PROSTATE CANCER

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EPIDEMIOLOGY

- **Approximately one American man in eight**
- **The most common cancer in American men other than skin cancer**
- **A majority of men with prostate cancer die of other causes**
- **Variable biology and clinical course**
- **Many prostate cancers do not require immediate intervention**
- **Metastatic disease develops in a small percentage of affected patients**

PATHOLOGY
AND
MOLECULAR PATHOGENESIS

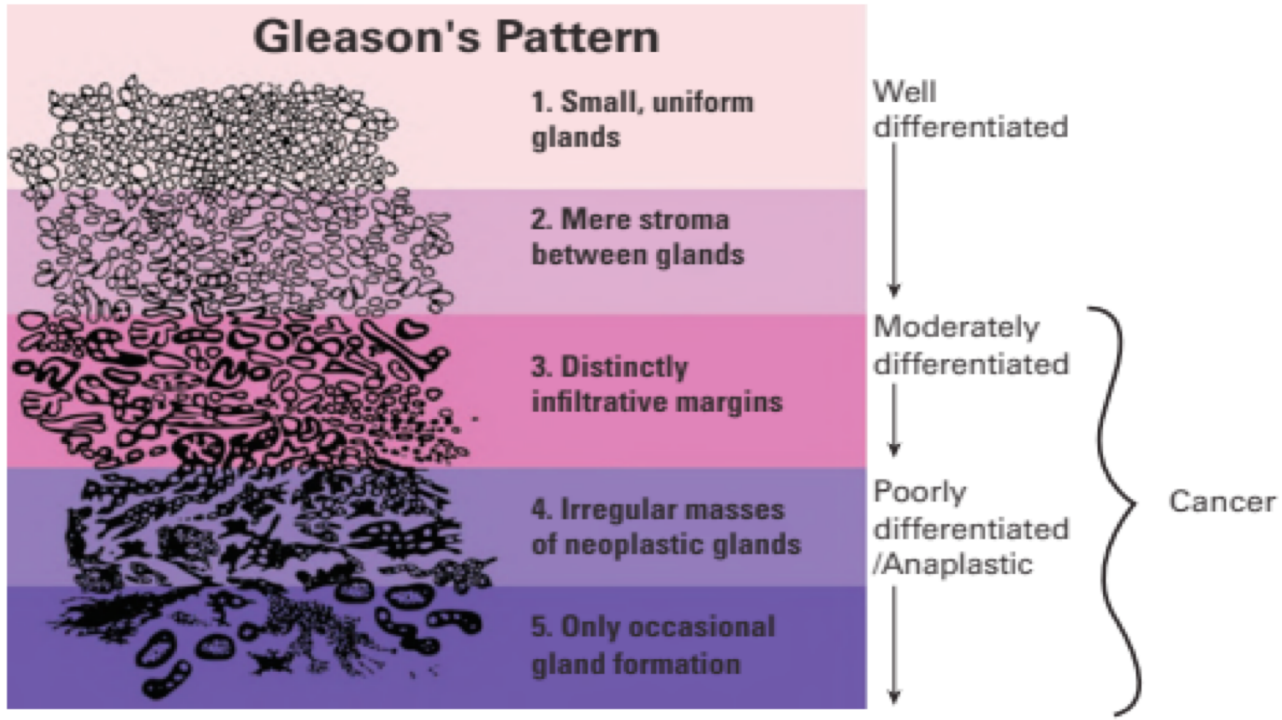
- ***Androgens*** are the primary drivers of prostate cancer cell growth and proliferation
- ***The AR***, located on chromosome Xq11-13, is a member of a superfamily of ligand-dependent transcription factors
- The development of prostate cancer involves a ***multistep*** process
- AR signaling plays a ***key role***
- Numerous molecular abnormalities that may ***differ*** between primary, metastatic, and CRPCs
- The targets relevant for the treatment of early-stage disease may not be the same as those for late-stage tumors

- The typical IHC profile of prostate cancer
- **Negative** for cytokeratins ***7 and 20***.
- **Positive** for ***AR and PSA***.
- **Positive** for the ***NKX 3.1*** homeobox protein
- **Help differentiate prostate cancer from urothelial cancer:**

➢ typically positive for cytokeratins 20 and (usually) 7 as well as GATA3 and negative for PSA and NKX 3.1

- The Gleason grading system applied to prostate biopsies **entire RP** specimens
- Should ***not*** be applied to **metastatic** biopsies or **after** preceding hormonal therapy
- The new system assigns grade groups from 1 through 5

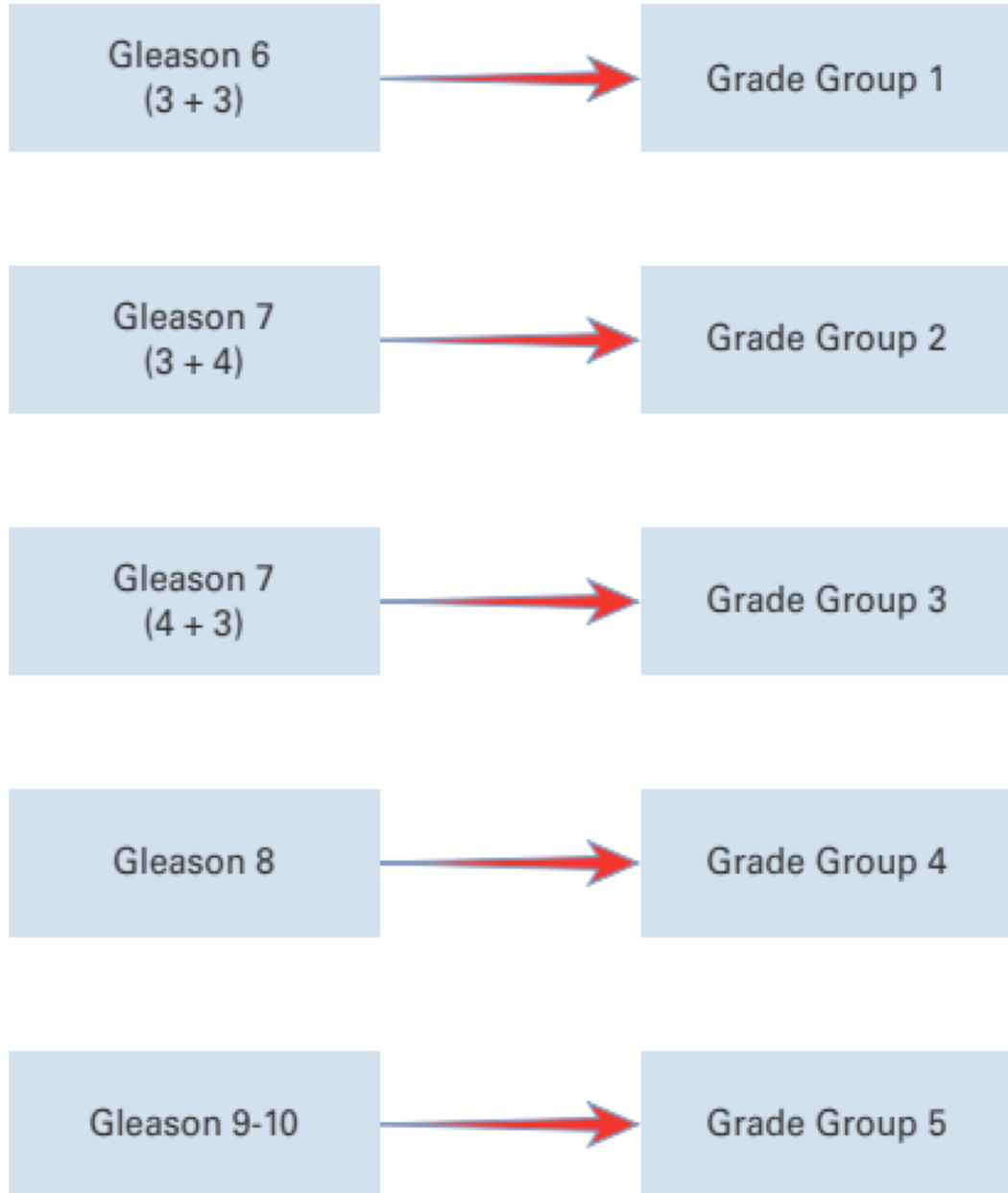
Fig. 14-3. Gleason's pattern.



Source. Wikimedia Commons

Primary Pattern (> 50%)		Secondary Pattern (< 50%)		Gleason Score
3	+	3	=	6
4		4		7
5		5		8
				9
				10

Fig. 14-5. The 2014 ISUP grade groups derived from Gleason scores.



- ***>99%*** of prostate cancers are adenocarcinomas; <1% are pure ductal and mucinous variants
- ***Other histologic*** subtypes include small cell carcinoma and rare mesenchymal tumor
- **Urothelial carcinomas** of the prostate are confined to the periurethral ducts and are more common among patients who have been successfully treated for non–muscle invasive bladder cancer
- **Lymphomas and leukemias** may rarely occur in the prostate gland.

- During the course of treatment of advanced prostate cancer, ***multiple*** genomic and transcriptomic **alterations** can occur
- Alterations in **RB1**, **PTEN**, and **p53**
- ***17%*** of patients with mCRPC developed treatment-associated **small cell/neuroendocrine** histology on metastatic tumor biopsies.
- Some, but not all, of these tumors may exhibit **neuroendocrine** differentiation with positive **synaptophysin** and/or **chromogranin A** staining
- The extreme of neuroendocrine differentiation is small-cell morphology, histology
- Small cell/neuroendocrine prostate cancer should be suspected in patients with a **rapid radiographic progression** or **new hepatic metastases** without PSA increase.

Fig. 14-4. Basic schematic of androgen receptor-directed therapies.

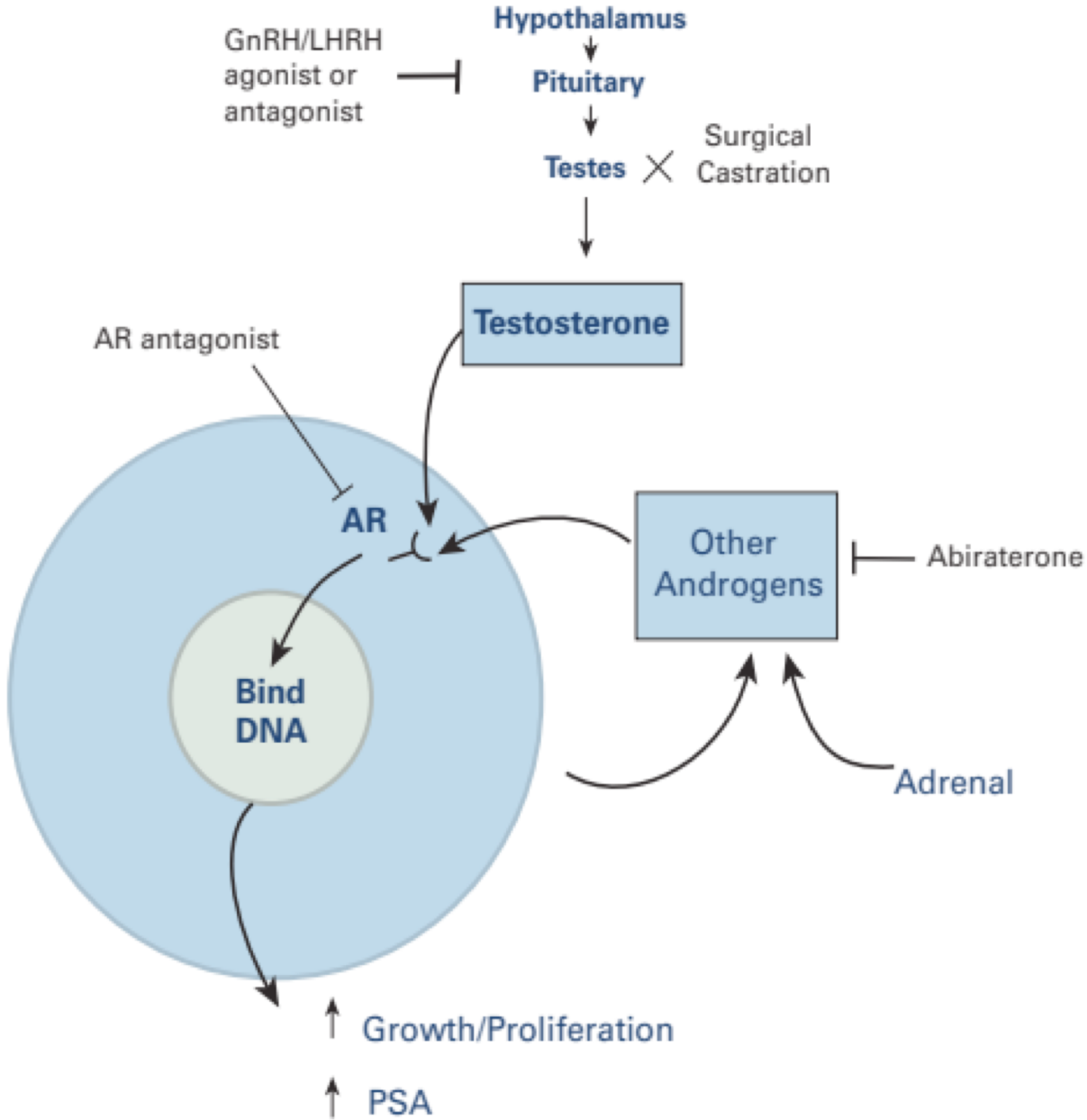
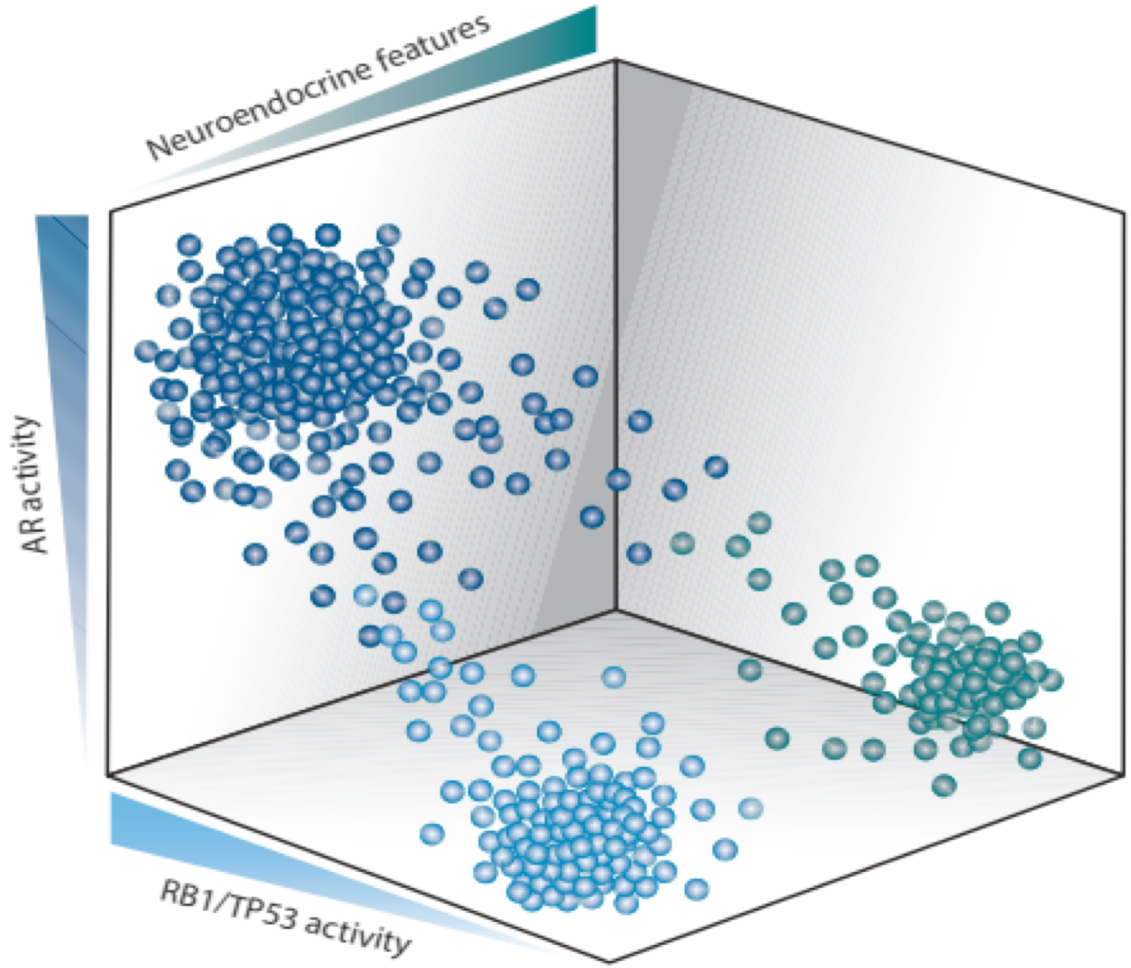


Fig. 14-6. Relationship between AR signaling, tumor-suppressor genes, and neuroendocrine features in metastatic castration-resistant prostate cancer.



This depicts a conceptual representation of the spectrum of profiles that include AR signaling, loss of tumor-suppressor genes and development of neuroendocrine features during prostate cancer progression. Individual dots represent hypothetic patients, but different subclones may also be present within one individual.
Abbreviation: AR, androgen receptor.

PREVENTION

- **Use of a 5-a reductase inhibitor for prevention of prostate cancer would result in one additional high-grade cancer to avert three to four potentially clinically relevant lower-grade cancers**
- **Finasteride and dutasteride do not have a favorable risk-benefit profile for chemoprevention of prostate cancer in healthy men**
- **PSA is expected to fall by approximately one half on 5-a reductase inhibitors**
- **Trials of vitamin supplementation have also not demonstrated benefit**
- **17% increased risk of prostate cancer in the vitamin E group but not in the selenium plus vitamin E group, suggesting that vitamin E supplementation at 400 IU daily significantly increases the risk of prostate cancer development**
- **No universally accepted protocols for prostate cancer prevention or screening.**

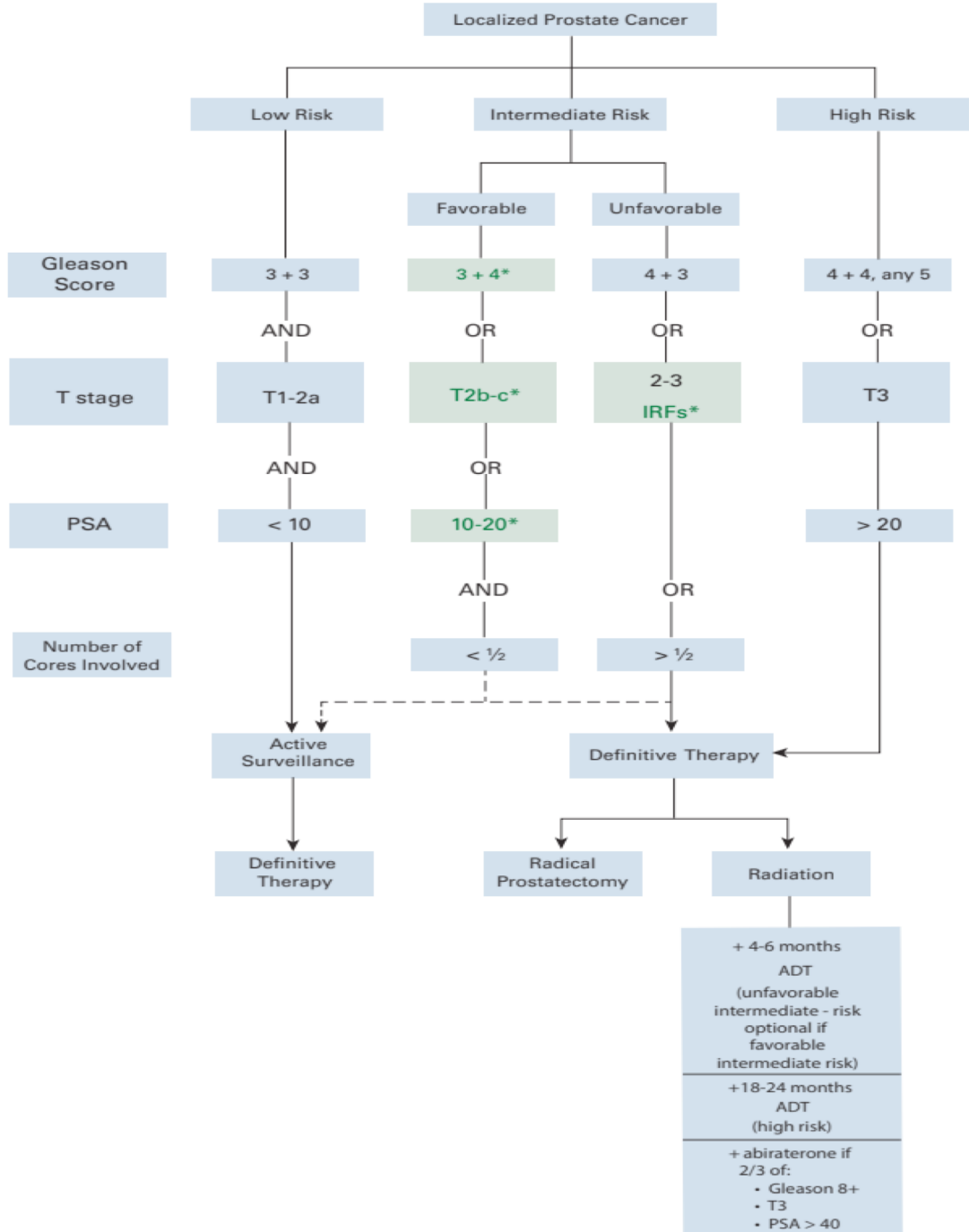
TUMOR STAGING

- Tumors detected in a biopsy specimen on the basis of an elevated PSA level and no palpable disease detected by DRE are designated ***T1c***
- ***T2*** disease is confined to the prostate
- ***T3*** disease, tumor extends through the prostate capsule (**T3a**) or invades the seminal vesicles (**T3b**)
- ***T4*** if they invade adjacent structures or organs.

RISK STRATIFICATION

- **Patients were categorized as low, intermediate, or high risk. However, these categories have been subdivided in more**
- **Using additional factors, such as PSA density, number of involved cores, and primary gleason pattern 5**
- **The DECIPHER test may have a role in determining the benefit of ADT in combination with salvage RT for patients with low PSA**

Approach to treatment options in newly diagnosed localized prostate cancer according to risk stratification.



MANAGEMENT OF PROSTATE CANCER BY RISK

- Localized prostate cancers are those confined to the prostate gland without nodal involvement or metastases
- Treatment selection:

1. the disease can be eradicated by a treatment directed solely
2. combined local and systemic approach
3. therapy is not needed or can be deferred

- Therapy:

1. complete local control
2. decrease the potential for recurrence

- Tumors confined to the prostate are generally managed by:

1. Radical prostatectomy
2. RT
3. In some cases active surveillance

- An assessment of:

1. The patient’s life expectancy
2. Overall health status
3. Tumor characteristics

- Life expectancy of < 5 years do not benefit from treatment of low-risk prostate cancer
- Should undergo watchful waiting and additional workup only if the patient becomes symptomatic

LOW RISK

- AS:

1. Very low risk localized prostate cancer
2. Low risk localized prostate cancer

- Patient preferences:

1. Interstitial prostate brachytherapy
2. EBRT
3. Radical prostatectomy
4. *Focal ablation or high-intensity focused ultrasound*

LOW RISK

- Prostate brachytherapy should not be offered to :

1. Significant lower urinary tract symptoms
2. Repeated episodes of prostatitis
3. Urinary infections

- ***Because brachytherapy may be more likely to exacerbate these symptoms***.

INTERMEDIATE AND HIGH RISK

- **Definitive therapy with:**

1. Prostatectomy

- Or

2. RT

- **The patient's life expectancy:**

1. 10 years or more (intermediate risk)

- Or

2. 5 years or more (high and very high risk)

- Or

3. If the patient is symptomatic

- **Long-term cancer control is equivalent between surgery and radiation**.

- Favorable intermediate-risk prostate cancer may be considered for ***active surveillance***, especially those with small proportions of Gleason pattern 4 disease
- **The addition of ADT to RT has not been shown to improve OS for patients with intermediate-risk disease**
- Improvement in biochemical DFS with 4 to 6 months of ADT
- **ADT is typically also offered to intermediate risk patients but for a relatively short course *(4 to 6 months)***
- **NCCN guidelines suggest ADT may be *optional* for patients who have favorable intermediate-risk disease**

- **ADT**: started approximately ***2 months before RT***
- Although earlier or later timing of RT relative to ADT does ***not seem to affect long-term outcomes***
- It is ***uncertain*** whether the ***addition of bicalutamide to ADT*** improves outcomes for localized prostate cancer
- ***In more advanced disease*** some clinicians will ***add bicalutamide*** for the first 4 to 6 months of ADT or until after RT is completed

- Prostatectomy :

1. Urinary incontinence : improving ***in the months*** after surgery
2. Erectile dysfunction: dependent on baseline function as well as surgical approach ***nerve-sparing vs. Non–nerve-sparing surgery***

- Radiotherapy :

1. irritative urinary
2. Bowel symptoms

- In the days/weeks after treatment (**acute**) or months to years later (**chronic**)

- **Prostatectomy** may be the preferred modality in patients with significant baseline ***urinary obstructive*** symptoms
- **RT** may ***worsen obstructive symptoms*** in the short term.
- **Erectile dysfunction** can occur as a result of **RT and especially surgery**.
- **All patients** in the ***protect study*** were noted to have **decreases** in **erectile function** over time, **even those in *AS*** highlighting that many men in this age range are expected to have decreases in erectile function for reasons other than prostate cancer treatment

- Optimal duration of ADT in conjunction with EBRT
  - ➢ Longer courses resulted in improved long-term survival with an optimal duration in the range of ***18 to 24 months***
- The recommended duration can be customized depending on patient tolerability and comorbidities

- **STAMPEDE protocol** indicated metastasis-free survival and OS benefit from the addition of ***2 years of abiraterone to ADT***
- **Standard-of-care RT** for men with newly diagnosed "high-risk" or relapsing with high-risk features,nonmetastatic prostate cancer
- Newly diagnosed high-risk nonmetastatic prostate cancer :

1. Node positive (Tx N1)

- or, if node negative

2. At least two of the following:

a) Tumor stage T3 or T4,

b) Gleason score of 8 to 10

c) PSA : 40 ng/mL or more

- Several trials : efficacy of ***adding docetaxel*** to ADT and EBRT
- Ultimately **none has shown an OS benefit** with long-term follow up
- **GETUG 12**, **RTOG 0521**, and a nonmetastatic subgroup of the **STAMPEDE** trial **improved relapse-free survival** for docetaxel in patients treated with EBRT and ADT.
- **only RTOG 0521** showed a survival difference with **improved 5-year OS** rate from 89% to 93% (HR, 0.69; 90% CI, 0.49–0.97; one-sided P 5 .034)
- **Neither GETUG 12 nor updated analysis of the STAMPEDE** study showed a difference in **metastatic PFS or OS** with docetaxel

- **NCCN recommends 2 years of abiraterone in addition to EBRT and ADT for very high-risk and regional-risk prostate cancer**

REGIONAL RISK PROSTATE CANCER (CN1) (STAGE IVA)

- Nodes located ***above the aortic bifurcation*** are staged as M1 disease (***stage IVB***) rather than N1 (***stage IVA***).
- Some nodes may be ***borderline*** ; obtain a ***biopsy*** specimen for clarification
- **Alternatively**, treatment with ***neoadjuvant ADT*** may be started before planned definitive RT
- If a repeated CT scan or MRI ***after approximately 3 months*** of ADT shows that any suspicious nodes have decreased in response to ADT
- **PSMA PET** may be helpful although, ***negative results do not rule out nodal involvement.***

- **(Stage IVA) without distant** metastases are ***not necessarily precluded*** from definitive therapy
- **No randomized trials** have established the role of definitive local therapy
- **Retrospective** analyses , **survival benefit** from definitive EBRT to prostate and pelvic nodes with ADT in men with clinical node-positive prostate cancer.
- The meta-analysis of two randomized controlled trials of the STAMPEDE protocols , TxcN1M0:

1) **Metastasis-free survival**
2) **OS benefit**
3) From adding **2 years** of abiraterone **to ADT** and standard-of-care **EBRT and ADT**

- **NCCN** recommends **EBRT plus ADT plus 2 years** of abiraterone for regional lymph node-positive
- ***Alternatively***, prostatectomy and extended lymphadenectomy
- With a likely plan for **adjuvant RT and ADT after surgery** (***trimodality therapy***) for selected patients

TREATMENT MODALITIES

1) **WATCHFUL WAITING AND ACTIVE SURVEILLANCE**
2) **RADICAL PROSTATECTOMY**
3) **RADIOTHERAPY**

WATCHFUL WAITING AND ACTIVE SURVEILLANCE

Watchful Waiting

- Limited life expectancy
- No therapeutic intervention
- Until symptomatic disease progression is evidenced by changes in symptoms, local tumor growth, or development of symptomatic metastases.

Active Surveillance

- Low-risk prostate cancer
- No immediate treatment interventions
- Reduce overtreatment
- Reduce resulting adverse effects of therapy
- Include scheduled

1. PSA testing
2. DREs
3. Periodic repeated prostate needle biopsies at 1 year
4. ***Or*** use of repeat mp-MRIs after the initial prostate biopsies

- Treatment is offered if or when changes in Gleason score, volume of tumor, or serum PSA

RADICAL PROSTATECTOMY

- **The goal of radical prostatectomy:**

1) completely excise the cancer
2) maintaining urinary control
3) preserving potency

- PSA should decline to ***undetectable*** levels
- ***Any detectable or increasing*** PSA levels after prostatectomy are an indication of **recurrent or residual cancer**
- **Cancer control is assessed by:**

1) PSA relapse-free survival
2) Time to objective progression (local or systemic)
3) Cancer-specific survival
4) OS

MANAGEMENT OF ERECTILE DYSFUNCTION

- Even in settings where one neurovascular bundle is spared during surgery
- Less frequent loss of erectile function both neurovascular bundles are spared
- Use of PDE-5 inhibitors (eg, Sildenafil and Tadalafil)
- Daily doses (“penile rehab”)
- Vacuum pumps
- Direct injections of alprostadil or insertion of drug pellets containing alprostadil into the penis or penile urethra
- Implantation of a penile prosthesis

MANAGEMENT OF URINARY INCONTINENCE

- **Most of the improvement after prostatectomy tends to happen within the first year**
- **Exercises of pelvic floor muscles**
- **Surgical approaches to reduce incontinence**
- **Urinary incontinence must be recognized as a potential complication before surgery to ensure that patient expectations**

RADIOTHERAPY

- External-beam techniques, an implant of radioactive seeds, or a combination of the two
- Protons; narrow bragg peak; has not improved clinical outcomes and is significantly more costly
- Treatment to pelvic lymph node for patients with substantial risk of lymph node involvement although including nodes in the radiation field was not associated with superior outcomes
- Radiographically evident lymph node involvement; long-term disease control or, at minimum, decreased chance of symptomatic local relapse.

- Brachytherapy; low- to intermediate-risk disease; a boost
- Acute toxicity; frequency
- Long-term complications, including stricture and irritative symptoms
- Less than 70 Gy; inadequate
- 78 to 79 Gy provide improved cancer control.
- ADT to RT (with or without a brachytherapy boost) suggest some improvements in local control and biochemical freedom from relapse
- RT is associated with bowel complications; irritative urinary symptoms; lower rates of urinary incontinence and sexual dysfunction
- Patients with significant baseline urinary obstructive symptoms may be better candidates for prostatectomy

THERAPY FOR RECURRENT OR ADVANCED DISEASE

PATHOLOGIC NODE-POSITIVE DISEASE (pN1)

- Patients undergo RP and pelvic LNDs
- Found to have pathologic nodal involvement (PN1) and undetectable PSA (< 0.1 ng/ml)
- The risks of biochemical and radiographic recurrence are high
- Adjuvant ADT is an option ➡️ improved OS and prostate cancer–specific survival
- This OS benefit of immediate over delayed ADT for PN1 patients could not be confirmed by another similar phase 3 study trial, EORTC 30846
- ASCO not recommend immediate ADT
- Adjuvant RT is often considered
- Salvage EBRT with ADT at time of BCR is an alternative option

BIOCHEMICAL RECURRENCE

- Rising PSA levels only without radiographic evidence of recurrence or metastatic disease after radical prostatectomy, RT, or both
- Primary radical prostatectomy; serum PSA 0.2 ng/ml or more, which is confirmed by a second determination
- Primary RT increased by 2 ng/dl above the nadir PSA
- Transiently increase after RT because of recovery of testosterone after ADT and/or the so-called PSA bounce

- Increasing PSA level represents micrometastatic disease
- Can be used to prognosticate regarding time to development of metastases

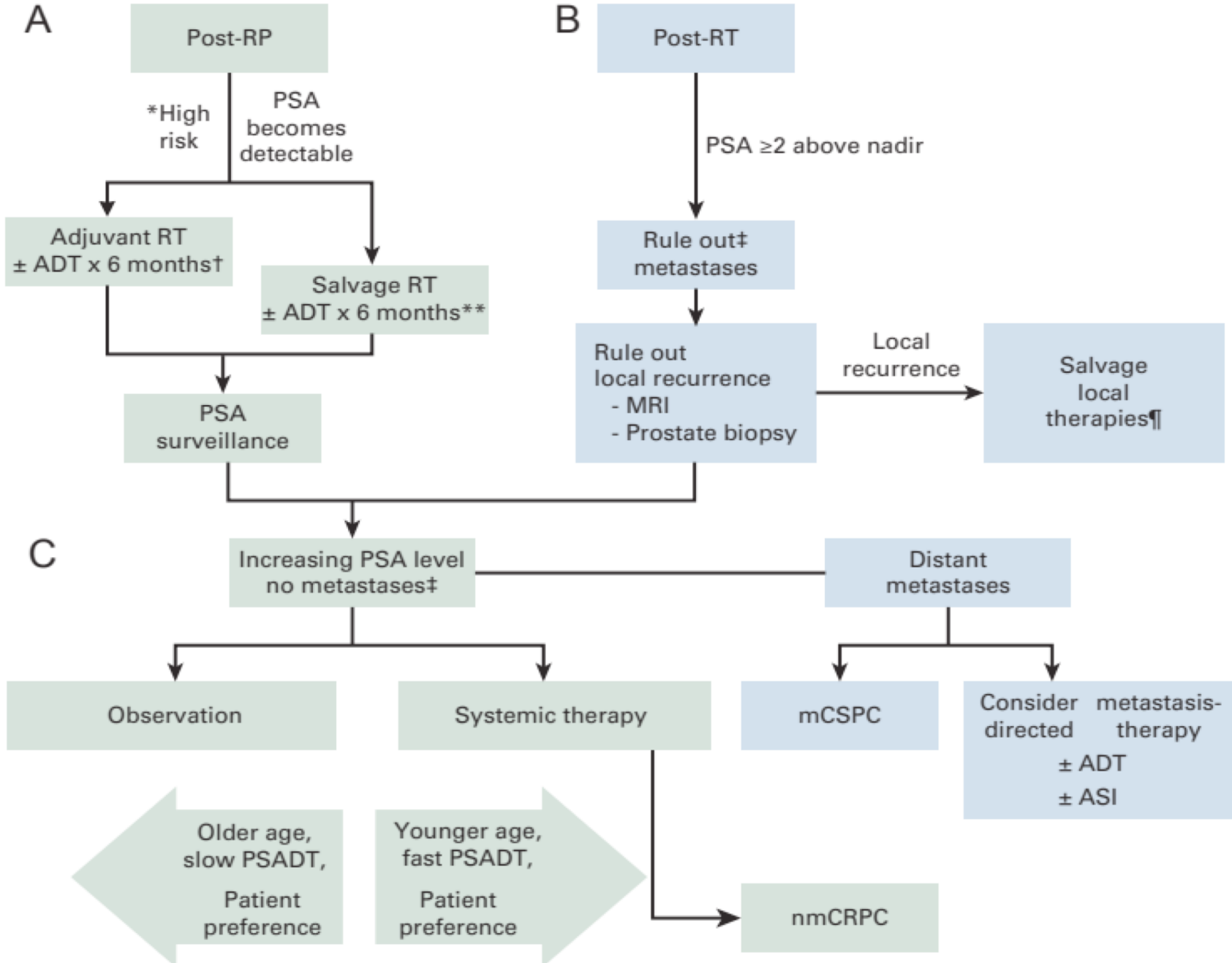
1. Prostate-specific antigen doubling time (PSADT)
2. Time to biochemical progression
3. Gleason score

- PSADT

1. Less than 9 to 10 month >>>development of metastases within months
2. 1.5 to 2 years are generally associated with many years of metastasis-free survival.

- Treatment is often targeted to those with the short PSA doubling times (less than 3 to 6 months)

Management options after primary therapy.



ROLE OF NEXT-GENERATION IMAGING IN EVALUATION OF PATIENTS WITH BIOCHEMICAL RECURRENCE

- The most common treatment failure occurs with undetected metastatic disease
- Detection of occult metastatic disease affects disease management
- Historically ; ^{99}T radionucleotide bone scan and CT scans limited sensitivity at low levels of PSA ***<10 ng/ml***
- In recent years ; ^{68}GA PSMA PET/CT, ^{18}F fluciclovine, or ^{11}C choline PET/CT improved the sensitivity at lower PSA levels

- The average rates of detection with ^{68}Ga PSMA PET/CT; PSA levels :

1. 51.5% < 1.0 ng/mL
2. 74% 1.0 to 2.0 ng/mL
3. 90.5% >2.0 ng/mL

- The average rates of detection with Fluciclovine PET/CT ; PSA levels :

1. 38% <1.0 ng/mL
2. 74% 1.0 to 2.0 ng/mL
3. 78% > 2.0 ng/mL ng/mL

- The rates of detection with ^{11}C choline ; with PSA levels :

1. 19.5% <1.0 ng/mL
2. 44.5% 1.0 to 2.0 ng/mL
3. 76% >2.0 ng/mL ng/mL

- PSMA PET/CT: staging of high-risk localized prostate cancer ; unfavorable intermediate risk.
- Early BCR postprostatectomy ; at PSAs around 0.2 ng/m ; the yield of PSMA PET/CT imaging is typically low
- Patient with PSA persistence postprostatectomy ; did not undergo initial staging PSMA PET/CT ; patient presenting for salvage radiation evaluation at higher PSAs, PSMA PET/CT may help guide the radiation treatment field
- PSMA PET/CT restaging should generally not be performed in patients with rising PSA after primary radiation until PSA reaches 2.0 ng/mL above nadir
- PSMA PET/CT may have false positives; benign rib lesions ; renal cell carcinoma and salivary gland tumors.

LOCAL FAILURE

ADJUVANT AND SALVAGE RADIOTHERAPY

- Adjuvant RT ; certain high-risk features at the time of radical prostatectomy, especially pathologically positive lymph nodes
- Salvage RT ; at the time of PSA recurrence (BCR) after prostatectomy ; limiting RT to only those patients with definitive evidence of recurrence
- Three randomized trials comparing immediate (adjuvant) versus early salvage RT indicated that early salvage is likely equally effective
- very high-risk pathology (eg, seminal vesicle involvement or positive lymph nodes; early salvage RT; when PSA becomes detectable; rising; PSA greater than 0.1 ng/mL; high Gleason score; extraprostatic extension; positive margins >>>> avoid the risk of overtreatment

- Early salvage RT at low PSA levels seems to be superior to later RT at higher PSA levels
- Salvage RT should not be delayed until there are positive findings on PSMA PET/CT
- Salvage RT may increase prostate cancer specific survival, but one study suggested the benefit was limited to men with a PSA doubling time of less than 6 months

- ***The role of hormonal therapy with RT in the salvage or adjuvant setting***:
- ***RTOG 9601***; 24 months of high-dose bicalutamide (150 mg orally daily); OS benefit; increased cardiac toxicity and gynecomastia
- No benefit; PSA < 0.6 ng/mL
- High score on the ***Decipher*** test, a 22-gene expression assay; risk of distant metastasis and prostate cancer–specific mortality; benefit of ADT even in the low-PSA subgroup

- ***GETUG-AFU16***; 6 months of ADT with GnRH agonist added to salvage RT improved 10-year PFS rate
- ***SPPORT***; multicenter trial ; PFS benefit; 4 to 6 months of ADT; extending the RT field to pelvic lymph node RT; compared with salvage RT only to the prostate bed
- ***RADICALS-HD***; evaluated the optimal duration of the ADT for postoperative RT, either immediate or salvage; randomization to either (1) 6 versus 0 months of ADT or (2) 24 versus 6 months of ADT
- No difference found between short-course versus no ADT
- Long-course ADT had prolonged metastasis-free survival versus short-course ADT
- Patients with higher risk factors (eg pT3b/4) could be considered for longer-course ADT
- Potential benefit to the addition of ARIs in patients with higher PSAs

SALVAGE PROSTATECTOMY

- Treated initially with RT; salvage prostatectomy if; life expectancy of more than 10 years; no metastatic disease
- Biopsy-specimen confirmation
- Incontinence rates remain high
- All patients are impotent

- Salvage treatments for post-RT recurrent, including

1. Cryotherapy
2. Brachytherapy

- MRI is most useful for detecting recurrence
- Confirmatory diagnosis is then made via prostate biopsy
- Biopsies should not be done for several months after RT because the effect of radiation is prolonged
- Cancer cells may persist at these earlier time

SYSTEMIC THERAPY FOR BIOCHEMICALLY RECURRENT PROSTATE CANCER

- Once local therapies have been exhausted
- Highly heterogeneous natural history
- Two approaches to persistent BCR

1. Surveillance
2. Systemic (noncurative intent)

- Prognostic factors:

1. Initial GS
2. Time to recurrence
3. Especially PSADT

- They do not necessarily predict who will most benefit from intervention versus surveillance

- PSA level almost always declines in response
- Clinical benefit of ADT in this setting has not been conclusively established
- One trial; randomly; patients who had BCR; early ADT at the time of BCR versus delayed ADT at the time of metastatic disease
- OS was improved with early ADT
- Decision of when to start ADT for BCR is a difficult one
- Historically, intermittent androgen suppression; 8 months in each cycle; restarting ADT when PSA is greater than 10 ng/mL
- Reasonable alternative to continuous androgen suppression, but only in the setting of nonmetastatic disease
- Goal is to minimize adverse effects
- Including hot flashes, loss of libido, bone loss, and muscle atrophy,

- ***EMBARK study*** randomized patients with BCR

1. PSADT < 9 months
2. postprostatectomy PSA > 1.0 ng/m
3. post primary RT > 2.0 ng/mL above nadir

i. ADT only

ii. Enzalutamide only

iii. The combination.

- Intermittent therapy was built into the protocol on all arms.
- Both enzalutamide alone and with ADT showed superior metastasis-free survival compared with ADT alone

NONMETASTATIC CASTRATION-RESISTANT PROSTATE CANCER

- Increasing PSA levels despite castration-level testosterone values but without overt radiographic evidence of metastases by conventional bone scan and CT imaging
- Several randomized trials; addition of second-generation AR antagonists; delay the onset of radiographic metastatic disease (metastasis-free survival) and OS compared with ongoing ADT alone
- Enzalutamide, apalutamide, and darolutamide for patients who have nmCRPC with PSA doubling time of 10 months or fewer
- It is not yet clear that starting men on early ADT and then proceeding to one of these agents before development of metastatic disease will prolong survival relative to starting ADT (and additional therapies) only at the time of metastatic disease.

- ***Apalutamide***:

1. Increased risk of rash
2. Hypothyroidism
3. Fracture

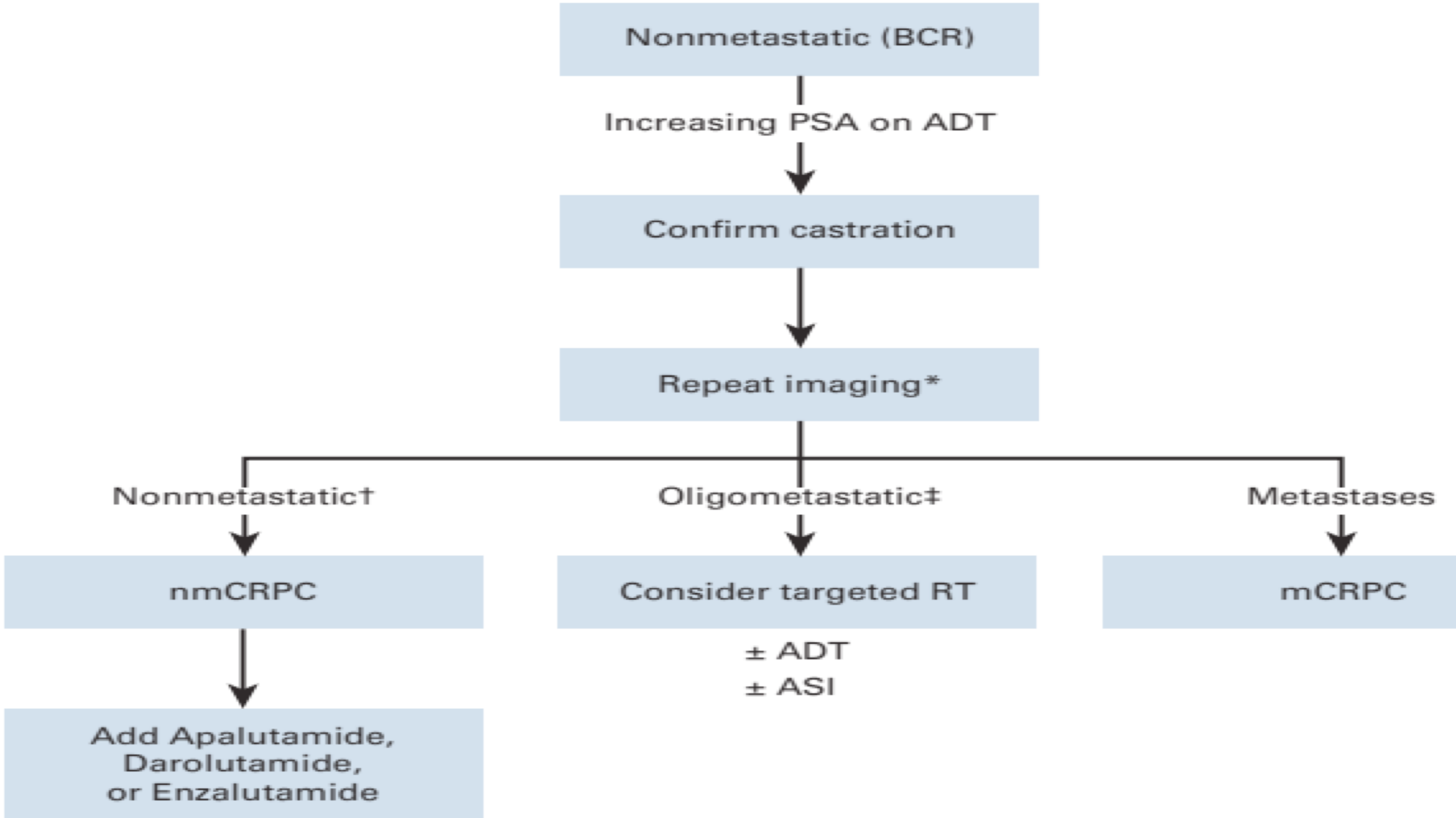
- ***Enzalutamide***

1. Increased risk of hypertension
2. Myocardial infarction
3. Fatigue
4. Falls
5. Fractures

- ***Darolutamide***

1. Increased risk of fatigue

Fig. 14-10. Treatment options for nmCRPC.



ROLE OF LOCAL THERAPY OUTSIDE THE PROSTATE FOR BIOCHEMICAL RECURRENCE

- Oligometastatic recurrence
- Targeted RT, cryoablation, or radiofrequency ablation
- Delay the need for ADT
- PSMA PET/CT may be particularly helpful for detecting early oligometastatic recurrences

THERAPY FOR METASTATIC PROSTATE CANCER

ANDROGEN-DEPRIVATION THERAPY FOR METASTATIC PROSTATE CANCER

- ADT(ie, castration therapy) is the backbone of systemic therapy
- Palliative
- PSA decline
- Objective tumor responses in **>90%**
- Metastatic “hormone-sensitive” or “castration-sensitive” prostate cancer
- Median time to castration-resistance or PSA progression on ADT monotherapy is about ***7 to 12 months***

- mCRPC all patients with mCSPC experience treatment resistance as evidenced by rising PSAs or radiographic progression despite castrated level of testosterone (< 50 ng/dL)
- ADT should be kept continuously even if patients develop castration resistance
- Two forms of ADT: surgical and medical castration
- Goal is to keep the testosterone level less than 50 ng/dL
- Bilateral orchiectomy
- Medical castration:

1. LHRH agonist (eg, leuprolide and goserelin)
2. LHRH antagonist (degarelix and relugolix).

- Medical or surgical castration is associated with:

1. Impotence
2. Loss of libido
3. Weakness
4. Fatigue
5. Hot flashes
6. Loss of muscle mass
7. Anemia
8. Depression
9. Cardiovascular toxicity
10. Loss of bone: osteoporosis or exacerbate underlying osteopenia
11. Risk of dementia : ***conflicting***

- ***Resistance and aerobic exercises can improve muscle mass, strength, and physical function***

- **Response to ADT can be measured by a decline in PSA values**
- ***60% to 70%* normalization; less than 4 ng/mL after castration**
- ***30% to 50%* of measurable tumor masses will regress by 50% or more**
- ***60%* of patients will have palliation of symptoms.**
- ***30% to 40%* Serial bone scans will show improvement**
- **scintigraphic flare on serial bone scans can occur after ADT between *3 and 6* months after initiation of therapy; this should *not be confused* with progression of skeletal metastases**
- ***PSA at 7 months after* initiating therapy is prognostic with dramatically shorter median survival for patients with a *PSA > 4 ng/mL* and dramatically longer median survival for those with a *PSA < 0.2 ng/mL* at this point**
- **Treatment with an LHRH agonist initially increases serum testosterone level**
- **an AR antagonist (eg, bicalutamide 50 mg daily) is sometimes used**
- **block potential effects of the testosterone surge, especially if a patient has high-risk metastatic lesions (eg, imminent spinal cord compression or urinary obstruction)**
- **LHRH antagonist or surgical castration could be used to avoid testosterone flare**
- **An AR antagonist as monotherapy is not a standard-of-care choice**

SECONDARY THERAPIES FOR METASTATIC CASTRATION-SENSITIVE PROSTATE CANCER

- ADT as a systemic therapy for advanced prostate cancer
- Intensification of systemic therapy for mCSPC by adding a secondary therapy to improve the clinical outcomes and OS
- Novel hormonal therapies (NHT) such as abiraterone, apalutamide, enzalutamide, and darolutamide

DOCETAXEL FOR METASTATIC CASTRATION-SENSITIVE PROSTATE CANCER

- CHAARTED and STAMPEDE
- Improvement in OS with the addition of docetaxel to ADT backbone.

TRIPLET THERAPY FOR mCSPC

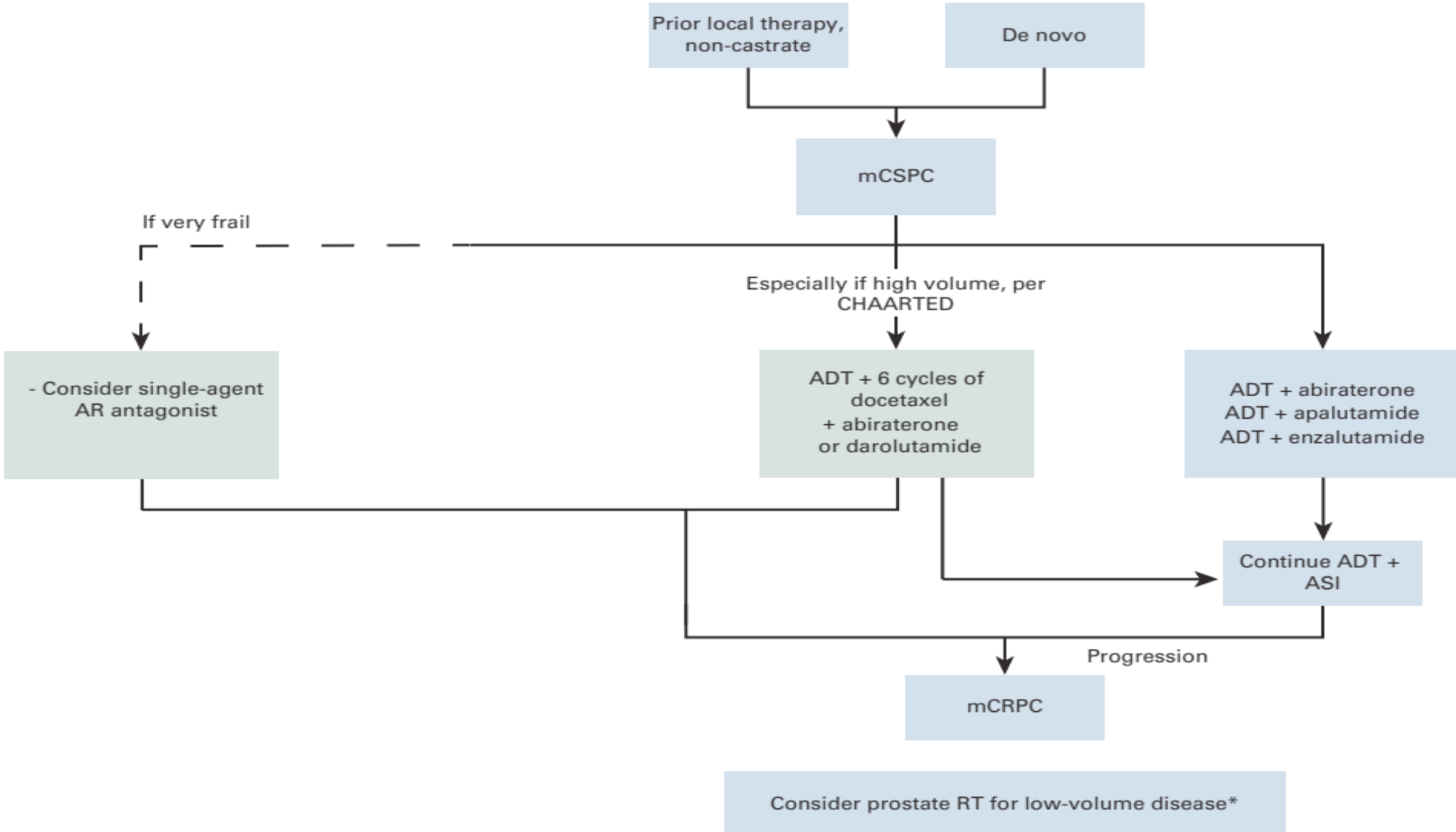
- ADT/docetaxel, addition of ARPI
- No trial; docetaxel is beneficial when added to an ADT/ARPI backbone
- ***PEACE-1 study***; adding abiraterone and/or local RT to prostate with a2×2 study design.
- Abiraterone added to ADT/docetaxel significantly improves median radiographic PFS in men with mCSPC by 2.5 years
- Both high- and low-burden metastatic disease
- 18% reduction in the risk of death and improvement in median OS
- The OS benefit was clearly seen in the subgroup with the high metastatic disease burden
- Immature for the low-burden
- Role of triple therapy in mCSPC is being established

Standards of care for mCSPC by disease volume

	High-Volume mCSPC	*Low-Volume mCSPC*
De Novo	*ADT +* * • *abiraterone* • *apalutamide* • *enzalutamide* • *docetaxel + abiraterone* • *docetaxel + darolutamide*	*ADT +* • *abiraterone* • *apalutamide* • *enzalutamide* *ADT + local RT to prostate* *+/- docetaxel* • *darolutamide + docetaxel*
Recurrent **	*less common*	*ADT +* • *apalutamide* • *enzalutamide*

High-volume **defined as presence** ***of >=4*** **bone metastases with one or more lesions in extra-axial skeleton or presence of visceral metastasis**

Fig. 14-12. Systemic treatment options for mCSPC.



- ***<u>ARASENS study</u>***
- Darolutamide is a potent AR antagonist that has shown efficacy in patients with nmCRPC
- darolutamide lowered the risk of death by 32.5%
- Darolutamide was approved by the FDA in combination with docetaxel for patients with mCSPC

ABIRATERONE FOR mCSPC

- Abiraterone acetate is an oral CYP17 inhibitor ; inhibits androgen and glucocorticoid biosynthesis.
- Feedback loops during treatment result in adrenocorticotropic hormone-mediated excess mineralocorticoid activity, including ***hypertension***, ***fluid retentio***n, and ***hypokalemia***
- Low-dose prednisone
- Potassium level, blood pressure, and liver function should be monitored during treatment
- Hepatotoxicity is managed with dose holds and resumption at lower dose levels
- Hypertension may be treated with standard antihypertensive mineralocorticoid receptor antagonists such as Eplerenone

- LATITUDE and STAMPEDE-G, demonstrated an improvement in OS with the addition of abiraterone and prednisone to ADT for mCSPC
- ***LATITUDE study*** included only patients with

1. de novo mCSPC with
2. high-risk features as defined by having two or three of the following:

a) visceral disease
b) at least three bone metastases
c) Gleason score of 8 or higher

- **improvement of median OS**
- ***STAMPEDE-G study***
- **improvement of 5-year survival rate**

Table 14-1 Randomized Trials of ADT Plus Abiraterone and Prednisone for mCSPC

Trial	No. of Participants	Study Population	Design	Outcome	Notes
LATITUDE	1199	De novo high-risk mCSPC	ADT plus placebo versus ADT plus abiraterone and prednisone	Improved OS with addition of abiraterone and prednisone (not reached versus 34.7 months)	High-risk based on 2 of 3: Gleason 8+, 3+ bone lesions, visceral metastase
STAMPEDE	1917	High-risk localized or high-risk BCR or mCSPC (recurrent or de novo)	ADT plus placebo versus ADT plus abiraterone and prednisone (plus RT for localized or N+ disease)	Improved 3-year OS with addition of abiraterone and prednisone (83% versus 76%)	Benefit was seen across subsets including M0 tumors, although there were few events in this group

- Three trials
- addition of either apalutamide or enzalutamide to standard ADT for mCSPC
- received FDA approval
- **none** was specifically designed to answer the question of whether **docetaxel plus AR antagonists** is more effective than either alone or in combination with ADT.

Table 14-2 **Randomized Trials of ADT Plus Androgen Receptor Antagonists for mCSPC**

Trial	No. of Participants	Study Population	Design	Outcome	Notes
ARCHES	1150	mCSPC (recurrent or de novo)	ADT versus ADT plus enzalutamide. Docetaxel allowed at investigator discretion in either trial arm	Improved radiographic PFS with addition of enzalutamide (not reached versus 19 months)	rPFS benefit seen regardless of docetaxel use and/or disease volume. OS data immature
ENZAMET	1125	mCSPC (recurrent or de novo)	ADT versus ADT plus enzalutamide. Docetaxel allowed at investigator discretion in either trial arm	Improved OS with addition of enzalutamide (median OS not yet estimable; 80% versus 72% OS at 3 years)	Possibly limited benefit of enzalutamide in docetaxel-treated patients. Possible increased docetaxel toxicity with addition of enzalutamide
TITAN	1052	mCSPC (recurrent or de novo)	ADT versus ADT plus apalutamide. Docetaxel allowed at investigator discretion in either trial arm	Improved OS and radiographic PFS with apalutamide (82% versus 74% OS; 68% versus 48% rPFS)	rPFS benefit seen regardless of docetaxel use and/or disease volume. Possibly limited OS benefit of apalutamide in docetaxel-treated patients

- ADT/docetaxel is superior to ADT alone, especially for high-volume mCSPC
- ADT/NHT (eg, abiraterone, apalutamide, or enzalutamide) is superior to ADT alone
- Do not know which of docetaxel or an NHT is superior as a secondary therapy
- no discernable difference in OS between the docetaxel cohort (n 5 5189) and abiraterone cohort (n 5 5377) of the multiarm STAMPEDE trial
- ADT/docetaxel/abiraterone or darolutamide is superior to ADT/docetaxel
- **A standard of care for a high-volume** mCSPC patient includes ADT//abiraterone or darolutamide or apalutamide or enzalutamide / docetaxel
- ***The standard of care for low-volume*** mCSPC is ADT/abiraterone or darolutamide or apalutamide or enzalutamide with consideration of radiotherapy to the prostate

PROSTATE-DIRECTED THERAPY FOR METASTATIC PROSTATE CANCER

- Conventionally, the presence of metastatic disease excluded consideration for radical prostatectomy or definitive prostate RT
- Interest in prostate-directed therapy is growing even in the setting of metastatic disease
- Long-term remissions using prostate-directed therapy with targeted RT and ADT for oligometastatic prostate cancer
- E HORRAD and STAMPEDE trial; increase in OS in patients with low-volume disease

SUPPORTIVE CARE FOR METASTATIC CASTRATION-SENSITIVE PROSTATE CANCER

CARDIOVASCULAR HEALTH

- long-course ADT has been associated with cardiovascular risks and metabolic syndrome
- further exacerbated by prednisone
- ***Relugolix*** may decrease major adverse cardiovascular events compared with GnRH agonists
- relugolix is a consideration, particularly in patients with prior major cardiovascular events,
- Surgical castration ; cost-effective, fewer injections

METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

- disease that progresses during ADT
- patient is medically castrate (defined as serum testosterone level less than 50 ng/dL)
- AR activation despite castrate testosterone levels include

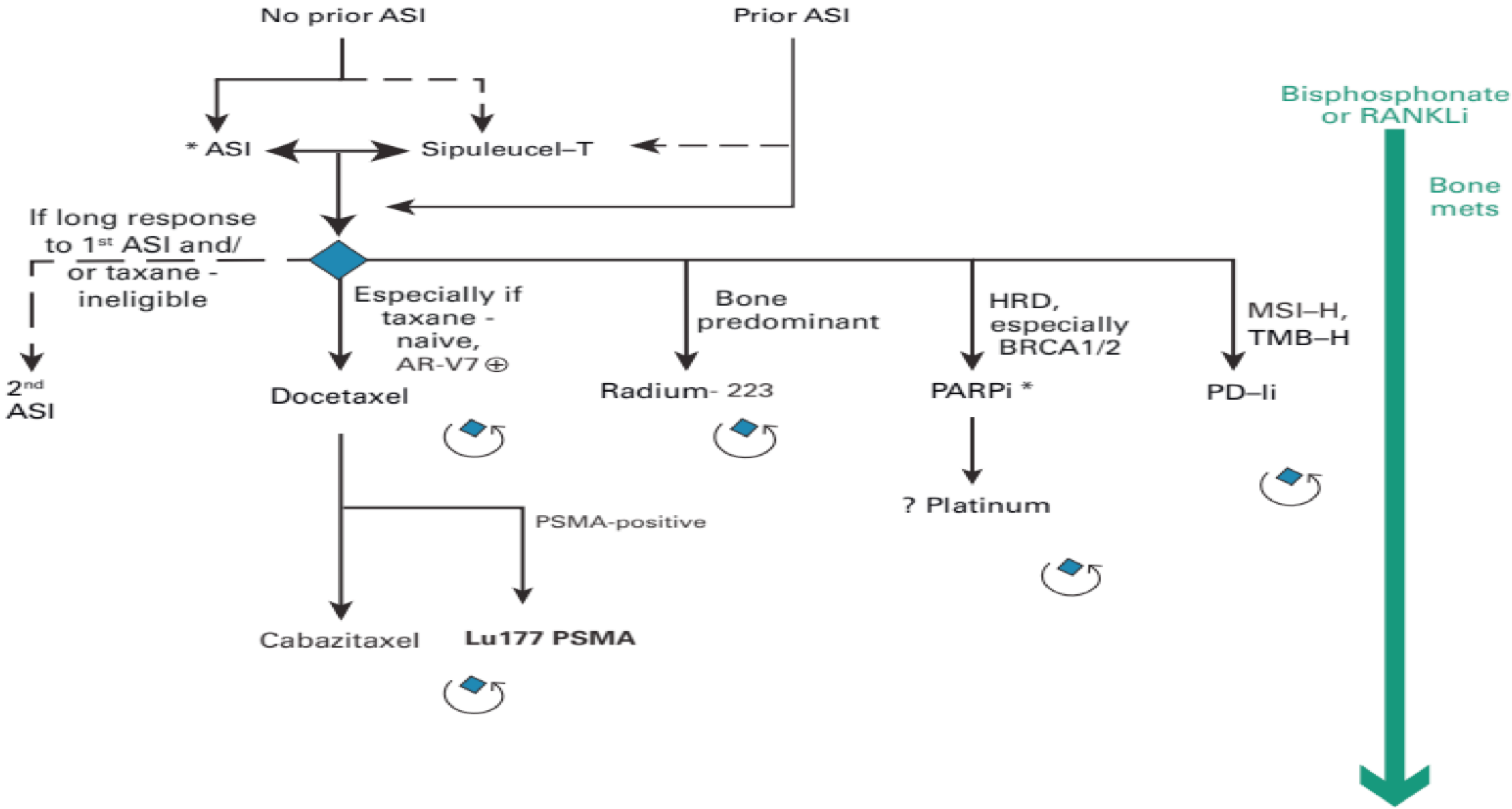
1. AR overexpression
2. ligand-independent activation
3. de novo synthesis of intratumoral androgens
4. alterations in the AR, including splice variants and circulating subcastrate levels of androgens

- Multiple classes of therapy that improve overall survival:

1. immunotherapy (sipuleucel-T)
2. taxane chemotherapy (docetaxel, cabazitaxel)
3. radiopharmaceuticals (radium-223, lutetium-177)
4. AR signaling inhibitors

- The development of new classes as novel hormonal therapies [NHT] or ARPIs) designed as cytochrome P450 (CYP) 17 inhibitors or inhibitors of the AR has that led to improvements in survival for patients with CRPC
- ARPIs includes abiraterone acetate, enzalutamide, apalutamide, and darolutamide
- repeated biopsy of a metastatic site may indicate a neuroendocrine or small-cell phenotype

Treatment options for mCRPC.



ANDROGEN RECEPTOR SIGNALING INHIBITORS FOR METASTATIC CASTRATION RESISTANT PROSTATE CANCER

- abiraterone, enzalutamide, apalutamide, and darolutamide
- the noninferiority of low-dose abiraterone (250 mg per day with a low-fat meal) to standard dosing
- for those who cannot afford the cost of the standard dose
- Enzalutamide is a highly potent oral AR antagonist; Toxicities include fatigue and hypertension
- interactions with; direct oral anticoagulants and fentanyl
- increased risk of falls and possibly seizures

- abiraterone and enzalutamide
- approximately 15% to 25% of patients have primary resistance and a high degree of cross-resistance
- Starting with abiraterone and then administering enzalutamide is associated with a better time to PSA progression with second-line therapy than enzalutamide followed by abiraterone, but overall survival is similar between the two sequences

CHEMOTHERAPY FOR METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

- 2004, two randomized trials
- docetaxel-based therapy with mitoxantrone and prednisone
- significant improvement in OS
- superior to mitoxantrone with respect to pain response rate, PSA response rate, and quality of life indices
- docetaxel (75 mg/m2 every 21 days) together with prednisone

- Cabazitaxel
- after prior docetaxel therapy
- 25 mg/m2
- Grade 3 to 4 neutropenic fever
- 20 mg/m2 is noninferior; less toxic

- In patients with small-cell histologies, platinum-containing chemotherapy
- ADT should be continued during treatment of small-cell carcinoma because of intratumoral and intertumoral heterogeneity

IMMUNOTHERAPY

- Sipuleucel-T
- activated autologous dendritic cells
- every 2 weeks
- asymptomatic patients
- 22% relative reduction in the risk of death

- Checkpoint inhibitors
- limited efficacy
- a small percentage of patients with metastatic prostate cancer have MSI-high/MMR-deficient

PARP INHIBITORS

- PARP, a critical enzyme in initiating repair machineries for single-strand DNA break
- somatic or germline deleterious mutations in BRCA1 or BRCA2 or other HRR-related genes
- olaparib and rucaparib
- radiographic PFS and OS

BONE-TARGETED THERAPY

- Bone metastases may be asymptomatic or painful
- can eventually lead to pathologic fracture, spinal cord compression, need for RT, or surgery; skeletal-related events (SREs)
- The a-emitter radium-223 (223Ra); no known visceral metastatic disease
- avoiding concurrent treatment with 223Ra and abiraterone plus prednisone
- Bisphosphonates or denosumab; approved by the FDA in two situations:

1. prevent osteoporosis related fractures.
2. Men with mCRPC and bone metastases:

- Monthly dosing or dosing every 3 months with zoledronic acid is indicated for bone metastases,
- yearly infusions can be used for treatment of osteoporosis.
- denosumab, a RANKL inhibitor; superior to zoledronic acid
- mCRPC (120 mg every month)
- fragility fracture prevention (60 mg every 6 months)
- Both denosumab and zoledronic acid are administered with calcium