Prostate Cancer Introductory Lecture

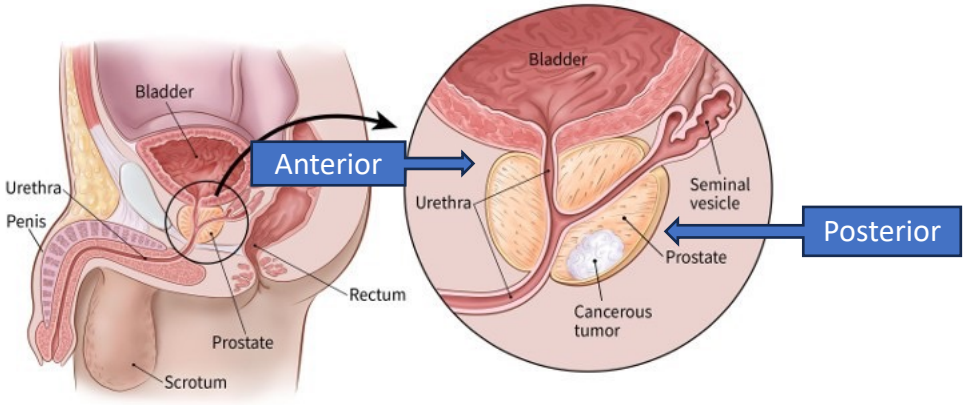
Prostate Cancer

General Information:

Lifetime risk 1/9 (~11%)

PSA Screening:

Annual PSA screening
Usually at age 50



American Cancer Society

Prostate Anatomy:

Prostate Zones:
Anterior, Peripheral, Central, Transitional

Most cancers occur in peripheral zones

Genetic Risk Factors:

High Penetrance
- BRCA2 > BRCA1
- PALB2

Moderate Penetrance
- CHEK2
- ATM
- HOXB13
- Lynch: MLH1, MSH2/6, PMS2

Prostate Cancer Diagnosis

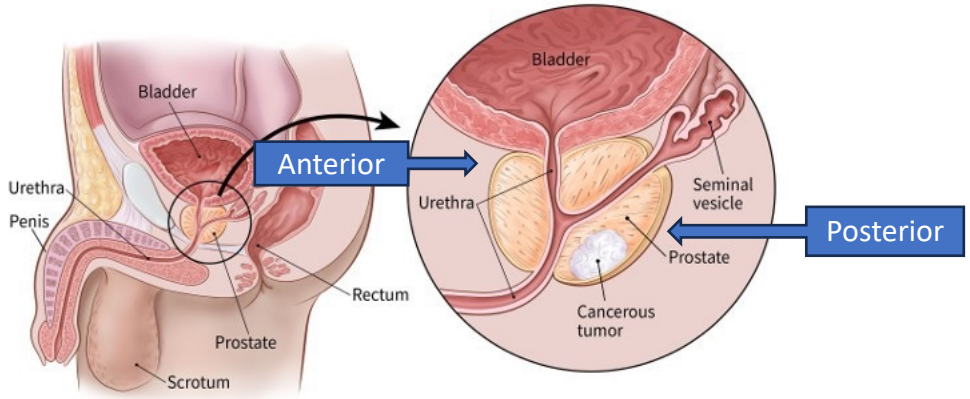
BIOPSY

12 core biopsies obtained
+ fusion biopsy = additional cores from regions of interest identified on MRI

IHC:

CK7-, CK20-, GATA3-

NKX3.1+ (negative in urothelial)
Androgen Receptor +
PSA+ (negative in urothelial)
* IHC markers can be lost if high-grade



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Anterior lesions are difficult to sample from rectal approach

If PSA elevated/rising and biopsies are benign consider:
MRI prostate, particular evaluation of anterior lesions

IMAGING

Abdominal/Pelvic Imaging:
MRI > CT

Systemic Imaging:
PSMA PET (prostate specific membrane antigen) or Bone Scan if intermediate or high-risk prostate cancer

Prostate Cancer Staging & Prognosis

T Stage

T1 = not palpable
T2 = palpable, confined to prostate
T3 = extracapsular
T3b = seminal vesicles
T4 = adjacent organs/structures

Lymph Nodes

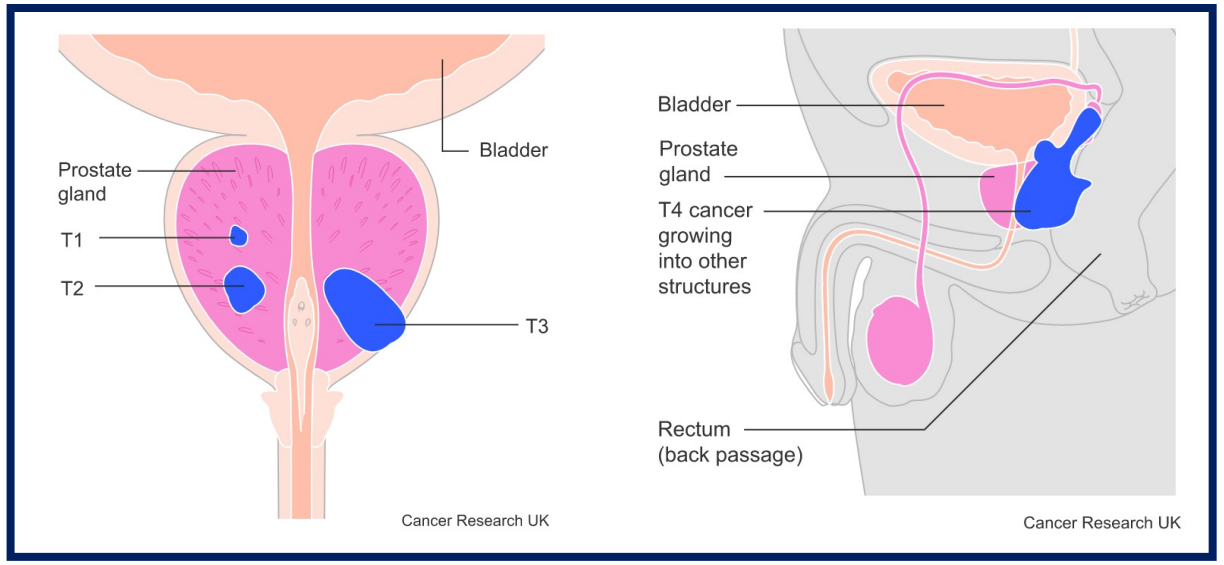
N1 = regional LN

Distant Mets

M1a = non-regional LN
M1b = bones
M1c = other sites

STAGE IV Disease

Stage IVA = N1
Stage IVB = M1



www.cancerresearchuk.org

T Staging:

Controversial if T staging should be based on DRE (digital rectal examination) vs MRI. MRI is more common

PROGNOSIS

5Y OS stage I-III disease = > 95%
5Y OS stage IV disease = 30%

Prostate Cancer Localized Disease

Gleason Grading

GLEASON SCORE

Composite path score of biopsies (≥ 12 total)

1-5 score = pathologic scoring of dysplasia
1 = well differentiated glands
5 = poorly differentiated glands

Grades 1-2 = benign
Grades 3-5 = malignant

Gleason Scores for each core are composites of:
Primary Grade + Secondary Grade
3 + 4 ≠ 4 + 3

Grade Group 1	Grade Group 1	Grade Group 1
Grade Group 1	≤ 6	≤ 3 + 3
Grade Group 2	7	3 + 4
Grade Group 3	7	4 + 3
Grade Group 4	8	4+4, 3+5, 5+3
Grade Group 5	9-10	4+5, 5+4, 5+5

RISK BY GLEASON SCORE GRADE GROUP

GLEASON 6 = LOW RISK
GLEASON 7 = INTERMEDIATE RISK
GLEASON 8+ = HIGH RISK

Risk Stratification for Localized Prostate Cancer (N0, M0)

if N+ or M+ risk categories don't apply

GLEASON SCORE

Composite path score of biopsies: 1^{o} + 2^{o}
1-5 score = pathologic scoring of dysplasia
1-2 = benign
3-5 = malignant

RISK BY GLEASON SCORE GRADE GROUP

GLEASON 6 = LOW RISK
GLEASON 7 = INTERMEDIATE RISK
GLEASON 8+ = HIGH RISK

PSA SCORE

Prostate Specific Antigen:
PSA is prostate specific NOT prostate cancer specific

Can be elevated for other reasons (ex: infection, BPH)
PSA > 4 ng/dl is not diagnostic

RISK BY PSA SCORE

PSA <10 = LOW RISK
PSA 10-20 = INTERMEDIATE RISK
PSA >20 = HIGH RISK

RISK STRATIFICATION: **Gleason score, PSA, and Stage are used in conjunction to risk stratify prostate cancer**
if conflicting, use whichever parameter is higher risk

Risk Stratification for Localized Prostate Cancer (N0, M0)

if N+ or M+ risk categories don't apply

LOW RISK	INTERMEDIATE RISK	HIGH RISK
SIZE: T1-T2	**SIZE:** T2	**SIZE:** T3-T4
GLEASON: 6	**GLEASON:** 7	**GLEASON:** 8+
PSA: < 10	**PSA:** 10-20	**PSA:** >20
VERY LOW RISK T1c < 3 core biopsies positive < 50% cancer/core biopsy PSA density <0.15 ng/ml/g	**UNFAVORABLE** > 50% cancer/core biopsy Gleason 4+3 (Grade Group 3)	**VERY HIGH RISK** T3b-T4 Primary Gleason grade 5 > 4 cores with Gleason 4-5

STAGING:

LOW RISK: Don't need systemic staging for low-risk disease. Get MRI or CT abdomen/pelvis

INTERMEDIATE UNFAVORABLE/HIGH RISK: (1) MRI or CT and (2) Bone Scan or PSMA scan

Localized Disease Treatment Overview (N0, M0)

LOW RISK

Surveillance or RP vs. RT

INTERMEDIATE RISK

Favorable
Surveillance or RP vs. RT

Unfavorable
RP vs. RT
+/- ADT x 4-6 months

HIGH RISK

RP vs RT
+/- ADT x 1-3Y
+/- Abiraterone

LOCAL TREATMENTS

Radical Prostatectomy (RP)
Robotic and non-robotic surgical options

Radiation Therapy (RT)
1. EBRT = external beam RT
2. Brachytherapy = internal RT via insertion of radioactive beads

SYSTEMIC TREATMENTS

ADT = Androgen Deprivation Therapy

Abiraterone = CYP17 Inhibitor

Local Treatments: Surgery vs. Radiation

Radical Prostatectomy (RP)

1. Robotic RP = minimally invasive
2. Non-Robotic RP = open

No difference in outcomes for robotic vs. non-robotic. Robotic = easier healing, less blood loss, possibly helps spare nerves. Requires skilled practitioner

* Pelvic lymph node dissection (PLND) is possible with RP

Radiation Therapy (RT)

1. External Beam RT (EBRT)
2. Brachytherapy (BT)

* Cannot assess pelvic lymph node involvement

SIDE EFFECTS of Surgery (RP) and Radiation Therapy (RT)

No difference in outcomes. Side effects vary.

Urinary retention or incontinence (recovery ~90-100%)
Erectile dysfunction (recovery ~60-70%)
Rectal proctitis, cystitis, colitis (only with RT)

RP:
more acute toxicity
higher risk of incontinence

RT:
more chronic toxicity
higher risk of irritation to bowel/bladder
lower risk of incontinence

Androgen Deprivation Therapy (ADT)

ADT mechanisms of action

1) Stop testosterone from interacting with androgen receptors
= Androgen receptor inhibitors

2) Lower testosterone level
= GNRH agonists, GNRH antagonists, surgical castration

Goal: Chemical Castration
Testosterone < 50 ng/dL (normal T 300-1000 ng/dL)

Side Effects:
Low libido, low energy, anemia, change in muscle/fat distribution, hot flashes, osteoporosis, gynecomastia, transaminitis

Androgen Receptor Inhibitor 1st Gen

Bicalutamide (Casodex) *PO*
Give 7D prior to GNRH agonist (not antagonist)
Can cause PSA flair

GNRH Agonists

Leuprorelin (Lupron) *IM*
Agonist causes initial testosterone flair
2-3 weeks to get castration T levels

GNRH Antagonists

Degarelix (Firmagon) *IM*
Antagonist does NOT cause testosterone flair
48-72H to get castration T levels

Relugolix (Orgovyx) *PO*
Oral GNRH Antagonist

Low Risk Treatment: Localized Disease (N0, M0)

LOW RISK

SIZE: T1-T2

GLEASON: 6

PSA: < 10

VERY LOW RISK
T1c
< 3 core biopsies positive
< 50% cancer/core biopsy
PSA density <0.15 ng/ml/g

LOW RISK Treatment Options

1. Active Surveillance <u>preferred</u>
2. RP (Radical Prostatectomy)
3. RT (EBRT or Brachytherapy)

* < 10Y life expectancy, consider observation

Active Surveillance Protocol

PSA maximum Q6M
DRE maximum Q12M
Prostate Biopsy maximum Q12M
Consider MRI

Intermediate Risk Treatment: Localized Disease (N0, M0)

INTERMEDIATE RISK

SIZE: T2

GLEASON: 7

PSA: 10-20

UNFAVORABLE
> 50% cancer/core biopsy
Gleason 4+3

FAVORABLE Treatment Options

1. RP: Radical Prostatectomy **+/- PLND**
2. RT: EBRT or Brachytherapy
3. Active Surveillance

UNFAVORABLE Treatment Options

1. RP: Radical Prostatectomy **+ PLND**
2. EBRT **+ ADT**
3. EBRT **+ Brachy +/- ADT**

* < 5-10Y life expectancy, consider observation

Androgen Deprivation Therapy
4-6 months ADT

After EBRT:
- Unfavorable-Intermediate Risk

After RP:
- Adverse features detected at surgery (consider EBRT +/- ADT)
- N1 disease detected

High Risk Treatment: Localized Disease (N0, M0)

HIGH RISK

SIZE: T3-T4

GLEASON: 8+

PSA: >20

VERY HIGH RISK
T3b-T4a
> 4 cores Gleason 4-5

HIGH RISK Treatment Options

1. RP: Radical Prostatectomy **+ PLND**
2. EBRT **+ ADT**
3. EBRT **+ Brachy + ADT**

VERY HIGH RISK Treatment Options

1. RP: Radical Prostatectomy **+ PLND**
2. EBRT **+ ADT**
3. EBRT **+ Brachy + ADT**
4. EBRT **+ ADT + Abiraterone**

* < 5Y life expectancy, consider observation or EBRT or ADT

Androgen Deprivation Therapy
1-3 Years ADT

After EBRT:
- High or Very High Risk

After RP:
- Adverse features detected at surgery (consider EBRT +/- ADT)
- N1 disease detected

CYP17 Inhibitor Therapy:
2 Years Abiraterone

After EBRT:
N1 or at least 2 of 3 factors present
- T3+
- Gleason ≥ 8 (Grade Group 4 or 5)
- PSA ≥ 40

Regional Disease (N1, M0)

REGIONAL NODAL

N1: regional LN

Regional Disease Treatment

1. EBRT **+ ADT + Abiraterone (preferred)**
2. EBRT **+ ADT**
3. RP: Radical Prostatectomy **+ PLND (for select patients)**

* < 5Y life expectancy, consider observation or ADT

Prostate Cancer Recurrence & Persistence

BIOCHEMICAL RECURRENCE

Biochemical Recurrence = rising PSA after local RP or RT
without evidence of disease on imaging

PSA: Rise of 2 ng/mL above nadir
Can have transient PSA rise after RT
Should not have PSA after surgery (1/2 life 2-3D)

PSA Doubling Time (PSADT)
Used for risk stratification

Imaging:
Consider PSMA PET to try to localize recurrence

Biochemical recurrence can pre-date clinical recurrence by a long time

CLINICAL RECURRENCE

Clinical Recurrence = evidence of disease on imaging

after local RP or RT
often detected iso rising PSA after RP or RT

Prostate Cancer Recurrence & Persistence

Recurrence After Radial Prostatectomy

Management options after RP

Biochemical Recurrence
EBRT +/- ADT

Pelvic Recurrence
EBRT + ADT +/- Abiraterone

Recurrence After Radiation Therapy

Management options after RT

Biochemical Recurrence
+/- ADT

Pelvic Recurrence
1. RP + PLND
2. Brachy or Cryotherapy
3. Pelvic LN RT
4. ADT

*** Not all recurrence requires immediate treatment. Can monitor.**

RESISTANCE

Non-Metastatic Castrate Resistant Prostate Cancer = M0 CRPC

Persistence = PSA rising on ADT

Management = Dependent on risk stratification, including PSA doubling time (PSADT)

Rapid PSA Doubling Time (< 10 months):
can trial 2nd generation AR antagonists
enzalutamide, apalutamide, darolutamide

Prostate Cancer Advanced Disease
Hormone Resistant or Metastatic

Agents Approved for Hormone Resistant or Advanced Disease

Hormone Resistance	Metastases: No	Metastases: Yes
No	**Biochemical Recurrence** • Surveillance • Intermittent ADT (GNRH agonist/antagonist)	**mHSPC: Metastatic Hormone Sensitive PC** • Abiraterone • Docetaxel • Enzalutamide Apalutamide Darolutamide
Yes	**M0 CRPC: Non-Metastatic Castrate Resistant PC** • Enzalutamide Apalutamide Darolutamide	**mCRPC: Metastatic Castrate Resistant PC** • Abiraterone • Docetaxel • Enzalutamide Apalutamide Darolutamide • Cabazitaxel • Sipuleucel-T • Ra-223 • PARP inhibitors

Agents for Hormone Resistant and/or Metastatic Disease

Androgen Receptor Signaling Inhibitor (ARSI)

Androgen Receptor Inhibitor 2nd Gen
Enzalutamide, Apalutamide, Darolutamide
Side effects: CNS (lower seizure threshold, except for Daro)

CYP17 Inhibitor
Abiraterone
Given with prednisone
Avoid if severe liver dysfunction
Side effects: HTN, fluid retention, hypokalemia

CHEMOTHERAPY

Docetaxel (Taxotere)
Only approved in high volume disease

Given with prednisone
Avoid if severe liver dysfunction
Side Effects: PSA can rise during initial tx, neuropathy, peripheral edema, skin/nail changes…

Systemic Tx Castrate Sensitive Prostate Cancer (CSPC)

ADT +

DOUBLET THERAPY

Androgen Receptor Inhibitor
Enzalutamide
Apalutamide

CYP17 Inhibitor
Abiraterone (+prednisone)

Chemotherapy
Docetaxel (+prednisone)

TRIPLET THERAPY

Chemo + ARI
Docetaxel + Darolutamide

Chemo + CYP17 Inhibitor
Docetaxel + Abiraterone

Indications for Triplet Therapy:
- De Novo MPC (no data in recurrent)
- High volume
- Good PS

Agents in Castrate Resistant Prostate Cancer (CRPC)

for use in Visceral Disease

Alternate Chemotherapy

Cabazitaxel
Only after front line taxane (docetaxel)

Alternate AR Signaling Inhibitor

ARSI Switch
CYP17 → ARI
Abiraterone → Enzalutamide

ARI → CYP17
Enzalutamide → Abiraterone

* Consider chemotherapy > ARSI switch if POD on first line ARSI

Nuclear Agents

Lutetium-PSMA (Lu 177)
If positive PSMA scan
Approved post-taxane therapy

Targeted Therapies

PARP Inhibitors (Olaparib, Niraparib, Talazoparib)
Used in HRR mutations (BRCA, RAD51, etc)
Can combine with abiraterone (Olaparib, Niraparib)
Can combine with enzalutamide (Talazoparib)

Immunotherapy

Pembrolizumab (Keytruda)
Approved for dMMR, MSI-H, TMB > 10 muts/mb

Agents in Castrate Resistant Prostate Cancer (CRPC)

cannot use in Visceral Disease

Immunotherapy

Sipuleucel-T (Provenge)
DC Vaccine (targets PAP = prostate acid phosphatase)
Not approved for visceral disease
Approved for asymptomatic or minimally symptomatic, life expectancy >6M, ECOG 0-1
PSA usually doesn't decrease

Bone Targeted Agents

Radium-223 (Xofigo)
Preferentially treats bone
Approved for symptomatic bone metastases
Not approved for visceral disease

Bone Supportive Agents

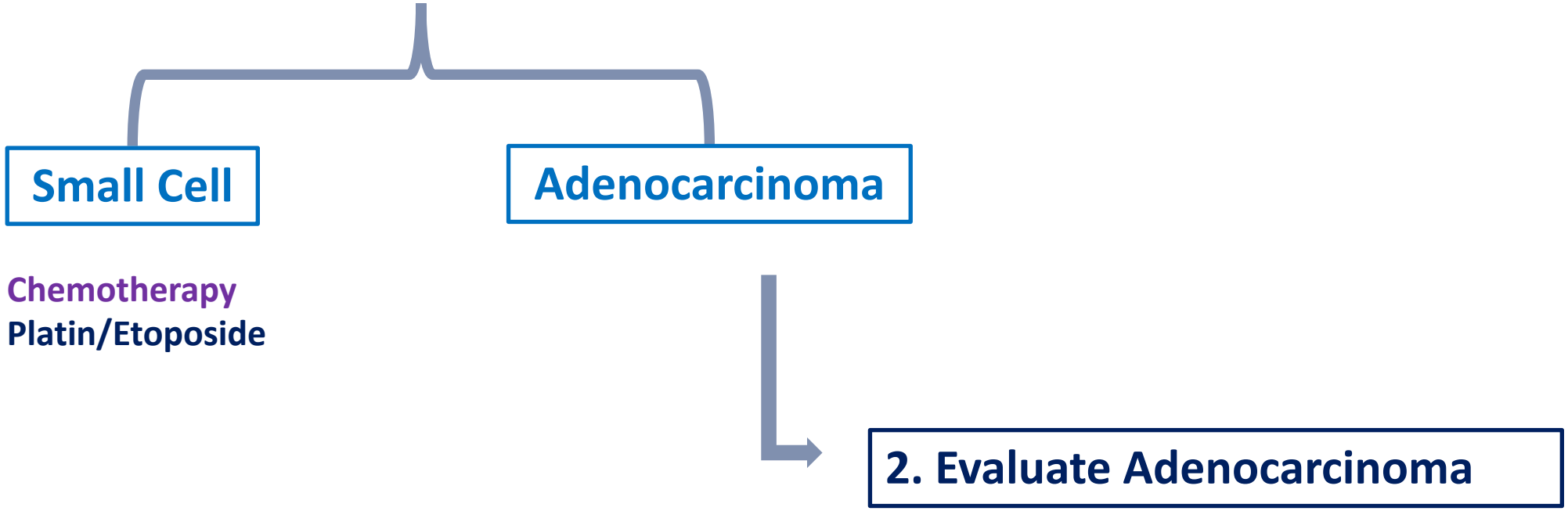
Bone Supportive Agents

RANKL Inhibitors (Denosumab)
Decreases skeletal related events > zoledronic acid
Rebound fractures if discontinued

Bisphosphonates (Zoledronic Acid)

Systemic Tx in Castrate Resistant Prostate Cancer (CRPC)

1. Biopsy to determine if transformation to small cell



Systemic Tx in Castrate Resistant Prostate Cancer (CRPC)

2. Evaluate Adenocarcinoma

1. Prior Exposures

No Prior Docetaxel
Docetaxel
Abiraterone
Enzalutamide
Sipuleucel-T

Prior Docetaxel
Cabazitaxel
Abiraterone
Enzalutamide
Sipuleucel-T

No Prior Hormone Tx
Docetaxel
Abiraterone
Enzalutamide
Sipuleucel-T

Prior Hormone Tx
Docetaxel

2. Disease Burden

Visceral
Docetaxel
Cabazitaxel
Abiraterone
Enzalutamide

Asymptomatic
Sipuleucel T

Sx Bone Mets
Radium-223

3. Molecular Characteristics

HRR Mutations
Olaparib +/- Abiraterone
Niraparib +/- Abiraterone
Talazoparib/Enzalutamide
Rucaparib

dMMR, MSI-H,
TMB >10
Pembrolizumab

PSMA+
Lu-177

Prostate Cancer Reference Handout

Prostate Cancer Dx & Risk Stratification

BIOPSY

12 or more core biopsies obtained

IHC:
CK7-, CK20-, GATA3-
Androgen receptor +
PSA+ (negative in urothelial)
NKX3.1+ (negative in urothelial)

IMAGING

Initial Staging:
MRI Abdomen (or CT)

Staging for Intermediate or High Risk:
PSMA PET scan or Bone Scan

STAGING

T Stage
T1 = no palpable
T2 = confined to prostate
T3 = extracapsular (3b = seminal vesicle)
T4 = adjacent organs/structures

Lymph Nodes
N1 = local pelvic LN
M1 = nodes outside pelvis (above aortic bifurcation)

STAGE IV Disease
Stage IVA = N1
Stage IVB = M1

Risk Stratification for Localized Disease (N0, M0)

LOW RISK

SIZE: T1-T2
GLEASON: 6
PSA: < 10

VERY LOW RISK
T1c
< 3 core biopsies positive
< 50% cancer/core biopsy
PSA density <0.15 ng/ml/g

INTERMEDIATE RISK

SIZE: T2
GLEASON: 7
PSA: 10-20

UNFAVORABLE
> 50% cancer/core biopsy
Gleason 4+3 (Grade Group 3)

HIGH RISK

SIZE: T3-T4
GLEASON: 8+
PSA: >20

VERY HIGH RISK
T3b-T4
Primary Gleason grade 5
> 4 cores with Gleason 4-5

Prostate Cancer: Localized Tx (N0, M0)

LOW RISK

1. **Active Surveillance preferred**
2. RP (Radical Prostatectomy)
3. RT (EBRT or Brachytherapy)

INTERMEDIATE RISK

Favorable:
1. RP **+/- PLND**
2. RT: EBRT or Brachy
3. Surveillance

Unfavorable:
1. RP **+ PLND**
2. EBRT **+ ADT**
3. EBRT **+ Brachy + ADT**

4-6 months ADT

HIGH RISK

High Risk:
1. RP: Radical Prostatectomy **+ PLND**
2. EBRT **+ ADT**
3. EBRT **+ Brachy + ADT**

Very High Risk:
1. RP: Radical Prostatectomy **+ PLND**
2. EBRT **+ ADT**
3. EBRT **+ Brachy + ADT**
4. EBRT **+ ADT + Abiraterone**

1-3 years ADT
2 years abiraterone

ADT

ADT = ANDROGEN DEPRIVATION THERAPY

Androgen Receptor Inhibitor

Bicalutamide (Casodex) *PO*
Give 7D prior to GNRH agonist (not antagonist)
Can cause PSA flair

GNRH Agonists

Lupron *IM*
Agonist causes initial testosterone flair
2-3 weeks to get castration T levels

GNRH Antagonists

Degarelix (Firmagon) *IM*
Antagonist does NOT cause testosterone flair
48-72H to get castration T levels

Relugolix (Orgovyx) *PO*

Goal: Chemical Castration
Testosterone < 50 ng/dL (normal 300-1000 ng/dL)

Side Effects:
Low libido, low energy, anemia, change in muscle/fat distribution, hot flashes, osteoporosis, gynecomastia, transaminitis

Metastatic Hormone Sensitive Prostate Cancer (mHSPC)

ADT +/-

DOUBLET THERAPY

Androgen Receptor Inhibitor
Enzalutamide
Apalutamide
AEs: Seizures

CYP17 Inhibitor
Abiraterone + Prednisone
AEs: HTN, Hypokalemia

Chemotherapy
Docetaxel + Prednisone
AEs: Neuropathy

TRIPLET THERAPY

Chemo + ARI
Docetaxel + Darolutamide

Chemo + CYP17 Inhibitor
Docetaxel + Abiraterone

Indications for Triplet Therapy:
- De Novo MPC (no data in recurrent)
- High volume
- Good PS

Metastatic Castrate Resistant Prostate Cancer (mCRPC)

1. Repeat Biopsy

Small Cell
Chemotherapy
Platin/Etoposide

Adenocarcinoma

2. Prior Exposures

Prior ARSI
Docetaxel

Prior Docetaxel
Cabazitaxel
ARSI

3. Disease Burden

Visceral
Docetaxel
Cabazitaxel
Abiraterone
Enzalutamide

Asymptomatic
Sipuleucel T

Sx Bone Only
Radium-223

4. Molecular Characteristics

HRRm
Olaparib +/- Abi
Niraparib +/- Abi
Talazoparib/Enza

dMMR, MSI-H
TMB >10
Pembrolizumab

PSMA+
Lu-177