



Prostate Cancer Board Review

The key with prostate cancer (abbreviated PAC for Prostatic Adenocarcinoma) is not that it is so deadly, its that **it happens so much**. In the US, for example, one of every 6 men will get Prostate Cancer. In 2008, that number was almost 200,000 men.

So, even if you only lose (i.e. people with Prostate Cancer who pass away from Prostate Cancer) only one out of every 8 men who have Prostate Cancer the number of men who die of PAC is nevertheless a huge number because it **occurs** in such a large amount of men.

That's why its the **2nd most common cause of death due to cancer**.

For example, if 1 out of every 6 people who get a cold die from it, the number of people who will die because of a cold would be HUGE because just about everyone gets a cold - well this is sort of what happens with Prostate Cancer.

Risk Factors in Prostate Cancer

I. Things which **INCREASE** one's risk for developing Prostate Ca

Things that increase a man's chances for developing PAC are basically

- 1) Family history/inheritance factors
- 2) Anything that \uparrow levels and/or time of exposure of the body to Androgens.

Just like Estrogens in Breast Cancer, in Prostate Cancer Androgens are the key.

So, with that in mind, let's look at some of the things that increase one's risk for developing Prostate Cancer

Genetics in Prostate Cancer

Genetically its a multi-step process: \downarrow GSTPI \rightarrow \downarrow C-CAM (9q13)

Just like the 9 \rightarrow 22 fusion gene in CML or the 15 \rightarrow 17 fusion gene in APML there is now identified a fusion gene in Prostate Cancer.

Genetics in Prostate Cancer (Cont'd)

- **7→21 fusion gene** in Prostate Ca (there is also a **17→21**)
Is a TMPRSS2 - ERG fusion gene part of the ETS transcription gene family
- Androgen Receptor Gene is on the X Chromosome (predictably)
- PTEN gene and ERG/ETV1 gene rearrangements → may predict which prostate cancers are more aggressive and cannot Tx w/ "watchful waiting"

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Inheritance Risk Factors in Prostate Cancer

1st degree relatives with Prostate Cancer (i.e. patient's dad or brother)	Risk of developing Prostate Ca compared with the general population
ONE with Prostate Ca	2x
TWO with Prostate Ca	9x
The more relatives a man has with PCa	The earlier in life he'll get PCA

Other Risk Factors for Prostate Cancer

Age 50 or older (30 year old guys typically do not get PAC → except see above)

African American Men (see "special group" below)

↑ fat in the diet → especially **αLinoleic Acids** = diets high in this → 2-3x risk

↓ fiber diet

↑ alcohol intake

Taking Androgens (i.e. by injection, patches, creams, etc)

Living in a Scandinavian Country (really?) - apparently b/o ↓ sunlight exposure

Special Group: An important group to be aware of when it comes to PAC is:

African American Men (abbreviated as AAM)

AAM have a *HUGE* risk for developing Prostate Ca

AAM develop **almost 2x as much** PAC as their white brethren in the USA

AAM have the **highest risk of any male population in the world** for PAC

-even more than the Scandinavian guys. (see above)

African American Men and Prostate Cancer

Prostate Cancer	For every 100,00 men	
	African American	Caucasian
Develop it	240	150
Die from it	55	22
Lifetime risk of death from it	1 in 10	

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II. Things which supposedly **DECREASE** one's risk for developing PCa

- Diets high in Selenium, Vitamin E, Tomatoes (because of Lycopene)
Carotenoids, Fish and Omega Fatty Acids, Soy
Cruciferous vegetables, Polyphenols.

Prevention in Prostate Cancer

The Finasteride Trial (Finasteride = 5 α reductase inhibitor)

There was a large Finasteride prevention trial performed in PAC

They gave 18,000 men Finasteride for 7 years to see if it would prevent PAC

Result:

There was a 25% reduction in PAC in the group treated with Finasteride

But those who DID get PAC had **higher grade** (more aggressive) tumors.

And there was **no difference in survival** between those who received Finasteride and those who did not.

Staging in Prostate Cancer

Gleason's Score (Gleason's Grading) of the Prostate Biopsy

Pathologists:

Grade a first biopsy specimen from 1 \rightarrow 5 =X

Grade a second biopsy specimen from 1 \rightarrow 5 =Y

To arrive at the **Gleason's Score** they then **add X + Y above**.

The **higher the number** = the **more aggressive** the Prostate Ca.

A Gleason Score of: **2 to 3** = **less** rapidly growing / less aggressive

8 to 10 = **more** rapidly growing / more aggressive

Pathology in Prostate Cancer

I. Adenocarcinoma = remember that just about all PAC is an AdenoCa

II. Others = there are other rare cancers that arise in the prostate
but these are very rare.

Pathology in Prostate Cancer (Cont'd)

III. Metastasis to the Prostate

An interesting side note is that of the rare tumors which metastasize **to** the prostate, **Lymphomas and Leukemias** are among the most common.

New Diagnostic developments in PAC

There is now an FDA approved Radio Immunoconjugate stain to image the prostate → its called **Copromab Penetide**.

TNM Staging in Prostate Cancer

TNM Staging in Prostate Cancer is very complex with many numbers and letters, but it makes sense to review it for the boards.

Its too long and complex to go over in detail here, but a few stages are:

T1c = Prostate Ca with ↑ PSA but **not palpable** via digital rectal exam (DRE).
Because of the widespread use of PSA screening, DRE and then biopsies,
This is the **stage at which most prostate cancer is diagnosed**.

T2c = Prostate Ca in **both lobes** of the prostate.

Cost Consciousness

In this day and age of cost consciousness, the boards are likely going to want you to know when to order an extensive work up or not.

Thus: Do not order a CT Scan of the Abdomen unless:

The **PSA > 20**

The Gleason's Score **is >7** →

Below these values the low

likelihood of a positive result
does not justify the expense.

Early detection of Prostate Cancer

Because of the widespread use of:

PSA + DRE (digital rectal exam) followed by biopsy of anything suspicious,
these days most prostate cancer is diagnosed at stage **T1c** (see above)

- which is a stage where the cancer is **non-palpable**.

Screening For Prostate Cancer

The key with early Dx in PCa is to use the PSA + DRE on a **Specific** population (i.e. for example, men with ↑ family histories)

To use PSA+DRE on everyone = screening - and this is controversial.

Controversies exist with screening because:

No randomized study has proven that screening = decreases mortality.

Note: Some things to remember if they ask you on the boards:

- Trans-rectal Ultrasound has **no role** in screening for PCa
- The DRE does not raise one's PSA by much (if anything at all).
- The half life of PSA = 2-3 days

Biopsy of the Prostate

When to do a biopsy of the prostate:

Do a biopsy If: **The DRE is abnormal on palpation**
or: **The PSA is > 4**

Sensitivity and Specificity of the PSA

If the PSA > 4 its **Sensitivity** in finding PCa = 80%
its **Specificity**, however, remains only = 15% - 20%

Thus there now are various **things to improve the specificity of PSA:**

A. PSA Density

This is because PAC produces less PSA than BPH does

Thus: PSA Density is: $\frac{\text{Serum PSA}}{\text{Volume of the Prostate}}$ if: its <0.15 = bad sign

B. PSA Velocity

This is the rate of change of the PSA level over time

Thus: $\frac{\text{Serum PSA}}{\text{Time}}$ If: it goes ↑ more than 0.75/yr = bad sign

Things to improve the specificity of PSA (Cont'd)

C. PSA Percent Free circulating

PSA circulates attached to β_2 macroglobulins or α_1 antichymotripsin

Thus:
$$\frac{\text{Free PSA}}{\text{Total PSA}}$$
 If: **lower** free PSA = bad sign (see below)

Percent probability of developing PAC			
Free : Total PSA ratio	50-59 years	60-69 years	> or =70 years
< or =0.10	49.2%	57.5%	64.5%
0.11-0.18	26.9%	33.9%	40.8%
0.19-0.25	18.3%	23.9%	29.7%
>0.25	9.1%	12.2%	15.8%

Source: Mayo Clinic Laboratories

Management of Prostate Cancer

As in all cancers, the key in decision making with regards to management is the amount of tumor spread at the time of diagnosis (i.e. the Stage)

Remember that in this day and age of DRE + PSA most Prostate Ca is diagnosed while it is still only confined to the Prostate → i.e. Stage T1c.

Therefore, a key aspect of therapy is therapy when the tumor is still located only to the Prostate - or Early Stage Prostate Cancer.

I. Management of **EARLY STAGE** Prostate Cancer

Remember that in this day and age of DRE + PSA, **most** Prostate Cancer is diagnosed in this early stage (i.e. stage T1c).

Early stage Prostate Cancer is basically prostate cancer that is diagnosed at a time when the tumor is entirely **confined only to the prostate gland**.

I. Management of EARLY STAGE Prostate Cancer (Cont'd)

For Stage T1c Prostate Ca one can do either:

- Surgery (radical prostatectomy)
- Radiation Therapy
- Watchful waiting

→ Any one of these choices are "ok" with the Am Urologic Association

The **choice** of which treatment modality one chooses depends on:

- The **age** of the man
 One should not do "watchful waiting" on a 'young' (<55 y/o) guy
 Younger patients tend to choose surgery rather than radiation.
- Patient **preference** - i.e.
 The **side effects** he is willing to tolerate (see table below)
 How strong his **fear of a recurrence**.

Arguments for / against either form of therapy for EARLY STAGE Prostate Ca		
	Surgery	Radiation
Impotence	Greatest right after surgery → but improves with time	Less right after radiation → but gets worse with time
Urinary Incontinence	Yes	No (or much less)
Urinary Frequency	No	Yes. (Implants cause it)
Diarrhea	No	Yes (radiation colitis)
Interrupts Work/Life	Yes. Needs to take time off for recovery after surgery	No. Can schedule radiation treatments around work
In order to be effective	Must remove ALL prostate tissue	Must give > 70 Gray
Combine with ADT	No. Adding ADT to surgery Does not improve effectiveness	Yes. Adding ADT to radiation therapy improves effectiveness
Cure Rate	About the same as Radiation	About the same as Surgery
	(some studies have suggested that over time - years - there is a small tendency to greater cure with surgery than with radiation)	

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I. Management of **EARLY STAGE** Prostate Cancer (Cont'd)

A. **Surgery for Early Stage** Prostate Cancer

This is typically a Radical Prostatectomy

Eliminates all Prostate tissue and thus, presumptively, all PAC

Incontinence risks are greater with surgery than with radiation therapy

Impotence: In this day and age with improved surgical techniques, the risk of impotence following radical prostatectomy is much less

Right after surgery, impotence if it is going to occur, is greatest → but it tends to improve over time (whereas with radiation therapy, impotence, when it develops, tends to worsen with time)

Younger men (<60 y/o) tend to choose surgery more frequently for their localized PAC rather than radiation therapy.

Over years surgery is a little statistically better for a cure than XRT

Surgery interrupts a man's work schedule (time off work for recovery)

B. **Radiation therapy for Early Stage** Prostate Cancer

Radiation (abbreviated as XRT) is considered equal to surgery.

Remember that it needs to be at least > 70 Gray

Remember that Radiation + ADT = improves results/response

Radiation sooner (rather than later) after the Dx is made = helps

XRT for PAC is usually the combination of external beam radiation + implants directly into the prostate.

The implants may cause radiation cystitis and ↑ urinary frequency

The radiation may cause radiation colitis and ↑ diarrhea

Older men (>60 y/o) tend to choose radiation more frequently for their localized PAC rather than surgery.

Radiation therapy does not interrupt a man's work schedule (he can schedule his radiation treatments around work hours).

C. **Watchful Waiting for Early Stage** Prostate Cancer

This is based on the idea that most men will die from other causes (such as heart disease) *with* their PAC and not *from* their PAC.

Thus in older men (>60 y/o), with "good risk" Prostate Cancer this approach advocates to do nothing about their PAC other than to monitor them closely until they develop reasons (symptoms, metastasis, etc) for which to start therapy → typically with ADT at that point.

This approach is considered in men >60 - not in men in their 50s

(Note: In recent articles [NEJM May 12, 2005], this approach has come into question).

II. Management of **ADVANCED** Prostate Cancer

Remember that PAC → osteoblastic bone metastasis (not osteolytic)
The treatment options for advanced PAC are basically:

- I. **ADT** (Androgen Deprivation Therapy)
- II. **XRT** (to painful bony mets)
- III. **Chemotherapy**
- IV. **Newer therapies**

→ The choice of therapy depends on clinical symptoms and disease progression

I. **ADT (Androgen Deprivation Therapy) in Advanced Prostate Ca**

ADT is typically used in metastatic and/or advanced Prostate Ca
Early Stage Exception: Remember that in Early Stage Prostate Ca
ADT + Radiation Therapy → better results than Radiation alone.
Prostate cancer which responds to ADT → "**Hormone Sensitive**"

A. Drugs which **PHYSICALLY LOWER** Testosterone levels

I. *LHRH Agonists*

- Leuprorelin (Lupron)
- Goserelin (Zoladex) → remember that these are *agonists* as such, when you first give these they produce an all-important **FLARE REACTION** (see below)
- Deslorelin
- Buserelin
- Histrelin
- Nafarelin

II. *Estrogens*

Important Note: **Flare Reaction** : Remember that the LHRH *agonists* are indeed agonists. This means that they initially *stimulate* the secretion of LHRH when you first give them with a resultant **initial sharp increase** in serum Testosterone (which is called the "Flare" reaction). Over time, of course, LHRH agonists cause LHRH to become depleted and to then go down and then Testosterone goes down as well - but initially they both go up. Thus, when you first give a LHRH agonist, it is best to **combine it with a Non-Steroidal Antiandrogen** in order to block the binding of all that initial excess Testosterone with its receptors. If you fail to do this, the initial start of a LHRH agonist could cause serious adverse problems (fractures, hypercalcemia, etc) because of this initial "Flare" reaction. (Note: see Degarelix on page 12 below)

B. Drugs which **BLOCK** Testosterone from binding to its receptor on the cells

I. The *Non-Steroidal Antiandrogens*

- Flutamide (Eulexin)
- Bicalutamide (Casodex)
- Nilutamide (Nilandron)

Remember*

Antiandrogens + **Surgery** = No

Antiandrogens + **Radiation** = Yes

* Surgery + ADT → does **not** improve response rate compared with surgery alone

Radiation Therapy + ADT → **yes** improves response rate compared with radiation alone.

C. Drugs which **BLOCK THE CONVERSION** of Testosterone in the tissues from weaker Testosterone to the more potent DiHydroTestosterone (DHT). These drugs are the:

I. *5 α Reductase Inhibitors*

Finasteride (Propecia or Proscar)

→

Note: These are

Dutasteride (Avodart)

mainly used in BPH

D. Chemical Castration

The key in ADT is that you need to decrease the serum testosterone level down to the level which it would be if you surgically remove the testicles → this is why it is called a **Castration Level** of Testosterone (which is < 50 ng/ml). Achieving this low level via the use of medications is called a **Chemical Castration** (i.e. versus a surgical castration).

The best way to achieve "castration levels" of serum Testosterone (which is < 50 ng/ml) is to give **both** a GnRH agonist + a Non-steroidal Antiandrogen.

In light of the above, this is why when a Prostate Cancer progresses/grows/spreads even while the patient is still receiving ADT, that cancer is then called a **Castration Resistant** Prostate Cancer.

Castration Levels of serum Testosterone

Getting the serum level of Testosterone down to "castration levels" is key. If one never gets the level of Testosterone down below 50 ng/ml, then it is not possible to say that the patient failed ADT.

Important Note: **Castration Resistant Prostate Cancer:** If a patient develops metastasis and/or tumor progression while on ADT, you **first need to draw and check a serum Testosterone level** to make sure that his serum level was indeed <50 ng/ml at the time of tumor Progression (i.e. that the patient had "castration levels" of serum Testosterone at the time of tumor progression and not that the tumor progression was, perhaps, due to poor compliance with the ADT medications) in order to be able to be certain that his Prostate Cancer is indeed now "Castration Resistant".

Important Note: **Antiandrogen withdrawal Therapy:** Over time it is sometimes possible that the Antiandrogens themselves may be stimulating the growth of the Prostate Cancer. Thus, once the initial diagnosis is made of a patient having becoming "castrate resistant", sometimes stopping the Antiandrogens → produces an antitumor response.

Second line Antiandrogen Therapy: If Antiandrogen withdrawal does not work, it sometimes helps to try *Second Line Antiandrogen Therapy* such as

- Ketoconazole + Hydrocortisone
- DES (estrogen)

Side Effects of Androgen Deprivation Therapy (ADT)	
Short Term Side Effects	
• ↓ Libido	• Impotence
• ↓ Muscle	• Osteoporosis → Important side effect
• ↑ Body Fat	Use: Zometa, Prolia, to ↑ bones
Long Term Side Effects	
• Insulin Resistance	• ↑ Cardiovascular Mortality
• Hyperglycemia and Diabetes	• Hyperlipidemia
• Metabolic Syndrome	• ↓ Penis size, ↓ Testicle size
• ↓ Male pattern baldness	• Anemia of 'chronic disease'
• Gynecomastia	• Fatigue, Depression, Emotional lability
• Liver Damage → this is especially a side effect of Non-Steroidal Antiandrogens	

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II. Radiation Therapy in Advanced Prostate Ca

This is usually reserved as therapy to decrease bone pain in mets.

For **extensive bone mets**, it is possible to give radiation therapy in the form of :

- Strontium 89 (Metastron)
- Phosphorus 32
- Samarium 153

III. Chemotherapy in Advanced Prostate Ca

Is shown to **only** be of benefit in pts with **known metastatic disease**

It has **NOT** shown to benefit "castrate resistant" pts with **no measurable Dz**

First Line Chemotherapy:

- A. Docetaxel Therapy → seems to offer an **↑ overall survival** benefit
→ is better than Mitoxantrone
→ Docetaxel + Prednisone
is **FDA approved as 1st Line** therapy for
"castrate resistant" prostate Ca

Second Line Chemotherapy:

- B. Mitoxantrone

Pain Control Chemotherapy:

- C. Mitoxantrone + Prednisone → **FDA approved** for pain control in PAC

IV. New Agents in Advanced Prostate Ca

A. Sipleucel-T (**Provenge**®)

Collects the person's white cells and then uses a vaccine approach to generate an immune antitumor response.

Was shown to **improve survival by 4 months** in patients with very advanced Prostate Cancer. It is very expensive.

Minimal side effects → flu-like symptoms such as:

(runny nose, watery eyes, mild bony aches) → Tx w Tylenol

IV. New Agents in Advanced Prostate Ca (Cont'd)

B. Ixempra

Is an Epithilone

Dec 2005 issue of JCO issue → possibly helps advanced PAC

C. Degarelix

FDA-Approved for **hormone-sensitive** PAC in December 2008

Blocks GnRH receptor on Prostate Cancer tissue

Works the same way as the LHRH agonists but avoids the "FLARE"