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Review Article

A Comprehensive Review of Prostate Cancer Including other Primary and Secondary Tumours Involving the Prostate Gland

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Abstract

Prostate cancer is the most common non-cutaneous malignancy in men in the Unites States, and the incidence in African American men appears to be on the rise. A somewhat similar trend has also been observed in Africa, especially in Sub-Saharan Africa. It is therefore critical for Pathologists, Urologist and other healthcare providers in Africa to be aware of the various advances in the field of prostate pathology. My goal with this very comprehensive review of prostate cancer is to educate all those in the healthcare community in Africa on the historic aspects of prostate pathology and recent advances in the field of prostate pathology and prostate cancer.

Keywords: Prostate cancer, tumour, review, *primary and secondary tumours*

Historical Background

Pathologists and surgeons alike have been intrigued by the prostate gland for over a century, and have worked tirelessly to better understand the clinicopathological characteristics of both benign and malignant entities involving this organ. The natural history of prostate cancer is that most men will die with the disease, rather than from it. On the other hand, the natural history of enlargement of the prostate gland due to benign prostatic hyperplasia (BPH) has long been known as a phenomenon that is typically associated with old age. Sir Benjamin C. Brodie one of the most respected surgeons and physiologists of the 19th century was quoted as follows "When the hair becomes grey and scanty, when specks of earthy matter begin to be deposited in the tunics of the arteries, and when a white zone is formed at the margin of the cornea, at this same period the prostate gland usually, I might perhaps say invariably, becomes increased in size" (Thompson, 1857). The urinary outlet obstruction usually associated with BPH was one of the symptoms that brought the prostate gland to the attention of physicians in general. Historically, patients with prostate cancer used to present late with metastatic disease typically with bone metastasis and died of their disease prior to diagnosis. Therefore, for several years most of the literature on prostate cancer was derived from autopsy based studies. One of the early large clinical (non-autopsy based) studies of prostate cancer was published by Hugh H. Young, MD, a surgeon at the Johns Hopkins Hospital in 1909 (Young, 1909). In his paper, he gave a detailed clinical, pathological and post-operative analysis of 111 patients with prostate cancer. Eleven years later, a Pathologist that would change our understanding of prostate cancer forever Donald F. Gleason, MD, PhD was born. In 1966 Dr Gleason in collaboration with colleagues at the Minneapolis Veterans Administration Hospital and the Veterans Administration Cooperative Urological Research Group described what is known today as the Gleason Grading system for prostatic adenocarcinoma (Gleason, 1966). The original description of this system was based on a study of 270 patients. Later in 1974, the study was expanded to include 1032 men. With additional experience, Gleason made further refinements to the system in 1974 and 1977 (Figure 1). In this architectural system, all tumours fall into a 5-grade system (1, 2, 3a, 3b, 3c, 4a, 4b, 5a & 5b) based on 9 architectural patterns, representing a continuum of progressively complex morphologies (Gleason, 1966; Baillar *et al*, 1966; Mellinger *et al*, 1967; Gleason and Mellinger, 1974). One of the unique features of this tumour grading system is the fact that it is based purely on architecture and not cytology. Another key and unique aspect of this system is the fact that the Gleason score is based on the sum of the two most common grades/patterns, and not only on the worst grade/pattern. Data obtained from the Gleason score on needle core biopsy in combination with serum prostate specific antigen (PSA) and clinical stage, have been utilized in the development of very powerful nomograms which are predictive of pathological stage and clinical outcome (Partin *et al*, 2001; Kattan and Scardino, 2002; Kattan and Eastham, 2003).

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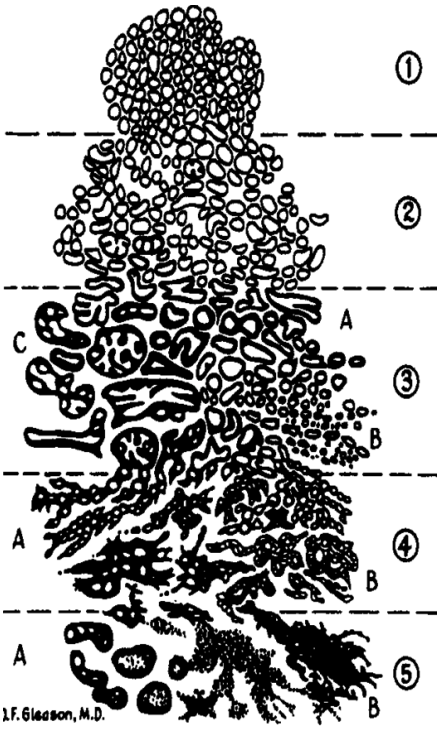

Figure 1:
Original Gleason grading system.

Our understanding of the anatomy of the prostate with regards to sites of origin of prostatic adenocarcinoma and benign prostatic hyperplasia, has also improved over the past several decades. The currently accepted concept of prostate zones (central zone, peripheral zone and transitional zone) is in large part credited to the work of John E. McNeal, M.D. between the late 1960s and early 1980s (McNeal, 1968; McNeal, 1969; McNeal, 1972; McNeal, 1978; McNeal, 1981).

Revisions to the Gleason grading system

The Gleason grading system has stood the test of time for over 40 years, and was revised in 2005 at the International Society for Urological Pathology (ISUP) consensus conference (Epstein *et al*, 2005a). The fields of urology and pathology have evolved over the past four decades with the discovery and utility of serum PSA, immunohistochemical stains, 18 gauge needle core biopsies, improved surgical techniques including open and robotic assisted radical prostatectomy. The vast majority of men enrolled in the Gleason studies presented with clinically advanced disease, due to lack of screening techniques such as the serum PSA. In the past, the majority of patients had prostate biopsies due to positive digital rectal examinations (DRE). Only large bore needles were available, and sampling was restricted to an area with a palpable nodule. The utility of thin 18-gauge needles for obtaining biopsies from consistent and specifically targeted sites, with the now routine ultrasound-guided sextant biopsies were not developed until three decades ago (Hodge *et al*, 1989). This has had an impact on Gleason grading on needle core biopsies, as will be discussed subsequently. The changes that have been made to the original Gleason grading system following the ISUP consensus conference have had a huge impact in contemporary pathology and urology practices worldwide as summarised in Figure 2 (Bjartell, 2006; Helpap and Egevad, 2006; Billis *et al*, 2008; Helpap and Egevad, 2008; Uemura *et al*, 2009; Helpap and Egevad, 2009; Zareba *et al*, 2009; Epstein, 2010). The major issues concerning the various Gleason grades/patterns are as follows:

Gleason grade/pattern 1:

These "glandular proliferations" are composed of a circumscribed nodule of distinct, closely packed, medium-sized glands that are round to oval and relatively uniform, with no infiltrating pattern. The utility of immunohistochemistry, specifically basal cell markers (p63, HMWCK and CK5/6) in routine practice over the years, has improved our understanding of the "glandular proliferations" that were originally assigned a Gleason score of 1+1=2. The vast majority of such cases are actually adenosis (atypical adenomatous hyperplasia) and not cancer (Epstein *et al*, 2005a; Young and Clement, 1987; Hedrick and Epstein, 1989; Jones *et al*, 1991; Gaudin and Epstein, 1994; Trpkov *et al*, 2009). It is therefore recommended that a Gleason score of 1+1=2 should not be assigned to prostatic adenocarcinoma in any specimen (with extremely rare exceptions).

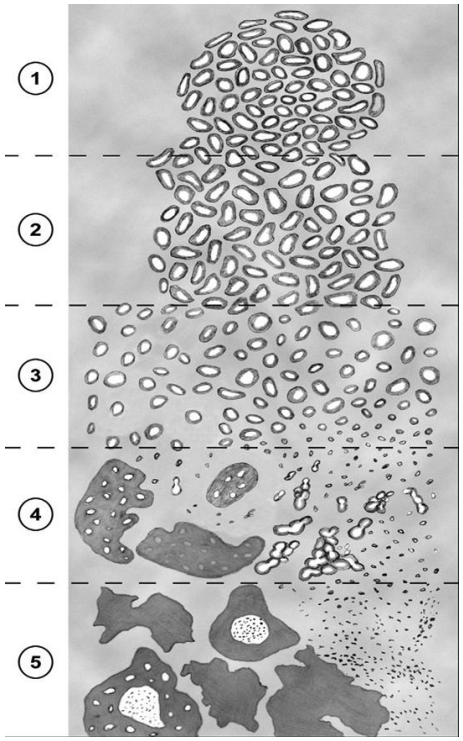

Figure 2:
Post-ISUP consensus conference modified Gleason grading system.

Gleason grade/pattern 2:

Similar to Gleason grade/pattern 1, the glands in Gleason grade/pattern 2 prostatic adenocarcinoma form a fairly circumscribed tumour nodule with rare focal infiltration at the edge of the tumour nodule. The glands are not as closely packed or uniform as Gleason grade/pattern 1. No cribriform glands are allowed in this grade/pattern. These tumours are typically seen on transurethral resection specimens (TURPs) and in multifocal low-grade tumours within radical prostatectomy specimens (transition zone or anterior aspect of the prostate). The utility of thin 18-gauge needles for obtaining needle core biopsies precludes the ability to sample

the entire tumour nodule or determine circumscription of Gleason grade/pattern 2 prostatic adenocarcinoma. The consensus is that a diagnosis of Gleason score 2+2=4 should ''rarely, if ever'' be made on needle core biopsies in contemporary practice (Epstein *et al*, 2005a; Shah, 2009; Latour *et al*, 2008). The corresponding radical prostatectomy specimens in the vast majority of cases assigned a Gleason score of 4 on needle core biopsies have a higher Gleason score, which confirms the inability to reproduce this result.

Gleason grade/pattern 3:

The glands in this category are typically smaller than those seen in Gleason grade/pattern 2. They are characterized by discrete glandular units that vary in size and shape, and have an infiltrating pattern in between benign glands when present. There is now consensus amongst the vast majority of urologic pathologists (post-ISUP consensus conference) that cribriform glands or glands with glomeruloid architecture should not be assigned Gleason grade/pattern 3, and more accurately reflect Gleason grade/pattern 4 (Helpap and Egevad, 2009; Zareba *et al*, 2009; Epstein, 2010; Shah, 2009; Latour *et al*, 2008; Lotan and Epstein, 2009).

Gleason grade/pattern 4:

The tumours in this category are composed of large cribriform glands, cribriform glands with irregular borders, fused microacinar glands, ill-defined glands with poorly formed glandular lumina or glomeruloid/hypernephromatoid glands. Perhaps the most difficult of these patterns for general pathologists to reproduce is "ill-defined glands with poorly formed glandular lumina". The best approach is to exclude the possibility of tangential sectioning of Gleason grade/pattern 3, which may occur in a small adjacent focus. If the glands are very small and with well-formed lumina, they should still be regarded as Gleason grade/pattern 3. It is also important to note that most tumours composed entirely of prostatic ductal adenocarcinoma are by convention assigned a Gleason score of 4+4=8. This variant will be discussed in more detail later.

Gleason grade/pattern 5:

Tumours in this category may have no glandular differentiation, and are composed of solid sheets, cords/files or single cells. The presence of true comedonecrosis (characterized by intraluminal necrotic cells and/or karyorrhexis) in a solid sheet of tumour cells or in cribriform glands (like those seen in Gleason grade/pattern 4), also falls into the Gleason grade/pattern 5 category.

An important issue is the reporting of Gleason score in needle core biopsies when there are three different Gleason grades/patterns present. The current recommendation is that if the worst Gleason grade/pattern is the least prevalent "tertiary pattern", it should influence the final Gleason score and must replace the secondary grade/pattern in the Gleason score. Therefore, the most predominant grade/pattern and the highest grade/pattern should both be incorporated into the Gleason score and there should be no more allusion to tertiary grade/pattern in needle core biopsy reports (Epstein *et al*, 2005a; Shah, 2009; Lopez-Beltran *et al*, 2006; Patel *et al*, 2007; Epstein *et al*, 2007; Trpkov *et al*, 2009). Our Urology colleagues insert the Gleason score into their prognostic tables and nomograms, with no documentation of the "tertiary" grade/pattern (Partin *et al*, 1997; Kattan and Scardino, 2002; Kattan and Eastham, 2003; Makarov *et al*, 2007). It is also recommended that in needle core biopsies with a predominantly higher Gleason grade/pattern and a small secondary component (<5%) of a lower Gleason grade/pattern, the latter should not be incorporated into the Gleason score. Finally, in cases of needle core biopsies with a predominantly lower Gleason grade/pattern and a small secondary component (<5%) of a higher Gleason grade/pattern, the latter should be incorporated into the Gleason score.

Review of handling and reporting of radical prostatectomy specimens

Most large academic institutions and non-academic medical centres have in recent years experienced a significant increase in the number of radical prostatectomies performed, due in part to early detection of prostate cancer and improved surgical techniques, including robotics. There has therefore been a concerted effort by the ISUP over the years to standardize the way radical prostatectomy specimens are handled, and microscopic findings reported. In 2009 the ISUP held a consensus conference on "Handling and Staging Radical Prostatectomy Specimens" at the United States and Canadian Academy of Pathology (USCAP) meeting in Boston (Egevad *et al*, 2011). The recommendations of the society will be the basis of this section. It is also important to note that the recommendations proposed at the ISUP consensus conference have already been incorporated into a number of international guidelines for the reporting of radical prostatectomy specimens (Srigley *et al*, 2009; Kench *et al*, 2011).

Handling of radical prostatectomy specimens:

There have been a number of key papers published over the past two decades that have described the importance of utilizing standardized techniques for handling, processing and reporting prostate cancer in radical prostatectomy specimens (Epstein, 1991; Bova *et al*, 1993; Sakr and Grignon, 1999; Bostwick and Montironi, 1997; Montironi *et al*, 2003; Epstein *et al*, 2005b; Srigley, 2006). The current recommendations for handling radical prostatectomy cases is based on the 2009 ISUP consensus conference (Samaratunga *et al*, 2011). Our clinical colleagues frequently correlate the preoperative radiologically estimated weight of the prostate with our measurements on the grossing bench (Myschetzky *et al*, 1991; Rathaus and Richter, 1991; Nunez-Nateras *et al*, 2010). It is therefore important that we measure the prostate in a standardized fashion. There was consensus that the weight of the prostate without the seminal vesicles should be obtained. In some circumstances (depending on requests by urologists), the weight of the prostate with attached seminal vesicles can also be obtained. The prostate should be measured in three dimensions; vertical (apical to basal), transverse (left to right) and sagittal (anterior to posterior). It is also recommended that the surface of the gland should be inked/painted with at least two colours (to designate laterality) prior to sectioning. This is very important for orientation and also for histologic assessment of "true" surgical margins (Bostwick and Montironi, 1997; Murphy *et al*, 1994; Bong *et al*, 2009). Once the specimen has been inked/painted, tissue can then be obtained for research/tumour banking. The prostate should be fully fixed in formalin prior to sectioning for routine histological review.

The benefits of adequate tissue fixation cannot be over emphasized. Adequate fixation can be achieved by overnight fixation or by enhanced fixation techniques (e.g. microwave fixation) within a few hours (Azumi *et al*, 1990; Leong, 1991; Hafajee and Leong, 2004). When sectioning the prostate, it is recommended that the apex and base regions should be sampled by the cone method/sagittal sectioning. This technique has a number of advantages, including maximizing the ability to adequately assess the margins in these regions. The prostate gland can be completely embedded or partially embedded for histologic examination, as long as the sampling methodology of the latter is clearly documented.

T2 sub staging and prostate cancer volume:

T2 sub staging of prostate cancer continues to be a somewhat controversial issue. Though it is still recommended in the 2010 TNM classification system, several studies have shown flaws in the correlation between T2 sub staging and prognosis (Chun *et al*, 2006; DeCastro *et al*, 2008; Hong *et al*, 2008; Osunkoya and Grignon, 2013; van der Kwast *et al*, 2011; Epstein, 2011). The current recommendation is that the reporting of pT2 sub stages of prostate cancer in radical prostatectomy specimens is optional. In contrast, there is correlation between tumour volume of prostate cancer in radical prostatectomy specimens and histological grade, tumour stage (extraprostatic extension and seminal vesicle involvement), tumour progression (development of metastasis) and patient survival (McNeal *et al*, 1986; Epstein *et al*, 1988; McNeal *et al*, 1988; Partin *et al*, 1989; Humphrey and Vollmer, 1990; Vollmer, 2009). Therefore, it is recommended that some quantitative measure of tumour volume is obtained. The dominant/index tumour was initially thought to be the tumour nodule with the largest volume, however this concept is evolving, and it likely represents the tumour with the highest grade and/or stage (van der Kwast *et al*, 2011; Epstein, 2011; McNeal *et al*, 1988). Incorporation of the location of the dominant/index tumour in the pathology report is acceptable if unequivocal.

Extraprostatic extension, lymphovascular invasion and locally advanced disease:

Extraprostatic extension of prostate cancer is defined as the presence of tumour beyond the confines of the prostate gland. The term extraprostatic extension is preferred to non-specific terms such as capsular invasion, capsular penetration or capsular perforation. Varying diagnostic criteria for extraprostatic extension apply in different regions of the prostate. In the posterior, posterolateral, and lateral regions of the prostate, tumour admixed with periprostatic adipose tissue is the most easily recognized manifestation of extraprostatic extension (Billis, 2004; Sung *et al*, 2006; Miller *et al*, 2010; Magi-Galluzzi *et al*, 2011). It is however important to note that rarely, adipose tissue may be found within the prostate gland (Cohen and Stables, 1998; Nazeer *et al*, 2009). In the anterior, apex and bladder neck regions, adipose tissue may not be present even beyond the confines of the prostate, thus other criteria have to be utilized in these regions. In view of the fact that in these regions, skeletal muscle may be intimately admixed with benign prostatic glands and stroma, the presence of prostate cancer in skeletal muscle does not constitute extraprostatic extension (Magi-Galluzzi *et al*, 2011; Evans *et al*, 2008; Ye *et al*, 2010). There is consensus amongst experts, that when extraprostatic extension is identified, the location and extent should be documented. There are a number of approaches to measuring the extent of extraprostatic extension (focal vs. established, unilateral vs. bilateral, unifocal vs. multifocal, greatest linear dimension, radial dimension, volumetric measurements etc.), each with its strengths and weaknesses (Epstein *et al*, 1993; Wheeler *et al*, 1998; Davis *et al*, 1999; Sohadya *et al*, 2000; Sung *et al*, 2007). In the past, bladder neck involvement by prostate cancer was staged as pT4, however several studies have demonstrated that bladder neck involvement is associated with a similar risk of progression as extraprostatic extension (pT3a) and lower risk of progression than seminal vesicle invasion (pT3b) (Greene 2002; Rodriguez-Covarrubias *et al*, 2008; Buschemeyer *et al*, 2008, Zhou *et al*, 2009; Ruano *et al*, 2009). There is now consensus that bladder neck involvement by prostate cancer should be staged as pT3a (Magi-Galluzzi *et al*, 2011; Edge *et al*, 2010).

Documentation of the presence of angiolymphatic invasion in radical prostatectomy is critical because of the strong association with higher Gleason score, positive surgical margins, extraprostatic extension, seminal vesicle invasion and poor outcome (Magi-Galluzzi *et al*, 2011; Cheng *et al*, 2005; McNeal and Yemoto, 1996; Shariat *et al*, 2004).

The highest pathological stage of prostate cancer (pT4) is defined as direct invasion of the urinary bladder (beyond bladder neck), rectum, pelvic floor muscles and pelvic side wall (Bates and Baithun, 2000; Bowrey *et al*, 2003; Lane *et al*, 2008; Hoffman *et al*, 2009).

Seminal vesicles and lymph nodes:

It has been known for several years that seminal vesicle invasion (pT3b) by prostatic adenocarcinoma is a predictor of poor outcome (Debras *et al*, 1998; Tefilli *et al*, 1998; Potter *et al*, 2000). Seminal vesicle invasion is currently defined as invasion of the muscular wall of the extraprostatic seminal vesicle by tumour (Berney *et al*, 2011). It is therefore recommended that the junction of the prostate and extraprostatic seminal vesicle should always be obtained for adequate evaluation of contiguous spread of tumour.

Documentation of lymph node metastasis is important for adequate staging of prostate cancer in radical prostatectomy specimens. As expected, this finding has also been associated with poor outcome in view of the fact that most of the patients with lymph node metastasis typically have high Gleason scores and tumour burden (Datta *et al*, 2010; Eggener *et al*, 2011). The size/diameter of the largest metastatic focus appears to be one of the most significant predictors of cancer specific survival (including number of positive lymph nodes and presence of extranodal extension) (Cheng *et al*, 1998; Boormans *et al*, 2008).

Surgical Margins:

Similar to other organ systems, it is critical to document margin status in radical prostatectomy specimens. A positive surgical margin is defined as tumour (extraprostatic or intraprostatic) that extends to the inked surface (surgical tissue plane) of the prostate gland (Epstein *et al*, 2005b; Chuang and Epstein, 2008; Tan *et al*, 2011). However, unlike other organs (e.g. breast) even if the tumour is within 1 mm from the surgical resection margin, it is still considered negative. Several studies have confirmed the lack of correlation between "close" negative margins and

postoperative biochemical failure or disease progression, typically associated with "true" positive margins (Bong *et al*, 2009; Epstein, 1990; Emerson *et al*, 2005). It is also recommended to document the location and extent of positive margins.

Update on variants of prostatic adenocarcinoma

Although the vast majority of prostate cancers are typical/conventional acinar prostatic adenocarcinoma, about 5-10% of cases are considered to be variants (Grignon, 2004; Mazzucchelli *et al*, 2008).

Mucinous Adenocarcinoma of the Prostate:

Mucinous adenocarcinoma of the prostate (also referred to as colloid carcinoma), is a rare morphologic variant of prostate cancer. The incidence of mucinous adenocarcinoma of the prostate, defined by the presence of more than 25% of the tumour composed of glands with extraluminal mucin, is approximately 0.2% (Epstein and Lieberman, 1985; Ro *et al*, 1990; Osunkoya and Epstein, 2007; Osunkoya *et al*, 2008). The presence of intraluminal mucin, seen in up to one-third of prostatic adenocarcinomas, should not be referred to as mucinous adenocarcinoma of the prostate. In the past, there was debate about whether to assign a Gleason score to these tumours. Recent data supports grading mucinous prostate carcinomas on the basis of the underlying architectural pattern (well-formed glands, poorly formed glands, cribriform glands etc.) rather than assuming that all of these tumours are aggressive (Osunkoya *et al*, 2008a). Data from recent large studies have demonstrated that mucinous adenocarcinoma of the prostate treated by radical prostatectomy is not more aggressive than usual non-mucinous prostatic adenocarcinoma, and is potentially even less aggressive (Osunkoya *et al*, 2008a; Lane *et al*, 2006; Osunkoya *et al*, 2008b).

Prostatic Ductal Adenocarcinoma:

Prostatic ductal adenocarcinoma is a rare variant of prostate cancer that was previously referred to as endometrioid carcinoma, endometrial carcinoma or papillary ductal carcinoma (Melicow and Pachter, 1967; Bostwick *et al*, 1985; Epstein and Woodruff, 1986; Ro *et al*, 1988). The incidence of the pure form of this variant is approximately 0.5-1.0 %, however the incidence of the more common mixed prostatic ductal adenocarcinoma and conventional acinar adenocarcinoma is approximately 5% (Grignon, 2004; Mazzucchelli *et al*, 2008). These tumours are composed of papillary fronds lined by pseudostratified columnar epithelial cells with amphophilic cytoplasm. Basal cells are typically absent, but may be present focally and identified by basal cell markers in a patchy distribution. Prostatic ductal adenocarcinoma typically arises from the periurethral region but can extend to the peripheral zone and extraprostatic tissue including the bladder, confirming the aggressive nature of the majority of these tumours. A Gleason score of 4+4=8 is assigned to tumours composed entirely of classic prostatic ductal adenocarcinoma. If comedonecrosis is present, then the Gleason score has to be increased accordingly. It should also be noted that a Gleason score of 3+3=6 should be assigned to tumours composed entirely of the recently described "High-grade prostatic intraepithelial neoplasia like ductal adenocarcinoma of the prostate" (Tagore and Epstein, 2008; Lee *et al*, 2010). Although immunohistochemical stains are typically positive for PSA and PSAP, serum PSA level may occasionally be normal.

Intraductal Carcinoma of the Prostate:

Although there are some similarities between prostatic ductal adenocarcinoma and intraductal carcinoma of the prostate (including bad prognosis), they are somewhat distinct entities. Intraductal carcinoma of the prostate is composed of an expansile proliferation of malignant prostatic epithelial cells that spans the entire lumen of prostatic ducts or acini, while the normal architecture of ducts or acini are still maintained (Kovi *et al*, 1985; McNeal and Yemoto, 1996; Guo and Epstein, 2006; Cohen *et al*, 2007; Henry and Evans, 2009). In contrast to prostatic ductal adenocarcinoma, in intraductal carcinoma of the prostate, basal cells are always present (distinguishes this from conventional cribriform Gleason pattern/grade 4 cancer), tumour cells are typically cuboidal, and may form cribriform structures with small rounded lumina and/or micropapillary tufts lacking fibrovascular cores. More importantly, intraductal carcinoma of the prostate should be distinguished from high grade prostatic intraepithelial neoplasia and urothelial carcinoma. Most cases of intraductal carcinoma of the prostate have a Gleason score of 4+4=8 or higher.

Other variants of prostatic adenocarcinoma include but are not limited to pseudohyperplastic adenocarcinoma, atrophic adenocarcinoma, adenosquamous carcinoma, foamy gland adenocarcinoma, adenocarcinoma with carcinoid-like morphology, adenocarcinoma with neuroendocrine differentiation, adenocarcinoma with Paneth-like neuroendocrine differentiation, signet ring cell adenocarcinoma, and adenocarcinoma with sarcomatoid differentiation.

Review of treatment effect on the prostate

Though the number of radical prostatectomy cases performed at most large academic institutions and non-academic medical centres is increasing, the rate of utility of other alternative therapeutic options including more recent modalities is also on the rise. The histology of both benign and neoplastic prostatic tissue may be significantly altered by these alternative therapeutic modalities. This can make accurate interpretation and reporting of post-treatment prostate specimens somewhat challenging. It is therefore important for pathologists to be aware of the changes and potential pitfalls typically associated with these various therapeutic modalities.

Androgen deprivation therapy:

Androgen deprivation therapy is also referred to as hormonal therapy or anti-androgen therapy. In the past, androgen deprivation therapy was achieved by bilateral orchiectomy with or without oestrogen therapy, for locally advanced or metastatic prostate cancer (Scott and Benjamin, 1948; O'Connor and Sokol, 1960; Klugo *et al*, 1981; Crawford, 1990).

A more effective approach which consists of a combination of luteinizing hormone-releasing hormone agonists such as Lupron and pure anti-androgens (steroidal, non-steroidal, or non-classic) such as flutamide, is used to achieve chemical castration (Faure *et al*, 1983; Crawford, 1989; Auclerc *et al*, 2000; Fluchter *et al*, 2007). Pathologists may come across needle core biopsies, TURP or radical

prostatectomy specimens from patients that have received these therapies. A number of characteristic changes may be identified following androgen deprivation therapy and these vary depending on the specific agents used, duration of therapy and dose of therapy (Petraki and Sfikas, 2007; Epstein and Netto, 2008; Tetu, 2008; Evans *et al*, 2011). The changes typically seen in benign glands include basal cell hyperplasia, urothelial metaplasia, squamous metaplasia and variable stromal fibrosis. Prostate cancer with androgen deprivation therapy effect is characterized by bland looking single cells in small clusters or files, composed of xanthomatous cytoplasm and pyknotic nuclei with inconspicuous nucleoli. These are typically seen in a background of variable stromal fibrosis, occasionally in between benign glands (retaining the infiltrative nature of the original cancer). Some cases of transformation to adenosquamous carcinoma have also been described (Grignon, 2004; Mazzucchelli *et al*, 2008; Parwani *et al*, 2004). Another interesting phenomenon is the development of neuroendocrine differentiation in tumours following androgen deprivation therapy (Ito *et al*, 2001; Hirano *et al*, 2004; Alberti, 2010; Berruti *et al*, 2010). Unfortunately, this finding tends to be associated with poor prognosis, tumour progression and androgen independence. In cases that are challenging on H&E, immunohistochemical stains for basal cell markers (p63, HMWCK, CK5/6) and P504S/alpha methyl acyl CoA racemase (AMACR) retain the typical immunohistochemical profile of hormone naive prostate cancer. Most importantly, tumours that show androgen deprivation therapy related changes should not be assigned a Gleason score.

Radiation therapy:

The use of radiation therapy (external beam and/or brachytherapy/interstitial therapy) in the management of localized prostate cancer with a curative intent is one of the most common alternatives to radical prostatectomy (Bagshaw *et al*, 1993; Zagars *et al*, 1993; Pollack *et al*, 2000; Kupelian *et al*, 2004; Nilsson *et al*, 2004; Pisansky, 2006). As pathologists, we have to familiarize ourselves with the various changes that occur in the prostate following radiation therapy, in view of the fact that we may encounter needle core biopsies, TURP or radical prostatectomy specimens with these changes. Prostate biopsies are typically performed in the post-radiation therapy setting in patients who have developed biochemical failure (elevated PSA levels). TURP may be performed to relieve urinary obstruction secondary to benign prostatic hyperplasia, in patients who have had prior radiation therapy (Patel *et al*, 1997; Kollmeier *et al*, 2005). Salvage radical prostatectomies may also be performed as a more definitive therapy in patients who have failed radiation therapy (Cheng *et al*, 1999; Leonardo *et al*, 2009; Seabra *et al*, 2009; Heidenreich *et al*, 2010). Changes typically seen in the benign prostatic glands include; atrophic cytoplasm of secretory cells, degenerative nuclear atypia and nuclear pleomorphism predominantly involving basal cells, multilayering of basal cells and preservation of glandular architecture (Epstein and Netto, 2008; Bostwick *et al*, 1982; Gaudin *et al*, 1999; Magi-Galluzzi *et al*, 2003; Bostwick and Cheng, 2008). Prostate cancer with radiation therapy effect is typically associated with the following changes; single cells or clusters of cells with abundant vacuolated cytoplasm and small nuclei without nucleoli. Other features typically associated with prostate cancer including perineural invasion and infiltrative growth pattern are preserved. Prostate cancer with radiation therapy effect also maintains the immunohistochemical profile of unradiated prostate cancer including negative expression of basal cell markers (p63, HMWCK, CK5/6) and positive expression of P504S/alpha methyl acyl CoA racemase (AMACR). It is also important to note that tumours which show radiation therapy related changes should not be assigned a Gleason score.

Cryotherapy:

Another therapeutic option for prostate cancer both in the initial and salvage setting is cryotherapy (cryoablation). The two main mechanisms of cell death produced by cryotherapy are by direct cellular toxicity from disruption of the cellular membrane by "iceball crystals" and vascular compromise from thrombosis and ischemia. Cryotherapy is a relatively inexpensive and somewhat effective treatment option for prostate cancer that can be applied to the whole gland (total) or a focal area/lobe (subtotal). There is some evidence to support the utility of whole-gland cryotherapy as a treatment option for localized prostate cancer, based on long-term biochemical results and post-treatment biopsy data (Shinohara, 2007; Ritch and Katz, 2009; Pisters, 2010). Focal or subtotal cryotherapy is more controversial, and is currently an experimental option for patients with small volume low-grade cancers (Truesdale *et al*, 2010; Tsivian *et al*, 2010; Jones, 2007; Yoon *et al*, 2008). The histopathological changes typically seen in prostate tissue following cryotherapy include; extensive necrosis, stromal hyalinization, stromal fibrosis, granulomatous inflammation, microcalcifications, squamous and/or urothelial metaplasia, hemosiderin deposition, stromal oedema, secondary bacterial colonization and haemorrhage (Epstein and Netto, 2008; Bostwick and Cheng, 2008; Borkowski *et al*, 1996; Chin *et al*, 2003; Izawa *et al*, 2006).

Unlike the previous therapeutic options discussed, residual prostate cancer identified in the post-cryotherapy setting does not typically have therapy related changes, and therefore a Gleason score should be assigned. This is due to the fact that in most of these cases, the areas with residual cancer were not adequately frozen, and may also represent new tumours.

Other therapeutic options for prostate cancer include but are not limited to; high intensity focused ultrasound, vascular targeted photo dynamic therapy, interstitial laser thermotherapy, microwave thermotherapy, chemotherapy, immunotherapy, nutritional/herbal therapy and targeted molecular therapy.

Review of other primary and secondary tumours involving the prostate

Although prostatic adenocarcinoma is the most common malignant neoplasm of the prostate that we encounter in routine practice, there are several other primary and secondary neoplasms that may involve the prostate gland.

Primary (Epithelial)

Small Cell Carcinoma: Primary small cell carcinoma of the prostate is a rare and aggressive neoplasm with distinctive clinicopathological characteristics, including disseminated metastasis (Grignon, 2004; Mazzucchelli *et al*, 2008; Tetu *et al*, 1987; Christopher *et al*, 1991; Oesterling *et al*, 1992;

Nadig *et al*, 2001; Wang and Epstein, 2008). Small cell carcinoma of the prostate was first described over three decades ago, and our understanding of the pathobiology of this aggressive tumour has improved over the years (Wenk *et al*, 1977). Small cell carcinomas irrespective of the site of origin have very similar morphological features. The determination of primary origin thus occasional poses a challenge in some cases, especially since immunohistochemical stains such as TTF-1, synaptophysin, chromogranin and CD56 are positive in most small cell carcinomas irrespective of site of origin. A characteristic feature of pure primary small cell carcinoma of the prostate is the fact that patients typically have low serum PSA levels and a poor response to androgen deprivation therapy. Interestingly, a number of patients have developed small cell carcinoma of the prostate following androgen deprivation therapy for conventional prostatic adenocarcinoma (Valle *et al*, 1996; Miyoshi *et al*, 2001; Nemoto and Tomita, 2007). One of the recent advances in our understanding of primary small cell carcinoma of the prostate, is the fact that gene fusions between members of the ETS-related gene (ERG) and transmembrane protease, serine 2 (TMPRSS2), have been identified in a significant number of these tumours, compared to small cell carcinoma from other sites (Han *et al*, 2009; Lotan *et al*, 2011; Williamson *et al*, 2011). This finding confirms the fact that primary small cell carcinoma of the prostate likely represents de-differentiation of conventional prostatic adenocarcinoma. There is also agreement amongst experts that a Gleason score should not be assigned to pure small cell carcinoma of the prostate.

Basal Cell Carcinoma: Prostatic adenocarcinoma arises from the secretory cells of the prostatic glands and acini. In contrast, basaloid proliferations of the prostate including basal cell hyperplasia and basal cell carcinoma arise from basal cells of glands typically located in the transition zone, though in some cases peripheral zone involvement may be seen. The distinction between these two entities may occasionally be challenging (Grignon *et al*, 1988; Iczkowski *et al*, 2003; McKenney *et al*, 2004; Hosler and Epstein, 2005; Ali *et al*, 2007). Basal cell carcinoma is characterized by variably sized basaloid nests with anastomosing areas, eosinophilic luminal lining and foci of necrosis. The nests typically have an infiltrative growth pattern, and may elicit a desmoplastic stromal response. Cribriform glands with adenoid cystic like areas may also be seen. Immunohistochemical stains are positive for p63, HMWCK, Bcl2, CD10, Ki-67 (increased expression) and negative for PSA and PSAP (Ali *et al*, 2007; Yang *et al*, 1998). A Gleason score should not be assigned to basal cell carcinoma.

Urothelial Carcinoma: Primary urothelial carcinoma of the prostate is rare and typically arises from the prostatic urethra or prostatic ducts and acini (Greene *et al*, 1976; Algaba *et al*, 1985; Cheville *et al*, 1998). Although a number of cases are composed of urothelial carcinoma in situ of the prostatic urethra or colonization of prostatic ducts and acini, a diligent search for possible foci of invasion into the periurethral soft tissue and prostatic stroma should be made. It is also important to note that prostatic stromal invasion due to primary urothelial carcinoma of the prostate and prostatic stromal invasion due to transmural invasion of a bladder primary are staged as pT2 and pT4a respectively (Edge *et al*, 2010).

Mucin-Producing Urothelial Type Adeno-carcinoma (Prostatic Urethral Adenocarcinoma): Rarely, in-situ and invasive tumours analogous to mucinous adenocarcinoma of the urinary bladder may arise from the prostatic urethra. These tumours are referred to as mucin-producing urothelial type-adenocarcinoma or prostatic urethral adenocarcinoma (Osunkoya and Epstein, 2007; Tran and Epstein, 1996; Ortiz-Rey *et al*, 2004; Curtis *et al*, 2005; Osunkoya *et al*, 2007). Mean patient age at diagnosis of this aggressive tumour is 72 years (range 58 to 93 years). In view of the fact that urothelial-type adenocarcinoma of the prostate is identical in its morphology and histogenesis to mucinous adenocarcinoma of the bladder, the latter must be excluded before this diagnosis is rendered. Other tumours that should be considered in the differential diagnosis and excluded include mucinous prostatic adenocarcinoma and mucinous colorectal adenocarcinoma involving the prostate (Osunkoya and Epstein, 2007; Osunkoya *et al*, 2008; Osunkoya *et al*, 2007). Immunohistochemical stains are typically positive in the tumour cells for CK7 and negative for PSA, PSAP, b-catenin and CDX2.

Other primary epithelial and epithelial-like tumours involving the prostate include but are not limited to squamous cell carcinoma, Wilms' tumour, clear cell adenocarcinoma, neuroblastoma, and melanoma.

Primary (Mesenchymal): Benign or malignant mesenchymal neoplasms of the prostate are rare. Apart from smooth muscle tumours involving the prostate, another group of tumours which arise from the specialized prostatic stroma are also recognized as distinct entities. These tumours have been classified into prostatic stromal tumours of uncertain malignant potential (STUMP) and prostatic stromal sarcoma (Eble *et al*, 2004; Herawi and Epstein, 2006; Hansel *et al*, 2007).

STUMP: These tumours arise from the specialized hormonally responsive stroma of the prostate. There are at least four main histological patterns of STUMP; hypercellular stroma with scattered atypical/ degenerative cells, hypercellular stroma with bland stromal cells, myxoid pattern and ''phyllodes'' like pattern, with the first two being the most common. The various histological patterns of STUMP may be confused with BPH. However it should be noted that some cases of STUMP may have the potential to undergo malignant transformation, or may be intimately associated with stromal sarcoma, and thus should be recognized as a distinct entity from BPH. STUMP may be associated with various epithelial proliferations, and it is therefore thought that this may represent epithelial-mesenchymal crosstalk (Nagar and Epstein, 2011). Prostatic adenocarcinoma may also occasionally be identified in cases of STUMP.

Stromal sarcoma: These aggressive tumours also arise from the specialized hormonally responsive stroma of the prostate. However, unlike STUMP these tumours are characterized by increased mitotic activity, non-degenerate nuclear pleomorphism and necrosis. Stromal sarcoma may also extend beyond the prostate and metastasize.

Other primary mesenchymal tumours of the prostate include but are not limited to inflammatory myofibroblastic tumour (IMT), solitary fibrous tumour (SFT), leiomyoma, leiomyosarcoma, and rhabdomyosarcoma.

Secondary Tumours: Secondary tumours involving the prostate excluding those from direct extension are rare. Metastasis from other sites to the prostate typically arise from the lung, gastrointestinal tract, skin (melanoma), kidney, testicle and endocrine organs, with an incidence ranging from 0.1-6% depending on the series (Johnson *et al*, 1974; Zein *et al*, 1985; Bates and Baithun, 2002). In view of the proximity to the prostate, the most common secondary tumour involving the prostate though direct extension is from the urinary bladder. Colorectal tumours including colorectal adenocarcinoma and gastrointestinal stromal tumour (GIST) may also occasionally involve the prostate.

Urothelial Carcinoma: The incidence of prostatic involvement by urothelial carcinoma of the bladder in radical cystoprostatectomy specimens ranges from 12% to 48% (Schellhammer *et al*, 1977; Revelo *et al*, 2004). Prostatic stromal invasion in this setting typically occurs by direct transmural extension of urothelial carcinoma from the bladder primary, and is designated as stage pT4a (Edge *et al*, 2010; Oliva *et al*, 2011). The challenge occurs if the tumour is detected first on needle core biopsy or TURP, in the absence of a known history of urothelial carcinoma. Making the distinction between urothelial carcinoma and prostatic adenocarcinoma is critical in view of the different therapeutic options and approaches for these tumours. In cases that are challenging on H&E, readily available immunohistochemical stains (PSA, PSAP, p63, HMWCK, uroplakin and thrombomodulin) can aid in the distinction between these two entities in most cases. In the few cases in which the distinction can still not be made with the previous markers, additional immunohistochemical stains (P501S, PSMA, NKX3.1 and pPSA) which are typically positive even in advanced prostatic adenocarcinoma, and negative in urothelial carcinoma are useful (Chuang *et al*, 2007).

Colorectal adenocarcinoma: Despite the proximity of the colorectum to the prostate, involvement of the prostate from this site in clinical specimens is rare with only very few case reports and series in the literature (Osunkoya *et al*, 2007). Although most patients present with classic symptoms of colonic cancer, patients may present with obstructive uropathy due to involvement of the prostatic urethra, and may therefore be diagnosed for the first time following TURP (Osunkoya *et al*, 2007). Histologically, the two most common entities that are in the differential diagnosis of colorectal adenocarcinoma invading the prostate are prostatic ductal adenocarcinoma and adenocarcinoma of the bladder. In addition, the various patterns of infiltrating colorectal adenocarcinoma, including mucinous, enteric, and signet-ring cell–type may also be seen in prostatic adenocarcinoma. Most colonic adenocarcinomas are positive for CDX2, villin, β-catenin, mucins (MUC1 and MUC3), CEA, and B72.3; and all are negative for prostate specific markers.

GIST: A challenging and well described scenario is one in which a patient has a positive DRE and on imaging appears to have a mass involving the prostate or extending in between the prostate and the colorectum. One of the entities to consider in this setting is GIST. Most cases of 'prostatic' GIST are sampled on needle core biopsy, and one of the clues to the diagnosis is the absence of prostatic glands and stroma in the cores that are involved. This is due to the fact that the vast majority of these tumours arise from the colorectal wall, and are not true GIST of prostatic origin. Unfortunately, if GIST is misdiagnosed as a sarcoma, patients may undergo unnecessary pelvic exenteration or chemo-radiation therapy (Madden *et al*, 2005). GISTs in this location are similar to those at other sites, thus the tumours are typically positive for CD117, CD34 and DOG1.

Update on biomarkers of prostate cancer

The majority of patients with prostate cancer are clinically asymptomatic with early-stage, organ-confined disease, and more than 50% of men who reach the age of 80 years develop clinically insignificant prostate cancer. However, a subpopulation of patients with prostate cancer progress to highly aggressive, androgen-independent metastatic disease, which is inevitably fatal (Long *et al*, 2011). One of the challenges in current prostate cancer research is to develop effective biomarkers to determine which patients are likely to progress to aggressive or metastatic disease, to aid clinicians in deciding on the appropriate course of treatment. In patients that have elevated serum PSA levels with or without a positive DRE, prostate needle core biopsies remain the gold standard for establishing the diagnosis of prostate cancer. Clinicopathological parameters including clinical stage, Gleason score, pathological stage and serum PSA levels continue to be important tools that aid in the management and prognostication of prostate cancer (Partin *et al*, 1997; Stephenson *et al*, 2005; Stephenson *et al*, 2006). However, it has also been recognized over the years that the diagnostic, prognostic and predictive power of prostate biopsies and the above parameters need improvement. Over the past two decades, several biomarkers have been identified that have enhanced our ability to diagnose and predict progression of prostate cancer.

Diagnostic markers in the form of immunohistochemical stains have been utilized over the years in cases in which the morphological findings are insufficient for a definitive diagnosis of prostate cancer at both primary and metastatic sites (especially when mimickers are being considered). These include markers that are typically positive in prostatic adenocarcinoma (PSA, PSAP, PSMA, p504s/AMACR, PSMA, P501s/prostein, NKX3.1) and basal cell markers (p63, HMWCK and CK5/6) which are typically negative in prostatic adenocarcinoma (Stein *et al*, 1982; Bates *et al*, 1982; Epstein, 1993; Wright *et al*, 1995; Green and Epstein, 1999; Luo *et al*, 2002; Shah *et al*, 2002; Rubin *et al*, 2002; Zhou *et al*, 2002; Zhou *et al*, 2003; Magi-Galluzzi *et al*, 2003; Sanderson *et al*, 2004; Farinola and Epstein, 2004; Hameed and Humphrey, 2005; Sheridan *et al*, 2007; Trpkov *et al*, 2009). These markers should however be interpreted with caution in view of the fact that several mimickers may stain like prostatic adenocarcinoma, and aberrant expression of basal cell markers may occasionally occur (Oliai *et al*, 2002; Ali and Epstein, 2008; Osunkoya *et al*, 2008). A relatively new addition to the panel of markers that are positive in prostate cancer is ERG. The recently discovered TMPRSS2: ERG gene rearrangement has been identified as a highly specific alteration in prostate cancer, present in 40%-

70% of cases (Tomlins *et al*, 2005; Clark and Cooper, 2009; Esgueva *et al*, 2010; Scheble *et al*, 2010). At the time of discovery and for the few years that followed, the ERG rearrangement status could only be assessed by fluorescence in situ hybridization (FISH). However, a number of recent studies have utilized a novel anti-ERG monoclonal antibody in the evaluation and diagnosis of prostate cancer with great success (Furusato *et al*, 2010; Park *et al*, 2010; Yaskiv *et al*, 2011; He *et al*, 2011).

The histological, clinical and molecular heterogeneity of prostate cancer poses a major challenge in the development of adequate prognostic markers. Prognostic and predictive factors in prostate carcinoma are stratified into three main categories. Category-I are factors that are considered proven to be useful in clinical practice (e.g. preoperative PSA, pathological stage, Gleason score and surgical margin status). Category-II are factors that have been extensively studied but await statistically robust trials (e.g. tumour volume, histological subtype and DNA ploidy analysis). Category-III are factors that still need additional studies to assure their prognostic utility prior to undergoing clinical trials (Bostwick *et al*, 1999; Netto and Epstein, 2010; Netto, 2011). Unfortunately, the majority of prognostic biomarkers available today fall into the latter category. Some of the prognostic biomarkers that have been studied, include but are not limited to; Ki-67 (proliferative index), tumour suppression genes (p53, p21, p27, NKX3.1, PTEN, retinoblastoma gene 'Rb'), oncogenes (Bcl2, c-myc, EZH2 and HER2/neu), adhesion molecules (CD44, E-Cadherin), PI3K/AKT/ mTOR pathway, apoptosis regulators (survivin and transforming growth factor beta-1), androgen receptor status, neuroendocrine differentiation markers, and prostate tissue lineage specific markers expression (PSA, PSAP and PSMA), including protein-coding genes and miRNA genes (RAD23B, FBP1, TNFRSF1A, CCNG2, NOTCH3, ETV1, BID, SIM2, LETMD1, ANXA1, miR-519d, and miR-647) (Long *et al*, 2011; Netto and Epstein, 2010; Wikstrom *et al*, 2000; Sanchez *et al*, 2006; Kremer *et al*, 2006).

Conclusions

Our understanding of prostate cancer has clearly improved over the years, and it is therefore important for pathologists in Africa to adopt current standard practices regarding handling and reporting of prostate cancer and accurately assigning Gleason scores to patients diagnosed with prostate cancer. It is also critical for pathologists in Africa to be aware of the variants of prostate cancer, and other primary and secondary tumours that may involve the prostate gland. Finally, it is also important for pathologists in Africa to be aware of the critical role of immunohistochemistry and other ancillary studies that may aid in the diagnosis and prognosis of prostate cancer.

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