Caring for Patients with Genitourinary Malignancies

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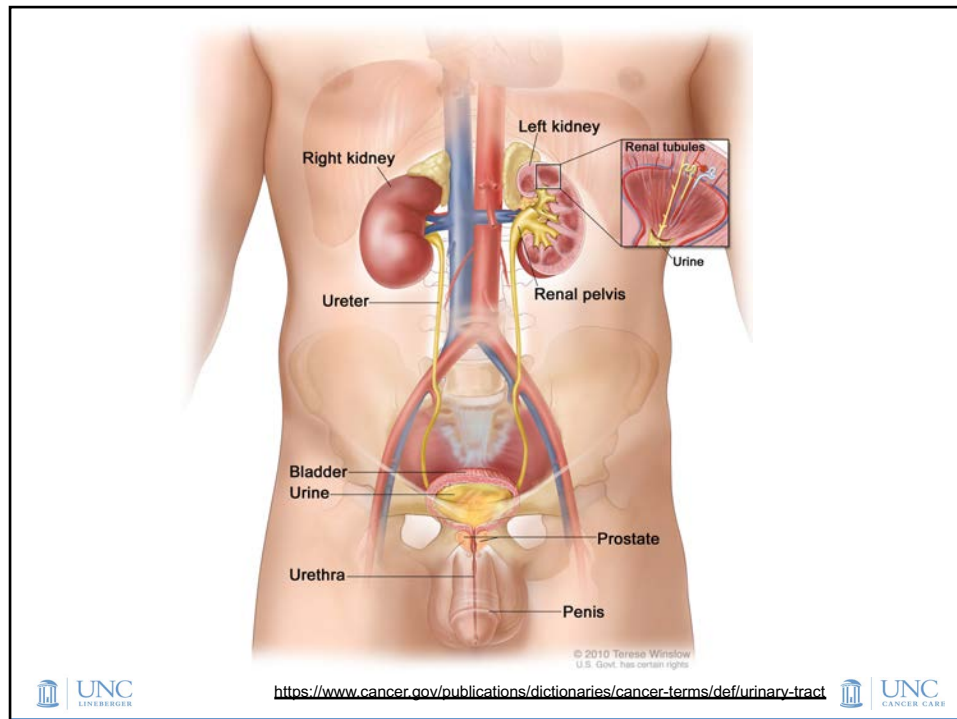
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Objectives

- Understand the breadth of genitourinary malignancies
- Recognize the role of each multidisciplinary team member
- Learn the basics of each major type of GU cancer: prostate, bladder, kidney, and testis
- Review types of cancer treatments used in GU malignancies

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Leading Causes of Death in the U.S.

- Heart disease: 635,206
- Cancer: 598,038
- Accidents (unintentional injuries): 161,374
- Chronic lower respiratory diseases: 154,596
- Stroke (cerebrovascular diseases): 142,142
- Alzheimer's disease: 116,103
- Diabetes: 80,058
- Influenza and Pneumonia: 51,537
- Nephritis, nephrotic syndrome and nephrosis: 50,046
- Intentional self-harm (suicide): 44,965

CDC.gov, accessed 10/12/18

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Cancer Statistics

Estimated New Cases

			Males	Females			
Prostate	161,360	19%		Breast	252,710	30%
Lung & bronchus	116,990	14%		Lung & bronchus	105,510	12%
Colon & rectum	71,420	9%		Colon & rectum	64,010	8%
Urinary bladder	60,490	7%		Uterine corpus	61,380	7%
Melanoma of the skin	52,170	6%		Thyroid	42,470	5%
Kidney & renal pelvis	40,610	5%		Melanoma of the skin	34,940	4%
Non-Hodgkin lymphoma	40,080	5%		Non-Hodgkin lymphoma	32,160	4%
Leukemia	36,290	4%		Leukemia	25,840	3%
Oral cavity & pharynx	35,720	4%		Pancreas	25,700	3%
Liver & intrahepatic bile duct	29,200	3%		Kidney & renal pelvis	23,380	3%
All Sites	**836,150**	**100%**		**All Sites**	**852,630**	**100%**

FIGURE 1. Ten Leading Cancer Types for the Estimated New Cancer Cases and Deaths by Sex, United States, 2017. Estimates are rounded to the nearest 10 and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

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Cancer Statistics

Estimated Deaths

			Males	Females			
Lung & bronchus	84,590	27%		Lung & bronchus	71,280	25%
Colon & rectum	27,150	9%		Breast	40,610	14%
Prostate	26,730	8%		Colon & rectum	23,110	8%
Pancreas	22,300	7%		Pancreas	20,790	7%
Liver & intrahepatic bile duct	19,610	6%		Ovary	14,080	5%
Leukemia	14,300	4%		Uterine corpus	10,920	4%
Esophagus	12,720	4%		Leukemia	10,200	4%
Urinary bladder	12,240	4%		Liver & intrahepatic bile duct	9,310	3%
Non-Hodgkin lymphoma	11,450	4%		Non-Hodgkin lymphoma	8,690	3%
Brain & other nervous system	9,620	3%		Brain & other nervous system	7,080	3%
All Sites	**318,420**	**100%**		**All Sites**	**282,500**	**100%**

FIGURE 1. Ten Leading Cancer Types for the Estimated New Cancer Cases and Deaths by Sex, United States, 2017. Estimates are rounded to the nearest 10 and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

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Most Common GU Cancers

- Prostate
- Bladder
- Kidney
- Testis (germ cell tumors)

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Prostate Cancer

Prostate cancer is a disease in which malignant (cancer) cells form in the prostate gland
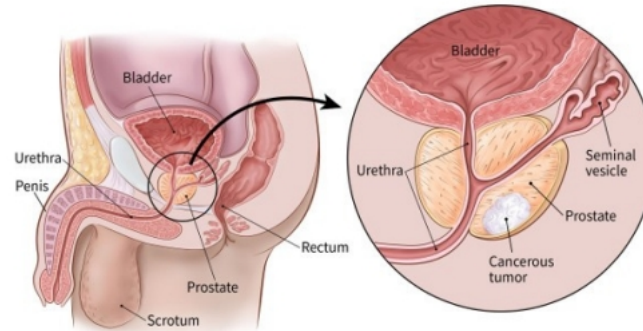
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Physiology of Prostate Cancer

- Partly glandular and muscular organ within lower pelvis
- Accessory reproductive gland
- Secretes alkaline fluid that forms a part of the ejaculate which aids in motility and nourishment of sperm
- 4 zones: peripheral (75%), central, transition, fibromuscular
- Size of a walnut in young men, but grows with age

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# Pathophysiology of Prostate Cancer

- ~90% are adenocarcinomas (formed from the gland cells)
  - Remaining ~10% are primarily neuroendocrine
- Typically spreads first to lymph nodes
- Metastasis = distant spread outside the prostate
  - Bone most common
  - Distant lymph nodes
  - Organs less common – and a bad sign!
- Commonly diagnosed by digital rectal exam or PSA

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Clinical Presentation

- **Usually asymptomatic**
- Lower urinary tract symptoms (LUTS)
- Bony pain
- Renal failure
- Spinal cord compression

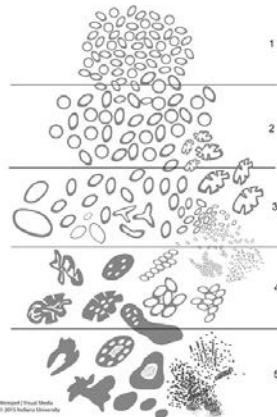UNC | LINEBERGER   UNC | CANCER CARE
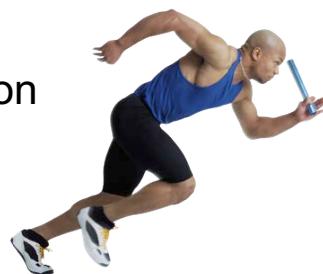
12

Diagnosis

- Shared decision making to screen
- PSA, DRE
- Prostate biopsy
  - Office procedure
  - transrectal ultrasound guided
  - 12 cores
  - Minor prep
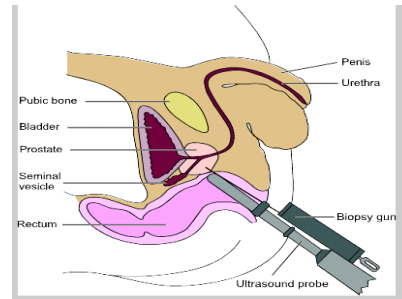
13

Grade = measure of the microscopic appearance (ie, how much does it resemble normal prostate?)

Epstein, J. Prostate cancer grading: a decade after the 2005 modified system. *Mod Pathol* **31,** 47–63 (2018). https://doi.org/10.1038/modpathol.2017.133

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Cancer Staging

- Define as precisely as possible the extent of disease

- Rationale: Staging will determine
  - Treatment
  - Prognosis
  - Surveillance

- A common currency for reporting treatment results

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Prostate Cancer Staging

Group	T	N	M	PSA	Gleason
I	T1a-c	N0	M0	PSA <10	Gleason ≤6
	T2a	N0	M0	PSA <10	Gleason ≤ 6
	T1-2a	N0	M0	PSA X	Gleason X
IIA	T1a-c	N0	M0	PSA <20	Gleason 7
	T1a-c	N0	M0	PSA ≥10<20	Gleason ≤ 6
	T2a	N0	M0	PSA≥10<20	Gleason ≤ 6
	T2a	N0	M0	PSA <20	Gleason 7
	T2b	N0	M0	PSA <20	Gleason ≤ 7
	T2b	N0	M0	PSA X	Gleason X
IIB	T2c	N0	M0	Any PSA	Any Gleason
	T1-2	N0	M0	PSA ≥ 20	Any Gleason
	T1-2	N0	M0	Any PSA	Gleason ≥ 8
III	T3a-b	N0	M0	Any PSA	Any Gleason
IV	T4	N0	M0	Any PSA	Any Gleason
	Any T	N1	M0	Any PSA	Any Gleason
	Any T	Any N	M1	Any PSA	Any Gleason

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Principles of Treatment

Local   vs   Locoregional   vs   Systemic

Surgery   Surgery

                                             Chemotherapy

Radiation   Radiation

Commonly we combine these approaches
= Multimodality treatment

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Prostate Cancer Treatment

Active Surveillance

- Typical criteria: PSA <10, Gleason 6, Stage T1c-T2a, >10 yr life expectancy, low volume
- Follow up: PSA & DRE every 3-6 months, biopsy annually
- Intervention: Change on biopsy, concerning PSA trend
- Not appropriate for all men meeting criteria
- Other: Age, comorbidities, anxiety, commitment to follow up schedule

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Prostate Cancer Treatment

Radical prostatectomy

- Surgical removal of the prostate gland and seminal vesicles
- Open, laparoscopic, robotic techniques
- Considerations: Age, comorbidities, prior abdominal surgeries
- 1 night in the hospital, leave with catheter
- Side effects: Erectile dysfunction, urine leakage, infertility
- Follow up: every 3 months x 1 year; every 6 months until year 5, annually until year 10

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Prostate Cancer Treatment

Radiation Therapy

- Intensity Modulated Radiation Therapy: gives higher dose to prostate and less to surrounding tissue
- Uses a machine outside the body to deliver radiation
- Usually 5 days/week, 4-6 weeks
- If >intermediate risk disease will get hormone shots too
- Side effects: urinary symptoms, diarrhea, rectal irritation, fatigue, erectile dysfunction

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Prostate Cancer Treatment

Brachytherapy

- Radioactive seeds implanted into the prostate
- Low risk disease; prostate size matters
- Side effects: Urinary retention, painful urination, erectile dysfunction

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Prostate Cancer Treatment

Cryotherapy

- Surgical freezing of the prostate
- Causes cell death
- Candidates: Unfit for surgery or radiation
- Side effects: Erectile dysfunction (near 100%), rectal pain, urinary symptoms

High-intensity focused ultrasound (HIFU)

- Ablates tissue using heat
- Side effects: urinary symptoms, erectile dysfunction

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Advanced Prostate Cancer Treatment

- Metastatic or stage IV prostate cancer is not curable
- Treatment focus is on prolonging as good a life as possible = PALLIATIVE
- Cornerstone of treatment is blocking the tumor's access to the male hormone testosterone – more to come!
- Also use standard chemotherapy

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Bladder Cancer

- Typically diagnosed in 5th-7th decade
- Global disease: ~350,000 new cases/year
  - The most common GU cancer in China
- Non-muscle-invasive: 75% at presentation
- **Highest recurrence rate** of any cancer
  - Substantial burden of health services
- Comparatively poor research funding

https://www.cancer.org/cancer/bladder-cancer/about/what-is-bladder-cancer.html
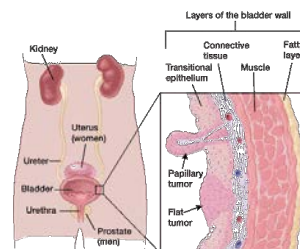
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Bladder Cancer – Risk Factors

- Male sex
- Cigarettes: 3x risk in current smokers
  - (50% reduction after quitting 5y)
  - Not just lung cancer
  - SMOKING CESSATION
- Family history and/or genetic mutations
- Age
- Chemical exposures
  - Aniline dye, gas/soot from coal, analgesic (phenacetin), dyes, rubber
  - Cyclophosphamide: Acrolein (urinary metabolite of Cytoxan) can cause hemorrhagic cystitis. Latency period 6-13 years
  - Occupations: Textile workers, truckers, leather/dye workers, painters, hairdressers, dry cleaners
- Pelvic Radiation
- Chronic cystitis
  - Long term indwelling catheters, chronic UTI, stones, schistosoma haematobium

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Bladder Cancer – Staging
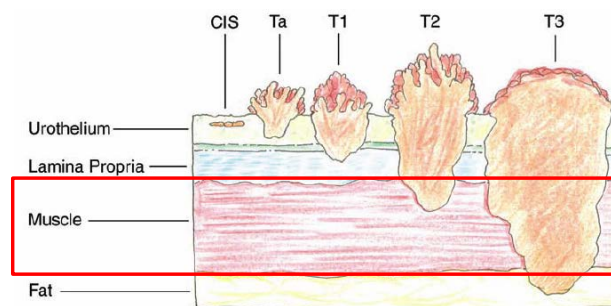
- Presence, Depth of Invasion
- ~25% muscle-invasive at presentation
- "Superficial"→ non-muscle invasive
  - T1: still invasive

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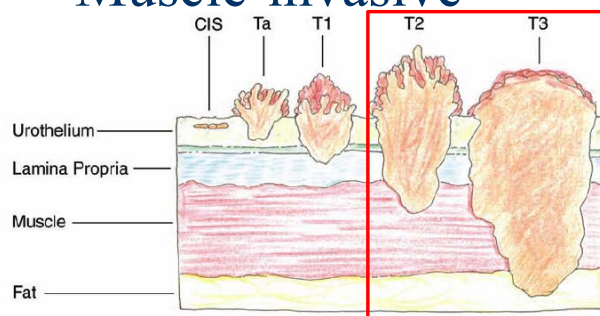
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Bladder Cancer Treatment – Non-muscle invasive
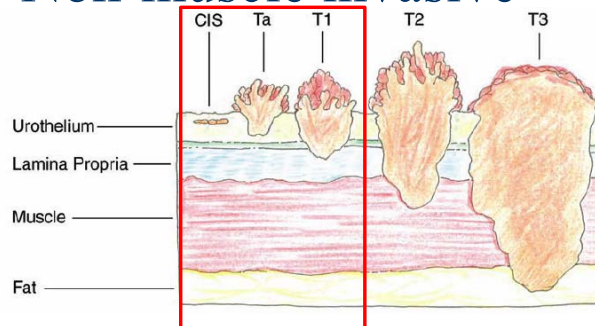
– Resect it via cystoscopy (via a camera in the bladder – "transurethral")

– Sometimes put BCG (yes, like the TB vaccine) or other therapy directly into the bladder

– Emerging data on intravenous treatments to retrain the immune system

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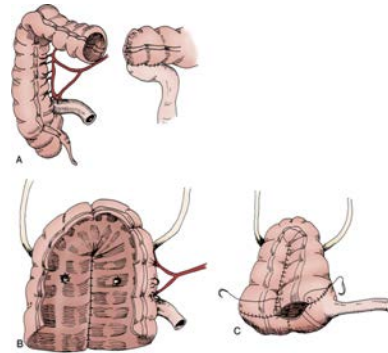# Bladder Cancer Treatment – Muscle-invasive

– A true multidisciplinary team approach

– Typically treat with chemotherapy followed by bladder removal ("cystectomy) or transurethral resection followed by chemotherapy plus radiation therapy

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Bladder Cancer Treatment – Cystectomy with Urinary Diversion
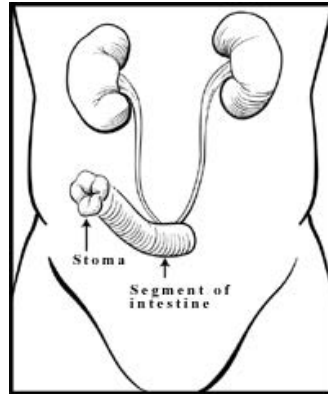
Ileal conduit   Continent cutaneous diversion

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Bladder Cancer Treatment – Ostomy Care

- Urinary diversion management
  - Skin irritation
  - Properly fitting appliance/leaking
  - Odor
  - Body image
  - Intimacy
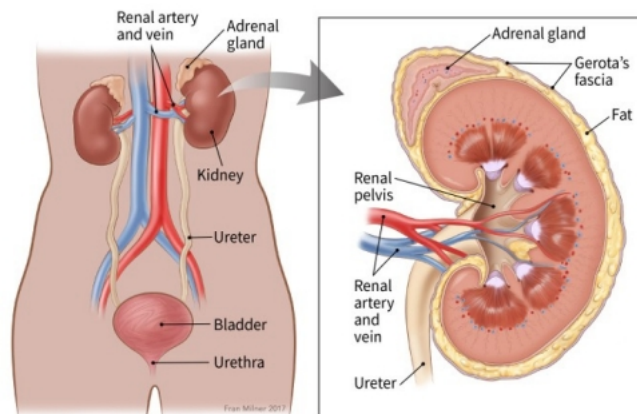 - Supplies
  - Consult WOCN

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Bladder Cancer Treatment – Advanced Disease

- Unresectable and metastatic bladder cancer remains incurable
- Chemotherapy historically was the cornerstone of treatment
- Finally some progress
  - 5 new immunotherapies, 1 targeted therapy, and 1 new "antibody-drug conjugate) approved in the last several years!
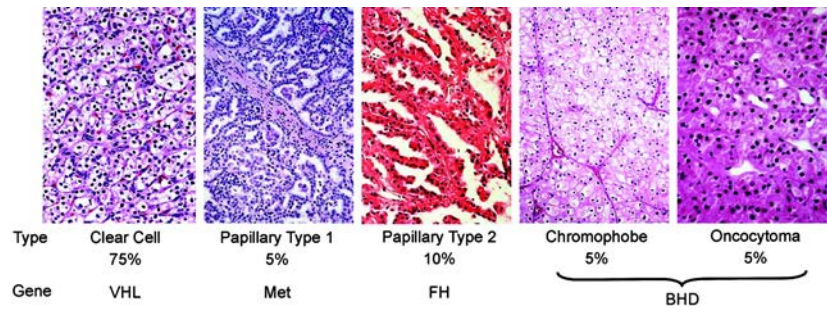- Supportive care is crucial

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Kidney Cancer

https://www.cancer.org/cancer/kidney-cancer/about/what-is-kidney-cancer.html

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Kidney Cancer = not a single disease

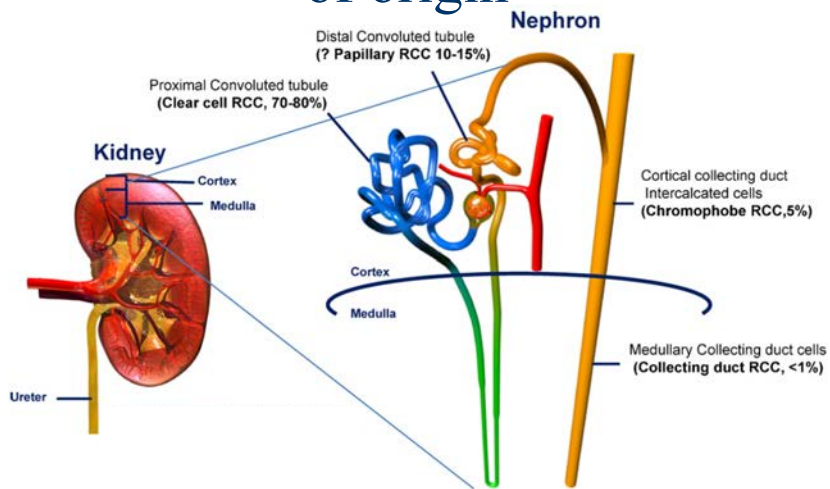| Type	Clear Cell 75%	Papillary Type 1 5%	Papillary Type 2 10%	Chromophobe 5%	Oncocytoma 5%
Gene	VHL	Met	FH		BHD

W. Marston Linehan et al. Clin Cancer Res 2004;10:6282S-6289S
©2004 by American Association for Cancer Research

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Kidney Cancer – Presumed cell of origin

Nephron

Distal Convoluted tubule
(? Papillary RCC 10-15%)

Proximal Convoluted tubule
(Clear cell RCC, 70-80%)

Kidney

Cortex

Medulla

Cortex

Medulla

Cortical collecting duct
Intercalated cells
(Chromophobe RCC,5%)

Medullary Collecting duct cells
(Collecting duct RCC, <1%)

Ureter

Morais et al, Int J Biochem & Cell Biol 43(2011):1537-1549.

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Kidney Cancer - Types

- The most common type is clear cell renal cell carcinoma (RCC)
- Clear cell RCC is almost universally characterized by loss of the von Hippel Lindau (VHL) gene
- A familial (autosomal dominant) cancer syndrome of germline VHL mutation can predispose to kidney cancer, although most cases of clear cell RCC as sporadic
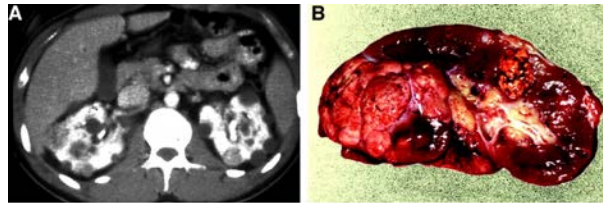
W. Marston Linehan et al. Clin Cancer Res 2004;10:6282S-6289S

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Kidney Cancer – Risk Factors

Risk Factor	Comment
Smoking	
Hypertension	Dose-response relationship
Obesity	Dose-response relationship
Acquired cystic kidney disease	Usually dialysis-associated
Occupational Exposures	Asbestos, Cadmium, Gasoline
Others: Familial cancer syndromes, analgesics, hepatitis C, cytotoxic chemotherapy, sickle cell trait (risk for renal medullary carcinoma)	

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Kidney Cancer – Symptoms

- "Classic triad" of symptoms for RCC:
  - Flank pain
  - Hematuria (blood in the urine)
  - Palpable abdominal mass.

- Other symptoms:
  - Scrotal varicocele
  - Lower extremity edema
  - Ascites

- Tumors can get BIG before they are detected
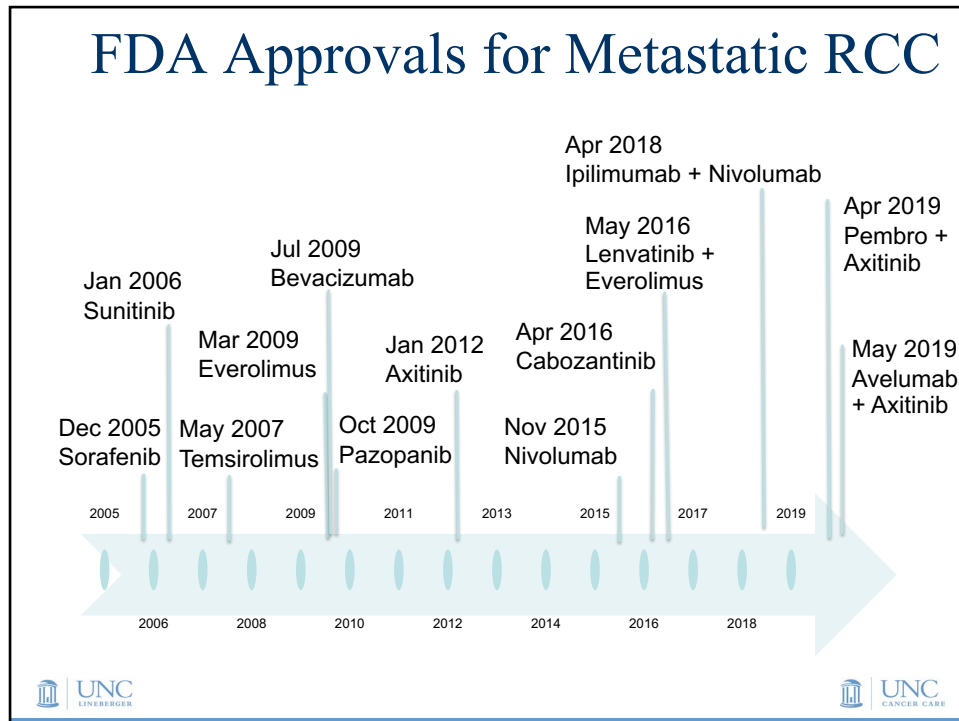- Common sites of metastases: lung, lymph nodes, bone, brain

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Kidney Cancer – Treatment

- Localized = Surgery
  - ie, if you can cut it out, do it

- Metastatic
  - Chemotherapy doesn't work
  - Immunotherapy or targeted therapy

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FDA Approvals for Metastatic RCC

Apr 2018
Ipilimumab + Nivolumab

Apr 2019
Pembro +
Axitinib

May 2016
Lenvatinib +
Everolimus

Jul 2009
Bevacizumab

Jan 2006
Sunitinib

Mar 2009
Everolimus

Jan 2012
Axitinib

Apr 2016
Cabozantinib

May 2019
Avelumab
+ Axitinib

Dec 2005
Sorafenib

May 2007
Temsirolimus

Oct 2009
Pazopanib

Nov 2015
Nivolumab

2005   2007   2009   2011   2013   2015   2017   2019

2006   2008   2010   2012   2014   2016   2018

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Testis Cancer in 1 Slide

- Most cases are "germ cell tumors" – meaning they start from the cells that make sperm

- 10,000 new cases per year

- Typically age 20s-40's

- VERY CURABLE

- Orchiectomy (removal of the testicle) cures many
- If has spread to lymph nodes, can get surgery, radiation or chemotherapy depending on type and extent of the cancer
- Advanced disease treated with chemotherapy, which is very effective

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Supportive Care

- Bone health
  - Drugs (such as those used for osteoporosis)
  - Calcium and Vitamin D
  - Weight Bearing exercise
- Pain control
- Depression/anxiety
- Treatment side effects
  - Nausea control, blood product support, etc
- Grief counseling

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Oncology drug approvals are skyrocketing.
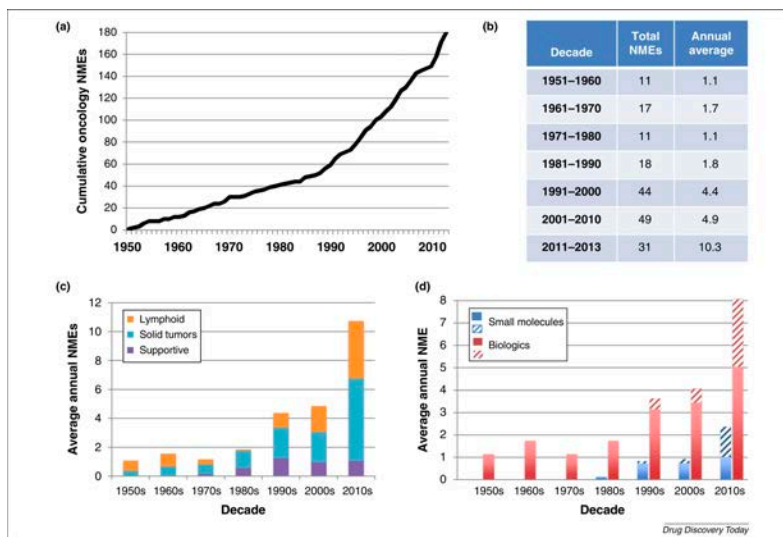
An analysis of FDA-approved drugs for oncology. Drug Discovery Today 2014 19(12):1831.

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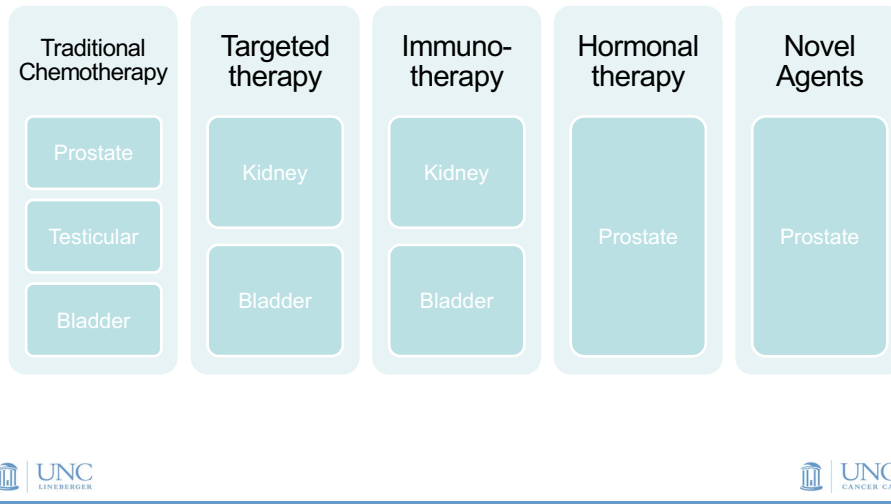Thanks for your attention

Tracy Rose
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Drug therapy in Genitourinary (GU) cancers

Katie Morgan, PharmD, BCOP, CPP

GU/Neuro Oncology Clinics

University of North Carolina Medical Center

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Classes of Drugs used in GU cancers

Traditional Chemotherapy	Targeted therapy	Immuno-therapy	Hormonal therapy	Novel Agents
Prostate	Kidney	Kidney		
Testicular			Prostate	Prostate
Bladder	Bladder	Bladder		

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Traditional Chemotherapy

- Classes of chemotherapy agents
  - Alkylating Agents
  - Antimetabolites
  - Antimicrotubule Agents
  - Topoisomerase inhibitors
  - Other "typical" chemotherapeutics

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The cell cycle

G1 - Growth

S - DNA synthesis

G2 - Growth and preparation for mitosis

M - Mitosis (cell division)
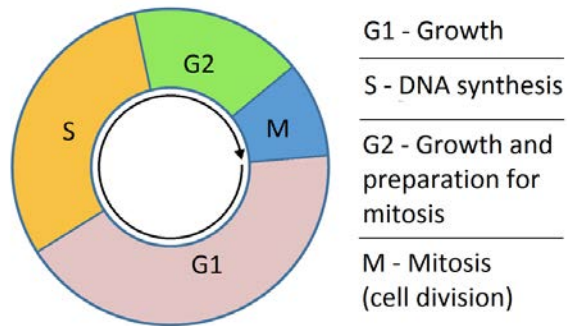
https://commons.wikimedia.org/wiki/File:Cell_cycle_simple.png

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Cell cycle non-specific agents

- Effects exerted at any phase of the cell cycle
- Toxic effects occur during cell cycle and are expressed during attempt at cell division
- May be more effective given as a bolus dose
  - Examples:
    - Alkylating agents
    - Anthracyclines
    - Platinum agents

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Cell Cycle specific agents

- Cell Cycle Specific
  - Effect exerted on dividing cells only
  - Not active in resting phase
  - Administration as continuous infusion or multiple divided doses
  - Examples:
    - Antimetabolites
    - Vincas
    - Taxanes
    - Topoisomerase Inhibitors

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Specific agents used in GU cancers

Alkylating Agents	Anti-metabolites	Anti-microtubules	Topoisomerase inhibitors	Other
Cisplatin	Gemcitabine	Docetaxel	Etoposide	Doxorubicin
Carboplatin		Cabazitaxel		
Ifosfamide	Methotrexate	Paclitaxel		Bleomycin
Doxorubicin		Vinblastine		
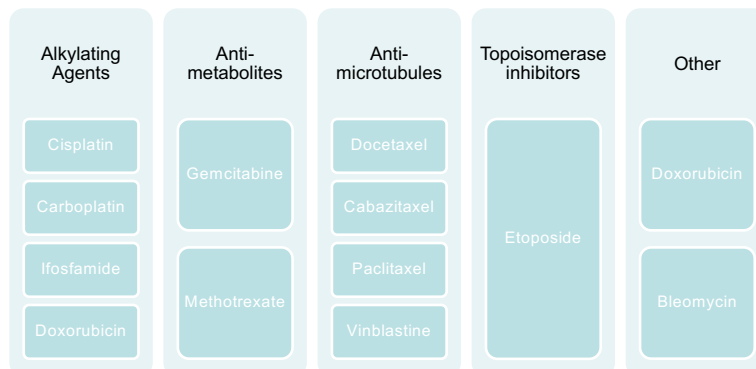
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Supportive Care for traditional Chemotherapy

- Chemotherapy induced nausea and vomiting (CINV)
- Myelosuppression
- Mucositis
- Organ toxicity
  - Renal
  - Liver
  - Cardiotoxicity
  - Lung toxicity

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Targeted Therapy

- Refers to newer generation of agents targeted at cellular processes
  - Monoclonal antibodies
  - Antibody drug conjugates
  - Tyrosine kinase inhibitors
  - Small molecule inhibitors
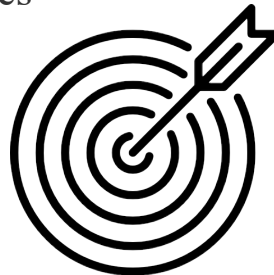
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Monoclonal Antibodies

Murine
100% mouse protein
*murom**onab***

Chimeric
33% mouse protein
*cetux**imab**,*
*ritux**imab***

Humanized
10% mouse protein
*bevaciz**umab**,*
*trastuz**umab***
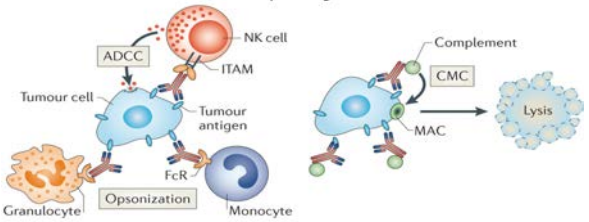
Human
0% mouse protein
*panitu**mumab***
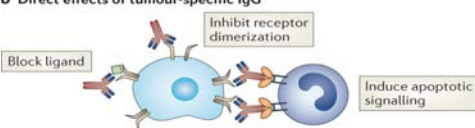
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Monoclonal Antibody Mechanism of Action

a Immune-mediated effects of tumour-specific IgG

- NK cell
- ADCC
- ITAM
- Tumour cell
- Tumour antigen
- Complement
- CMC
- MAC
- Lysis
- FcR
- Granulocyte
- Opsonization
- Monocyte

b Direct effects of tumour-specific IgG

- Inhibit receptor dimerization
- Block ligand
- Induce apoptotic signalling

Nature Reviews | Cancer

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Antibody Drug Conjugates
Mechanism of Action

Tsuchikama, K., An, Z. Protein Cell. 2016; DOI 10.1007/s13238-016-0323-0.
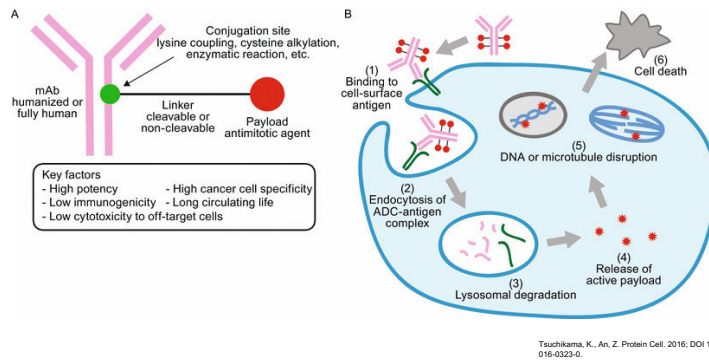
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Tyrosine Kinase Inhibitors (TKIs) and
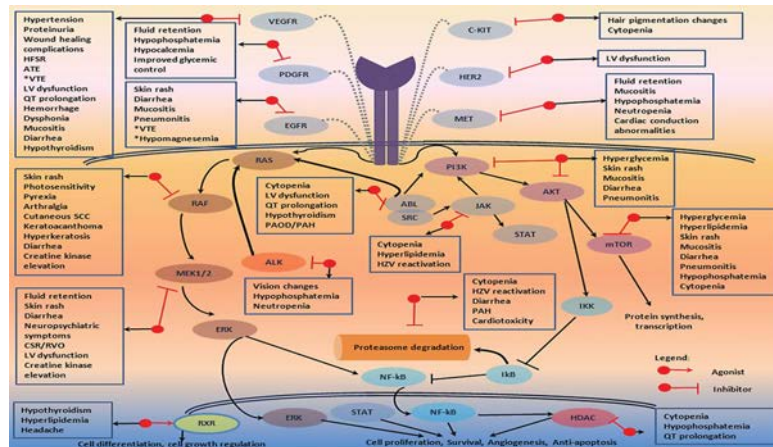## Small Molecules

Cancer Research UK

https://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/targeted-cancer-drugs/types/cancer-growth-blockers
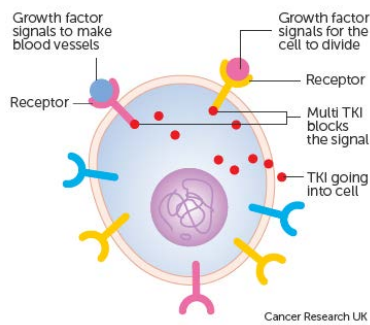
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Targeted Therapy and Downstream Effects

Dy GK, Adjei, A. CA Cancer J Clin 2013;63:249-279.

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Molecular Targets in GU

Kidney

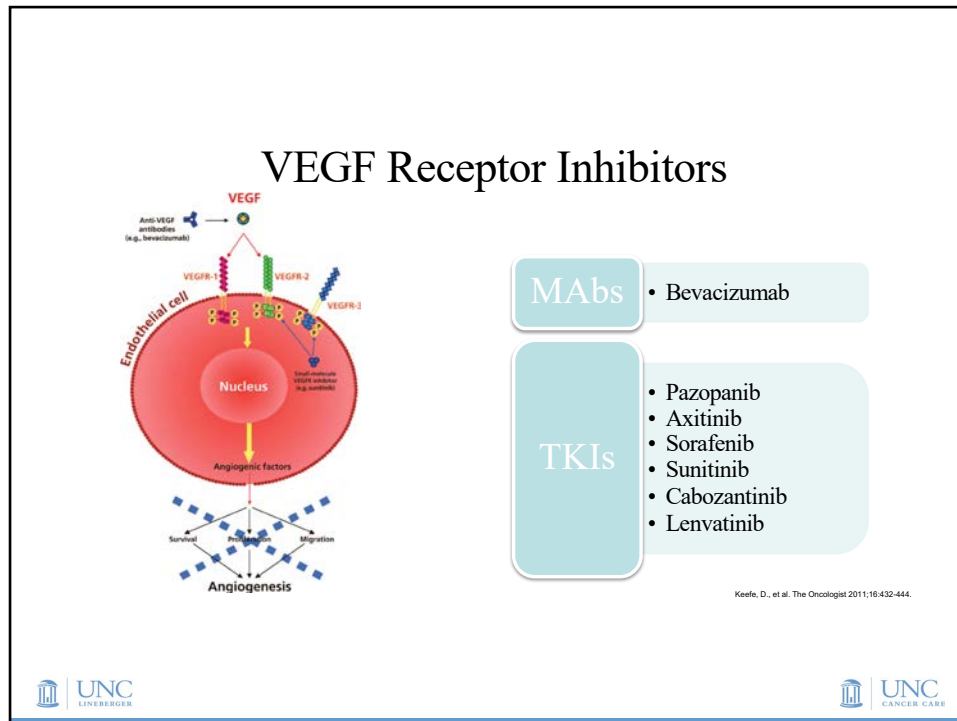Vascular endothelial growth factor (VEGF)

Mammalian target of rapamycin (mTOR)

Bladder

Fibroblast growth factor receptor (FGFR)

Nectin-4

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VEGF Receptor Inhibitors

MAbs	• Bevacizumab
TKIs	• Pazopanib • Axitinib • Sorafenib • Sunitinib • Cabozantinib • Lenvatinib

Keefe, D., et al. The Oncologist 2011;16:432-444.

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VEGF Receptor Inhibitors Side Effects

- Target Side Effects
  - Hypertension, heart failure, impaired wound healing, proteinuria, bleeding complications, thrombosis, GI perforation
- Monoclonal Antibodies- infusion reactions
  - Bevacizumab
- Tyrosine Kinase Inhibitors- diarrhea, hand foot syndrome
  - Pazopanib: changes in liver function
  - Sorafenib/Sunitinib: decreased blood counts
  - Axitinib: stomatitis, thyroid disorders
  - Cabozantinib: changes in liver function, thyroid disorders
  - Lenvatinib: thyroid disorders

Keefe, D., et al. The Oncologist 2011;16:432-444.

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mTOR inhibitors-
Everolimus/Temsirolimus

- mTOR inhibitors decrease intracellular signaling downstream of PI3-K/Akt pathway resulting in decreased protein synthesis and apoptosis
- Everolimus- oral mTOR inhibitor
  - Used typically second or third line, monotherapy or in combo with VEGF-Inhibitor
  - Toxicities – mucositis, diarrhea, hyperlipidemia, hyperglycemia, pneumonitis
  - Dexamethasone mouth rinse recommended as prophylaxis
- Temsirolomis – IV mTOR inhibitor
  - Favored in poor risk disease (historically)
  - Toxicities- rash, anemia, nausea, peripheral edema, hyperlipidemia, hyperglycemia

Battelli, C., Cho, D.C., Therapy 2011;8(4):359-367.

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FGFR inhibitor- Erdafitinib

- Targets gene mutations in FGFR
  - inhibits downstream signaling and tumor growth
- Incidence of FGFR mutations/alterations is about 20% in bladder cancer
- 40% response rates vs. 9% with alternative therapy
- Toxicity
  - Hyperphosphatemia, fatigue, diarrhea, nail toxicity, ocular toxicity, dry mouth, dry eyes, decreased appetite
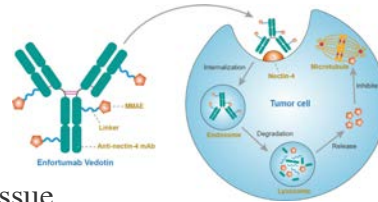 - Lubricating eye drops recommended when starting treatment

Casadei C, et al. TherAdv Med Oncol. 2019; 11: 1758835919890285.
Loriot, Y., et al. N Engl J Med 2019;381:338-48.

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NECTIN-4 inhibitor-Enfortumab-vedotin

- Nectin involved in polarity, proliferation, differentiation and migration in epithelial, endothelial, immune and nervous systems.
- High expression on bladder cancer cells but low expression in normal tissue
- 40% response rates
- Toxicity
  - Rash, peripheral neuropathy, hyperglycemia, fatigue, diarrhea, nausea, decreased appetite
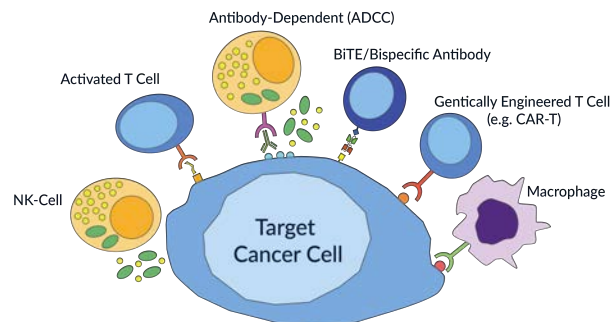
https://www.creativebiolabs.net/enfortumab-vedotin-overview.htm
Rosenberg JE, et al. J Clin Oncolo 2019;10.1200/JCO.1901140.

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Immunotherapy

Antibody-Dependent (ADCC)

BiTE/Bispecific Antibody

Activated T Cell

Gentically Engineered T Cell (e.g. CAR-T)

NK-Cell

Target Cancer Cell

Macrophage

https://www.aceabio.com/applications/cancer-immunotherapy/

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Immunotherapy

IL-2	CTLA-4 Inhibitors
PD-1 inhibitors	PD-L1 inhibitors

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CTLA-4 Inhibitor: Ipilimumab

Weber et al. J Clin Onclo 2012;30;2691-97.
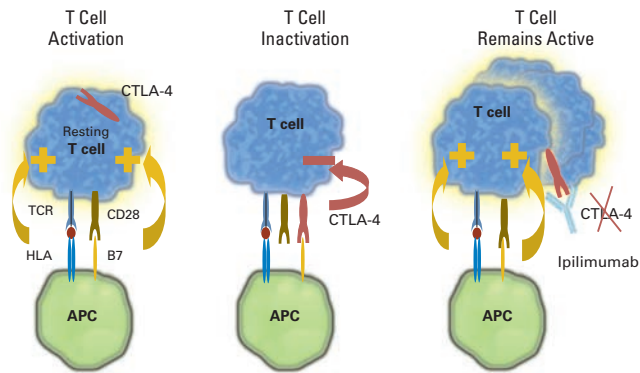
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PD-1/PD-L1 Inhibitors

| PD-1 Inhibitor | • Pembrolizumab • Nivolumab |
| PD-L1 Inhibitors | • Atezolizumab • Avelumab • Durvalumab |

http://labiotech.eu/pfizer-merck-ovarian-cancer-trial-avelumab-pd1-immunooncology/

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Immune Related Toxicity/Management

Evans, B., Evans, S. The Pharmaceutical Journal. 2018. https://www.pharmaceutical-journal.com/cpd-and-learning/learning-article/immune-checkpoint-inhibitors-in-cancer-pharmacology-and-toxicities/20204831.article?firstPass=false

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Hormonal Therapy for Prostate Camncer

Androgen Deprivation Therapy (ADT)	CYP17 inhibitor	Androgen receptor inhibitors
GnRH agonists	Abiraterone	Enzalutamide
GnRH antagonists		Apalutamide
		Darolutamide
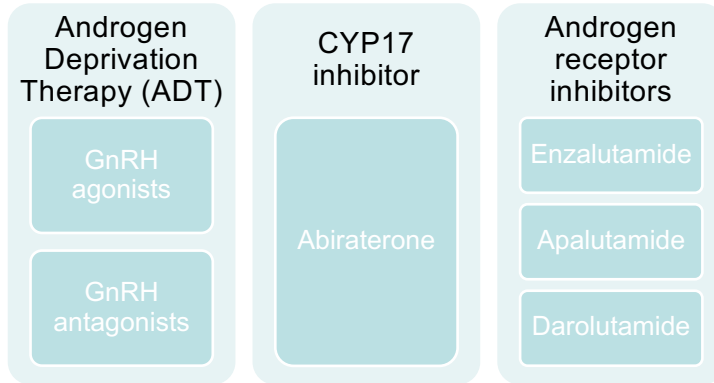
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GnRH Agonists and Antagonists
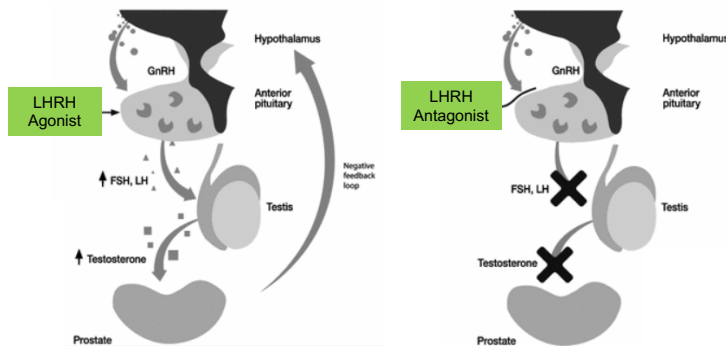
Rosario et al. World J Urol 2016;34:1601-09.
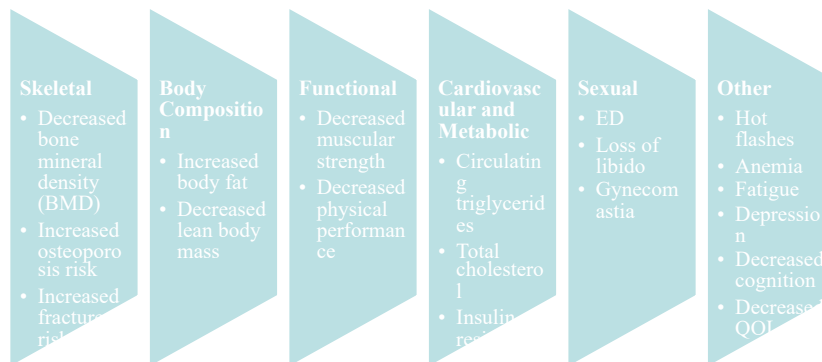
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LHRH Agonists and Antagonists

- GnRH Agonists
  - Leuprolide, histrelin, goserelin, triptorelin
    - Injections can be given every 1, 3, or 6 months depending on formulation
    - Tumor flare a concern with initial increase in testosterone
    - Can take up to 30 days to reach castration levels of testosterone
- GnRH Antagonist
  - Degarelix
    - SC injection given every 1 month
    - Reduces testosterone to castration levels within 3 days
    - Preferred for patients with advanced disease where testosterone flare would lead to worsening pain, urinary obstruction or spinal cord compression

Rosario DJ, et al. *World J Urol* 2016;34:1601-1609;
Crawford ED, et al. *Prostate Cancer Prostatic Dis.* 2019;22(1):24-38.

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Effects of Androgen Deprivation Therapy

Skeletal	Body Composition	Functional	Cardiovascular and Metabolic	Sexual	Other
• Decreased bone mineral density (BMD) • Increased osteoporosis risk • Increased fracture risk	• Increased body fat • Decreased lean body mass	• Decreased muscular strength • Decreased physical performance	• Circulating triglycerides • Total cholesterol • Insulin resistance	• ED • Loss of libido • Gynecomastia	• Hot flashes • Anemia • Fatigue • Depression • Decreased cognition • Decreased QOL

Gardner JR, et al. *J Clin Oncol.* 2014;32(4)335-346.

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Abiraterone Acetate

- Anti-androgen therapy
- Inhibits steroid 17-hydroxylase/17,20-lyase
- Decreases adrenal androgen synthesis
  - Testosterone→DHT
- Decreases cortisol synthesis
- Results in increased ACTH production and mineralocorticoid excess

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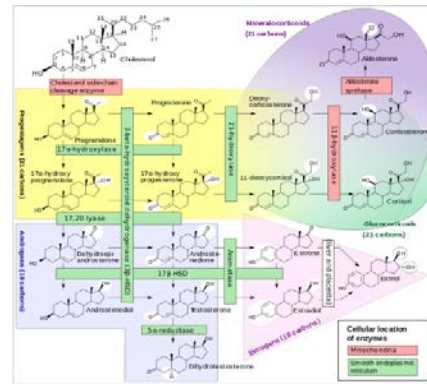
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Abiraterone Acetate

- Approved in mCSPC and mCRPC with data in high risk localized/nodal disease
- Adverse Events
  - **Mineralocorticoid excess syndrome** (hypertension, hypokalemia, edema)
    - PREDNISONE REQUIRED- mimics normal cortisol production and minimizes AEs
      - Dose of 5-10 mg per day
    - Caution in patients with CHF, recent MI, CVD, ventricular arrhythmia
  - Hepatic toxicity requires close monitoring of LFTs for first 3 months
  - Androgen deprivation AEs
- Administration- taken on an empty stomach, fat increases AUC x 10 fold
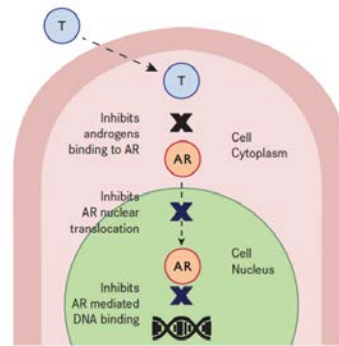- Cost- $12,000/m

Auchus et al. Oncologist 2014;19:1231-40.

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Androgen Receptor Inhibitors

Enzalutamide, Apalutamide, and Darolutamide
- Mechanism of Action
  - Binds to AR receptor
  - inhibits translocation of AR receptor into nucleus
  - inhibits DNA binding and coactivator recruitment
- Common side effects; fatigue, dizziness, hot flashes, arthraligias
- Blood brain barrier penetration; Seizure risk highest with enzalutamide
  Enzalutamide > Apalutamide > Darolutamide

Ammannagari et al. AJHO 2015;11(2):15-19.

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Novel Agents for Prostate Cancer
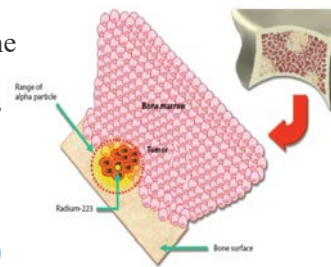
Radium 233   Sipuleucel-T

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Radium-223 (Xofigo)

- Alpha-emitter calcium mimetic
  - Selectively binds to areas of high bone turnover
  - Induces double stranded DNA breaks
- Treatment of mCRPC with **bone only metastasis**
- ADE- hematologic toxicities, N/V
- Cost - 1000 kBq/mL vial is **$13,800**
 - One dose could be 4 or more vials x 6 treatments

Nilsson et al. Lancet Oncol 2013;369:213-23.

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Sipuleucel – T (Provenge)

- APCs stimulate T-cell immune response targeted against prostatic acid phosphatase (PAP), which is highly expressed in prostate cancer cells
- Treatment of **asymptomatic or minimally symptomatic** mCRPC
- ADE- infusion related reactions
- Cost- $93 K (3 doses)
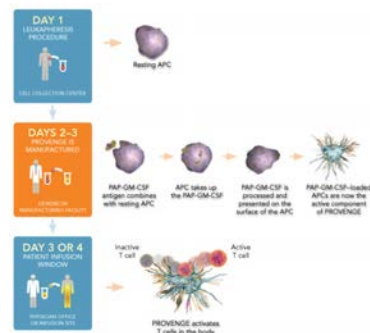
Kantoff et al. NEJM 2010;363:411-22.

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Sipuleucel – T (Provenge) Process

- Complicated approval and process
  - Application sent to company who then if patient is eligible they do insurance approval
  - Vein assessment by Red cross
  - Peripheral collection vs apheresis catheter
  - Collection via leukapheresis and antigen presenting cells (APCs) isolated ex vivo
  - Sent to Dendreon's manufacturing facility in New Jersey
  - Harvested APCs are incubated with recombinant fusion protein antigen, which contains both PAP and GM–CSF
  - The activated, antigen-loaded APCs are transported back to the infusion center and are infused into the patient
  - From apheresis to administration takes 4 days

Kantoff et al. NEJM 2010;363:411-22.
Anassi et al. PT 2011;36(4):197-202.

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