INTRODUCTION

Cancer prostate continue to be a major health problem all over the world, in fact the rates of this disease in US African American and Caucasian men are the highest in the world. Prostate cancer is now of the leading cause of cancer death in men, exceeded only by lung cancer. It accounts for 29% of all male cancer and 11% of male cancer related death ***(Parkin et al., 2005).***

This considerable progress in the diagnosis of prostate cancer will be translated into better patient care and decrease in the mortality from prostate cancer.

Prostate cancer is one of the most important cancers in men with a worldwide incidence of 25.3 per 100,000. This makes prostate cancer the fifth most common cancer and the second most common cancer in, with large differences between countries men ***(Parkin et al., 2005)***.

In Egypt the **GLOBOCAN 2002 database** compiled by for the International Agency for Research on Cancer) estimated the number of new cases per year to be 867 cases. In the period 2002-03 the Egyptian National Cancer Institute at Cairo University reported seeing 238 new cases of prostate cancer out of a total of 9,340 new cancer cases in males (2.6 %) ***(Ferlay et al., 2002).***

Chances of developing cancer in men and women are increasing with age. In Egypt aged population represents about 6% of overall population (age 60 years and more) in 2006, it is expected that this percent will be about 9% and 15% in 2015 and 2030 respectively. In spite of the low incidence of prostate cancer in Egypt the increase of the aging population, makes that prostate cancer will become ever more an enormous challenge ***(Ibrahim et al., 2011).***

Incidence can be influenced by several risk factors including genetic susceptibility, environmental exposure in its largest sense and differences in health care and cancer registration (or a combination of these) ***(Schroder et al., 2003).***

Prostate cancer is a glandular malignant neoplasia (adenocarcinoma), the origin of such neoplasia is not to be searched for in the secretory cells (that are final differentiation cells that will disappear after serving their purpose) but in the precursor (or stem) cells. This hypothesis called (stem cell model). The stem (basal) cells of prostate acini are considered the origin of prostate cancer. Between these cells and the final secretory cells, different intermediate or transit cells can be observed, and every one of them can evolve into malignant cells, explaining the biological variability of prostatic cancer. The exact changes between normal gland and prostatic intraepithelial neoplasia (PIN) are not yet known, but a post-inflammatory atrophy lesion is being studied in this respect. The PIN lesion is considered the pre-invasive change of

prostatic cancer and its presence in needle biopsy is clinically used for follow-up of the patient. The progressive knowledge of the stromal invasion in prostate cancer (loss of some cell–cell adhesion molecules and expression of others) can be correlated with the Gleason grading system and the molecular changes in the progression to androgen independent carcinoma can be used as a prognostic marker in conjunction with the classical pathological markers ***(Pardal et al., 2003)***.

The main diagnostic tools used to look for evidence of prostate cancer include digital rectal examination (DRE), trans rectal ultrasonography (TRUS) and serum prostate specific antigen (PSA). PSA is the most common tumor marker for prostate cancer, for screening, diagnosis, following therapy and for early detection of relapse. However, the PSA levels can also be affected by various benign conditions like certain medical procedures, an enlarged prostate and a prostate infection. PSA is an organ specific volume marker and does not reveal any information about the aggressiveness of the disease.

A positive test only indicates that further evaluation of the patient is necessary. Prostate-specific antigen is the most important tumor marker in patient with prostate cancer, reflecting tumor stage and response to treatment. However, it suffers limitations in different clinical situations. Since PSA is a tumor volume marker patients with clinically progressive disease will generally show rising PSA levels. Following successful androgen blockade PSA synthesis decreases.

However, PSA expression is reported to be under hormonal control indicating that changes in serum level may be independent of tumor response ***(Caspo et al., 1988).***

These findings are explained because a direct effect on serum PSA is caused by androgen deprivation. This may result in a discrepancy between clinical findings and PSA values ***(Leo et al., 1911).***

Moreover PSA values in hormonally treated patients may differ from values in non-treated patients with similar disease status (stage and extent of metastases) ***(Miller et al., 1922).***

Secondly, it was shown that normal PSA values (levels smaller or equal to 4 ng/ml) are observed in up to 13% of patients with progressive disease following androgen ablation ***(Dupont et al., 1991).***

This indicates that low serum PSA after androgen ablation does not always indicate no evidence of progressive disease ***(Bruchovsky et al., 1987).***

Finally, although elevated PSA levels reflect increased tumor burden and may lead to adverse outcome the prognostic significance of pretreatment PSA values in metastatic patients is controversial ***(Mulders et al., 1990).***

Although high pretreatment PSA values (>60 ng/ml) are reported to be of prognostic significance with respect to both

survival ***(Matzkin et al., 1993)*** and development of metastases ***(Stokkel et al., 1997)*** other studies show no relation between pretreatment PSA and survival ***(Kawakami et al., 1997)*** or disease progression ***(Zagars et al., 1994)***.

Because of these three limitations continuous search for additional tumor markers is of great value. Tissue polypeptide-specific antigen (TPS) has been reported to be additional tumor marker ***(Bjorklund et al., 2015)***.

TPS is a 18 –cytokeratin –associated tumor proliferation marker with increased serum levels at time of rapid divisions.

TPS is detected by a specific monoclonal antibody against the M3 epitope of the tissue polypeptide antigen molecule ***(Tarle et al., 1994).*** It is measured in serum and is released in the circulation during the process of cellular degradation ***(Polito et al., 2014)***.

Although TPS is not tumor- specific, its measurement is potentially of additional value together with PSA because it is androgen –independent ***(Tarle et al., 1993)***. Its value was previously determined in patient with hormone refractory metastatic prostate cancer ***(Kramer et al., 1997)*** and in patients under intermittent hormonal therapy ***(Theyer et al., 2012).***

AIM OF THE WORK

The aim of this study is to evaluate the prognostic significance of Tissue polypeptide specific-antigen. as proliferation marker together with and as compared to PSA in patients with metastatic prostate cancer.

And correlate the TPS with clinical progression in patients on maximal androgen blockade.

Chapter 1

ANATOMY OF THE PROSTATE

The basic anatomy

The prostate gland develops after puberty as a result of the testosterone surge. It reaches a size of 20cc in the normal adult, measuring 3 cm in length, 4 cm in width, and 2 cm in depth. Its size and shape can be approximated to that of a walnut. It is located at the base of the bladder, where it surrounds the proximal urethra. In this position, it lies above the urogenital diaphragm between the rectum and the symphysis pubis (Figure 1). It is described as having anterior, posterior, and lateral surfaces. Its base is contiguous with the bladder and its apex narrows inferiorly. There is no 'true' capsule to the prostate, but rather a 'false' capsule of fibromuscular stroma which disappears towards the apex of the gland. The prostate is surrounded by fascial structures (Figure 2) anteriorly and anterolaterally by the prostatic fascia, and posteriorly by Denonvillier's fascia which separates it from the fascia propria of the rectum. Laterally, the prostatic fascia merges with the endopelvic fascia (also called the lateral pelvic or levator fascia). The prostatic base is covered with a posterior layer of detrusor apron from the bladder muscle. Abutting the prostate posteriorly are the seminal vesicles and vasa (ducti) deferentia (Figure 3) ***(Walz et al., 2010)***.

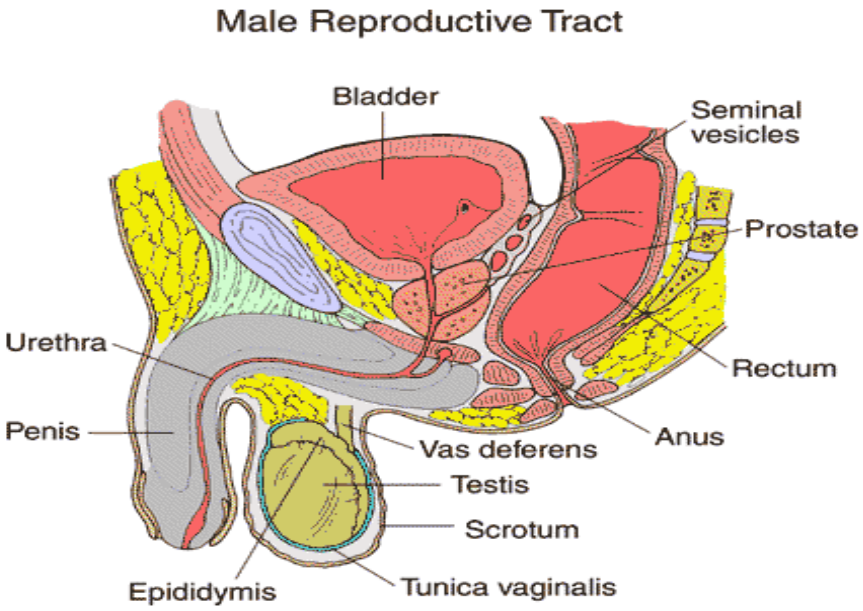

Fig. (1): Sagittal section of the male pelvis ***(Tewari et al., 2003).***

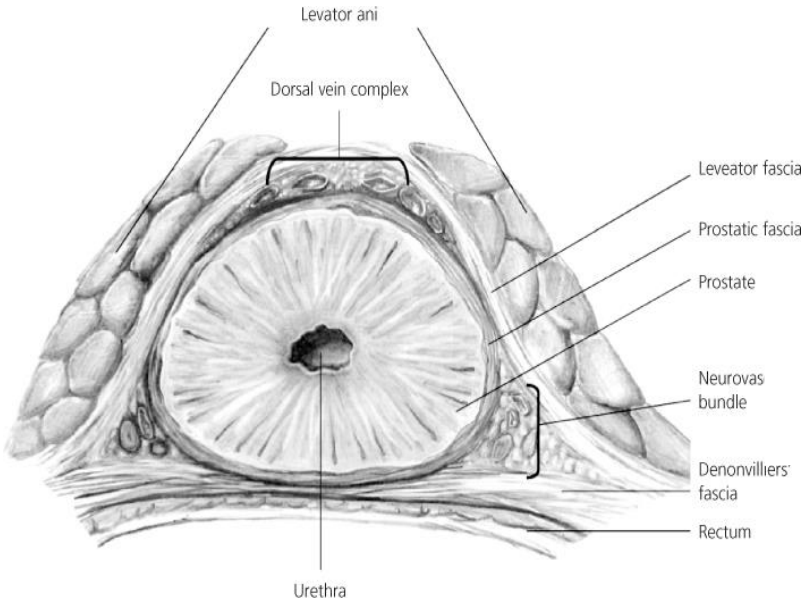

Fig. (2): Fascial relations of the prostate ***(Takenaka et al., 2006).***

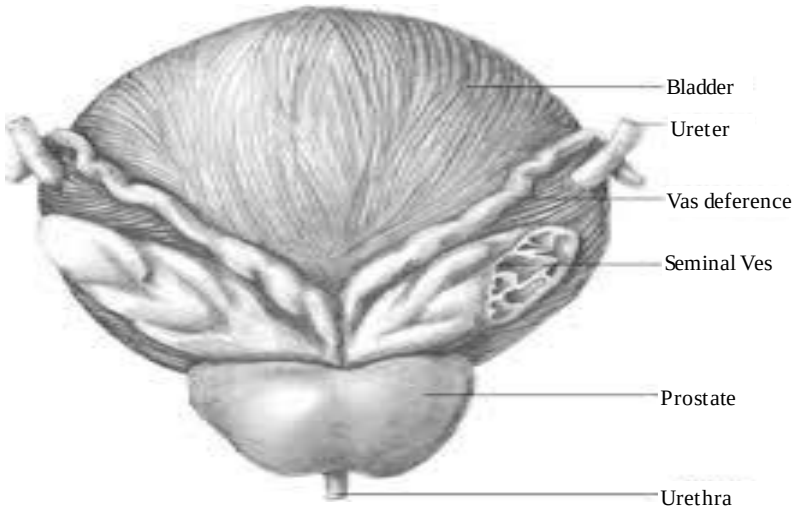

Fig. (3): The posterior relations of the prostate ***(Walz et al., 2010)***.

The prostate gland itself is composed of ducts and alveoli that are lined by tall columnar epithelium (70%) within a stroma of fibromuscular tissue (30%). The urethra takes a curved course, running anteriorly as it proceeds from proximal to distal, such that it ends up close to the prostate's anterior surface. It is lined by transitional epithelium throughout most of its length, and squamous epithelium at its distal end, hence, cancer of the urethra is either transitional cell or squamous cell carcinoma, and not adenocarcinoma as for the prostate. Those urothelial cancers are highly aggressive ***(Tewari et al., 2003).***

A urethral crest runs the length of the prostate and disappears in the striated external urethral sphincter (rhabdosphincter).The prostatic sinuses run alongside the crest and all the prostatic glands discharge into this. The small slit of the prostatic utricle is found on the verumontanum (colliculus).

The ejaculatory ducts open just lateral to the verumontanum and this is where the seminal vesicle contents are discharged (via the vasa) during emission (Figure 4). This allows the seminal fluid to mix with the prostatic secretions such that the final ejaculate is a mixture of these two components ***(Tewari et al., 2003).***

Just proximal to the verumontanum is the external urethral sphincter (EUS) which is a horseshoe-shaped structure which surrounds the prostatic apex craniodorsolaterally, is deficient posteriorly, and has both striated (voluntary) and smooth muscle (involuntary) components. Hence, during a transurethral resection of the prostate (TURP) for benign prostatic enlargement (BPE), the verumontanum serves as the limit for proximal resection so that the EUS is not damaged. The internal urethral sphincter is located at the bladder neck where the prostato-vesical junction is, and is purely under involuntary control (hence, it is composed of smooth muscle). It not only completes the continence mechanism but also makes antegrade ejaculation possible ***(Wang et al., 2005).***

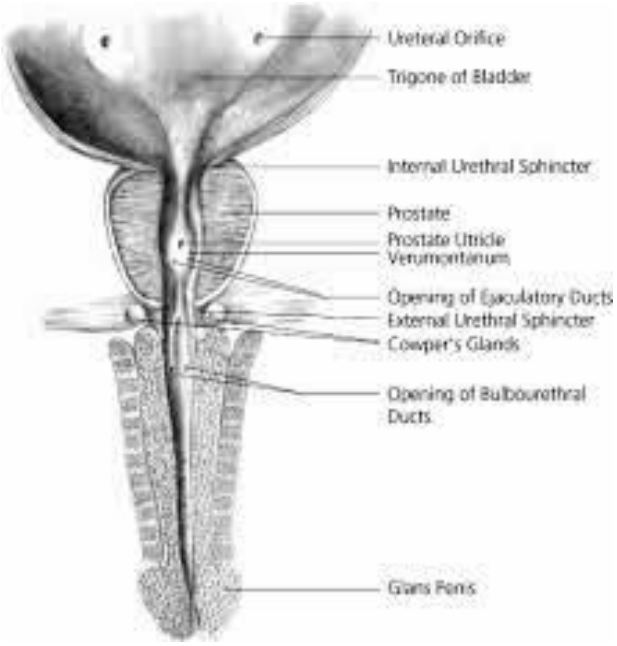

Fig. (4): Cross-sectional anatomy of the male lower urina tract ***(Warde et al., 2011).***

Lymphovascular supply

The arterial supply to the prostate arises from the inferior vesical artery (a branch of the internal iliac artery). As the inferior vesical artery approaches the prostate gland, it becomes the prostatic artery. This then divides into two main groups of arteries: the urethral group and the capsular group. The urethral arteries penetrate the prostato-vesical junction posterolaterally and travel inward, perpendicular to the urethra. They approach the bladder neck in the 1- to-5 o'clock and 7- to-11 o'clock positions, with the largest branches located posteriorly. The capsular artery gives off few small branches to the false capsule of the prostate, but, in the main, runs posterolaterally to the

prostate along with the cavernous nerves (to form the so-called neurovascular bundle), before ending at the urogenital diaphragm ***(Takenaka et al., 2006).***

The venous drainage of the prostate is via the periprostatic plexus of veins to both the dorsal venous complex (of Santorini) superiorly and the inferior vesical vein to the hypogastric vein. These then both drain into the internal iliac vein. The dorsal venous complex (DVC) lies over the anterior aspect of the prostate and is the commonest source of bleeding during a radical prostatectomy. Just lateral to the DVC are the puboprostatic ligaments (PPL) which are condensations of the endopelvic fascia and attach the prostate to the pubic symphysis. The PPL may be important in maintaining continence, and are thus often spared during radical prostatectomy ***(Sylvester et al., 2007).***

As is true of much human anatomy, the lymphatic drainage of the prostate follows that of the veins. Hence, for the prostate, this is to the obturator and hypogastric nodes, and then on to the internal iliac and aortic nodes. It is important to note, however, that prostatic lymphatic drainage is not always predictable in a stepwise manner, and 25% of cases of prostate cancer drain directly to nodes outside the pelvis (internal iliac or higher), making the extent of pelvic lymphadenectomy in high-risk prostate cancer a subject of much debate ***(Wang et al., 2005).***

Zonal anatomy

Throughout the nineteenth century, the prostate was described as having two lobes, with each lobe having its own ducts. In 1906, Howe described a middle (or median) lobe. In 1912, Lowsley described five lobes: two lateral lobes, a posterior lobe, the middle lobe, and an atrophied embryological anterior lobe. However, these lobes were visible only in BPE and not the normal prostate. This lobar concept thus left much to be desired, and in 1968, McNeal replaced it with his concentric zones concept (Figure 5) ***(Green et al., 1992)***.

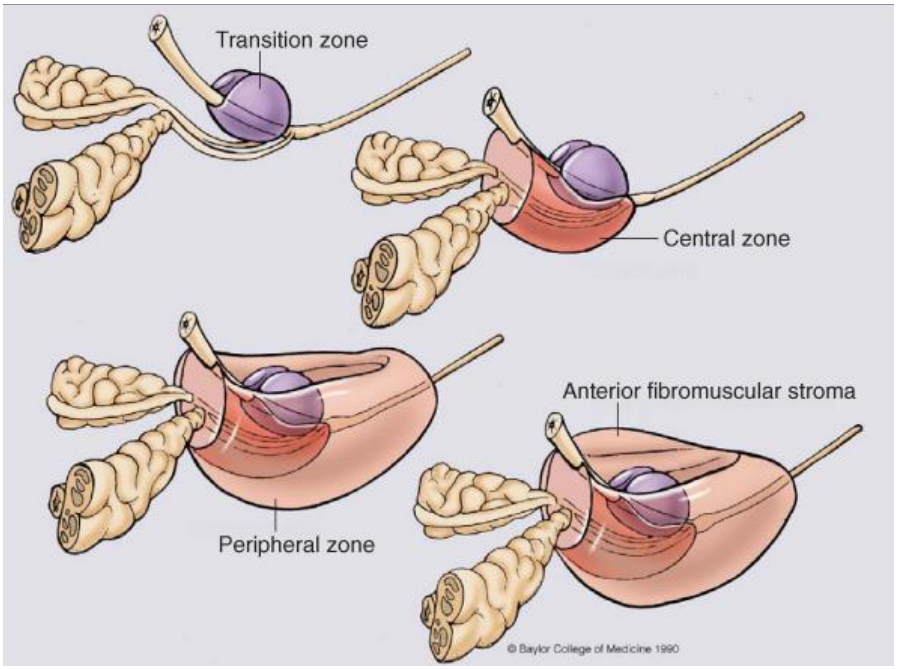

Fig. (5): Zones of the prostate ***(Green et al., 1992).***

The transition zone consists of 5–10% of the glandular tissue of the prostate and is responsible for most of the BPE

that affects the prostates of older men. The prostatic ducts lead into the junction of the pre-prostatic and prostatic urethra, and travel on the posterolateral aspects of the EUS.

The central zone consists of ducts which arise circumferentially around the openings of the ejaculatory ducts. These glands are histologically distinct and appear to be Wolffian (mesonephric) in embryological origin. Only 1–2% of prostate cancers arise from this zone.

The peripheral zone makes up 60% of the prostatic volume. Its ducts drain into the prostatic sinus along the entire length. Some 70% of carcinomas arise from this zone which is also commonly affected by prostatitis (hence, prostatitis and cancer can co-exist in men).

The anterior fibromuscular stroma makes up approximately 30% of the gland, and extends from the bladder neck to the EUS anteriorly. It is compressed in BPE and rarely involved in prostate cancer, though anterior cancers should be suspected when repeat conventional prostatic biopsies which do not sample the anterior aspects well come back negative; hence, the use of saturation or template biopsies to sample these anterior aspects ***(Zelefsky et al., 2011).***

Neuroanatomy

Using dissections of male fetuses and newborn cadavers, Walsh and Donker first demonstrated the course of the

cavernous nerve (the main nerve responsible for erectile function). This led to the concept of the macroscopic neurovascular bundle (NVB) that is located between the endopelvic and prostatic fasciae and runs along the posterolateral aspect of the prostate until it enters the urogenital diaphragm. By Using intraoperative electrical stimulation of intracavernosal pressure revealed that the distribution of cavernous nerves was wider than that of the neurovascular bundle,So the distribution of these nerves can be thought of forming three broad zones: the trizonal concept ***(Takenaka et al., 2007).***

The first zone is the proximal neurovascular plate (PNP) which is located lateral to the bladder neck, seminal vesicles, and branches of the inferior vesical vessels. Proximally, the PNP is derived from the pelvic (inferior hypogastric) plexus and cavernous nerves run in its most distal part. It is not only composed of parasympathetic nerves as commonly thought, but also has sympathetic contributions from the hypogastric nerve. The second zone is the predominant neurovascular bundle (PNB) which corresponds with the classical NVB. The PNB is located between the endopelvic and prostatic fasciae at the posterolateral aspect of the prostate (the same as the NVB). The third zone is the accessory distal neural pathways (ANP). These smaller accessories off the PNB travel in the prostatic and Denonvillier's fasciae, and may serve as additional conduits for