



Prostate Cancer Management: Where Do We Stand in 2022

Shawn Dason, MD
Urologic Oncologist

Assistant Professor of Urology
The Ohio State University Wexner Medical Center

MedNet21
Center for Continuing Medical Education

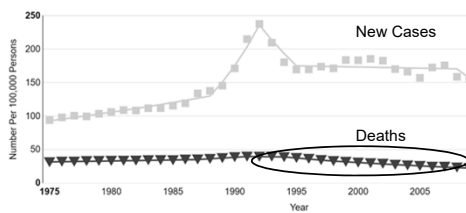
THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

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% |
| All Sites | 321,670 | 100% |

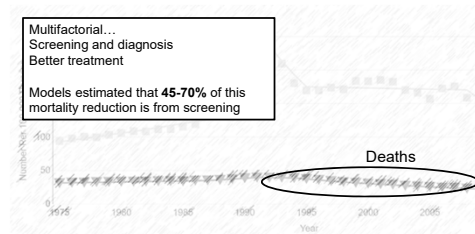
American Cancer Society Statistics, CA Cancer J Clin 2019, non-melanoma skin not included

Prostate cancer mortality has halved



SEER Registry Public Data

Prostate cancer mortality has halved



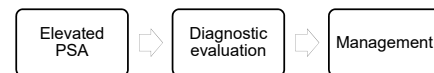
Cancer Causes Control, 2008 Mar;19(2):175-81. Epub 2007 Nov 20.

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

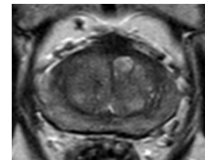
Eastham, JAMA, 2003

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

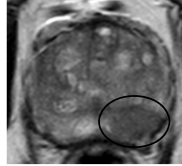


PRECISION, NEJM, 2018; STHLM3, NEJM, 2021.

Diagnostic evaluation – risk stratification

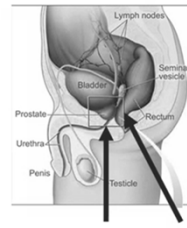
- An abnormal MRI lesion can be targeted during biopsy, clinically significant prostate cancer diagnosis (12-22%)

- 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%)

Transperineal Transrectal

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 findings

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, right 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:

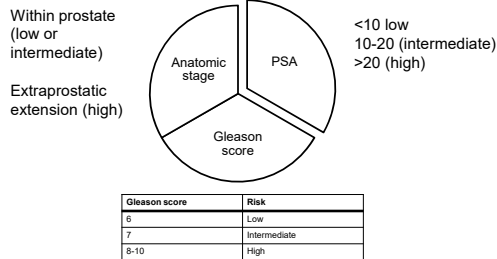
- Prostate tissue with no significant pathologic change

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



Staging

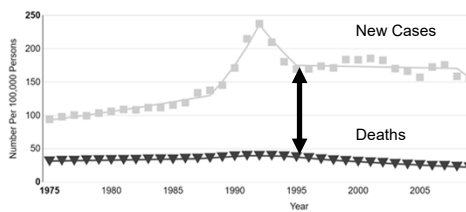
Most patients are assumed to be localized staging is only for high risk (select intermediate risk)

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, Witt 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 | Essentially all low-risk (e.g. Gleason 6) patients 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

Bir-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

Bir-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

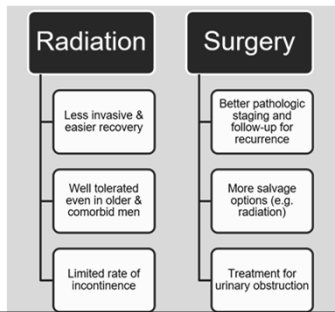
Studies of radiation have demonstrated a survival benefit

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

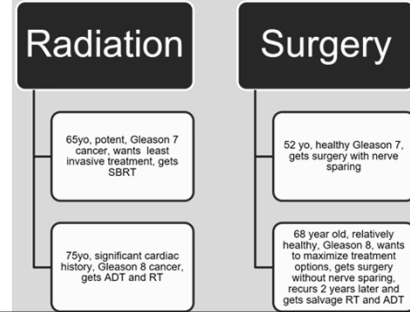
Studies of systemic therapy demonstrate clear survival benefit

SPCG-4, SPCG-7, PROTECT, PIVOT

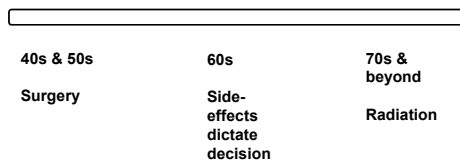
Patients with localized disease can generally select...



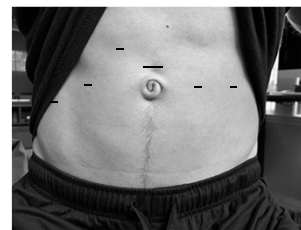
Patients with localized disease can generally select...



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



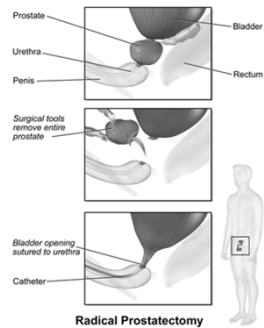
Surgery – robot assisted radical prostatectomy



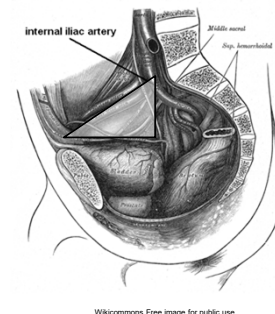
5 incisions 5-12mm
Extraction 3-4 cm
New SP robot
1 incision

Author: SwirlyDude (CC BY-SA 4.0)

Prostatectomy



Lymphadenectomy



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

Shang-Jui Wang, MD, PhD

Assistant Professor

Department of Radiation Oncology

Ohio State University Comprehensive Cancer Center

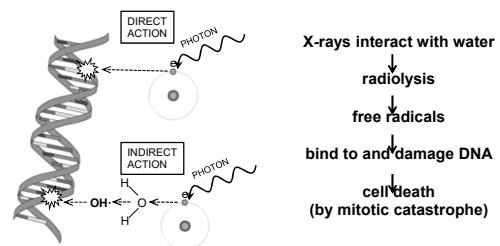
James Cancer Hospital and Solove Research Institute

The Ohio State University Wexner Medical Center

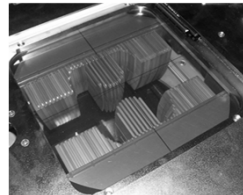
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How does radiation work?

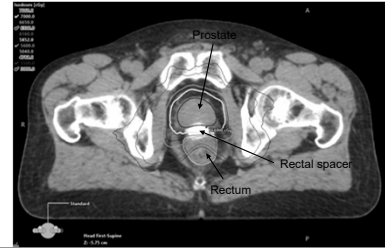


External beam radiotherapy

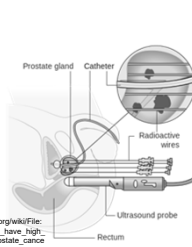


External beam radiotherapy

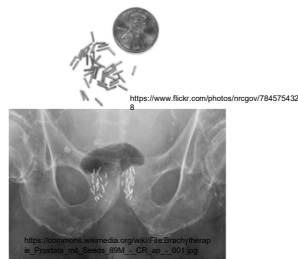
Volumetric modulated arc therapy (VMAT)



Brachytherapy



High-dose rate

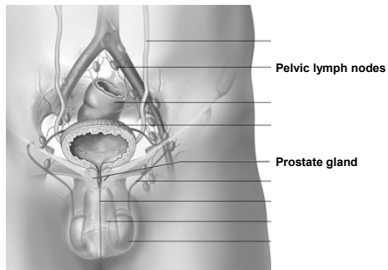


Low-dose rate

Definitive radiotherapy

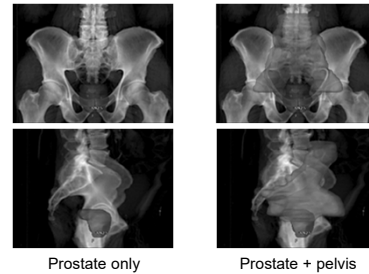
Salvage radiotherapy

Radiation target for prostate cancer



Source: cancer.gov

Radiation target for prostate cancer



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

Brachytherapy boost

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

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 |
|--------------------|------|---------------------------------------|---|---|
| EORTC 22961 | 970 | RT + ADT x 6 mo vs. RT + ADT x 36 mo | <ul style="list-style-type: none"> High risk or N+ | <ul style="list-style-type: none"> 5-yr PCSM: 4.7% v 3.2% (p=0.002) |
| RTOG 9202 | 1521 | RT + ADT x 4 mo vs. RT + ADT x 28 mo | <ul style="list-style-type: none"> High risk | <ul style="list-style-type: none"> 10-yr DSS: 83.9% v 88.7% (p=0.0042) 10-yr non-DM rate: 77.2% v 85.2% (p<0.0001) |
| DART 01/05 | 355 | RT + ADT x 4 mo vs. RT + ADT x 28 mo | <ul style="list-style-type: none"> Int risk 47% High risk 53% | <ul style="list-style-type: none"> 5-yr OS: 86% v 95% (p=0.009) 5-yr MFS: 83% v 94% (p=0.01) |
| PCS IV | 630 | RT + ADT x 36 mo vs. RT + ADT x 18 mo | <ul style="list-style-type: none"> High risk 100% | <ul style="list-style-type: none"> Similar 10-yr OS and DM rate 10-yr BF rate: 25% v 31% (p=0.02) |

Node-positive prostate cancer

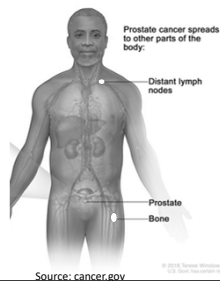
- Treat prostate + pelvic nodal RT
 - External beam radiotherapy + ADT 2-3 yr
 - CFRT
 - HFRT

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

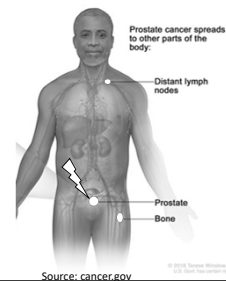
- Clinical definition of ≤ 3-5 metastatic lesions
- Early phase of metastasis with better prognosis



STAMPEDE Arm H

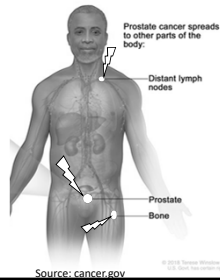
Ali et al., JAMA Oncol 2021

- 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



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

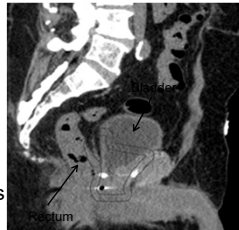
- | | |
|------------------------|---------------------------|
| ➤ Hot flashes | ➤ Metabolic |
| ➤ Decreased libido | ▪ Insulin resistance |
| ➤ Erectile dysfunction | ▪ Changes in blood lipids |
| ➤ Loss of bone density | ➤ Cardiovascular risks |
| ➤ Loss of muscle mass | ➤ Weight gain |
| ➤ Mood swings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

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

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

M1^{ss,tt,uu,vv,ww} → ADT^t with one of the following:

- Preferred regimens:
 - Abiraterone (category 1)^{t,ff}
 - Apalutamide (category 1)^t
 - Docetaxel 75 mg/m² for 6 cycles^{xx} (category 1)^{y,y}
 - Enzalutamide (category 1)^t
- EBRT^o to the primary tumor for low-volume M1^{xx}

or
ADT^{t,rr}



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 3.2022
Prostate Cancer

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 ≥ 1500/μL
 - Platelet ≥ 100,000/μL
 - Hgb ≥ 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