Prostatic Carcinoma: Fundamental Reduction

EPIDEMIOLOGY

GENERAL

Lifetime male risk is 1:6
Mortality: 10% of all male cancer deaths
33% of new cancer diagnoses in males
Incidence of diagnoses peaked in late 90s, and is now declining
95% of prostate tumors are adenocarcinomas

NATURAL HISTORY

Approximately 65% of PCA is diagnosed in males > 65 yrs
In a randomly sampled 50 yr male: 30% risk of T1 (subclinical) disease
10% risk of symptomatic prostate cancer
3% disease-specific mortality
At Dx: 58% local disease, 18% regional nodal disease, 11% metastatic
The survival at 10 yrs is 95% for low-grade neoplasms
67% for neoplasms across all grades
15 yrs is 52% for neoplasms across all grades
Survival is primarily determined by: Age, Performance Status, Tumor Size, Tumor Grade
PCA is likely to be the mechanism of death (87%) in untreated high-grade tumors

Sites of Metastases: **bone** (85%) > **LN** (15%) > Lung, Liver, CNS
Extracapsular extension → considered incurable disease

ESTABLISHED RFs for PROSTATE CANCER

Age : the incidence increases sharply at > 50 yrs
Ethnicity : **AA** and **African Jamaicans** have higher incidence, earlier onset, higher tumor burden, increased mortality, and increased rates of distant metastases
Lowest incidence in Asians and South Americans
FHx : single FDR → 2x increased risk
10% of cases are familial, and most can be mapped to specific loci

EQUIVOCAL RFs for PROSTATE CANCER

Geography : highest in Scandanavia, lowest in Asia
Obesity : associated with higher-grade cancers
Genotype : associated with polymorphisms in 8q24

Benign Prostatic Hyperplasia or **SES** do NOT seem to be a risk factors

PATHOGENESIS

The exact sequence of tumorigenesis is unknown, but androgens (testosterone) are both permissive and proliferative

Most adenocarcinomas are derived from the subcapsular glandular tissue of the **posterior peripheral zone** → palpable though anterior rectal wall

The disease is **NOT** considered malignant transformation of BPH

HISTOPATHOLOGY and STAGING

THE GLEASON SCORE

On a scale of 1 – 5 (most dysplastic): assign score to the **dominant** and **minor** patterns for each core Bx

Gleason Score = **Dominant Score** + **Minor Score**

- **2 – 4**: well-differentiated
- **5 – 7**: moderately differentiated
- **8 – 10** : poorly differentiated

Prostatic Intraepithelial Neoplasia is confined within the basal cell layer

The epithelium is hypertrophic, and becomes stratified (piled cell layers)

Adenocarcinoma is defined by loss of the basal epithelium (basement membrane) surrounding the individual glands

STAGING

The accepted standard is the TMN system

TUMOR EXTENT

- T1: carcinoma is subclinical (**microscopic**); the mass is silent on imaging and non-palpable
  - (T1a: ≤ 5% of sample ; T1b > 5%)
  - (T1c: +ve core needle Bx and elevated PSA on screening)
- T2: carcinoma is palpable and **confined to the prostate** capsule
  - T2a: < 1/2 of single lobe
  - T2c: both lobes involved
  - T2b: otherwise
- T3a: **extracapsular** extension
  - T3b: invasion of the seminal vesicles
- T4: **fixed mass** or **invasion of structures** more remote that the seminal vesicles

NODAL DISEASE

- N0: no regional nodes
- N1: mets in **regional nodes** only

METASTASIS

- M0: none
- M1: mets anywhere (including non-regional nodes)

Prostate cancer is rather unique: the **GRADE** is an integral determinant of the **STAGE**

Also, it is possible to have STAGE IV disease **without** metastasis!
Metastatic disease includes confirmation of disease in non-regional nodes

T1a + N0 + M0 + G1 : **STAGE I**

T1a + N0 + M0 + G2-4 : **STAGE II**
T1b – T2 + N0 + M0 + any G

T3 + N0, M0 + any G : **STAGE III**

T4 + N0 + M0 : **STAGE IV**
Any T + N1 and/or M1

SCREENING

It is known that PSA screening has reduced the mortality due to prostate cancer
However, the risk of false positives may detect disease that is not destined to be clinically significant
There is no established standard for screening

CURRENT ACS RECOMMENTATIONS

In general male population

Begin screening ≥ 40 yrs if ≥ 10 yr life expectancy
Indications for core Bx: Abnormal DRE
PSA ≥ 4
PSA velocity > 0.75
Repeat q. 2 -4 yrs

In the high-risk male population
(AA, FHx of 2 FDRs)

Begin screening ≥ 45 yrs if ≥ 10 yr life expectancy
Indications for core Bx: Abnormal DRE
PSA ≥ 2.5
PSA velocity > 0.75

Screening should be **DISCONTINUED** at 70 – 75 yrs

INDICATIONS for ACTIVE SURVEILANCE

These patients may be followed q. 12 – 18 mos.

PSA < 10
PSA density < 0.15 (normalized to prostate volume)
Gleason ≤ 6 *and* no Gleason 4 – 5
< 3/12 core needle Bx containing carcinoma
No single core with > 50% involvement

CLINICAL PRESENTATION

Local Disease

Usually asymptomatic!

More extensive local invasion results in urinary retention, hematuria, and UTIs

Advanced Disease (Including Mets)

Bone pain from mets, neurologic deficits due to cord compression, leg edema due to lymphatic obstruction, constitutional symptoms

TREATMENT of LOCAL DISEASE

SURGICAL RESECTION

Radical Prostatectomy

en bloc resection of the prostate, capsule, seminal vesicles, vas deferens, vesicular fascia

Indicated for T1 – T2 tumors with no nodal (N0) disease

Retropubic

- Node sampling and nerve-sparing
- A more invasive procedure with longer recover time
  - (but this is a single procedure)

Perineal

- Less morbidity in the elderly
- Exploration of lymphatic bed requires second laproscopic procedure

Survival (DSS): 75 – 95% at 10 – 15 yrs for ideal candidates

Adverse Outcomes: urethral strictures, urinary incontinence, impotence

RADIATION

3D conformal XRT and **IMRT** have allowed for dose escalation to the tumor while decreasing collateral toxicity

Brachytherapy: radioactive seeds implanted; *efficacy is comparable to surgery* and *external beam* modalities (used for small tumors only)

- More convenient: seed placement may be done as a single-day procedure
- Limitations: due to sharp dose fall-off, brachytherapy can only be used for small (early) tumors
  - Preferred: Gleason Score < 7 and PSA < 10

Neoadjuvant Androgen Deprivation: increases disease-free survival (DFS) for large, locally advanced, and high-grade tumors

In general, the local recurrence rate for XRT is higher than that of surgical methods

- Thus: Younger patients often elect to undergo radical prostatectomy

Acute Radiation Toxicity: diarrhea, rectal pain, hematochezia, dysuria, enteroproctitis, frequency, nocturia
Delayed Radiation Toxicity: proctitis, rectal ulcers, colonstomy, chronic cystitis, vesicular outlet stricture, incontinence, impotence (20 – 40%)
Erectile Dysfunction is the most common adverse outcome of both surgery and radiation.

As a side effect of XRT, the risk is **age-dependent!**
The risk does not depend on age as an adverse outcome of surgery

TREATMENT of **ADVANCED DISEASE**

DEFINED as *biochemical failure* (recurrent elevation of PSA following initial treatment), *new primary lesions,* or *metastatic disease*

ANDROGEN DEPRIVATION THERAPY

There are several methods of ADT : Bilateral Orchiectomy
GnRH-R agonists
GnRH-R antagonists
Estrogens
Antiandrogens

The goal is to suppress serum free testosterone < 50 ng/dL

MECHANISM: GnRH **agonists** cause a transient spiking of free testosterone levels → massive inhibition of the HPG axis → dropped testosterone

The breakthrough rise in testosterone may be controlled with anti-androgen agents

OUTCOMES: if the carcinoma remains sensitive to deprivation, **ADT increases survival in patients with metastatic PCA**
However, all PCA eventually become hormone-refractory. Growth is then independent of androgen regulation.

CASTRATE-RESISTANT PROSTATE CANCER (CRPC): With prolonged hormone therapy, the tumor will begin to escape ADT and grow autonomously. The mean survival is reduced by 1 yr.

For refractory disease: consider initiating chemotherapy

CHEMOTHERAPY

There are two approved chemotherapeutic agents

MITOXANTRONE is a DNA intercalating agent → inhibits S phase progression
DOCETAXEL is a mitotic apparatus poison → inhibits M phase progression

Both are DOCs for Hormone-Refractory Prostate Cancer (HRPC)

However, MITOXANTRONE only palliated symptoms while DOCETAXEL actually increases survival by 2.5 mos and improves QoL

PREVENTION

In high-risk patients with PSA > 2.6, **5α-reductase inhibitors** (Dutasteride) prevent the occurrence of PCA

- A risk reduction was seen for development of low-grade cancers (Gleason < 7)
- A risk increase was seen for development of higher grade cancers (Gleason ≥ 7)