Rare Tumours of the Prostate Gland

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CHAPTER 1

ADENOCARCINOMA OF THE PROSTATE GLAND: A PREAMBLE OVERVIEW INTRODUCTION TO RARE TUMOURS OF THE PROSTATE GLAND

BLURB

Adenocarcinoma of the prostate gland is a common malignant neoplasm that is encountered throughout the world and its treatment options have been well-outlined. Nevertheless, there are other types of neoplasms of the prostate gland that are rare and there are no guidelines regarding the treatment of these rare neoplasms. Furthermore, difficulties tend to be experienced in establishing the diagnosis of a number of these rare neoplasms as well as at times the diagnosis of some rare neoplasms of the prostate gland are missed or the neoplasms are misdiagnosed. Before learning about rare neoplasms of the prostate gland, it is important for all clinicians to be familiar with the features of the more common adenocarcinoma of the prostate gland in order to appreciate the differences. This chapter contains details about the common adenocarcinoma of the prostate gland.

INTRODUCTION

Adenocarcinoma of the prostate gland is the most common type of prostate cancer that afflicts men all over the world. Nevertheless, there are rare types of prostate cancer which tend to be reported sporadically throughout the world. Before going on to learn and update knowledge about rare types of prostate cancer, it would be important that clinicians are up to date with their bird's eye view information and knowledge about adenocarcinoma of the prostate gland. The ensuing documentation contains an overview information related to adenocarcinoma of the prostate gland as a preamble introduction to the book on rare tumours of

prostate cancer which have been narrated in detail in the subsequent chapters of the book.

OVERVIEW OF ADENOCARCINOMA OF THE PROSTATE GLAND

Definition / general statement

- Adenocarcinoma of the prostate gland is the most common malignancy of the prostate gland. [1]
- Adenocarcinoma of the prostate gland does originate from prostatic secretory epithelium. [1]

Essential features of adenocarcinoma of prostate gland [1]

- It has been pointed out that clinical and radiology imaging features are neither sensitive nor specific for confirmation of the diagnosis of adenocarcinoma of the prostate gland.
- Adenocarcinoma of the prostate gland has often been diagnosed based upon pathology examination of non-targeted needle biopsies investigating raised serum prostate specific antigen (PSA) levels in men.
- It has been pointed out that absence of the basal cell layer is a pathognomonic histological feature of adenocarcinoma of the prostate gland.
- It has been iterated that pathognomonic diagnostic features of adenocarcinoma of the prostate gland include the following: circumferential perineural invasion, glomerulations and collagenous micronodules (mucinous fibroplasia).
- It has been stated that other histopathology examination features of adenocarcinoma of the prostate gland include the following: logical features, infiltrative architecture, nucleolar prominence, amphophilic cytoplasm and some intraluminal contents (crystalloids, blue mucin, pink amorphous material).

Terminology

The terminologies that had been utilised for adenocarcinoma of the prostate gland had been summated as follows: [1]

- Prostate cancer.
- Prostate adenocarcinoma.

- Subtypes of prostatic adenocarcinoma include: acinar adenocarcinoma, ductal adenocarcinoma, atrophic adenocarcinoma, pseudo-hyperplastic adenocarcinoma, microcystic adenocarcinoma, foamy gland adenocarcinoma, mucinous adenocarcinoma, signet ring variant of adenocarcinoma, pleomorphic giant cell adenocarcinoma, sarcomatoid adenocarcinoma.

Epidemiology

The epidemiology of adenocarcinoma of the prostate gland had been summated as follows: [1]

- Adenocarcinoma of the prostate gland is the second most common cancer and second leading cause of cancer related death in American men. [2]
- Ninety-two percent (92%) of United States of America (U.S.A) cases of adenocarcinoma of the prostate tend to be diagnosed in men who are older than 55 years and in 19.5% in men who are older than 75+ years. [2]
- It has been stated that adenocarcinoma of the prostate gland is found at autopsy in 40% of men who are more than 60 years of age. [3]
- It has been iterated that incidental adenocarcinoma of the prostate gland had been reported in about 25% of cystoprostatectomies which had been undertaken for the treatment of urinary bladder cancer. [4]
- It has been iterated that globally, highest age standardized rates of adenocarcinoma of the prostate gland had been documented in Oceania, North America, and Europe. [5]
- It has been pointed out that lower rates of adenocarcinoma of the prostate gland have been documented within developing countries. This might be due to different screening programs and diagnostic pathways. [1]
- It has been documented that there is a higher incidence of adenocarcinoma of the prostate gland in men of African heritage. [5]

Sites

The sites of adenocarcinoma of the prostate gland had been summated as follows: [1]

- Majority of adenocarcinomas of the prostate gland are multifocal. [6]
- 75% to 80% of adenocarcinomas of the prostate gland are found within the posterior / posterolateral peripheral zone of the prostate gland. [1]
- About 13% to 20% of adenocarcinomas of the prostate gland are found within the transition (periurethral) zone. [7] [8]
- It has been iterated that most clinically significant adenocarcinomas of the prostate gland arise within the peripheral zone that is sampled by needle biopsies. [1]
- It has been iterated that transition zone adenocarcinoma of the prostate gland is associated with favourable pathology features and better recurrence free survival. [9]
- It has been iterated that adenocarcinoma of the prostate gland less frequently involves the anterior prostate most likely due to inadequate sampling using standard biopsy approach. [10]

Pathophysiology [1]

The pathophysiology of adenocarcinoma of the prostate gland has been summated as follows: [1]

- Germline variants can increase the risk of adenocarcinoma of the prostate gland.
- Somatic mutations in genes such as *ERG, ETV1/4, FLI1, SPOP, FOXA1, IDH1, PTEN, TP53, MYC, CDH1* had been found in patients afflicted by adenocarcinoma of the prostate gland. [11] [12]
- The Most common somatic genomic rearrangement that are found in patients afflicted by adenocarcinoma of the prostate gland is fusion of the androgen regulated gene *TMPRSS2* with a member of the *ETS* transcription family. [12]

Aetiology [1]

The ensuing summations had been made regarding the aetiology of adenocarcinoma of the prostate gland: [1]

- Obesity increases risk for the development of adenocarcinoma of the prostate gland. [13]
- Nonmodifiable risk factors for the development of adenocarcinoma of the prostate gland include: age, race and family history. [14]

  - Genetic susceptibility to the development of adenocarcinoma of the prostate gland is linked to African heritage. [14]
  - There is an increased risk for the development of adenocarcinoma of the prostate gland with first degree relative with prostate cancer. [14]
  - *BRCA2* mutations increase the risk for the development of adenocarcinoma of the prostate gland by 5-fold; *BRCA2* associated cancers occur at a lower age and have worse survival outcomes. [12] [15]
  - Additional germline variants associated with increased cancer risk occur in *HOXB13* [12]
  - Increased risk for the development of adenocarcinoma of the prostate gland had been noted in Lynch syndrome. [16]
- Numerous single nucleotide polymorphisms (SNPs) that have a low to moderate effect on risk/progression have been identified in patients afflicted by adenocarcinoma of the prostate gland [17]
- High levels of IGF1 may confer increased risk for the development of adenocarcinoma of the prostate gland. [18]

Clinical features [1]

The ensuing summations had been made regarding the clinical manifestations of adenocarcinoma of the prostate gland: [1]

- Adenocarcinoma of the prostate gland is generally asymptomatic unless locally advanced or metastatic.
- Adenocarcinoma of the prostate gland is often diagnosed pursuant to investigation of non-specific lower urinary tract symptoms.
- Digital rectal examination (DRE): the prostate may feel normal or may be enlarged/asymmetrical/hard/have a palpable nodule present.

Diagnosis [1]

The ensuing summations had been made regarding the diagnosis of adenocarcinoma of the prostate gland: [1]

- Adenocarcinoma of the prostate gland is generally diagnosed by systematic transrectal ultrasound guided prostate biopsies.
- Trans-perineal needle biopsies of the prostate gland are increasingly being used as the biopsies are associated with lower risk of infection.

- Pre-biopsy MRI scan followed by systematic biopsies supplemented with targeted biopsies from any radiological abnormality leads to better identification of clinically significant prostate cancer than systematic prostate biopsy alone. [19]
- Incidental prostate cancer sometimes has tended to be diagnosed in transurethral resections of the prostate gland.
- Immunohistochemistry with basal cell markers (HMWCK, p63) and AMACR is used to establish the diagnosis of adenocarcinoma of the prostate gland in equivocal cases of adenocarcinoma of the prostate gland.

Laboratory tests [1]

The ensuing summations had been made regarding the laboratory tests that are undertaken in cases of adenocarcinoma of the prostate gland with the results: [1]

- Raised serum PSA level tends to be seen in cases of adenocarcinoma of the prostate gland.
- Different serum PSA cutoffs have been used to prompt prostate needle biopsy.
- Age specific cutoffs, PSA velocity (rate of change in PSA over time) and PSA density (PSA per unit prostate volume - ng/mL/cc) may increase sensitivity and specificity of PSA testing. [20]
- U.S. Preventative Services Task Force (USPSTF) recommends against PSA based screening for prostate cancer in men 70 and over.
    - For men aged 55 - 69, periodic PSA based screening should be an individual choice.
    - Screening in this age group offers a small potential benefit of reducing the chance of death from prostate cancer in some men; however, many men will experience potential harm. [20]
- American Urological Association (AUA) does not recommend serum PSA screening in men under age 40 years or in men aged 40 - 54 years at average risk:
    - For men age 55 - 59 years, shared decision making is desirable.
    - For men aged 70 years and over or men with < 10 - 15 -year life expectancy, PSA screening is not recommended. [21]
- Potential urine biomarker for prostate cancer is PCA3. [12]

Radiology description [1]

The ensuing summations had been made regarding the radiology image features of adenocarcinoma of the prostate gland: [1]

- Ultrasound scan (USS) generally is used to guide prostate biopsies; prostate cancer may appear hypoechoic but USS neither sensitive nor specific.
- Multiparametric MRI commonly is used for local tumour staging; may also be used to identify abnormalities for targeting at biopsy
- MRI scan abnormalities are generally reported using either PI-RADS (Prostate Imaging - Reporting and Data System) or Likert score.
- CT scan is utilised to identify metastatic disease in lymph nodes
- Isotope Bone scan is utilised to detect bony metastases.
- PET/CT scan is utilised to detect micro-metastatic disease in selected patients, such as men with raised PSA levels after treatment.

Prognostic factors [1]

The ensuing summations had been made regarding the prognostic factors of adenocarcinoma of the prostate gland: [1]

- Biopsy results: tumour extent (mm or percentage core involvement), grade (Gleason score and grade group), perineural invasion, and extra-prostatic extension tend to predict the prognosis of adenocarcinoma of the prostate gland.
- Radical prostatectomy specimen findings: tumour size, Gleason score and grade group, stage, and margin status determine the prognosis of adenocarcinoma of the prostate gland.
- Cribriform morphology and intraductal carcinoma associated with invasive prostate cancer are adverse prognostic indicators associated with adenocarcinoma of the prostate gland. [22]
- The small cell carcinoma component of primary adenocarcinoma of the prostate gland is associated with aggressive behaviour and treated differently.
- Some expert groups recommend incorporating the intraductal component into the Gleason score while others recommend reporting it separately in a comment. [23] [24] [25]

Treatment [1]

The ensuing summations had been made regarding the treatment of adenocarcinoma of the prostate gland: [1]

- Pre-operative risk stratification is based upon serum PSA, clinical stage, biopsy parameters (tumour extent, grade, cribriform morphology, intraductal carcinoma, perineural invasion).
- Primary treatment options for primary adenocarcinoma of the prostate gland are based upon pre-operative risk stratification as follows:
  - Active surveillance.
  - Focal therapy (cryotherapy, high intensity ultrasound).
  - Radical prostatectomy.
  - Brachytherapy.
  - External beam radiotherapy.
  - Hormone therapy (e.g., luteinizing hormone releasing hormone [LHRH] analogues, antiandrogens).
  - Orchidectomy (rare in contemporary practice)
  - Chemotherapy (for metastatic disease).
  - Immunotherapy. Some patients are also offered immunotherapy in collaboration with some of the aforementioned treatment options
- Postprostatectomy options:
  - Generally, PSA monitoring and early salvage therapy if rising serum PSA.
  - Less commonly adjuvant therapy for high stage disease or margin positivity.

Macroscopy Gross description [1]

The ensuing had been iterated about macroscopy examination features of adenocarcinoma of the prostate gland: [1]

- Adenocarcinoma of the prostate gland is often grossly inapparent.
- Adenocarcinoma of the prostate gland may form a cream mass.

Microscopic (histopathology examination) description [1]

The ensuing had been iterated about microscopy examination features of adenocarcinoma of the prostate gland: [1]

- Gleason grading is based on the architecture of the tumour
- Gleason grades represent a morphological spectrum from well-formed glands (pattern 3) to increasingly complicated glandular proliferations (pattern 4) to almost no glandular differentiation (pattern 5). [26]
- Glandular crowding and infiltrative growth pattern.
- Nuclear enlargement, nucleolar prominence.
- Round generally monomorphic nuclei.
- Amphophilic cytoplasm.
- Mitoses.
- Apoptotic bodies.
- Stromal desmoplasia.
- Intraluminal contents: crystalloids, pink amorphous secretions, blue mucin.
- Glomerulations, collagenous micronodules (mucinous fibroplasia).
- Absence of basal cell layer (generally requires immunohistochemical confirmation). [27]

Cytology examination description [1]

The ensuing had been iterated about cytology examination features of adenocarcinoma of the prostate gland: [1[

- Urine cytology for detecting prostate cancer has a very low sensitivity. [28]
- Urine cytology is not utilised clinically in the diagnosis of prostate cancer.
- FNA of metastatic prostate cancer to a lymph node may show micro-acinar complexes / cell clusters / single cells with fragile cytoplasm and prominent nucleoli. [29]

Positive stains

Adenocarcinoma of the prostate gland tumour cells tend to exhibit positive staining upon immunohistochemistry staining studies to the following: tumour markers: [1]

- **PSA.**
- **NKX3.1.**
- **AMACR** (P504S, racemase).
- **Prostein** (P501S).

- **PSMA.**

Rare tumours may have aberrant expression of:

- p63. [30] [31]

Negative stains [1]

Adenocarcinoma of the prostate gland tumour cells tend to exhibit negative staining upon immunohistochemistry staining studies to the following tumour markers:

- **CK7.**
- **CK20.**
- High molecular weight cytokeratins **(34 beta E12, CK5, CK5/6**).
- **p63.**
- **CDX2.**
- **GATA3.**
- **TTF1.** [31]

Molecular / cytogenetics description [1]

The ensuing had been iterated about the molecular / cytogenetics features of adenocarcinoma of the prostate gland: [1]

- Prostate cancer is a heritable disease.
- Family history of a first degree relative with prostate cancer increases the risk of developing prostate cancer by 2-fold. [32]
- 30 - 40% of familial risk is due to genetic factors). [32]
- Genetic factors include highly penetrable rare variants and more common low to moderate risk variants. [32]
- Highly penetrant variants occur in *BRCA2* and *HOXB13*
- Over 280 SNPs have been identified as prostate cancer risk factors. [32]
- For most SNPs, the molecular mechanism of cancer association is generally unknown, as they occur in noncoding regions of the genome. [32]
- Somatic mutations occur in genes such as *ERG, ETV1/4, FLI1, SPOP, FOXA1, IDH1, PTEN, TP53, MYC, CDH1*. [32] [33]
- The most common somatic genomic rearrangement is fusion of the androgen regulated gene *TMPRSS2* with a member of the *ETS* transcription family. [32]

- Somatic mutation profiles of prostate cancer are associated with clinical and pathological outcomes:
  - There are 7 major subtypes, which are defined by either specific gene fusions of *ETS* transcription family members (*ERG, ETV1, ETV4* and *FLI1*) or mutations (*SPOP, FOXA1, IDH1*). [34]
- Different subtypes have different molecular profiles, for example: [34]
  - *ETS* subset (59% of cases) are enriched in *PTEN* mutations.
  - *SPOP* mutant subset (11%) of cases have distinct somatic copy number alteration profiles, including deletions of *CHD1*, 6q and 2q.
- Radical prostatectomy:
  - Histological tumour type: acinar adenocarcinoma.
  - Gleason score:
    - Primary Gleason grade: 3.
    - Secondary Gleason grade: 3.
    - Tertiary Gleason grade (< 5%): not applicable.
    - Gleason score: 3+3=6.
    - Grade group: 1.
  - Location of dominant tumour: right apex.
  - Extra-prostatic extension: not identified.
  - Bladder neck: not involved.
  - Seminal vessels: not involved.
  - Margin status: not involved.
  - Lympho-vascular invasion: not identified.
  - Regional lymph node status:
    - Number of nodes examined: 9.
    - Number of positive lymph nodes: 0.
  - Primary tumour: pT2 pN0.

Differential diagnoses [1]

The ensuing had been iterated about the differential diagnoses of adenocarcinoma of the prostate gland: [1]

- **Benign prostate tissue:**
  - Pale cytoplasm.
  - Corpora amylacea.
  - No other intraluminal contents.
  - Basal cell marker immunoreactivity.
- **Prostatic atrophy**:
  - Lobular architecture.

- Scant cytoplasm.
- Basal cell marker immunoreactivity.

❖ **Adenosis:**
- Lobular architecture.
- Basal cell marker immunoreactivity (often scattered).

❖ **Atypical small acinar proliferation (ASAP):**
- Small size.
- Lack of significant cytological atypia, including a lack of macro-nucleoli.

❖ **High grade prostatic intraepithelial neoplasia**:
- Less architectural atypia.
- Maintained basal cells.

❖ **Post-atrophic hyperplasia**:
- Some glands atrophic.
- Basal cell marker immunoreactivity (often scattered).

❖ **Partial atrophy**:
- Atrophic glands with abundant lateral pale.
- Cytoplasm.
- Irregularly distributed nuclei.
- Basal cell marker immunoreactivity (often scattered).

❖ **Radiation atypia:**
- Glandular atrophy.
- Nuclear irregularity and pleomorphism.
- Atypical stromal cells.
- Basal cell marker immunoreactivity.

❖ **Urothelial carcinoma:**
- Nuclear irregularity and pleomorphism.
- Hyaline dense eosinophilic cytoplasm.
- Desmoplastic stromal reaction.
- Immunoreactivity for urothelial markers (**GATA3, CK7, p63,**).
- No expression of prostatic immunomarkers (**PSA, PSAP, NKX3.1**).

REFERENCES

[1] Short E, Varma M. Adenocarcinoma. PathologyOutlines.com website. https://www.pathologyoutlines.com/topic/prostateadenoNOS.html. Accessed January 13th, 2024. https://www.pathologyoutlines.com/topic/prostateadenoNOS.html

[2] NIH National Cancer Institute Surveillance Epidemiology, and End Results Program. Cancer Stat Facts: Common Cancer Sites. https://seer.cancer.gov/statfacts/html/common.html

[3] Zlotta AR, Egawa S, Pushkar D, Govorov A, Kimura T, Kido M, Takahashi H, Kuk C, Kovylina M, Aldaoud N, Fleshner N, Finelli A, Klotz L, Sykes J, Lockwood G, van der Kwast TH. Prevalence of prostate cancer on autopsy: cross-sectional study on unscreened Caucasian and Asian men. J Natl Cancer Inst. 2013 Jul 17;105(14):1050-8. doi: 10.1093/jnci/djt151. Epub 2013 Jul 11. PMID: 23847245. https://pubmed.ncbi.nlm.nih.gov/23847245/

[4] Fahmy O, Khairul-Asri MG, Schubert T, Renninger M, Stenzl A, Gakis G. Clinicopathological Features and Prognostic Value of Incidental Prostatic Adenocarcinoma in Radical Cystoprostatectomy Specimens: A Systematic Review and Meta-Analysis of 13,140 Patients. J Urol. 2017 Feb;197(2):385-390. doi: 10.1016/j.juro.2016.08.088. Epub 2016 Aug 26. PMID: 27569436. https://pubmed.ncbi.nlm.nih.gov/27569436/

[5] Rawla P. Epidemiology of Prostate Cancer. World J Oncol. 2019 Apr;10(2):63-89. doi: 10.14740/wjon1191. Epub 2019 Apr 20. PMID: 31068988; PMCID: PMC6497009. https://pubmed.ncbi.nlm.nih.gov/31068988/

[6] Løvf M, Zhao S, Axcrona U, Johannessen B, Bakken AC, Carm KT, Hoff AM, Myklebost O, Meza-Zepeda LA, Lie AK, Axcrona K, Lothe RA, Skotheim RI. Multifocal Primary Prostate Cancer Exhibits High Degree of Genomic Heterogeneity. Eur Urol. 2019 Mar;75(3):498-505. doi: 10.1016/j.eururo.2018.08.009. Epub 2018 Sep 1. PMID: 30181068. https://pubmed.ncbi.nlm.nih.gov/30181068/

[7] Reissigl A, Pointner J, Strasser H, Ennemoser O, Klocker H, Bartsch G. Frequency and clinical significance of transition zone cancer in prostate cancer screening. Prostate. 1997 Feb 1;30(2):130-5. doi: 10.1002/(sici)1097-0045(19970201)30:2<130::aid-pros8>3.0.co;2-s. PMID: 9051151. https://pubmed.ncbi.nlm.nih.gov/9051151/

[8] Urology 1994; 43:11 [8] Matzkin H, Patel JP, Altwein JE, Soloway MS. Stage T1A carcinoma of prostate. Urology. 1994 Jan;43(1):11-21. doi: 10.1016/s0090-4295(94)80254-8. PMID: 8284869. https://pubmed.ncbi.nlm.nih.gov/8284869/

[9] Lee JJ, Thomas IC, Nolley R, Ferrari M, Brooks JD, Leppert JT. Biologic differences between peripheral and transition zone prostate cancer. Prostate. 2015 Feb;75(2):183-90. doi: 10.1002/pros.22903. Epub 2014 Oct 18. PMID: 25327466; PMCID: PMC4270836. https://pubmed.ncbi.nlm.nih.gov/25327466/

[10] Fine SW, Reuter VE. Anatomy of the prostate revisited: implications for prostate biopsy and zonal origins of prostate cancer. Histopathology. 2012 Jan;60(1):142-52. doi: 10.1111/j.1365-2559.2011.04004.x. PMID: 22212083. https://pubmed.ncbi.nlm.nih.gov/22212083/

[11] Cancer Genome Atlas Research Network. The Molecular Taxonomy of Primary Prostate Cancer. Cell. 2015 Nov 5;163(4):1011-25. doi: 10.1016/j.cell.2015.10.025. PMID: 26544944; PMCID: PMC4695400. https://pubmed.ncbi.nlm.nih.gov/26544944/

[12] Faisal FA, Lotan TL. The Genomic and Molecular Pathology of Prostate Cancer: Clinical Implications for Diagnosis, Prognosis, and Therapy. Adv Anat Pathol. 2020 Jan;27(1):11-19. doi: 10.1097/PAP.0000000000000245. PMID: 31503032. https://pubmed.ncbi.nlm.nih.gov/31503032/

[13] Lavalette C, Trétarre B, Rebillard X, Lamy PJ, Cénée S, Menegaux F. Abdominal obesity and prostate cancer risk: epidemiological evidence from the EPICAP study. Oncotarget. 2018 Oct 2;9(77):34485-34494. doi: 10.18632/oncotarget.26128. PMID: 30349643; PMCID: PMC6195387. https://pubmed.ncbi.nlm.nih.gov/30349643/

[14] Gann PH. Risk factors for prostate cancer. Rev Urol. 2002;4 Suppl 5(Suppl 5):S3-S10. PMID: 16986064; PMCID: PMC1476014. https://pubmed.ncbi.nlm.nih.gov/16986064/

[15] Junejo NN, AlKhateeb SS. BRCA2 gene mutation and prostate cancer risk. Comprehensive review and update. Saudi Med J. 2020 Jan;41(1):9-17. doi: 10.15537/smj.2020.1.24759. PMID: 31915789; PMCID: PMC7001059. https://pubmed.ncbi.nlm.nih.gov/31915789/

[16] Haraldsdottir S, Hampel H, Wei L, Wu C, Frankel W, Bekaii-Saab T, de la Chapelle A, Goldberg RM. Prostate cancer incidence in males with Lynch syndrome. Genet Med. 2014 Jul;16(7):553-7. doi: 10.1038/gim.2013.193. Epub 2014 Jan 16. PMID: 24434690; PMCID: PMC4289599. https://pubmed.ncbi.nlm.nih.gov/24434690/

[17] Allemailem KS, Almatroudi A, Alrumaihi F, Makki Almansour N, Aldakheel FM, Rather RA, Afroze D, Rah B. Single nucleotide polymorphisms (SNPs) in prostate cancer: its implications in diagnostics and therapeutics. Am J Transl Res. 2021 Apr 15;13(4):3868-3889. PMID: 34017579; PMCID: PMC8129253. https://pubmed.ncbi.nlm.nih.gov/34017579/

[18] Roberts CT Jr. IGF-1 and prostate cancer. Novartis Found Symp. 2004; 262:193-9; discussion 199-204, 265-8. PMID: 15562830. https://pubmed.ncbi.nlm.nih.gov/15562830/

[19] Ahmed HU, El-Shater Bosaily A, Brown LC, Gabe R, Kaplan R, Parmar MK, Collaco-Moraes Y, Ward K, Hindley RG, Freeman A, Kirkham AP, Oldroyd R, Parker C, Emberton M; PROMIS study group. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet. 2017 Feb 25;389(10071):815-822. doi: 10.1016/S0140-6736(16)32401-1. Epub 2017 Jan 20. PMID: 28110982. https://pubmed.ncbi.nlm.nih.gov/28110982/

[20] NCCN Guidelines. Prostate Cancer, Early Detection. Version 1 2024; https://www.nccn.org/guidelines/guidelines-detail?category=2&id=1460

[21] Carter HB, Albertsen PC, Barry MJ et al: Early detection of prostate cancer: AUA Guideline. J Urol 2013; **190:** 419. https://www.auanet.org/guidelines-and-quality/guidelines/prostate-cancer-early-detection-guideline

[22] Kweldam CF, van der Kwast T, van Leenders GJ. On cribriform prostate cancer. Transl Androl Urol. 2018 Feb;7(1):145-154. doi: 10.21037/tau.2017.12.33. PMID: 29594028; PMCID: PMC5861292. https://pubmed.ncbi.nlm.nih.gov/29594028/

[23] van Leenders GJLH, van der Kwast TH, Grignon DJ, Evans AJ, Kristiansen G, Kweldam CF, Litjens G, McKenney JK, Melamed J, Mottet N, Paner GP, Samaratunga H, Schoots IG, Simko JP, Tsuzuki T, Varma M, Warren AY, Wheeler TM, Williamson SR, Iczkowski KA; ISUP Grading Workshop Panel Members. The 2019 International Society of Urological Pathology (ISUP) Consensus Conference on Grading of Prostatic Carcinoma. Am J Surg Pathol. 2020 Aug;44(8):e87-e99. doi: 10.1097/PAS.0000000000001497. PMID: 32459716; PMCID: PMC7382533. https://pubmed.ncbi.nlm.nih.gov/32459716/

[24] Epstein JI, Amin MB, Fine SW, Algaba F, Aron M, Baydar DE, Beltran AL, Brimo F, Cheville JC, Colecchia M, Comperat E, da Cunha IW, Delprado W, DeMarzo AM, Giannico GA, Gordetsky JB, Guo CC, Hansel DE, Hirsch MS, Huang J, Humphrey PA, Jimenez RE, Khani F, Kong Q, Kryvenko ON, Kunju LP, Lal P, Latour M, Lotan T, Maclean F, Magi-Galluzzi C, Mehra R, Menon S, Miyamoto H, Montironi R, Netto GJ, Nguyen JK, Osunkoya AO, Parwani A, Robinson BD, Rubin MA, Shah RB, So JS,

Takahashi H, Tavora F, Tretiakova MS, True L, Wobker SE, Yang XJ, Zhou M, Zynger DL, Trpkov K. The 2019 Genitourinary Pathology Society (GUPS) White Paper on Contemporary Grading of Prostate Cancer. Arch Pathol Lab Med. 2021 Apr 1;145(4):461-493. doi: 10.5858/arpa.2020-0015-RA. PMID: 32589068. https://pubmed.ncbi.nlm.nih.gov/32589068/

[25] Varma M, Epstein JI. Head to head: should the intraductal component of invasive prostate cancer be graded? Histopathology. 2021 Jan;78(2):231-239. doi: 10.1111/his.14216. Epub 2020 Sep 12. PMID: 32692448. https://pubmed.ncbi.nlm.nih.gov/32692448/

[26] Short E, Warren A Y, Varma M. Gleason Grading of Prostate Cancer: A pragmatic approach. Diagnostic Histopathology, 2019; 25(10): 371 – 378. https://www.diagnostichistopathology.co.uk/article/S1756-2317(19)30087-8/fulltext

[27] Humphrey PA. Histopathology of Prostate Cancer. Cold Spring Harb Perspect Med. 2017 Oct 3;7(10):a030411. doi: 10.1101/cshperspect.a030411. PMID: 28389514; PMCID: PMC5629988. https://pubmed.ncbi.nlm.nih.gov/28389514/

[28] Eskra JN, Rabizadeh D, Pavlovich CP, Catalona WJ, Luo J. Approaches to urinary detection of prostate cancer. Prostate Cancer Prostatic Dis. 2019 Sep;22(3):362-381. doi: 10.1038/s41391-019-0127-4. Epub 2019 Jan 17. PMID: 30655600; PMCID: PMC 6640078. https://pubmed.ncbi.nlm.nih.gov/30655600/

[29] Rosa M, Chopra HK, Sahoo S. Fine needle aspiration biopsy diagnosis of metastatic prostate carcinoma to inguinal lymph node. Diagn Cytopathol. 2007 Sep;35(9):565-7. doi: 10.1002/dc.20693. PMID: 17703448. https://pubmed.ncbi.nlm.nih.gov/17703448/

[30] Tan HL, Haffner MC, Esopi DM, Vaghasia AM, Giannico GA, Ross HM, Ghosh S, Hicks JL, Zheng Q, Sangoi AR, Yegnasubramanian S, Osunkoya AO, De Marzo AM, Epstein JI, Lotan TL. Prostate adenocarcinomas aberrantly expressing p63 are molecularly distinct from usual-type prostatic adenocarcinomas. Mod Pathol. 2015 Mar;28(3):446-56. doi: 10.1038/modpathol.2014.115. Epub 2014 Sep 12. PMID: 25216229; PMCID: PMC4344845. https://pubmed.ncbi.nlm.nih.gov/25216229/

[31] Epstein JI, Egevad L, Humphrey PA, Montironi R; Members of the ISUP Immunohistochemistry in Diagnostic Urologic Pathology Group. Best practices recommendations in the application of immunohistochemistry in the prostate: report from the International Society of Urologic Pathology consensus conference. Am J Surg

Pathol. 2014 Aug;38(8):e6-e19. doi: 10.1097/PAS.0000000000000238. PMID: 25029122.
https://pubmed.ncbi.nlm.nih.gov/25029122/

[32] Faisal FA, Lotan TL. The Genomic and Molecular Pathology of Prostate Cancer: Clinical Implications for Diagnosis, Prognosis, and Therapy. Adv Anat Pathol. 2020 Jan;27(1):11-19. doi: 10.1097/PAP.0000000000000245. PMID: 31503032.
https://pubmed.ncbi.nlm.nih.gov/31503032/

[33] Cancer Genome Atlas Research Network. The Molecular Taxonomy of Primary Prostate Cancer. Cell. 2015 Nov 5;163(4): 1011-25. doi: 10.1016/j.cell.2015.10.025. PMID: 26544944; PMCID: PMC4695400.
https://pubmed.ncbi.nlm.nih.gov/26544944/

[34] Inamura K. Prostatic cancers: understanding their molecular pathology and the 2016 WHO classification. Oncotarget. 2018 Feb 16;9(18):14723-14737. doi: 10.18632/oncotarget.24515. PMID: 29581876; PMCID: PMC5865702.
https://pubmed.ncbi.nlm.nih.gov/29581876/

CHAPTER 2

STROMAL TUMOUR OF UNCERTAIN MALIGNANT POTENTIAL (STUMP) OF THE PROSTATE GLAND: REVIEW AND UPDATE

ABSTRACT

Stromal tumour of uncertain malignant potential (STUMP) of the prostate gland is an extremely uncommon tumour which has been associated with a variable and unpredictable clinical biological behaviour. Many cases of STUMPs had been diagnosed incidentally and never progressed, while cases of STUMPS had been identified to have invaded locally and rapidly recurred pursuant to surgical intervention, and yet others had emanated in the development of distant metastasis and death. Generally; STUMPS manifest with non-specific symptoms including: lower urinary tract voiding symptoms, haematuria, retention of urine, and loin pain. A wide array of histology patterns is encompassed by STUMP, and distinguishing these tumours from prostatic stromal sarcoma or other malignant lesions of the prostate gland that are more common had quite often proven to be difficult. In view of the rarity of this tumour, there is at the moment no consensus opinion of the management of STUMP. Some cases of STUMP had been treated by (a) trans-urethral resection of prostate (TURP) to relief voiding symptoms or by resection of the tumour only, followed by regular follow assessments of patients by a combination of clinical assessments, laboratory tests including serum prostate specific antigen testing as well as various types of radiology imaging assessments and others had been treated by the undertaking of radical prostatectomy. Following the undertaking of TURP for a number of patients who have STUMP, a number of patients have tended to be identified by radiology imaging assessments to have residual tumours within the prostate gland and if the patients remain asymptomatic many of these patients are not offered any further treatment of curative but instead the patients are then offered

regular surveillance follow-up assessments to ascertain if the residual tumours would subsequently increase in size or develop further and invade the urinary bladder or the rectum without being sure which of the tumours would eventually portend an aggressive behaviour and this option has been adopted due to the understanding that radical prostatectomy for tumours, majority of which may not progress may be too aggressive and invasive. This approach is aimed at early diagnosis of progress but does not prevent the development of local recurrence or distant metastasis. Nevertheless, there are a number less-invasive treatment procedures of curative intent that can be used to destroy the tumours immediately pursuant to their initial diagnosis which hopefully would prevent development of subsequent local recurrence or distant metastases. These less-invasive treatment options for localised STUMPs include the ensuing radiology-image guided procedures: [1] Radiology-image-guided cryotherapy of the tumour, [2] Radiology-image-guided radiofrequency ablation of the prostate tumour, [3] Radiology image-guided irreversible electroporation of the residual prostate tumour, and [4] Selective prostate arteriography and super-selective embolization of the prostate artery branch supplying the tumour. If these procedures are included as treatment options, it is likely that the outcome of these procedures would improve the prognosis and even though the patients would still need to be followed-up, almost invariably because of the good outcome of these procedures, the interval of follow-up assessments of the patients would be prolonged. It would also be important that urologists, oncologists, and pharmacotherapy research workers globally should endeavour to undertake research work that is aimed at the discovery or identification of new chemotherapy medicaments that would safely and effectively destroy STUMP tumour cells and which would enable patients afflicted by STUMP to live longer and enjoy a good quality of life. In some scenarios, STUMPs may be diagnosed contemporaneously with primary adenocarcinoma of the prostate such that the multi-disciplinary team would also discuss the treatment options of the associated contemporaneous tumour.

KEYWORDS

Prostatic stromal tumour of uncertain malignant potential; adenocarcinoma of prostate; Prostate biopsy; trans-urethral resection of prostate; enucleation of the prostate lesion, radical prostatectomy, local recurrence; metastasis; Histopathology, immunohistochemistry; difficulties in diagnosis; differential diagnosis; consensus opinion, multi-disciplinary team.

INTRODUCTION

It has been iterated that: prostatic stromal tumours of uncertain malignant potential (STUMPs), are distinct and quite rare lesions which do afflict specialized prostatic stroma. [1] [2] Classically, STUMPs are stated to manifest in the sixth and seventh decades of life [1] [3] and they also have the potential to infiltrate the whole prostate gland, as well as adjacent tissues. [1] [3] [4] [5] [6] STUMPs can also afflict younger age groups of men including some men who are in their twenties or 3rd decades of life. The clinical course of STUMP has tended not to be predictable, ranging from a focal incidental finding based upon the pathology examination features of prostate biopsy specimens which had been undertaken for raised serum prostate specific antigen level, abnormal digital examination finding of an abnormality within the prostate gland or radiology image mass finding in the prostate gland when the radiology imaging scan had been undertaken for a different reason or for lower urinary tract symptoms associated with an enlarged prostate gland. Some cases of STUMP portend an innocuous, benign type of biological behaviour and cases of STUMP manifest with lower urinary tract symptoms, visible haematuria, retention of urine or loin pain due to ureteric obstruction. Some cases though not many tend to be highly aggressive lesions that emanate in the development of widespread metastases and death of the patients. Some cases of STUMP do not recur after their resection or excision but other STUMP tumours recur locally and develop to invade nearby organs including the urinary bladder and rectum.[1] [7] The clinical, laboratory, and radiology imaging abnormalities associated with STUMPs are generally non-specific. The most manifesting symptoms and signs and include: lower urinary tract obstructive symptoms, abnormal digital rectal examination findings, visible haematuria, hematospermia, rectal dysfunction and/or a sensation of fullness within the rectum, acute urinary retention, and elevated prostate specific antigen levels. [1] [4] [7] [8] [9] [10] [11] Upon digital rectal examination, the prostate might be found to be diffusely enlarged, nodular, or soft, spongy, and cystic. [1 [4] Histopathology examination of STUMPs may demonstrate four distinct patterns based upon the degree of stromal cytologic atypia. The presence and appearance of a non-neoplastic epithelial component and patterns may coexist in the same STUMP specimen. The first type of pattern, degenerative atypia, demonstrates marked cellular atypia, is the commonest pattern which has been iterated to accounts for at least 50% of cases. It is composed of normal to slightly hypercellular stroma with scattered cytologically atypical cells interdigitating between benign prostatic glands. The second histological pattern is hypercellular, and consists of hypercellular stroma which is

composed of bland and fusiform cells with eosinophilic cytoplasm. The third pattern is composed of an expanded stroma and proliferating benign glandular elements, which simulate the features of phyllodes tumour of the breast. [1] [4],[10], [12] [13] The stroma has tended to be hypocellular, fibrotic, leaf-like with regard to its configuration, as well as it tends to be devoid of mitotic activity or mitotic figures. The fourth pattern, myxoid, is composed of an expansive overgrowth of the bland stromal cells within a myxoid background. [1] [3], [8] [9], [11], [12] [14] Clinical and histological features of STUMP might closely simulate benign prostatic hyperplasia (BPH), but recognition of this entity tends to be associated with an important treatment as well as prognostic implication in view of the risk of local recurrence of the tumour and the likelihood of subsequent emanation of progression to malignant prostatic stromal sarcoma. Considering the rarity of Stump, and difficulties in differentiating STUMPS based upon their pathology examination features other more common prostate lesions, it is important for all clinicians globally to be aware of the diagnostic features, management and outcome so that they can have a high index of suspicion for STUMP. The ensuing updating article on STUMP, is divided into two parts: (A) Overview which has discussed the general overview aspects of STUMP, and (B) Miscellaneous narrations and discussions from some case reports, case series and studies relate to STUMPs.

AIM

To review and update the literature on prostatic stromal tumour of uncertain malignant potential (STUMP).

METHODS

Internet databases were searched including: Google; Google Scholar; Yahoo; and PUBMED. The search words that were used included: prostatic stromal tumour of uncertain malignant potential; STUMP; stromal hyperplasia of prostate with atypia. Thirty-eight (38) references were identified which were used to write the article which has been divided into two parts: (A) Overview which has discussed the general overview aspects of STUMP, and (B) Miscellaneous narrations and discussions from some case reports, case series and studies relate to STUMPs.

RESULTS

[A] OVERVIEW

Definition / general statements [15]

- It has been iterated that stromal tumour of uncertain malignant potential (STUMP) is a terminology which should be reserved for a category of benign lesions that almost never metastasize. [15] [16]
- It has been pointed out that stromal neoplasms that involve only the prostate gland are a heterogeneous group including: [15]
  - 2 benign entities including: STUMP, leiomyoma with atypia.
  - 2 malignant entities including: stromal sarcoma, phyllodes tumour of the prostate gland.

Essential features [15]

- Prostatic stromal rumours of uncertain malignant potential are stated to be rare prostatic tumours with stromal degenerative atypia featuring vacuolated nuclei. [15]
- It has been stated that some cases of prostatic tumours of uncertain malignant potential are stated to contain cyst spaces, which need to be excluded from phyllodes tumour, which represent differential diagnosis. [15] [17]
- It has been pointed out that prostatic stromal rumours of uncertain malignant potential may recur rapidly pursuant to incomplete resection; rarely progress to stromal sarcoma. [15]

Terminology

- It has been pointed out that the terminology stromal hyperplasia with atypia, which is a synonym that some scholars consider preferable to STUMP, is a useful terminology which more distinctly separates it from malignant neoplasms. [15] [18]

Epidemiology

With regard to the epidemiology of STUMP. It has been iterated that STUMP afflicts a broad age range of males with median age of between 58 years and 61 years. [4] [12] [19]

Clinical features [15]

- It has been iterated that STUMP, usually manifests with urinary obstruction, followed by haematuria, hematospermia and sensation of fullness of the rectum. [15]
- It has been pointed out that many STUMPs had tended to be incidental findings and they do or have tended to portend an indolent biological behaviour. [15]
- It has been stated that tumour recurrence could develop after transurethral resection of STUMP, if definitive surgery is not pursued. [15] [20]
    - Local recurrence rate has been reported as 6 of 13 cases (46.2%), 2 of 12 cases (16.7%), and 3 of 18 cases (16.7%); nevertheless, metastasis should not occur in cases of STUMP. [12] [16] [19]

Diagnosis

- It has been iterated that for the confirmation of the diagnosis of STUMP. CD34, Ki67 and cytokeratin are the most helpful immunostaining agents that are used by the pathologist. [15]

Radiology description

The radiology image features of STUMP had been summarized as follows: [15]

- STUMP as a solid/cystic lesion, does have high signal intensity upon diffusion weighted images; diagnosis of STUMP is favoured by restricted diffusion of FDG or low FDG accumulation by ^{18}F-FDG-PET, correlating with no recurrence or metastasis. [15] [21]
- It has been pointed out that conversely, a malignant lesion with proven metastases, classifiable as phyllodes tumour, which is also referred to as cystic epithelial tumour, would demonstrate high diffusion and FDG accumulation. [15] [17]

Prognostic factors

- It has been iterated that with regard to factors of progno0stication of STUMP, proliferative index as measured by mitotic count or Ki67 may presage worse outcome, even though if high enough, sarcoma should be considered as the diagnosis. [15]

Treatment

- With regard to the treatment options of STUMP, it has been iterated that simple excision is the usual approach. [15]

Other treatment options which should quickly be discussed by multi-disciplinary teams globally

- Considering that follow-up assessments based upon wait and see or active surveillance approach would only identify tumours that develop local recurrence or further growth of getting bigger to invade nearby organs like the urinary bladder and rectum or would help identify metastasis early, this follow-up approach would not prevent the development of local recurrence or distant metastasis.
- Prevention of local recurrence and distant metastasis emanating ensuing treatment of localised STUMP whether low-grade, intermediate-grade, or high-grade should be the priority concern for all clinicians including, urologists, interventional radiologists, oncologists, and pathologists who generally discuss cases of STUMP at their regular intervals. MDTs should discuss the treatment of all cases of localised STUMP by less-invasive treatments of curative intent including the ensuing radiology-image guided procedures: [1] Radiology-image-guided cryotherapy of the tumour, [2] Radiology-image-guided radiofrequency ablation of the prostate tumour, [3] Radiology image-guided irreversible electroporation of the residual prostate tumour, and [4] Selective prostate arteriography and super-selective embolization of the prostate artery branch supplying the tumour. If these procedures are included as treatment options, it is likely that the outcome of these procedures would improve the prognosis and even though the patients would still need to be followed-up, almost invariably because of the good outcome of these procedures, the interval of follow-up assessments of the patients would be prolonged.
- It would also be important that Urologists, oncologists, and pharmacotherapy research workers globally should endeavour to undertake research work that is aimed at the discovery or identification of new chemotherapy medicaments that would safely and effectively destroy STUMP tumour cells and which would enable patients afflicted by STUMP to live longer and enjoy a good quality of life. In some scenarios, STUMPS may be diagnosed contemporaneously with primary adenocarcinoma of the prostate