In this issue of Clinical Cancer Research, Saito and colleagues (1) expanded upon the potential applicability of $^{13}$C-pyruvate hyperpolarized magnetic resonance imaging (HP-MRI) to assess the radioresistance of tumors as driven by intrinsic tumor microenvironment and oxygenation characteristics in SCCVII and HT-29 tumor cell line models. Otto Warburg first described that most cancer cells produce energy at a high rate using the glycolytic pathway rather than the oxidative phosphorylation pathway (2), and the "Warburg effect" has become a hallmark of tumor growth. The development of $^{13}$C-pyruvate HP-MRI has led to increased interest in the use of lactate, the final metabolite in the glycolysis pathway, as a biomarker of disease progression and treatment response (3). Day and colleagues reported that HP-MRI could detect radiation-induced changes in tumor lactate levels within 96 hours of irradiation (4). Sandulache and colleagues hypothesized and demonstrated that $^{13}$C-pyruvate HP-MRI could be used to detect changes in tumor reducing potential induced by metabolic agents (5) and that HP-MRI could detect radiation-induced effects on tumor lactate levels within hours of irradiation (6). Thind and colleagues demonstrated that HP-MRI can also detect radiation-induced toxicity to normal tissue within days of irradiation (7, 8). The biochemical model for these effects reflects the parallel and inverse relationship between reducing potential and radiation-induced free radicals or reactive oxygen species. Because the conversion of pyruvate into lactate requires reducing equivalents, $^{13}$C-pyruvate HP-MRI can provide an indirect measure of radiation-induced free radical stress.

The biochemical model put forth by Sandulache and colleagues, with the preclinical data by Saito and colleagues, provides support for continued innovations in the delivery of targeted radiotherapy (Fig. 1). Because radiation is the primary nonsurgical treatment modality for the management of solid tumors, elucidating radiation response via HP-MRI has generated enthusiasm for clinical implementation of this technology through adaptive irradiation algorithms and personalized dosimetric planning.

However, several important caveats should be considered. Imaging irradiation of solid tumors must take into account spatial as well as temporal resolution. Because tumors are heterogeneous, spatial resolution is essential for appropriate targeting; moreover, as tumors undergo clonal regression based on relative radiosensitivity during radiation treatment, spatial resolution becomes even more important. As demonstrated by Sandulache and colleagues, irradiated tumors exhibit significant spatial heterogeneity with respect to viability. Consequently, imaging pyruvate metabolism in irradiated tumors requires a detailed voxel-by-voxel map with which clonal regression can be tracked over time. This issue is also a significant concern in the current report, because clinical implementation of HP-MRI in adaptive irradiation algorithms cannot proceed without adequate spatial resolution of changes in the pyruvate-to-lactate conversion rate. Because the conversion of pyruvate into lactate is a dynamic process, temporal resolution is also essential. Golman and colleagues demonstrated the heterogeneity of pyruvate-to-lactate conversion in tumors by using timed snapshots. Progress in the development of algorithms with adequate spatial and temporal resolution should allow continued improvements leading to clinical translation.

HP-MRI can provide "real-time" imaging of tumor metabolism and overcomes several limitations of metabolic imaging with positron emission tomography (PET), such as poor temporal-spatial resolution or dynamic PET assessments that can require more than 20 minutes to obtain in clinical settings. Furthermore, serial HP-MRI measurements are safe and feasible to obtain without additional exposure to radiation, facilitating high-frequency radiation response assessment in patients undergoing therapy.

The first-in-human imaging studies using HP-MRI in men with prostate cancer have demonstrated its safety and efficacy for...
Reactive oxygen species (ROS) have important roles in tumor growth and metastasis. Although low levels of ROS can have oncogenic effects, high levels of ROS, such as those resulting from ionizing radiation or chemotherapy, are cytotoxic, and thus are crucial role for treatment effectiveness. Treatment-related ROS are also responsible for some of the toxicity to normal tissue associated with treatment of solid tumors. Metabolic interrogation, whether invasive (biochemical analysis) or noninvasive (metabolic imaging) could be used to devise treatment regimens that generate tumoricidal levels of ROS while maximally sparing normal tissues.

Noninvasively characterizing tumor metabolism (9). The current study further supports the ability of HP-MRI to monitor energy metabolism in both tumors and normal tissue and provides useful findings along the temporal continuum of radiation-induced effects on tumor lactate levels. These findings may provide a better understanding of early response to radiotherapy in the definitive, recurrent, and palliative settings.

However, we would caution that additional work is required before HP-MRI can be implemented in the clinic. First, as detailed above, future studies must use imaging algorithms with sufficient spatial and temporal resolution. Spatial resolution is particularly important because of normal tissue toxicity (7, 8). Second, preclinical studies must reproduce clinically relevant radiation doses. The most commonly accepted biologic model for radiation effects in solid tumors involves a free radical mechanism that triggers aberrant DNA repair and programmed cell death. As the authors acknowledge, the 10-Gy doses used by Saito and colleagues or the 15-Gy doses used by Day and colleagues are far higher than the radiation doses typically used in radiotherapy (indeed, they approach the doses used in stereotactic ablative radiotherapy) and carry significant risks such as direct DNA and protein damage. Third, future studies must fully investigate temporal effects. Sandulache and colleagues showed lactate perturbations within hours of irradiation. Saito and colleagues and others showed lactate perturbations within days of irradiation. Future studies should combine measurements during the acute, delayed and chronic phases after irradiation to provide a more comprehensive understanding of radiation-driven lactate perturbations in solid tumors. Finally, other hyperpolarized biomarkers interrogating pH imaging, ROS pathway, and the tricarboxylic acid cycle may provide insight into chemoresistance and changes in energy metabolism due to therapy (10).

The translational implications of HP-MRI for precision radiotherapy approaches are exciting. Not only can HP-MRI be coupled with anatomic MRI, but it can also be merged with functional multiparametric MRI, providing simultaneous assessment of perfusion or cell density through combination with same-visit dynamic contrast-enhanced or diffusion-weighted MRI sequences. Thus, "perfusion-weighted" metabolomic imaging, already done in animal models (11), may be a reality in the near-intermediate term. The advent of MRI-guided radiotherapy, as commercial vendors transition to MR-only treatment planning, coupled with adaptive strategies for tumor volume reduction, underscore the intriguing possibility of combining serial HP-MRI with adaptive MRI-based radiation planning (12). As the current body of literature has shown, 13C-pyruvate HP-MRI has great promise as a quantitative imaging-based biomarker of early radiation response. Immediate clinical applications in tumors currently treated with high radiation doses per fraction (e.g., 5–20 Gy) within the brain, lung, liver, kidney, prostate, or spine may provide an opportunity to monitor the immediate response to radiotherapy, providing clinical evidence for the use of concurrent radiosensitizing targeted agents or surgical resection of radioresistant tumors. HP-MRI thus warrants further investigation as a promising imaging biomarker for future clinical trials and personalized treatment approaches, especially within the context of translational radiotherapy.

Disclosure of Potential Conflicts of Interest

C.D. Fuller reports receiving commercial research grants from General Electric and Elekta AB, and is a consultant/advisory board member for Elekta AB. S.J. Frank reports receiving a commercial research grant from Elekta AB and is founder of, is on the Board of Directors for, and has ownership interest (including patents) in C4 Imaging. No potential conflicts of interest were disclosed by the other authors.

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Development of methodology: S.Y. Lai, S.J. Frank
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S.Y. Lai
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S.Y. Lai, C.D. Fuller, S.J. Frank
Writing, review, and/or revision of the manuscript: S.Y. Lai, C.D. Fuller, S.J. Frank

Figure 1.
A model of therapeutic optimization using metabolic interrogation. Reactive oxygen species (ROS) have important roles in tumor growth and metastasis. Although low levels of ROS can have oncogenic effects, high levels of ROS, such as those resulting from ionizing radiation or chemotherapy, are cytotoxic, and thus are crucial role for treatment effectiveness. Treatment-related ROS are also responsible for some of the toxicity to normal tissue associated with treatment of solid tumors. Metabolic interrogation, whether invasive (biochemical analysis) or noninvasive (metabolic imaging) could be used to devise treatment regimens that generate tumoricidal levels of ROS while maximally sparing normal tissues.
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Metabolic Imaging as a Biomarker of Early Radiation Response in Tumors


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