PROSTATE CANCER

- Prostate cancer is a malignant neoplasm that arises from the prostate gland. Prostate cancer has an indolent course; localized prostate cancer is curable by surgery or radiation therapy but advanced prostate cancer is not yet curable.

- The endocrine dependence of this tumor is well documented, and hormonal manipulation to decrease circulating androgens remains the basis for the treatment of advanced disease.

- The major pathologic cell type is adenocarcinoma (more than 95% of cases). Prostate cancer can be graded. Well-differentiated tumors grow slowly, whereas poorly differentiated tumors grow rapidly and have a poor prognosis.

EPIDEMIOLOGY AND ETIOLOGY:

Prostate cancer is the most frequent cancer among American men and represents the second leading cause of cancer- related deaths in all males.

Although prostate cancer incidence increased during the late 1980s and early 1990s owing to widespread prostate-specific antigen (PSA) screening, deaths from prostate cancer have been declining continuously since 1995.

- Metastatic spread can occur by local extension, lymphatic drainage, or hematogenous dissemination.

- Skeletal metastases from hematogenous spread are the most common sites of distant spread.

- The lung, liver, brain, and adrenal glands are the most common sites of visceral involvement, but these organs are not usually involved initially.

Risk Factors Associated with Prostate Cancer:

Factor Possible Relationship:

Probable Risk Factors:

Age More than 70% of cases are diagnosed in men greater than 65 years old.

Race African Americans have higher incidence and death rate.

Genetic Familial prostate cancer is inherited in an autosomal dominant manner.

Mutations in *p53, Rb*, E-cahedrin, *a*-catenin, androgen receptor,,microsatellite instability. Candidate prostate cancer gene locus identified on chromosome 1.

Environmental Clinical carcinoma incidence varies worldwide.

Latent carcinoma similar between regions. Nationalized males adopt intermediate incidence rates between that of the United States and their native country.

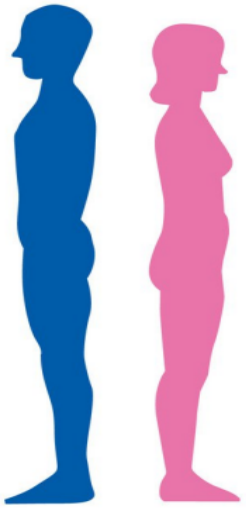
Occupational Increased risk associated with cadmium exposure.

Diet Increased risk associated with high-meat and high-fat diets. Decreased intake of 1, 25-dihydroxyvitamin D, vitamin E, lycopene, and *b*-carotene increases risk.

Hormonal Does not occur in eunuchs. Low incidence in cirrhotic patients **(why?)**. Up to 80% are hormonally dependent. African-Americans have 15% increased testosterone. Japanese have decreased 5-*a*-reductase activities. Polymorphic expression of the androgen receptor.

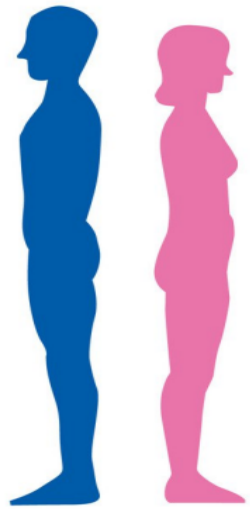
Estimated New Cases

Males			Females		
Prostate	191,930	21%	Breast	276,480	30%
Lung & bronchus	116,300	13%	Lung & bronchus	112,520	12%
Colon & rectum	78,300	9%	Colon & rectum	69,650	8%
Urinary bladder	62,100	7%	Uterine corpus	65,620	7%
Melanoma of the skin	60,190	7%	Thyroid	40,170	4%
Kidney & renal pelvis	45,520	5%	Melanoma of the skin	40,160	4%
Non-Hodgkin lymphoma	42,380	5%	Non-Hodgkin lymphoma	34,860	4%
Oral cavity & pharynx	38,380	4%	Kidney & renal pelvis	28,230	3%
Leukemia	35,470	4%	Pancreas	27,200	3%
Pancreas	30,400	3%	Leukemia	25,060	3%
All Sites	**893,660**	**100%**	**All Sites**	**912,930**	**100%**



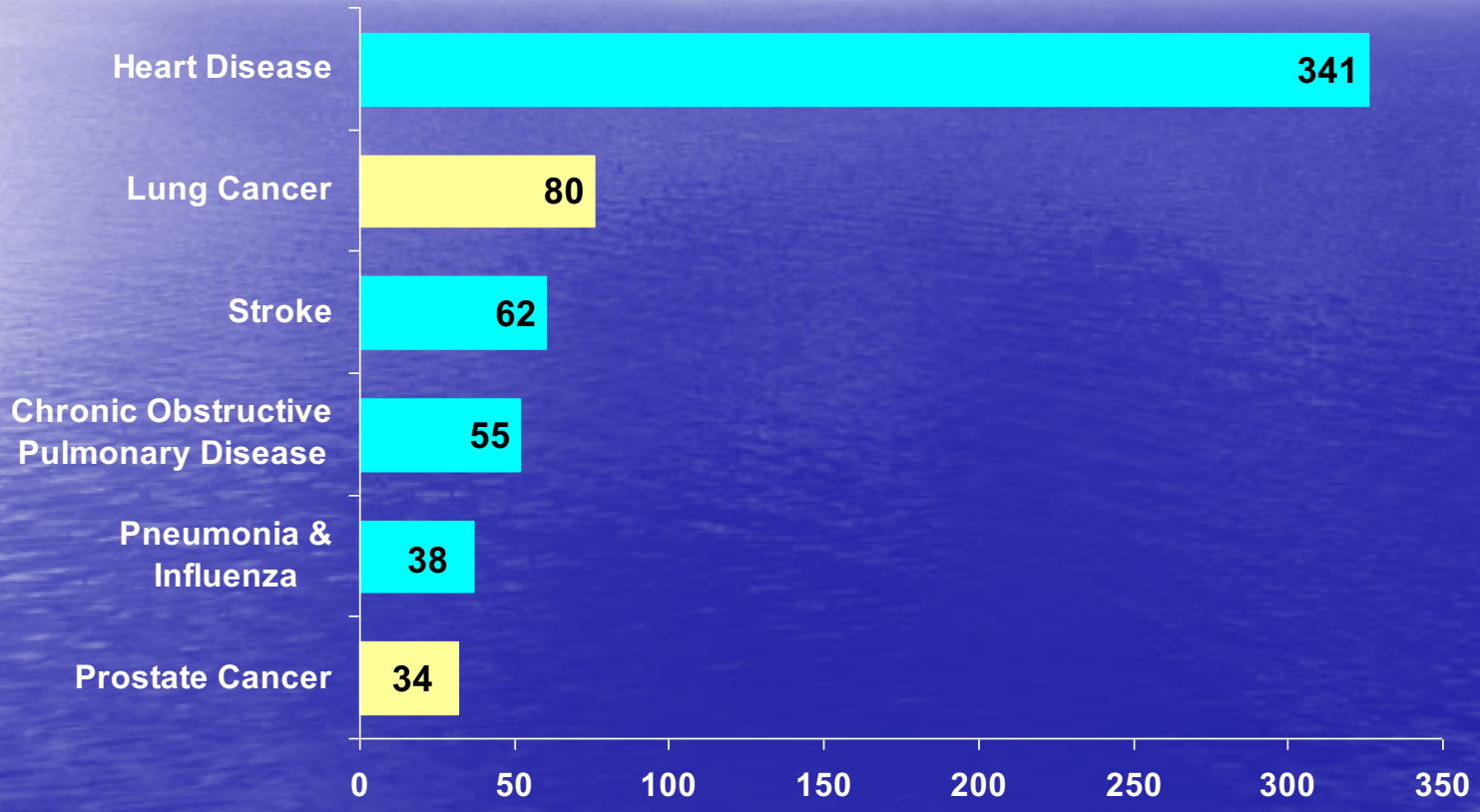
Estimated Deaths

Males			Females		
Lung & bronchus	72,500	23%	Lung & bronchus	63,220	22%
Prostate	33,330	10%	Breast	42,170	15%
Colon & rectum	28,630	9%	Colon & rectum	24,570	9%
Pancreas	24,640	8%	Pancreas	22,410	8%
Liver & intrahepatic bile duct	20,020	6%	Ovary	13,940	5%
Leukemia	13,420	4%	Uterine corpus	12,590	4%
Esophagus	13,100	4%	Liver & intrahepatic bile duct	10,140	4%
Urinary bladder	13,050	4%	Leukemia	9,680	3%
Non-Hodgkin lymphoma	11,460	4%	Non-Hodgkin lymphoma	8,480	3%
Brain & other nervous system	10,190	3%	Brain & other nervous system	7,830	3%
All Sites	**321,160**	**100%**	**All Sites**	**285,360**	**100%**



Risk of Death for 40 year old U.S. Men, to End of Life, by Leading Causes:

Note Smoking Related Disease



Screening:

Early detection of potentially curable prostate cancers is the goal of prostate cancer screening.

1- Digital rectal examination (DRE).
2- Prostate specific antigen (PSA).

PATHOPHYSIOLOGY:

The growth and development of the prostate is under control of androgens, and it is well known that men who undergo castration prior to puberty do not develop prostate cancer.

Antiandrogens inhibit the formation of the DHT-receptor complex and thereby interfere with androgen-mediated action at the cellular level.

CLINICAL PRESENTATION, DIAGNOSIS, AND STAGING:

Localized Disease

Asymptomatic.

Locally Invasive Disease

- Ureteral dysfunction, frequency, hesitancy, and dribbling
- Impotence.

Advanced Disease

- Back pain
- Cord compression
- Lower extremity edema
- Pathologic fractures
- Anemia
- Weight loss

AUS[a] Stage (A–D)	AJC-UICC[b] Classification (TNM)
A (Occult, nonpalpable)	$T_xN_xM_x$ (Cannot be assessed)
A_1: Focal	$T_0N_0M_0$ (Nonpalpable)
A_2: Diffuse	T_0: Focal or diffuse
B (Confined to prostate)	$T_1N_0M_0$, $T_2N_0M_0$
B_1: Single nodule in one lobe, less than 1.5 cm	T_1 (Clinically inapparent tumor not palpable or visible by imaging)
	T_{1a}: Tumor incidental histologic finding in 5% or less of tissue resected
	T_{1b}: Tumor incidental histologic finding in 5% or more of tissue resected
	T_{1c}: Tumor identified by needle biopsy (e.g., because of elevated prostate-specific antigen)
B_2: Diffuse involvement of whole gland, greater than 1.5 cm	T_2: (Tumor confined within the prostate[c])
	T_{2a}: Tumor involves half of a lobe or less
	T_{2b}: Tumor involves more than half a lobe, but not both lobes
	T_{2c}: Tumor involves both lobes
C (Localized to periprostatic area)	$T_3N_0M_0$, $T_4N_0M_0$
C_1: No seminal vesicle involvement, less than 70 g	T_3: (Tumor extends through the prostatic capsule[d])
	T_{3a}: Unilateral extracapsular extension
	T_{3b}: Bilateral extracapsular extension
	T_{3c}: Tumor invades the seminal vesicle(s)
C_2: Seminal vesicle involvement, greater than 70 g	T_4: (Tumor is fixed or invades adjacent structures other than the seminal vesicles)
	T_{4a}: Tumor invades any of bladder neck, external sphincter, or rectum
	T_{4b}: Tumor invades levator muscles and/or is fixed to the pelvic wall
D (Metastatic disease)	Any T, N_{1-4}, M_0, or N_{0-4}, M_1
D_1: Pelvic lymph nodes or ureteral obstruction	N_1: Metastasis in a single lymph node, 2 cm or less in greatest dimension
D_2: Bone, distant lymph node, organ, or soft tissue metastases	N_2: Metastasis in single lymph node more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph node metastases, none more than 5 cm in greatest dimension
	N_3: Metastasis in lymph node more than 5 cm in greatest dimension
	M_{1a}: Nonregional lymph node(s)
	M_{1b}: Bone(s)
	M_{1c}: Other site(s)

Diagnostic and Staging Work-Up for Prostate Cancer

Diagnostic Tests

- Digital rectal examination (DRE)
- Prostate-specific antigen (PSA)
- Transrectal ultrasonography (TRUS) if either DRE is positive

or PSA is elevated

- Biopsy

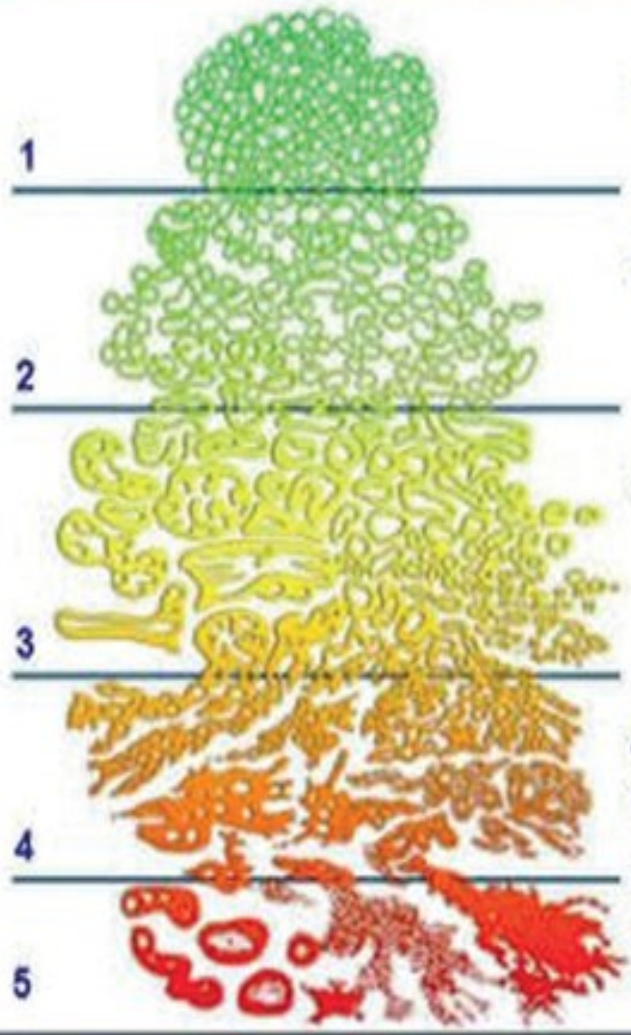
Staging Tests

- Gleason score on biopsy specimen
- Bone scan
- Complete blood count
- Liver function tests
- Serum phosphatases (acid/alkaline)
- Excretory urogram
- Chest x-ray

Additional Staging Tests

- Depends on tumor classification, PSA, and Gleason score.
- Skeletal films
- Lymph node evaluation
- Pelvic computed tomography
- 111In-labeled capromab pendetide scan
- Bipedal lymphangiogram
- Transrectal magnetic resonance imaging

Gleason's Pattern Scale



1. Small, uniform glands.
2. More space (stroma) between glands.
3. Distinctly infiltration of cells from glands at margins.
4. Irregular masses of neoplastic cells with few glands.
5. Lack of or occasional glands, sheets of cells.

Well differentiated

Moderately differentiated

Poorly differentiated
Anaplastic

TREATMENT:

The desired outcome in early-stage prostate cancer is to minimize morbidity and mortality owing to prostate cancer.

The initial treatment for prostate cancer depends primarily on the disease stage, the gleason score, the presence of symptoms, and the life expectancy of the patient.

Initial Management of Prostate Cancer with Low and Intermediate Recurrence Risk:

Recurrence Risk	Expected Survival	Initial Therapy
Low	Less than 10 years	Expectant management or RT
T1–2a, Gleason 2–6, PSA less than 10	Greater than or equal to 10 years	Expectant management or RP with or without pelvic lymph node dissection or RT
Intermediate	Less than 10 years	EM, RT or RP with or without pelvic lymph node dissection
T2b–2c, or Gleason 7, or PSA 10–20	Greater than or equal to 10 years	RP with or without pelvic lymph node dissection or RT

Chemoprevention:

Currently, the most promising agent for the prevention of prostate cancer is finasteride, a 5-α-reductase inhibitor used for BPH.

Other agents, including selenium, vitamin E, lycopene, green tea, nonsteriodal anti-inflammatory agents, isoflavones, and statins, are under investigsation for prostate cancer and show promise.

Prostate cancer diagnosed in patients on finasteride is more aggressive, making its use in men without BPH controversial.

Management of Prostate Cancer with High and Very High Recurrence Risk

Recurrence Risk	Initial Therapy
High	
T3a, or Gleason 8–10, or PSA greater than 20 ng/mL Locally advanced	Androgen deprivation for 2 years and RT or RT or RP
Very high	RT + androgen deprivation
T3b–T4	or Androgen deprivation
Metastatic	
Any T, N1	Androgen deprivation or RT
Any T, any N, M1	Androgen deprivation

Nonpharmacologic Therapy:

Expectant Management:

Expectant management, also known as *observation* or *watchful waiting,* involves monitoring the course of disease and initiating treatement if the cancer progresses or the patient becomes symptomatic.

Orchiectomy:

Bilateral **orchiectomy,** or removal of the testes, rapidly reduces circulating androgens to castrate levels (androstenedione less than 50 ng/mL, 1.7 nmol/L).

Radiation:

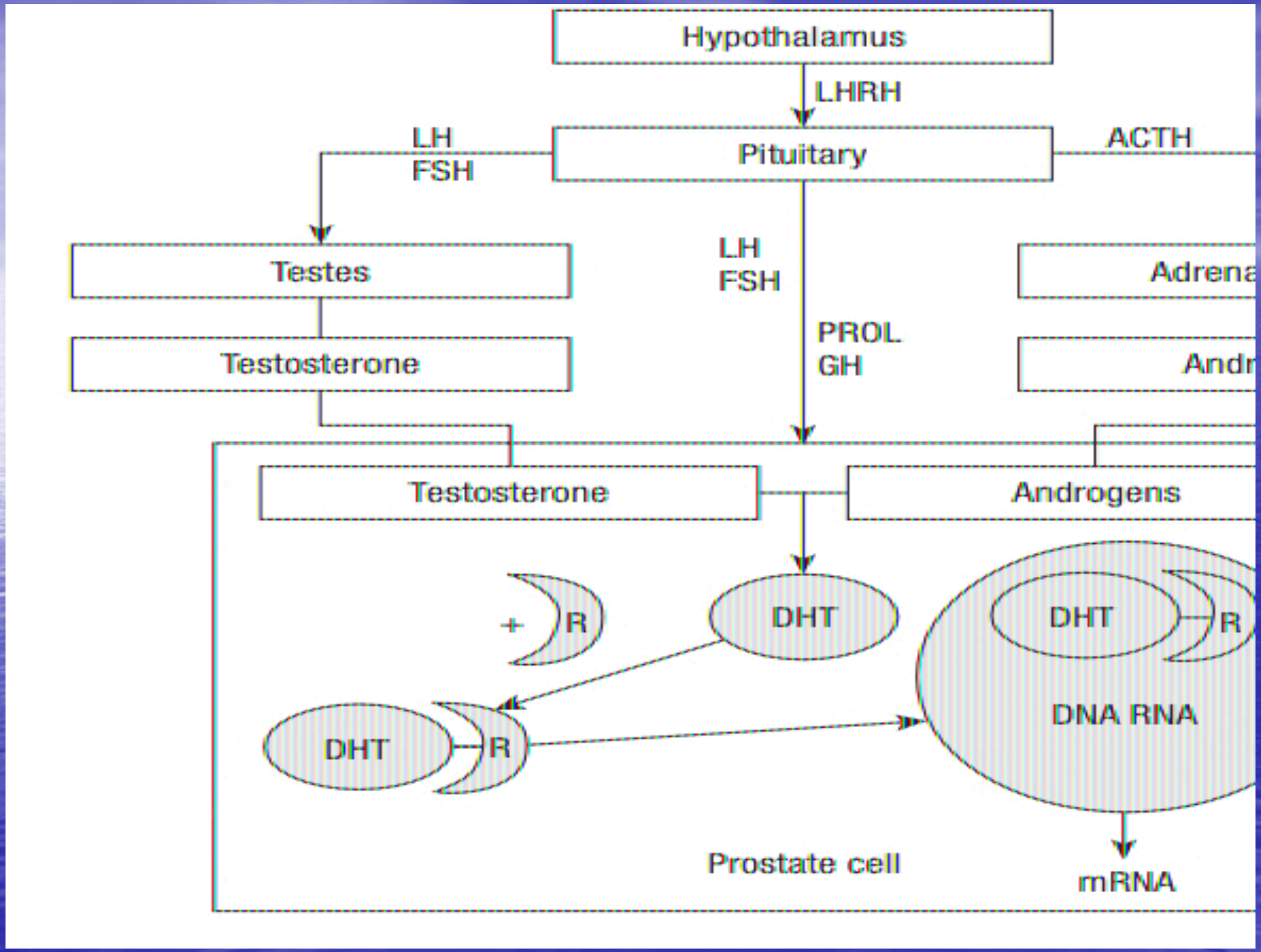
- The two commonly used methods for radiation therapy are **external-beam radiotherapy** and **brachytherapy.**

- Acute complications of radiation therapy include cystitis, proctitis, hematuria, urinary retention, penoscrotal edema, and impotence.

- Chronic complications of radiation therapy include proctitis, diarrhea, cystitis, enteritis, impotence, urethral stricture, and incontinence.

Radical Prostatectomy:

Complications from radical **prostatectomy** include blood loss, stricture formation, incontinence, lymphocele, fistula formation, anesthetic risk, and impotence.


Hypothalamus
LHRH
LH
FSH
Pituitary
ACTH
Testes
LH
FSH
Adrena
Testosterone
PROL
GH
Andr
Testosterone
Androgens
+
R
DHT
DHT
R
DHT
R
DNA RNA
Prostate cell
mRNA

Pharmacologic Therapy:

LHRH Agonists:

LHRH agonists are a reversible method of androgen ablation and are as effective as orchiectomy in treating prostate cancer. Currently available LHRH agonists include leuprolide, leuprolide depot, leuprolide implant, and goserelin acetate implant.

Leuprolide acetate is administered once daily, whereas leuprolide depot and goserelin acetate implant can be administered either once monthly, once every 12 weeks, or once every 16 weeks (leuprolide depot, every 4 months).

The most common adverse effects reported with LHRH agonist therapy include a disease flare-up during the first week of therapy, hot flashes, erectile impotence, decreased libido, and injection-site reactions.

LHRH antagonists:

- LHRH antagonists can be used to treat advanced prostate cancer. These drugs work in a slightly different way from the LHRH agonists, but they lower testosterone levels more quickly and don't cause tumor flare like the LHRH agonists do. Treatment with these drugs can also be considered a form of medical castration.

- Degarelix (Firmagon) is given as a monthly injection under the skin. Some men may notice problems at the injection site (pain, redness, and swelling).

- Relugolix (Orgovyx) is taken as pills, once a day, so it might allow for less frequent office visits.

Antiandrogens:

- Three antiandrogens, flutamide, bicalutamide, and nilutamide, are currently available.

- Antiandrogens have been used as monotherapy in previously untreated patients, but a recent meta-analysis determined that monotherapy with antiandrogens is less effective than LHRH agonist therapy.

- Objective responses are manifested as decreased bone pain, decreased prostate size, decreased PSA, and/or improved performance status.

Antiandrogen	Usual Dose	Adverse Effects
Flutamide	750 mg/day	Gynecomastia, Hot flushes, Gastrointestinal disturbances (diarrhea) Breast tenderness, Methemoglobinemia Liver function test abnormalities,
Bicalutamide	50 mg/day	Gynecomastia, Hot flushes, Gastrointestinal disturbances (diarrhea) Liver function test abnormalities, Breast tendernes.
Nilutamide	300 mg/day for first month, then 150 mg/day.	Gynecomastia, Hot flushes, Gastrointestinal disturbances (nausea or constipation) Liver function test abnormalities, Breast tenderness, Visual disturbances impaired dark (adaptation) Alcohol intolerance, Interstitial pneumonitis

Combined Hormonal Blockade:

Although up to 80% of patients with advanced prostate cancer will respond to initial hormonal manipulation, almost all patients will relapse within 2 to 4 years of initiating therapy.

The rationale for combination hormonal therapy is to interfere with multiple hormonal pathways to completely eliminate androgen action.

The combination of LHRH agonists or orchiectomy and antiandrogens is the most extensively studied combined androgen-deprivation approach. Combining an LHRH agonist with flutamide demonstrated response rates greater than 90% in previously untreated patient.

Estrogens:

DES was once a mainstay of prostate cancer therapy. While very effective in androgen ablation, DES-treated patients experienced increased cardiovascular mortality.

Second-Line Therapy:

Secondary or salvage therapies for patients who progress after their initial therapy depend on what was used for initial management.

Supportive care, chemotherapy, or local radiotherapy can be used in patients who have failed all forms of androgen-ablation manipulations because these patients are considered to have androgen-independent disease.

Androgen withdrawal, for patients having progressive disease while receiving combined hormonal blockade with an LHRH agonist plus an antiandrogen, can provide additional symptomatic relief. Mutations in the androgen receptor have been documented that cause antiandrogen compounds to act like receptor agonists.

Patient responses to androgen withdrawal manifest as significant PSA reductions and improved clinical symptoms.

Adding an agent that blocks adrenal androgen synthesis, such as aminoglutethimide, at the time that androgens are withdrawn may produce a better response than androgen withdrawal alone.

Androgen synthesis inhibitors, such as aminoglutethimide and ketoconazole, can provide symptomatic relief for a short time in approximately 50% of patients with progressive disease despite previous androgen-ablation therapy.

Data are emerging that demonstrate that bisphosphonates such as pamidronate and zoledronic acid may prevent skeletal morbidity, such as pathologic fractures and spinal cord compression, in men with hormone-refractory prostate cancer; however, other studies have shown no benefit.

Chemotherapy, with docetaxel and prednisone or docetaxel and estramustine, improves survival in patients with hormone refractory prostate cancer.

- ✓ The combination of **estramustine** 280 mg by mouth three times daily on days 1 to 5 and docetaxel 60 mg/m2 on day 2 of a 21-day cycle also improves survival in hormone-refractory metastatic prostate cancer.

- ✓ Estramustine causes a decrease in testosterone and a corresponding increase in estrogen, which results in an increase in thromboembolic events, gynecomastia, and decreased libido.

- For definitive, curative therapy, objective parameters to monitor include primary tumor size, involved lymph nodes, and tumor markers such as PSA. PSA level is checked every 6 months for the first 5 years, and then annually.
- With metastatic disease, clinical benefit can be documented by evaluating performance status, weight, quality of life, analgesic requirements, and PSA or DRE at 3-month intervals.
- Patients should be monitored for treatment-related adverse events, especially events that are amenable to intervention.

Thanks for listening