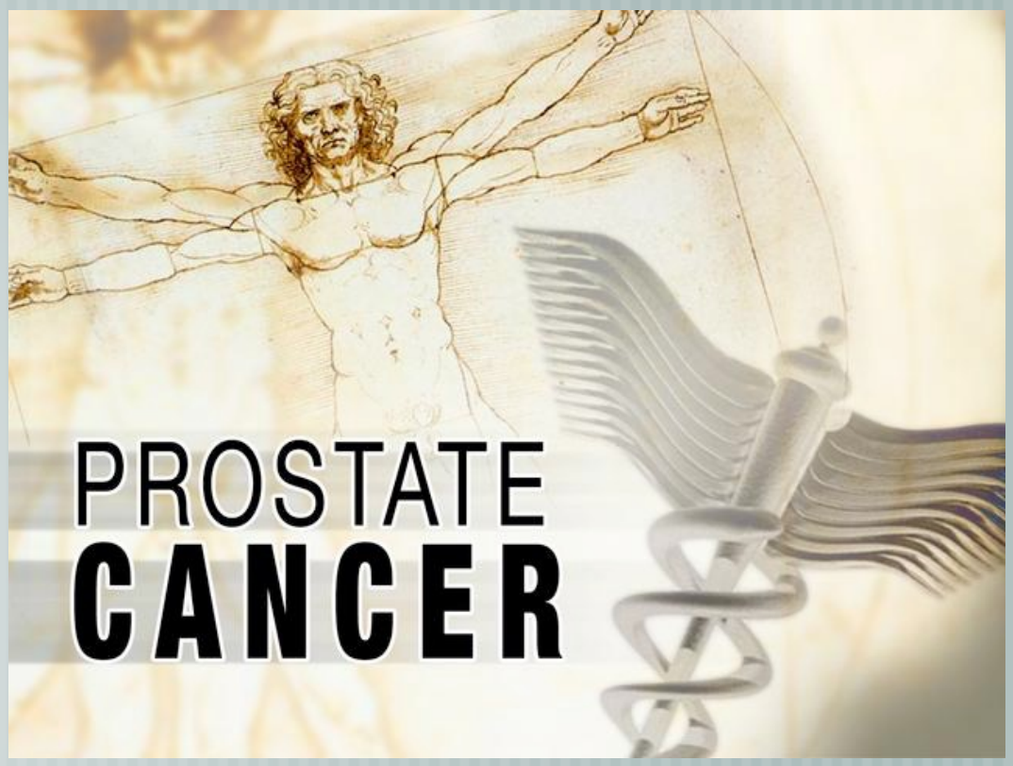
ADENOCARCINOMA OF THE PROSTATE

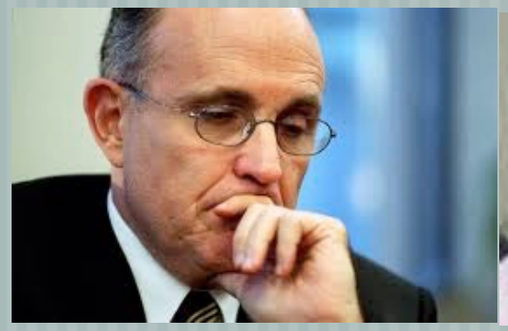
WHAT IS NEW

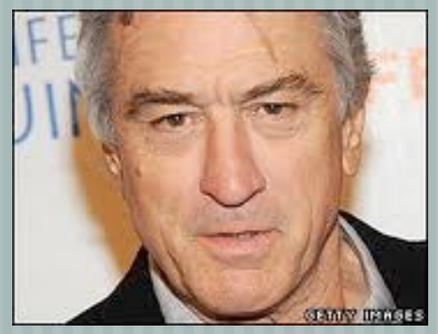
STEVEN PALETSKY M.D.

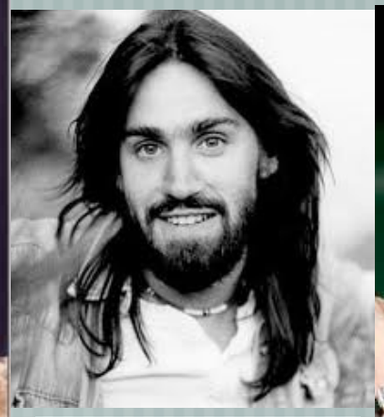
FLORIDA SPECIALISTS IN UROLOGY

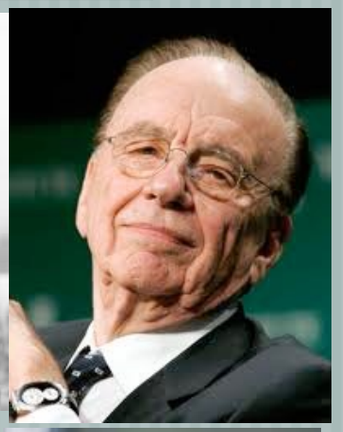


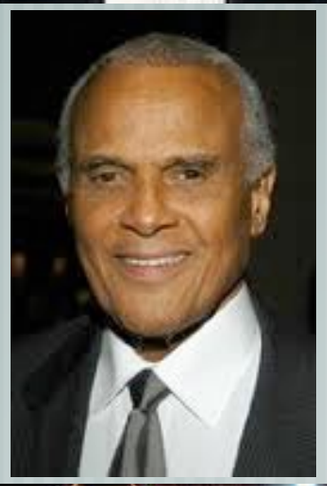
FAMOUS MEN WITH PROSTATE CANCER

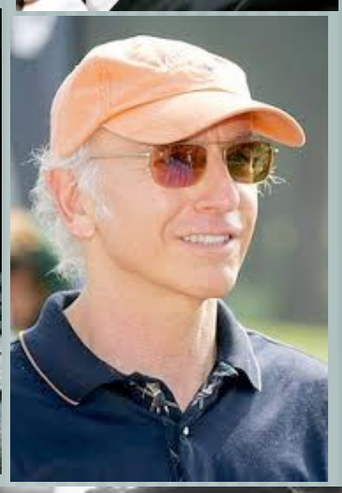


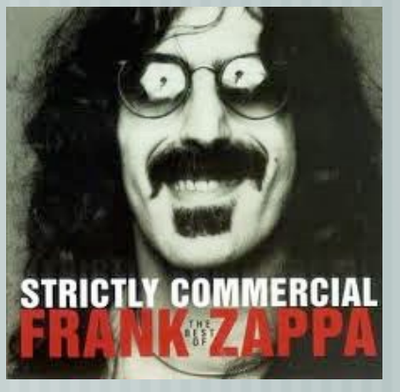


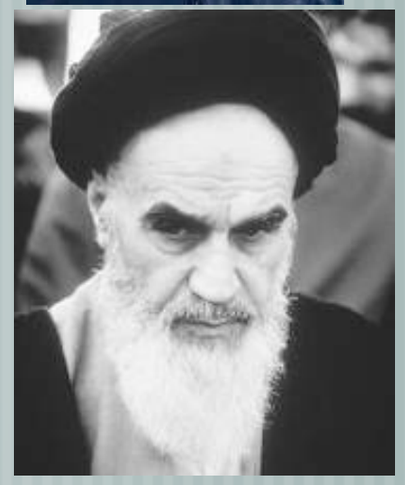












PROSTATE RISK CALCULATOR

Individualized Risk Assessment of Prostate Cancer

Enter Your Information

Race

Age

PSA Level ? ng/ml

Family History of Prostate Cancer ?

Digital Rectal Examination ?

Prior Prostate Biopsy ?

Calculate Cancer Risk

Adjusted Prostate Cancer Risk Calculators

BMI
PCA3
Finasteride
%freePSA
[-2]proPSA
%freePSA and [-2]proPSA

Useful Links for Prostate Cancer

National Cancer Institute
American Cancer Society

Other Individualized Risk Assessment Tools for the Family

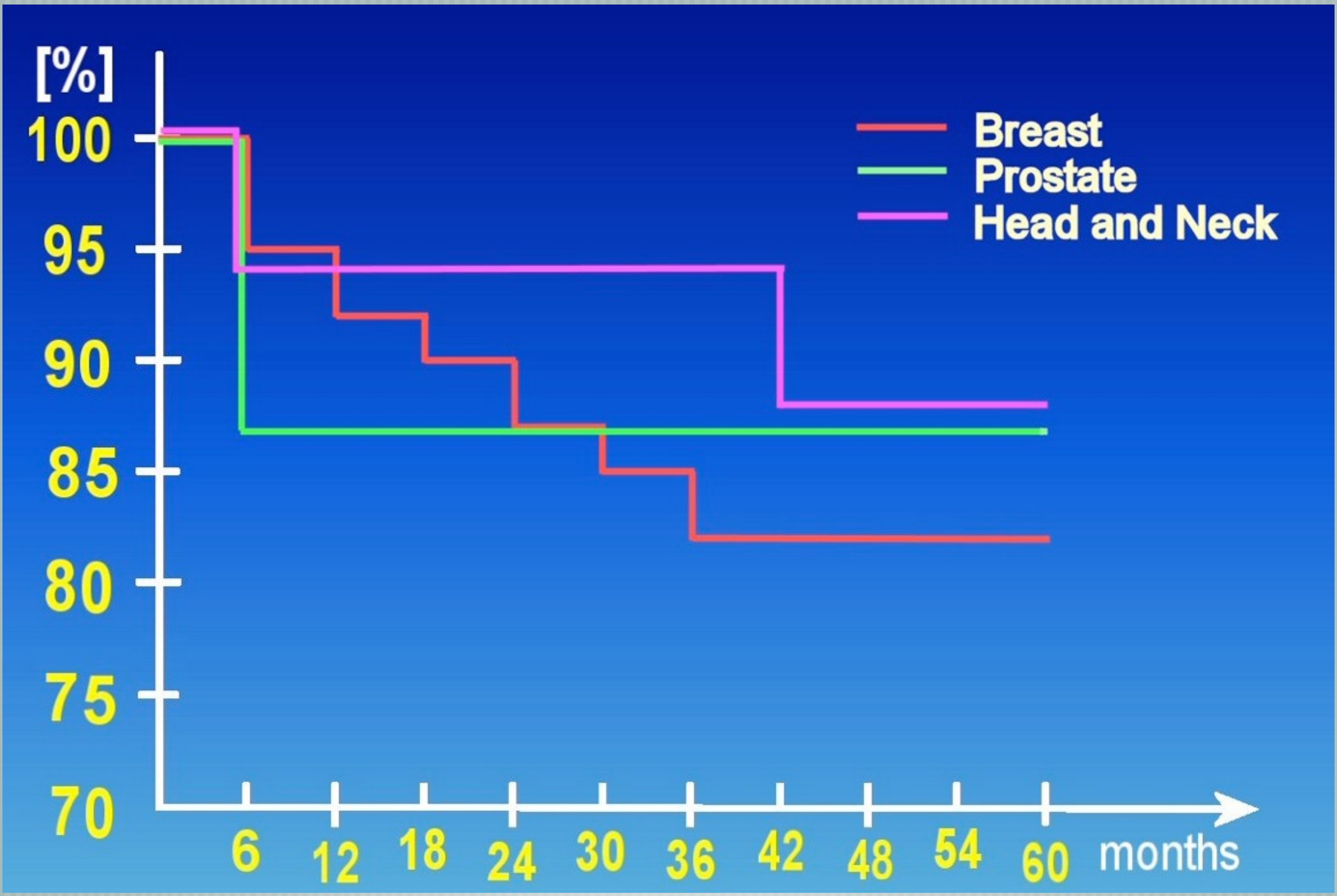
Breast Cancer
Colorectal Cancer
Lung Cancer

Figures Formulas R Code Disclaimer

Incidence Rate by Race

Race/Ethnicity	Male
All Races	156.0 per 100,000 men
White	149.5 per 100,000 men
Black	233.8 per 100,000 men
Asian/Pacific Islander	88.3 per 100,000 men
American Indian/Alaska Native	75.3 per 100,000 men
Hispanic	107.4 per 100,000 men

SURVIVAL FROM DIAGNOSIS



Prostate Cancer
Autopsy studies

- 40 - 50 Y.O. - 1/3 risk of harboring small cancers

- 60 - 70 Y.O. - 60% risk of Prostate cancer

- Lifetime Risk of being diagnosed with prostate cancer is 1 in 7

- Highest Risk - Westernized Nations
  Lowest Risk - Asian Nations

DIAGNOSIS

DIAGNOSING PROSTATE CANCER

PSA

- Glycoprotein
- Produced by prostate epithelial cells
- Free or Complexed (bound to protein) = Total PSA

CANCER	< 5%	F/T ratio
BENIGN	>28%	F/T ratio

FOLLOWING THE PATIENT

PSA value - age related values

PSA velocity - increase of 0.4 ng/ml for patients under 60 yrs old
0.75 ng/ml for patients over 60 yrs old

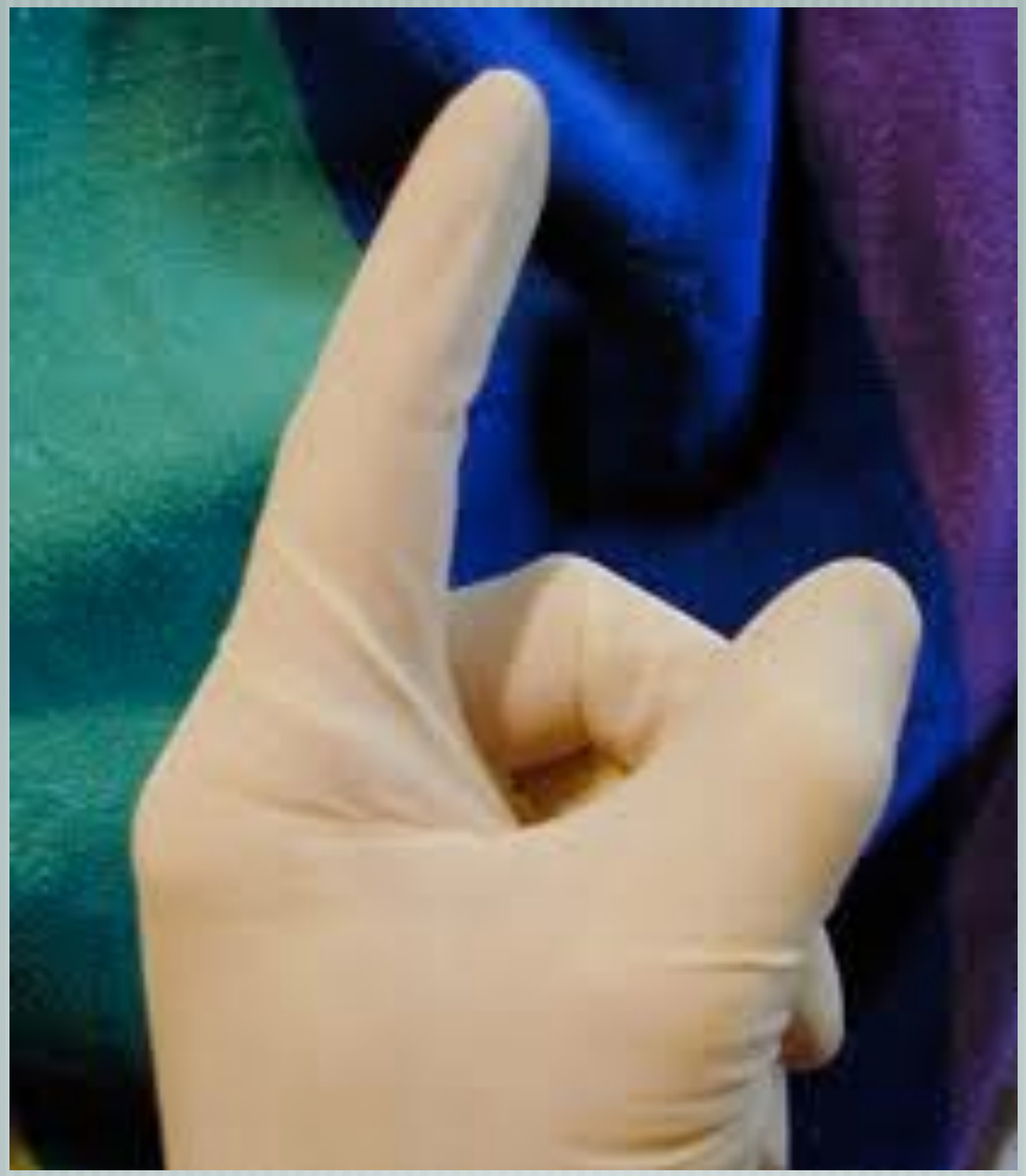
PSA density - PSA / prostate volume (0.15 ng/ml)

AGE RELATED PSA

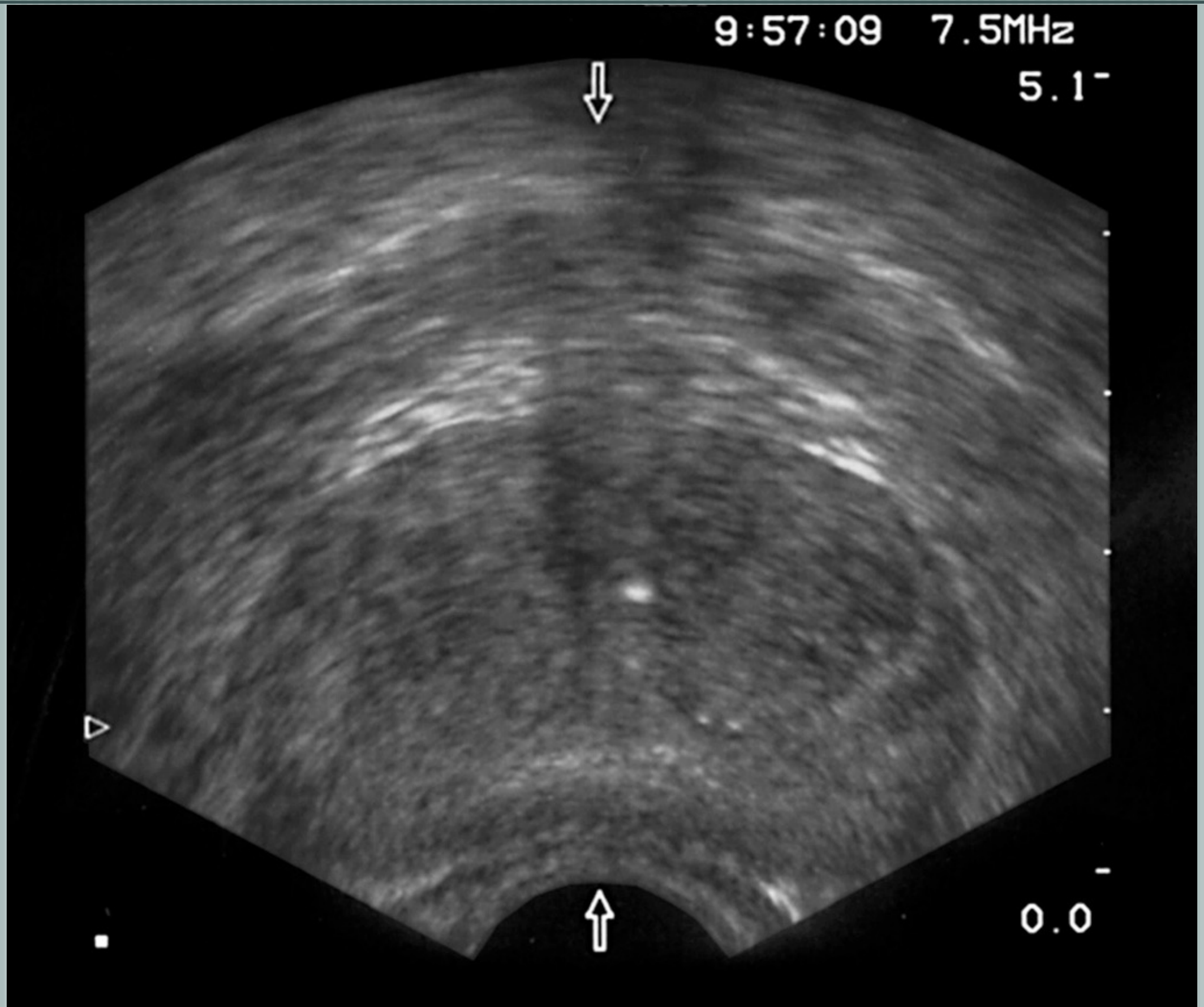
AGE (years)	PSA cut-off (mg/ml)
50 - 59	> 3.0
60 - 69	>4.0
70 +	>5.0

Note: For patients taking finasteride consider doubling the PSA results

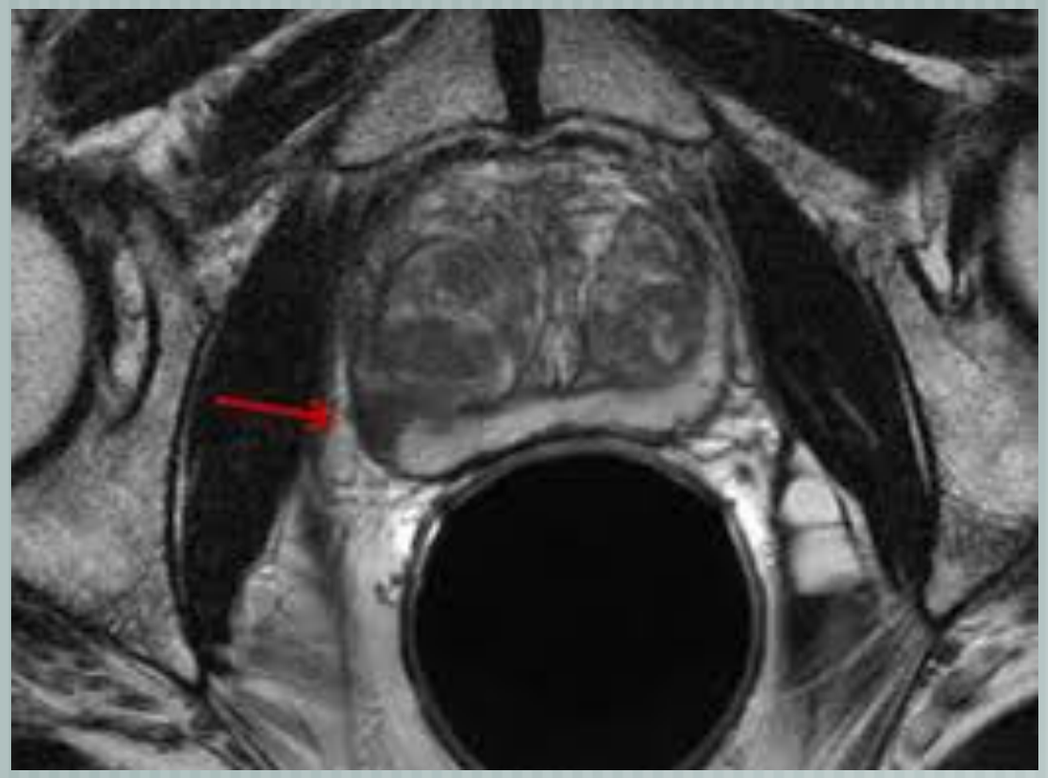
DRE

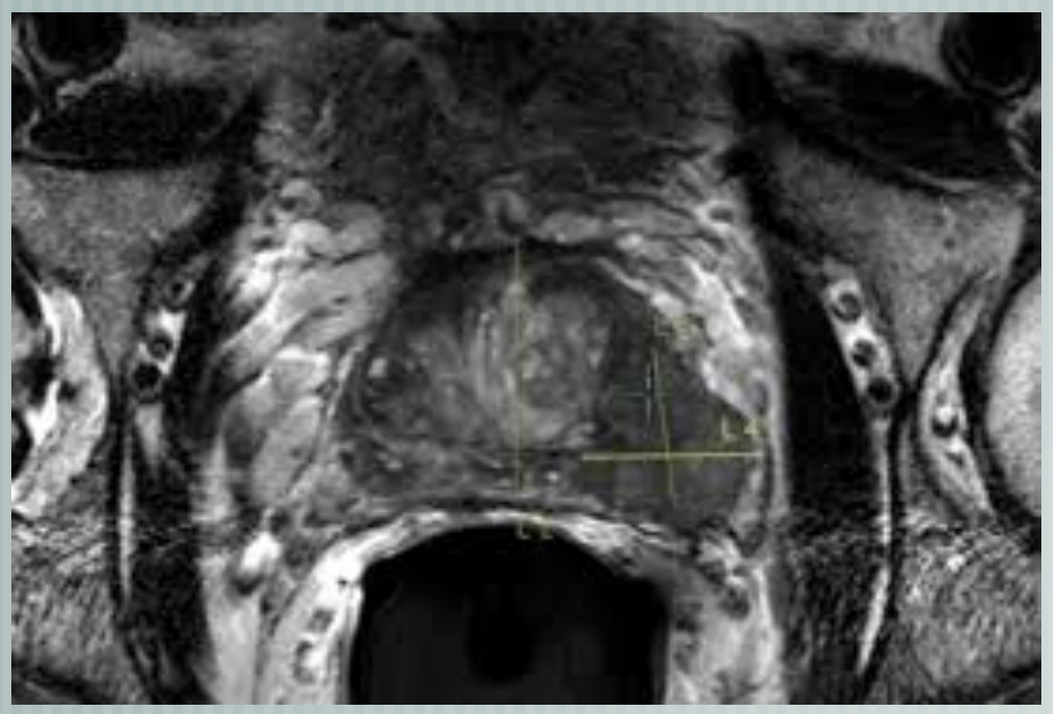


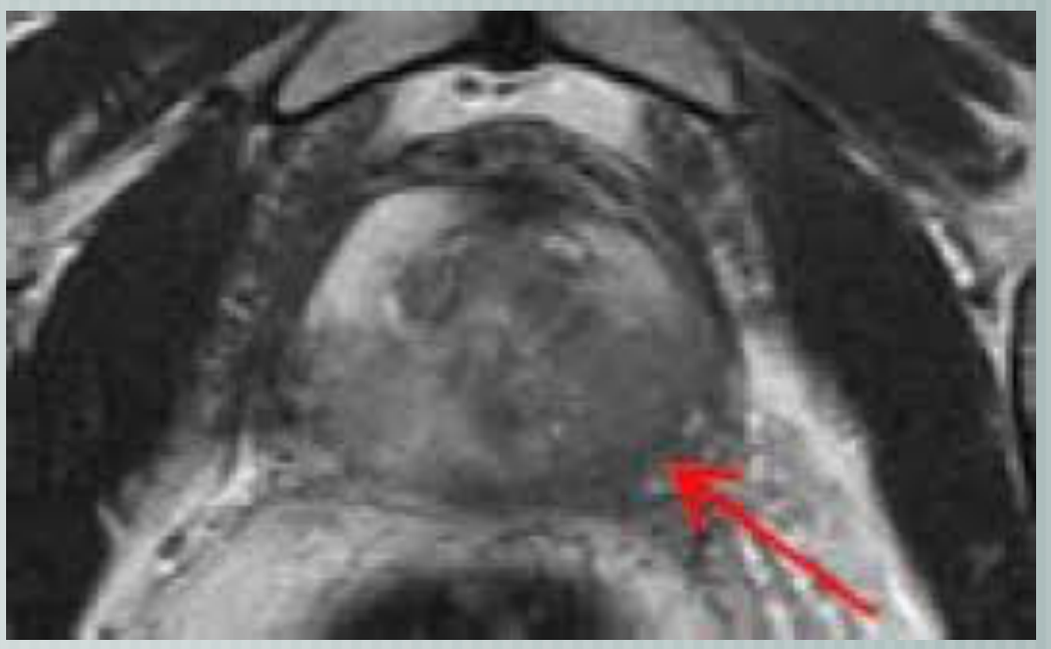
ULTRASOUND



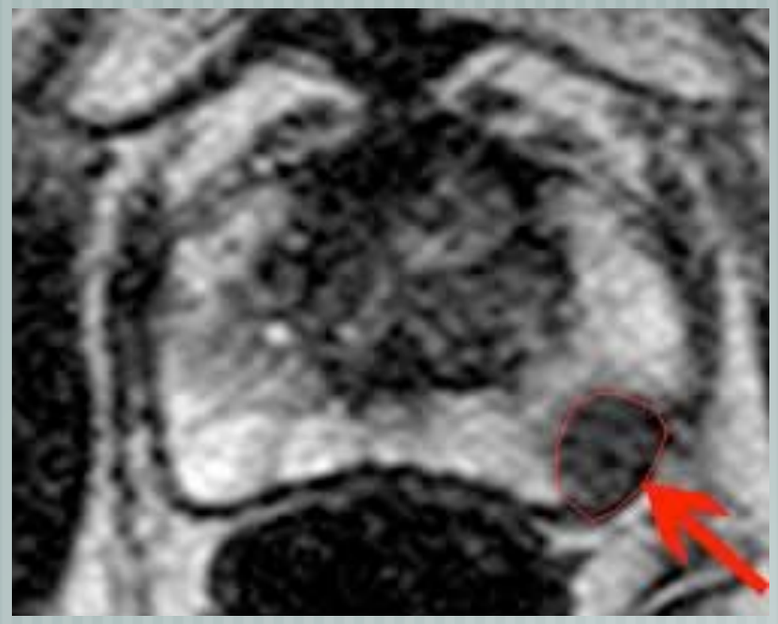
MRI

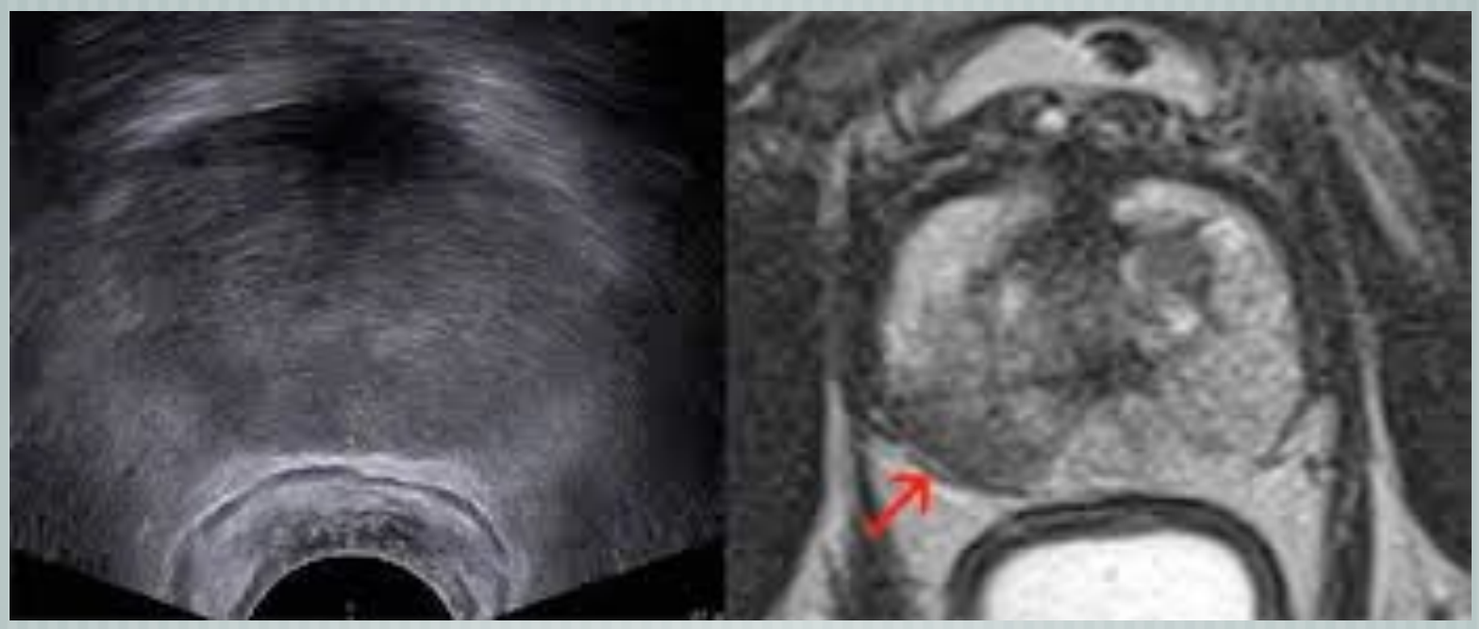






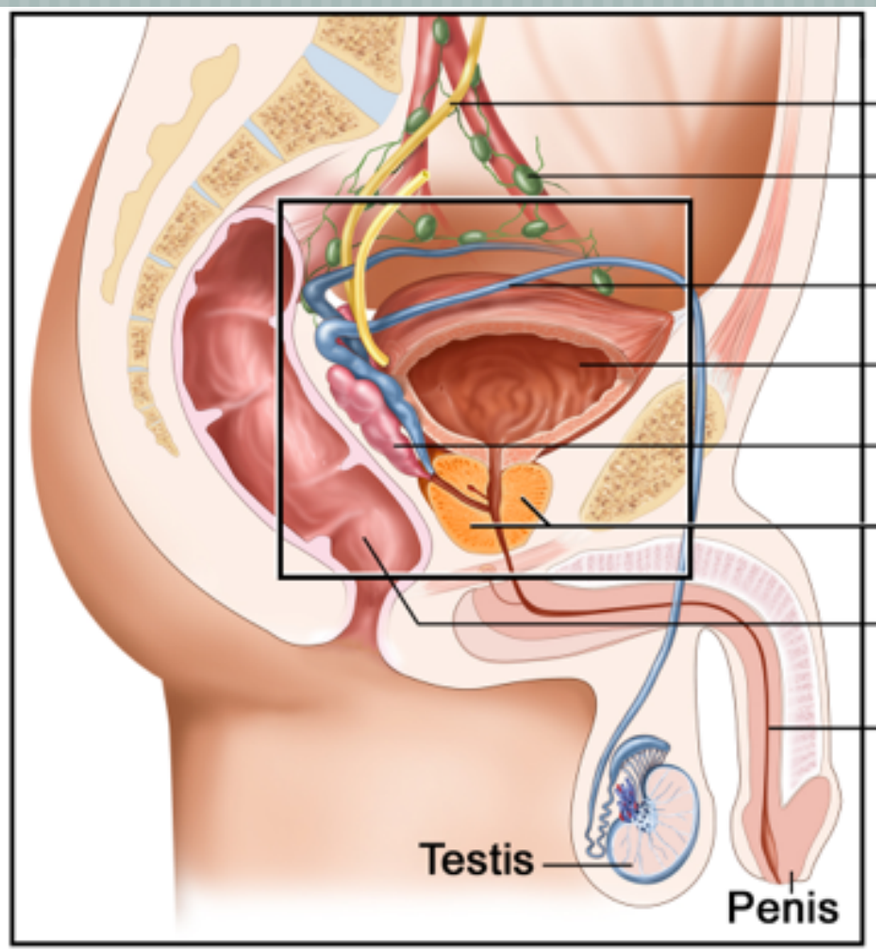
MRI - ULTRASOUND FUSION

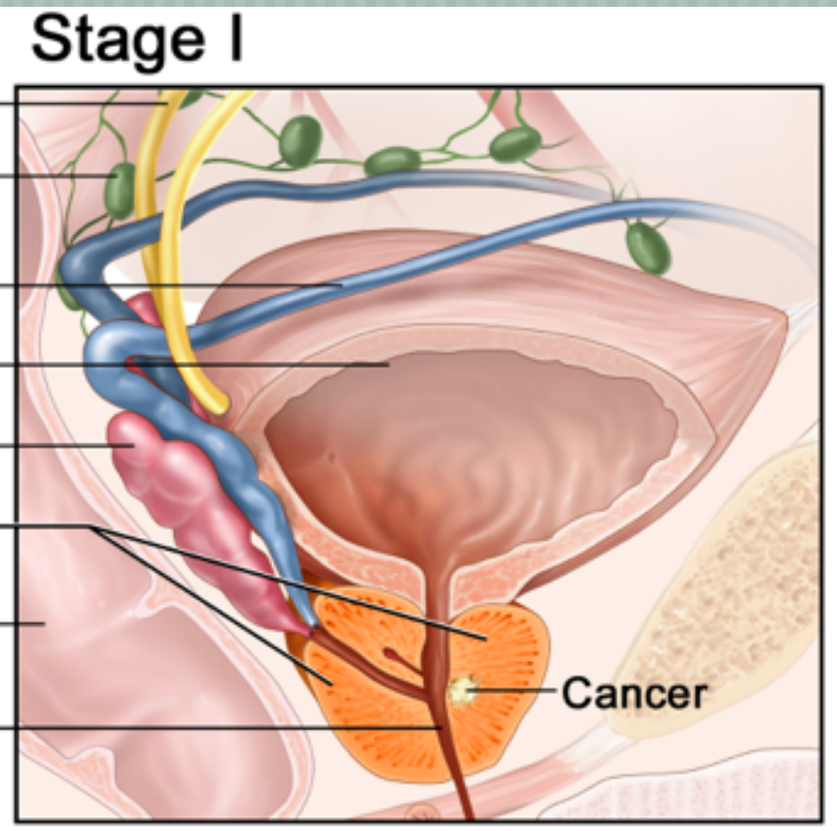


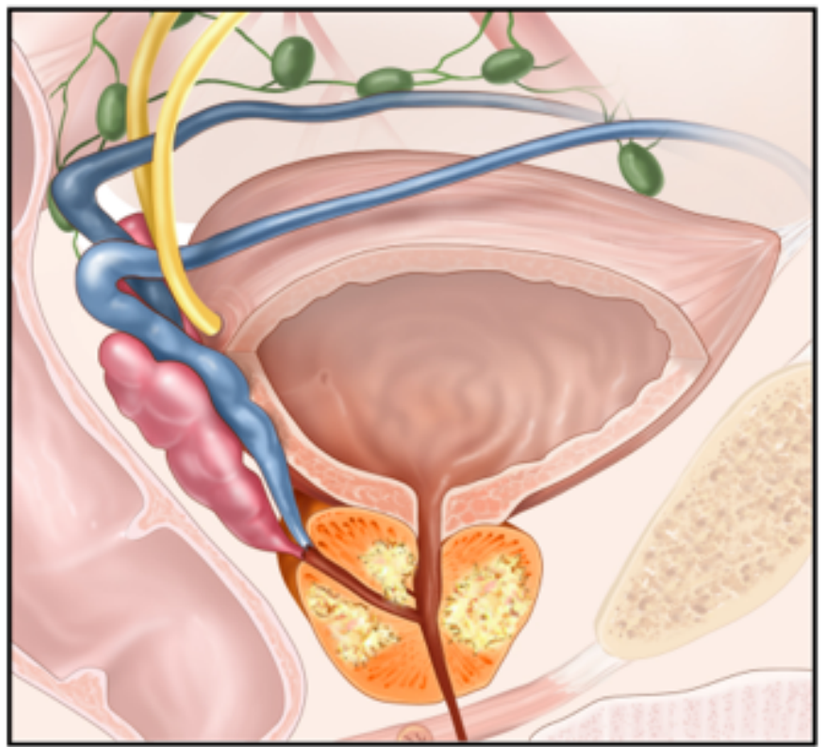


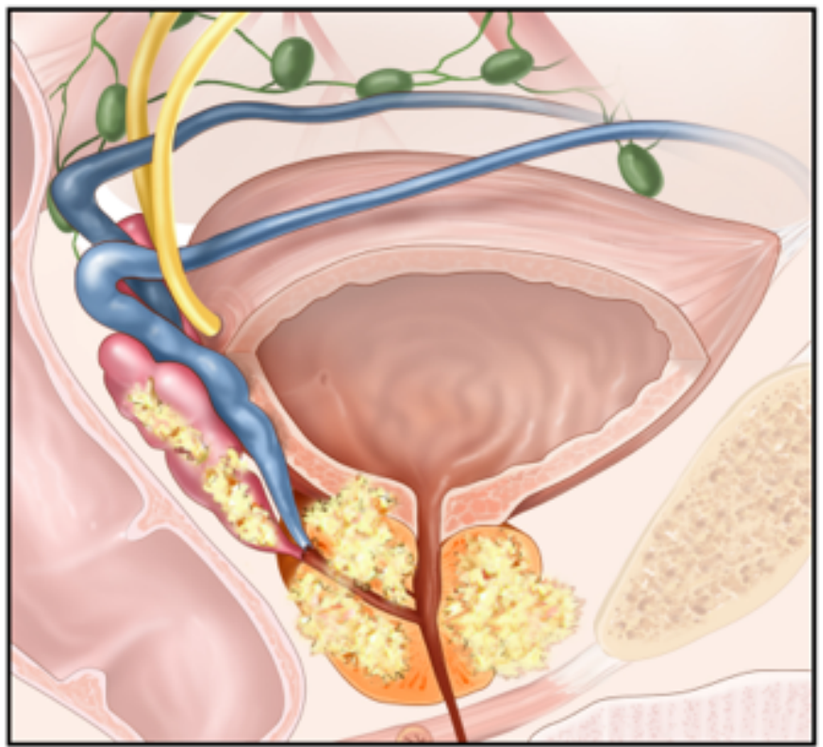
STAGING

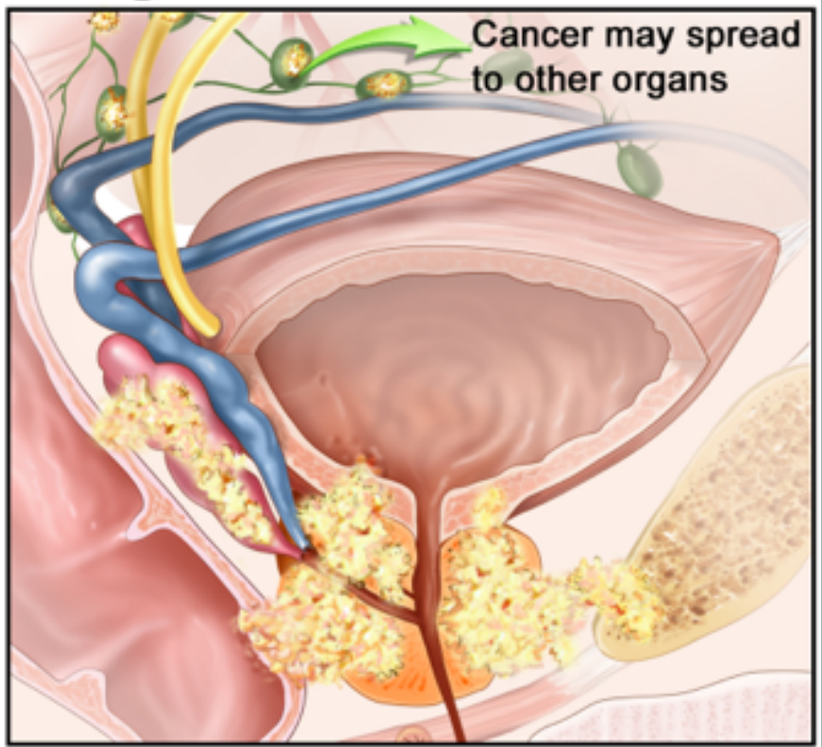
PROSTATE STAGING









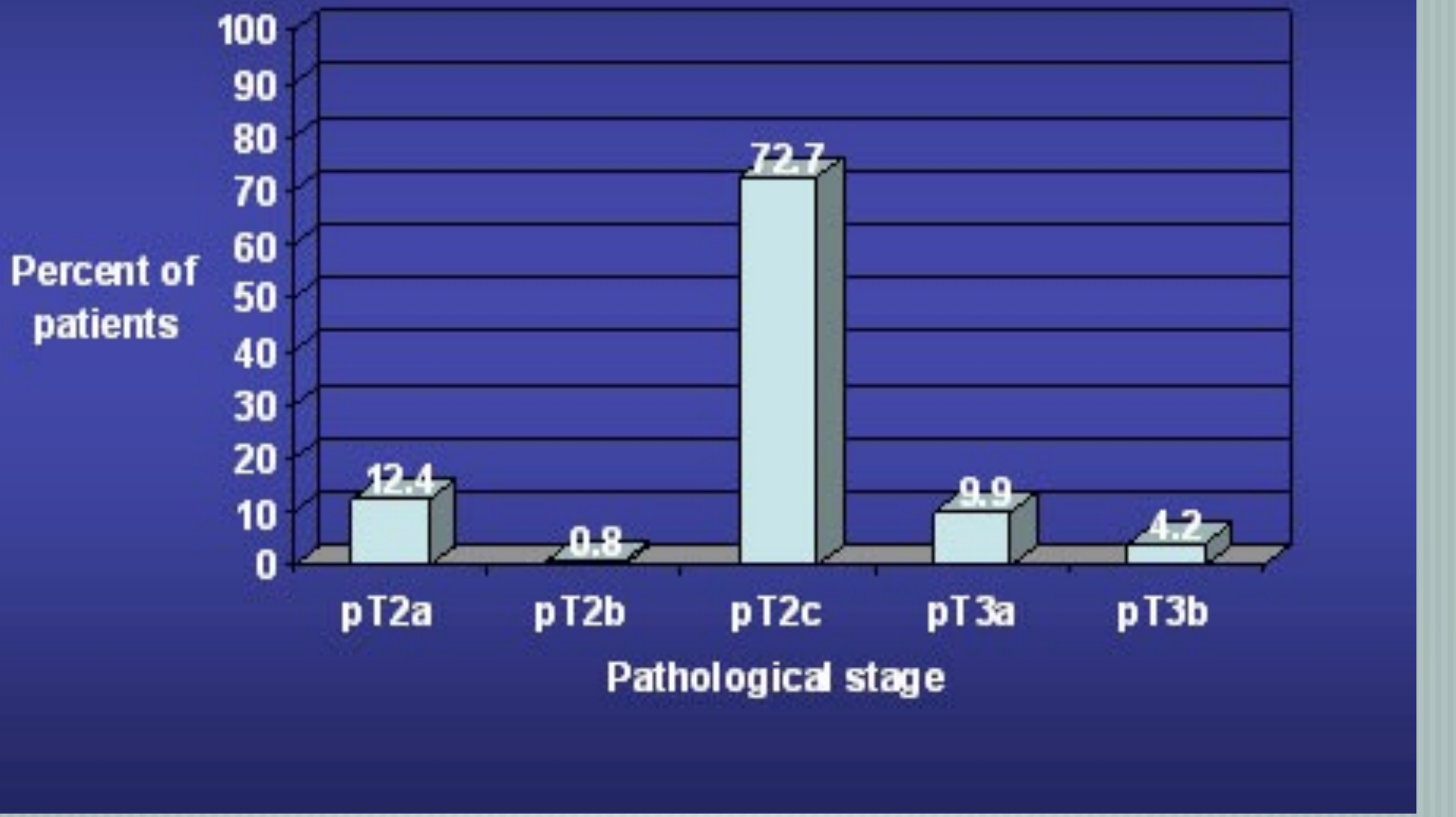


T (tumor)	TX: tumor cannot be assessed TO: no evidence of primary tumor
	T1: tumor not clinically apparent T1a: tumor found in resected specimen (<5%) T1b: tumor found in resected specimen (>5%) T1c: tumor found at biopsy for elevated PSA
	T2: tumor confined to prostate T2a: tumor involves one lobe of prostate T2b: tumor involves both lobes of prostate T3: tumor palpable, extends beyond capsule T3a: tumor extends beyond capsule (unilateral, bilateral) T3b: tumor invades seminal vesicles T4: tumor is fixed or invades adjacent anatomy (other than seminal vesicles)
N (node)	NX: regional lymph nodes cannot be assessed NO: no regional lymph node metastasis N1: metastasis to regional lymph node(s)
M (metastasis)	MX: presence of distant metastasis cannot be assessed M1: distant metastasis M1a: metastasis to nonregional lymph nodes M1b: metastasis to bone M1c: metastasis to other distant sites

Used with the permission of the American Joint Committee on Cancer (AJCC). Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Manual, Sixth Edition* (2002) published by Springer-Verlag, New York.

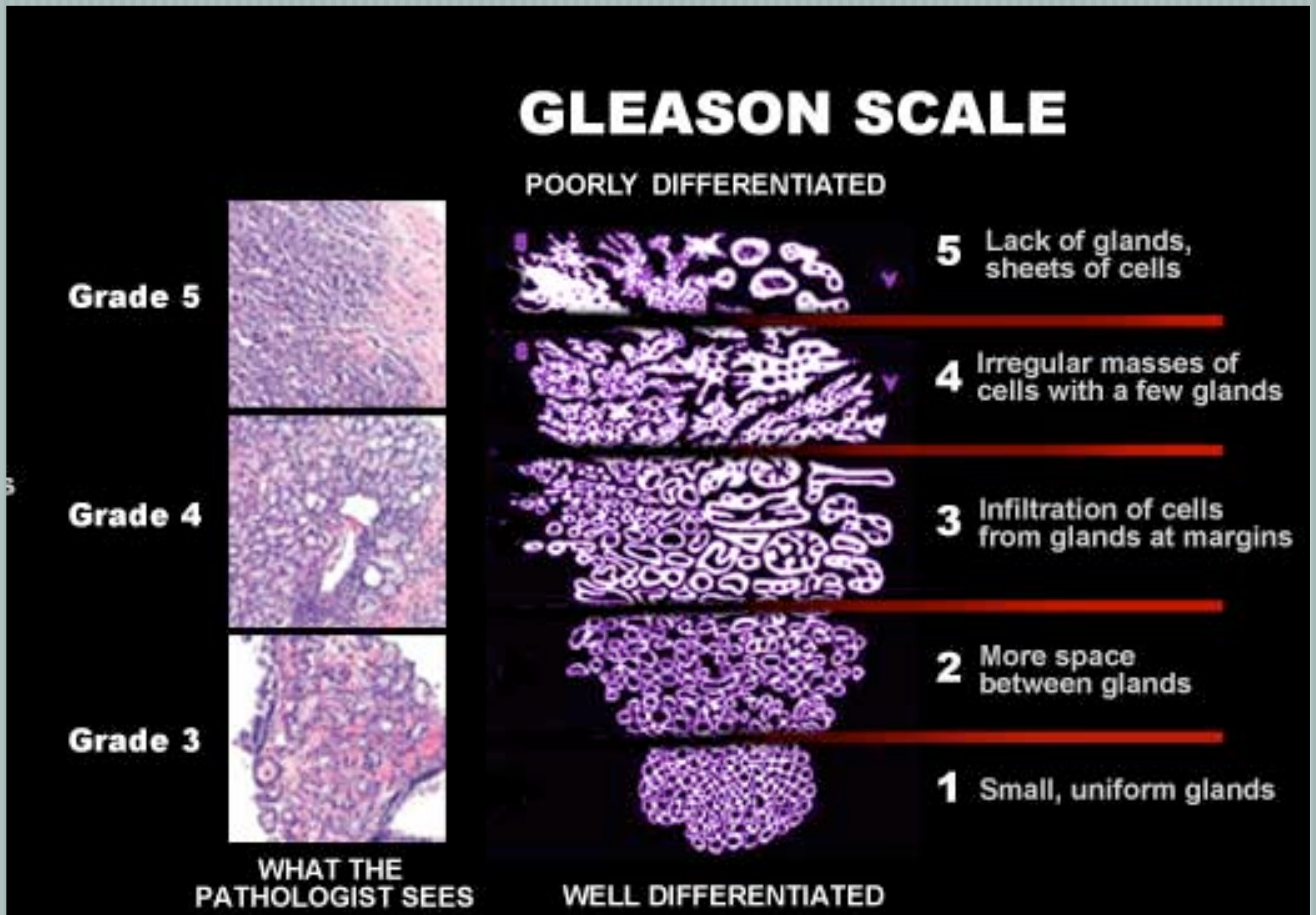
STAGING - TNM

Pathologic staging



GRADING

GRADING


GLEASON SCALE
POORLY DIFFERENTIATED
Grade 5
Grade 4
Grade 3
5 Lack of glands, sheets of cells
4 Irregular masses of cells with a few glands
3 Infiltration of cells from glands at margins
2 More space between glands
1 Small, uniform glands
WHAT THE PATHOLOGIST SEES
WELL DIFFERENTIATED

PROGRESSION TO MALIGNANCY

BENIGN

HGPIN - HIGH GRADE PROSTATE INTRAEPITHELIAL HYPERPLASIA

ASAP - ATYPICAL SMALL ACINAR PROLIFERATION

ADENOCARCINOMA

PARTIN TABLES

TABLE I. *Clinical Stage T1c (nonpalpable, PSA elevated)*

PSA Range (ng/mL)	Pathologic Stage	Gleason Score 2–4	5–6	3 + 4 = 7	4 + 3 = 7	8–10
0–2.5	Organ confined	95 (89–99)	90 (88–93)	79 (74–85)	71 (62–79)	66 (54–76)
	Extraprostatic extension	5 (1–11)	9 (7–12)	17 (13–23)	25 (18–34)	28 (20–38)
	Seminal vesicle (+)	—	0 (0–1)	2 (1–5)	2 (1–5)	4 (1–10)
	Lymph node (+)	—	—	1 (0–2)	1 (0–4)	1 (0–4)
2.6–4.0	Organ confined	92 (82–98)	84 (81–86)	68 (62–74)	58 (48–67)	52 (41–63)
	Extraprostatic extension	8 (2–18)	15 (13–18)	27 (22–33)	37 (29–46)	40 (31–50)
	Seminal vesicle (+)	—	1 (0–1)	4 (2–7)	4 (1–7)	6 (3–12)
	Lymph node (+)	—	—	1 (0–2)	1 (0–3)	1 (0–4)
4.1–6.0	Organ confined	90 (78–98)	80 (78–83)	63 (58–68)	52 (43–60)	46 (36–56)
	Extraprostatic extension	10 (2–22)	19 (16–21)	32 (27–36)	42 (35–50)	45 (36–54)
	Seminal vesicle (+)	—	1 (0–1)	3 (2–5)	3 (1–6)	5 (3–9)
	Lymph node (+)	—	0 (0–1)	2 (1–3)	3 (1–5)	3 (1–6)
6.1–10.0	Organ confined	87 (73–97)	75 (72–77)	54 (49–59)	43 (35–51)	37 (28–46)
	Extraprostatic extension	13 (3–27)	23 (21–25)	36 (32–40)	47 (40–54)	48 (39–57)
	Seminal vesicle (+)	—	2 (2–3)	8 (6–11)	8 (4–12)	13 (8–19)
	Lymph node (+)	—	0 (0–1)	2 (1–3)	2 (1–4)	3 (1–5)
>10.0	Organ confined	80 (61–95)	62 (58–64)	37 (32–42)	27 (21–34)	22 (16–30)
	Extraprostatic extension	20 (5–39)	33 (30–36)	43 (38–48)	51 (44–59)	50 (42–59)
	Seminal vesicle (+)	—	4 (3–5)	12 (9–17)	11 (6–17)	17 (10–25)
	Lymph node (+)	—	2 (1–3)	8 (5–11)	10 (5–17)	11 (5–18)

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

Screening for Prostate Cancer — The Controversy That Refuses to Die

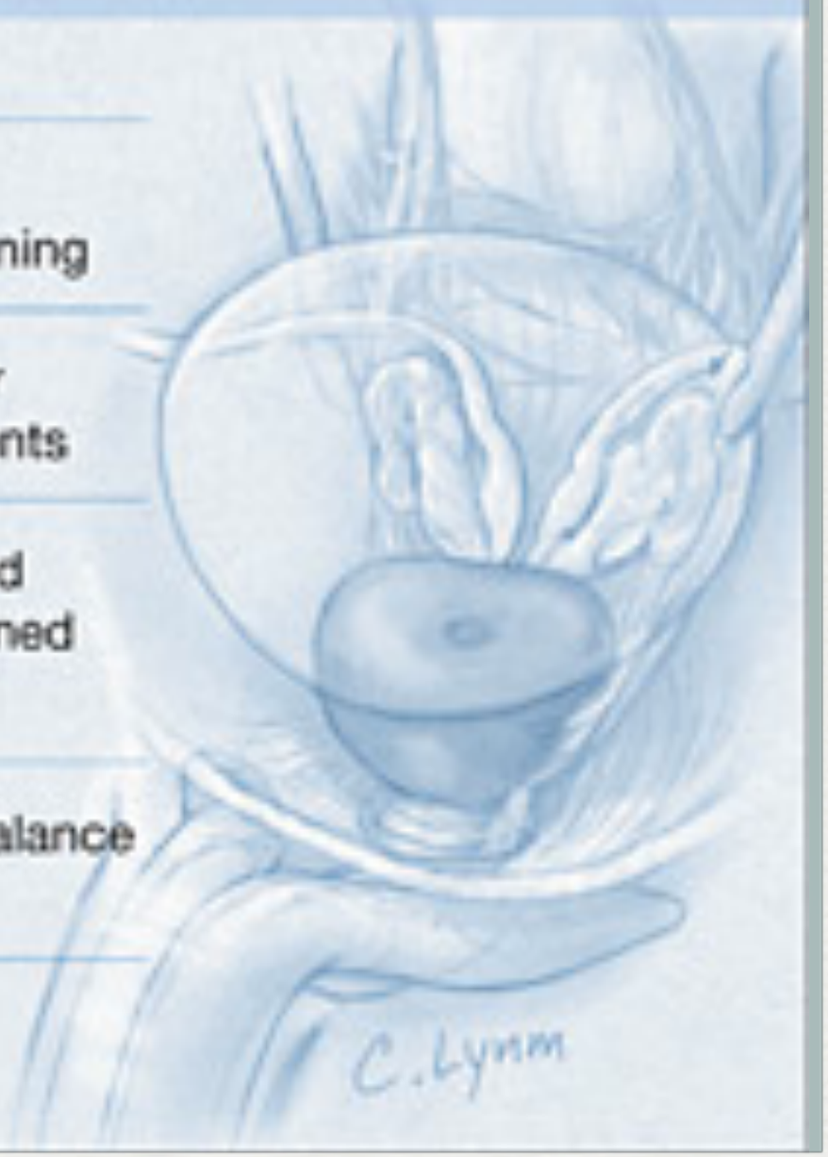
Michael J. Barry, M.D.

N Engl J Med 2009; 360:1351-1354 | March 26, 2009

Screening

Expert Assessment Regarding Prostate Cancer Screening in Asymptomatic Men Aged <75 y at Low Risk

Organization	Assessment
American Academy of Family Physicians	Evidence is insufficient to assess the balance of benefits and harms of screening
American Cancer Society	Offer annual screening at age 50 y after discussing risks and benefits with patients
American Urological Association	Offer baseline screening at age 40 y and subsequent testing at intervals determined by the baseline result
US Preventive Services Task Force (USPSTF)	Evidence is insufficient to assess the balance of benefits and harms of screening
American College of Physicians	Suggests physicians follow USPSTF recommendations



American Urologic Society
Prostate Cancer Screening Guidelines

- Beginning at age of 50, all men with a ten year life expectancy should be offered both PSA and DRE annually
- Men in high risks groups, such as African-Americans or those with a family history should start at age 40

PLCO SCREENING TRIAL
PROSTATE, LUNG, COLORECTAL, OVARIAN

- ENROLLMENT - Men between 55 & 74 yrs.
- STUDY- 1993 - 2001 enrollment
- RANDOMIZED - Prostate cancer screening group vs control group
- SCREENING GROUP - Annual PSA for 6 yrs. plus DRE for 4 yrs.
- PSA - PSA over 4 ng/ml considered positive
- SAMPLE SIZE - 76,693 men
- DURATION OF FOLLOW-UP - 11.5 yrs, 2/3 followed for 10 yrs.
- COMPLIANCE - 85% in the screening group. Control group PSA screening 40% in 1st yr., 52% by yr. 6

PLCO RESULTS

- Incidence of Prostate Cancer higher in screening group than control group
- Trend of increased cancer detection in screening group remained steady between year 2 and 10
- Rate ratio for prostate cancer in comparing both groups at 10 yrs. was 1.17
- Most Cancers - stage 2, Gleason 6 at discovery
- Advanced cancer detection - similar in both groups
- At 7 years - incidence of death was similar in both groups
- Overall mortality similar in both groups

ERSPC STUDY

European Randomized Study of Screening for Prostate Cancer

- Enrollment - men between 55 and 69 years
- PSA - cut off for a positive PSA between 2.5 and 4.0 ng/ml
- Sample Size - 162,243 men
- 82% of men in screening group received prostate cancer screening at least once. 16% of all PSA tests were positive at F/U
- Incidence rates of prostate cancer during a median of 9 years of F/U was: screening group 8.2% & control group 4.8 %
- Main difference between PLCO and ERSPC outcomes was the significant decrease in the risk of prostate cancer mortality in the screening vs control group

PSA Screening

ERSPC (European Randomized Study of Screening for Prostate Cancer) 13 yr follow-up

- Increase in the relative reduction of prostate cancer mortality in 9 & 11 yr follow-up
- 27% decrease in prostate cancer mortality among the screening cohort
- Equaling 1 prostate cancer death avoided per 27 cancer diagnosis in 781 men screened

PSA Screening Study – Goteborg

20,000 nonrandomized patients - 10,000 control / 10,000 screened
Screening - every 2 yrs from 1995 to 12/31/12 — 18 yr follow-up
Prostate bx if PSA >2.5

At 18 yrs

1,396 men dx'd with Prostate Ca – 79 died of prostate ca in screening group
936 men dx'd with Prostate Ca – 122 died of prostate ca in the control group

Screen – incidence/ mortality 16%/0.98%
Control – incidence/ mortality 11%/1.5%

Conclusion

Organized screening reduces Prostate Ca mortality but is associated with over diagnosis

SHOULD WE SCREEN FOR PROSTATE CANCER ?

- Ecology studies suggest that screening with PSA testing can reduce the risk for mortality due to prostate cancer.

- Surgery, radiation therapy, & androgen - deprivation therapy can all improve survival outcomes among men with prostate cancer, but all of these treatments are associated with significant rates of adverse events.

- In the PLCO trial, screening for prostate cancer failed to significantly improve the risk of prostate cancer mortality. However, this trial was limited by the high rate of crossover into screening for prostate cancer among the control group.

- The ERSPC trial found a significant 20% decrease in the risk of prostate cancer mortality associated with a PSA screening protocol.

- Clinicians should discuss risks and benefits of screening for prostate cancer before screening begins (ie. not after the information from screening test is available).

WHAT'S NEW

Prostate Cancer Genomic Test

OncotypeDX - Personalized risk assessment, Bx based, 17 gene based
GPS (Genomic Prostate Score)

ConfirmMDx - Prostate tissue based to determine need for additional Bx.
3 gene methylation

Polaris - Post prostatectomy based to determine relative risk of recurrence or
Prostate tissue based to evaluate for active surveillance, 46 gene based

Decipher - Post prostatectomy based to determine need for additional treatment,
pT2 with positive margins or pT3 disease, 22 gene based

4 K score Test

% risk of having aggressive prostate cancer

- Total PSA
- Free PSA
- Intact PSA - Proprietary, OPKO lab

  h - K2 (human Kallikrein protein)
- Age, DRE, Prior Bx Status

Androgen Receptor Splice Variant 7 - Taxanes in mCRPC

CTC (Circulating tumor cells) from men with castrate - resistant P. Ca examined using reverse- transcription polymerase chain rxn assay for androgen receptor splice variant 7

To determine relationship between AR-V7 status and response to treatment with Taxanes vs treatment with Enzalutamide or Abiraterone

Treatment with Taxanes resulted in a better response then Enzalutamide or Abiraterone in AR - V7 positive men.

Outcomes similar in AR - V7 negative men

Taxanes; diterpenes produced by the plants of the genus Taxus(yews), use as chemotherapy, ie Taxotere

Antonarakis, ES JAMA 2015; 1(5):582-591 – Johns Hopkins

METASTATIC PROSTATE CANCER

WHAT IS NEW

SEQUENCING

Guideline Recommendations from the American Urological Association (AUA)

In April 2014, the AUA updated its guideline recommendations based on updated literature and FDA guidance regarding treatment options for metastatic castration-resistant prostate cancer (mCRPC). The FDA issued a safety announcement in July 2013 related to the use of ketoconazole in oral form, noting side effects that include hepatotoxicity, adrenal insufficiency, and potential drug–drug interactions. In addition, in July 2014, the FDA issued a recommendation that healthcare providers should consider the alcohol content of docetaxel when prescribing the drug.

The updated guideline was based on a review of the literature relevant to prostate cancer and castration resistance. The report included English-language, peer-reviewed literature published between January 1996 and February 2013. Evidence was graded as A (high), B (moderate), or C (low). Below are the recommendations based on six common patient scenarios, followed by evidence grade.

Patient Scenario #1

Asymptomatic, nonmetastatic castration-resistant prostate cancer (nmCRPC)

- Recommend observation with continued androgen deprivation to patients with nmCRPC (C)
- Offer treatment with first generation anti-androgens or first generation androgen synthesis inhibitors to select patients with nmCRPC who do not want observation (C)
- Should not offer systemic chemotherapy or immunotherapy to patients with nmCRPC outside the context of a clinical trial (C)

Patient Scenario #2

Asymptomatic or minimally symptomatic mCRPC without prior docetaxel chemotherapy

- Offer abiraterone plus prednisone, docetaxel, or sipuleucel-T to patients with asymptomatic or minimally symptomatic mCRPC with good performance status and no prior docetaxel chemotherapy (A for abiraterone; B for docetaxel and sipuleucel-T)
- Offer first generation and anti-androgen therapy, ketoconazole plus steroid or observation to patients with asymptomatic or minimally symptomatic mCRPC with good performance status and no prior docetaxel chemotherapy who do not want or cannot have standard therapies (C)

Patient Scenario #3

Symptomatic mCRPC with good performance status and no prior docetaxel chemotherapy

- Offer docetaxel (B)
- Offer abiraterone plus prednisone (C)
- Offer ketoconazole plus steroid, mitoxantrone, or radionuclide therapy for patients who do not want or cannot have standard therapies (B for mitoxantrone; C for ketoconazole and radionuclide therapy)
- Offer radium-223 dichloride (Ra-223) to patients with symptoms from bony metastases without known visceral disease (B)
- Should not offer treatment with either estramustine or sipuleucel-T (C)

Patient Scenario #4

Symptomatic mCRPC with poor performance status and no prior docetaxel chemotherapy

- Offer treatment with abiraterone plus prednisone (C)
- Offer treatment with ketoconazole plus steroid or radionuclide therapy for those who are unable or unwilling to receive abiraterone plus prednisone (C)
- Offer docetaxel or mitoxantrone chemotherapy in select cases, specifically when the performance status is directly related to cancer (expert opinion)
- Offer Ra-223 to patients with symptoms from bony metastases and without known visceral disease in select cases, specifically when the performance status is directly related to symptoms related to bone metastases (expert opinion)
- Should not offer sipuleucel-T (C)

Patient Scenario #5

Symptomatic mCRPC with good performance status and prior docetaxel chemotherapy

- Offer treatment with abiraterone plus prednisone, cabazitaxel, or enzalutamide (A for abiraterone and enzalutamide; B for cabazitaxel)
- Offer ketoconazole plus steroid if abiraterone plus prednisone, cabazitaxel, or enzaluatamide is unavailable (C)
- Offer treatment with docetaxel for patients who were benefitting at the time of discontinuation of docetaxel chemotherapy (C)
- Offer Ra-223 to patients with symptoms from bony metastases without known visceral disease (B)

Patient Scenario #6

Symptomatic mCRPC with poor performance status and prior docetaxel chemotherapy

- Offer palliative care; for select patients, offer abiraterone plus prednisone, enzalutamide, ketoconazole plus steroid, or radionuclide therapy (expert opinion)
- Should not offer systemic chemotherapy or immunotherapy (expert opinion)

SOURCE

American Urological Association. Castration-resistant prostate cancer: AUA guideline. https://www.auanet.org/education/guidelines/castration-resistant-prostate-cancer.cfm. Accessed May 17, 2015.

Treatment for Prostate Cancer Guidelines

Treatment for Metastatic Prostate Cancer
First Options

LHRH agonist (GnRH analog)

Lupron Depot, Eligard, Trelstar (triptorelin)

With/without

Antiandrogen

Casodex (Bicalutamide)

or

Firmagon (GnRH antagonist)

Continuous vs Intermittent Hormonal therapy

Continuous : Traditional
Possibly slight survival advantage

Intermittent : Increased quality of life
No reduction of embolic or bone related adverse effects

SWOG trial - 1134 patients, mean age 71.5 yrs

FDA Approved Treatment Options for Prostate Cancer

- Casodex (Bicalutamide)
- Firmagon (Degarelix)
- Jevtana (Cabazitaxel)
- Lupron (Leuprolide Acetate)
- Mitoxantrone Hydrochloride
- Prednisone
- Provenge (Sipuleucel-T)
- Taxotere (Docetaxel)
- Viadur (Leuprolide Acetate)
- Xofigo (Radium-223 Dichloride)
- Xtandi (Enzalutamide)
- Zoladex (Goserelin Acetate)
- Zytiga (Abiraterone Acetate)

mCRPC Treatment options

newer options

Provenge (sipuleucel-T)	Dendreon Corp.	$93,000/R't
Zytiga (abiraterone acetate)	Janssen Biotech, Inc.	$110,000/yr
Xtandi (enzalutamide)	Astellas Pharma US, Inc.	$110,000/yr

Xofigo (radium Ra 223 dichloride) — Bayer HealthCare Pharmaceuticals

6 sc injections ($ 12,500 - 34,500/injection)

Total cost $75,000 - $207,000

PROVENGE

Designed to induce an immune response targeted against PAP (prostatic acid phosphatase).

Consists of autologous peripheral blood mononuclear cells, including antigen-presenting cells (APC) that have been activated ex vivo with a recombinant antigen.

NOTE: The antigen PAP is found on > 95% of prostate tumors.

Used in Castrate - Resistant metastatic patients.

Well tolerated. Adverse events <15%.

Chills, fatigue, fever, back pain, nausea, joint aches, headaches

Improvement in median survival in mildly symptomatic CRPC pt's is 4.1 mos. (21.7 to 25.8 mos.)

Three cycles of treatment costs about $105,000.

ZYTIGA Abiraterone

Used for metastatic castrate -resistant prostate cancer

Dose 1,000 mg orally qd + prednisone 5 mg bid.

A CYP 17 inhibitor. Hepatotoxic.

Caution in pt's with cardiovascular disease, liver disease,adrenocortical insufficiency, hypertension, hypokalemia

Median survival increase between 3.9 to 4.6 mos.

Cost $110,000/yr

Xifigo (radium Ra 223 Dichloride)

- alpha radioactive emitter
- 11.4 day half-life (more commonRa 226 - 1601 yr half-life)
- For only bone metastasis
- Extends life 30% (14.9 mos. vs 11.3 mos. in controls)

- 6 SC injections
- Can be used in concert with other agents
- Can lower blood cells
- generally well tolerated
- cost $12,500/inj (billed at $34,500) = Total cost $75,000 (bill $207,000)

What is new?

Docetaxel (Taxotere) + Hormonal therapy

- STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate cancer: Evaluation and Drug Efficacy) - United Kingdom

- Early metastatic prostatic cancer, and High risk nonmetastatic disease

- 25% Life survival improvement = 10 mos. more life
  2 of 3 risk factors: Stage T3/4, PSA>40, Gleason=>8

- Hormone naive patients

- 6 cycles of Taxotere

- 31% grade 3-5 adverse events

★ FEATURED
Published in Oncology
Expert Opinion / Interview · August 11, 2015

At What Point Does Cancer Treatment Cost Too Much? Part 1

Interview with  Jeffrey J. Kirshner MD, FACP Interview by  Jarushka Naidoo MD

Dr. Jeffrey Kirshner, a partner of Hematology Oncology Associates of Central New York in East Syracuse and a member of the advisory board of *PracticeUpdate Oncology*, speaks with Dr. Jaruska, an advanced fellow in medical oncology at Memorial Sloan Kettering Cancer Center, about his views on the recently published ASCO statement on assessing the value of cancer treatment.

What's the point of the ASCO statement?

Dr. Naidoo: Dr. Kirshner, in June, the *Journal of Clinical Oncology* published an ASCO statement, "A Conceptual Framework to Assess the Value of Cancer Treatment Options," written by the ASCO Value in Cancer Care Task Force. What are your thoughts on this in general, and, in particular, on the purpose of the statement?

Dr. Kirshner: I think that the point is to emphasize the cost of cancer care, which is increasing daily. Costs are becoming out of control, and we've got to do something about it or we're not going to have adequate resources to treat cancer patients. I think the responsible thing to do as a professional organization is to acknowledge the problem and then start to address it. This statement represents one of the first examples of oncologists attempting to deal with this issue at an organizational level.

Dr. Naidoo: What do you think was the rationale behind about approaching this as a conceptual framework? Has ASCO participated in initiatives in the past that highlight this issue?

Dr. Kirshner: ASCO participated in the Choosing Wisely Campaign, which was initiated by the American Board of Internal Medicine and which I think was an excellent initiative. As part of the Choosing Wisely Campaign, ASCO highlighted the results of studies that showed that certain treatments and tests are clinically useless because they cost money but they don't contribute to, or play an essential role in, patient care. I believe that the experience has been very valuable and ASCO's participation has shown its commitment to addressing cost and

TABLE 5: Hormonal approaches to the treatment of advanced prostate cancer

Method	Mechanism of action	Side effects
Surgical castration	Removal of testicular androgens	Hot flashes (50%), psychological effects
Diethylstilbestrol (DES)	Inhibition of gonadotropin secretion	Gynecomastia, cardiovascular risks at high doses
LHRH analogs (agonists and antagonists) (goserelin, leuprolide, degarelix)	Inhibition of gonadotropin secretion	Hot flashes (50%), less gynecomastia than with DES, fatigue
Antiandrogens (bicalutamide, flutamide, nilutamide)	Blockade of binding of dihydrotestosterone to its receptor	Abnormal liver function studies, diarrhea (10%)
Ketoconazole	Adrenal androgen synthesis inhibitor, possible autocrine/paracrine androgen inhibition	LFT abnormalities, nausea, drug interactions
Abiraterone acetate	Adrenal androgen synthesis inhibitor, possible autocrine/paracrine androgen synthesis inhibition	LFT abnormalities, fluid retention, hypokalemia, hypertension, fatigue
Glucocorticoids	Inhibition of androgen receptor activity, adrenal androgen synthesis inhibition, independent cytotoxic effects	Weight gain, immunosuppression, ulcers, bone density loss/fracture, hyperglycemia

Treatment for Metastatic Prostate Cancer

When to Treat

No need to treat

Treat when - Progressive disease ie. increasing PSA (how high?)

Patient having symptoms

Prostate Cancer Prevention

- Dietary fat reduction
- Vitamins D & E
- Selenium
- Statins, Metformin
- Intake of Soy, Green tea, Lycopene (tomato rich products)
- 5 alpha Reductase (Proscar/Finasteride, Avodart/Dutasteride)
- Avoid Pesticide exposure, Agent Orange
- Non-steroidal anti-inflamatories . Cyclo-oxypenase (COX)

PCPT Prostate Cancer Prevention Trial

- Study Group- men over 55, PSA under 3 ng/ml, normal DRE
- Allocation - Placebo vs Finasteride 5 mgm daily
- Enrollment - 18,882 American men, 7 year intervention
- Plan - Annual DRE & PSA. Biopsy at year 7
- Exclusion - "for cause" biopsies if abnormal DRE or significant PSA rise (PSA rise of 2.3 to factor in finasteride adjustment)

RESULTS

PCPT stopped prematurely

Placebo group cancer 24.4%

Finasteride group cancer 18.4%

Testosterone

Testosterone Replacement

Benefits

- Quality of life
- Sexual function - libido, mood
- Increase muscle mass
- Increase bone mineral density
- Cognitive ability - not shown

Risks

- Dyslipidemia
- Polycythemia
- Liver dysfunction (?)

Testosterone Replacement in Older Men

- Document hypogonadism - **Free + Total Testosterone, SHBG** (Sex hormone binding globulin) - morning sample, fasting
- Testosterone levels **reduced during acute illness**, up to several months.
- If no symptoms - **no need to treat**
- **Erectile dysfunction** in the absence of other symptoms is not a symptom of hypogonadism
- Gonadotropins (FSH & LH) can distinguish **primary vs secondary** hypogonadism
- **Weight reduction** - testosterone levels can double in morbidly obese patients after bariatric surgery

Testosterone Replacement Contraindications

- Prostate cancer - prostate nodule, increasing/elevated PSA
- Breast cancer
- Polycythemia
- Untreated sleep apnea
- Severe lower urinary symptoms
- Poorly controlled CHF
- Aggressive behavior

Testosterone - CV Risks

To date- No long term, prospective studies to determine safety

Recent study

509 men - median age 54, follow-up 10 yrs

284 on testosterone (80 injection, 204 transdermal)

225 off testosterone

Results

19 deaths - 9 (3.2%) on testosterone

10 (4.4%) not on testosterone

Conclusion

No change in mortality

Eieseberg, Herden, Lipshutz

Testosterone Replacement

- **Topical Gels** - daily dosing, steady state, variable absorption, avoid children & females, expensive (nongenerics $500/mo.)
- **Transdermal patches** - steady state, irritation, expensive
- **Subcutaneous pellets** - steady state, expensive
- **Nasal Gel** - use 1 pump,each nostril, t.i.d, new product
- **Injections** - every 2-3 weeks, least expensive

Defending Testosterone - Debunking the Myths

March 2014 - FDA issued warnings about Testosterone's possible CV risks. Advised testosterone not to be used in "Age Related" symptoms

Precautions derived from Vigen & colleagues, 2013 JAMA

8709 men from VA Health system. Evaluated strokes, MI, Death

25.7% of pts on testosterone

19.9% of controls

Error: Number of adverse events divided by the number of patients was incorrect

Later JAMA published a 2nd correction of several data errors of 1,000 pts. Revealed the "all male" study population also comprised of women

Abraham Morganthaler M.D., Professor of Urology, Harvard Medical School

Test study group - Abraham Morganthaler M.D., Harvard Medical School

- Low T levels are associated with increased mortality, atherosclerosis, CAD
- Mortality is decreased in T-deficient men treated with Testosterone
- Exercise capacity is increased testosterone treated vs placebo in men with CV disease
- There is uniform improvement in CV risk factors with testosterone replacement vs placebo (ie. body fat, waist circumference, insulin resistance)

No large long term study has been preformed

Morganthaler conclusion: Weight of evidence supports T replacement in hypogonadal men

Plaintiff 's attorneys advertise for men on Testosterone replacement who have experienced CV issues

Flibanserin ("female viagra")

- Sold under the name Addyi
- Used for premenopausal women - not used in postmenopausal
- Drug class: antidepressant
- Potential serious interaction with alcohol - hypotension, syncope
- Most common side effects; dizziness, somnolence, nausea, fatigue
- Reacts with CYP3A4 inhibitors
- Need to be a certified prescriber to use - hypotension, syncope
- Mechanism of action is unknown - Serotonin 1A agonist, Serotonin 2A antagonist
- 100 mg dose at bedtime
- Tested in 2400 premenopausal women: increased satisfying events by 0.5-1/mo.
- Does not improve sexual performance
- Sprout Pharmaceutical - product of Boehringer-Ingelheim
- "Even The Score" campaign

FLORIDA SPECIALISTS IN UROLOGY

STEVEN PALETSKY, M.D.

THANK YOU FOR LISTENING

QUESTIONS

Table **Efficacy of Treatment Options for Metastatic Castrate-Resistant Prostate Cancer**

Drug	Prior docetaxel	ORR by RECIST (vs placebo)	rPFS (vs control)	Median OS (vs control)
Abiraterone (Zytiga)[8]	Yes	14% (vs 3%) $P < .001$	5.6 mos (vs 3.6 mos) HR, 0.67 (95% CI, 0.58–0.78)	14.8 mos (vs 10.9 mos) HR, 0.65 (95% CI, 0.54–0.77)
Abiraterone[10]	No	36% (vs 16%) $P < .0001$	Not reached (vs 8.3 mos) HR, 0.43 (95% CI, 0.35–0.52)	Not reached (vs 27.2 mos) HR, 0.75 (95% CI, 0.61–0.93)
Enzalutamide (Xtandi)[13]	Yes	29% (vs 4%) $P < .0001$	8.3 mos (vs 2.9 mos) HR, 0.40 (95% CI, 0.35–0.47)	18.4 mos (vs 13.6 mos) HR, 0.63 (95% CI, 0.53–0.75)
Sipuleucel-T (Provenge)[37]	Some in both arms	NR	3.7 mos (vs 3.6 mos) HR, 0.95 (95% CI, 0.77–1.17)	25.8 mos (vs 21.7 mos) HR, 0.77 (95% CI, 0.61–0.98)
Cabazitaxel (Jevtana)[38]	Yes	14.4% (vs 4.4%) $P < .0005$	8.8 mos (vs 5.4 mos) HR, 0.61 (95% CI, 0.49–0.76)	15.1 mos (vs 12.7 mos) HR, 0.70 (95% CI, 0.59–0.83)
Docetaxel (Taxotere)[39]	No	17% (vs 11%) $P < .30$	6.3 mos (vs 3.2 mos) $P < .001$	17.5 mos (vs 15.6 mos) HR, 0.80 (95% CI, 0.67–0.97)
Alpharadin[a] (radium-223 chloride)[26]	Yes	NR	NR	14.9 mos (vs 11.3 mos) HR, 0.70 (95% CI, 0.58–0.83)

[a] This agent has not received regulatory approval for routine use.

CI = confidence interval; HR = hazard ratio; mos = months; NR = not reported; ORR = overall response rate; OS = overall survival; RECIST = response evaluation criteria in solid tumors; rPFS = radiographic progression-free survival.

New Therapeutic Treatments

Table 3

Comparison of newer pharmacologic agents for the treatment of metastatic castration-resistant prostate cancer (mCRPC)

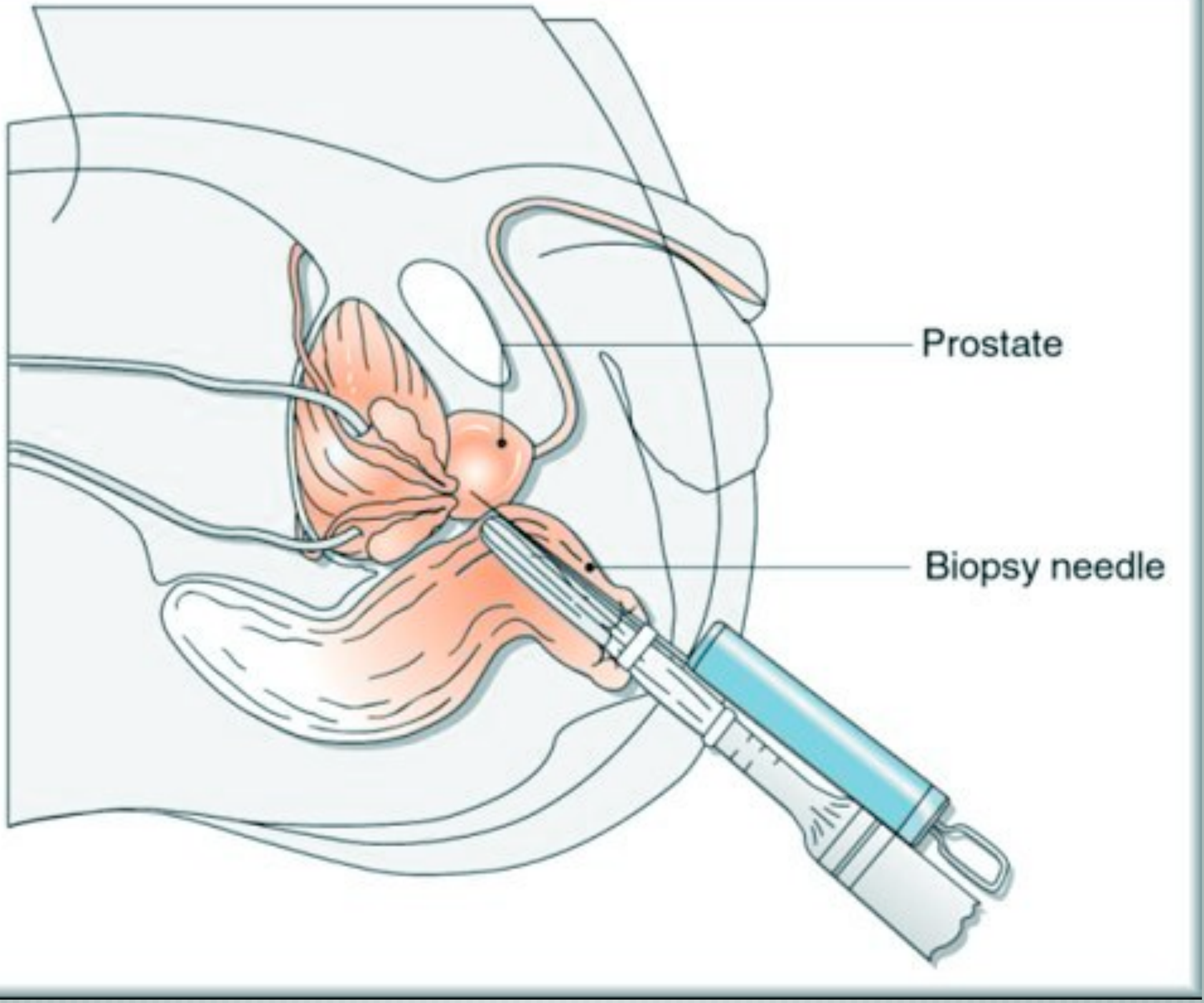
Drug	Class	Indications*	Dosing	Dosing
Abiraterone (Zytiga)	Androgen biosynthesis inhibitor	mCRPC before or after docetaxel	1,000 mg PO daily with prednisone 5 mg by mouth twice daily	Hypertension, edema, hypokalemia
Cabazitaxel (Jevtana)	Cytotoxic chemotherapeutic agent	mCRPC after docetaxel	25 mg/m^2 IV every 3 weeks with prednisone 10 mg by mouth daily	Allergic reactions, neutropenia, febrile neutropenia, diarrhea, renal failure
Enzalutamide (Xtandi)	Second-generation antiandrogen	mCPRC before or after docetaxel	160 mg by mouth daily	Seizures, fatigue, diarrhea, hot flashes
Sipuleucel-T (Provenge)	Autologous cellular immunotherapy	Asymptomatic or minimally symptomatic mCRPC without visceral metastases	IV infusion every 2 weeks for 3 total doses	Infusion-related reactions, chills, fever, fatigue, pain

* Labeled indications according to the FDA

Formulary/Source Ref 8

PSA 3

- Preformed in a urine collection after prostate message
- Attempts to establish early prostate cancer
- Useful in patients who have negative prior biopsies , with a high suspicion for cancer
- Measures the PSA gene (a segment of noncoding mRNA from chromosome 9q21-22; overexpressed in 95% P Ca pts)
- PSA3 cut off is 35 (54% sensitivity & 74% specificity)
- Has not obtained wide spread acceptance by urologists
- Long term place in the workup of prostate cancer is uncertain



PROSTATE BIOPSY

PROSTATE CANCER STAGING

- **CAT** - useful if PSA over 20 ng/ml
- **Bone scan** - useful if PSA over 20 ng/ml
- **Endorectal MRI** - useful for local tumor outside the prostate
- **Prostascint** - no value for initial staging, possible use for metastatic lesions
- **Blood studies** - acid phos, alkaline phos, CBC, CMP

IN THE REAL WORLD

- ATTORNEYS ARE ANXIOUS TO SUE FOR MISSED DIAGNOSIS

- PATIENTS EXPECT TO BE EVALUATED NO MATTER HOW OLD THEY ARE

  Are you giving up on me?

  What kind of a doctor doesn't check the PSA ?

  My last doctor aways check it !

- PATIENTS DO NOT WANT CHANGE

Treatment Differences and Outcomes of ERSPC Rotterdam

The Journal of Urology

1 Expert Comment

TAKE-HOME MESSAGE

- Researchers evaluated the differences in treatment between the screening and control arms of ERSPC Rotterdam. Initial treatment differed in all risk groups except the metastatic group, and the relative risk of prostate cancer incidence and mortality correlated 1:1 per group.
- Researchers suggest that the differences in prostate cancer mortality between the control and screening arms are more likely to be due to favorable stage through screening than differences in treatment.

JC1

Prostate Cancer Genomic Tests

Test	Indication	Science	Results	Cost
OncotypeDX Genomic Health	• Biopsy tissue based test • NCCN Very Low, Low & Intermediate Risk • Provides Personalized Risk Assessment	Assay looks at 17 genes within 4 pathways (androgen signaling, stromal response, cellular organization, proliferation) to assess tumor aggressiveness	• Genomic Prostate Score (GPS) from 0 to 100 • Likelihood of freedom from Dominant 4 or higher-GS and/or non-organ confined disease • GPS is reflective of the biology of the tumor at the time of biopsy	• $3,820 • Medicare = No ABN required* • Other ins: If estimated out-of-pocket cost>$100, company will contact the patient to offer financial assistance program. • 866-662-6897
Prolaris Myriad Genetics	• Biopsy tissue based test for patients who are Active Surveillance candidates -or- • Post-Prostatectomy tissue based test to determine relative risk of BCR	46-gene expression signature includes cell cycle progression genes selected based upon correlation with prostate tumor cell proliferation	• Prolaris score • Biopsy is < or = or > than AUA risk group & est. 10y mortality risk • Post-surgical is similar but 10y risk for BCR	• $3,400 • Medicare = No ABN required* • Other ins: If estimated out-of-pocket cost>$375, company will contact patient to make arrangements…they have a financial assistance program. • 800-469-7423
Decipher® GenomeDx Biosciences	• Post-Prostatectomy tissue based test used for patients who are candidates for secondary therapy post prostatectomy • pT2 with positive margins or pT3 or BCR	Analyzes the activity of 22 genetic markers in multiple pathways across the genome to measure the tumor's biological potential for metastasis after surgery	• Decipher reports the probability of metastasis at 5y after surgery and 3yafter PSA recurrence. • AUC 0.79 HR: 7.3 (Decipher high risk) NPV 98.5%	• $4250 • Medicare =No ABN required* • Other ins: Financial assistance program available for out of pocket expenses. • 888-792-1601
ConfirmMDx MDxHealth	• Biopsy tissue based test for patients who are repeat biopsy candidates • Provides risk stratification on decision for repeat biopsy • Eligibility: Prior negative or HGPIN biopsy result in past 24 months	Three-gene methylation assay to detect an epigenetic field effect associated with the cancerization process at the DNA level	• Negative ConfirmMDx result: Avoid repeat biopsy and monitor with routine screening. • Positive ConfirmMDx result: Hypermethylated areas are marked as positive providing repeat biopsy guidance on a prostate map.	• $2,473 ($206 core/block) • Medicare = No ABN required* • Other ins: Financial assistance program is available for out of pocket expenses. • 866-259-5644
Know Error® Strand Diagnostics	• Oral swab and biopsy tissue based test provides DNA tissue matching • Confirms pathology and/or confirms Biomarker is performed on correct patient • Increases diagnostic accuracy	Buccal swab in the clinic sent for DNA match to pathology specimen; may be used with all tissues. STR profiles assessed from multiplex panel of 16 genetic markers	• DNA Match • DNA Non-match • Contamination	• $1780 (out-of-network billed charge amount per test) • Medicare =$293/No ABN required* • Other ins: Patient is only responsible for 'in-network' copays/deductibles. As of Mar/2014, only 2.4% of patients had any out-of-pocket costs and average is $65. • 888-924-6779 ex. 2

ASCO/AUA - CHEMOPREVENTION OF PROSTATE CANCER

ASCO/AUA Special Announcement on FDA Decision Re:Dutasteride

Special Announcement (2/22/11): On January 26, 2011 FDA issued a Complete Response letter for the supplemental New Drug Application for dutasteride for prostate cancer chemoprevention. A Complete Response letter is issued by the FDA's Center for Drug Evaluation and Research when the review of a file is completed and it cannot be approved in its present form. The notification refers only to the supplemental file regarding an indication to reduce prostate cancer risk and not the existing FDA-approved uses. Dutasteride is currently approved to treat symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate.

In December, 2010, the FDA's Oncologic Drugs Advisory Committee (ODAC) voted against recommending dutasteride (Avodart, GlaxoSmithKline) for the indication to reduce prostate cancer risk because in the view of the ODAC members, the risk for more aggressive tumors outweighed the potential for chemoprevention.

ODAC recommended against prostate cancer chemoprevention labeling for the 5-alpha reductase inhibitors - dutasteride (vote 14 (no) to 2 (yes), with 2 abstentions) and finasteride (vote 17 (no) to 0 (yes), with 1abstention).

As part of ASCO's scheduled updates to its guidelines, an ASCO-AUA Update Panel for the Clinical Practice Guideline published in 2008, "Use of 5-alpha Reductase Inhibitors for Prostate Cancer Chemoprevention" will convene shortly and will consider all the evidence bearing on the question of 5-ARIs for chemoprevention of prostate cancer, including the data and discussions that occurred at the ODAC meeting.

Active Surveillance vs Watchful Waiting

Active Surveillance

PSA q 3-6 mos.
DRE q3-6 mos.
- Bx 6 mos., 1yr, then if PSA rises

Watchful Waiting

PSA q 3-6 mos.
DRE q 3-6 mos.
Bx Only if PSA rises

Patient Scenario #1

Asymptomatic, nonmetastatic castration-resistant prostate cancer (nmCRPC)

- Recommend observation with continued androgen deprivation to patients with nmCRPC (C)
- Offer treatment with first generation anti-androgens or first generation androgen synthesis inhibitors to select patients with nmCRPC who do not want observation (C)
- Should not offer systemic chemotherapy or immunotherapy to patients with nmCRPC outside the context of a clinical trial (C)

Patient Scenario #2

Asymptomatic or minimally symptomatic mCRPC without prior docetaxel chemotherapy

- Offer abiraterone plus prednisone, docetaxel, or sipuleucel-T to patients with asymptomatic or minimally symptomatic mCRPC with good performance status and no prior docetaxel chemotherapy (A for abiraterone; B for docetaxel and sipuleucel-T)
- Offer first generation and anti-androgen therapy, ketoconazole plus steroid or observation to patients with asymptomatic or minimally symptomatic mCRPC with good performance status and no prior docetaxel chemotherapy who do not want or cannot have standard therapies (C)

Patient Scenario #3

Symptomatic mCRPC with good performance status and no prior docetaxel chemotherapy

- Offer docetaxel (B)
- Offer abiraterone plus prednisone (C)
- Offer ketoconazole plus steroid, mitoxantrone, or radionuclide therapy for patients who do not want or cannot have standard therapies (B for mitoxantrone; C for ketoconazole and radionuclide therapy)
- Offer radium-223 dichloride (Ra-223) to patients with symptoms from bony metastases without known visceral disease (B)
- Should not offer treatment with either estramustine or sipuleucel-T (C)

Patient Scenario #4

Symptomatic mCRPC with poor performance status and no prior docetaxel chemotherapy

- Offer treatment with abiraterone plus prednisone (C)
- Offer treatment with ketoconazole plus steroid or radionuclide therapy for those who are unable or unwilling to receive abiraterone plus prednisone (C)
- Offer docetaxel or mitoxantrone chemotherapy in select cases, specifically when the performance status is directly related to cancer (expert opinion)
- Offer Ra-223 to patients with symptoms from bony metastases and without known visceral disease in select cases, specifically when the performance status is directly related to symptoms related to bone metastases (expert opinion)
- Should not offer sipuleucel-T (C)

Patient Scenario #5

Symptomatic mCRPC with good performance status and prior docetaxel chemotherapy

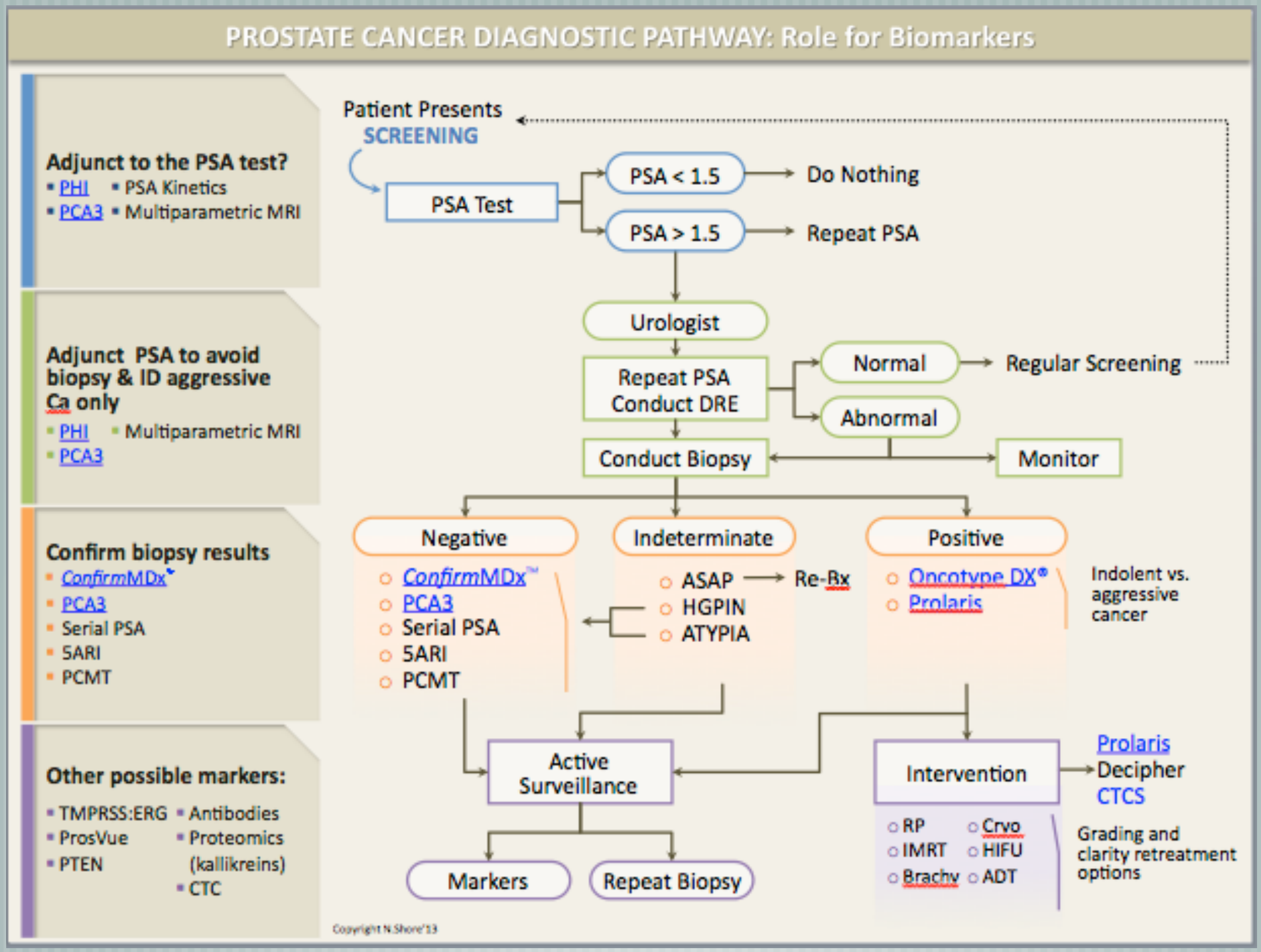
- Offer treatment with abiraterone plus prednisone, cabazitaxel, or enzalutamide (A for abiraterone and enzalutamide; B for cabazitaxel)
- Offer ketoconazole plus steroid if abiraterone plus prednisone, cabazitaxel, or enzaluatamide is unavailable (C)
- Offer treatment with docetaxel for patients who were benefitting at the time of discontinuation of docetaxel chemotherapy (C)
- Offer Ra-223 to patients with symptoms from bony metastases without known visceral disease (B)

Patient Scenario #6

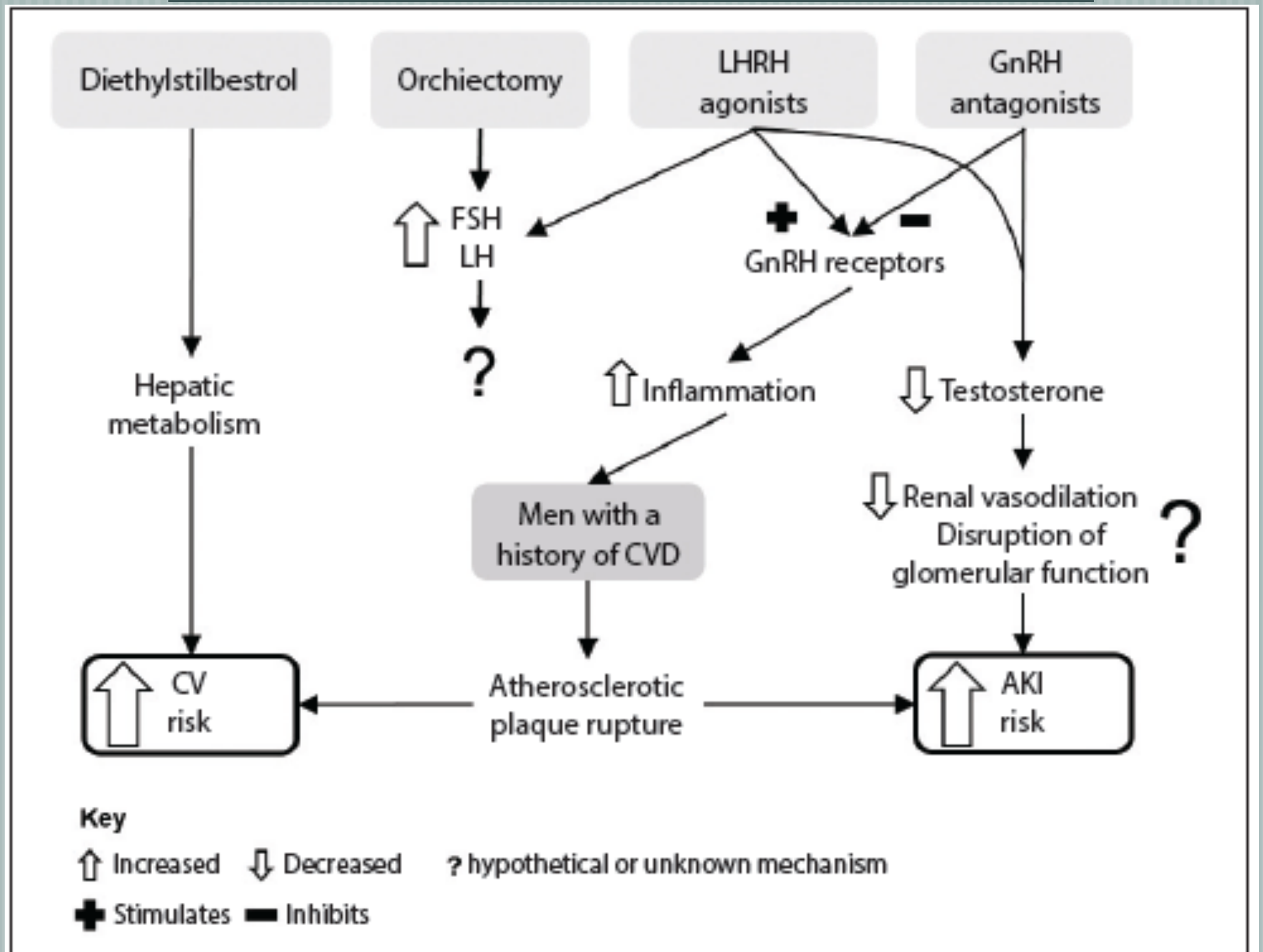
Symptomatic mCRPC with poor performance status and prior docetaxel chemotherapy

- Offer palliative care; for select patients, offer abiraterone plus prednisone, enzalutamide, ketoconazole plus steroid, or radionuclide therapy (expert opinion)
- Should not offer systemic chemotherapy or immunotherapy (expert opinion)

PROSTATE CANCER DIAGNOSTIC PATHWAY



Decreasing Testosterone



Active ingredient	Trade Name	Strength	Manufacturer
Anti-androgens			
Bicalutamide	Bicalinn	50mg	Helsinn Birex
	Bicalutamide Teva	50mg	Teva
	Biluta	50mg	Rowex
	Casodex	50mg	AstraZeneca
	Casomide	50mg	Clonmel
Flutamide	Drogenil	250mg	Schering-Plough
Cytoproterone	Androcur 100	100mg	Bayer Schering
LHRH agonists			
Buserelin	Suprefact Depot	6.6mg	sanofi-aventis
	Suprefact Solution for Injection	1mg/ml	sanofi-aventis
	Suprefact Nasal Spray	100mcg/dose	sanofi-aventis
Goserelin	Zoladex	3.6mg	AstraZeneca
	Zoladex LA	10.8mg	AstraZeneca
Leuprorelin	Eligard	7.5mg, 22.5mg, 45mg	Astellas
	Prostap SR	3.75mg	Takeda
	Prostap 3	11.25mg	Takeda
Triptorelin	Decapeptyl SR	3mg	Ipsen
	Decapeptyl 3-month	11.25mg	Ipsen
	Gonapeptyl Depot	3.75mg	Ferring
LHRH antagonist			
Degarelix	Firmagon	80mg, 120mg	Ferring

PROSTATE CANCER PREVENTION

Table 1. Roster of Major Prevention Trials by Agent and Design

Study type	Population	Sponsor	Agent	Sample size (approximate)	Estimated completion
General risk	Healthy	SWOG	Selenium & Vitamin E (SELECT)	32,400	2012
		Merck	Refocoxib	8000	Cancelled
		SWOG	Finasteride	19,000	Completed
Higher risk	Elevated PSA-negative biopsy	Glaxo Smith Kline	Dutasteride	8200	2010
Preneoplastic	High-grade prostatic intraepithelial neoplasia	GTX	Toremifene	1200	2010
		SWOG	Selenium	700	2011
		NCIC	Soy, Vitamin E, selenium	325	2008

SWOG indicates Southwest Oncology Group; NCIC, National Cancer Institute of Canada.

No Advantage to Screening

Problem: Study contamination by large number of patients from control group wanting to be screened