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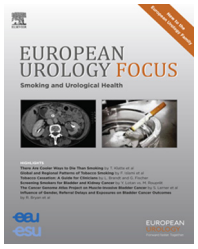

Platinum Priority – Prostate Cancer
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Nuclear Shape and Architecture in Benign Fields Predict Biochemical Recurrence in Prostate Cancer Patients Following Radical Prostatectomy: Preliminary Findings

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Abstract

Background: Gleason scoring represents the standard for diagnosis of prostate cancer (PCa) and assessment of prognosis following radical prostatectomy (RP), but it does not account for patterns in neighboring normal-appearing benign fields that may be predictive of disease recurrence.
Objective: To investigate (1) whether computer-extracted image features within tumor-adjacent benign regions on digital pathology images could predict recurrence in PCa patients after surgery and (2) whether a tumor plus adjacent benign signature (TABS) could better predict recurrence compared with Gleason score or features from benign or cancerous regions alone.
Design, setting, and participants: We studied 140 tissue microarray cores (0.6 mm each) from 70 PCa patients following surgery between 2000 and 2004 with up to 14 yr of follow-up. Overall, 22 patients experienced recurrence (biochemical [prostate-specific antigen], local, or distant recurrence and cancer death) and 48 did not.
Intervention: RP was performed in all patients.
Outcome measurements and statistical analysis: The top 10 features identified as most predictive of recurrence within both the benign and cancerous regions were combined into a 10-feature signature (TABS). Computer-extracted nuclear shape and architectural features from cancerous regions, adjacent benign fields, and TABS were evaluated via random forest classification accuracy and Kaplan-Meier survival analysis.
Results and limitations: Tumor-adjacent benign field features were predictive of recurrence (area under the receiver operating characteristic curve [AUC]: 0.72). Tumor-field nuclear shape descriptors and benign-field local nuclear arrangement were the predominant features found for TABS (AUC: 0.77). Combining TABS with Gleason sum further improved identification of recurrence (AUC: 0.81). All experiments were performed using threefold cross-validation without independent test set validation.
Conclusions: Computer-extracted nuclear features within cancerous and benign regions predict recurrence following RP. Furthermore, TABS was shown to provide added value to common predictors including Gleason sum and Kattan and Stephenson nomograms.
Patient summary: Future studies may benefit from evaluation of benign regions proximal to the tumor on surgically excised prostate cancer tissue for assessing risk of disease recurrence.

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1. Introduction

Each year, nearly 75 000 radical prostatectomies (RPs) are performed in the United States for the purpose of curing prostate cancer (PCa) [1]. Despite the effectiveness of RP, 20–40% of men will experience recurrence following surgery, manifested as biochemical, local, or distant cancer recurrence or cancer death [2–4]. There is an urgent need for improved methods of accurately predicting which men with PCa will have recurrence following surgery. Early identification of PCa patients at elevated risk for recurrence after surgery and prior to prostate-specific antigen (PSA) rising could help improve treatment management and monitoring.

Although high Gleason scores (ie, PCa with a Gleason score of 8–10) are typically associated with more aggressive disease and thus a higher risk of recurrence, its diagnosis is made solely based on the visual appearance of the morphology within the cancerous foci. There has been evidence to suggest that the microenvironment surrounding the prostate tumor may play a role in cancer progression [5,6], a phenomena known as the *field effect*. Epigenetic changes within the benign regions surrounding the tumor have been shown to be capable of initiating PCa [5]. This begs the question of whether morphometric attributes within tumor-adjacent benign regions can provide additional complementary features to Gleason scoring for better prediction of disease risk and recurrence.

There has been significant recent interest in investigating histomorphometric features of benign regions adjacent to the tumor and evaluating the association of these features with disease aggressiveness and outcome. Veltri et al [7] and Gann et al [6] showed that there are quantifiable morphometric attributes within tumor-adjacent benign regions that can provide additional information related to disease outcome. These studies, however, have been limited to the correlation of outcome and nuclear shape parameters alone. Although there has been substantial interest in computer-based evaluation of nuclear architecture in the context of developing better methods for automated Gleason scoring, there has been little to no work looking at the association with disease aggressiveness and outcomes.

Computer-based analysis of digital pathology images has allowed for extraction of image-based features from histologic tissue that have been shown to be able to predict biochemical recurrence following RP.

Graph-based algorithms allow for capturing the spatial architecture of nodes via connected edges. There has been recent interest in developing quantitative histomorphometry algorithms that use these graph-based approaches for assessing nuclear architecture. Quantitative measurements that can be extracted from these nuclear graphs include Voronoi and Delaunay tessellation graphs [8] and local cell cluster graphs [9]. These features summarize distance statistics between nuclei and have been shown to be useful in discriminating between different Gleason grades of PCa histopathology [10]. However, these features thus far have been evaluated within the tumor epithelium alone, whereas features from the tumor-adjacent benign regions have never been explicitly interrogated in the context of association with disease recurrence and outcome.

The primary objectives of this study were to identify (1) whether histomorphometric features relating to the nuclear architecture within the tumor-adjacent benign regions can predict recurrence following RP and (2) whether a combination of nuclear shape and architectural features from within the cancer and from adjacent benign regions can better predict disease progression compared with Gleason score.

In this work, we developed a tumor plus adjacent benign signature (TABS) for differentiating PCa patients who will develop recurrence from those who will not. The reported results represent a preliminary study in lieu of independent validation of TABS.

2. Materials and methods

2.1. Study population

Two tissue microarrays (TMAs; TMA681 and TMA682) were recruited for this study, each prepared using a Beecher MT1 manual arrayer (Beecher Instruments, Silver Spring, MD, USA) under the supervision of the Prostate Cancer Biorepository Network. The patients included in this TMA were selected independently of this work and based on an Early Detection Research Network grant to recruit a Gleason grade–stratified PCa cohort to study quantitative histomorphometry and molecular biomarkers.

Each TMA was composed of hematoxylin and eosin (H&E)–stained 0.6-mm samples of tumor, adjacent benign, and control regions. The formalin-fixed, paraffin-embedded RP PCa tissues and normal (benign) cancer-adjacent controls to be included in the two TMAs were selected and reviewed by a pathologist at Johns Hopkins University School of Medicine (J.I.E.). H&E-stained slides from all selected cases were reviewed by the pathologist: The tumor-adjacent normal-appearing regions along with staged and/or graded index tumor areas were identified and marked on the H&E slide for each case. Benign region selection was confined to that of normal-appearing prostatic glands and did not include any atypical benign pathology such as atrophy, basal cell hyperplasia, or high-grade prostate epithelial neoplasia.

The two TMAs included 80 unique PCa patients. Among the 80 patients, 5 from TMA681 and 5 from TMA682 were removed from this study due to lack of follow-up data following RP. This resulted in 70 patients remaining for this study identifying relationships between recurrence and features extracted from tumor-adjacent benign tissue.

All patients from this cohort underwent RP between 2000 and 2004 and were followed for PSA updates for up to 14 yr. Average time to biochemical recurrence after surgery was 6.6 yr. Moreover, 22 patients displayed recurrence (in the form of biochemical, local, or distant recurrence or cancer death), whereas 48 did not. Demographic information for the study cohort is summarized in Table 1.

The TMA samples were scanned at $\times$20 magnification with a resolution of 0.5 μm per pixel using an Aperio whole-slide scanner (Leica, Wetzlar, Germany). The scanning resulted in a 1670 $\times$ 1670-pixel RGB color image for each TMA core, similar to the one shown in Figure 1a. For this study, a single randomly selected core was chosen from each of the tumor and benign sets to represent each patient.

In total, we identified 140 fields of view from the surgically excised histopathology specimens of 70 PCa patients, corresponding to regions

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