The Role of Complexed Prostate-Specific Antigen in the Detection of Prostate Carcinoma

Assay

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✍ Tarek Ismail Abushloa

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List of Abbreviations

AAH	Atypical adenomatous hyperplasia
ACT	Alpha-1-antichymotrypsin
API	Alpha-1-protease inhibitor
A2M	Alpha-2- macroglobulin
BPH	Benign prostatic hyperplasia
CZ	Central zone
cPSA	Complexed prostate-specific antigen
cPSAD	Complexed prostate-specific antigen density
DRE	Digital rectal examination
fPSA	Free prostate-specific antigen
f/tPSA	Ratio of free to total prostate-specific antigen
hK	Human glandular kallikrein
IGF-1	Insulin-like growth factor-1
PCa	Prostate cancer
PIN	Prostatic intraepithelial neoplasia
PPV	Positive predictive value
PSA	Prostate-specific antigen
PSAD	Prostate-specific antigen density
PSADT	Prostate-specific antigen doubling time
PSAV	Prostate-specific antigen velocity
PZ	Peripheral zone

ROC curve	Receiver-operating characteristic curve
TZ	Transition zone
TZ-cPSAD	Transition zone complexed prostate-specific antigen density
TRUS	Transrectal ultrasonography
TNM	Tumor, node, and metastasis

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Introduction

Prostate-specific antigen (PSA) has become the most useful tool for detecting, staging, and monitoring prostate cancer in the past decade. However, it has a lack of specificity in detecting prostate cancer, as using the most widely applied cut-off level of 4.0 ng/mL will result in a low cancer detection rate of between 25–33% for transrectal ultrasonography-guided biopsies ***(Obort, 2013)***.

There have been several approaches to improve PSA performance. These have included age-referenced PSA ranges, PSA velocity, PSA density, PSA transition zone density, and free-to-total PSA ratio (f/t PSA). However, none of these have gained universal acceptance ***(De Angelis, 2007)***. This has led to further research until it was observed that once PSA enters the systemic circulation, it becomes complexed to protease inhibitors and circulates in serum in several molecular forms. Total PSA (tPSA) is comprised of the complexed forms and the free unbound form. The complexed forms include α1-antichymotrypsin (ACT), α1-protease inhibitor, and α2-macroglobulin ***(Stenman et al., 2005)***.The major complex that is PSA-ACT comprises between 65% and 95% of tPSA. Other

molecular forms also have been identified in vitro, such as protein C inhibitor, interα1-trypsin inhibitor, and pregnancy zone protein ***(Martınez et al., 2002)***.

There has been a lot of interest in the PSA-ACT form, as early on it was noted that its percentage is increased in the serum of men with prostate cancer ***(Zhu et al., 2013)***. Numerous studies have been performed analysing the performance of complexed PSA (cPSA) assays. Most have shown promising results with an increased specificity over tPSA in the detection of prostate cancer while other studies have shown equivalence to the f/t PSA **(*Strittmatter et al., 2011)***. There is also a cost advantage in using cPSA, In comparison to the measurement of the f/t PSA, which requires two assays; the measurement of cPSA requires only one assay. It also has been shown to have a cost benefit over tPSA in prostate cancer early detection and screening ***(Ekwueme et al., 2007)***.

Aim of the Assay

The aim of this assay is the evaluation of the role of complexed-prostate specific antigen (cPSA) in the detection of early prostate adenocarcinoma.

Anatomy of the Prostate Gland

Gross Appearance

The prostate gland is the male organ most commonly afflicted with either benign or malignant neoplasms. The prostate is a firm, partly glandular and partly fibro-muscular structure that comprises the most proximal aspect of the urethra. Anatomically, it resides in the true pelvis separated from the pubic symphysis anteriorly by the retropubic space (space of Retzius). The posterior surface of the prostate is separated from the rectal ampulla by Denonvillier`s fascia. The base of the prostate is continuous with the bladder neck, and the apex rests on the upper surface of the urogenital diaphragm. Laterally, the prostate is related to the levator ani musculature ***(Chung et al., 2012)***.

The normal prostate is approximately 20 g in volume. It measures 3-4 cm at the base, 4-6 cm in cephalocaudal, and 2-3 cm in anteroposterior dimensions **(**Figure 1).

The prostate is perforated by the urethra and the ejaculatory ducts. The urethra usually lies along the junction of its anterior with its middle third. The ejaculatory ducts pass obliquely downward and forward through the posterior part of the prostate, and open into the prostatic portion of the urethra.

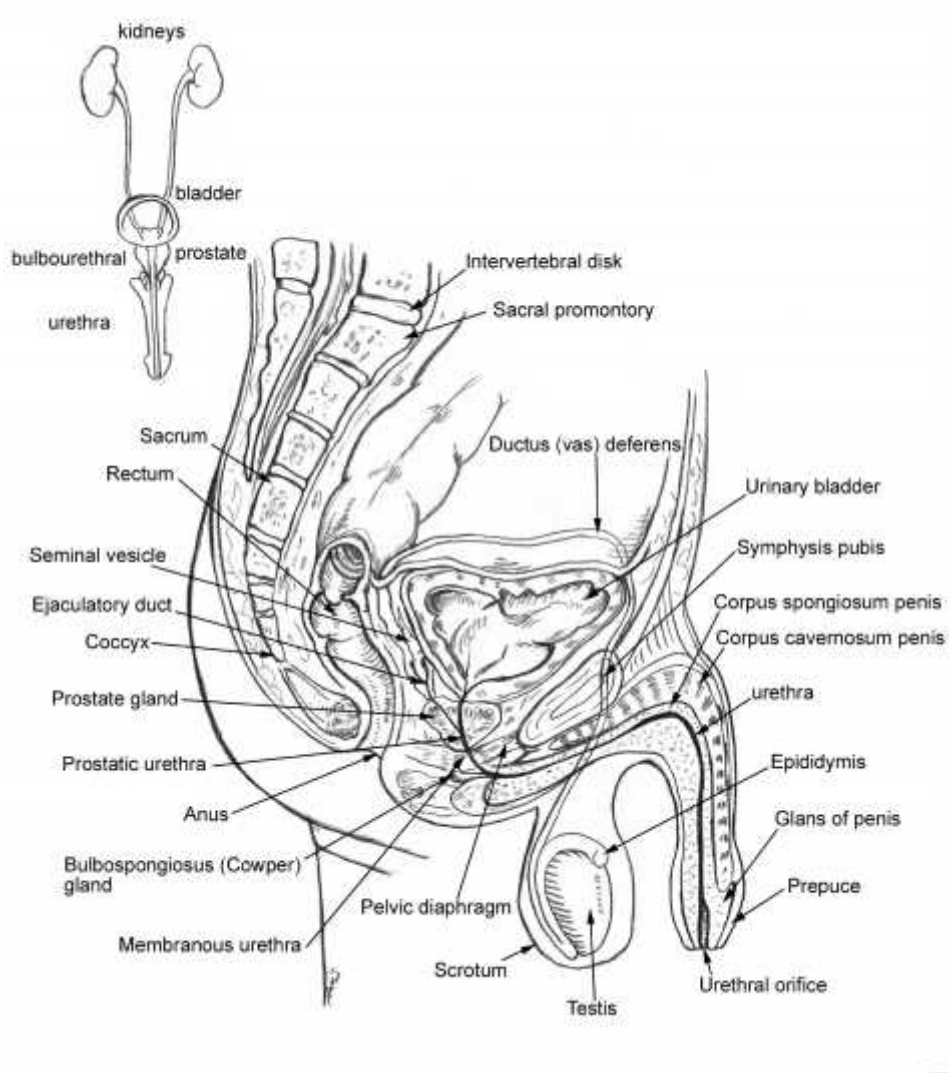

Figure (1): Male Reproductive System.

McNeal has popularized the concept of zonal anatomy of the prostate. Three distinct zones have been identified. Peripheral, central and transition zone (Figure 2). The peripheral zone accounts for 70% of the volume of the young adult prostate, the central zone accounts for 25%, and the transition zone accounts for 5%. Sixty to seventy

percent of carcinomas of the prostate originate in the peripheral zone, 10-20% in the transition zone, and 5-10% in the central zone. The peripheral zone is the most common site for prostate carcinoma and the transition zone is the exclusive site for benign prostatic hyperplasia (BPH) ***(McNeal, 1988)***.

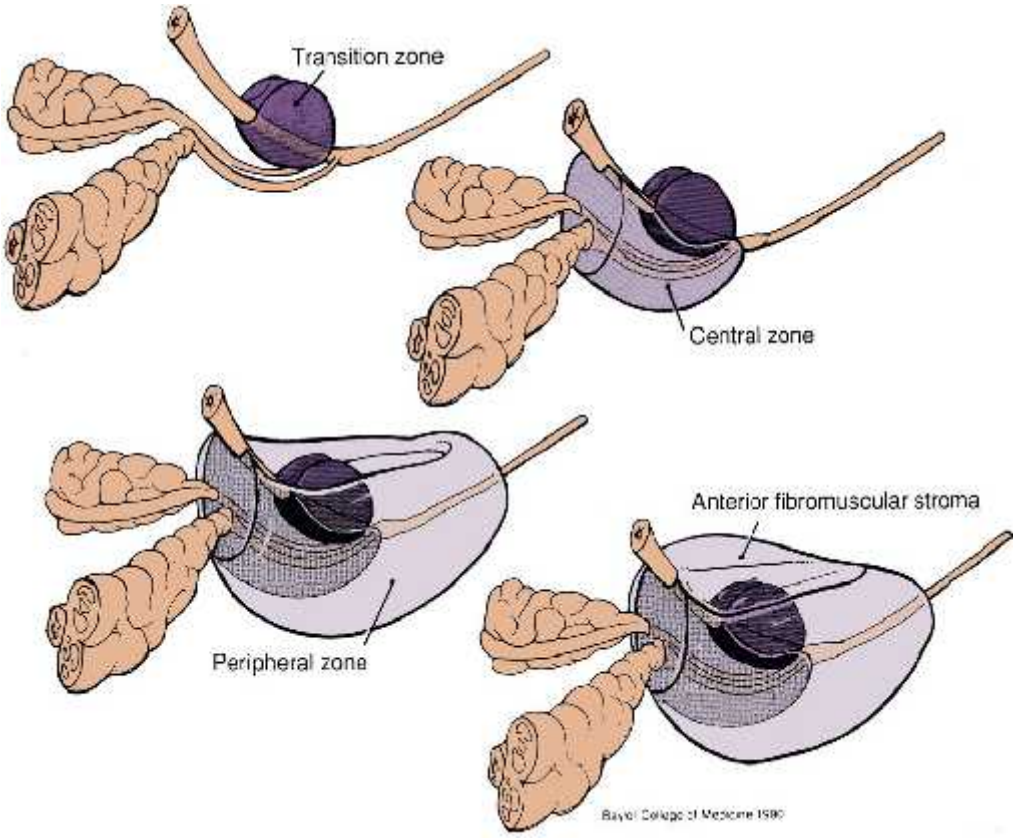

Figure (2): Zonal anatomy of the prostate as described by McNeal ***(Chung et al., 2012)***.

Microscopic Structure

Microscopically, the prostate consists of approximately 70% glandular tissue and 30% fibromuscular stroma. The glandular substance is composed of numerous follicles (acini), the lining of which frequently shows papillary elevations. The acini open into elongated canals which join to form 12-20 small excretory ducts. Both the follicles and the canals are lined by columnar epithelium and the ducts are enclosed in a delicate capillary plexus **(*Chung et al., 2012)***.

The prostatic ducts open into the floor of the prostatic portion of the urethra, and are lined by two layers of epithelium, the inner layer consisting of columnar epithelium and the outer layer of small cuboidal cells. Small colloidal masses, known as corpora amylicia, are often found in the gland acini. The prostatic secretion and the secretion of the seminal vesicles together form the bulk of the seminal fluid **(*Tanagho, 2008)***.

Vascular Supply and Innervation

The arterial blood supply of the prostate is derived from branches of the internal iliac artery (inferior vesical and middle rectal arteries). Venous drainage is via the dorsal venous complex, which receives the deep dorsal vein