We believe that oxygen-sensitive MRI can be used to evaluate tumor hypoxia so that therapy may be individualized and optimized for the characteristics of an individual patient. Specifically, we foresee a simple test based on breathing hyperoxic gas to characterize tumor hypoxia and the potential for modulating tumor hypoxia and hence therapeutic response.

Radiology has become the mainstay for clinical diagnosis and together with pathology underpins clinical medicine. Imaging has come a long way from the revolutionary, but crude x-rays of Roentgen at the turn of the 20th century to the exquisite temporal and spatial revolution offered by modern computed tomography, providing multislice (or 3D) sub-millimeter spatial and sub-second temporal resolution. Beyond x-rays, MRI has revolutionized soft-tissue analysis by providing tissue contrast based on multiple parameters identified by varying repetition and echo times and gradients to reveal T₁-, T₂-, T₂*- , diffusion- and flow-weighted images. Nonetheless, the discipline hitherto remained essentially an anatomical analysis providing tumor location, size and spread.

A new vision foresees prognostic radiology, whereby tumors are not only identified with high sensitivity and specificity, but there is stratification of tumors according to expected response to therapy, as well as early evaluation of therapeutic efficacy. Clinically, we are privileged to have a wide range of therapeutic choices, but this presents the challenge of selecting the right therapy. Societally, we are demanding greater efficacy at reduced cost. Increasingly, it has been realized that tumors that may outwardly appear quite similar may exhibit very different responses to therapy. As a result, there is increasing emphasis on tumor characterization using genomic, proteomic and metabolic techniques with the promise of assessing tumor aggressiveness and predicting response to therapy: generally, they require biopsy. A notable example is the evaluation of Her2-neu expression for efficacy of Herceptin®. Noninvasive assessments are even more attractive.

One tumor characteristic that has come to the forefront of attention is tumor hypoxia and, more generally, oxygenation. Since the fundamental studies of Gray et al. [1] 50 years ago, it has been accepted that cellular response to radiation is oxygen dependant with a three-fold increase in radiation resistance when pO₂ declines from approximately 10 mmHg to hypoxia (<1 mmHg). The original work used cultured cells in vitro, but noting the inefficient tortuous nature of tumor vasculature hypoxia was expected in vivo. A meta-analysis of some 10,000 patients indicated a marginal clinical benefit for manipulating tumor hypoxia [2]. However, the overall conclusion was that there was a pressing need to identify those patients (viz. tumors) who would actually benefit from the added cost and complexity of addressing hypoxia. The importance and relevance of hypoxia and feasibility of imaging hypoxia in tumors are drawing increasing interest. There is a consensus that while many methods have been proposed there is currently no gold standard available for assessing tumor hypoxia in patients. Criteria considered important for a useful technique include invasiveness, radiation exposure, resolution, safety, availability, imaging time and lead time to effective implementation in the clinic [3].

The development of the Eppendorf electrode system permitted measurement of pO₂ (mean, median, hypoxic percentiles and distributions) in vivo and several studies have now shown distinctly poorer prognosis for patients with large hypoxic tumors in the cervix and head and neck [4,5]. Moreover, hypoxia has
been reported in the brain, lung and prostate. However, the needle electrode was sufficiently invasive to discourage widespread use and it is no longer manufactured. Fluoromisonidazole and similar agents such as EF5 based on 18F as well as 64Cu-ATSM have been applied in clinical trials and promise insight into identifying tumor hypoxia using PET [6]. However, the associated radioactivity and inability to undertake rapid dynamic studies are limiting factors. 19F MRI efficiently measures pO2 in preclinical studies based on perfluorocarbon-reporter molecules such as hexafluorobenzene and fluorocarbon relaxometry using echo planar imaging for dynamic oxygen mapping (FREDOM) has been successfully used to assess tumor hypoxia and interventions to modulate radiotherapy in rats [7]. Based on FREDOM, we have found three categories of tumor: category I hypoxic tumors, which do not respond to hyperoxic gas intervention; category II hypoxic tumors, which do respond to hyperoxic gas intervention; and category III, well-oxygenated tumors. In every case examined to date, well-oxygenated tumors became even better oxygenated with hyperoxic gas breathing. However, the lack of 19F MRI in human scanners has stymied development.

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Ideally, tumor oxygenation would be characterized noninvasively generating prognostic criteria for therapy without the need for exogenous reporter molecules. The fundamental reports of Thulborn [8] and Ogawa [9] suggested that blood could reveal vascular oxygenation based on T2* -weighted MRI. Deoxygenhemoglobin is paramagnetic and induces signal loss in T2* -weighted images and blood-oxygen-level-dependant (BOLD) contrast proton nuclear magnetic resonance forms the basis of so-called functional MRI in brain activation studies, where it is thought to reflect changes in perfusion. In tumors, a BOLD response is more difficult to interpret, since it may also be influenced by blood flow, as investigated extensively by Howe et al. [10], who coined the term flow-and-oxygen-level-dependant (FLOOD) contrast. In addition, variation in vascular volume can introduce signal perturbation. In tumors, BOLD effects are often evaluated in response to a challenge such as hyperoxic gas breathing, and several studies have indicated a correlation with relative pO2 [11–13]. There was always a positive correlation, but a 10% change in relative signal intensity in the BOLD experiment could correspond to an increase in pO2 of less than 25 torr or more than 100 torr. We contend that either change would be radiobiologically pertinent. Once pO2 exceeds 10 torr there is relatively little further oxygen enhancement achieved by increasing pO2 further. It has been suggested that BOLD measurements are only useful in well-vascularized tumors since the changes depend on deoxyhemoglobin concentration. However, we believe that the ability to oxygenate a tumor depends strongly on vascular supply and that a small BOLD response due to low vascularization will itself be indicative of hypoxic tumors.

Nonetheless, BOLD changes alone may not be definitive for tumor hypoxia. Recently, Matsumoto et al. showed that a T1 response accompanied breathing hyperbaric oxygen for squamous cell carcinoma xenografts in mice [14]. The so-called tissue-oxygen-level-dependant (TOLD) response is sensitive to changes in tissue pO2, as opposed to vascular oxygenation. Since many additional factors such as protein concentrations and ions may influence the absolute T1 value, it is not a reliable quantitative assay of absolute pO2, but we are finding it to be a robust surrogate of changes in pO2 in response to interventions.

We propose that combined assessment of T1 and T2* changes in tumors accompanying breathing hyperoxic gas will allow noninvasive characterization of tumor hypoxia. In preliminary investigations we have identified distinct characteristics for tumor oxygenation and dynamics: category I tumors show essentially no signal response to breathing hyperoxic gas; category II tumors show modest response; and category III show large BOLD and TOLD responses. As expected, BOLD responses precede TOLD since vascular oxygen delivery is required before changes in tissue pO2.

We are already able to examine patients and have preliminary data in breast, cervix, head and neck and lung tumors. Lung tumors are most challenging owing to respiratory and cardiac motion. We should note that others are also pursuing such measurements, notably Padhani et al. (Mount Vernon, London, UK) in prostate based on T2* [15] and O’Connor et al. (Manchester, UK) characterizing TOLD in multiple organs and tissues [16]. We note that Rodrigues et al. reported relationships between baseline T2* and response to radiation [17].
Bibliography