Chapter 12
Computer-Aided Image Analysis and Detection of Prostate Cancer:
Using Immunostaining for Alpha-Methylacyl-CoA Racemase, p63, and High-Molecular-Weight Cytokeratin

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ABSTRACT

Immunohistochemistry (IHC) is an adjunct tool for clinical histologic diagnosis of diseases. A common IHC technique for prostate cancer diagnosis is a triple-antibody cocktail with Alpha-Methylacyl-CoA Racemase (AMACR), p63, and High-Molecular-Weight Cytokeratin (HMWCK), which stains certain types of cells into two distinct colors. The authors have developed an automated computer technique that detects prostate cancer in prostate tissue sections processed with the triple-antibody cocktail. Test and validation of the authors' technique on digital images obtained from conventional microscopes (region of interest images) showed that the computer technique can recognize prostatic adenocarcinoma with both high sensitivity and high specificity. The authors also used this computer technique to analyze whole-slide images of prostate biopsy and the initial results are promising. With further development and refinement, this computer technique could become a useful tool for pathologists to detect prostate cancer foci in histologic sections of tissue processed with the triple-antibody cocktail.

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BACKGROUND

As the most frequently diagnosed non-skin cancer in adult men, prostate cancer has been—and likely will remain in the near future—a major public health concern in the United States. In 2010, the estimated number of newly diagnosed prostate cancer cases is 217,730 and the estimated number of deaths from this disease is 32,050 (Jemal, Siegel, Xu, & Ward, 2010). In the current clinical practice, prostate cancer is typically detected through age-based asymptomatic screening of serum level of Prostate-Specific Antigen (PSA), frequently also Digital Rectal Examination (DRE), and histologic analysis of thin-needle core biopsy samples, the last of which provides the definitive diagnosis (Bostwick, 1990; Epstein & Yang, 2002).

Histologic diagnosis of prostate cancer is often rendered based on morphological features in tissue sections processed with the routine hematoxylin and eosin (H&E) staining. However, in cases that morphological features are not sufficient enough to determine, definitively, whether cancer is present, Immunohistochemistry (IHC) can be a valuable tool that identifies the presence of specific types of cells or molecules, taking advantage of antibody and antigen reactions (Wojon & Epstein, 1995). For example, both p63 and High-Molecular-Weight Cytokeratin (HMWCK) are markers for basal cells, a strong indication that rules out prostatic adenocarcinoma. Therefore, both p63 and HMWCK, individually or jointly, can help distinguish non-malignant prostatic glands from prostatic adenocarcinoma (Ramnani & Bostwick, 1999; Weinstein, Signoretti, & Loda, 2002; Zhou, Shah, Shen, & Rubin, 2003). More recently, a prostate cancer marker, Alpha-Methylacyl-CoA Racemase (AMACR, also known as P504S), was found to be overexpressed in the cytoplasm of prostatic adenocarcinoma cells (Jiang et al., 2001; Rubin et al., 2002; Adley & Yang, 2006). In current clinical practice, a triple-antibody cocktail, which combines AMACR and the basal cell markers, p63 and HMWCK, are used to improve the diagnosis of prostatic adenocarcinoma (Jiang, Li, Fischer, Dresser, & Woda, 2005; Ng, Koh, Tan, & Tan, 2007). The triple-antibody cocktail uses two chromogens—one marks malignant secretory cell cytoplasm red and the other marks benign basal cells brown—to provide a simple means for the identification of prostatic adenocarcinoma. This technique is used widely in difficult or questionable cases in which the diagnosis is not clear based on H&E staining alone, and is especially useful in cases of small malignant foci in limited biopsy materials.

Computer methods can be developed to extract quantitative information from medical images to help physicians with diagnostic decision-making. Computer-aided diagnosis (CAD) methods have been developed for the detection of breast, lung, and colon cancers in radiographs, CT images, and MR images (Kobayashi, Xu, MacMahon, Metz, & Doi, 1996; Jiang, et al., 1999; Yoshida & Dachman, 2005). It has been shown that with the aid of CAD, radiologists' performance in the interpretation of mammograms can be improved (Freer & Ulissey, 2001). The clinical effects of CAD continue to be investigated (Fenton, et al., 2007; Nishikawa, Schmidt, & Metz, 2007; Feig, Birdwell, & Linver, 2007; Gromet, 2008). Similarly, computer methods for quantitative image analysis can be developed for the analysis of pathology images (Thompson, Bartels, Bartels, & Montironi, 1995; Bartels, et al., 1995; Diamond, Anderson, Bartels, Montironi, & Hamilton, 2004; Saidi, Cordon-Cardo, & Costa, 2007; Tabesh, et al., 2007). However, no CAD technique has been developed for clinical diagnosis of prostate cancer. Our purpose in this work was to test the feasibility of developing an automated computer technique for the detection of prostatic adenocarcinoma in tissue sections stained with the AMACR/p63/HMWCK triple-antibody IHC cocktail.