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Diffusion-weighted Imaging of Prostate Cancer:

Revisiting Occam's Razor

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MRI is playing an ever-increasing role in the management of prostate cancer. The Gleason grading system, along with the more recently introduced International Society of Urological Pathology grade groups that are based on the Gleason grading system, represent the current standard for assessing prostate cancer aggressiveness from histologic tissue sampling. Pathologic grading systems capture key aspects of the malignant transformation of healthy prostatic tissue by means of admixtures of fluid-filled glands, stroma, fibrosis, and cancerous cellularity. These systems are supported by a strong evidence base relating each Gleason grade to prognosis (1), such that treatment selection in healthy patients is overwhelmingly driven by cancer grade.

Aggressive prostate lesions have conventionally been managed with radical prostatectomy or radiation therapy, although an array of ablative therapies are also being adopted. Patients with presumed indolent cancers are increasingly being treated with active surveillance. Active surveillance forestalls definitive intervention until there is greater confidence in the presence of an aggressive cancer, thereby reducing surgical comorbidities. However, this paradigm inherently depends on a means of differentiating indolent from aggressive cancers, which is not possible with traditional systematic biopsy given the extent of undersampling with this procedure. MRI-targeted biopsy stands to improve upon this limitation but requires a mechanism to identify the most aggressive areas at imaging to direct the biopsy. The Prostate Imaging Reporting and Data System (PI-RADS) strives to reliably identify aggressive cancers with MRI. However, limitations of PI-RADS have been recognized (2), raising the possibility that quantitative MRI metrics may have added value in optimizing risk assessment. Diffusion-weighted MRI is an ideal tool in this space given the microscopic sensitivity of diffusion-weighted imaging to the cellular compartmentation making up the Gleason grade. Indeed, diffusion-weighted imaging has a leading role in the characterization of peripheral prostate lesions.

The apparent diffusion coefficient (ADC) has been the most widely investigated metric by far, but a variety of diffusion-weighted imaging techniques of higher complexity have also been explored in prostate imaging. Intravoxel incoherent motion (3) separates

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microcirculation and microstructure components according to their apparent diffusivities. Diffusion kurtosis imaging (4) collects higher-order cumulants of the diffusion propagator to characterize microstructural complexity. Time-dependent diffusion (5) varies the time allotted for water diffusion to observe its progressive reduction by microscopic barriers. Each of these techniques may be viewed as probing one “dimension” of a tissue microenvironment that contains multiple overlapping features of malignancy. These advanced techniques may provide additional insight into tissue properties beyond that of ADC maps.

The study by Johnston et al in this issue of *Radiology* (6) challenges the use of only a single quantitative diffusion-weighted imaging method. The authors use multifactorial data sampling and analysis to assess microcirculation, microstructural complexity, and diffusion time dependence. Their mathematical and biophysical framework is termed Vascular, Extracellular, and Restricted Diffusion for Cytometry in Tumors (VERDICT). The parameters of VERDICT include apparent fractions of the vascular space, intracellular space, and extracellular space. The acquisition time (12 minutes) is acceptable, and image processing is performed with a previously described software. The authors also performed test-retest benchmarking and interreader variability studies. The performance of the VERDICT measures in the differentiation of tumors at a threshold impacting patient treatment (Gleason grade ≥3+4 vs Gleason grade 3+3) is compared with that of ADC.

Repeatability (intraclass correlation coefficients) was determined to be high for VERDICT MRI, particularly for the intracellular space fraction (intraclass correlation coefficients: 0.87–0.95). A key finding is that the intracellular volume fraction outperforms ADC in the differentiation of Gleason grades; ADC did not significantly differentiate these two classes. Radiologist-graded image quality of the VERDICT maps was similar to that of the ADC maps. Thus, the authors argue that fractional intracellular volume has diagnostic potential that meets and possibly exceeds that of the ADC standard while retaining some degree of clinical feasibility.

The study by Johnson et al is noteworthy in that it combines multiple features known to contribute to malignancy in a quantitative biophysical model. In that spirit, it represents a strong advance toward the incorporation of more specific biomarkers from quantitative imaging into clinical routine—in this case for prostate cancer management. Examples like this study are reminders that efficiency and complexity need not be fundamental opponents in clinical imaging. VERDICT MRI demonstrates that multiple tissue features can be captured in diffusion MRI assessment to increase diagnostic benefit.

The study by Johnston et al (6) has several limitations. First, test-retest repeatability was not computed from the conventional ADC measurements. Second, the concepts underpinning the VERDICT model still bear discussion. Both parsimonious model selection and biophysical fidelity are important priorities. Several approaches have been pursued that balance these aspects in different ways. As detailed by Panagiotaki et al (7), the VERDICT approach focuses more on the three volume fractions than on their diffusivities, fixing the latter to values that minimize global fitting error (equal intra- and extracellular bulk diffusivities). Conversely, another tissue model from Gilani et al (8) fixes fractional volume

trends from histology literature and determines compartmental diffusivities to account for ADC data within the peer-reviewed literature. A model from Chatterjee et al (9) determines properties of three relaxation-weighted Gaussian-diffusion compartments (stroma, epithelial, and lumen) from a joint diffusion-weighted and relaxation-weighted acquisition. Finally, Lemberskiy et al (10) built a model employing joint time-dependent diffusion and relaxation weighting along with topological principles of prostate microstructure to provide imaging-based prostate lesion grading. The microstructural assumptions on degree of cell permeability, the role of stromal anisotropy, the contribution of microvascularity, and the time-dependent character of each compartment's diffusion remain controversial and are under active investigation by these and other groups. Further research in this area is warranted to understand which model assumptions are most appropriate and diagnostically beneficial for prostate cancer management.

Taken together, the studies by Johnston et al (6) and others indicate that quantitative diffusion-weighted imaging is undergoing active investigation for prostate cancer. However, quantitative modeling applied to characterize prostate tissue is clearly feasible. Ongoing research should continue to value both practicality and tissue specificity to gain maximum clinical benefit from MRI.

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