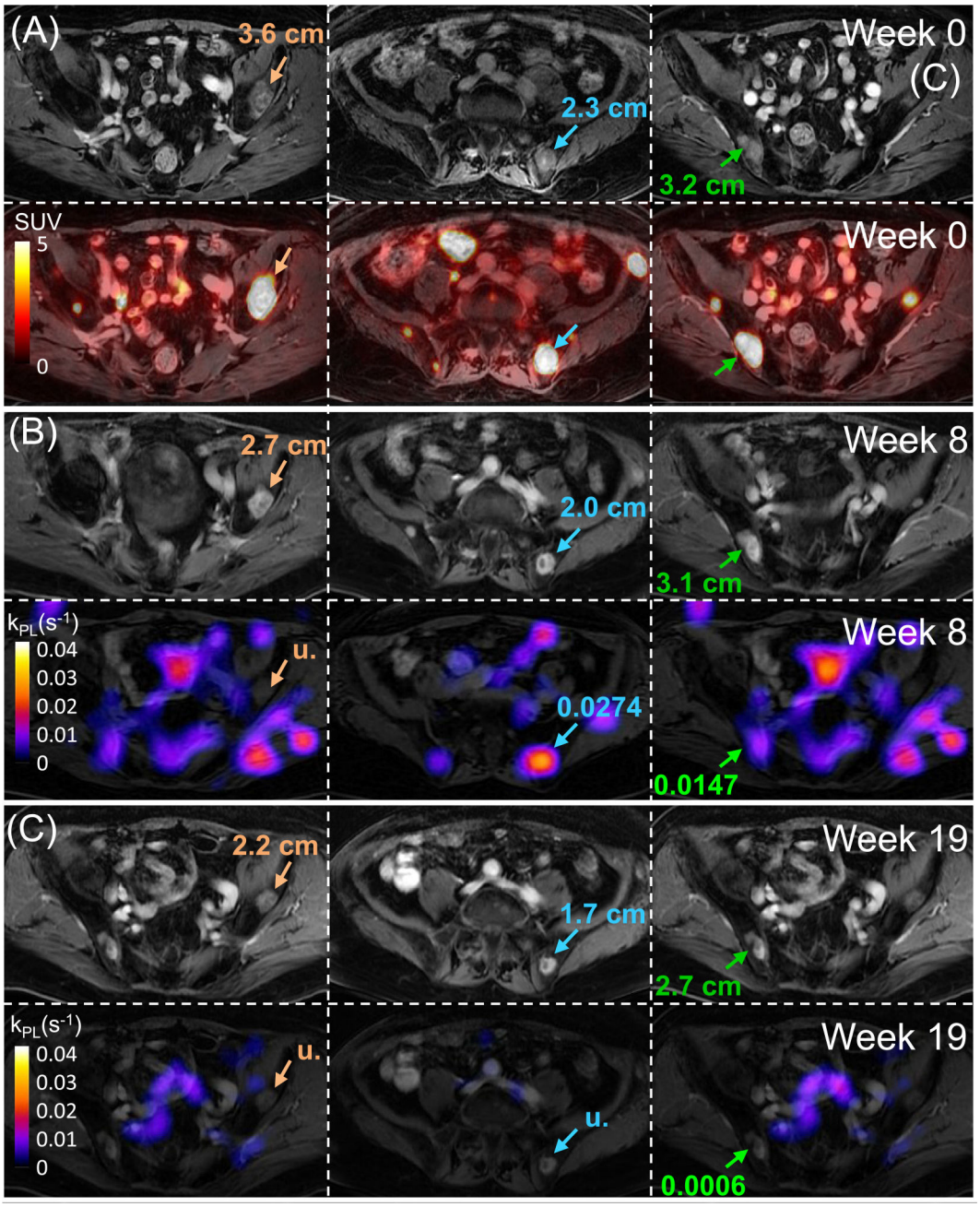

Fig. 1 –.

Representative axial T1-weighted post-contrast (T1W-P) anatomic images (A, top row) and corresponding prostate-specific membrane antigen positron emission tomography images (A, bottom row) before therapy. Corresponding axial T1W-P (top row) and T1W-P with overlaid pyruvate-to-lactate metabolic conversion rate (k_{PL}) images (bottom row) after (B) 8 wk and (C) 19 wk of pembrolizumab therapy. A left acetabular lesion (orange, left column) exhibited undetectable (u) k_{PL} levels and tumor shrinkage after only 8 wk of therapy (B), with further tumor shrinkage (total 39%) and persistently undetectable k_{PL} after 19 wk of therapy (C). A left (blue, middle row) and right (green, right row) iliac lesion exhibited

elevated k_{PL} and minimal tumor shrinkage after 8 wk of therapy (B). After an additional 11 wk of therapy (C), both lesions showed a marked (>95%) reduction in k_{PL} and decreases in lesion diameter (16% and 26% reductions, respectively, in maximum diameter from baseline). SUV = standardized uptake value.