HISTOPATHOLOGY UPDATE
Prostate Cancer

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How common is Prostate Cancer (PC)?
- In South Africa, in 2013, the age standardised incidence rate of PC was 44.30 per 100 000 people and accounted for 18.86% of all histologically diagnosed cancers.
- In the USA, the lifetime risk of developing PC is approximately 1 in 9, and it is the second most common cause of cancer-related deaths in American men, after lung cancer.
- The socio-economic impact of PC is substantial and growing due to:
  - An aging population
  - Increased utilisation of Prostate Specific Antigen (PSA) screening
  - Increasing demands for PC diagnosis and treatment

What causes PC?
Whilst far less is known about the cause and pathogenesis of PC than any other common human cancer, a new understanding of disease diagnosis and treatment has expanded our knowledge.

A. Genetics
- A positive family history amongst first degree relatives confers patients with an increased risk of PC.
- Certain genetic risk factors have been recognised, but these are not as strongly associated with disease as the genetic risk factors associated with colon and breast carcinoma.

B. Endocrine factors
- Male sex hormones play an important role in the development and growth of PC.
- Research into genetic polymorphisms affecting these pathways has implicated certain genes e.g. SRD5A2 and the androgen receptor gene, which lead to an increased risk of PC.

C. Environmental factors
- Despite extensive research, the environmental risk factors for PC are not well understood.
- Possible culprits include dietary fat and the intake of animal products, especially red meat.
- There is little evidence for a link between PC and obesity.
- No significant occupational exposures have been defined.

PSA screening:
- Current methods for screening and diagnosis remain controversial, as there are inherent problems with PSA screening.
- Notwithstanding, PSA screening has become widespread with a significantly raised PSA level resulting in a prostate biopsy.
- PC remains the only tumour where a random, rather than a directed biopsy is undertaken.

How is PC diagnosed by the pathologist?
Pathology is the gold standard for the diagnosis of PC. In the hands of experienced pathologists, diagnosing even limited quantities of PC has become a routine task. The basic tenets of PC diagnosis are based on the identification of:
- A haphazard growth pattern
- The lack of basal cells
- Nuclear atypia with prominent nucleoli

Numerous benign and non-neoplastic mimics exist that the pathologist must be aware of in order to prevent an erroneous diagnosis. Mimickers include atrophic benign glands, adenosis, high grade prostatic intraepithelial neoplasia (PIN), basal cell lesions and normal histological structures of the prostate gland.

Why and how is PC graded?

Pathological grading, through the use of the Gleason grading system, is the most robust method to assess the aggressiveness of the tumour. The Gleason grading system has a proud history, being embraced almost universally as an integral part of prostate cancer reporting.

The grading system has been correlated with:
• Biochemical failure
• The development of distant metastases
• Survival following radiotherapy or with deferred treatment
• Progression free survival and overall survival

What does a diagnosis of high grade prostatic intraepithelial neoplasia (HG PIN) mean?
• HG PIN is the only accepted precursor of PC.
• The mean incidence of HG PIN in biopsies is 9%, with carcinoma developing in most patients with PIN within 10 years.
• PIN is characterised by progressive phenotypic and genotypic abnormalities intermediate between normal prostatic epithelium and carcinoma.
• The only method of diagnosing HG PIN is biopsy, as it does not significantly alter the serum PSA level and cannot be detected by ultrasound examination.
• Most authors agree that the identification of PIN should not influence/dictate therapeutic decisions, but that its diagnosis necessitates vigorous diagnostic follow-up.
• Studies to date have not determined whether PIN remains stable, regresses or progresses, although the implication is that it can progress.

What are the tools that pathologists use to diagnose PC?
• There are various non-malignant conditions that may mimic PC, necessitating the use of immunohistochemistry to reach a definitive diagnosis.
• The immunohistochemical cornerstone of prostate cancer diagnostics involves the use of markers that:
  • Delineate the basal cells of the prostate gland, as prostate carcinomas are exclusively characterised by a loss of these cells.
    • The most commonly used markers include p63, 34βE12, CK5/6 (Please see images on the next page).
    • Other markers that may be used diagnostically include P-cadherin, D2-40, CD109 and BCL-2, though they have not been extensively validated.
  • Positively mark the malignancy.
    • AMACR (alpha-methylacyl-CoA racemase) is so far the only biomarker that has gained clinical acceptance.
    • Other markers that have been suggested include GOLM1, FASN and ERG.

Does molecular pathology have anything to offer the field of PC?

The most fundamental challenge in PC management is in delineating indolent tumours that need limited treatment from those that will advance/metastasise. Prognostication allows for the individualisation of therapy and triaging of patients to identify those who should NOT be treated as a significant number of patients with low grade carcinoma will not experience clinically relevant disease progression, even if left untreated.

Potential markers that may meet this need include TMPRSS2-ERG rearrangements (TER) (which is purported to be a molecular correlate of lethal PC by some authors), deep sequencing and epigenetic alteration prognostic markers e.g. PITX2. It is important to note that thus far, NO clinically significant markers have been found as there has been limited translation of this information into clinically useful interventions.

What are the future developments in the field of PC?
• Benign epithelium adjacent to PIN or malignancy may exhibit subtle, non-morphologic changes and attempts have been made to detect these "malignancy-associated changes" by identifying certain markers e.g. Mcm-2, caspase-3, racemase, pS2, EPCA-1, P2X, with the aim of predicting subsequent prostate cancer.
• Some tests are already commercially available e.g. the mitochondrial DNA deletion assay.
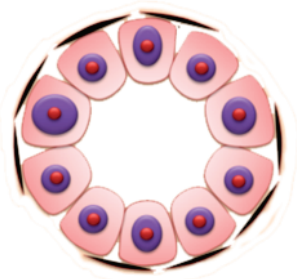
Prostatic Adenocarcinoma Diagnostics

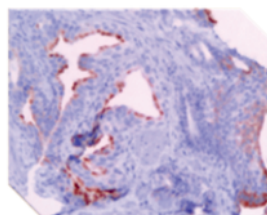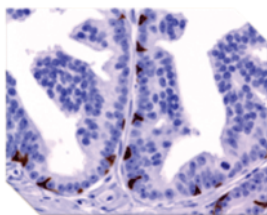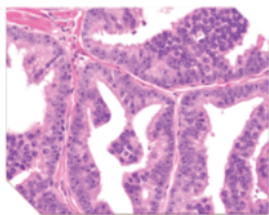An illustrated guide by Dr Julian Deonarain


NORMAL PROSTATIC ACINUS
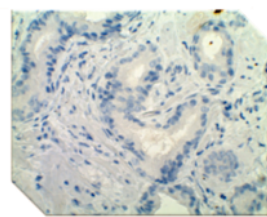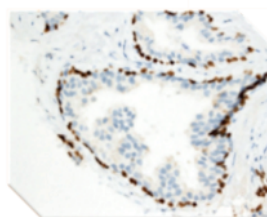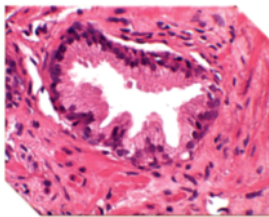
A normal bilayered prostate acinus (left) with intact basal layer highlighted on CK5/6 staining (centre). Normal prostate acini are racemase negative (right).
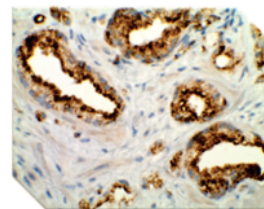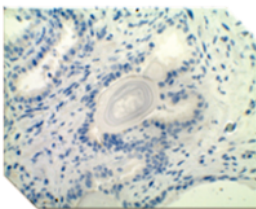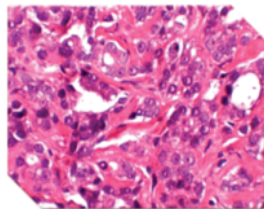

HIGH GRADE PROSTATIC INTRAEPITHELIAL NEOPLASIA

High grade PIN (left) commonly shows atypical epithelial cells with prominent nucleoli with a partially intact basal layer (centre). The cells are typically racemase positive (right).
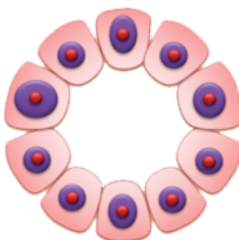
PROSTATIC ADENOCARCINOMA

Prostatic adenocarcinoma comprises a monolayered proliferation of cells with prominent nucleoli (left). CK5/6 is negative around the adenocarinoma, highlighting the absence of a basal layer (centre). Racemase is typically positive in the tumour cells (right).

KEY

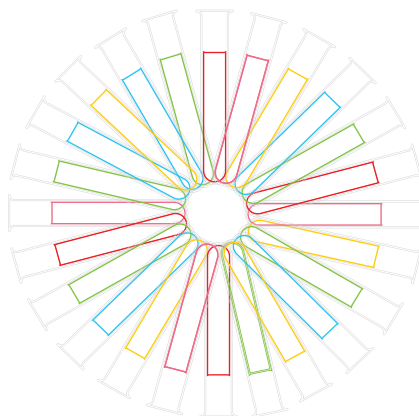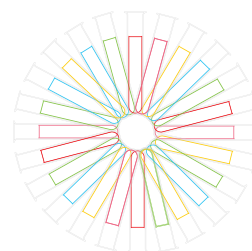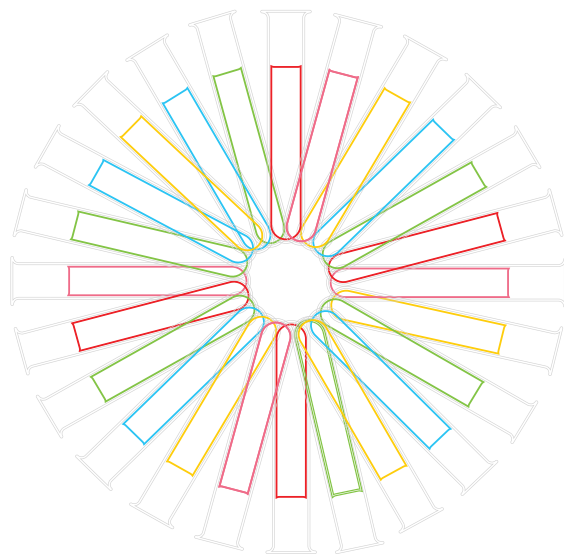acinar cell membrane and cytoplasm

basal cell

acinar cell nucleus

acinar cell nucleolus

Key references:

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