Metabolic Imaging as a Biomarker of Early Radiation Response in Tumors

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Summary

[13]C-pyruvate hyperpolarized magnetic resonance imaging (HP-MRI) is emerging as a viable quantitative biomarker for solid tumor response and normal tissue toxicity following radiation therapy. This technology effectively predicts response related to metabolic agents or alterations in the tumor microenvironment, but challenges remain to be addressed to ensure successful translational implementation.

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 et al. 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

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within hours of irradiation (6). Thind et al. 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 et al., with the pre-clinical data by Saito et al., provides support for continued innovations in the delivery of targeted radiation therapy (Fig. 1). Since radiation is the primary non-surgical 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. Since 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 et al, radiated 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-lactate conversion rate. Since 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 for continued improvements leading to clinical translation.

HP-MRI can provides "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 greater 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 non-invasively 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 radiation therapy 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 employ 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 biological 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 et al. or the 15-Gy doses used by Day et al. are far higher than the radiation doses typically used in radiation therapy (indeed, they approach the doses used in stereotactic ablative radiation therapy) and carry significant risks such as direct DNA and protein damage. Third, future studies must fully investigate temporal effects. Sandulache et al showed lactate perturbations within hours of irradiation. Saito et al. and others showed lactate perturbations within days of irradiation. Future studies should combine measurements during the acute, delayed and chronic phases following irradiation to provide a more comprehensive understanding of radiation-driven lactate perturbations in solid tumors. Lastly, 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 multi-parametric 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" metabolic 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, ^{13}C-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 radiation therapy, 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.

Acknowledgments

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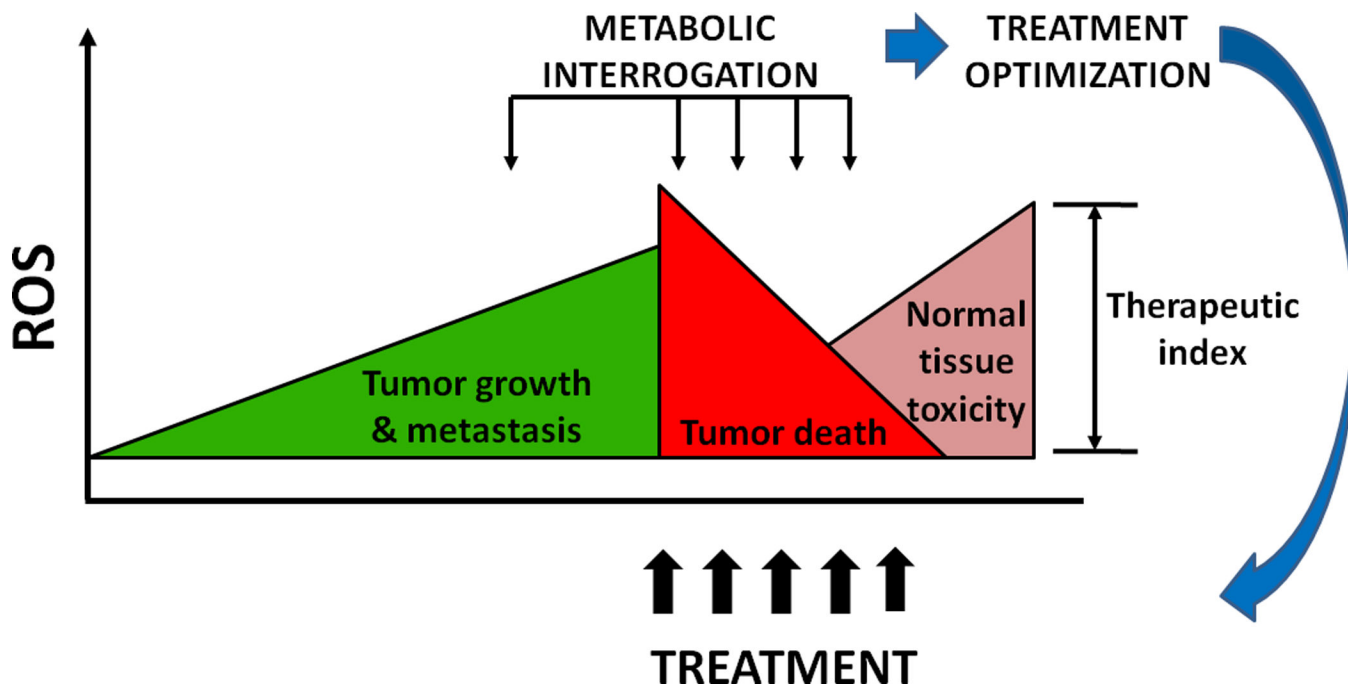
Figure 1. A model of therapeutic optimization using metabolic interrogation
Reactive oxygen species (ROS) have important roles in tumor growth and metastasis. Although low levels of ROS can have oncogenic effects, high levels of ROS, such as those resulting from ionizing radiation or chemotherapy are 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.