A Quantitative Exploration of Efficacy of Gland Morphology in Prostate Cancer Grading

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Abstract—Currently, prostate cancer diagnosis is done qualitatively by pathologists who visually analyze tissue architecture while largely ignoring gland morphology. In this study we have developed an automated image analysis scheme for grading prostate cancer by quantitatively analyzing morphological features of individual glands from digitized histological images. Following automated gland boundary segmentation via level sets, 7 boundary features are extracted. Non-linear dimensionality reduction is then applied to the set of extracted features. A Support vector machine (SVM) classifier is then used to classify tissue patches corresponding to benign epithelium, and prostate cancer grades 3 and 4 in a lower dimensional embedding space. We obtained an accuracy of 75.00% in distinguishing benign epithelium and grade 3, 85.71% between benign epithelium and grade 4, and 72.73% between grade 3 and grade 4. Our results strongly suggest that quantitative analysis of gland boundary morphology may play a significant clinical role in distinguishing different prostate cancer Gleason grades.

I. INTRODUCTION
Prostate cancer is a major problem in United States with 218,890 new predicted cases and 27,050 deaths in 2007 (American Cancer Society.) Definitive diagnosis of prostate cancer is done via visual diagnosis of prostate core biopsy specimens by trained pathologists. Gleason grading system describes five increasingly malignant stages of prostate cancer based on tissue architecture, where grade 1 corresponds to early stage cancer and grade 5 to highly infiltrative cancer [1]. Manual grading of prostate tissue is extremely time consuming and subject to inter-observer and intra-observer variations [1]. In previous work [2], we presented a successful computer-aided diagnostic (CAD) system to automatically distinguish between different prostate cancer Gleason grades by quantitatively integrating tissue architecture and texture attributes. Our work complements [2] by exploring the discriminability of gland morphology in distinguishing different Gleason grades. The overall motivation for this work is to quantitatively analyze prostate tissue to help reduce variability in cancer grading by pathologists, leading in turn to more accurate and consistent diagnosis and thus to better treatment options for the patient.

II. MATERIALS
Hematoxylin and eosin stained prostate biopsy cores were scanned into a computer using a high resolution whole slide scanner at 40x optical magnification at the University of Pennsylvania. Tissue regions within each image were labeled as belonging to benign epithelium, Gleason grade 3 or 4 by an expert pathologist.

III. METHODS
An overview of our methodology is shown in Fig. 1. Inner boundaries of the individual glands from a total of 29 tissue patches were automatically segmented using the level set algorithm [3]. A user-defined estimate of boundary was used as the initial contour to the algorithm. A total of 7 boundary features were defined and implemented, including,

1. Area overlap ratio: Ratio of gland area to area of smallest circle enclosing the gland boundary.
2. Distance ratio: Ratio of average distance to maximum distance from the centroid of the gland to the points lying on the boundary.
4. Variance of the distances as defined in 2.
5. Perimeter ratio: Ratio of estimated perimeter to actual perimeter. Estimated perimeter is computed using linear interpolation between 5-10 points randomly sampled from the segmented gland boundary, while actual perimeter is computed using all the points lying on the boundary.
6. **Compactness:** Actual perimeter$^2$/gland area.

7. **Smoothness:** For points $i-1$, $i$, and $i+1$ on the gland boundary $B$, $S_i = |d(i, c) - (d(i-1, c) + d(i+1, c))/2|$, where $c$ is the centroid of the gland and $d(c,i)$ is the Euclidean distance between $c$ and $i$. Smoothness is then defined as $\sum_i S_i$ for $i \in B$ [4].

A non-linear dimensionality reduction method (graph embedding (GE) [5]) was used to reduce the dimensionality of the feature set and an SVM classifier was then used to identify the 29 tissue patches as either benign epithelium, grade 3, or 4.

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**IV. RESULTS AND DISCUSSION**

Fig. 2 illustrates variations in gland appearance from tissue patches corresponding to benign epithelium and Gleason grades (3, 4). SVM classification accuracy in distinguishing the 3 pairs of classes is listed in Table 1.

**Table 1.** SVM classification accuracy for the 29 patches.

<table>
<thead>
<tr>
<th>Class Distinction</th>
<th>Accuracy</th>
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<tbody>
<tr>
<td>Benign Epithelium vs. Grade 3</td>
<td>75.00%</td>
</tr>
<tr>
<td>Benign Epithelium vs. Grade 4</td>
<td>85.71%</td>
</tr>
<tr>
<td>Grade 3 vs. Grade 4</td>
<td>72.73%</td>
</tr>
</tbody>
</table>

The results indicate that not only can gland morphology discriminate between benign epithelium and cancer, but can also distinguish between intermediate prostate cancer Gleason grades (3, 4). Note that most inter-observer variability among pathologists and diagnostic error occurs in discriminating between intermediate Gleason grades (3, 4) [2]. Fig. 3 displays the tissue patches in a lower dimensional space following application of GE on the feature set. Note that (Fig. 3(b)) while better discriminability is achieved between benign epithelium and grade 4 patches, larger overlap is observed between grade 3 and grade 4 patches (Fig. 3(a)) revealing the difficulty of this clinical problem. However, our automated classifier was still able to distinguish grades 3 and 4 with an accuracy of 73%.

**Fig. 3** Tissue patches corresponding to (a) grade 3 (x’s), and grade 4 (circles), and (b) benign epithelium (x’s) and grade 4 (circles) in the lower dimensional embedding space.

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**V. CONCLUSIONS**

In this paper, we demonstrated an automated scheme to quantify prostate gland morphology for distinguishing different Gleason cancer grades with the aim of reducing intra- and inter-observer variability among pathologists. The results indicate that gland morphology may be a useful feature to help discriminate between different Gleason cancer grades. In future work, we plan to integrate architectural, textural, and morphological gland features to attain even better discriminability between prostate cancer Gleason grades.

**ACKNOWLEDGMENT**

This work was possible due to grants from the Coulter Foundation, the Busch Biomedical Award and Technology Commercialization Fund at Rutgers University.

**REFERENCES**


