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Radio-pathomic Maps of Epithelium and Lumen Density Predict the Location of High-Grade Prostate Cancer

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Summary

This study aims to combine whole-mount prostate pathology with multiparametric magnetic resonance imaging from 39 patients to generate predictive maps of epithelium and lumen density in magnetic resonance imaging space. We show that the new image contrasts generated stratify high-grade tumors from low-grade tumors and healthy tissue. Future studies will explore targeted radiation therapy and clinical

Purpose: This study aims to combine multiparametric magnetic resonance imaging (MRI) and digitized pathology with machine learning to generate predictive maps of histologic features for prostate cancer localization.

Methods and Materials: Thirty-nine patients underwent MRI prior to prostatectomy. After surgery, tissue was sliced according to MRI orientation using patient-specific 3-dimensionally printed slicing jigs. Whole-mount sections were annotated by our pathologist and digitally contoured to differentiate the lumen and epithelium. Slides were co-registered to the T2-weighted MRI scan. A learning curve was generated to determine the number of patients required for a stable machine-learning model. Patients were randomly stratified into 2 training sets and 1 test set. Two partial least-squares regression models were trained, each capable of predicting lumen and epithelium density. Predicted density values were calculated for each patient in the test dataset, mapped into the MRI space, and compared between regions confirmed as high-grade prostate cancer.

Results: The learning-curve analysis showed that a stable fit was achieved with data from 10 patients. Maps indicated that regions of increased epithelium and decreased lumen density, generated from each independent model, corresponded with pathologist-annotated regions of high-grade cancer.

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disease staging using the radio-pathomic mapping technique.

Conclusions: We present a radio-pathomic approach to mapping prostate cancer. We find that the maps are useful for highlighting high-grade tumors. This technique may be relevant for dose-painting strategies in prostate radiation therapy.

Introduction

Prostate cancer will be diagnosed in 1 in 7 men, although not all cases are clinically significant (1). Gleason grade 3 (G3) cancers often never progress to metastatic cancer, while Gleason grade 4 (G4) and grade 5 (G5) cancers are more likely to progress and cause death (2). Differentiation of indolent from aggressive disease is therefore a major focus of ongoing radiologic studies.

Multiparametric (MP) magnetic resonance imaging (MRI) including diffusion and perfusion imaging has recently shown promise in improving the diagnostic accuracy in high-grade prostate cancer (3, 4). Ongoing standardization efforts have also improved the consistency of radiologist reports (5, 6). Studies have shown that MP-MRI is useful for biopsy guidance (7) and potentially selective radiation therapy boost strategies (8). Noninvasive imaging is therefore becoming standard for staging and localizing prostate cancer.

Radiomics describes the field of study in which images are treated as mineable databases to solve classification problems (9, 10). Image features, which can be a statistical expression of pixel neighborhood or tumor morphometry, as well as clinical variables (9, 11, 12), are used as inputs to classification algorithms. Models can then be used to detect and characterize a clinically relevant outcome (12-15).

"Rad-path" correlation is the integration of radiology and pathology, in which diagnostic information from tissue is aligned with medical imaging. Whole-mount tissue alignment has allowed the measurement of tissue heterogeneity across large regions that include many voxels and various degrees of cancer aggressiveness (16-18).

This study presents a technique, radio-pathomic mapping, that combines whole-mount prostate rad-path with machine learning to generate predictive maps of pathologic features based on noninvasive imaging alone. Two machine-learning models were generated from separate training datasets and subsequently applied to a naive test dataset. We hypothesized that radio-pathomic maps of epithelium and lumen density would highlight regions of high-grade prostate cancer, which has direct implications for the radiation oncology community.

Methods and Materials

Patient population

We prospectively recruited 39 patients undergoing MP-MRI prior to prostatectomy for this institutional review board—approved study. Written consent was obtained from all patients, who ranged in age from 45 to 72 years (mean, 60 years). The average prostate-specific antigen score measured prior to surgery was 8.2 ng/mL, with a range of 2.8 to 27.5 ng/mL. Eligible patients were identified and recruited consecutively. The distribution of tumor burden in the cohort is shown in Table E1 (available online at www.redjournal.org).

Imaging

MP-MRI was acquired on a 3-T MRI scanner (General Electric, Waukesha, WI) using an endorectal coil. MP-MRI included field-of-view optimized and constrained undistorted single shot (FOCUS) diffusion weighted imaging with 10 b values (0, 10, 25, 50, 80, 100, 200, 500, 1000, and 2000), dynamic contrast-enhanced imaging, and T2-weighted imaging (19). A summary of imaging parameters is shown in Table E2 (available online at www.redjournal.org).

MRI preprocessing

To correct for intersubject intensity variation, T2-weighted images were intensity normalized using previously published techniques (12). Apparent diffusion coefficient (ADC) maps were calculated from different combinations of b values. The image with b = 0 was aligned with the T2 image using FMRIB's Linear Image Registration Tool (Functional Magnetic Resonance Imaging of the Brain Library, Oxford, UK), and all resulting diffusion maps were transformed into the T2 space using the calculated transformation matrix (20). Alignment was verified and manually corrected if misregistration occurred by use of the tkregister tool from FreeSurfer (surfer.nmr.mgh.harvard.edu). Contrast uptake was calculated from the dynamic contrast-enhanced imaging.

Surgery

Robotic prostatectomy was performed using the da Vinci robotic system (Intuitive Surgical, Sunnyvale, CA). All surgical procedures were performed by a single fellowship-trained surgeon (KJ) using a robotic surgical technique (21, 22). Surgical specimens were extracted en bloc and fixed in formalin.

Tissue sectioning

Prostate samples were inked and sectioned using patient-specific tissue-slicing molds (16, 23). Prostate masks were manually segmented from the patient's T2-weighted scan