Basics of prostate cancer

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Plan of our seminar

- Epidemiology
- Risk factors
- Signs and symptoms
- Screening and diagnosis
- Staging
- Risk stratification
- Management: early stage/ locally advanced/ disseminated prostate ca

Epidemiology

Epidemiology

- 2nd most common cancer in men
- Estimated 1,100,000 cases and 307,000 deaths in 2012
- Following the introduction of PSA testing, the incidence or prostate cancer peaked in 1992, declined between 1992 and 1995, and has risen since then at a rate of about 1 percent per year
- The incidence is higher in blacks than in whites in the United States


Risk factors

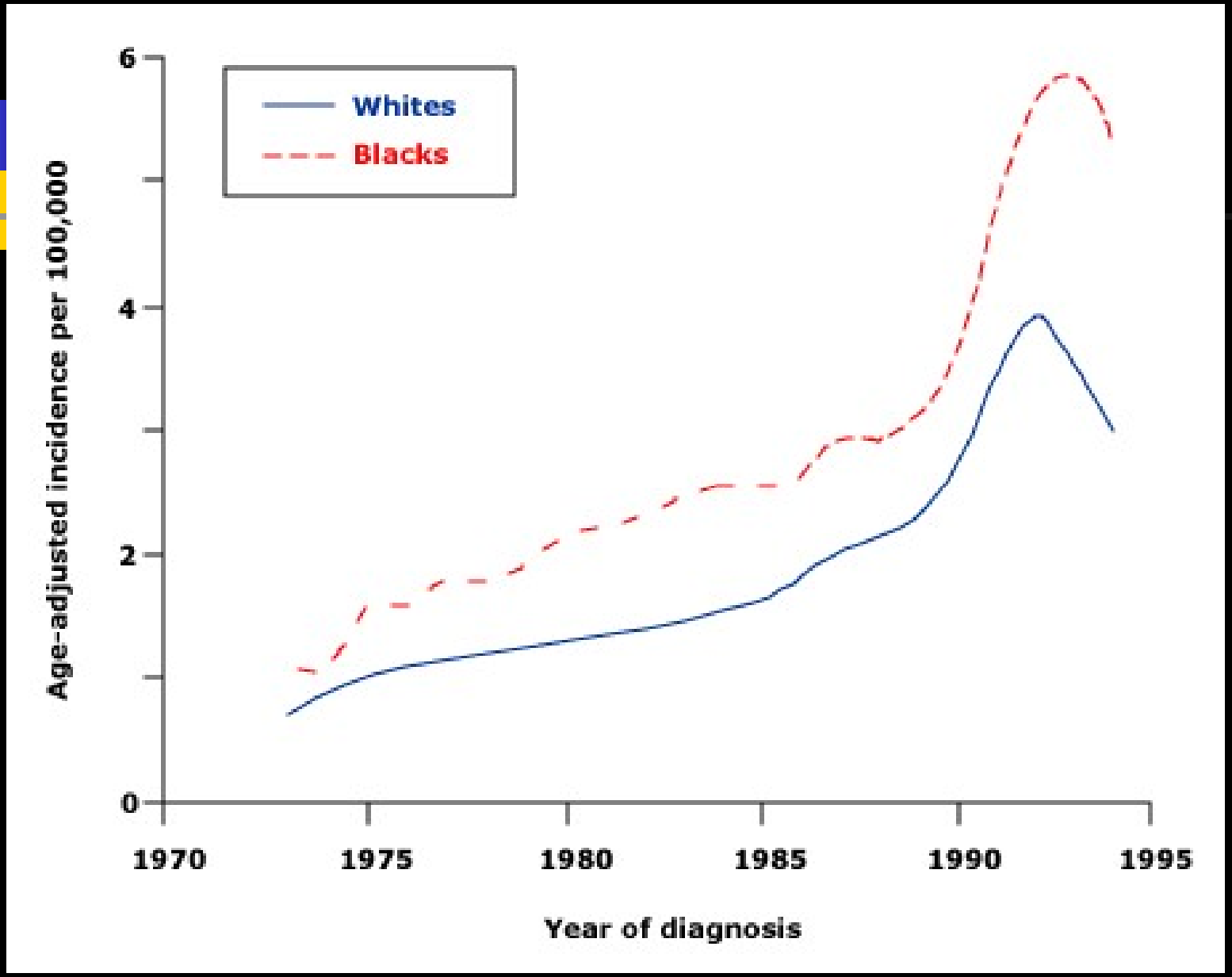
Risk factors

- Age!!!

- The incidence is higher in blacks than in whites in the United States. African-Americans: prostate ca occurs at an earlier age and is associated with a more aggressive clinical course than in other ethnic groups.

- The incidence of prostate cancer is highest in Scandinavian countries (22 cases per 100,000 population) and lowest in Asia (5 per 100,000) - the Japanese and mainland Chinese populations have the lowest rates of prostate cancer

- Family history: Men who have a first-degree relative with prostate cancer have approximately a 2-fold increased risk of developing prostate cancer during their lifetime. An individual who has two first-degree relatives with prostate cancer has a 9-fold increase in lifetime risk


Whites
Blacks
Age-adjusted incidence per 100,000
6
4
2
0
1970
1975
1980
1985
1990
1995
Year of diagnosis

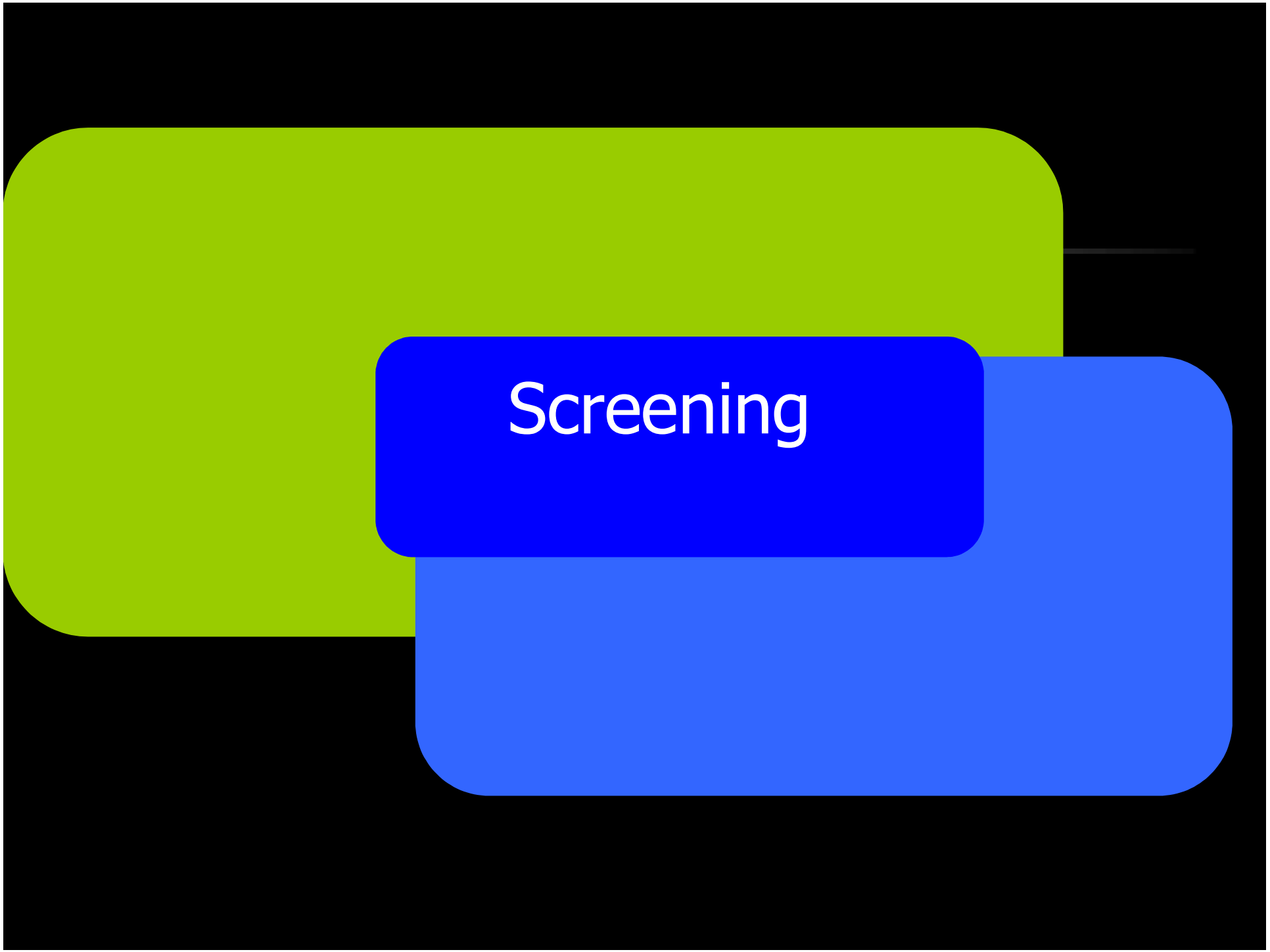
Risk factors

- Mutations in BRCA1 and BRCA2 appear to play an important role in the development certain prostate cancers
- Sexual Activity/Sexually Transmitted Disease: A large prospective study of more than 29,000 men demonstrated an association between high ejaculatory frequency (more than 21 ejaculations/month) and a decreased risk of prostate cancer, with a lifetime relative risk of 0.67.
- Diet? Probably
- Prevention? finasteride or dutasteride (dual 5-α reductase inhibitors that inhibit conversion of testosterone to dihydrotestosterone (DHT)) ? Reduction in the risk of PC in RCT but ... not recommended!


Signs and symptoms

Signs and symptomes

- Early disease- asymptomatic!
  - Almost 80 percent of men currently diagnosed with prostate cancer undergo a biopsy because of a suspicious PSA level. However, digital rectal examination retains an important role for early detection as 20 percent of cases have a prostate nodule that prompts the biopsy.
  - Symptoms usually related to a concomitant benign prostate enlargement
- Locally advanced disease: bladder outlet obstruction is the most common sign of locally advanced prostate cancer. Less commonly: hematuria, urinary tract infections, and irritative voiding symptoms secondary to bladder outlet obstruction.
- Disseminated disease: depending on meastases location! Bone metastases: pain, pathological fracture, SCC.
- On DRE, asymmetric areas of induration or frank nodules are suggestive of PC. In contrast, symmetric enlargement and firmness of the prostate are more frequent in men with BPH


Screening

Screening

- Screening for prostate cancer with PSA can reduce mortality from PC
- The absolute risk reduction is very small.
- Given limitations in the design and reporting of RCT, there remain important concerns that the benefits of screening are outweighed by the potential harms to QoL (overdiagnosis, treatment complications)
- Health care providers should periodically discuss prostate cancer screening with men who are expected to live at least 10 years and are old enough to be at significant risk for prostate cancer.
- Men who are at increased risk of prostate cancer because of race or family history may be more likely to benefit from screening, however there is relatively little evidence addressing this

When to talk about screening with PSA?

In average-risk men

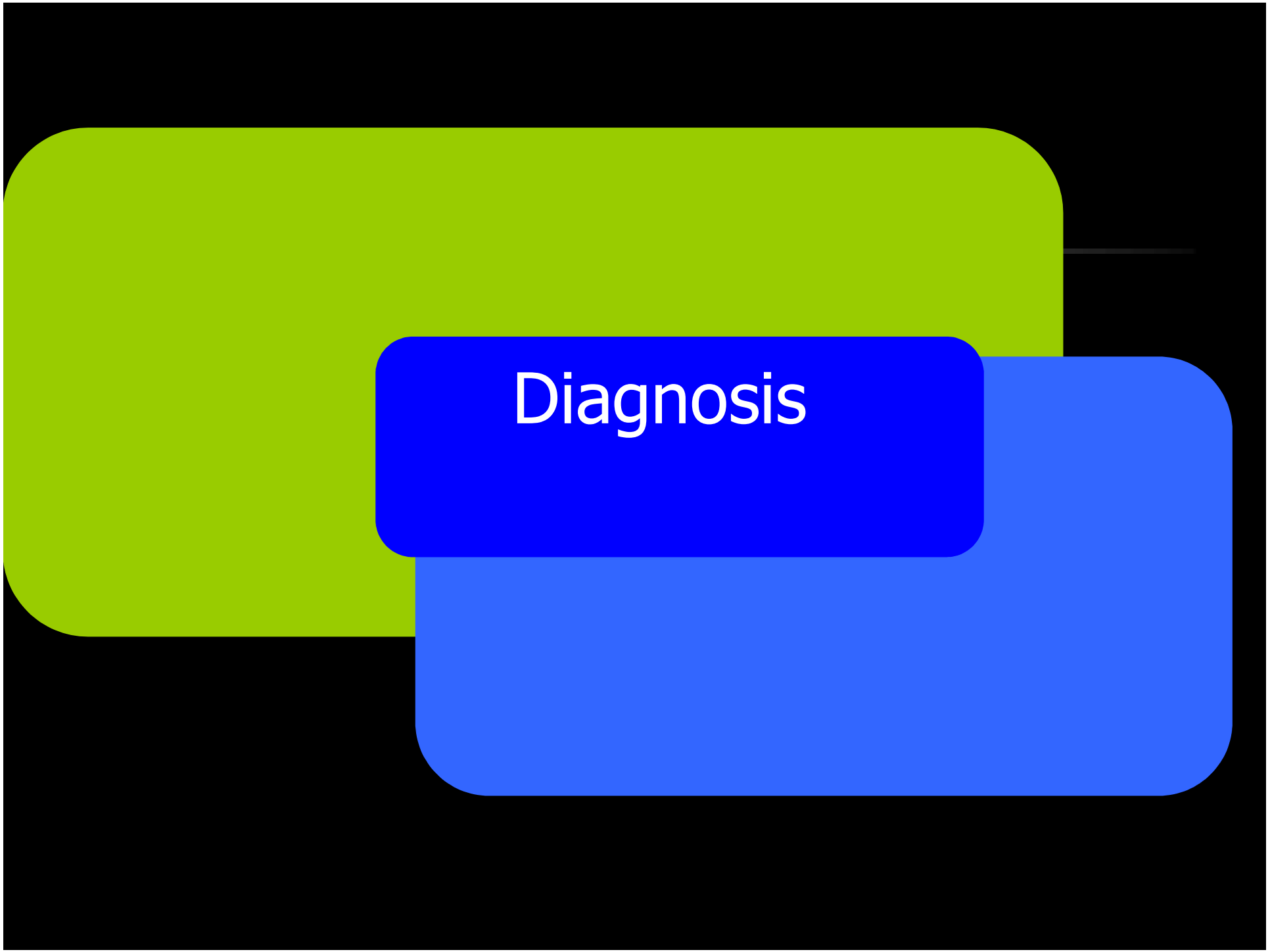
- The discussion should begin at age 50

In men at high risk, including black men, men with a family history of prostate cancer, particularly in relatives younger than age 65, and men who are known or likely to have the BRCA1 or BRCA2 mutations

- The discussion begin at age 40-45

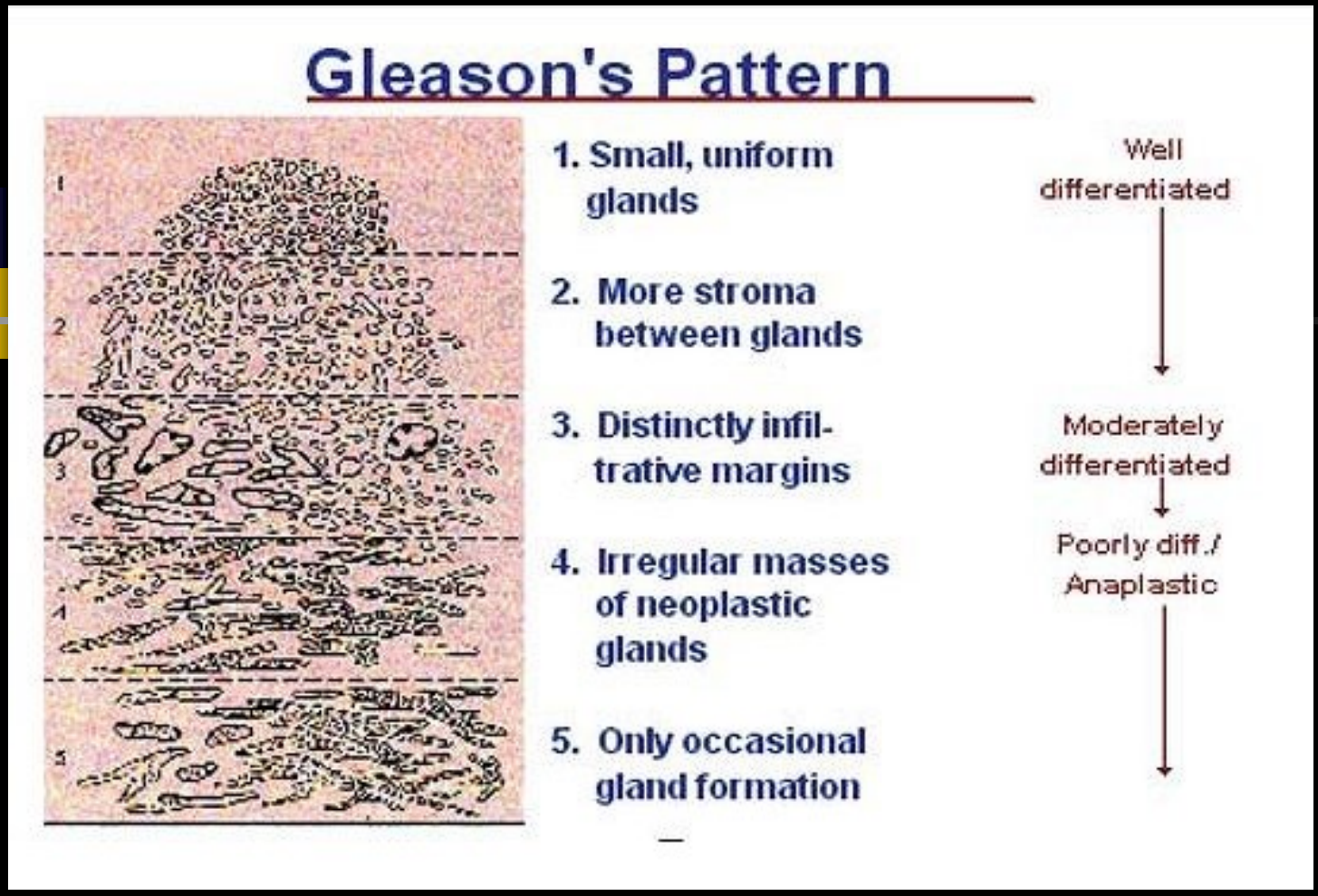
Screening

- Screening should stop after age 69 or earlier when comorbidities limit life expectancy to less than 10 years, or the patient decides against further screening
- Men with an abnormal DRE or PSA > 7 ng/mL should be referred, without further testing, to an interventional specialist who can evaluate them for a transrectal ultrasound-guided prostate biopsy.
- Men with PSA 4 to 7 ng/mL undergo repeat testing several weeks later. Men with a repeat PSA level above 4 ng/mL should be referred for transrectal ultrasound-guided prostate biopsy
- Prior to repeat PSA testing, men should abstain from ejaculation and bike riding for at least 48 hours

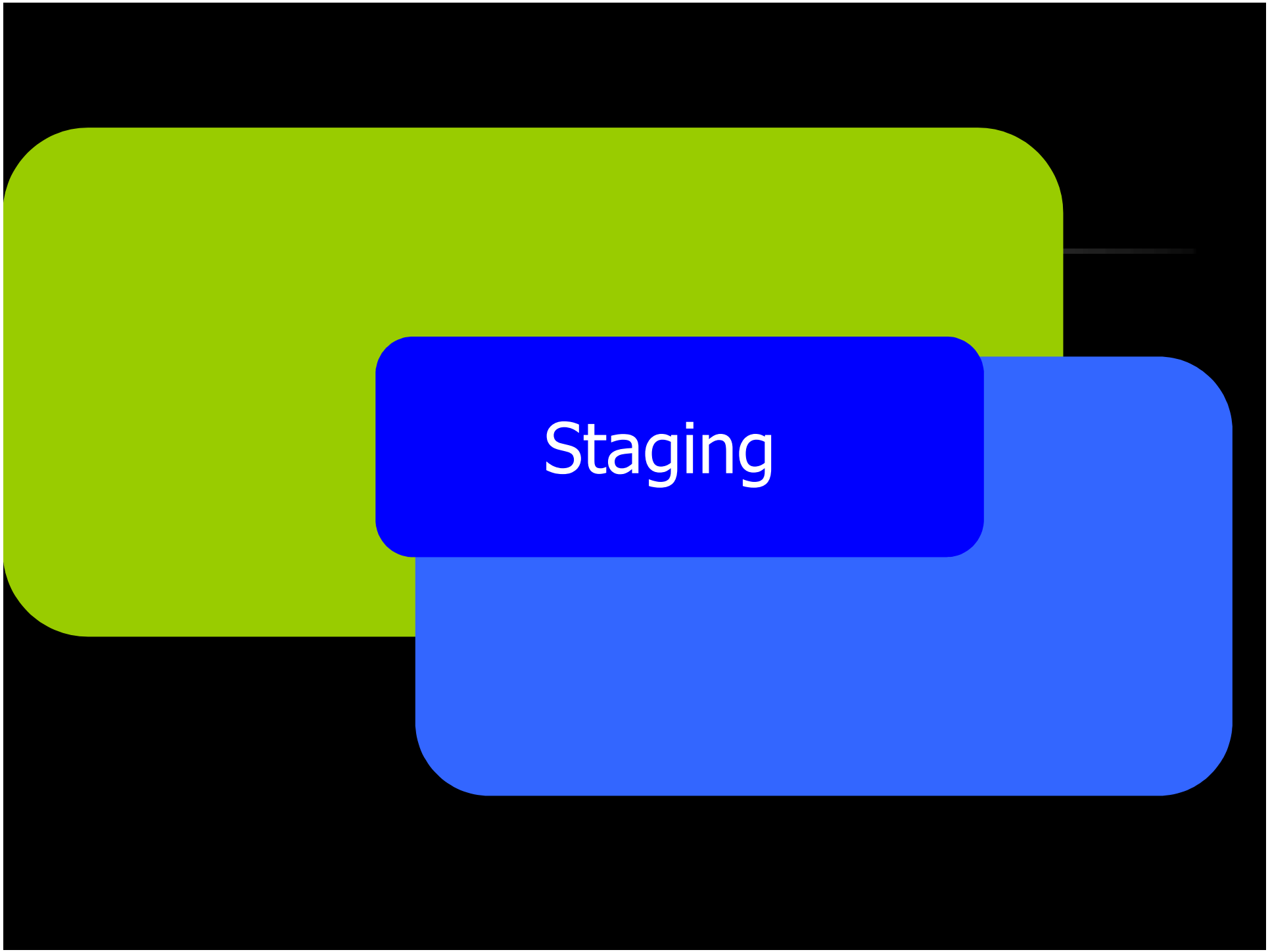

Diagnosis

Diagnosis

- Men with abnormal prostate exams should be referred to a urologist for a prostate biopsy. A prostate biopsy may also be indicated based upon abnormal PSA values.
- A transrectal biopsy typically is performed with transrectal ultrasound (TRUS) guidance
- MRI targeted prostate biopsy is being evaluated as a method to improve the accuracy of TRUS biopsy
- A minimum of 12 cores should be obtained in most situations
- Repeat biopsy may be indicated if the PSA level increases further.



- Adenocarcinoma- 95 percent of malignancies arising in the prostate
- Gleason score is derived by adding together the numerical values for the two most prevalent differentiation patterns (a primary grade and a secondary grade).


Staging

Tumor node metastasis (TNM) stage definitions for prostate cancer

Primary tumor (T)	
Clinical (cT)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor neither palpable nor visible by imaging
T1a	Tumor incidental histologic finding in 5% or less of tissue resected
T1b	Tumor incidental histologic finding in more than 5% of tissue resected
T1c	Tumor identified by needle biopsy (eg, because of elevated PSA)
T2	Tumor confined within prostate*
T2a	Tumor involves one-half of one lobe or less
T2b	Tumor involves more than one-half of one lobe but not both lobes
T2c	Tumor involves both lobes
T3	Tumor extends through the prostate capsule¶
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall
Pathologic (pT)Δ	
pT2	Organ confined
pT2a	Unilateral, one-half of one side or less
pT2b	Unilateral, involving more than one-half of side but not both sides
pT2c	Bilateral disease
pT3	Extraprostatic extension
pT3a	Extraprostatic extension or microscopic invasion of bladder neck◇
pT3b	Seminal vesicle invasion
pT4	Invasion of rectum, levator muscles, and/or pelvic wall

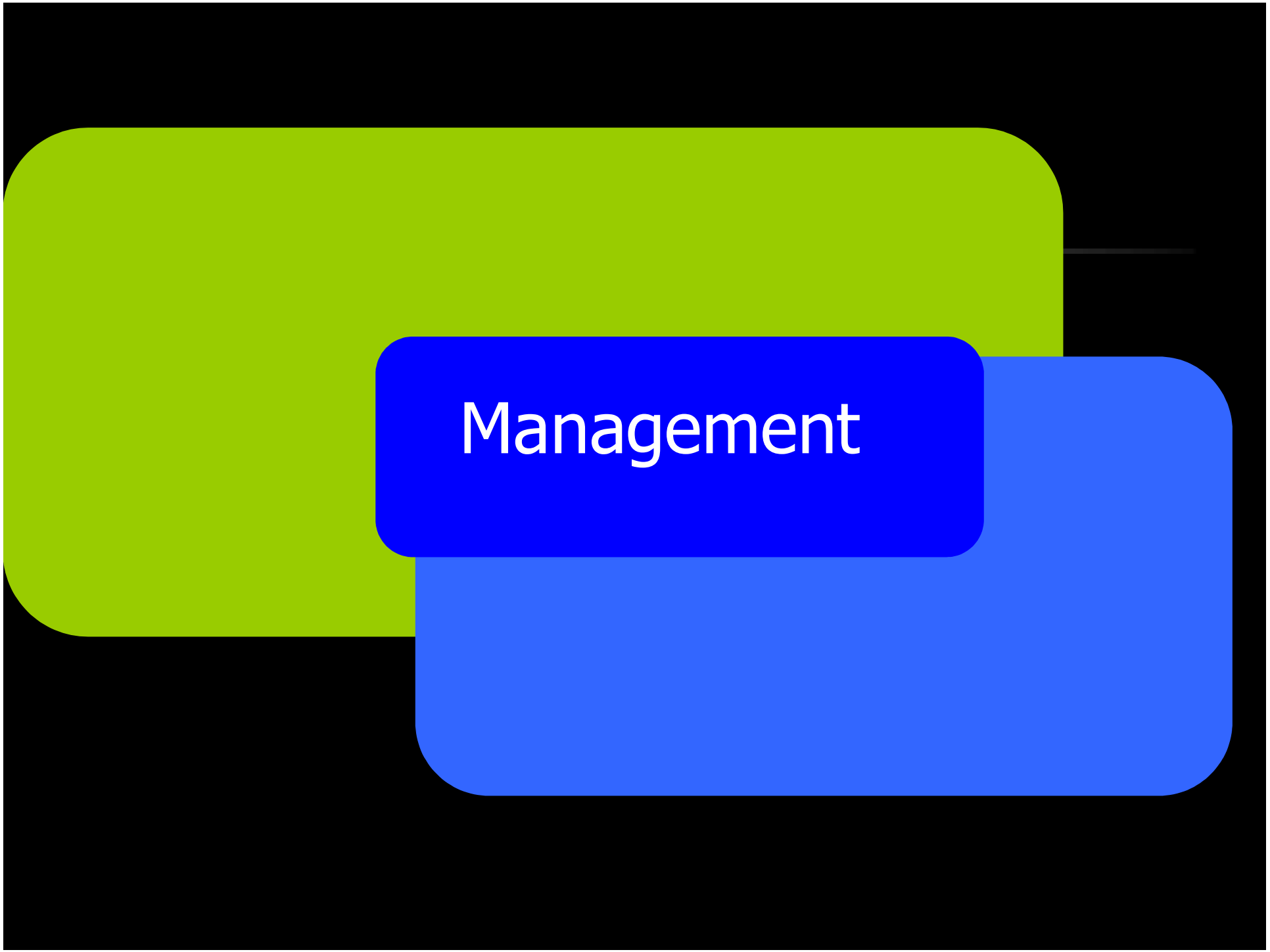
Regional lymph nodes (N)	
Clinical	
NX	Regional lymph nodes were not assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)
Pathologic	
pNX	Regional nodes not sampled
pN0	No positive regional nodes
pN1	Metastases in regional node(s)
Distant metastasis (M)[§]	
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional lymph node(s)
M1b	Bone(s)
M1c	Other site(s) with or without bone disease


Risk
stratification

Risk stratifiction

- Patients are divided into three risk groups (low, intermediate, or high) of occult micrometastases and relapse after initial local therapy

	Low Risk	Moderate Risk	High Risk
Primary Tumor, cT	cT1 / 2a	cT2b	cT2c[1] / 3
	and	or	or
PSA Value (ng/ml)	≤ 10	> 10 ≤ 20	> 20
	and	or	or
Gleason Score	≤ 6	7	≥ 8


Management

Initial approach to low-risk clinically localized PC

- For men with low-risk prostate cancer and a life expectancy of greater than 10 years, definitive therapy (radical prostatectomy, brachytherapy, or external beam radiation therapy (RT)), or active surveillance may all be appropriate options.
- For patients with a more limited life expectancy (less than 10 years) - active surveillance
- Urinary symptoms and bowel symptoms are more common after RT. Incontinence is more frequent after RP.
- Erectile dysfunction is most frequent immediately after prostatectomy, but is also common after RTH. At 24 months, sexual symptom scores are similar among men treated with RP and RTH.

Active surveillance

- = Observation rather than immediate therapy, with curative-intent treatment deferred until there is evidence that the patient is at an increased risk for disease progression
- ≠Watchful waiting
- For patients who are being managed with active surveillance, the optimal schedule for monitoring and the criteria for initiating therapy have not been defined :
  - Measurement of the serum PSA at 3month intervals, to calculate the PSA doubling time. A doubling time of three years or less as a criterion for active intervention.
  - A repeat prostate biopsy is performed at one year. Following this, biopsies are repeated every 4-5 years to look for evidence of biologic progression to Gleason 4+3 or higher.

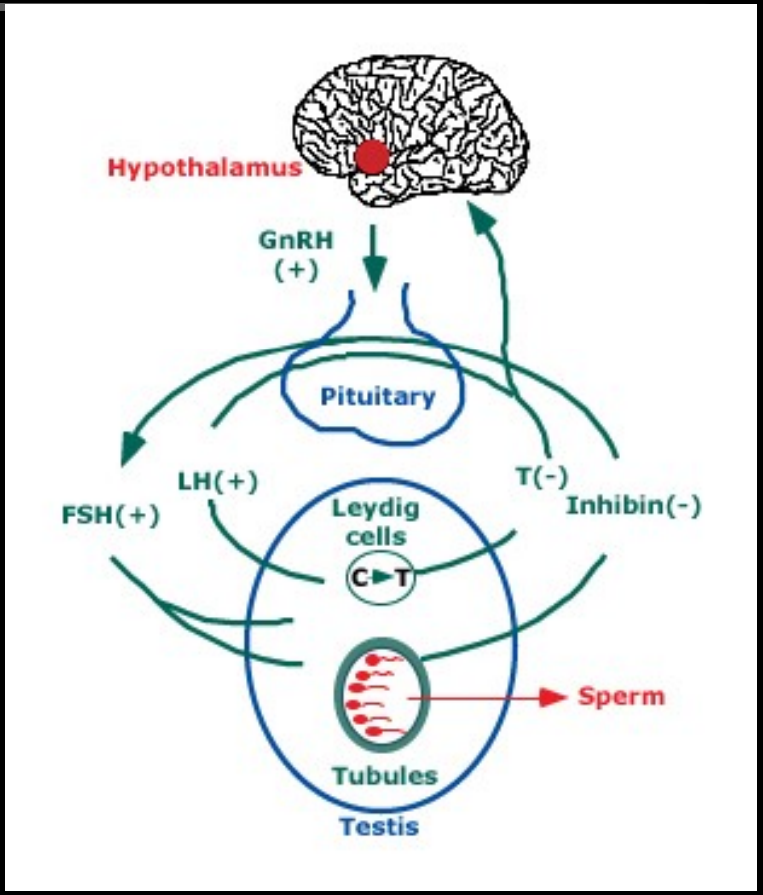
Initial management of regionally localized intermediate and high-risk PC

- Intermediate-risk with life expectancy >10 years and without serious comorbidities- RTH or RP
- Intermediate-risk with life expectancy <10 years RTH or RP vs active surveillance are also alternatives
- High-risk prostate cancer - definitive therapy with RTH (EBRT or EBRT plus brachytherapy) or radical prostatectomy

Management of metastatic disease

- First line: androgen supression (castration) using bilateral orchiectomy or an LHRH agonist/antagonist

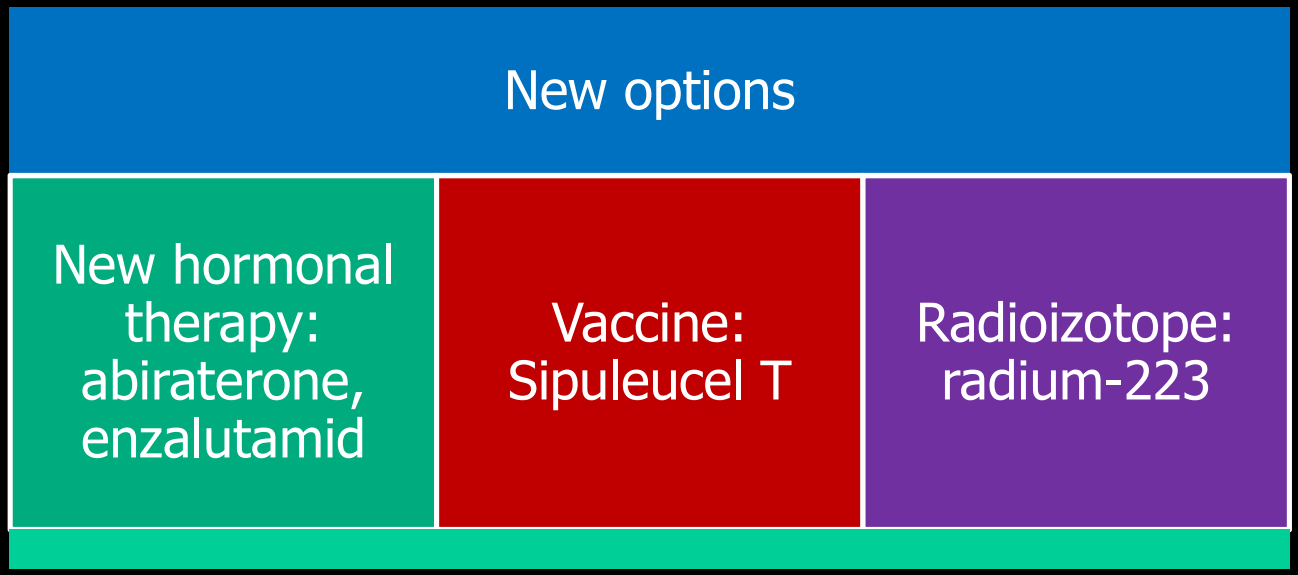
- Second line hormonal manipulations in castrate resistant prostate cancer (CRPC): - adding and withdrawing antiandrogen (eg flutamid, bicalutamid)



Management of metastatic disease

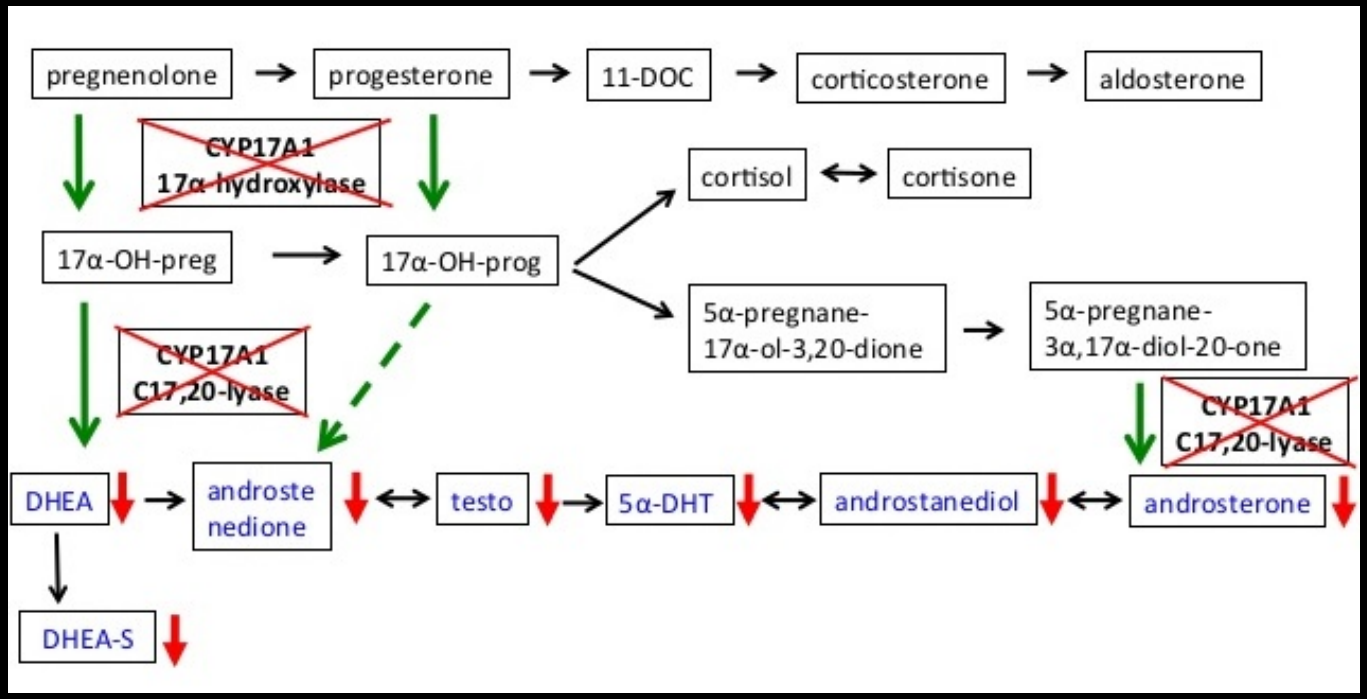
- In castrate resistant prostate cancer (CRPC) – Chemotherapy
  - Docetaxel (BUT! Chemo+AD is also earlier option!)
  - Cabazitaxel
  - Mitoxantrone

or...



Abiraterone

- A selective inhibitor of androgen biosynthesis that potently blocks cytochrome P450 c17 (CYP17), a critical enzyme in testosterone synthesis, thereby blocking androgen synthesis by the adrenal glands and testes and within the prostate tumor



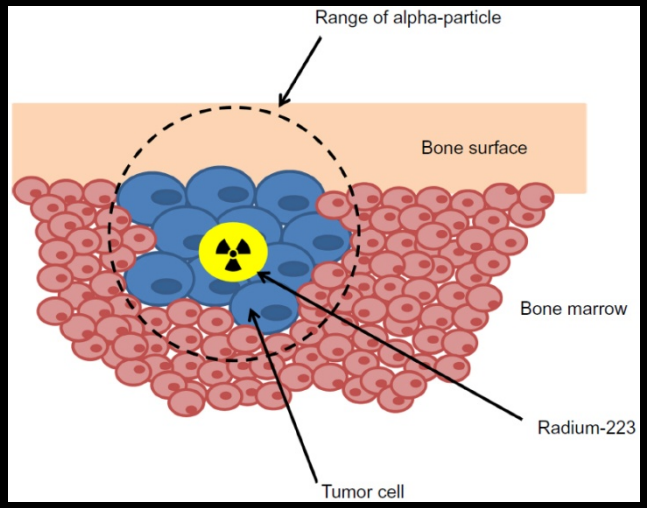
Sipuleucel T

- Day 1: Mononuclear cells are harvested from the patient and shipped to the manufacturing facility
- Day 2-3: centrifugation · incubation for 36-48 h with a chimeric antigen GM-CSF to activate antigen presentation + prostatic acid phosphatase tumor associated antigen
- Days 3-4: final wash before shipment and reinfusion into the patient
- Process repeated every 2 weeks for a complete course of 3 cycles

Radium 223

- Radium-223 dichloride (radium-223) is a novel targeted α-emitter that selectively binds to areas of increased metabolic activity in bone metastases

- It emits high-energy αparticles with ultra-short penetration (<100 µm; 2–10 cell diameters) to effectively induce cytotoxicity in target areas, while limiting damage to surrounding normal tissue, including bone marrow



Bone metastases

- Bisphosphonates
- Denosumab
- Radiotherapy
- Surgery

Question

Screening for prostate cancer:

A. Should be routinely offered to every man aged 50-79 y/o

B. Is strongly supported by results of multiple trials

C. May be recommended in men 50-69 y/o after shared decision making

D. Should be offered to every men with prostate cancer symptoms

E. Should be routinely offered to every man aged 50-69 y/o

Question

The first-line therapy for metastatic prostate cancer is:

A. Chemotherapy with docetaxel
B. Chemotherapy with cabazitaxel
C. Sipuleucel T
D. Hormonal therapy +/- docetaxel
E. Radium-223