



# Prostate Cancer Management: Where Do We Stand in 2022

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**MedNet21**  
Center for Continuing Medical Education

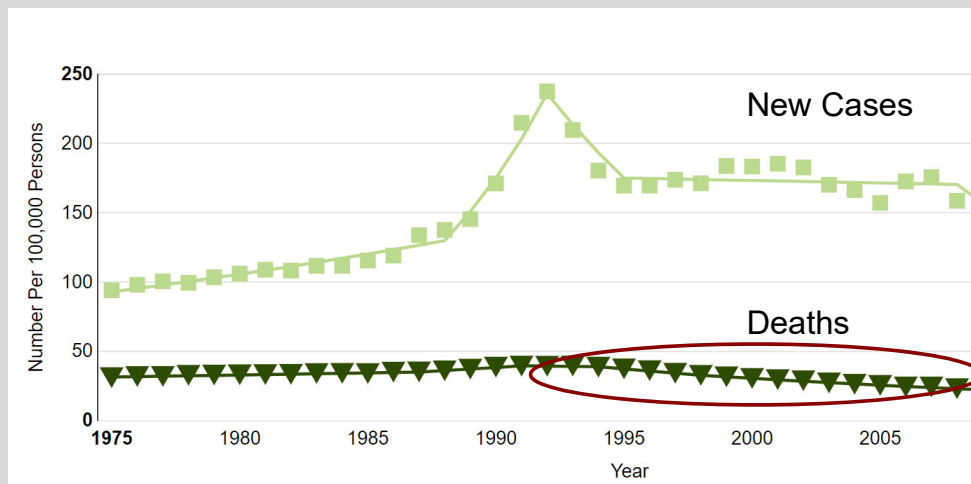
**THE OHIO STATE UNIVERSITY**  
WEXNER MEDICAL CENTER

## Yearly male cancer deaths (2019)

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%
<b>All Sites</b>	<b>321,670</b>	<b>100%</b>

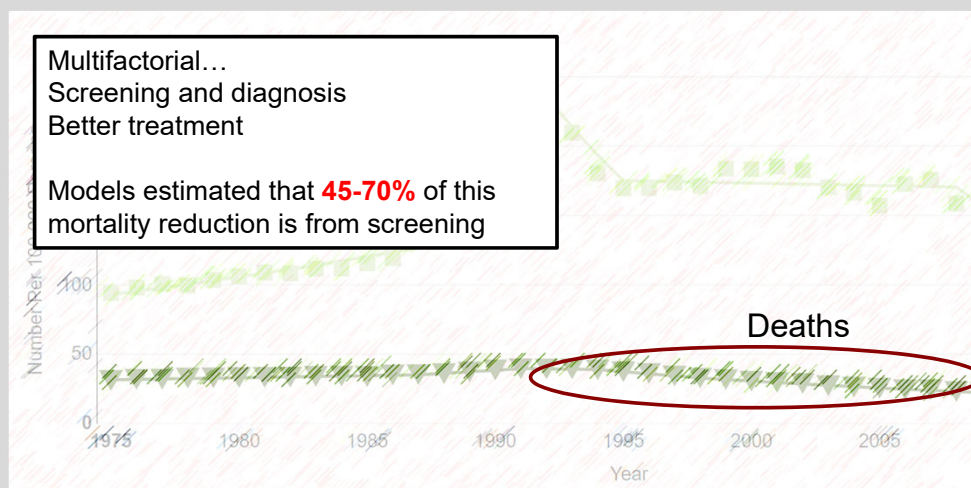
American Cancer Society Statistics, CA Cancer J Clin 2019, non-melanoma skin not included

## Prostate cancer mortality has halved



SEER Registry Public Data

## Prostate cancer mortality has halved



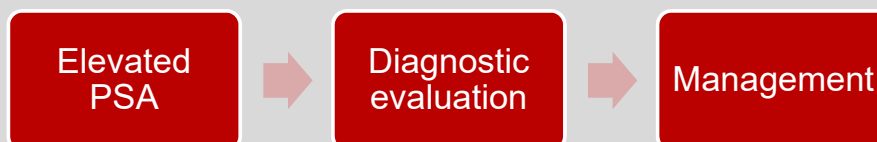
Cancer Causes Control. 2008 Mar;19(2):175-81. Epub 2007 Nov 20.

## Latest PSA screening recommendations

Society	Shared decision making for men
USPSTF	55-69
AUA	55-69
NCCN	45-75
ACS	Starting 40-50 based on risk
ACP	50-69
AAFP	55-69

Society Websites

## Next steps...



## Diagnostic evaluation

- History and physical examination
  - including digital rectal exam
- Ensure PSA is truly elevated
  - False positive causes are common (e.g. UTI)
  - Single marginally elevated PSA may normalize in 40%
  - Consider patient factors in deciding in threshold for workup

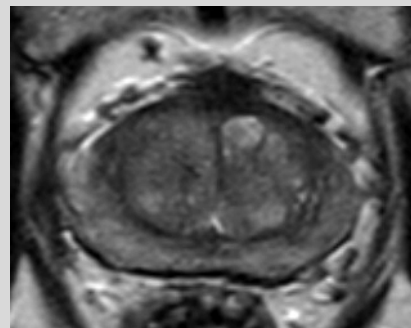
Eastham, JAMA, 2003

## Diagnostic evaluation – risk stratification

- MRI more frequently done before biopsy
  - MRI may reduce number of biopsies by 1/3

Normal MRI → low chance of clinically significant prostate cancer

- 63 yo WM, no family history
- PSA 5 and normal rectal exam
- Likely <10% risk of clinically significant prostate cancer with normal MRI, decision made to forego biopsy

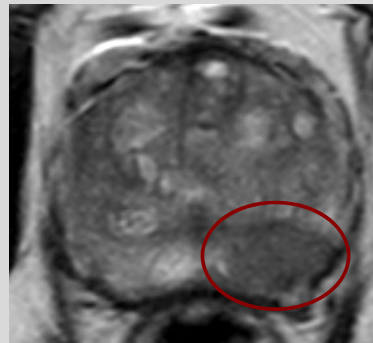


PRECISION, NEJM, 2018. STHLM3, NEJM, 2021.

## Diagnostic evaluation – risk stratification

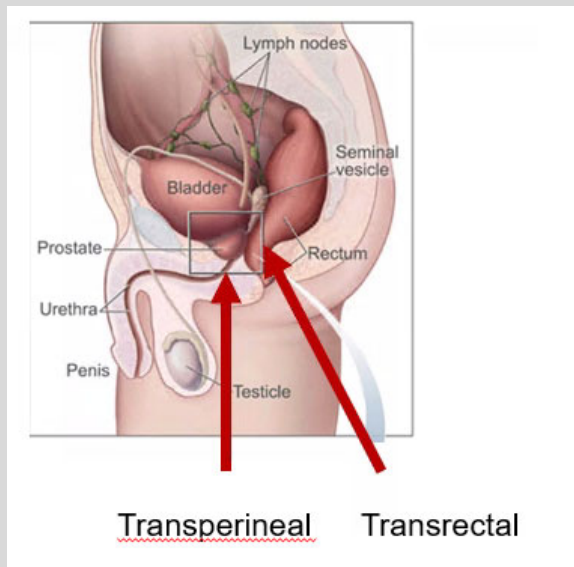
- An abnormal MRI lesion can be targeted during biopsy, clinically significant prostate cancer diagnosis (12-22%)

- 73 yo WM, no family history
- PSA 10 slightly abnormal rectal exam
- Cardiac history on warfarin
- Gleason 8 prostate cancer on MR fusion biopsy



PRECISION, NEJM, 2018. STHLM3, NEJM, 2021.

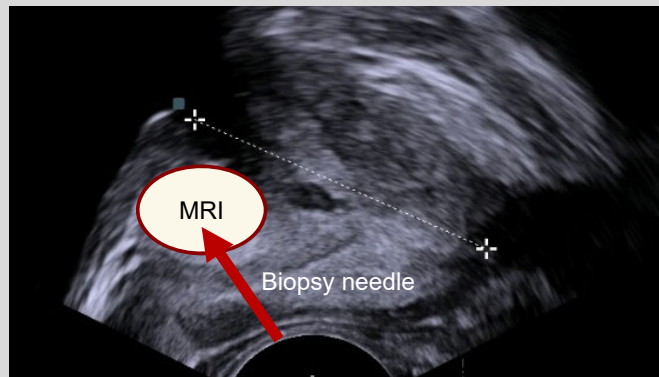
## Diagnostic evaluation – biopsy



Prostate biopsy can be done from the rectum or the perineum

National shift towards transperineal due to a much lower infection rate (<<1%)

## Diagnostic evaluation – biopsy



Biopsy probe

Around 12 cores are taken, plus any MRI areas

## Biopsy report

- Overall Gleason score is the highest
- Generally the only important “take-away”

### Pathologic Diagnosis

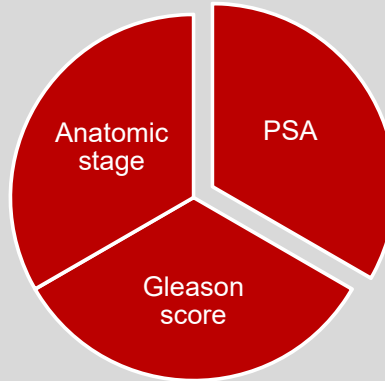
- A. Prostate, left base, needle biopsy:
  - Prostate tissue with no significant pathologic change
- B. Prostate, left mid, needle biopsy:
  - Prostate tissue with no significant pathologic change
- C. Prostate, left apex, needle biopsy:
  - Prostate tissue with no significant pathologic change
- D. Prostate, left lateral base, needle biopsy:
  - Prostate tissue with chronic inflammation
- E. Prostate, left lateral mid, needle biopsy:
  - Prostate tissue with no significant pathologic change
- F. Prostate, left lateral apex, needle biopsy:
  - Prostate tissue with chronic inflammation
- G. Prostate, right base, needle biopsy:
  - Prostate tissue with no significant pathologic change
- H. Prostate, right mid, needle biopsy:
  - Prostatic adenocarcinoma, Gleason score 3+5=8, involving 1 of 1 core and 20% of the tissue
- I. Prostate, right apex, needle biopsy:
  - Prostate tissue with no significant pathologic change
- J. Prostate, right lateral base, needle biopsy:
  - Prostatic adenocarcinoma, Gleason score 4+5=9, involving 1 of 1 core and 80% of the tissue
- K. Prostate, right lateral mid, needle biopsy:
  - Prostatic adenocarcinoma, Gleason score 4+5=9, involving 1 of 1 core and 60% of the tissue
- L. Prostate, right lateral apex, needle biopsy:
  - Prostatic adenocarcinoma, Gleason score 4+5=9, involving 1 of 1 core and 80% of the tissue
- M. Prostate, ROI 1, needle biopsy:
  - Prostatic adenocarcinoma, Gleason score 4+5=9, involving 4 of 5 cores and 85% of the tissue
- N. Prostate, right transition, needle biopsy:
  - Prostate tissue with no significant pathologic change
- O. Prostate, left transition, needle biopsy:
  - Prostate tissue with no significant pathologic change

Comment: PSA 11 ng/mL on 10/15/2021 per the electronic medical record.

## Localized PCa risk stratification

Within prostate  
(low or  
intermediate)

Extraprostatic  
extension (high)



<10 low  
10-20 (intermediate)  
>20 (high)

Gleason score	Risk
6	Low
7	Intermediate
8-10	High

## Staging

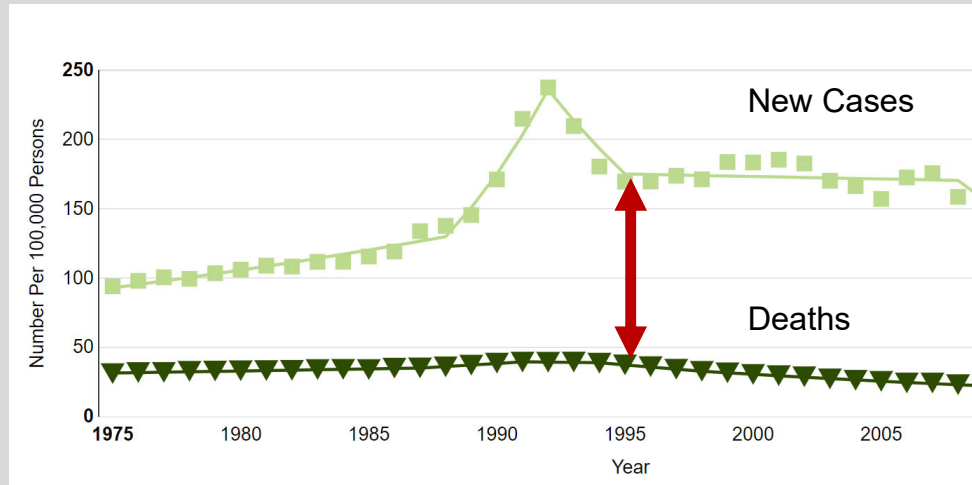
Most patients are assumed to be localized staging is only for high risk (select intermediate risk)

Conventionally CT scan and bone scan

Within the next few years MRI and PSMA-PET CT will be standard

## Expectant management

- Generally the first question in a new diagnosis of prostate cancer



SEER Registry Public Data

## Low risk focused studies have not found a survival benefit for treatment

### PROTECT

- 1643 men, 17 PCa deaths at 10 years
- >70% Gleason 6
- Randomized to active monitoring, radiation, or surgery
- No difference in 10 year survival but a reduction in metastases noted with surgery and radiation

### PIVOT

- 731 men, 69 PCa deaths at 19.5 years
- >70% Gleason 6
- Randomized to surgery or watchful waiting
- No difference in mortality with surgery

PROTECT (UK, Hamdy et al NEJM 2016) PIVOT (US, Wilt et al NEJM 2017)



## Expectant management

	Active surveillance	Watchful waiting
Goal	Detect progression and treat cancer before metastasis	Await symptoms and palliate symptoms
Patient population	<b>Essentially all low-risk (e.g. Gleason 6) patients</b> regardless of age, family history Some Gleason 7 patients	More limited life expectancy (e.g. <10 years) particularly with more favorable cancers
Protocol	Routine PSA, MRI, biopsies to detect progression	Infrequent clinical assessment and testing

## Treating the right patients is beneficial

### SPCG-4 study

- 695 men in Sweden in a pre-PSA era
- 69% Gleason 7 or higher
- Randomized to prostatectomy vs. watchful waiting
- Reported when 80% had died with 29 year follow-up

Bill-Axelsson et al NEJM 2018

## Treating the right patients is beneficial

SPCG-4 study

**2.9 years** mean life expectancy increase with surgery

Number needed to treat of **8.4**

**6.6 if <65**

12% absolute risk reduction in all cause and prostate cancer specific mortality

17% absolute risk reduction in metastatic disease

Bill-Axelsson et al NEJM 2018

## Treating the right patients is beneficial

Prior low-risk focused studies demonstrated a signal to benefit in certain patients

- Distant metastasis reduction in PROTECT at 10 years
- Certain subgroups of PIVOT were positive

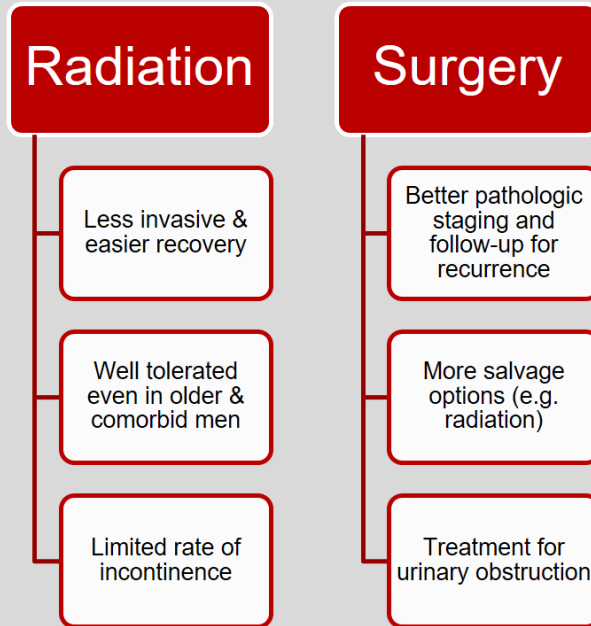
Studies of radiation have demonstrated a survival benefit

- Addition of radiation to ADT alone (SPCG-4)

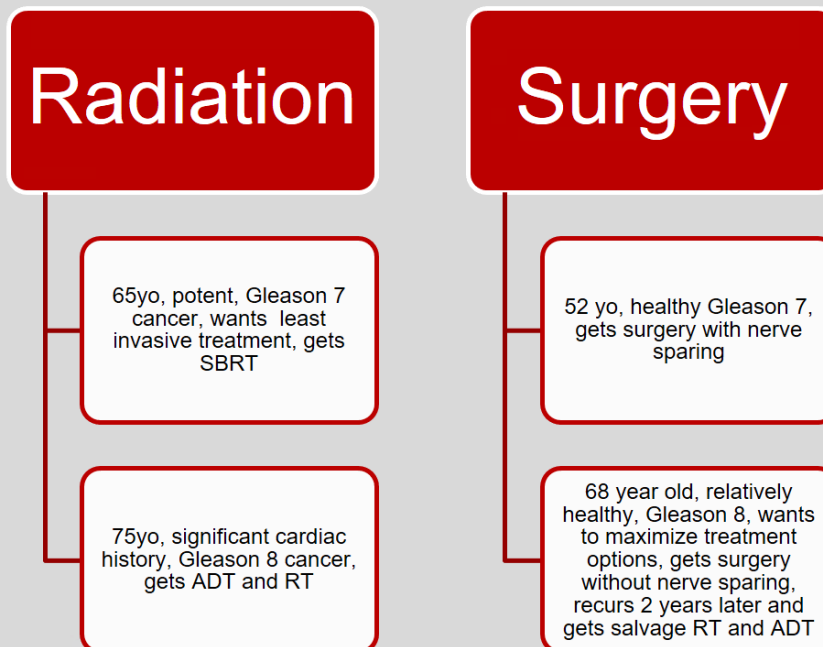
Studies of systemic therapy demonstrate clear survival benefit

SPCG-4, SPCG-7, PROTECT, PIVOT

## Patients with localized disease can generally select...



## Patients with localized disease can generally select...



## In my experience...after select decision making patients select...



40s & 50s

Surgery

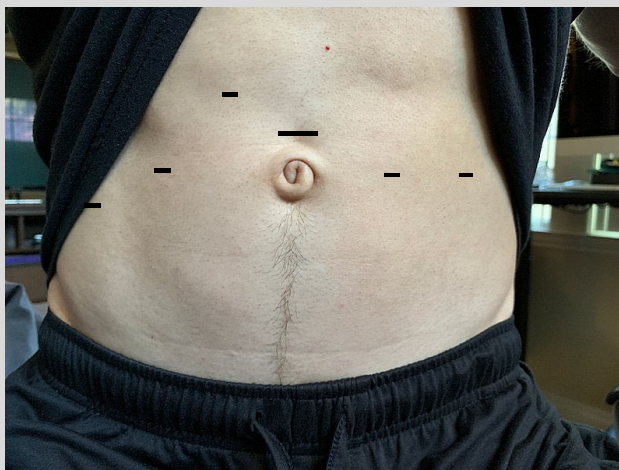
60s

Side-effects  
dictate  
decision

70s &  
beyond

Radiation

## Surgery – robot assisted radical prostatectomy

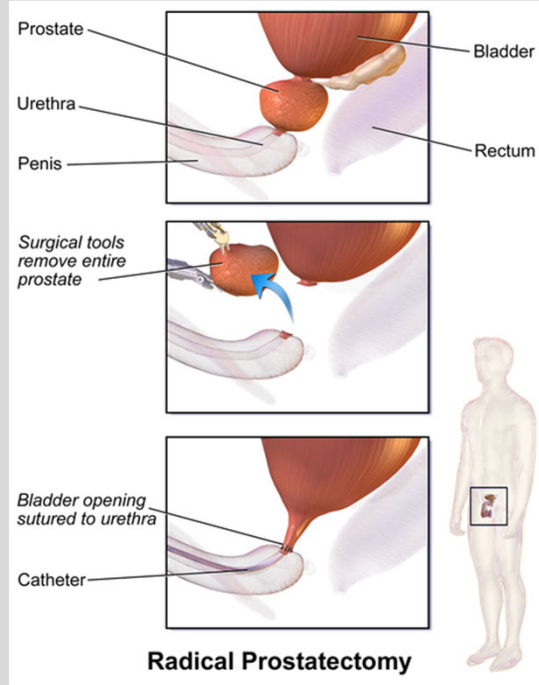


5 incisions 5-12mm  
Extraction 3-4 cm

New SP robot  
1 incision

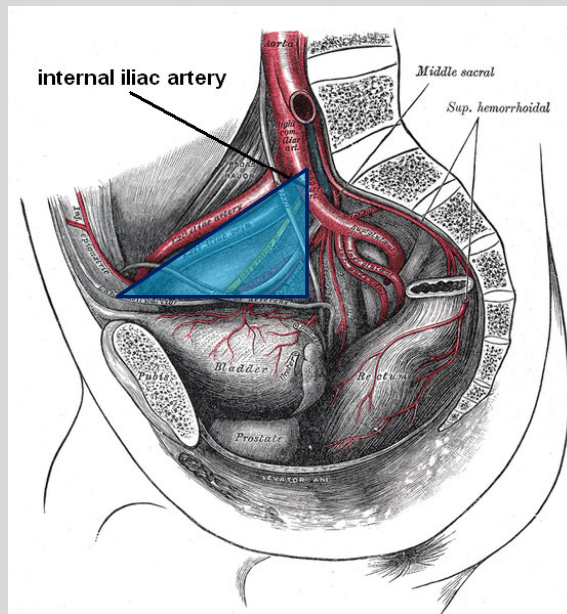
Author: SwirlyDude (CC BY-SA 4.0)

# Prostatectomy



Wikicommons Free image for public use

# Lymphadenectomy



Wikicommons Free image for public use

## Perioperative course

- 2-4 hour operation, 0-1 night in hospital
- Catheter for around 7 days
- Recovery 4-6 weeks

## Perioperative complications

- Medical complications
- Lymphocele requiring drainage <5%
- Urine leak (prolonged catheter and / or drain) <5%
- Rectal or ureteral injury <<1%

## Postoperative function

- Stress urinary incontinence
  - Due to loss of sphincteric function
  - Essentially all men after surgery
  - Resolves in 90% by 1 year
  - Multiple options to help with non-resolving incontinence
- Erectile dysfunction
  - Due to neurovascular compromise
  - Essentially all men after surgery
  - May resolve, dependent upon many factors
  - Effectively treated with ICI (intracavernosal injection)

## Cancer surveillance

- Follow-up PSA testing should reveal undetectable or stable very low PSA (<0.1 or so)
- Recurrence is highly dependent on pathology, but even those with adverse pathology may not recur
- Rising PSA generally indicates recurrence, particularly with rise above 0.1-0.2
- Still potentially curable with salvage treatment
- Even if not cured, salvage treatment, metastases, symptoms, and death are delayed
  - Goal: convert to a chronic disease



# Prostate Cancer

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*The Ohio State University Wexner Medical Center*

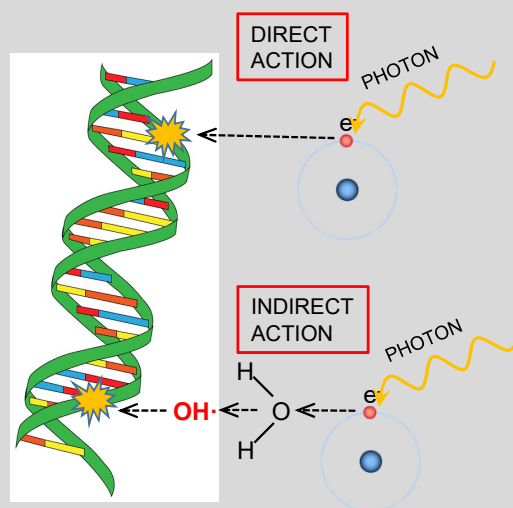
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## How does radiation work?



**X-rays interact with water**

↓  
**radiolysis**

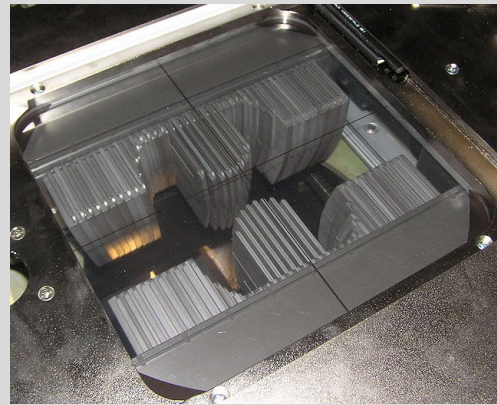
↓  
**free radicals**

↓  
**bind to and damage DNA**

↓  
**cell death**  
(by mitotic catastrophe)

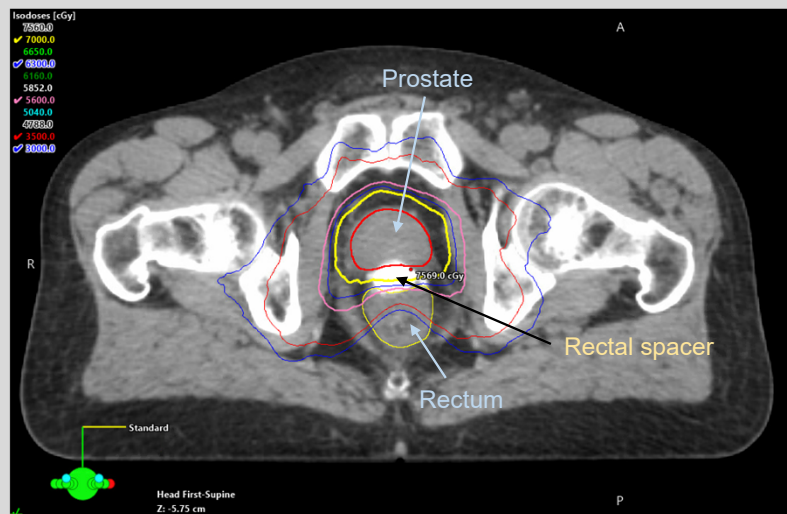


# External beam radiotherapy

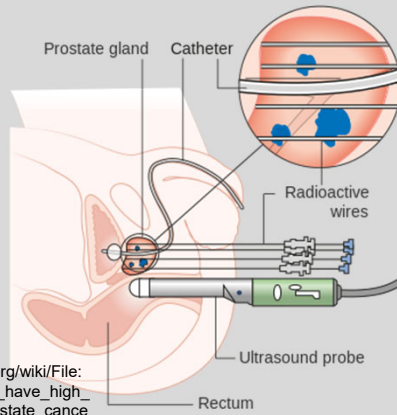


# External beam radiotherapy

## *Volumetric modulated arc therapy (VMAT)*



# Brachytherapy



[https://commons.wikimedia.org/wiki/File:Diagram\\_showing\\_how\\_you\\_have\\_high\\_dose\\_brachytherapy\\_for\\_prostate\\_cancer\\_CRUK\\_419.svg](https://commons.wikimedia.org/wiki/File:Diagram_showing_how_you_have_high_dose_brachytherapy_for_prostate_cancer_CRUK_419.svg)

High-dose rate



<https://www.flickr.com/photos/nrcgov/7845754328>

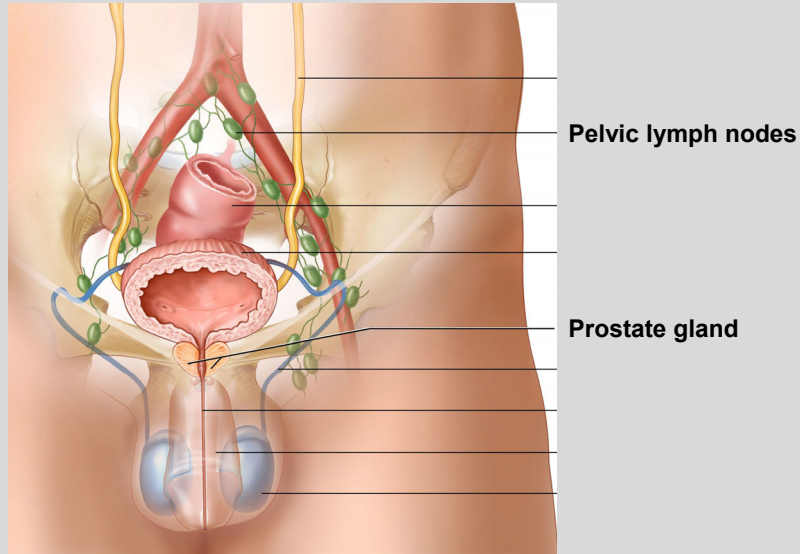


Low-dose rate

## Definitive radiotherapy

Salvage radiotherapy

# Radiation target for prostate cancer

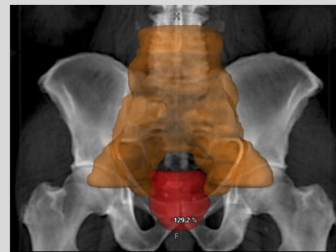


Source: cancer.gov

# Radiation target for prostate cancer



Prostate only



Prostate + pelvis

## Nomogram prediction

- Memorial Sloan Kettering Pre-Radical Prostatectomy nomogram
  - Age
  - Pretreatment PSA
  - Gleason score
  - Clinical tumor stage
  - Number of biopsy cores involved

## Nomogram prediction

- Memorial Sloan Kettering Pre-Radical Prostatectomy nomogram
- Provides extent-of-disease probability
  - Extracapsular extension
  - Seminal vesicle invasion
  - Lymph node involvement

## Definitive RT dose-fractionation

- Gray (Gy) is the unit of radiation dose
- Conventional fractionation (CFRT)
  - 74-81 Gy in 1.8-2 Gy/fx (8-9 weeks)
- Hypofractionation (HFRT)
  - 60-70 Gy in 2.5-3 Gy/fx (4-5.5 weeks)
- Ultra-hypofractionation (SBRT)
  - 36.25-40 Gy in 7.25-8 Gy/fx (1-2 weeks)

## Definitive RT dose-fractionation

	N	Arms	Patients	Outcome
CHHiP	3216	74 Gy (2 Gy/fx) vs. 60 Gy (3 Gy/fx)	• Low to high risk	• 5-yr BCFF 88.3% v 90.6% • 60 Gy non-inf to 74 Gy
PROFIT	608	78 Gy (2 Gy/fx) vs. 60 Gy (3 Gy/fx)	• Int risk	• 5-yr BCFF 85% in both arms • 60 Gy non-inf to 78 Gy
RTOG 0415	1115	73.8 Gy (1.8 Gy/fx) vs. 70 Gy (2.5 Gy/fx)	• Low risk	• 5-year DFS 85.3% v 86.3% • 70 Gy non-inf to 73.8 Gy
HYPO-RT-PC	1200	78 Gy (2 Gy/fx) vs. 42.7 Gy (6.1 Gy/fx) [3 fx/week]	• Int to high risk	• 5-yr FFS 84% v 84% • 42.7 Gy non-inf to 78 Gy

## Androgen deprivation therapy (ADT)

- Gonadotropin-releasing hormone (GnRH) agonists
  - Leuprolide, goserelin, triptorelin, histrelin
- GnRH antagonists
  - Degarelix, relugolix (oral)
- Androgen receptor blockers
  - Bicalutamide, enzalutamide, apalutamide, darolutamide
- ❖ “Standard” ADT
  - GnRH (ant-)agonist ± bicalutamide

## Prostate radiation indications

- Low risk
- Intermediate risk
  - Favorable intermediate risk
  - Unfavorable intermediate risk
- High / very-high risk
- Node-positive
- Oligometastatic

## Low-risk prostate cancer

- Treat prostate alone
  - External beam radiotherapy
    - CFRT
    - HFRT
    - SBRT
  - Brachytherapy alone
    - Low-dose rate
    - High-dose rate

## Intermediate-risk prostate cancer

- Heterogeneous cohort
- Stratified as favorable vs. unfavorable
- Unfavorable disease
  - Primary Gleason pattern 4
  - $\geq 50\%$  positive biopsy cores
  - $\geq 2$  intermediate-risk factors

## Favorable intermediate risk

❖ *Essentially treat like low-risk!*

➤ Treat prostate alone

❑ External beam radiotherapy

- CFRT
- HFRT
- SBRT

❑ Brachytherapy alone

- Low-dose rate
- High-dose rate

## Unfavorable intermediate risk

➤ Treat prostate + consider pelvic nodal RT

❑ External beam radiotherapy + ADT 4-6 mo

- CFRT
- HFRT
- SBRT (if treat prostate alone)

❑ Consider brachytherapy boost

- Low-dose rate
- High-dose rate



## Androgen deprivation therapy (ADT) for intermediate risk

	N	Arms	Patients	Outcome
<b>RTOG 9408</b>	1979	RT + ADT x 4 mo vs. RT alone	<ul style="list-style-type: none"> <li>Low/int risk 89%</li> <li>High risk 11%</li> </ul>	<ul style="list-style-type: none"> <li>Improved OS at 10 yr: 62% v 57% (p=0.03)</li> </ul>
<b>DFCI 95-096</b>	206	RT + ADT x 6 mo vs. RT alone	<ul style="list-style-type: none"> <li>Int/high risk</li> </ul>	<ul style="list-style-type: none"> <li>Improved OS at 8 yr: 74% v 61% (p=0.01)</li> </ul>
<b>EORTC 22991</b>	819	RT + ADT x 6 mo vs. RT alone	<ul style="list-style-type: none"> <li>Int risk 75%</li> <li>High risk 25%</li> </ul>	<ul style="list-style-type: none"> <li>5-yr biochem DFS: 82.6% v 69.8% (p&lt;.001)</li> <li>5-yr clinical DFS: 88.7% v 80.8% (p=.001)</li> </ul>
<b>GETUG-14</b>	377	RT + ADT x 4 mo vs. RT alone	<ul style="list-style-type: none"> <li>Int risk 100%</li> </ul>	<ul style="list-style-type: none"> <li>5-yr DFS: 84% v 76% (p=0.02)</li> </ul>
<b>RTOG 9910</b>	1489	RT + ADT x 4 mo vs. RT + ADT x 9 mo	<ul style="list-style-type: none"> <li>Int risk 85%</li> <li>High risk 15%</li> </ul>	<ul style="list-style-type: none"> <li>No difference in OS, DM rate or BF rate</li> </ul>

## Brachytherapy boost

	N	Arms	Patients	Outcome
<b>ASCENDE-RT</b>	398	<u>DE-EBRT</u> 46 Gy pelvis → 78 Gy 3D-CRT prostate boost vs. <u>LDR-PB</u> 46 Gy pelvis → 115 Gy I <sup>125</sup> boost	<ul style="list-style-type: none"> <li>Int risk 32%</li> <li>High risk 68%</li> </ul>	<ul style="list-style-type: none"> <li>9-yr bPFS: 62% v 83% (p&lt;.001)               <ul style="list-style-type: none"> <li>Int risk: 69.8% v 93.9%</li> <li>High risk: 58.2% v 78.0%</li> </ul> </li> </ul>

## High risk prostate cancer

- Treat prostate + consider pelvic nodal RT
  - ❑ External beam radiotherapy + ADT 2-3 yr
    - CFRT
    - HFRT
    - SBRT (if treat prostate alone)
  - ❑ Consider brachytherapy boost
    - Low-dose rate
    - High-dose rate

## Androgen deprivation therapy (ADT) for high risk

	N	Arms	Patients	Outcome
<b>EORTC 22961</b>	970	RT + ADT x 6 mo vs. RT + ADT x 36 mo	• High risk or N+	• 5-yr PCSM: 4.7% v 3.2% (p=0.002)
<b>RTOG 9202</b>	1521	RT + ADT x 4 mo vs. RT + ADT x 28 mo	• High risk	• 10-yr DSS: 83.9% v 88.7% (p=0.0042) • 10-yr non-DM rate: 77.2% v 85.2% (p<0.0001)
<b>DART 01/05</b>	355	RT + ADT x 4 mo vs. RT + ADT x 28 mo	• Int risk 47% • High risk 53%	• 5-yr OS: 86% v 95% (p=0.009) • 5-yr MFS: 83% v 94% (p=0.01)
<b>PCS IV</b>	630	RT + ADT x 36 mo vs. RT + ADT x 18 mo	• High risk 100%	• Similar 10-yr OS and DM rate • 10-yr BF rate: 25% v 31% (p=0.02)

## Node-positive prostate cancer

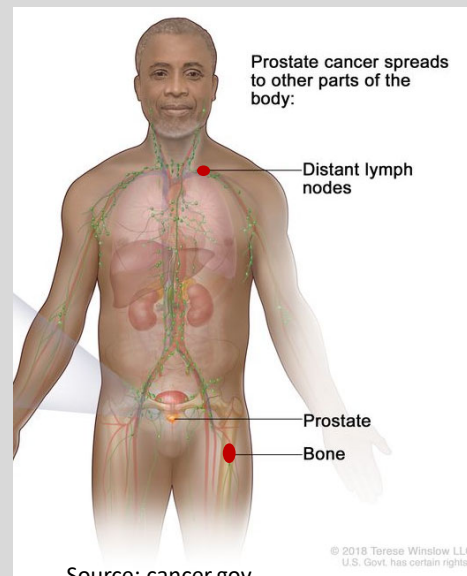
- Treat prostate + pelvic nodal RT
  - External beam radiotherapy + ADT 2-3 yr
    - CFRT
    - HFRT

## STAMPEDE Arm G+J

- High risk non-metastatic patients
- Addition of abiraterone to standard ADT improves outcome:
  - 6-yr MFS: 69% → 82%
  - 6-yr OS: 77% → 86%
  - 6-yr PCSS: 85% → 93%

## Oligometastatic prostate cancer

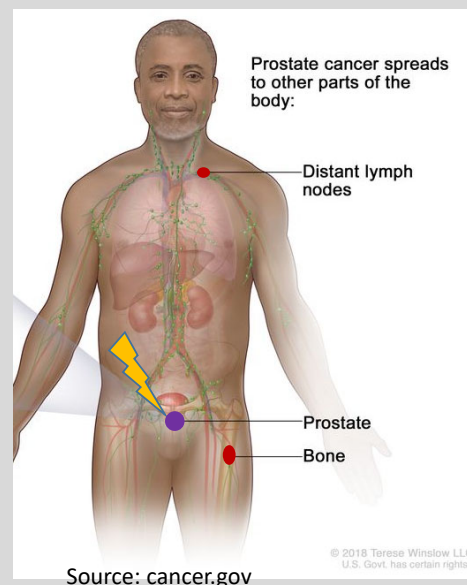
- Clinical definition of  $\leq 3$ -5 metastatic lesions
- Early phase of metastasis with better prognosis



## STAMPEDE Arm H

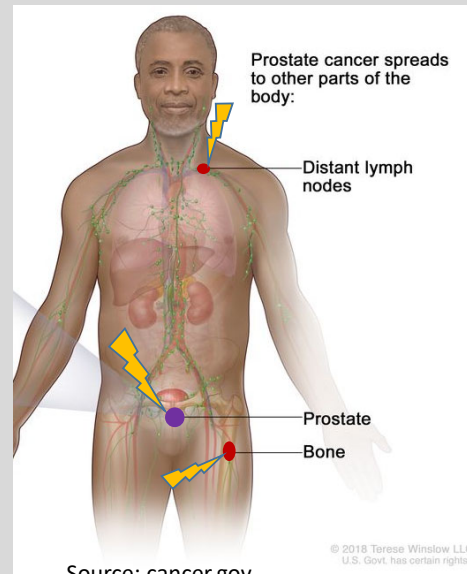
Ali et al., JAMA Oncol 2021

- Patients with low metastatic burden benefit from prostate RT:
  - 3-yr OS: 75% → 85%
  - 3-yr FFS: 33% → 53%



## Future of oligometastatic management

- Future trials evaluating the role and benefit of total disease eradication with radiation/surgery



Source: cancer.gov

## Radiation side effects

### Acute effects

- Fatigue
- Urinary symptoms
  - Frequency/urgency
  - Straining/weak stream
  - Dysuria
- Bowel symptoms
  - Diarrhea
  - Tenesmus

### Chronic effects

- Erectile dysfunction
- Radiation proctitis
- Radiation cystitis
- Secondary malignancy

## ADT side effects

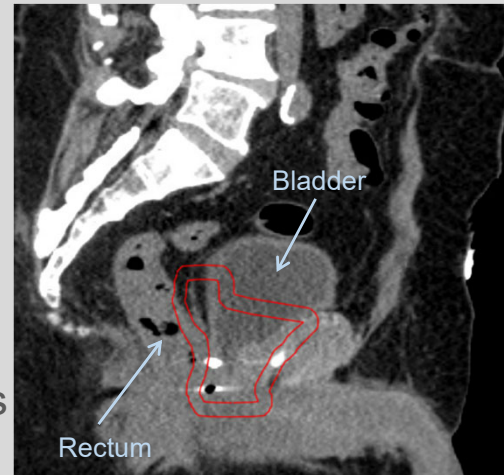
- Hot flashes
- Decreased libido
- Erectile dysfunction
- Loss of bone density
- Loss of muscle mass
- Mood swings
- Gynecomastia
- Metabolic
  - Insulin resistance
  - Changes in blood lipids
- Cardiovascular risks
- Weight gain
- Fatigue

Definitive radiotherapy

**Salvage radiotherapy**

## Salvage radiotherapy

- Prostate cancer recurrence after radical prostatectomy
- Mostly PSA-detected
  - Detectable PSA without gross disease on imaging
  - Gross disease recurrence limited to the pelvis
- Radiation target: prostate bed ± pelvis
- Not candidate for salvage with metastatic recurrence



## Adjuvant therapy replaced

	N	Arms	Patients	Outcome
<b>RADICALS-RT</b>	1396	Adjuvant RT vs. Early salvage	<ul style="list-style-type: none"> <li>Post-RP PSA <math>\leq 0.2</math></li> </ul>	<ul style="list-style-type: none"> <li>5-yr bPFS: 85% v 88% (p=0.56, NS)</li> <li>At 8 years, only 33% of patients on early salvage arm received treatment</li> </ul>
<b>RAVES</b>	333	Adjuvant RT vs. Early salvage	<ul style="list-style-type: none"> <li>Post-RP PSA <math>\leq 0.1</math></li> </ul>	<ul style="list-style-type: none"> <li>8-yr FFBF: 79% v 76%</li> <li>50.3% of salvage arm patients met criteria for salvage RT</li> </ul>

## Salvage RT dose-fractionation

- Conventional fractionation (CFRT)
  - 64-72 Gy in 1.8-2 Gy/fx (6.5-8 weeks)
- Hypofractionation (HFRT)
  - 62.5 Gy in 2.5 Gy/fx (5 weeks) [NRG GU-003]
    - Greater acute GI toxicity

## ADT for salvage therapy

### GETUG-16

- SRT ± 6-month GnRH antagonist (goserelin)
- ADT improved 5-yr PFS 62% → 80%



## Radiation side effects

### Acute effects

- Fatigue
- Urinary symptoms
  - Frequency/urgency
  - Incontinence
  - Dysuria
- Bowel symptoms
  - Diarrhea
  - Tenesmus

### Chronic effects

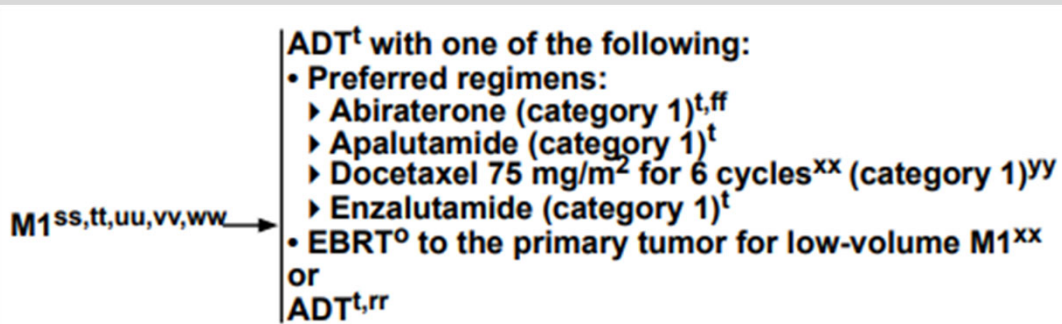
- Erectile dysfunction
- Radiation proctitis
- Radiation cystitis
- Secondary malignancy

## Advanced prostate cancer

## Advanced prostate cancer

- Metastatic castration-sensitive prostate cancer (mCSPC)
- Metastatic castration-resistant prostate cancer (mCRPC)

## Systemic therapy



## Chemotherapy

- Docetaxel
  - mCSPC and mCRPC
- Cabazitaxel ± carboplatin
  - mCRPC
- Mitoxantrone
  - mCRPC

## Radium-223 (Xofigo)

- Alpha particle-emitting radiopharmaceutical absorbed by bone
- Improved survival in mCRPC patients with prior docetaxel (ALSYMPCA)
- For patients without visceral disease
- Intravenous delivery monthly x 6 months
- Sufficient baseline blood count
  - ANC  $\geq$  1500/ $\mu$ L
  - Platelet  $\geq$  100,000/ $\mu$ L
  - Hgb  $\geq$  10 g/dL

## PSMA-Lu177

- Targets prostate-specific membrane antigen (PSMA) on cell surface of prostate cancer cells
- Delivers payload beta-emitter Lu177
- Improves survival and delayed progression in mCRPC (TheraP and VISION trials)
- Currently undergoing priority review for FDA approval

## Other systemic therapy options

- PARP inhibitors (olaparib)
  - Prevents DNA damage repair
  - Synthetic lethality with BRCA1/2 mutations
- Sipuleucel-T
  - Prostate cancer “vaccine”
  - Isolate patient’s dendritic (antigen-presenting) cells
  - Train dendritic cells against prostate cancer antigen PAP
  - Reinfuse “trained” dendritic cells to activate immune response against prostate cancer

## Palliative radiotherapy

- Tumor and pain control for bone or visceral metastases
- Conventional external beam
  - 20 Gy in 5 fx
  - 30 Gy in 10 fx
- Stereotactic ablative radiotherapy
  - 24 Gy in 2 fx
  - 24-30 Gy in 3 fx
  - 30-50 Gy in 5 fx