

Prostate, bladder and testicular cancers

Mark M Pomerantz, MD
Medical oncologist, Clinical Director
Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute
Associate Professor of Medicine
Harvard Medical School

Mark Pomerantz, MD

**Titles:**

Senior Physician, Dana-Farber Cancer Institute
Associate Professor, Harvard Medical School
Clinical Director, Lank Center for Genitourinary
Oncology

Education and Training:

- Yale University, BA, History
- Stanford University, MD
- Brigham and Women's Hospital, Residency in Internal Medicine
- Dana-Farber Cancer Institute, Fellowship in Medical Oncology

Clinical Specialty: Genitourinary Medical Oncology

**No financial disclosures
or conflicts to report**

Prostate Cancer

Objectives

- To describe the pros and cons of PSA screening
- To define the approach to newly diagnosed bladder cancer
- To outline diagnosis and management of testicular cancer

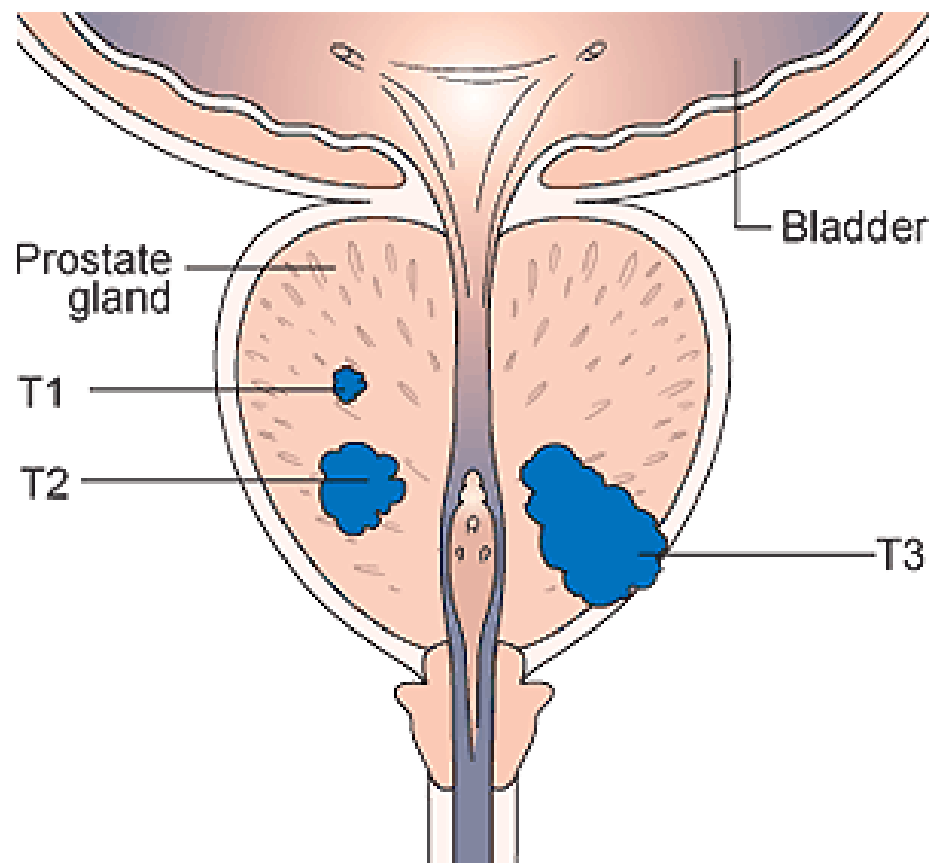


Diagram showing T1-3 stages of prostate cancer
© CancerHelp UK

Prostate cancer statistics

#1 in Incidence (males)

#2 in cancer-related mortality among U.S. men

1 in 7 men will be diagnosed in the U.S.

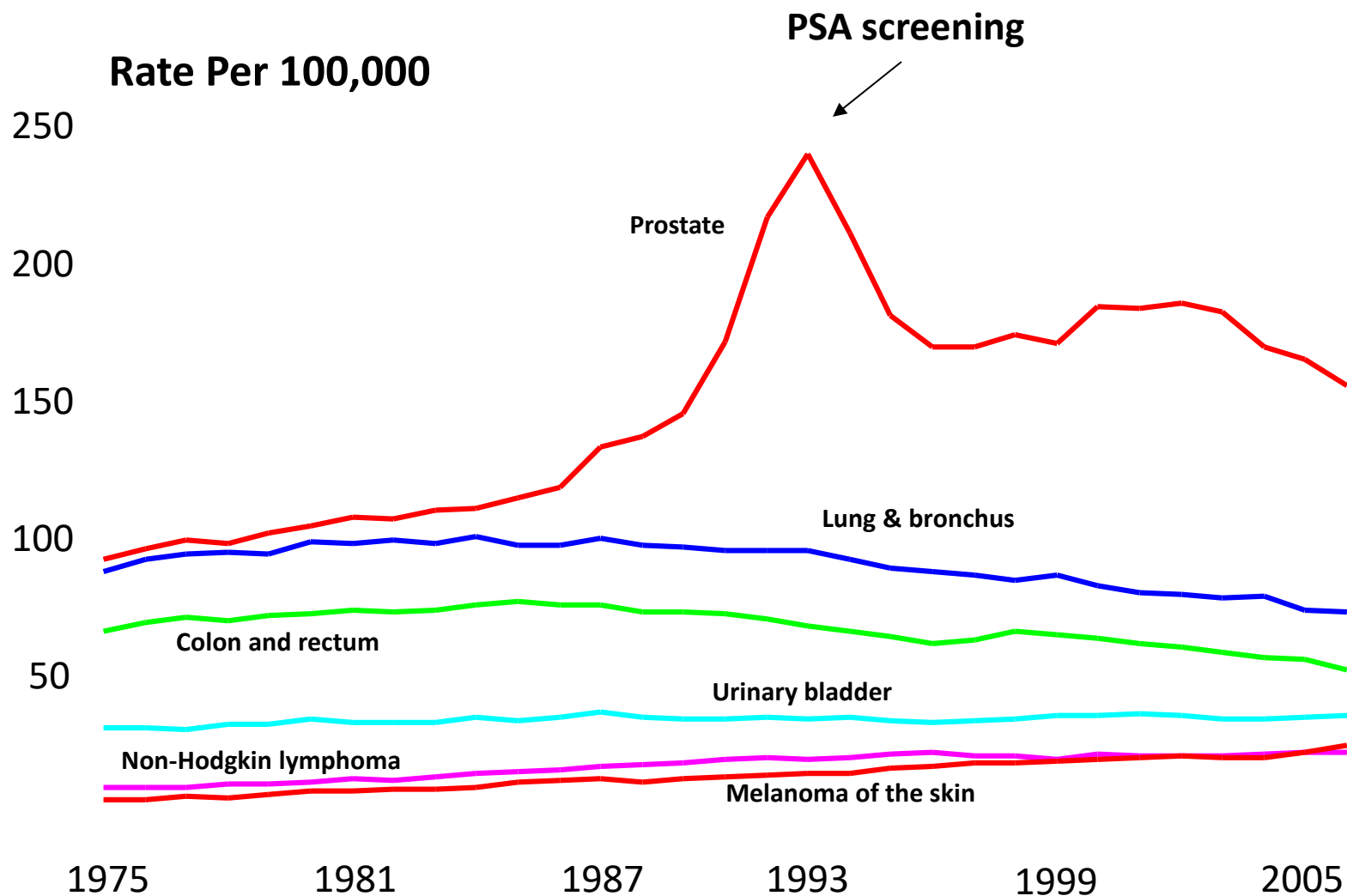
Risk Factors:

- Age
- Family history
- Ancestry: **African American men** at highest risk
- Genetic syndromes
 - BRCA 1/2, Lynch syndrome

Estimated New Cases	Male			
	● Prostate	333,830	31%	
	Lung & bronchus	110,910	10%	
	Colon & rectum	84,160	8%	
	Melanoma of the skin	65,400	6%	
	Urinary bladder	64,730	6%	
	Kidney & renal pelvis	50,770	5%	
	Non-Hodgkin lymphoma	43,770	4%	
	Oral cavity & pharynx	43,070	4%	
	Leukemia	39,070	4%	
	Pancreas	35,190	3%	
	All sites	1,094,070		

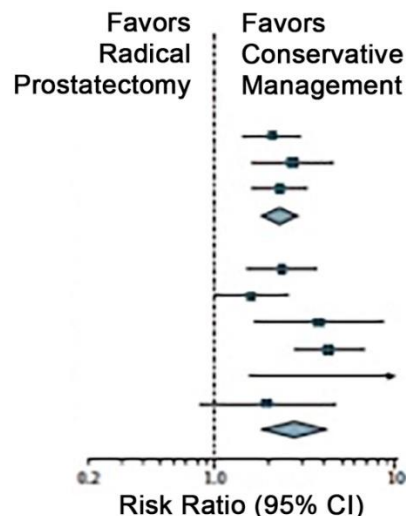
Estimated Deaths	Male			
	Lung & bronchus	63,040	19%	
	● Prostate	36,320	11%	
	Colon & rectum	30,110	9%	
	Pancreas	27,230	8%	
	Liver & intrahepatic bile duct	19,650	6%	
	Leukemia	13,900	4%	
	Esophagus	12,940	4%	
	Urinary bladder	12,640	4%	
	Non-Hodgkin lymphoma	11,710	4%	
	Kidney & renal pelvis	10,200	3%	
	All sites	327,290		

Prostate cancer incidence 1975-2005



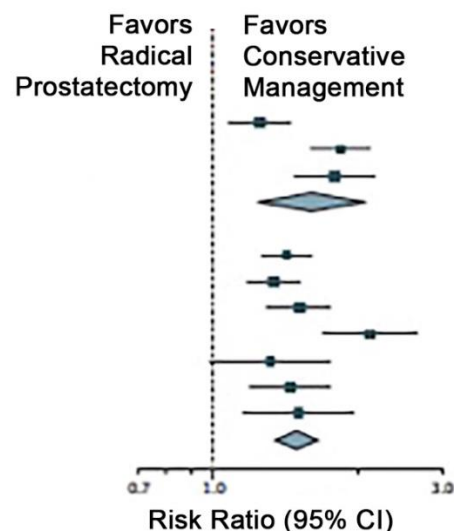
Urinary incontinence

Source	Risk Ratio (95% CI)
RCT	
Donovan et al, ⁶⁶ 2016	2.07 (1.44-2.98)
Wilt et al, ⁶⁸ 2012	2.69 (1.61-4.51)
Johansson et al, ⁶⁹ 2011	2.29 (1.63-3.22)
Subtotal ($P = 0.0%$)	2.27 (1.82-2.84)
Cohort study	
Barocas et al, ⁷¹ 2017	2.34 (1.49-3.65)
Chan et al, ⁷⁰ 2017	1.58 (0.99-2.53)
Smith et al, ⁷⁷ 2009	3.77 (1.68-8.46)
Hoffman et al, ⁶⁹ 2003	4.27 (2.76-6.60)
Schapira et al, ⁷⁵ 2001	11.11 (1.57-78.47)
Litwin, ⁷³ 1995	1.94 (0.82-4.58)
Subtotal ($P = 63.0%$)	2.75 (1.78-4.23)



Erectile dysfunction

Source	Risk Ratio (95% CI)
RCT	
Donovan et al, ⁶⁶ 2016	1.25 (1.08-1.45)
Wilt et al, ⁶⁸ 2012	1.84 (1.59-2.12)
Johansson et al, ⁶⁹ 2011	1.79 (1.48-2.16)
Subtotal ($P = 87.5%$) ^b	1.60 (1.23-2.07)
Cohort study	
Barocas et al, ⁷¹ 2017	1.42 (1.27-1.59)
Chan et al, ⁷⁰ 2017	1.33 (1.18-1.51)
Smith et al, ⁷⁷ 2009	1.51 (1.29-1.76)
Hoffman et al, ⁶⁹ 2003	2.11 (1.69-2.64)
Schapira et al, ⁷⁵ 2001	1.31 (0.98-1.76)
Siegel et al, ⁷⁶ 2001	1.44 (1.19-1.75)
Litwin, ⁷³ 1995	1.50 (1.15-1.96)
Subtotal ($P = 59.2%$)	1.49 (1.34-1.65)



Does PSA screening benefit patients?

>50% of men diagnosed via DRE
have disease outside the prostate

<35% of men diagnosed via PSA
have disease outside the prostate

Mortality rate per 100,000 population -
39.3 in 1993 and **24.6** in 2005

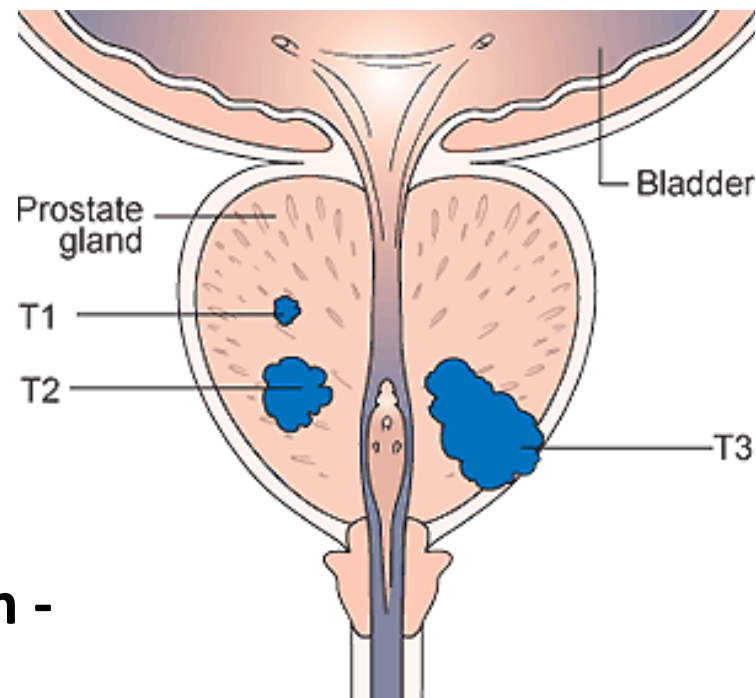


Diagram showing T1-3 stages of prostate cancer
© CancerHelp UK



Prostate cancer screening RCTs



PLCO

38,343

38,350

PSA screening

No PSA screening

Men aged 55-74 years
PSA <4

ERSPC

82,816

99,184

PSA screening

No PSA screening

Men aged 50-74 years
PSA <3



Prostate cancer screening RCTs



PLCO

38,343

38,350

PSA screening

No PSA screening

>80% contamination of control arm

**Only 20% increase in dx in
screened arm**

ERSPC

82,816

99,184

PSA screening

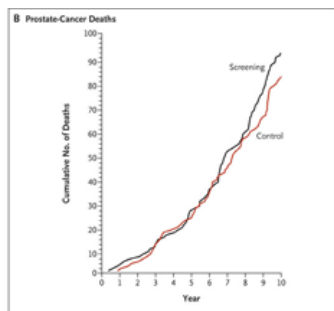
No PSA screening

~25% in *screening* arm did not
receive appropriate testing

~25% of screening dx's did not
receive RP/RT

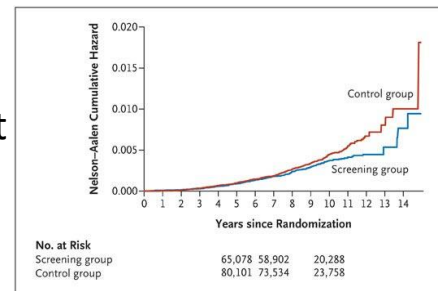
PLCO

No mortality benefit at median follow-up 11 yrs

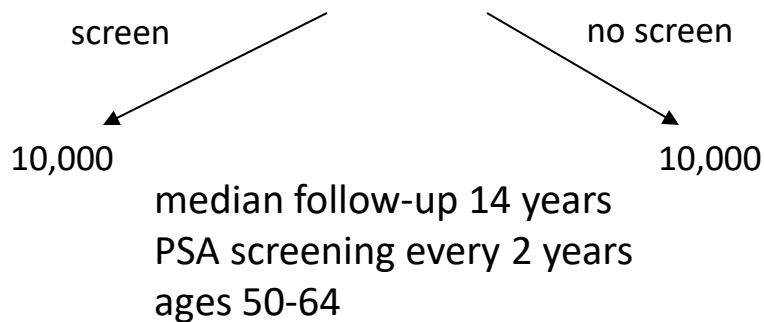


ERSPC

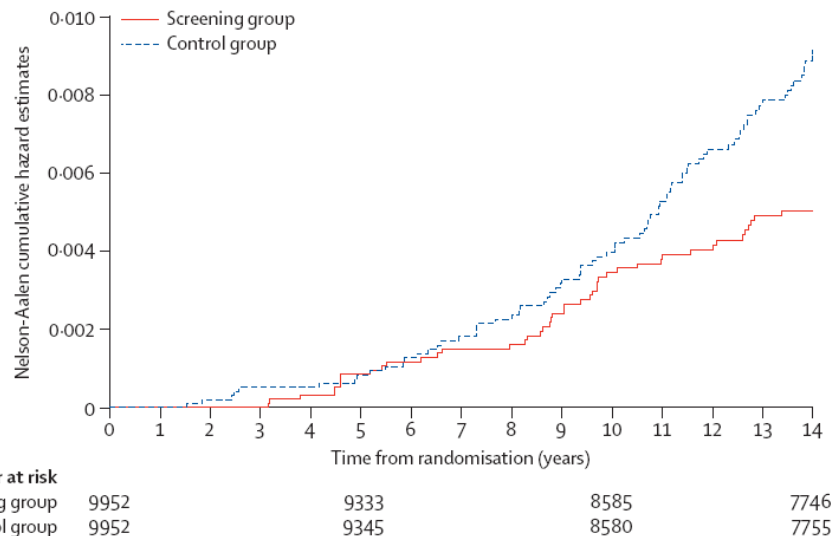
20% mortality benefit at median follow-up 9 yrs
NNS: 1,400 NNT: 48



Göteborg randomized population-based prostate-cancer screening trial



rate ratio for prostate cancer death = **0.56**
number needed to screen = **293**
number needed to treat = **12**



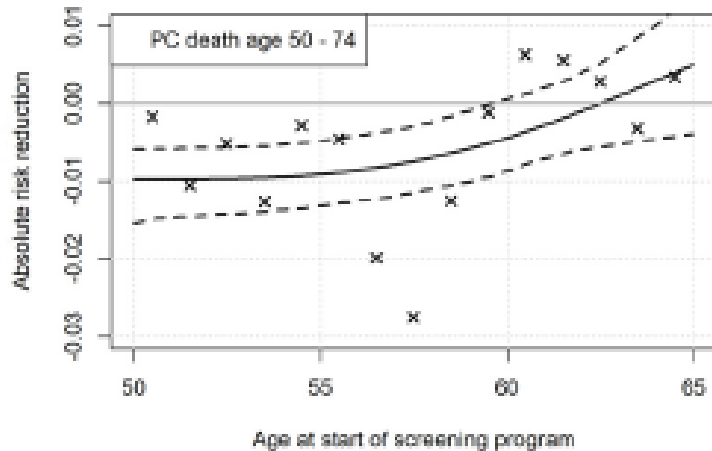
Attendee setting

Screening versus control, attendees first round

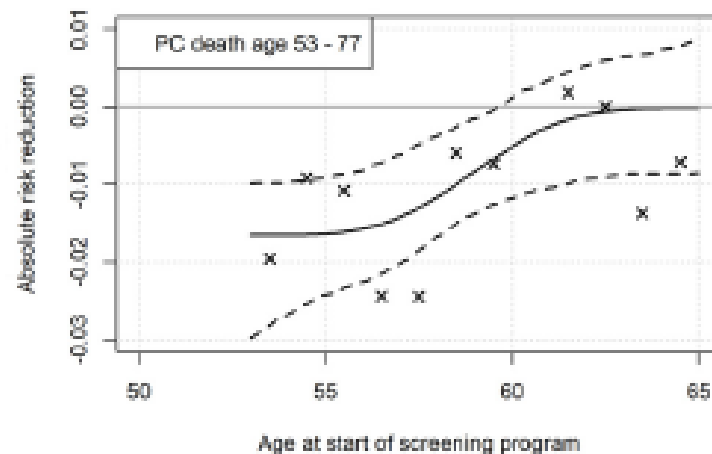
Ages 50–74 yr (screening $n = 5855$, control $n = 5857$)

Ages 53–77 yr (screening $n = 4481$, control $n = 4448$)

E



F



Göteborg randomized population-based prostate-cancer screening trial

Younger age on starting PSA testing was associated with a greater reduction in PC mortality

Risk of developing metastatic prostate cancer **reduced by 30%**

Fenton et al, Agency for Healthcare Research and Quality, 2018



Modeling number needed to PSA screen and treat to prevent one prostate cancer death

The NEW ENGLAND
JOURNAL of MEDICINE

SOUNDING BOARD

Reconsidering the Trade-offs of Prostate Cancer Screening

Jonathan E. Shoag, M.D., Yaw A. Nyame, M.D., M.B.A., Roman Gulati, M.S., Ruth Etzioni, Ph.D., and Jim C. Hu, M.D., M.P.H.

Table 1. Estimates of the Number Needed to Screen and the Number of Excess Prostate Cancer Diagnoses to Prevent One Death from Prostate Cancer during the Indicated Follow-up Interval.*

Variable	No. Needed to Screen (95% CI)	No. of Excess Diagnoses (95% CI)
16 Yr of follow-up: empirical estimate from ERSPC	570 (380–1137)	18 (12–35)
25 Yr of follow-up: conservative model estimate	385 (273–687)	11 (8–20)

Recommendations



2012

U.S. Preventive Services Task Force

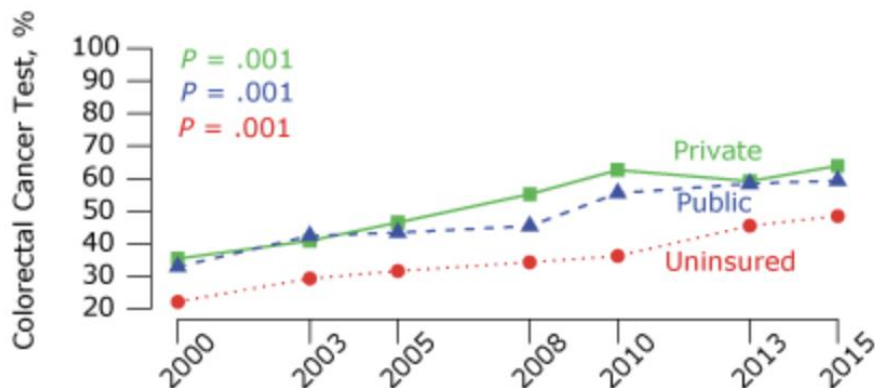
“There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.”

Recommend against any screening in men >75

Trends in PSA screening after the USPSTF 2012 recs

Men

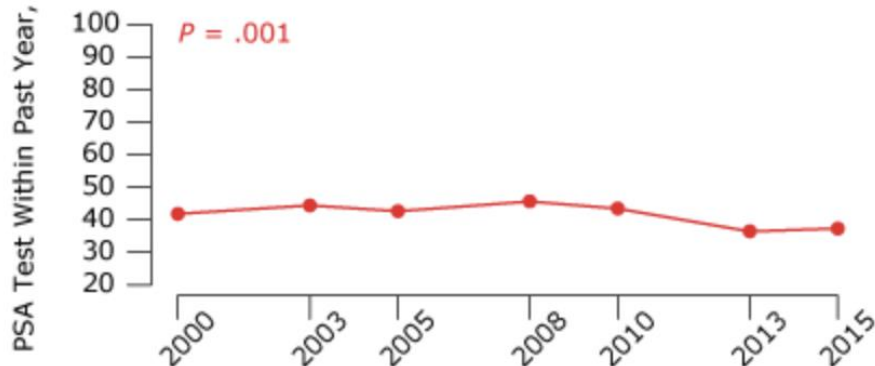
D. Recent Colorectal Test by Insurance Coverage



Use of an annual PSA test
declined (9.2%) from 2008
through 2013



E. Recent PSA Test



Annual Report to the Nation on the Status of Cancer, Part II: Recent Changes in Prostate Cancer Trends and Disease Characteristics

Serban Negoita, MD, DrPH¹; Eric J. Feuer, PhD¹; Angela Mariotto, PhD¹; Kathleen A. Cronin, PhD¹;
Valentina I. Petkov, MD, MPH¹; Sarah K. Hussey, MS ¹; Vicki Benard, PhD²; S. Jane Henley, MSPH²;
Robert N. Anderson, PhD³; Stacey Fedewa, PhD⁴; Recinda L. Sherman, MPH, PhD, CTR⁵; Betsy A. Kohler, MPH⁵;
Barbara J. Dearmon, BS, CTR⁶; Andrew J. Lake, BS⁷; Jiemin Ma, PhD, MHS⁴; Lisa C. Richardson, MD, MPH²;
Ahmedin Jemal, DVM, PhD ⁴; and Lynne Penberthy, MD, MPH¹

BACKGROUND: Temporal trends in prostate cancer incidence and death rates have been attributed to changing patterns of screening and improved treatment (mortality only), among other factors. This study evaluated contemporary national-level trends and their relations with prostate-specific antigen (PSA) testing prevalence and explored trends in incidence according to disease characteris-

“...the incidence of distant stage disease increased from 2010 to 2014...After years of significant decline (from 1993 to 2013), the overall prostate cancer mortality trend stabilized from 2013 to 2015).”

...the cancer mortality has leveled off since 2010, the most recent data available. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

KEYWORDS: Gleason score, incidence, mortality, prostate cancer, prostate-specific antigen, trends.

Prostate Cancer Incidence 5 Years After US Preventive Services Task Force

Recommendations Against Screening

Ahmedin Jemal, DVM, PhD*, MaryBeth B.
Culp, MPH, Jiemin Ma, PhD, Farhad Islami,
MD, PhD, Stacey A. Fedewa, PhD

JNCI J Natl Cancer Inst (2021) 113(1): djaa068

Surveillance and Health Services
Research, American Cancer Society,
Atlanta, GA, USA

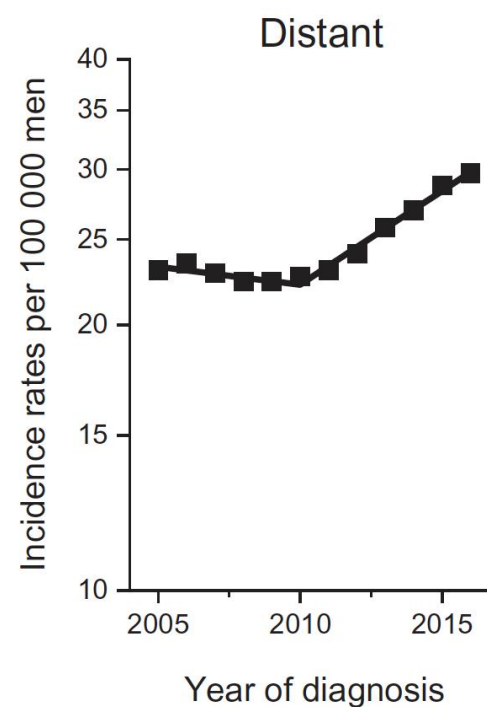
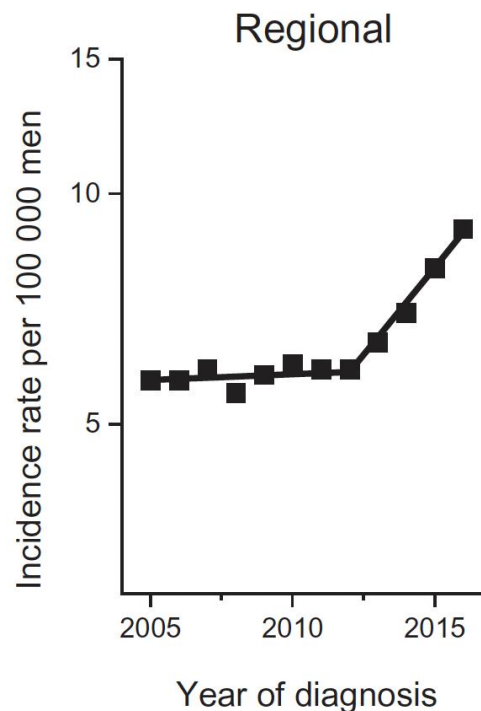
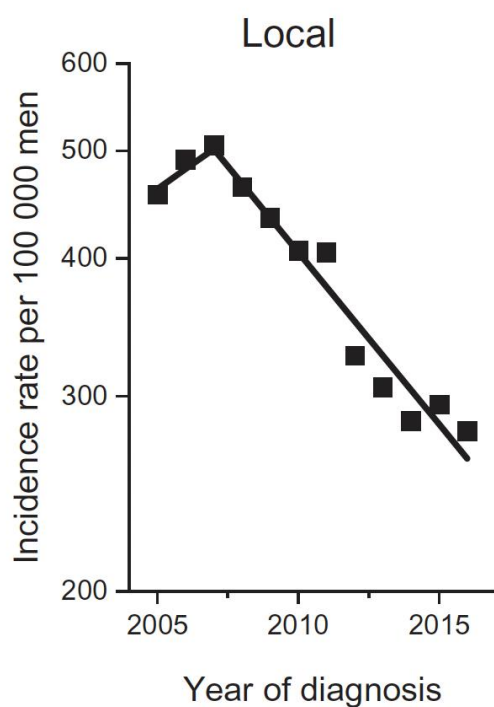
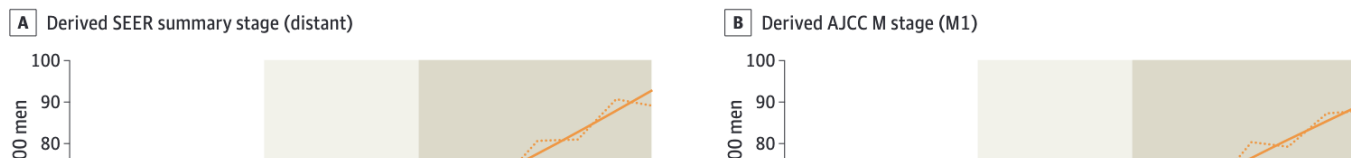
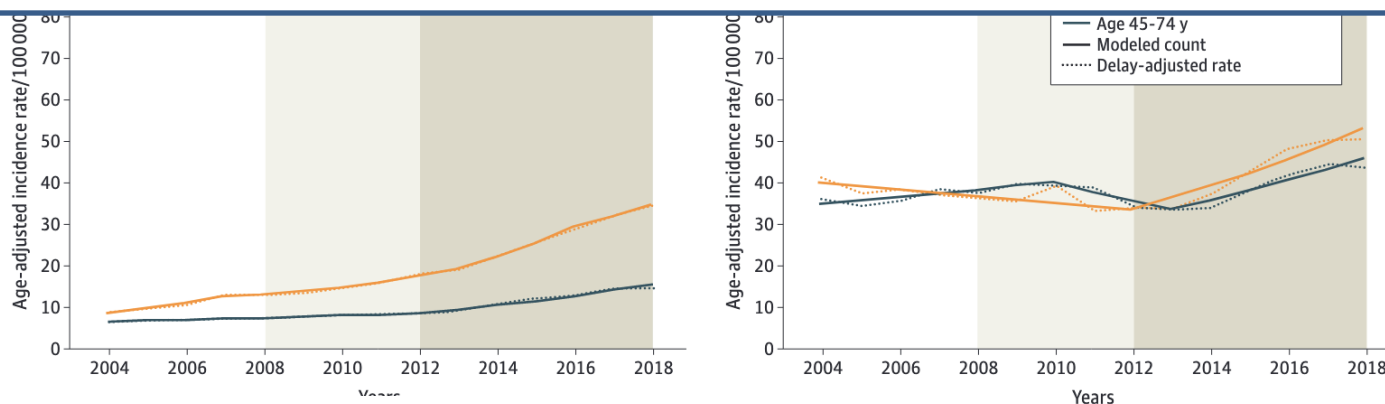


Figure. Trends in Invasive Prostate Cancer: Surveillance, Epidemiology, and End Results 18 Registries 2004-2018 for All Races



CONCLUSIONS AND RELEVANCE Analysis of the emerging trends from the most recently released SEER data set (2004-2018) suggests that the incidence rates of mPCa have increased significantly and coincide temporally with the USPSTF recommendations against PCa screening across races and age groups. These mPCa trends are associated with reported changes in screening practices following the USPSTF recommendations.



Recommendations



2012

U.S. Preventive Services Task Force

“There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.”

Recommend against any screening in men >75

2018

U.S. Preventive Services Task Force

Men between the ages of 55 and 69 should discuss the test’s potential benefits and harms with their physicians and make decisions based on their own values and preferences.

The USPSTF recommends against PSA-based screening for prostate cancer in men 70 years and older.

Guidelines

American Urological Association

Age <40: No PSA screening

Age 40-54: average risk: No routine PSA screening

Age 55-69: Shared decision-making with physician

Age 70 and above (or life expectancy <10 yrs): No PSA screening



American Cancer Society

All men ≥ 50 with 10 yr life expectancy

Discuss age ≥ 45 for African Americans and men with family history

Discuss age ≥ 40 for those with mult. family members dx'ed young

Screen yearly for PSA ≥ 2.5 , every other year for <2.5

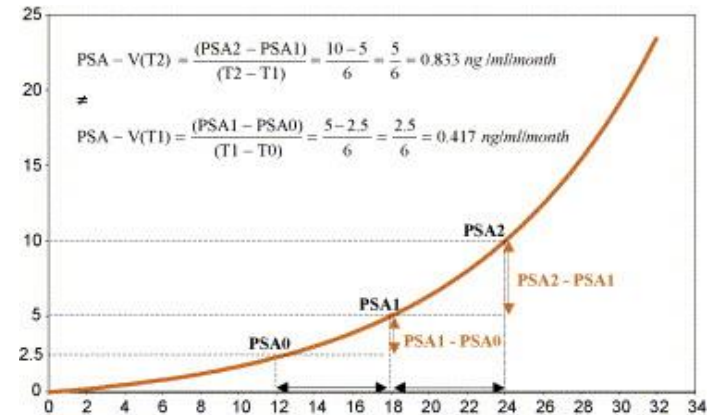


Additional factors that may refine our approach

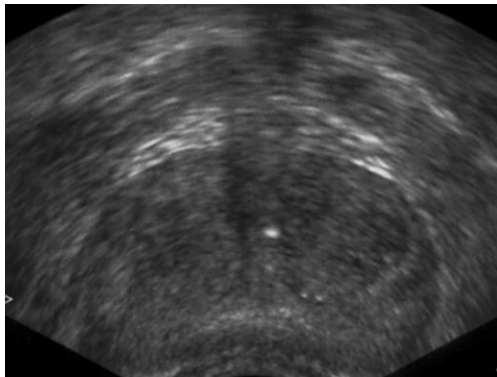
Family history/Ethnicity/Genetics



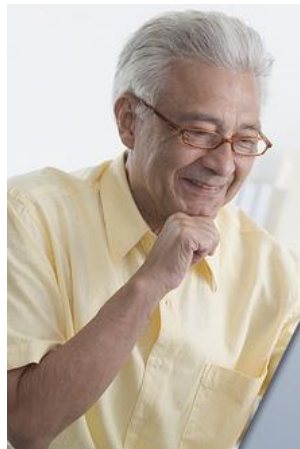
PSA velocity



PSA density



Age



% free PSA



Improving prostate cancer screening PRECISION trial

500 men randomized to standard prostate biopsy or **prostate MRI** followed by MRI-guided biopsy of suspicious lesion

The NEW ENGLAND
JOURNAL of MEDICINE

Comparison of cancer detection between groups:

	MRI-targeted Bx	Standard Bx
Low-grade	9%	22%
Clinically significant	38%	26%



Treatment of newly diagnosed localized prostate cancer

radical prostatectomy

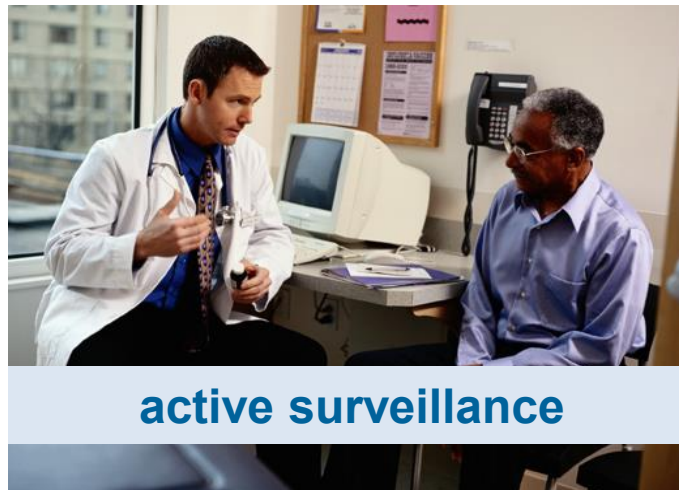


radiation therapy

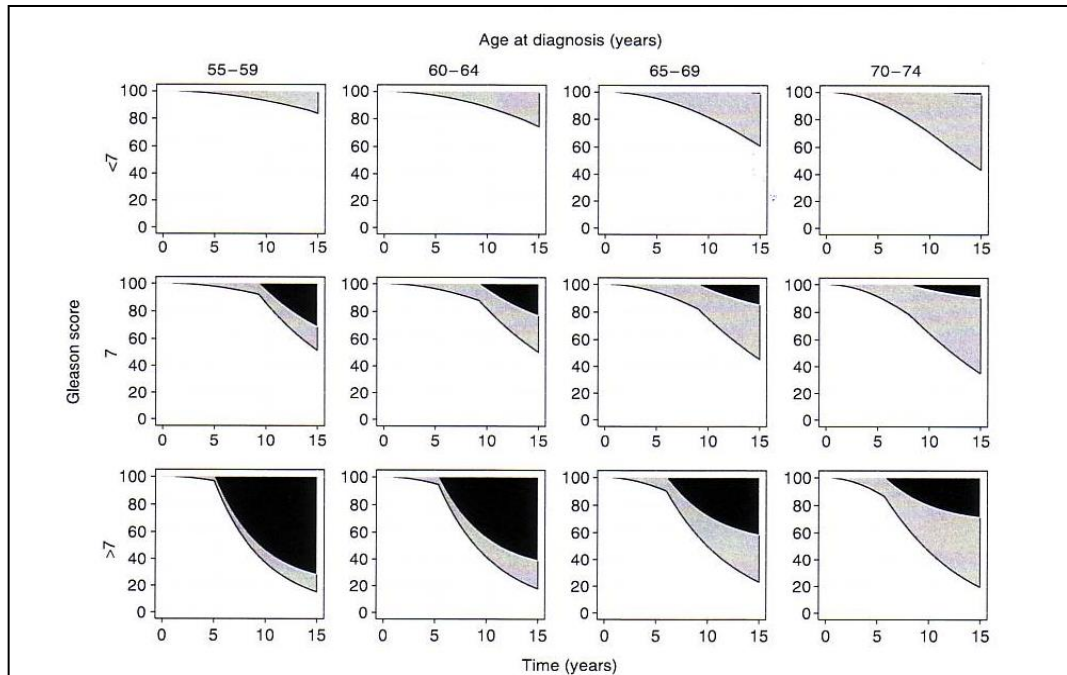
with or without androgen deprivation therapy



active surveillance



Treatment of newly diagnosed localized prostate cancer



Modeling screen-detected prostate cancer without any intervention

Key:

Grey: death to other cause
Black: death due to PC

Take home:

GS <7: few deaths from PC
GS ≥7 and >10 yr LE: no AS

Parker et al, BJC 2006



- No initial treatment; treat only those men who need it
- Good AS candidate: GS <7, PSA <10, <T2b, <1/3 bx cores positive
- Close monitoring: PSA, physical exam, serial re-biopsy
- Treat to cure at a sign of more aggressive disease
 - e.g., Increase in Gleason score, PSADT, increasing volume of disease
- Cons: anxiety, chance of progression to incurable state

Treatment of newly diagnosed localized prostate cancer

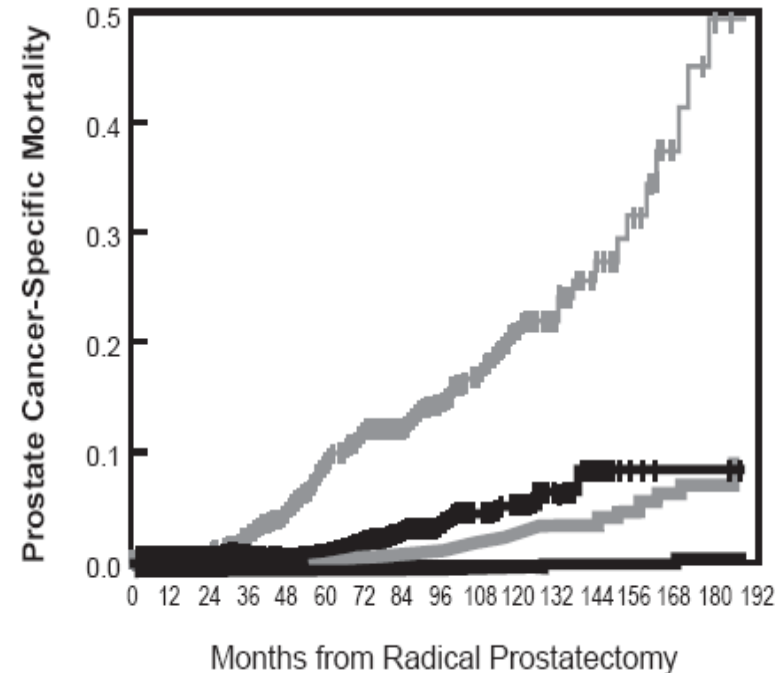
radical prostatectomy



Gleason 8-10: 10% of all cases
49% 15-year PCSM
45% of all cancer deaths

Gleason 7: 40% of all cases
8% 15-year PCSM
50% of all cancer deaths

Gleason 6: 50% of all cases
<1% 15-year PCSM
1 of 3756 patients with organ-confined,
Gleason 6 cancer died from prostate cancer



G8-10

G4+3

G3+4

G3+3

High cure rate in GS ≤ 7
Surgery for select cases of GS 8-10

Treatment of newly diagnosed localized prostate cancer

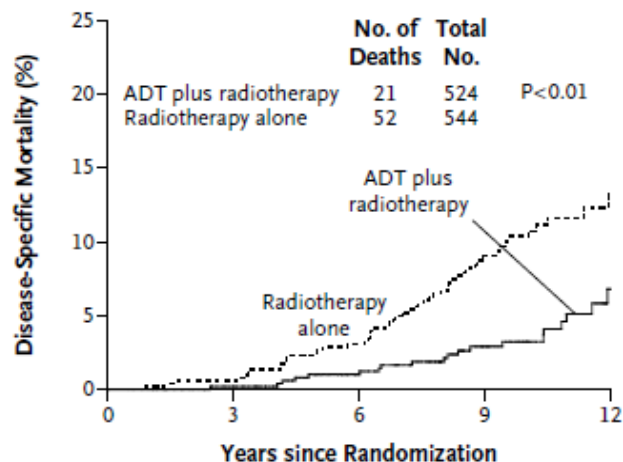


Intermediate-risk prostate cancer

4-6 months neoadjuvant ADT

- RTOG Trial
 - Enrolled all risk patients
 - XRT +/- Short term ADT
 - Intermediate risk
 - Decrease PC mortality
 - Increase OS
 - No benefit for low risk
 - High risk likely need longer course ADT
- Two other trials with similar results
 - TROG Lancet 2011
 - DFCI JAMA 2008

Intermediate-Risk Patients



No. at Risk					
ADT plus radiotherapy	524	471	380	220	46
Radiotherapy alone	544	489	369	202	47

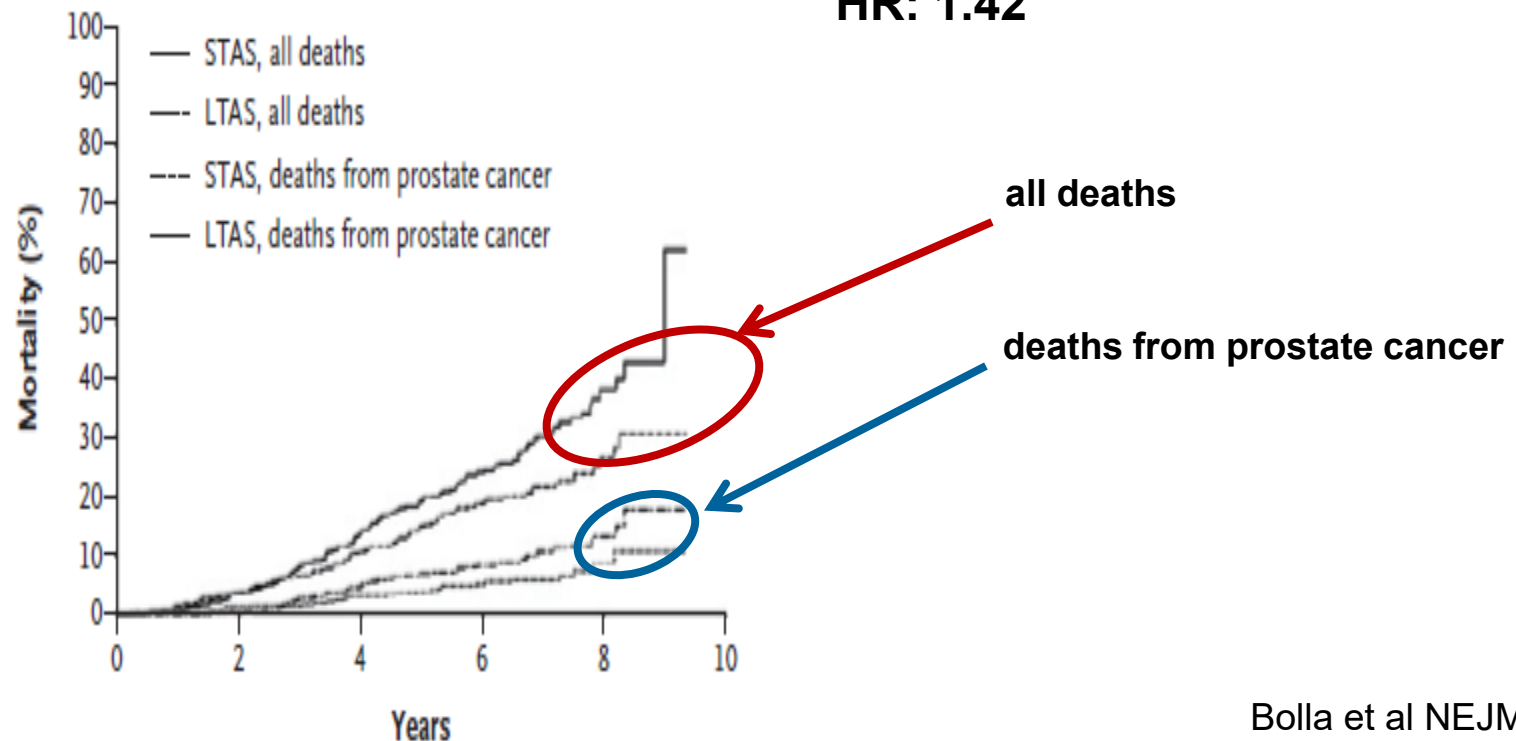
Treatment of newly diagnosed localized prostate cancer



High-risk prostate cancer

36 vs. 6 months neoadjuvant ADT

- ↓all deaths (increased OS)
- ↓ prostate Ca deaths
- 5 yr mortality: 19% vs. 15.2%
HR: 1.42



Treatment of newly diagnosed localized prostate cancer - weighing toxicity risks

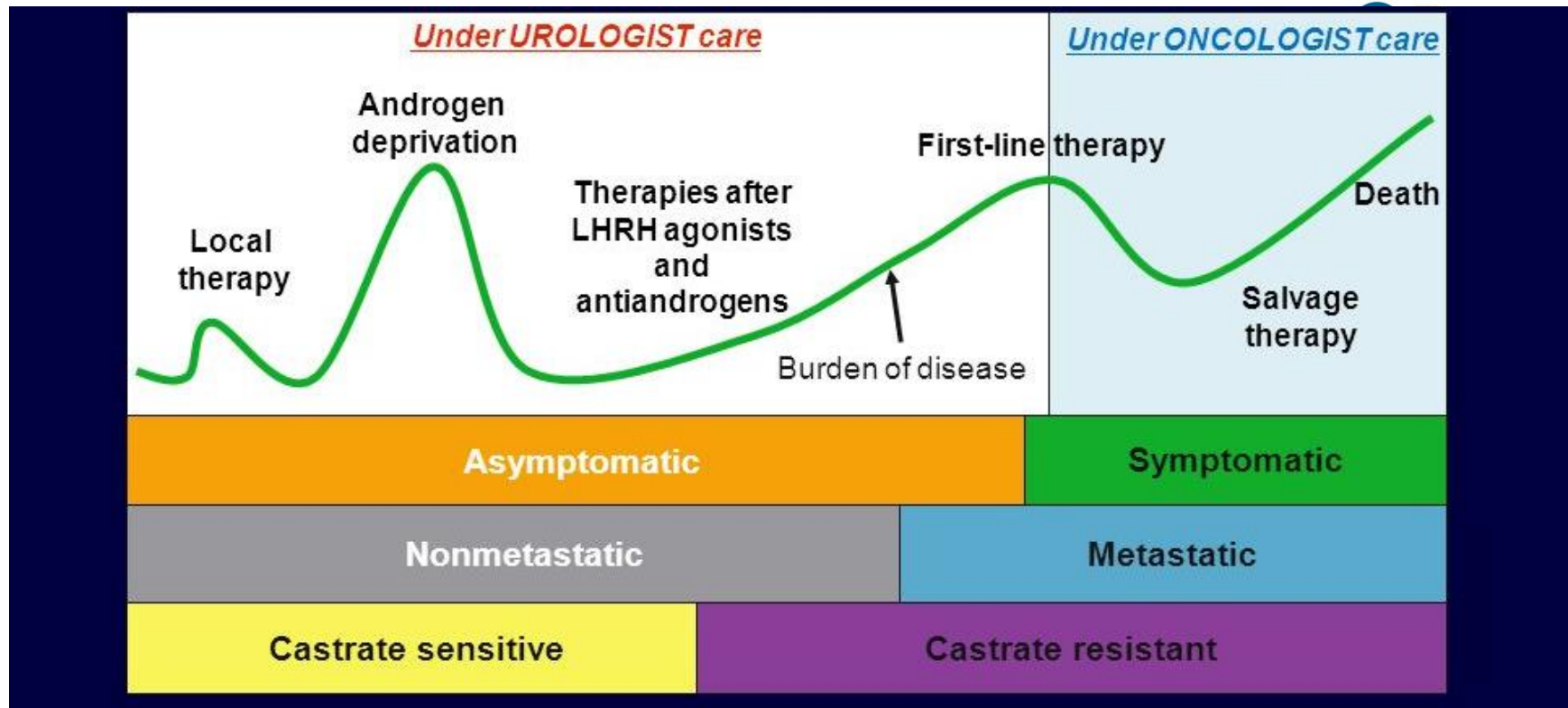
Surgery	Radiation	ADT
• Surgical complications - Wound healing - Infection - Anesthesia risks • Erectile dysfunction • Urinary Incontinence	• Irritative urinary Sx • Bowel dysfunction • Erectile dysfunction • Risk of second cancer	• Hot flashes • Fatigue • Weight gain • Bone density loss • Loss of libido • Emotional changes • Metabolic insults: insulin resistance • ?Cardiac toxicity • ?Dementia

Surgery: radical prostatectomy (robotic, open, laparoscopic)

Radiation: external beam, brachytherapy

ADT: GnRH agonist or antagonist +/- antiandrogen

Natural history of advanced prostate cancer



Higano et al in Figg et al 2010, Pound et al JAMA 1999

Duration of response to first-line androgen deprivation therapy varies substantially among advanced prostate cancer patients.

Treatment decisions require balancing the risk of progression and morbidity secondary to treatment toxicity with life expectancy.

Summary of Prostate Cancer

- **Prostate cancer mortality has decreased significantly in the PSA era**
 - Screening appears most beneficial in the 55-69 age group with life expectancy >10 yrs (shared decision making is key)
 - Overtreatment is a valid concern, but diagnosis does not mean we have to treat the patient
- **Active surveillance reasonable in low-risk disease—goal: delay or prevent toxicity**
- **Both surgery and radiation + ADT can lead to cure and improve outcomes in patients with intermediate or high-risk disease**
- **Wealth of agents now available that improve survival in metastatic disease, but cure is exceedingly rare**
 - ADT (e.g., leuprolide acetate, degarelix) is backbone of first-line treatment
 - Advanced androgen pathway targeted therapy (abiraterone, enzalutamide and others) play an increasingly central role
 - Chemotherapy (docetaxel, cabazitaxel) remains effective
 - Immunotherapy, radiopharmaceuticals and PARP inhibitors for some subsets of disease
 - **Clinical trials remain imperative to improve outcomes**

Bladder Cancer

Bladder Cancer

- **80,470 cases will be diagnosed**
 - **61,700 males/ 18,770 females (3:1)**
 - **#4 cancer in incidence**
 - **50-60% superficial disease**
 - **Median age: 73-74 yrs**
- **17,670 estimated deaths**
 - **10% present with metastatic disease**
 - **4% of all cancer deaths**

Estimated New Cases

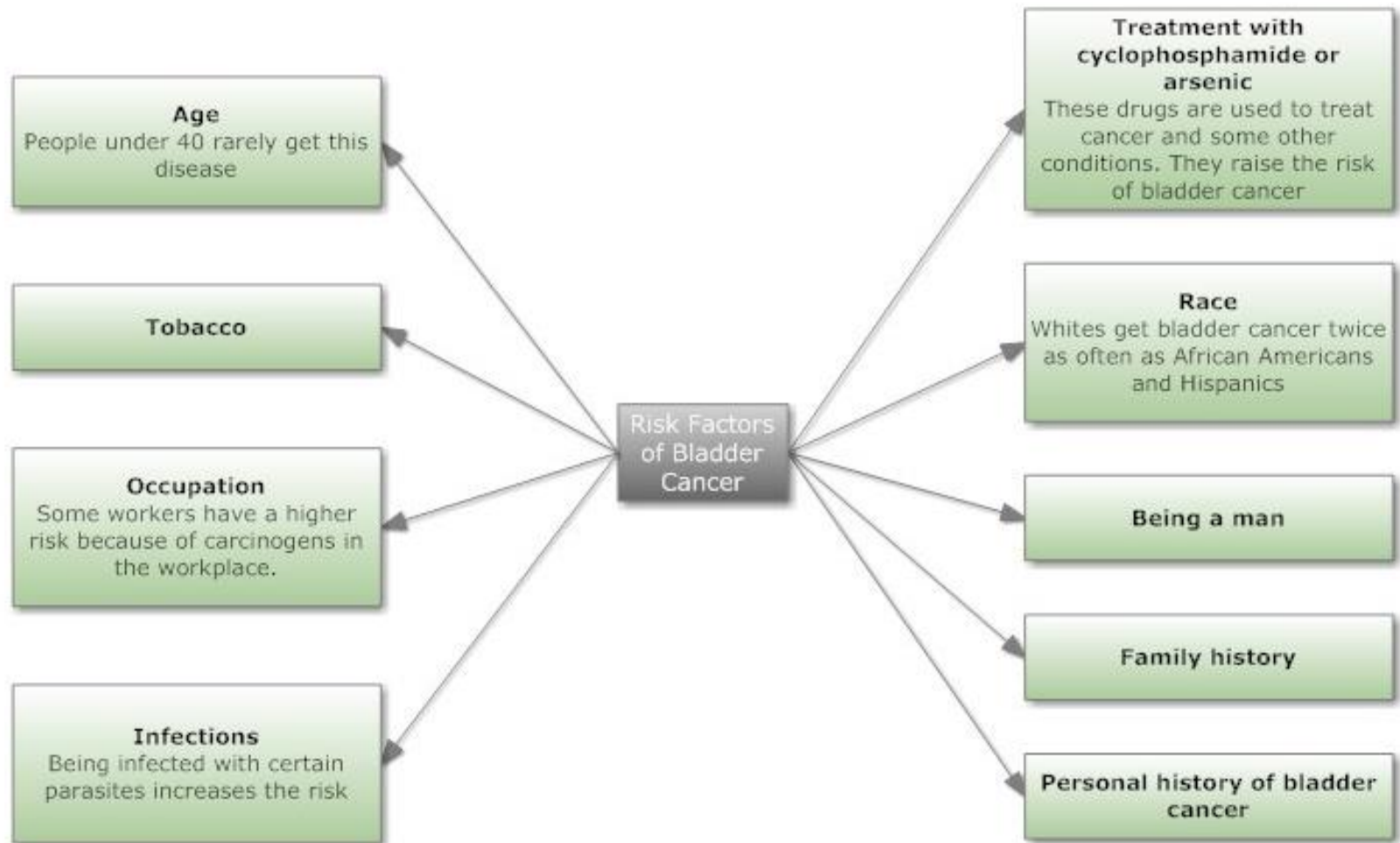
			Males
Prostate	174,650	20%	
Lung & bronchus	116,440	13%	
Colon & rectum	78,500	9%	
Urinary bladder	61,700	7%	
Melanoma of the skin	57,220	7%	
Kidney & renal pelvis	44,120	5%	
Non-Hodgkin lymphoma	41,090	5%	
Oral cavity & pharynx	38,140	4%	
Leukemia	35,920	4%	
Pancreas	29,940	3%	
All Sites	870,970	100%	

Estimated Deaths

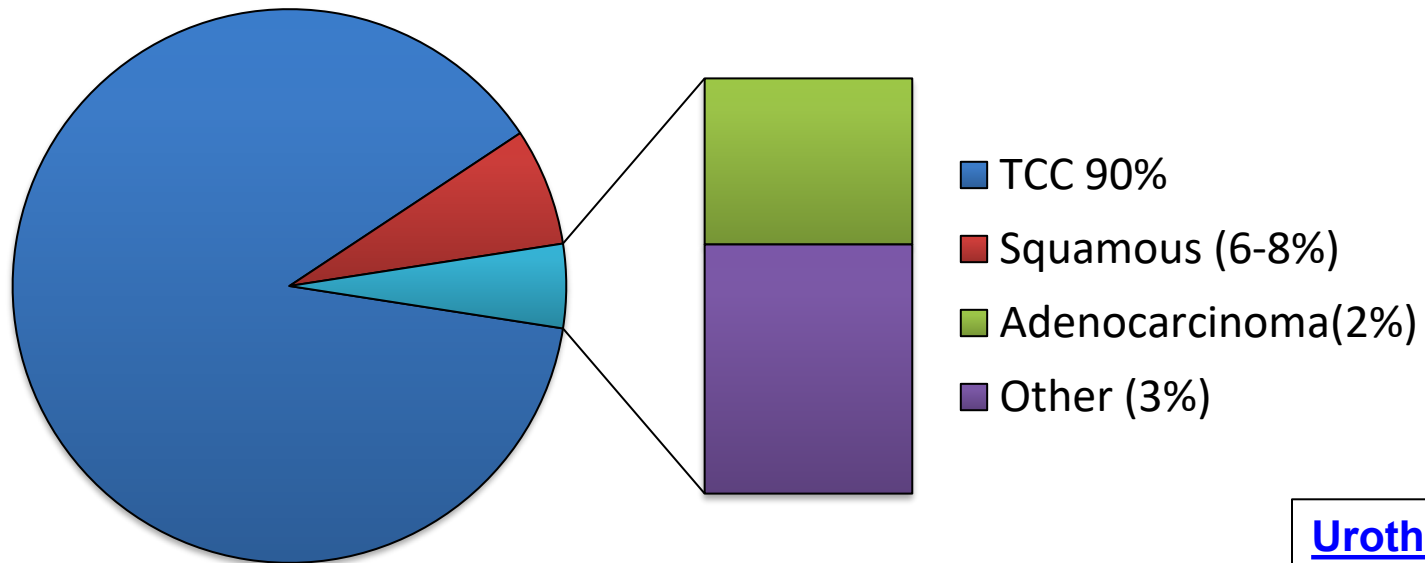
			Males
Lung & bronchus	76,650	24%	
Prostate	31,620	10%	
Colon & rectum	27,640	9%	
Pancreas	23,800	7%	
Liver & intrahepatic bile duct	21,600	7%	
Leukemia	13,150	4%	
Esophagus	13,020	4%	
Urinary bladder	12,870	4%	
Non-Hodgkin lymphoma	11,510	4%	
Brain & other nervous system	9,910	3%	
All Sites	321,670	100%	

Bladder Cancer

Risk factors



Bladder Cancer - subtypes



- **Urothelial cell or transitional cell-carcinoma (TCC) (90%)**
- **Squamous (6-8%)**
 - Schistosomiasis
 - Non-schistosomiasis cases: chronic catheterization patients
- **Adenocarcinoma (2%)**
 - Urachal
 - Non-urachal (chronically irritated transitional epithelium)
- **Small cell (<1%, treat like lung cancer)**

Bladder Cancer - diagnosis

Hematuria: gross or microscopic

UTI like or irritative symptoms: frequency, dysuria, blood

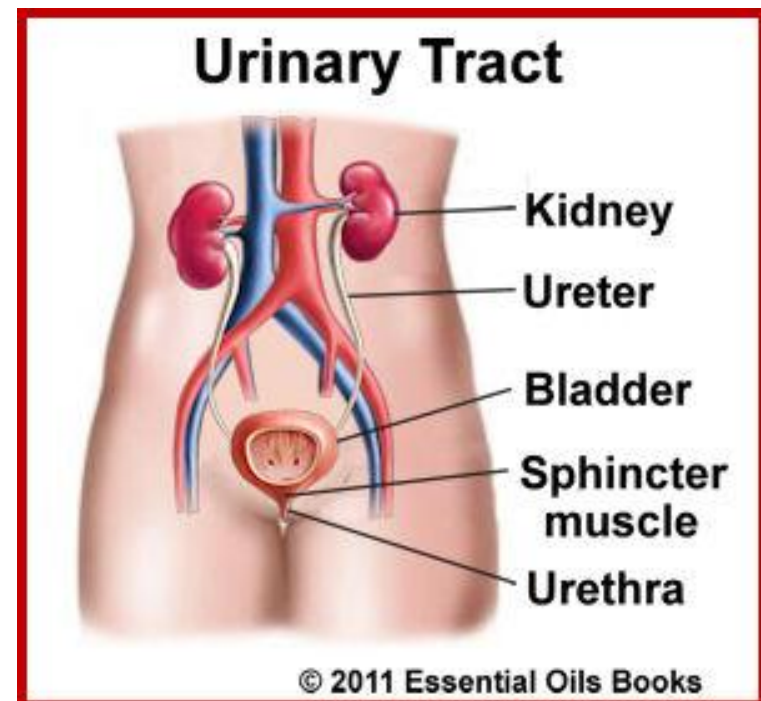
Patients are often treated with 2-3 courses of antibiotics before they are referred to a urologist

If not clearly a UTI on UA or culture:

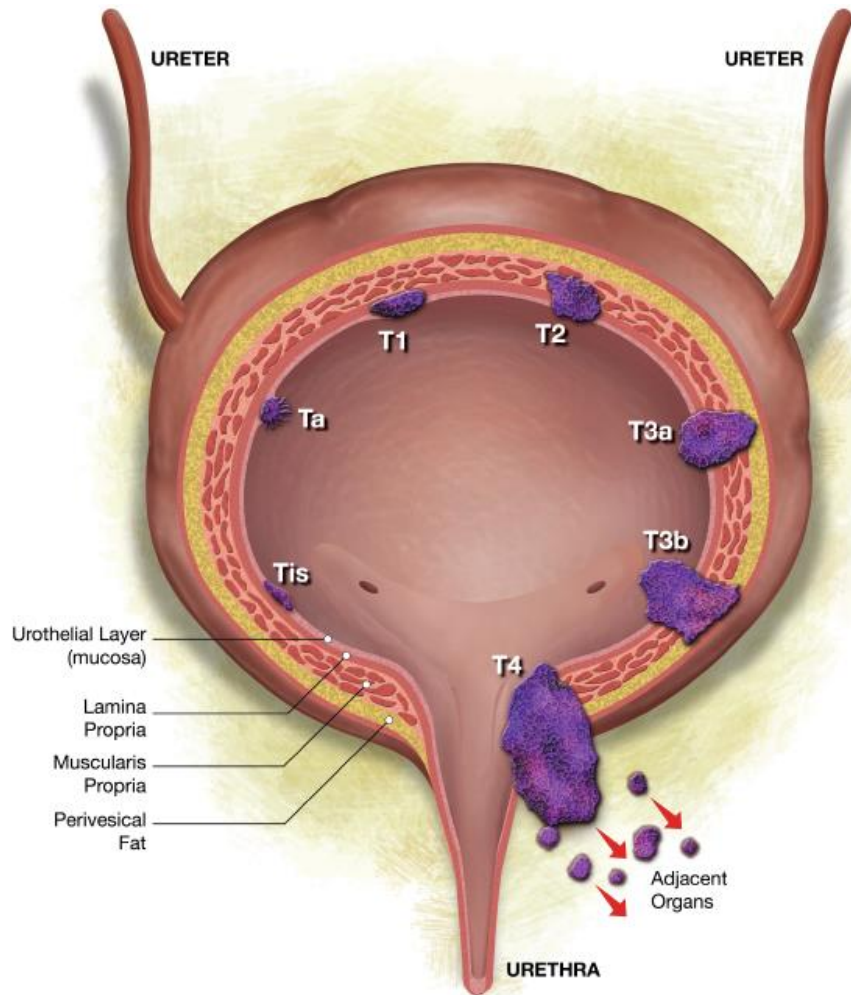
Refer to urology for cystoscopy
and upper tract evaluation

Send urine cytology

Consider CT abdomen/pelvis



Bladder Cancer - staging



- T1 = superficial, non-invasive
- T2 = muscle invasion
- T3 = into/through perivesicular fat
- T4b = invasion of pelvic/abdom wall
- N1 = Involved regional lymph nodes
- M1 = Distant metastasis

Critical that TURBT samples the muscle layer!

Bladder Cancer

**Non-muscle
Invasive (60%)**

**TURBT
and
Intravesical tx
if high grade**

**Muscle Invasive
(30%)**

**Radical cystectomy +/-
neo/adjuvant chemo
or
Chemoradiation**

**Metastatic
(10%)**

**Chemotherapy
and/or
Immunotherapy**

Bladder Cancer

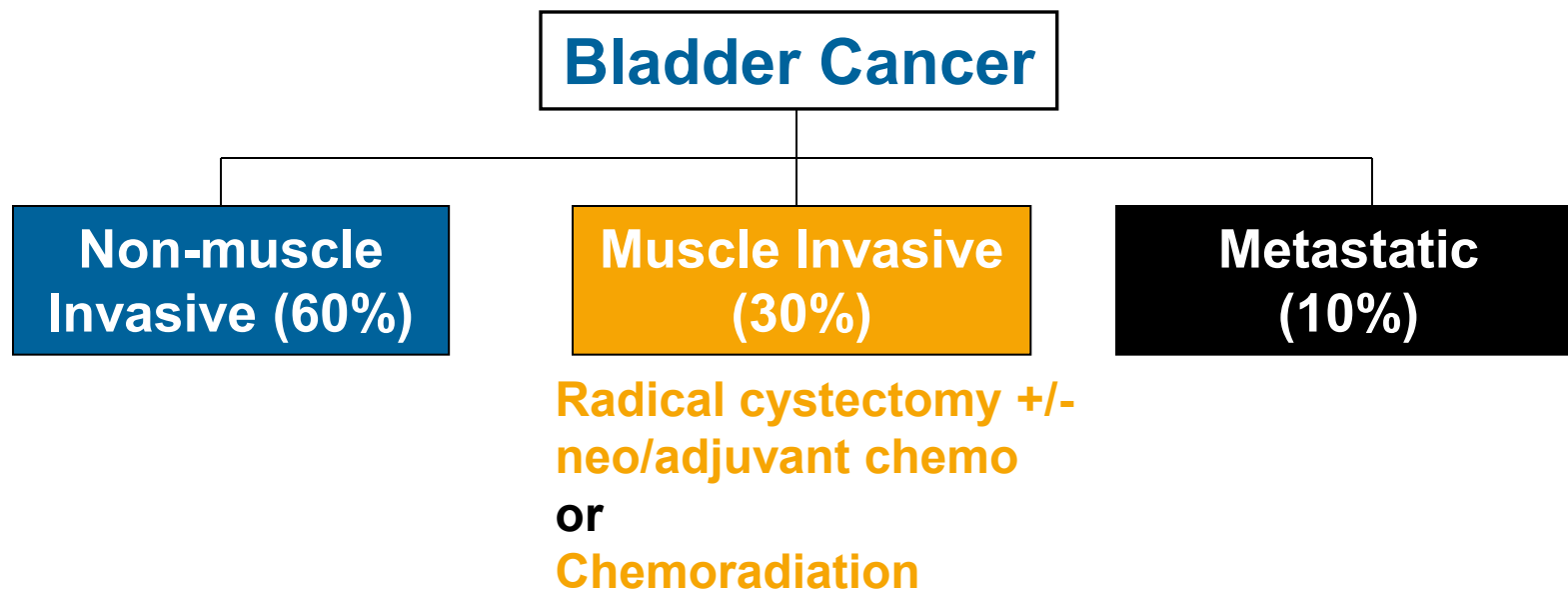
**Non-muscle
Invasive (60%)**

**Muscle Invasive
(30%)**

**Metastatic
(10%)**

**TURBT
and
Intravesical tx
if high grade**

- Risk of progression to muscle invasive
 - High grade, T1a - 48% rate of progression
 - Low grade Ta - 2% rate of progression
- Managed by cystoscopy and TURBT
 - Transurethral resection of bladder tumor
 - BCG instillations weekly x 6 then q3mos for “high risk” lesions
 - Improved disease-free survival compared with no tx
 - Decreases need for “salvage” cystectomy
 - No improvement in overall survival because often cured with cystectomy



- Organ confined (T2, ~35%): **5 yr OS: 74%**, median OS ~15 yrs
- Extravesicular (>T2): **5 yr OS: 37%**, median OS ~4.5 yrs
- Regional nodal disease: **5 yr OS: 31%**, median: OS ~2 yrs

Bladder Cancer

**Non-muscle
Invasive (60%)**

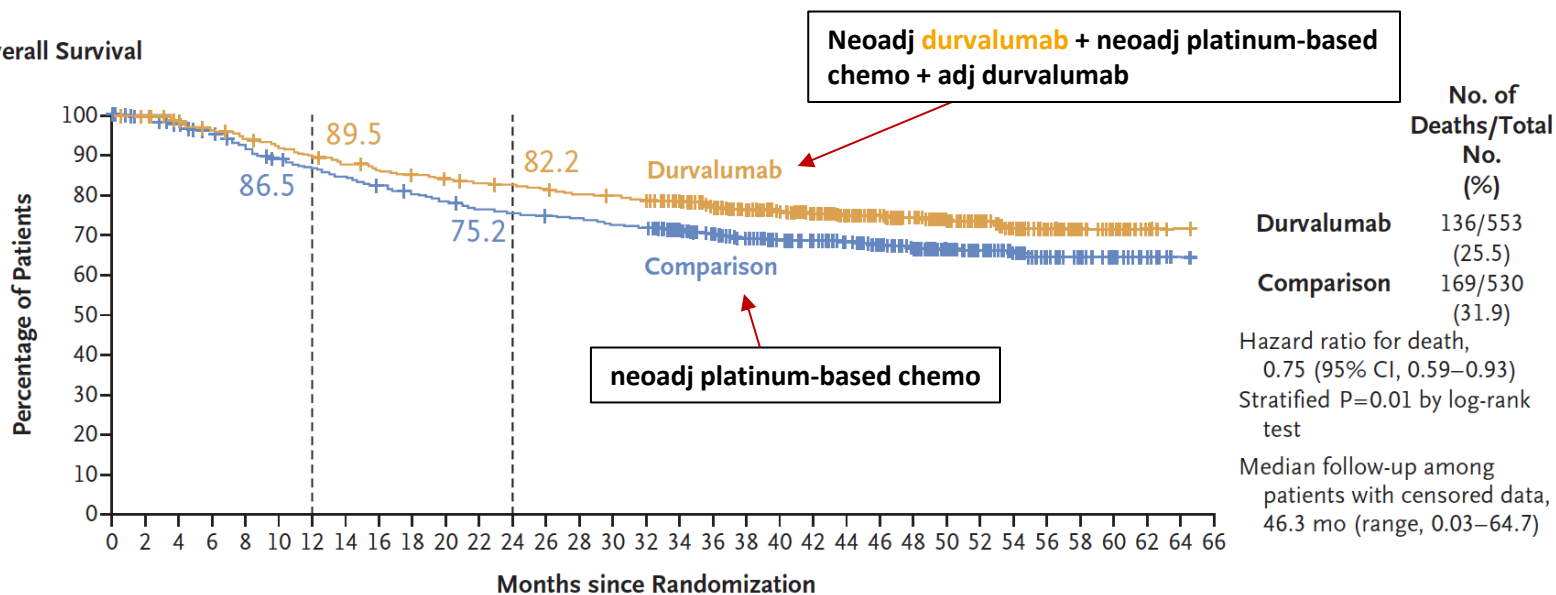
**Muscle Invasive
(30%)**

**Metastatic
(10%)**

**Radical cystectomy +/-
neo/adjuvant chemo**

Durvalumab: Anti-PD-L1 Monoclonal Antibody

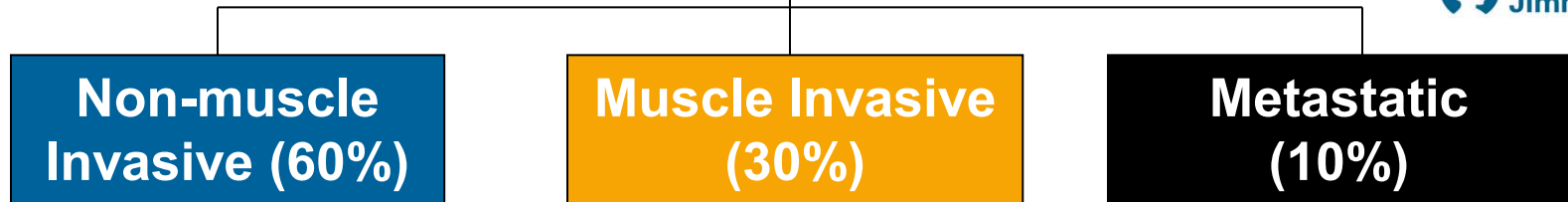
A Overall Survival



No. at Risk

Durvalumab	533	517	492	468	446	434	423	410	400	349	295	238	182	125	96	68	34	21	7	1	0
Comparison	530	507	467	438	413	392	378	368	358	311	259	215	174	113	90	60	38	21	10	2	0

Bladder Cancer



Chemoradiation as alternative to cystectomy

- Optimal candidates: **small solitary lesions** (<5cm), **T2 or T3** disease, no hydronephrosis, ability to perform a complete TURBT, and minimal to no carcinoma in situ
- Bladder preservation approach:
 - **Maximal TURBT** to remove all residual disease
 - **Radiation**: 64-65 Gy bladder, 44-45 Gy adj pelvic nodes
 - **Cisplatin** based therapy: weekly vs. every 3 wks
 - Cisplatin unfit: 5FU/Mitomycin, carbo/taxol
 - Repeat TURBT: if residual cancer → salvage cystectomy
- Outcomes
 - ~50% of patients long term control with intact bladder
 - 20-30% require salvage cystectomy

Bladder Cancer

**Non-muscle
Invasive (60%)**

**Muscle Invasive
(30%)**

**Metastatic
(10%)**

**Chemotherapy
and/or
Immunotherapy**

Current recommendation for 1st line therapy for eligible patients
Enfortumab + pembrolizumab

Anti-PD-1 Monoclonal Antibody

antibody targeting the cell adhesion molecule nectin-4 linked to a microtubule inhibitor conjugate

Other options:

Cisplatin eligible

- Nivolumab + cisplatin + gemcitabine
- Cisplatin-based combo tx + avelumab followed by maintenance avelumab

Cisplatin ineligible

- Carboplatin + gemcitabine followed by maintenance avelumab
- Pembrolizumab

Summary of Bladder Cancer

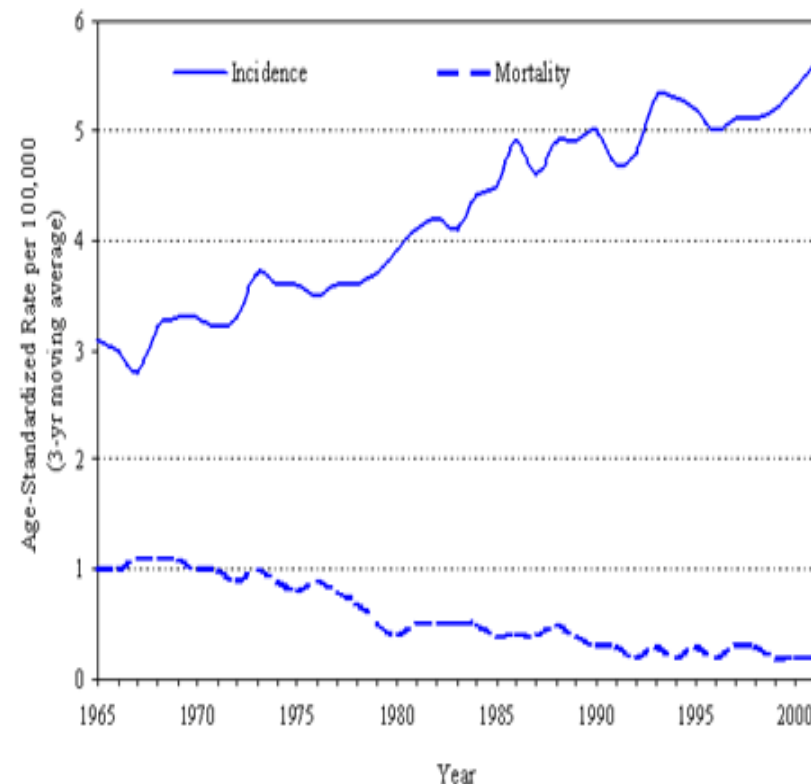
- **Multidisciplinary approach essential to cure/long term management**
- **For patients with muscle-invasive bladder cancer: survival benefit to neoadjuvant cisplatin-based chemotherapy + immunotherapy**
- **Metastases: can be highly sensitive to chemotherapy and immunotherapy**
Landscape of recommended therapies is changing
- **Cure/long term control possible in node positive (stage IV) disease**
- **Novel therapies imperative to improve outcomes: SUPPORT CLINICAL TRIALS**

Testicular Cancer (germ cell tumors)

Testicular cancer statistics

- most common solid malignancy affecting **males 15-35**
 - but only 1% of all solid tumors in men
- USA: ~ **9,000** new cases diagnosed
 - ~ 350 men will die per year
- Lifetime risk of
 - being diagnosed: 1 in 300
 - of dying of the disease: 1 in 5000
- 95% are **Seminoma or NSGCT**
- Children: NSGCT > Seminoma
- Adults: Seminoma > NSGCT
- Risk factors: Family hx, cryptorchidism, previous GCT

Trends in Testicular Cancer (ICD9 186) Incidence and Mortality Rates, Ontario, 1964-2001



Presentation and work-up

Most often - nodule or painless swelling of one testicle, noted incidentally

~30% of cases - dull ache or heavy sensation in the abdomen, perianal area, scrotum

~10% of cases - acute scrotal pain

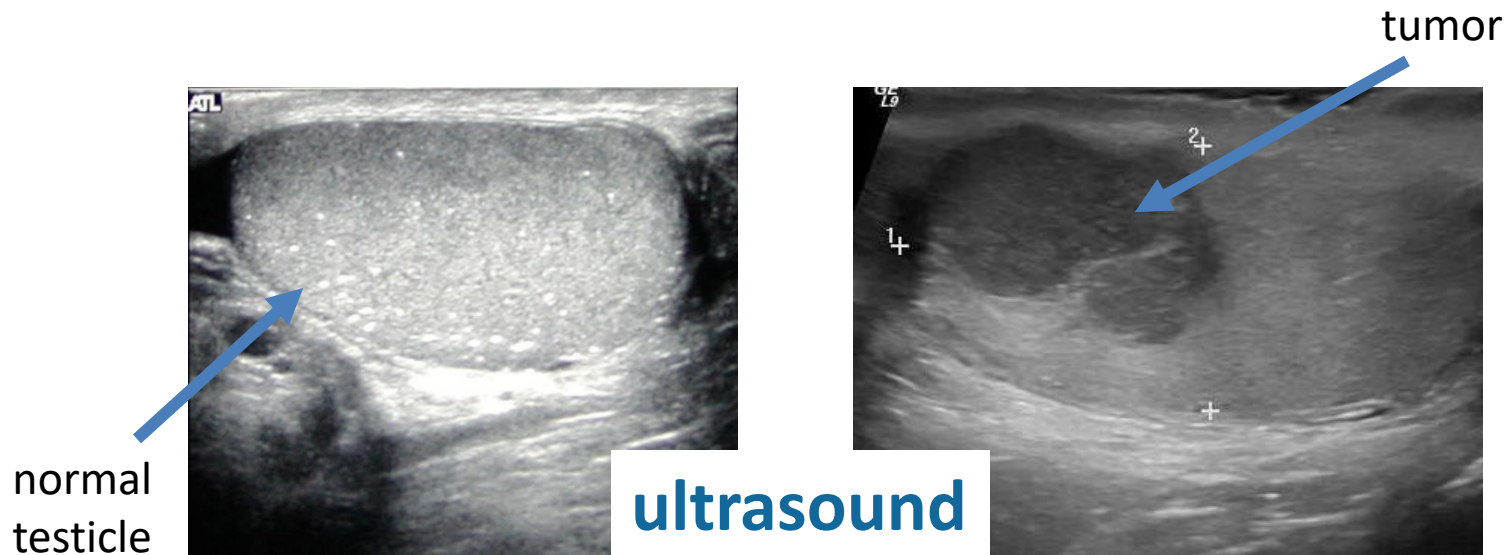
~10% of cases – symptoms related to metastatic disease

~5% of cases - gynecomastia.

If exam or symptoms concerning for testicular cancer, next step is **scrotal ultrasound**

Presentation and work-up

- Most often** - nodule or painless swelling of one testicle, noted incidentally
- ~30% of cases** - dull ache or heavy sensation in the abdomen, perianal area, scrotum
- ~10% of cases** - acute scrotal pain
- ~10% of cases** – symptoms related to metastatic disease
- ~5% of cases** - gynecomastia.



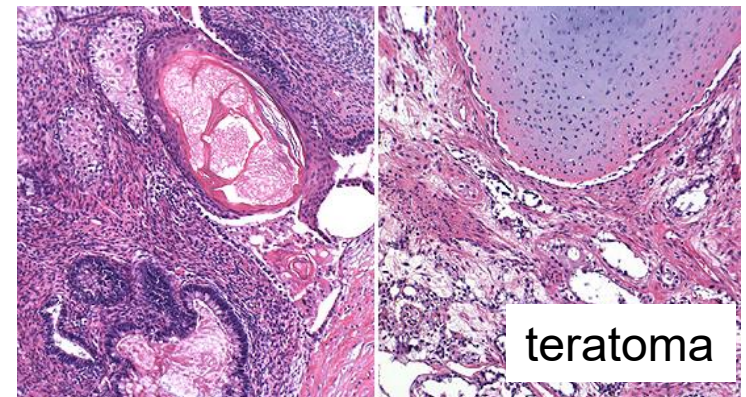
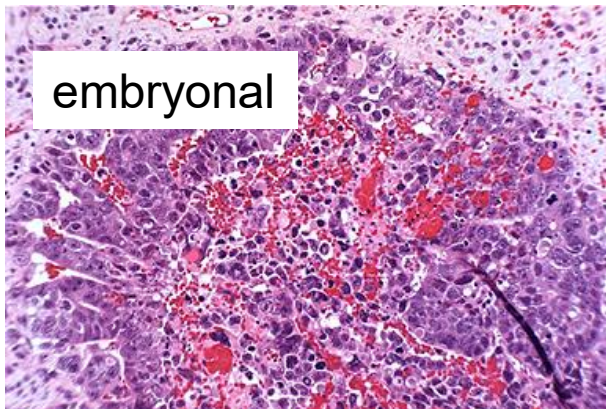
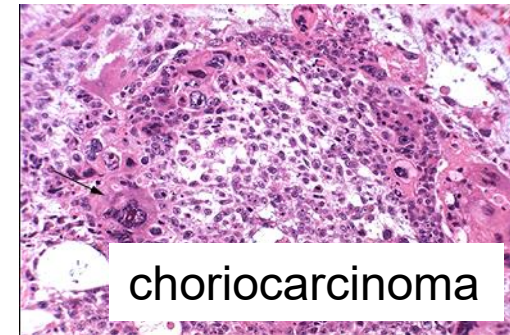
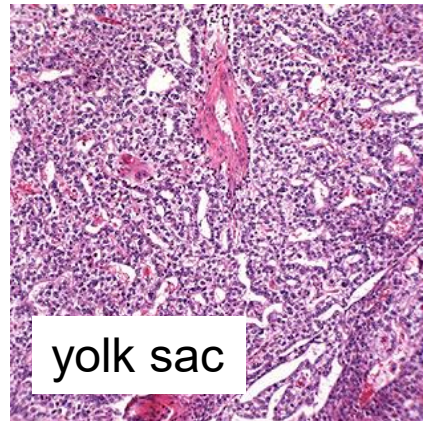
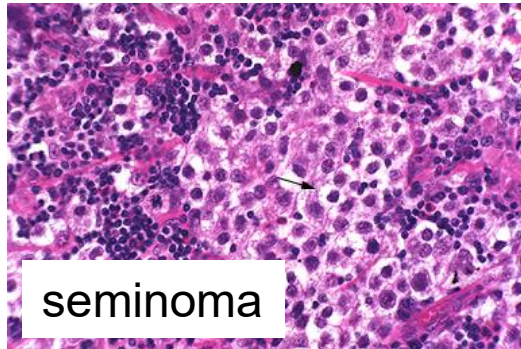
If ultrasound demonstrates testicular cancer, next steps are:
blood draw for tumor markers (**AFP, beta-HCG, LDH**)
followed by **orchiectomy**

Staging with CT scan

- **Lymphatic spread common to all GCTs**
 - Choriocarcinoma : vascular dissemination also common
- **Primary drainage of testis is to its embryological origin, the retroperitoneum; lungs are the second most common site**



Germ cell tumor histology

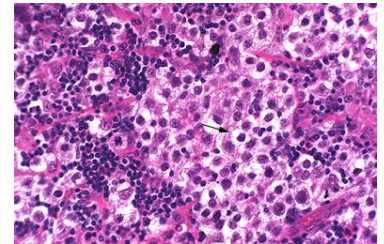


GCTs display patterns of differentiation that mimic stages normally undergone by the developing zygote

Broadly...

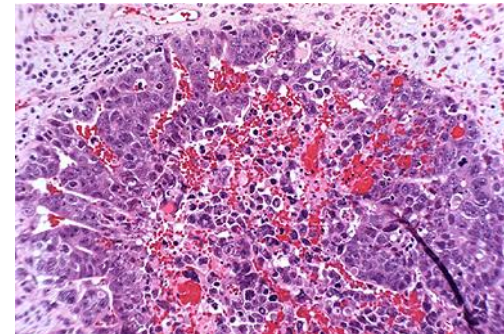
Seminoma

- **Presents as a single histology**
 - Can make bHCG and LDH (never AFP)
 - Radiosensitive
 - No teratoma, and surgery less of a role than in NSGCT

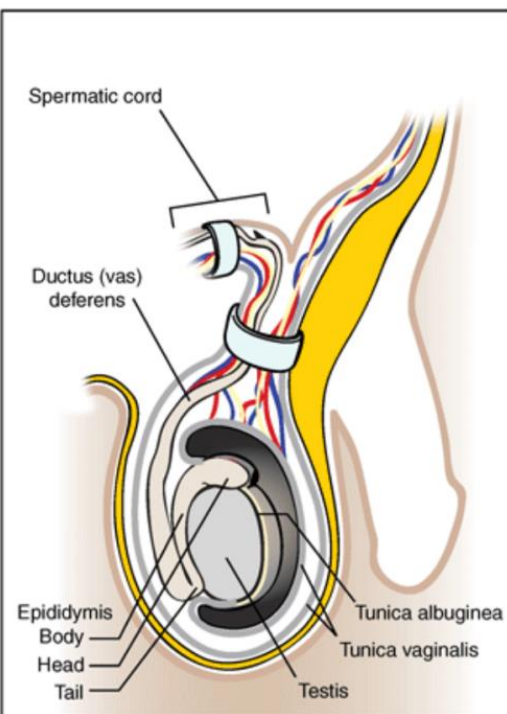


Non-seminoma

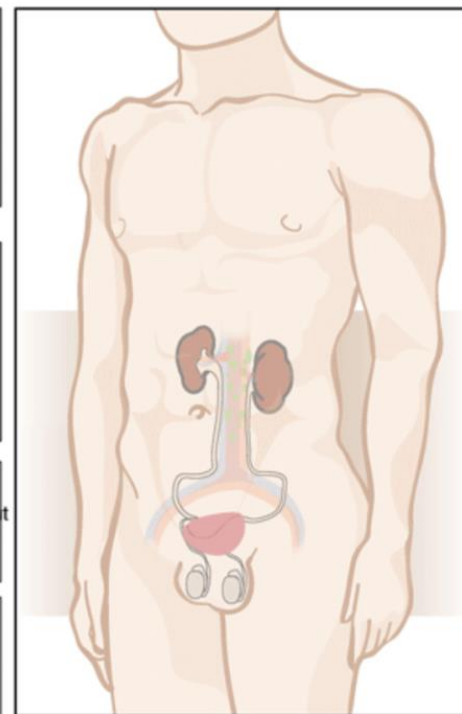
- **One or many histologies:** embryonal, seminoma, yolk sac, teratoma, choriocarcinoma
 - Makes AFP, LDH, and/or bHCG (or none)
- **Teratoma**
 - Chemoinsensitive – surgery often needed
 - Mature and immature
 - Can de-differentiate to sarcoma, carcinomas



Testicular cancer staging



Stage	Extent of Disease
pT1	Tumor limited to the testis and epididymis without vascular/lymphatic invasion; tumor may invade into the tunica albuginea but not the tunica vaginalis
pT2	Tumor limited to the testis and epididymis with vascular/lymphatic invasion; tumor extending through the tunica albuginea with involvement of the tunica vaginalis
pT3	Tumor invades the spermatic cord with or without vascular/lymphatic invasion
pT4	Tumor invades the scrotum with or without vascular/lymphatic invasion



Stage	Extent of Disease
IA	Testis only, no vascular/lymphatic invasion (T1)
IB	Testis only, with vascular/lymphatic invasion (T2), or extension through tunica albuginea (T2), or involvement of spermatic cord (T3) or scrotum (T4)
IIA	Retroperitoneal Nodes < 2 cm
IIB	Retroperitoneal Nodes 2-5 cm
IIC	Retroperitoneal Nodes > 5 cm
Distant Metastases	
III	Common sites include distant (or extra-abdominal) lymph nodes, lung, liver, bone, and brain

Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com
Copyright © The McGraw-Hill Companies, Inc. All rights reserved.

Stage I

CT unremarkable and tumor markers normalized

- Seminoma
 - Most (~75-85%) **cured** with radical orchiectomy
 - risk for recurrence: large tumor (>4 cm) and/or rete testis involvement
- Non-seminomatous GCT
 - Most (~60-80%) **cured** with radical orchiectomy
 - risk for recurrence: lymphovascular invasion and/or embryonal predominance

Stage I

CT unremarkable and tumor markers normalized

Seminoma

~75-85% cured by
orchiectomy alone

Options

- Active surveillance
- Adjuvant radiation therapy to retroperitoneum
- Adjuvant single dose carboplatin

Non-seminomatous GCT

~60-80% cured by orchiectomy alone

Options

- Active surveillance
- Adjuvant RPLND
- Adjuvant bleomycin, etoposide, cisplatin x1

RPLND = retroperitoneal lymph node dissection

Stage I

CT unremarkable and tumor markers normalized

Options

- Active surveillance
15-25% → need BEPx3 (or EPx4)
- Adjuvant radiation therapy to RP
8-10% → need BEPx3 (or EPx4)
- Adjuvant single dose carboplatin
5% → need BEPx3 (or EPx4)

Options

- Active surveillance
20-40% → need BEPx3 (or EPx4)
- Adjuvant RPLND
8-15% → need BEPx3 (or EPx4)
- Adjuvant bleomycin, etoposide, cisplatin X1
5% → need BEPx3 (or EPx4)

No matter what approach is taken, in the end, >97% of patients are cured even if BEP x3 is required in the setting of progression

RP = retroperitoneum

RPLND = retroperitoneal lymph node dissection

Advanced testicular cancer

pure seminoma

good prognosis

- any primary site
- no non-pulmonary visceral mets
- normal AFT, any beta-HCG or LDH

90% of all advanced seminomas

5-year Progression Free Survival 82%

5-year Overall Survival 86%

intermediate prognosis

- any primary site
- non-pulmonary visceral mets
- normal AFT, any beta-HCG or LDH

10% of all advanced seminomas

5-year Progression Free Survival 67%

5-year Overall Survival 72%

NSGCT

good prognosis

- testis or RP primary
- no non-pulmonary visceral mets
- AFP <1000, beta-HCG <5000 and LDH <1.5x

56% of all advanced non-seminomas

5-year Progression Free Survival 88%

5-year Overall Survival 92%

intermediate prognosis

- testis or RP primary
- no non-pulmonary visceral mets
- AFP 1-10K, beta-HCG 5-50K and LDH 1.5-10x

28% of all advanced non-seminomas

5-year Progression Free Survival 75%

5-year Overall Survival 80%

poor prognosis

any of the following

- mediastinal primary
- non-pulmonary visceral mets
- AFP >10K, beta-HCG >50K and LDH >10x

16% of all advanced non-seminomas

5-year Progression Free Survival 41%

5-year Overall Survival 48%

Testicular cancer treatment and risk of cardiovascular disease

990 men treated 1980-1994 and followed for twenty years (Norway) compared with age and gender-matched controls -Haughnes (2010)

Risk of Atherosclerosis

Treatment	Hazard Ratio	95% Confidence Interval
RT	2.3	1.04-5.3
Chemotherapy	2.6	1.1-5.9
Both	4.8	1.6-14.4
BEP	5.7	1.9-17.1

Testicular cancer treatment and risk of secondary cancers

Dutch Tumor Registry Data 2707 5-year survivors of GCTs

	HR	95% CI
Surgery only	1	
Subdiaphragmatic RT	2.6	1.7-4.0
Sub. and Mediastinal RT	3.6	2.1-6.0
Cisplatin-based Chemo	2.1	1.4-3.1
Smoking	1.8	1.4-2.4

Summary of Testicular Cancer

- Approach to testicular cancer is guided by disease histology, broadly dichotomized into seminoma and non-seminomatous germ cell tumors.
- An “active surveillance” approach is often recommended for stage I testicular cancers
- Risk category determines approach to advanced disease; risk categories are based on presence/absence of extra-pulmonary organ involvement and tumor marker levels.
- Post-chemotherapy surgery often indicated for residual disease to consolidate cure and remove any teratoma.

Review Question – GU Oncology

69 y o Hispanic, healthy man with no known family history of cancer has been undergoing PSA screening. His PSA two years ago was 2.4 mg/mL. This year it was 3.9. It was re-checked eight weeks later and was 4.1. Digital rectal exam was normal. He underwent prostate MRI that showed a 0.6 cm lesion at the right apex of the prostate (PI-RADS 3, indicating that presence of clinically significant cancer is equivocal). There were areas of BPH and there was no evidence of extra-prostatic disease. He was referred for prostate biopsy, which was remarkable for Gleason 3+3 adenocarcinoma of the prostate in 2 of 12 biopsy cores. Each positive core demonstrated 5-10% tumor involvement. The next best course of action is which of the following:

- A. Maintain routine screening, repeating PSA and MRI in one year
- B. Active surveillance - PSA every 3-6 months, with MRI and repeat biopsy in one year
- C. Neoadjuvant androgen deprivation therapy for three months followed by radical prostatectomy
- D. Neoadjuvant androgen deprivation therapy for six months, with external-beam radiation therapy to the prostate during the third and fourth months of medical treatment.
- E. Androgen deprivation therapy + docetaxel chemotherapy x6 cycles.

Review Question – GU Oncology

69 y o Hispanic, healthy man with no known family history of cancer has been undergoing PSA screening. His PSA two years ago was 2.4 mg/mL. This year it was 3.9. It was re-checked eight weeks later and was 4.1. Digital rectal exam was normal. He underwent prostate MRI that showed a 0.6 cm lesion at the right apex of the prostate (PI-RADS 3, indicating that presence of clinically significant cancer is equivocal). There were areas of BPH and there was no evidence of extra-prostatic disease. He was referred for prostate biopsy, which was remarkable for Gleason 3+3 adenocarcinoma of the prostate in 2 of 12 biopsy cores. Each positive core demonstrated 5-10% tumor involvement. The next best course of action is which of the following:

- A. Maintain routine screening, repeating PSA and MRI in one year
- B. Active surveillance - PSA every 3-6 months, with MRI and repeat biopsy in one year
- C. Neoadjuvant androgen deprivation therapy for three months followed by radical prostatectomy
- D. Neoadjuvant androgen deprivation therapy for six months, with external-beam radiation therapy to the prostate during the third and fourth months of medical treatment.
- E. Androgen deprivation therapy + docetaxel chemotherapy x6 cycles.

ANSWER

B. Active surveillance - PSA every 3-6 months, with MRI and repeat biopsy in one year

The patient has low-grade, low-volume prostate cancer. Risk of prostate cancer-specific mortality is remarkably low. Rate of prostate cancer mortality is 0.1% at 15 years among men undergoing active surveillance. Curative treatments may be associated with significant long-term side effects. These include erectile dysfunction and urinary incontinence. Complications from treatment may outweigh the medical and psychological benefits of cure. Nonetheless, curative treatment with surgery, radiation therapy or focal treatments such as high frequency ultrasound are reasonable. In setting of low-grade, low-volume prostate cancer, systemic treatments are not indicated.

Review

Question 2

- Which pairing of treatment and clinical scenario is incorrect?
 - A. Prostatectomy for 57 yo with T1c (no nodule on DRE), Gleason score 7 disease in 4 of 6 cores and PSA 5
 - B. Active surveillance for 73 yo with Gleason score 6 in 5% of 1 core out of 12 cores and PSA 4.5, T1c (no nodule on DRE)
 - C. 2-3 years of androgen suppression and radiation for 65 yo with 6 of 12 cores with Gleason score 8 and T2b (nodule on DRE)
 - D. Radiation alone for 60 yo with Gleason score 4+3 =7 disease in 8 of 12 cores, PSA 8, and T2a (small nodule) disease

Board Review

Question 2

- Which pairing of treatment and clinical scenario is incorrect?
 - A. Prostatectomy for 57 yo with T1c (no nodule on DRE), Gleason score 7 disease in 4 of 6 cores and PSA 5
 - B. Active surveillance for 73 yo with Gleason score 6 in 5% of 1 core out of 12 cores and PSA 4.5, T1c (no nodule on DRE)
 - C. 2-3 years of androgen suppression and radiation for 65 yo with 6 of 12 cores with Gleason score 8 and T2b (nodule on DRE)
 - D. Radiation alone for 60 yo with Gleason score 4+3 =7 disease in 8 of 12 cores, PSA 8, and T2a (small nodule) disease

Radiation plus short-term testosterone suppression alone for intermediate risk prostate cancer results in superior prostate cancer specific and superior overall survival compared to radiation alone.

Board Review

Question 3

Which pairing of treatment and clinical scenario is incorrect?

- A. Neoadjuvant cisplatin combination therapy + duvalumab followed by cystectomy then adjuvant durvalumab for muscle invasive urothelial bladder cancer in a “fit” 60 yo
- B. Transurethral resection of bladder tumor (TURBT) alone for grade 1, Ta solitary urothelial cancer
- C. Concurrent chemotherapy with radiation for multifocal high grade T1 (lamina propria invasion but not muscle) urothelial cancer
- D. Chemotherapy plus XRT for 78 yo female with muscle invasion and not “fit” for cystectomy

Board Review

Question 3

Which pairing of treatment and clinical scenario is incorrect?

- A. Neoadjuvant cisplatin combination therapy followed by cystectomy for muscle invasive urothelial bladder cancer in a “fit” 60 yo
- B. Transurethral resection of bladder tumor (TURBT) alone for grade 1 Ta solitary urothelial cancer
- C. Concurrent chemotherapy with radiation for unifocal high grade T1 (lamina propria invasion but not muscle) urothelial cancer
- D. Chemotherapy plus XRT for 78 yo female with muscle invasion and not “fit” for cystectomy

TURBT with intravesical therapy (most commonly BCG to decrease risk of recurrence) is appropriate management for non-muscle cancers at high risk for recurrence. Radiation is not appropriate for T1 (superficial) disease outside of a clinical trial.

Selected References

- Bill-Axelson A, Holmberg L, Ruutu M et al. Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med 2011.
- Bolla M, de Reijke TM, Van Tienhoven G, et al. Duration of androgen suppression in the treatment of prostate cancer. N Engl J Med 2009.
- Hamdy FC, Donovan JL, Lane LA et al. 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. N Engl J Med 2016
- Hussain M, Tangen CM, Berry DL, et al. Intermittent versus continuous androgen deprivation in prostate cancer. N Engl J Med. 2013.
- Powles T, Catto JWF, Galsky MD, et al. Perioperative Durvalumab with Neoadjuvant Chemotherapy in Operable Bladder Cancer. N Engl J Med. 2024.
- Powles T, Valderrama BP, Gupta S, et al. Enfortumab Vedotin and Pembrolizumab in Untreated Advanced Urothelial Cancer. N Engl J Med. 2024.
- Chovanec et al, Management of stage I testicular germ cell tumours. Nat Rev Urol. 2016 Nov;13(11):663-673.
- Litchfield et al, The genomic landscape of testicular germ cell tumours: from susceptibility to treatment. Nat Rev Urol. 2016 Jul;13(7):409-19.
- Nichols et al, Active surveillance is the preferred approach to clinical stage I testicular cancer. J Clin Oncol. 2013 Oct 1;31(28):3490-3.