10.1148/radiol.2017160906

Appendix E1

MR Imaging Protocol

Multiparametric MR imaging of the prostate was performed with the aforementioned 3-T MR imager by using the anterior half of a 32-channel sensitivity encoding cardiac coil and an endorectal coil. Pre-examination bowel preparation was not required. The balloon of each endorectal coil was distended with approximately 45 mL of perfluorocarbon (Fluorinert FC-770; 3M, St Paul, Minn) to reduce imaging artifacts related to air-induced susceptibility. Multiparametric MR imaging of the prostate consists of high-spatial-resolution T2-weighted (T2W) MR imaging in three orthogonal planes, axial diffusion-weighted (DW) MR imaging, and high-*b*-value DW imaging. Parameters for T2W MR imaging are as follows: repetition time msec/echo time msec, 2925/120; field of view, 140 × 140 mm; resolution, 0.27 × 0.27 mm; matrix, 304 × 234; 26 sections; section thickness, 3 mm; imaging time, 1 minute 51 seconds; flip angle, 90° or 100°. Standard DW images are acquired with five evenly spaced *b* values (0–750 sec/mm^2), and a map of the apparent diffusion coefficient (ADC) is calculated with monoexponential fitting per MR imaging voxel. High-*b*-value DW images are acquired with a *b* value of 2000 sec/mm^2. Parameters for the standard and high-*b*-value DW images are presented in Table E1.

The whole prostate, peripheral zone, transition zone, and cancer lesions are delineated and recorded with an MR imaging coordinate system. The whole prostate is first automatically segmented by research software (iCAD, Nashua, NH), and the resulting segmentation is manually adjusted by the radiologists.

T2W MR imaging and high-*b*-value DW imaging are normalized. We identify potential outliers as the voxels with intensities below the first percentile or above the 99th percentile of the voxel intensities in the prostate. We exclude these outlier voxels and compute the median and standard deviation of the voxel intensities in the prostate by using the whole prostate segmentation (semiautomated and manually adjusted by the radiologists) and divide the intensity of each voxel by median + 2 × standard deviation. Then, the ADC map and high-*b*-value DW images are rigidly registered with T2W MR images by using MR imaging coordinate information (27). The registration result is visually examined for the correspondence (S.S., 2 years of experience). Image normalization and registration are performed per MR imaging section.

Appendix E2

Tissue Specimen Preparation

The patient-specific mold (PSM) is printed based on presurgical MR imaging findings in each patient, ensuring that the tissue blocks correspond to the MR imaging sections (28). The PSM is created in SolidWorks, a three-dimensional computer-aided detection software (Dassault Systems SolidWorks, Waltham, Mass), and printed with a three-dimensional printer by using acrylonitrile butadiene styreneplastic plastic. The PSM is designed with sectioning slots that are positioned such that each tissue block matched the location of a 3-mm-thick MR imaging section. After prostatectomy, a whole-mount prostate tissue specimen was fixed in formalin for 2–24 hours at room temperature. The tissue specimen was serially sectioned in the PSM from apex to base at 6-mm intervals by using a 10-inch-long (25.4-cm) autopsy knife (Scientific Supplies, Pakistan). The resulting tissue blocks are labeled and allowed to fix in formalin for an

additional 48–72 hours. The formalin is removed via a wax addition, and graded alcohol is added to dehydrate the specimen. Adding xylene and paraffin to the media clears the alcohol. Tissue slices are cut with a thickness of 5 μm (approximate dimensions, 5 × 4 cm) and stained with hematoxylin-eosin for histopathologic evaluation. Robot-assisted radical prostatectomy is performed within 180 days of imaging, without any intervening treatment. This may cause differences between MR imaging and tissue specimen images due to tumor growth or internal structural changes in the interim.

Appendix E3

Image Registration

In-house semiautomated registration, implemented in OncoNav software (Center for Interventional Oncology, National Institutes of Health), completes the registration based on the outer shape or internal structures of the prostate. Given the prostate segmentation contours of both the tissue specimen image and the MR image, manual rigid body registration with six degrees of freedom is performed to match the oblique plane of the three-dimensional MR image with the tissue specimen image. Thirty landmarks are sampled from each of the segmentation contours, paired, and used to conduct two-dimensional thin-plate spline deformable registration (29). The landmarks are obtained by calculating the intersections between the prostate contour and 30 evenly angled rays (an interval of 12°), which start from the center of the prostate segmentation contour. In addition, internal anatomic landmarks, such as the urethra, ejaculatory ducts, and benign prostatic hyperplasia nodules can be added to improve the quality of registration. Smoothing is incorporated in the deformable registration to prevent overfitting. The registration result is visually inspected by a radiologist (S.S., 2 years of experience) to ensure

that the overall shape and the internal anatomic landmarks at histology match the identified regions (peripheral zone [PZ], transition zone [TZ], and tumor).

Appendix E4

Tissue Segmentation

We convert a tissue specimen image I (in RGB: red, green, and blue) into three different color forms: *(a)* histogram equalization, *(b)* HSV (hue, saturation, and value) color space, and *(c)* La*b* (L, illumination; a* and b*, color-opponent dimensions) color space, generating nine color channels. For a pixel $x \in I$, intensity- and texture-based features are computed within a w x w rectangular window around the pixel x. Intensity-based features include average, standard deviation, kurtosis, and skewness. Texture-based features use local binary pattern (LBP) (30), local directional derivative pattern (31), and variance measurement (30). Texture features are computed for the two color channels (HSV value and La*b* illumination) by using two neighborhood topologies $(P,R) = [(16,2),(24,3)]$ where P and R are the number of neighboring pixels and the radius, respectively. The features are computed for seven different sizes of w x w window (w = 1, 3, 7, 15, 27, 43, and 63 pixels). For w = 1, the intensity value of nine color channels constitutes nine features. For w = 3, 36 features (average, standard deviation, kurtosis, and skewness per color channel) are computed. For $w \geq 7$, we compute 36 intensity-based features and 216 texture-based features ($[P,R] = [16,2]$: 18 features for local binary pattern and local directional derivative pattern and 10 features for variance measure per color channel; $[P,R] = (24,3)$: 26 features for local binary pattern and local directional derivative pattern and 10 features for variance measure per color channel). We adopt multiview boosting algorithm (32) to cooperatively integrate the seven different sets of features and to construct a classifier for tissue

segmentation in a boosting scheme. It maintains a cost matrix (or distribution) C of data for each view and a global cost matrix C_G in a way that the harder cases for one view are managed by the other views. At each booting round, it learns a weak classifier on each view and selects the best one. At the end of the boosting iterations, a weighted vote of the chosen weak classifiers forms the final classifier. Details of the multiview boosting algorithm are available elsewhere (32).

A tissue specimen image is segmented into lumen, nucleus, epithelium, and stroma in a cascaded fashion. The tissue image is first segmented into lumen and nonlumen areas. Lumens are determined by using a threshold value (th_L, >0.5) on the output of the lumen versus nonlumen multiview boosting classification (+, lumen; -, nonlumen) followed by a size constraint (s_L, >50 um^2). Second, nonlumen areas are classified into nuclei and nonnuclei areas. By thresholding (th_N, > 0.5) the output of the nuclei versus nonnuclei multiview boosting classification (+, nuclei; -, nonnuclei), initial nuclei are identified. The size and shape of the initial nuclei are examined. If a nucleus is smaller than 5 μm^2 or if the ratio of the major and minor axes is greater than 5 when its size is smaller than 25 μm^2, the nucleus is considered to be an artifact. Third, nonnuclei areas are grouped into epithelium and stroma. We identify epithelium by using a threshold value (th_{ES}) on the output of the epithelium versus stroma multiview boosting classification (+, epithelium; -, stroma), followed by a size constraint (s_{ES}). To reflect and correct the variability in staining and improve the segmentation, we adjust the threshold value and size constraint (th_E, 0.4–0.6; s_E, 500–1500 um^2) per slice. Fourth, nuclei that are present in the epithelium are designated *epithelial nuclei*. Finally, the perimeter of lumens is examined. By definition, epithelial cells enclose lumens in tissue. If less than 40% of the perimeter is surrounded by epithelium, such lumens are excluded.

This approach has been validated based on expert pathologists' annotations and has been shown to be effective in segmenting tissue components (33,34).

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Table E1. Parameters for Standard DW Imaging and High-*b*-Value DW Imaging

Parameter	Standard DW Imaging	High-*b*-value MR Imaging
Technique	Multisection single-shot spin-echo echo planar imaging	Multisection single-shot spin-echo echo planar imaging
Field of view (mm)	140 × 140	140 × 140
Resolution (mm)	1.25 × 1.25	1.80 × 1.80
Matrix	112 × 108	76 × 75
Recon matrix	256 × 256	256 × 256
No. of sections	26	26
Section thickness (mm)	2.73	2.73
Section gap (mm)	0.27	0.27
Orientation	Axial	Axial
Half scan	0.737	0.732
Water fat shift	Minimum (22| 482 pixels)	Minimum (13|319 pixels)
Bandwidth in echo planar imaging frequency direction (Hz)	1987	2850
Fat suppression	Spectral attenuated inversion recovery	Spectral attenuated inversion recovery
Sensitivity encoding	2 (right-left)	2 (Right-Left)
Gradient overplus	Yes	Yes
b factor (sec/mm²)*	0 (3, 41), 188 (3, 41), 375 (3, 41), 563 (6, 82), 750 (6, 82)	0 (1, 40), 1000 (5, 102), 2000 (5, 102)
Repetition time (msec)	4873	6805
Echo time (msec)	52	52
Imaging time	4 minutes 47 seconds	3 minutes 44 seconds
Diffusion gradient timing DELTA (diffusion time)/delta(pulse width) (msec)	26.0/7.2	25.7/12.4

* Data in parentheses are signals acquired and imaging duration (in seconds), respectively.

Table E2. Relationship between MR Imaging and Tissue Component Density in Region-based Analysis

MR Imaging Sequence and Region	Lumen	Epithelium	Stroma	Epithelial Nucleus
T2W				
PZ and TZ	0.35 (<.01)	–0.34 (<.01)	0.12 (.07)	–0.22 (<.01)
PZ	0.49 (<.01)	–0.45 (<.01)	0.16 (.06)	–0.32 (<.01)
TZ	0.54 (<.01)	–0.47 (<.01)	0.13 (.14)	–0.48 (<.01)
ADC				
PZ and TZ	0.50 (<.01)	–0.53 (<.01)	0.24 (<.01)	–0.37 (<.01)
PZ	0.58 (<.01)	–0.48 (<.01)	0.13 (.13)	–0.32 (<.01)
TZ	0.62 (<.01)	–0.76 (<.01)	0.44 (<.01)	–0.68 (<.01)
High *b* value				
PZ and TZ	–0.44 (<.01)	0.52 (<.01)	–0.26 (<.01)	0.39 (<.01)
PZ	–0.46 (<.01)	0.49 (<.01)	–0.21 (.02)	0.33 (<.01)
TZ	–0.46 (<.01)	0.61 (<.01)	–0.37 (<.01)	0.50 (<.01)

Note.—Data are correlation coefficient (γ), with *P* value in parentheses.

Table E3. Gleason Score versus MR Imaging and Tissue Component Density

MR Imaging and Tissue component	PZ and TZ	PZ	TZ
T2W	–0.08 (.53)	–0.34 (.03)	0.51 (.02)
ADC	–0.25 (.05)	–0.36 (.02)	0.25 (.26)
High *b* value	0.18 (.17)	0.21 (.20)	0.36 (.10)
Lumen	–0.35 (<.01)	–0.37 (.02)	–0.33 (.14)
Epithelium	0.27 (.04)	0.29 (.07)	0.11 (.64)
Stroma	–0.15 (.24)	–0.18 (.27)	0.03 (.91)
Epithelial nucleus	–0.06 (.66)	0.12 (.46)	–0.36 (.11)

Note.—Data are correlation coefficients (γ), with *P* value in parentheses.