GU TUMORS

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Renal cell carcinoma

ETIOLOGY:

- **CIGARETTE SMOKING**
- **OBESITY**
- **ANALGESIC ABUSE (phenacetin)**
- **INDUSTRIAL SOLVENT, TRICHLOROETHYLENE**
- **EXPOSURE TO CADMIUM**
- **ACQUIRED CYSTIC DISEASE**

Renal cell carcinoma

Clinical presentation:

- Pain
- Hematuria
- Flank mass

metastatic disease – 30% (75% - lung mets)

locally advanced - 25%

localized disease - 45%

Renal cell carcinoma

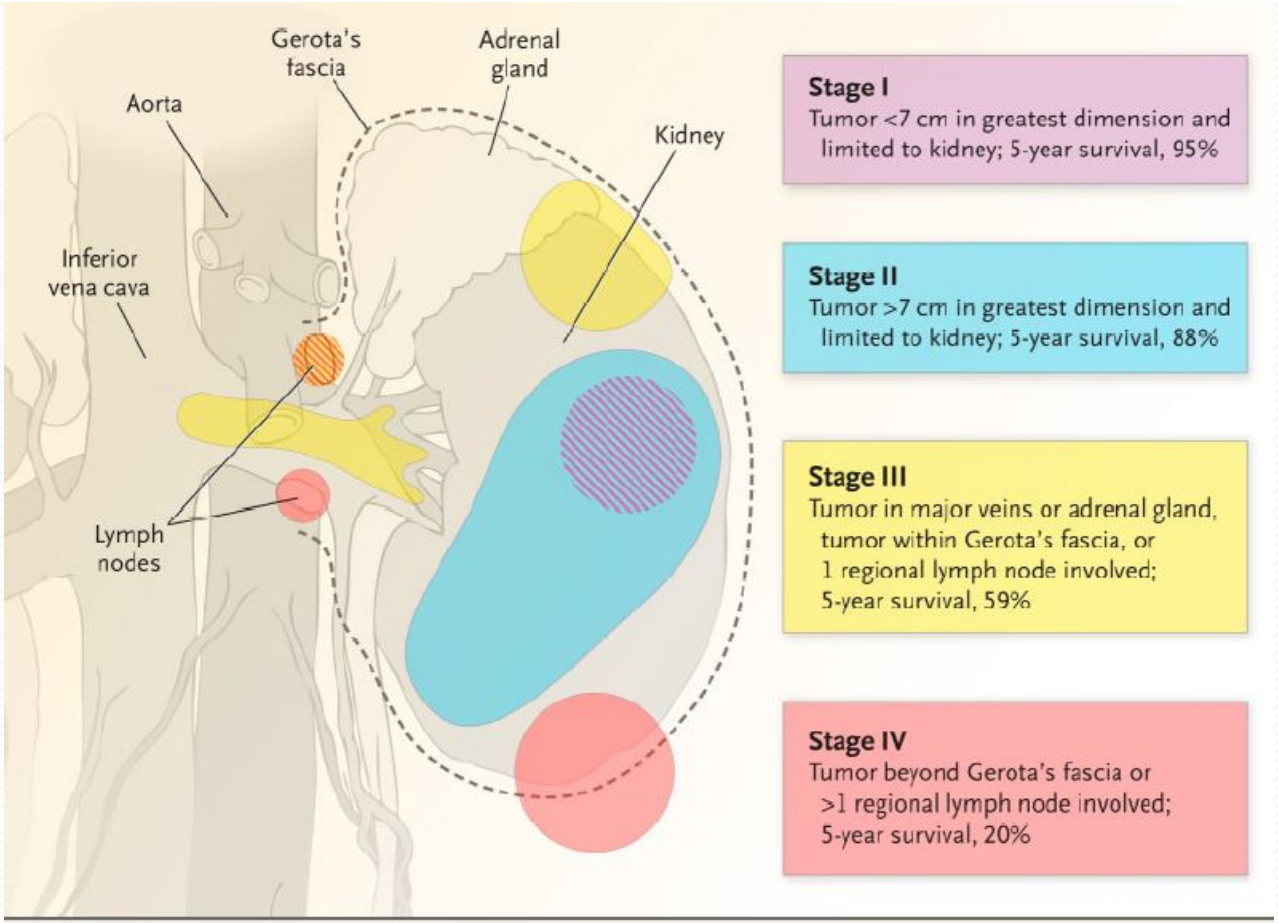


Figure 1. Staging Overview and Five-Year Survival Rates for Renal Cancer.

Survival data[3] are based on the 1997 tumor–node–metastasis (TNM) staging guidelines.[4] More recent renal-cancer staging is described elsewhere.[5]

Table 1. Sporadic and Hereditary Renal-Cell Carcinomas and Genetic Defects According to Histologic Appearance.*

Sporadic Renal-Cell Carcinomas			Renal-Cell Carcinomas in an Inherited Syndrome	
Histologic Appearance	Incidence	Gene and Frequency	Rare Syndrome†	Gene
		percent		
Conventional	75	*VHL*, 60	VHL disease FCRC Hereditary paraganglioma	*VHL* Chromosome 3p translocation *SDHB*
Papillary	12	*MET*, 13 *TFE3*, <1	HPRC HLRCC	*MET* *FH*
Chromophobe	4		Birt–Hogg–Dubé syndrome	*BHD*
Oncocytoma	4		Birt–Hogg–Dubé syndrome	*BHD*
Collecting duct	<1			
Unclassified	3–5			

* *VHL* denotes von Hippel–Lindau, FCRC familial clear-cell renal cancer, *SDHB* succinate dehydrogenase B, HPRC hereditary papillary renal carcinoma, HLRCC hereditary leiomyomatosis and renal-cell cancer, and *FH* fumarate hydratase.
† Additional rare syndromes or infrequent associations are not included.

Biology of RCC

- Von Hippel-Lindau (VHL) syndrome is characterized by germline mutation of chromosome 3p, development of renal cell carcinoma (RCC)
- Noninherited clear-cell RCC characterized by VHL gene tumor suppressor gene inactivation, leads to
  - Constitutive expression of oxygen-regulated transcription factor (HIFa)
  - Induction of hypoxia-inducible genes, including vascular endothelial growth factor (VEGF)
- VEGF overexpression promotes tumor angiogenesis

Motzer. Five variables as risk factors for short survival

- Low KPS (<80%)
- High LDH (>1.5 upper limit)
- Low hemoglobin
- High corrected serum calcium (>10mg/dL)
- Time of metastatic desease from diagnosis (less than a year)

Renal cell carcinoma

- Radiographic evaluation:

- CT is the modality of choice for imaging a renal mass
- MRI
- US
- Renal arteriography

Renal cell carcinoma - treatment

- Localized RCC

  - surgical treatment

- Metastatic RCC

  - palliative nephrectomy (in patients with pain, hemorrhage, malaise, hypercalcemia, erythrocytosis or hypertension).

  - resection of metastasis (lung)

Renal cell carcinoma - treatment

- Chemotherapy -

Chemotherapy currently has little to no role in the treatment of metastatic RCC

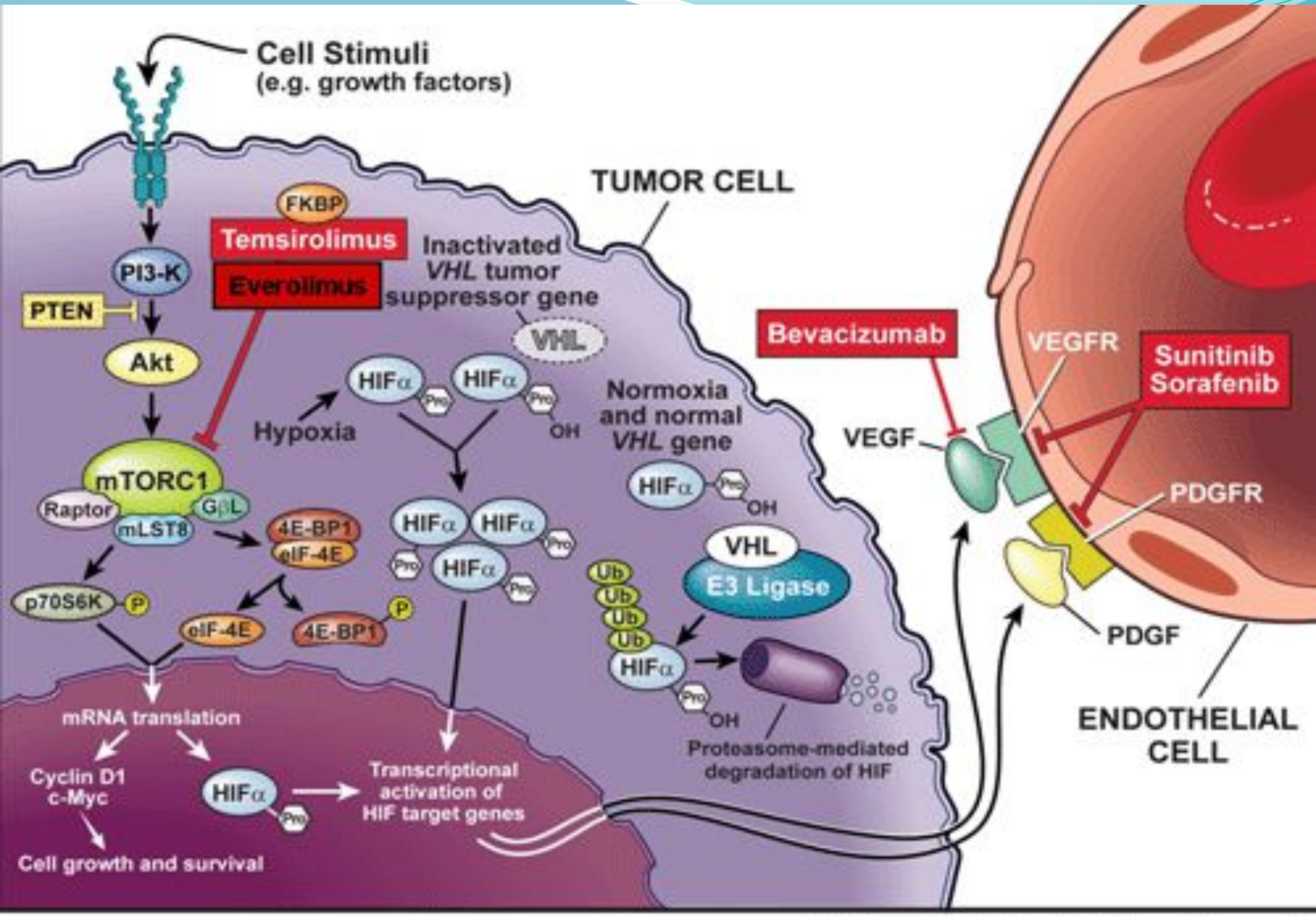
Renal cell carcinoma - treatment

VEGF Targeted therapy

- VEGF receptor:
  - Sunitinib
  - surafenib
  - Pazopanib
  - Axitinib
- VEGF ligand:
  - Bevacizumab

immunotherapy

- Opdivo (Nivolumab) - anti PD1



Rini, Campbell, Escudier. *Lancet* (in press)

Bladder cancer

- Pathology - transitional cell carcinoma (TCC) – 90%
  adenocarcinoma
  squamous Cell carcinoma
- Risk factors – gene abnormalities (protooncogene Ras p21 protein)
  chemical exposure
  chronic irritation (SqCC)

Bladder cancer

- Clinical presentations:

  gross painless hematuria

- Workup:

  cytology

  cystoscopy

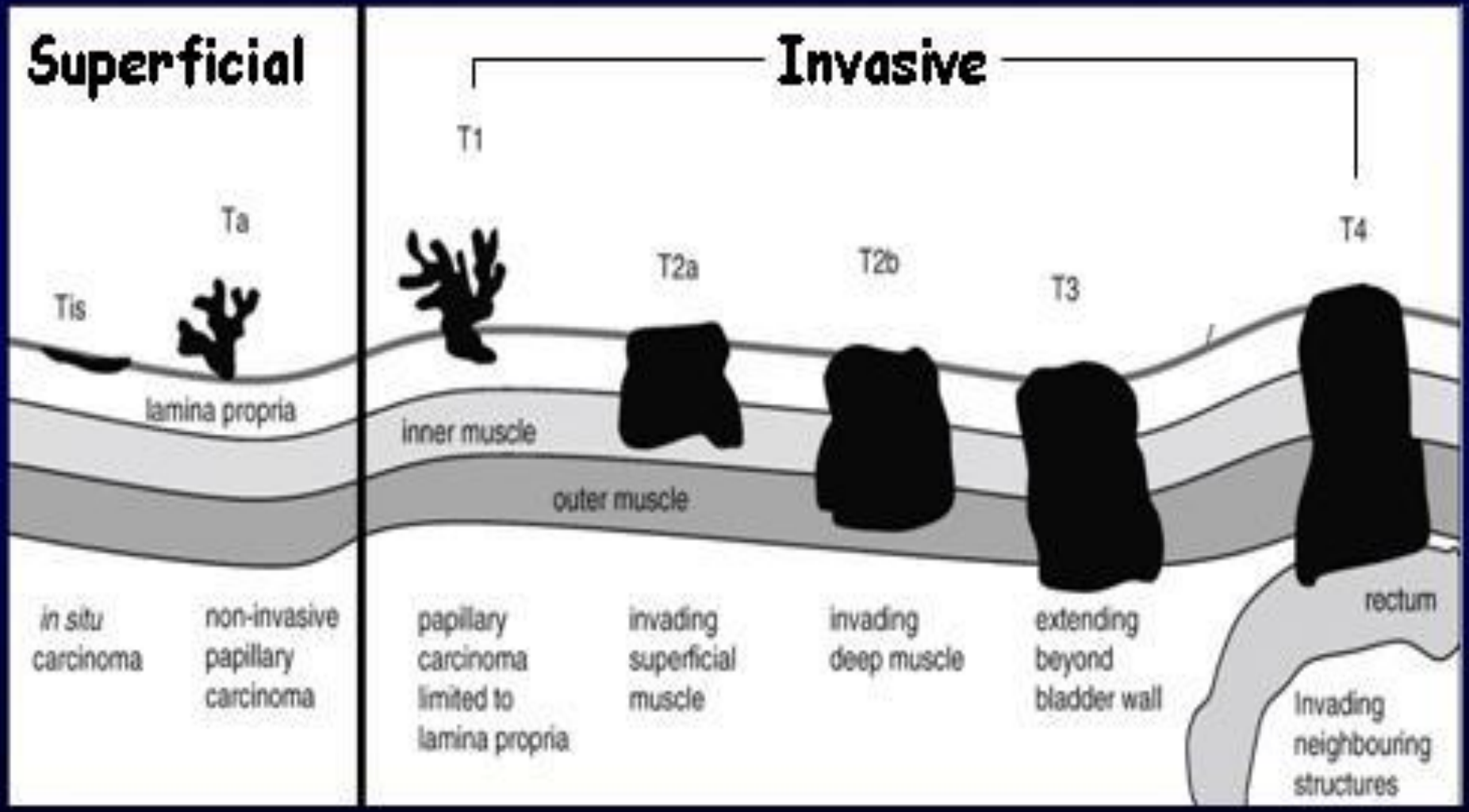
  upper truct study (CT)

- Clinical stage of the primary tumor - TURBT

Stages

56% of the patients

44% of the patients



Bladder cancer - treatment

- Ta, Tis, T1 – 70%
  - TURBT
  - Intravesical drug therapy:
    - BCG
    - MITOMYCIN C
    - DOXORUBICIN
    - GEMCITABINE
    - THIOTEPA

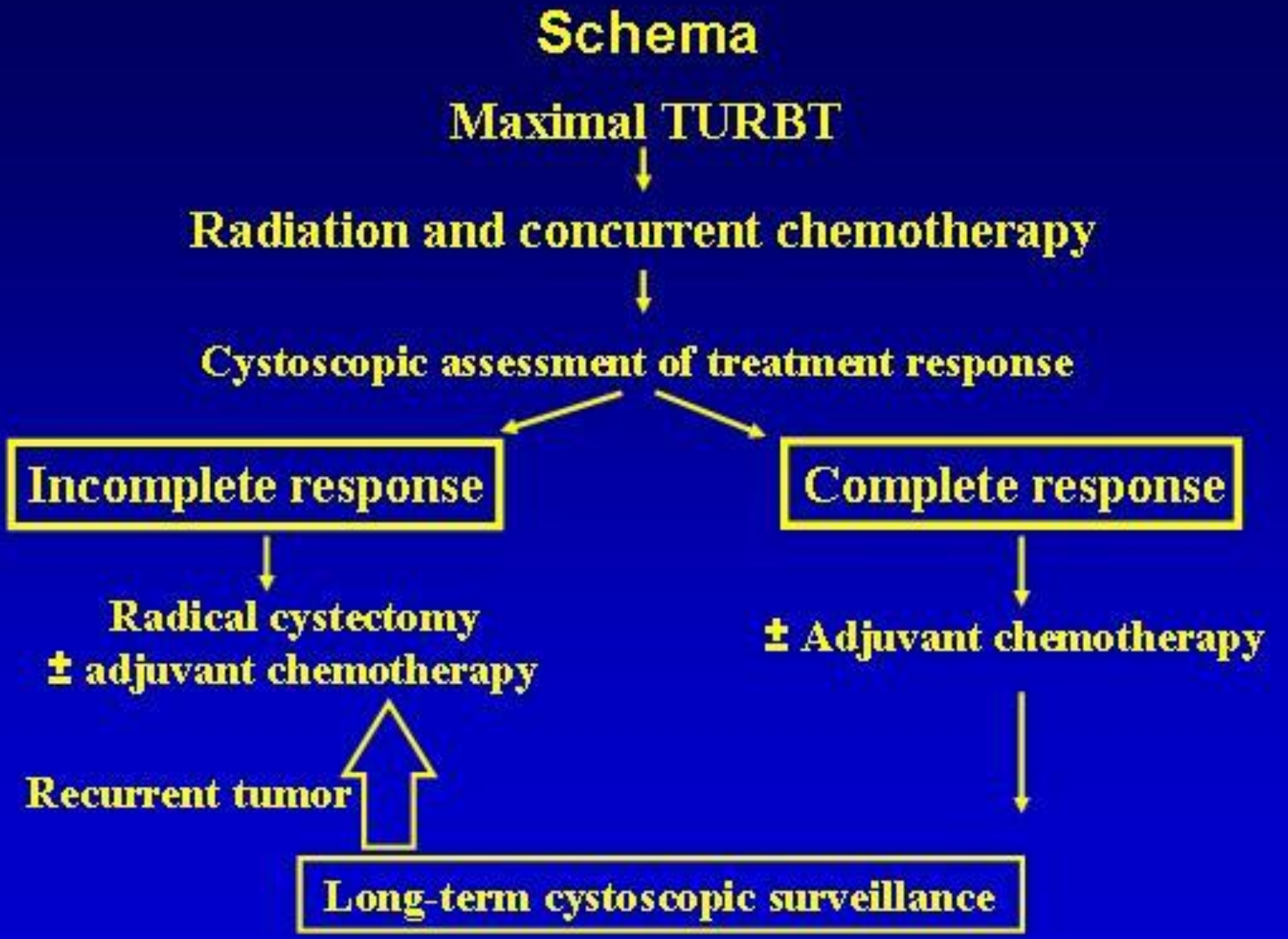
Bladder cancer - treatment

- Muscularis propria-invasive disease

Radical cystectomy

- Complications of Cystectomy (ileal Conduit):
- Metabolic acidosis
- Increase Cl
- Decrease K,CA, MG

Bladder Preservation treatment


Schema
Maximal TURBT
Radiation and concurrent chemotherapy
Cystoscopic assessment of treatment response
Incomplete response
Complete response
Radical cystectomy
± adjuvant chemotherapy
± Adjuvant chemotherapy
Recurrent tumor
Long-term cystoscopic surveillance

Bladder cancer - treatment

- <u>Adjuvant chemotherapy?</u>

  4 cycles of Cisplatin plus gemcitabine or MVAC?

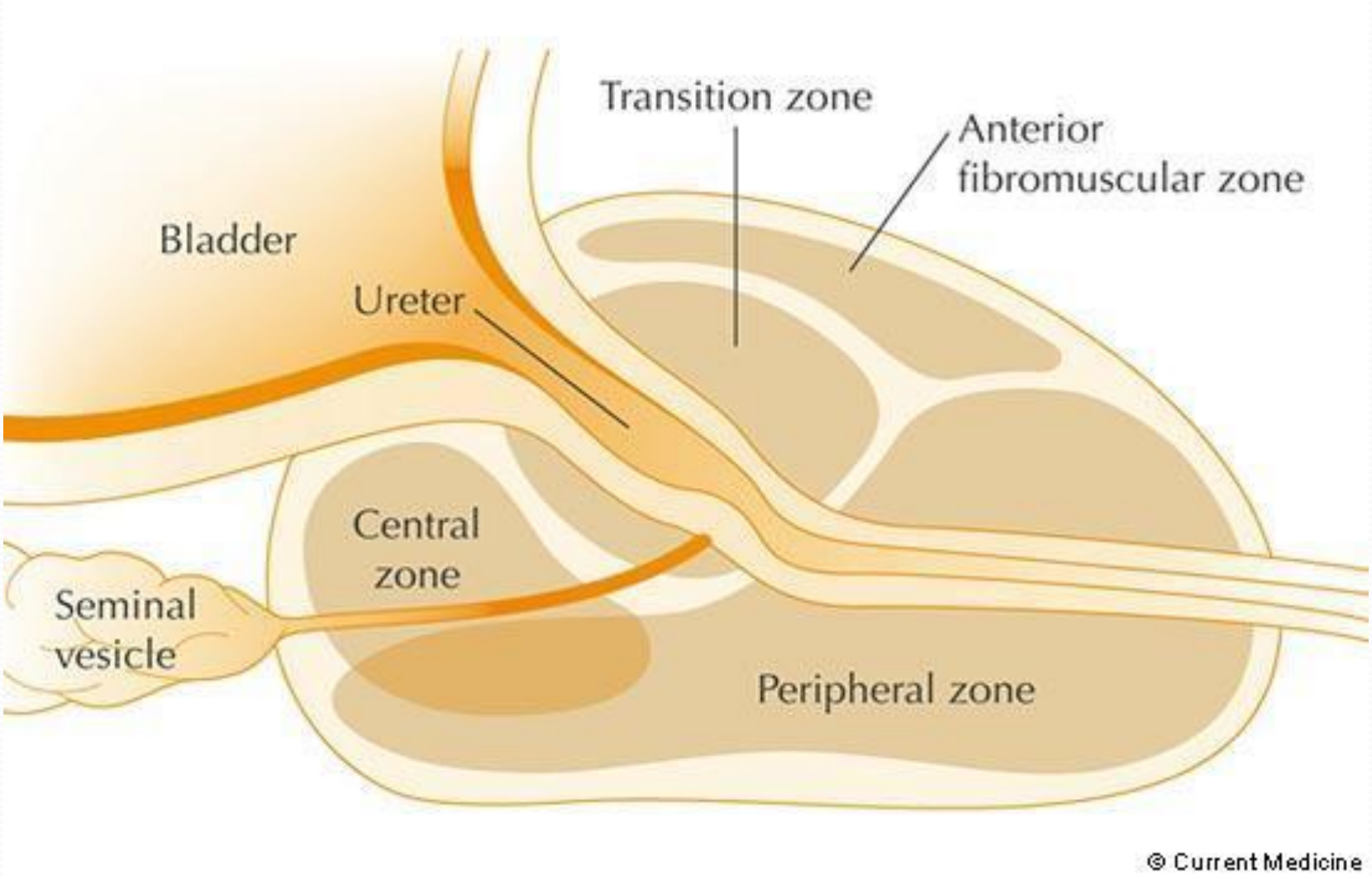
- <u>Metastatic Bladder Cancer</u>

  MVAC MS - 15.2 m

  gemcitabine/cisplatin –MS - 14.0 m (more less toxicity)

Prostate cancer

Prostate cancer is the most common cancer in American men except for non-melanoma skin cancer.

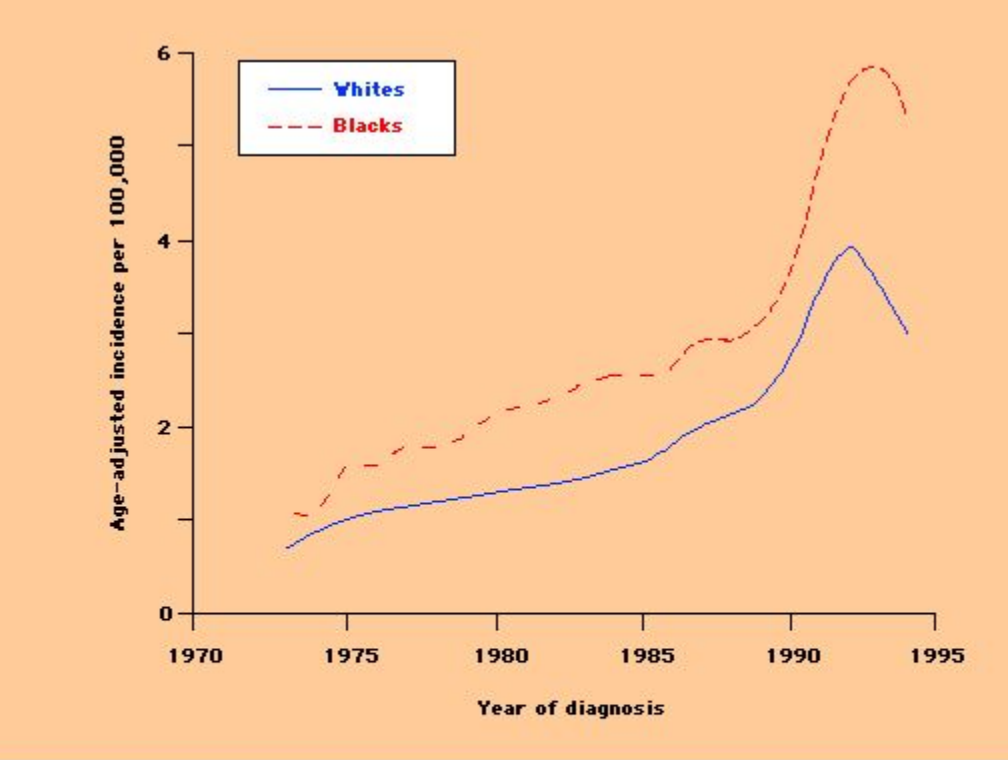


Risk factors

- **GENETIC FACTORS**
  - **two-fold** elevated in men with an affected first degree relative (brother, father), compared to those without an affected relative
  - trend toward increasing risk with a greater number of affected family members; men with two or three affected first-degree relatives had a 5- and 11-fold increased risk of prostate cancer
  - In a study of 45,000 Scandinavian twin pairs, concordance for cancer in identical twins was higher for prostate cancer than either breast or colorectal cancer

Risk factors

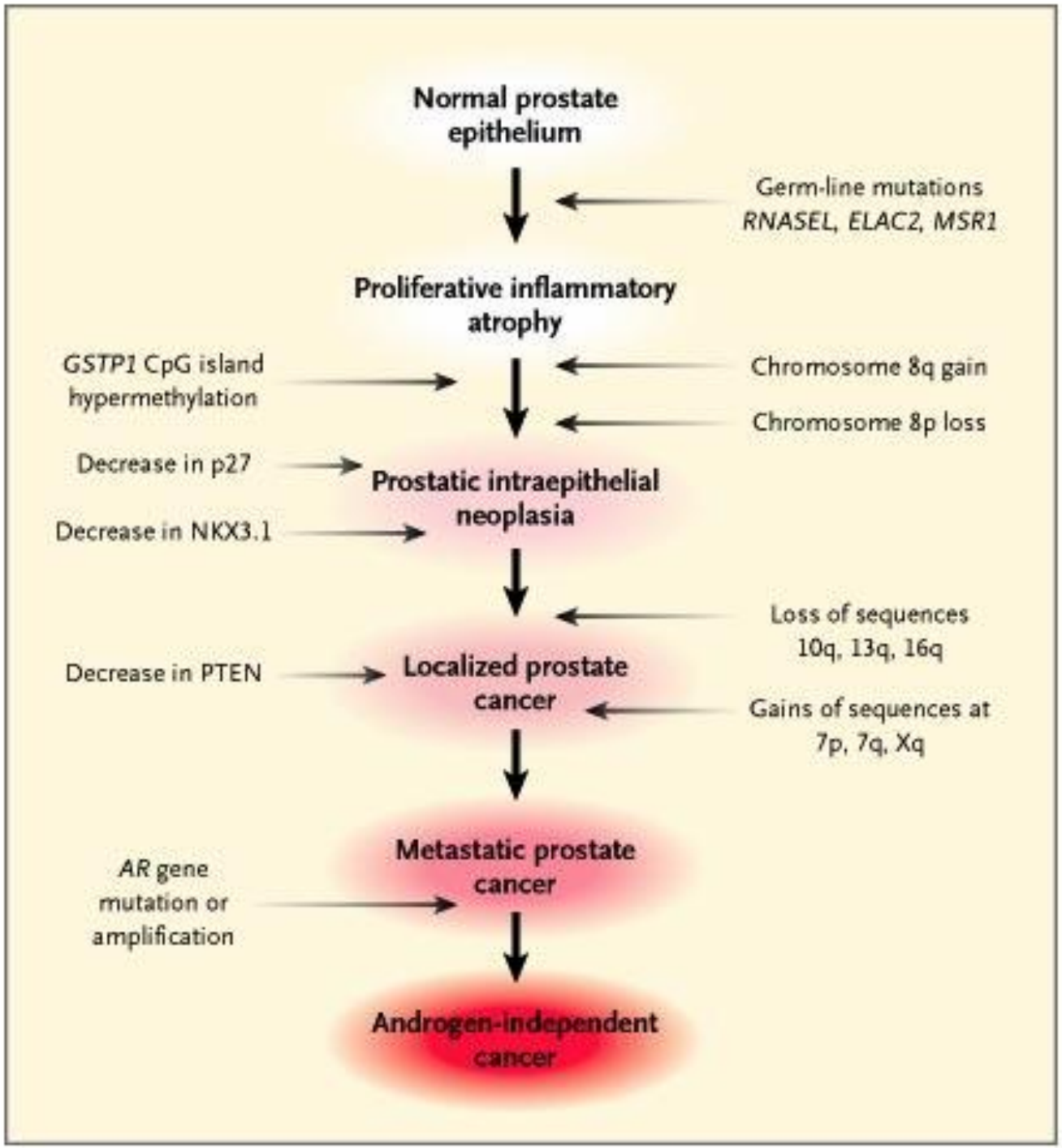
- **AGE** :rarely occurs before the age of 45
- **RACE, ETHNICITY**



Prostate cancer is more common in black men Age-adjusted incidence r
for prostate cancer by race from 1973 to 1994 in the National Cancer Institute'
Surveillance Epidemiology and End Results (SEER) data base. Screening in the 19

BRCA1/2 mutations

- The presence of BRCA1/2 mutations may increase the risk of developing prostate cancer at least two to five-fold


Normal prostate epithelium
Germ-line mutations
RNASEL, ELAC2, MSR1
Proliferative inflammatory atrophy
GSTP1 CpG island hypermethylation
Chromosome 8q gain
Chromosome 8p loss
Decrease in p27
Prostatic intraepithelial neoplasia
Decrease in NKX3.1
Loss of sequences 10q, 13q, 16q
Decrease in PTEN
Localized prostate cancer
Gains of sequences at 7p, 7q, Xq
Metastatic prostate cancer
AR gene mutation or amplification
Androgen-independent cancer

PRETREATMENT STAGING

- Serum PSA
- Biopsy of the tumor
- Digital rectal examination :
  - to detect the presence of extraprostatic extension or seminal vesicle invasion
- Computed tomography (CT) of the abdomen and pelvis and radionuclide bone scan are used selectively
- endorectal coil MRI may be useful in selected patients

TNM staging

Staging of Prostate Cancer by 2002 AJCC Staging System†

Clinical tumor (cT) stage

Stage cT1
Clinically inapparent tumor neither palpable nor visible by imaging

Substage
T1a Tumor incidental histologic finding in five percent or less of tissue resected
T1b Tumor incidental histologic finding in more than five percent of tissue resected
T1c Tumor identified by needle biopsy (eg, because of elevated PSA)

Stage cT2*
Tumor confined within the 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 involving both lobes

Stage cT3**
Tumor extends through the prostate capsule

T3a Extracapsular extension (unilateral or bilateral)
T3b Tumor invades the seminal vesicle(s)

Stage cT4
Tumor is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall.

Pathologic Tumor (pT) Stage

Stage pT2
Organ confined

pT2a Unilateral, involving one-half of one lobe or less
PT2b Unilateral, involving more than one-half of one lobe, but not both lobes
pT2c Bilateral

Stage pT3
Extraprostatic extension

pT3a Extraprostatic extension
pT3b Seminal vesicle invasion

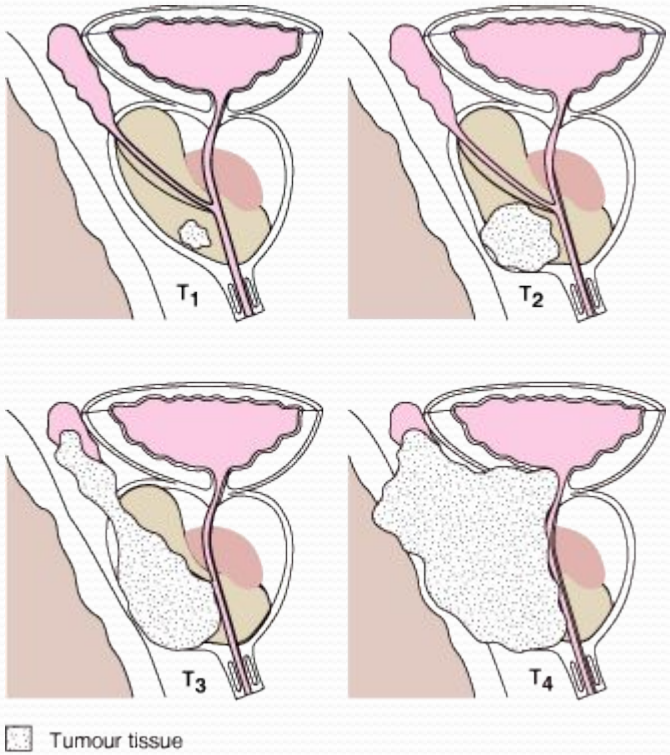
Stage pT4
Invasion of bladder, rectum

Regional lymph nodes

NX Regional lymph nodes not assessed
N0 No regional lymph node metastases
N1 Metastasis in regional lymph nodes

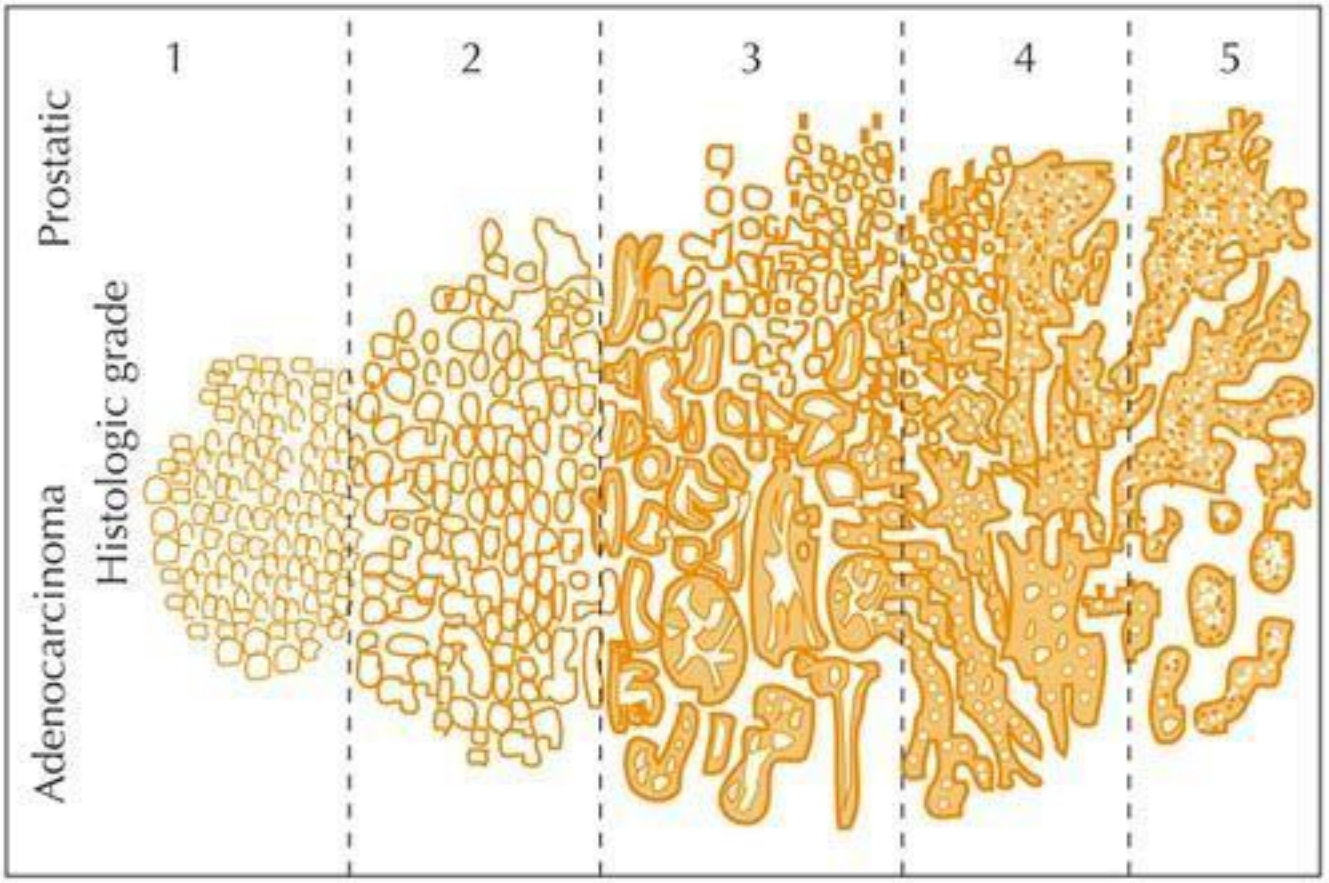
Distant metastasis

M0 No distant metastases
M1 Distant metastases present
M1a Non-regional lymph nodes
M1b Bone(s)



PREDICTING ORGAN CONFINED DISEASE

- **Biopsy Gleason grade**



Pretreatment Risk Assessment in Localized Disease

Recurrence Rate after Local Therapy	Criteria	Risk group
20%-6%	PSA < 10 ng/mL Gleason <6 T1, T2a	Lo
60%-34%	PSA 10-20 ng/mL Gleason 7 T2b, T3a	Intermediate
100%-50%	PSA >20 ng/mL Gleason 8-10 T3b	H

The most effective therapy for clinically localized prostate cancer

- Surgery
- radiation therapy (RT)
- androgen deprivation therapy (ADT)
- observation (also termed watchful waiting).

Increased PSA After Radical Prostatectomy

- ***Risks Factor for Clinical Relapse***

1. <u>1. Doubling time</u>

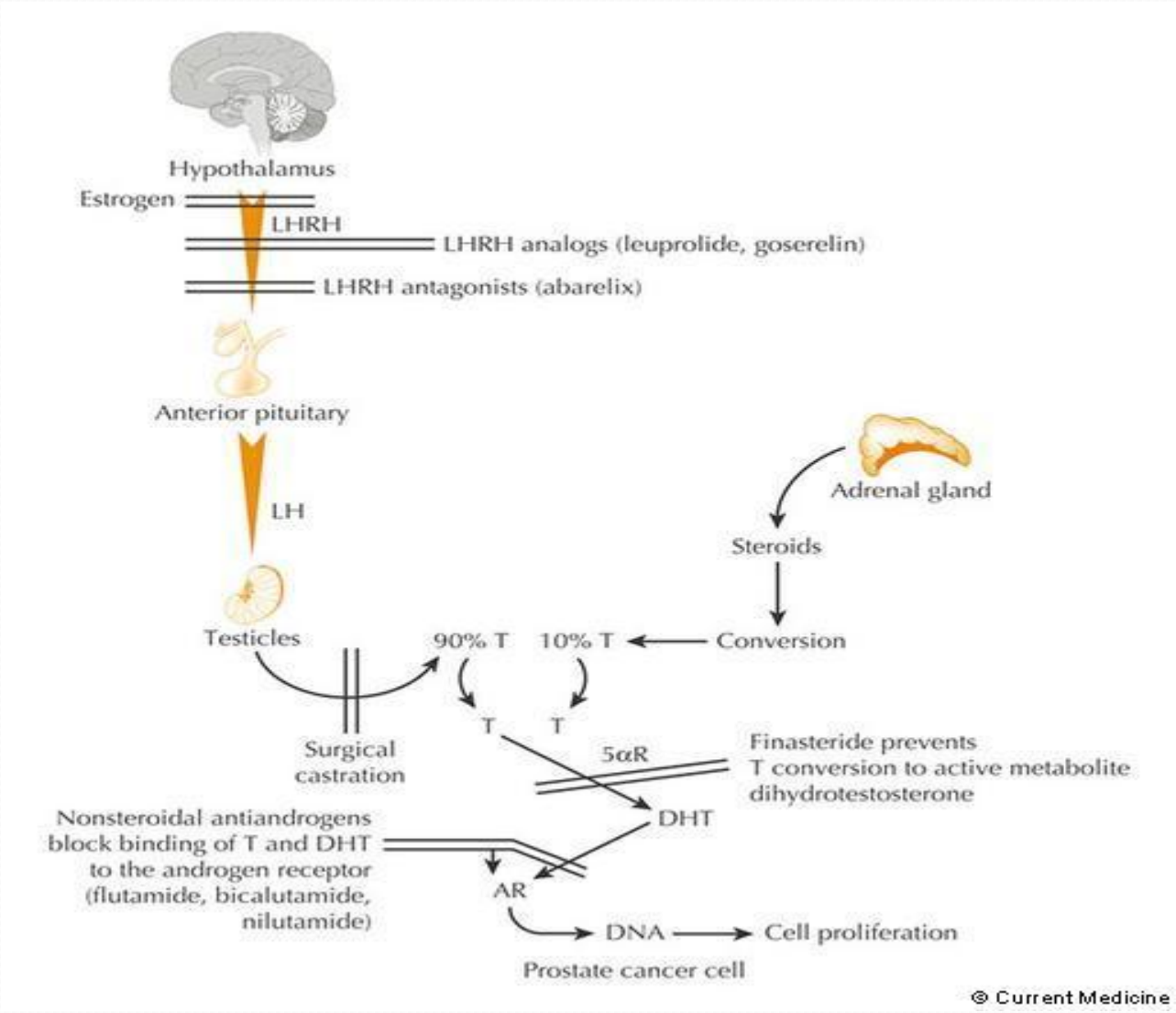
   The shorter the time, the higher the risk

2. <u>2. Time to biochemical failure</u>

   The shorter the time, the higher the risk

3. <u>3. Gleason score</u>

   higher scores reflect more aggressive tumors


Hypothalamus
Estrogen
LHRH
LHRH analogs (leuprolide, goserelin)
LHRH antagonists (abarelix)
Anterior pituitary
LH
Testicles
Adrenal gland
Steroids
Conversion
90% T
10% T
T
T
Surgical castration
5αR
Finasteride prevents T conversion to active metabolite dihydrotestosterone
DHT
Nonsteroidal antiandrogens block binding of T and DHT to the androgen receptor (flutamide, bicalutamide, nilutamide)
AR
DNA
Cell proliferation
Prostate cancer cell
© Current Medicine

OTHER THERAPIES

- **Cryotherapy**
- **Laparoscopic and robotic prostatectomy**

Cancer of Testis

- Pure germ cell tumor – one site of hystology
- Mixed germ cell tumor – more than one hystologic pattern

SEMINOMA

NON-SEMINOMA: - embrional carcinoma
- teratoma
- choriocarcinoma
- yolk sac tumor

Cancer of Testis

	Non- Seminoma	Seminoma
Good progn	**55%**	**90%**
5y PFS	90%	80%
5y OS	92%	85%
Interm progn	**30%**	**10%**
5y PFS	75%	67%
5y OS	80%	72%
Poor progn	**15%**	
5y PFS	40%	
5y OS	50%	

Cancer of Testis - Staging

- T1- without involv of tunica vaginalis
- T2 –vascular/lumphovascul inv., involv tunica vaginalis
- T3- spermatic cord inv.
- T4- scrotum
- c N – number of LN not important, size!:
- C N1 <2cm
- C N2 2-5 cm
- C N3 >5 cm
- PN- number and size important!:
- P N1- 1-5 LN-s , <2cm
- PN2- single 2-5 cm, or 2-5 : <5cm
- PN3->5cm

Cancer of Testis - Staging

- M1a – non-regional nodes oo pulmonary mts
- M1b – non-pulmonary methastasis
- S0- normal markers
- S1 LDH < 1.5 X UNL; HCG < 5000; AFP<1000
- S2 LDH 1.5-10XUNL; HCG 5 000-50 000; AFP1000-10 000
- S3 LDH > 10 X UNL; HCG >50 000; AFP>10 000

- Normal LDH 60 – **225** 90 – 337 S2

- T1/2 AFP 5-7 days
- T1/2 HCG 1-2 days

Cancer of Testis - Staging

- **St I – N0**
- St IA – *pT1* N0 M0 S0
- St IB – *p T2-4* N0 M0 S0
- St IS – any T N0 M0 *S1-3*
- **St II – N1-3**
- St IIA – any T *N1* M0 S0 -1
- St IIB – any T *N2* M0 S0 -1
- St IIC – any T *N3* M0 S0 -1
- **St III – M1 or S2-3**
- St IIIA – any T any N *M1a* S0 -1
- St IIIB - //-// N1-3 M0 *S2*
- //-// any N M1a *S2*
- St IIIC //-// N1-3 M0 *S3*
- //-// any N M1a S3
- //-// any N *M1b* S3

Cancer of Testis – Prognostic Group

- Any primary, Normal alfa-FP, any HCG, LDH for both prognostic group

Good prognosis

No non-pulmonary visceral metastasis – whole exclude M1b

Intermediate prognosis

Yes non-pulmonary visceral metastasis - M1b

Seminoma St I

RT para-aortic (*Fossa) (*Jones)

or

Carbo-single dose (*Oliver)

or

sirveillance (*Ward)

Seminoma St II- Low- tumor burden (St IIA-B = <5 cm retroperit LN)

Dog-leg 25-30 Gy + boost 5 -7.5 Gy

Seminoma St II - III – (High tumor burden= N3, supradiaphragm LN, visceral mts) Good progn. Group--- BEP X3

- ***de Wit *JCO 2001* 812 pts**

	2y DFS		2y DFS
BEP X 3	90.4%	3 days	88.8%
BEP X 4	89.4%	5 days	89.7%
	(1% differ)		(0.9% diff)

5 day: Bleo 30mg d1, 8, 15
Etoposide 500mg/m2 (100mg/m2 d1-5)
Platinum 100mg/m2 (20mg/m2 d1-5)

3 day: Bleo 30mg d1, 8, 15
Etoposide 500mg/m2 (165mg/m2 d1-3)
Platinum 100 mg/m2 (50mg/m2 d1-2)

Conclusion:
BEPX3 sufficient for good prognosis;
3-day –administration not decrease effect.

Seminoma St II-III High- tumor burden

- Chemo +/- surgery RPLND
- * good prognosis BEPX3 (PEX4)
- *interm -risk (nonpulmonary visceral metastasis) - BEPX4 (VIPX4)
- Residual retroperitoneal disease:
- <3cm- observed
- >=3cm=>PET=> positive =>surgery
- Residual lung, mediast tumor- resection

Seminoma metast – inferiority of carbo vs cis

- Bokemeyer Br J Cancer 204

361 pts

	cisplat-based	vs carbo-single
5y PFS	92%	72%
5y OS	94%	89% - 5% infer

Non-Seminoma

Good and interm progn:

- testis/retroperitoneal primary

And

- No nonpulmonary visceral metastasis

And :

S1 for good

S2 for interm

Poor progn:

- Mediast primary or
- Yes non-pulmonary visceral metastasis or
- S3

Non-Seminoma St I

RPLND bilateral +/- chemo

or

Chemo BEP x 2– not USA standard (for high risk – St IB - T2-4 N0M0S0)

or

Surveillance (for low risk St IA - T1 S0)

Non-Seminoma St II – Low tumor burden

* <3 cm ipsilat. solitary LN- RPLND

*>=3cm , increas markers, bilater- initial chem => RPLND,

-For >6 +LN-s, >2cm, extracaps extens => BEP or EP x 2

Non-Seminoma St II - III – (High tumor burden= N3, supradiaphragm LN, visceral mts) Good progn. Group--- BEP X3

*de Wit BEP x 4 vs PE x 4 – inferiority 8% in DFS

*Horwich BEP x 4 vs CEB x 4 – inferiority 7% of carbo in 3y OS

Non-Seminoma St II - III – (High tumor burden= N3, supradiaphragm LN, visceral mts) Poor progn. Group--- BEP X 4

CT => PET => +/- RPLND; if viable malignancy in specimen => PEX2 post-op.