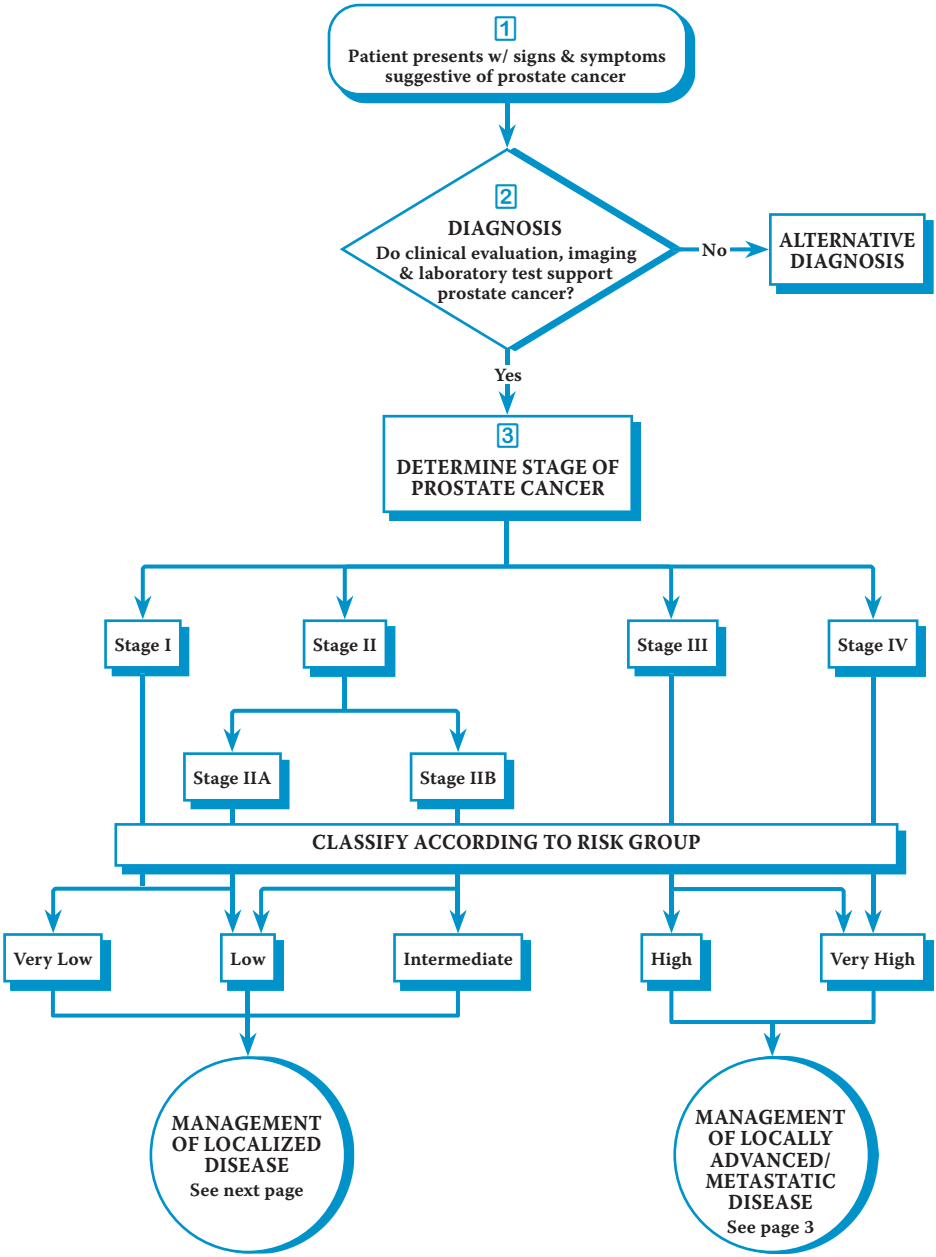
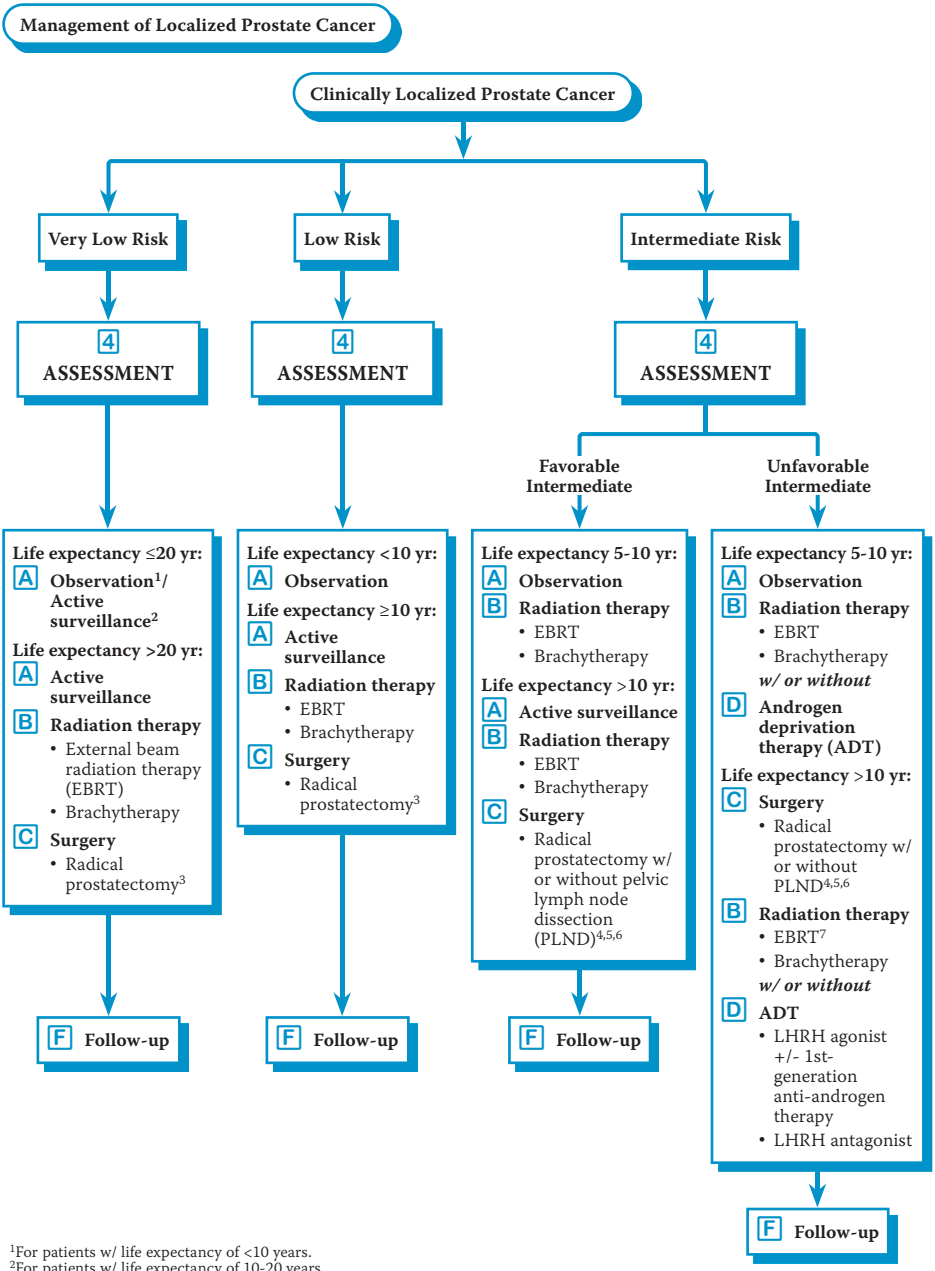
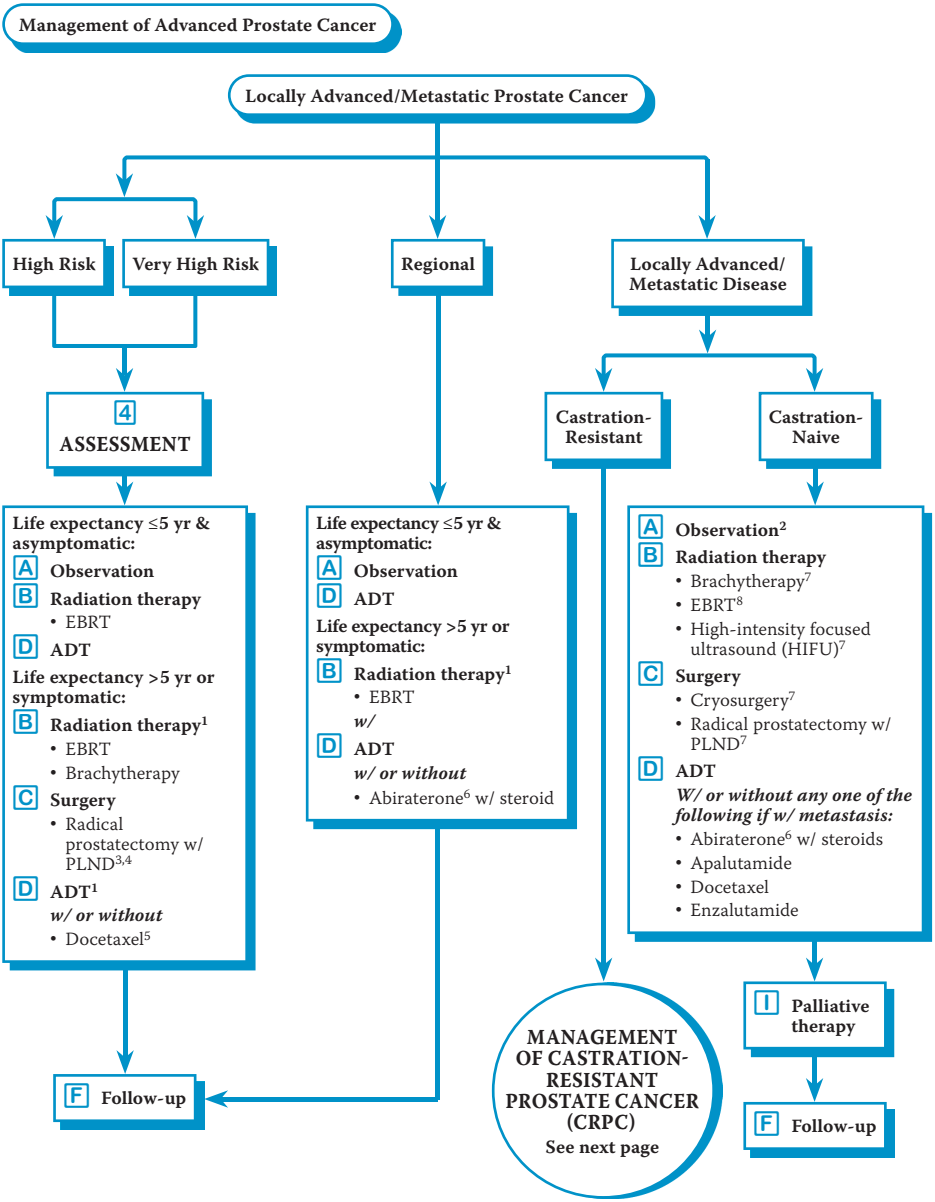
Prostate Cancer (1 of 30)

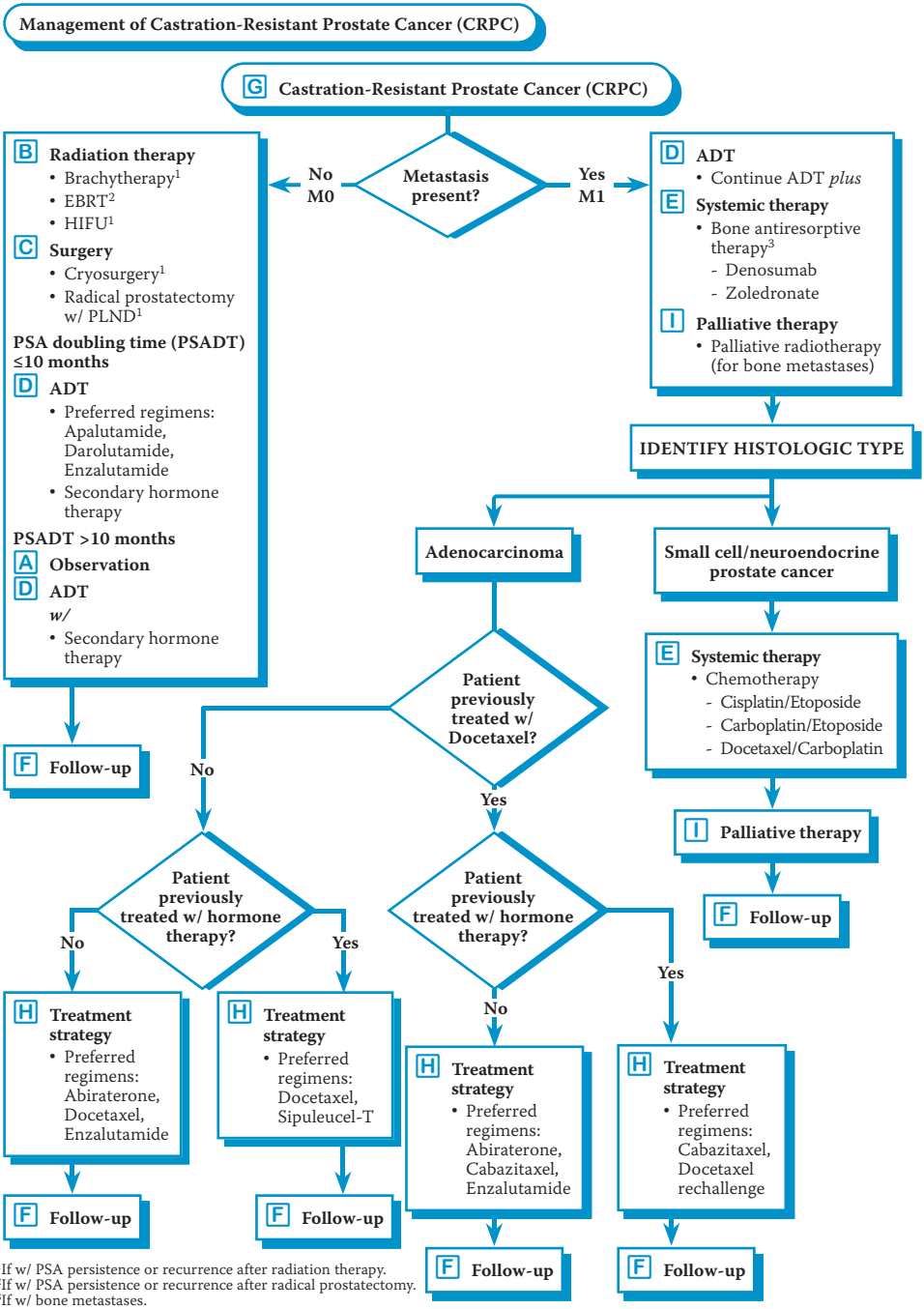




[1]For patients w/ life expectancy of <10 years.
[2]For patients w/ life expectancy of 10-20 years.
[3]May be given adjuvant EBRT w/ or without ADT or may be observed if w/ adverse events.
[4]May be given adjuvant EBRT w/ or without ADT or may be observed if w/ adverse events & no lymph node metastases.
[5]W/ PLND if w/ ≥2% predicted probability of lymph node metastasis.
[6]May be given adjuvant ADT w/ or without EBRT or may be observed if w/ lymph node metastasis.
[7]Treatment duration for EBRT given w/ either brachytherapy or ADT: 4-6 months.



[1]Combination of EBRT + ADT w/ or without brachytherapy is recommended.
[2]For patients without distant metastasis only.
[3]May be given adjuvant EBRT w/ or without ADT for 6 months or may be observed if w/ adverse events & no lymph node metastasis.
[4]May be given adjuvant ADT w/ or without EBRT or may be observed if w/ lymph node metastasis.
[5]Optional treatment for very high risk patients.
[6]Fine-particle Abiraterone may also be considered.
[7]If w/ PSA persistence or recurrence after radiation therapy in patients w/ life expectancy >10 years.
[8]If w/ PSA persistence or recurrence after radical prostatectomy.



[1]If w/ PSA persistence or recurrence after radiation therapy.
[2]If w/ PSA persistence or recurrence after radical prostatectomy.
[3]If w/ bone metastases.

Not all products are available or approved for above use in all countries.
Specific prescribing information may be found in the latest MIMS.

1 PROSTATE CANCER

- Second most common cancer in men; one of the most common cancers in men >50 years of age

Risk Factors

- Age (increased risk in men >50 years)
- Positive family history: 1st- or 2nd-degree relatives diagnosed w/ metastatic prostate, ovarian, breast (female ≤45 years old), colorectal, endometrial (≤50 years old) or pancreatic cancer, & those w/ ≥2 1st- or 2nd-degree relatives diagnosed w/ prostate, breast, colorectal or endometrial cancer at any age
- Ethnicity (African ancestry, Ashkenazi Jewish descent)
- Chemical exposures (toxic combustion products)
- Genetic mutations: *BRCA1*, *BRCA2, ATM*, *CHEK2*, *HOXB13*, *EPCAM*, *RAD51D*, *PALB2* mutations, DNA mismatch repair genes (MSH2, MLH1, Lynch syndrome), IGF-1
- Genetic mutations: Breast cancer gene 1 (*BRCA1*), breast cancer gene 2 (*BRCA2*) mutations, ataxia telangiectasia mutated (*ATM*), checkpoint kinase 2 (*CHEK2*), homeobox B13 (*HOXB13*), epithelial cellular adhesion molecule (*EPCAM*), nibrin (*NBN*), tumor protein 53 (*TP53*), partner & localizer of *BRCA2* (*PALB2*), deoxyribonucleic acid (DNA) mismatch repair genes [mutS homolog 2 (*MSH2*), mutL homolog 1 (*MLH1*), Lynch syndrome, mutS homolog 6 (*MSH6*), post-meiotic segregation increased 2 (*PMS2*)], insulin-like growth factor-1 (IGF-1)
- Other risk factors under research include a positive medical history of inflammation of the prostate gland [eg prostatitis, sexually transmitted diseases (STDs), proliferative inflammatory atrophy (PIN)] & vasectomy

Signs & Symptoms

- Weak urinary stream, incomplete bladder emptying
- Polyuria, nocturia
- Hematuria
- Erectile dysfunction
- Pelvic pain, back pain, chest pain
- Lower extremity weakness or numbness
- Loss of bladder or bowel control

2 DIAGNOSIS

- Key examinations for the diagnosis of prostate cancer include prostate-specific antigen (PSA) level, digital rectal examination (DRE) & prostate biopsy

Prostate-Specific Antigen (PSA) Level

- A kallikrein-like serine protease produced by prostatic epithelial cells
- Organ specific but not specific to cancer & may be elevated in benign conditions (eg benign prostatic hypertrophy, prostatitis)
- Risk for prostate cancer increases w/ increasing level of PSA & may warrant a prostate biopsy
- Predicts extension outside the prostate gland, seminal vesicle invasion, & lymphadenopathies
- Baseline results should be obtained prior to starting treatment as it is also a good measurement for therapeutic efficacy
- Other parameters (PSA testing derivatives) include free PSA level, PSA velocity & PSA density

Digital Rectal Examination (DRE)

- Detects prostatic enlargement w/ volume of ≥0.2 mL
- Abnormal DREs are associated w/ high Gleason scores & may be considered for prostate biopsy

Prostate Biopsy

- Most common method used in diagnosing prostatic carcinoma
- Should only be offered if PSA levels & DRE highly suggest prostate cancer
- Transrectal ultrasound (TRUS)-guided core-needle prostate biopsy is highly recommended for men w/ PSA levels of >4 ng/mL
- Indications:
  - Increased risk for prostate cancer & w/ PSA levels of 2.5-4 ng/mL
  - Increased PSA levels of >0.35 ng/mL within 1 year from baseline of <4 ng/mL
  - Increased PSA levels of >0.75 ng/mL within 1 year from baseline of 4-10 ng/mL
  - PSA levels too high for age range
- Obtaining a minimum of 10-12 cores are recommended
- Should be done under antibiotic coverage
- The perineal approach (transperineal 3D prostate mapping biopsy) is a useful option for special circumstances (eg rectal amputation)

2 DIAGNOSIS (CONT'D)

Prostate Biopsy (Cont'd)

- Transperineal biopsies are favored compared to TRUS-guided biopsies due to reduced risk of infection
- Confirmatory prostate biopsy, w/ or without multiparametric MRI (mpMRI), may be considered if active surveillance is being considered for very low-risk patients & w/ or without molecular tumor analysis in low- to favorable intermediate-risk patients
- Indications for repeat biopsy after previously negative results:
  - Persistently elevated &/or increasing PSA levels
  - Suspicious DRE
  - Positive mpMRI findings

Imaging Procedures

- Should be based on age, risk, PSA results, Gleason score & patient's health status
- Pelvic &/or abdominal imaging is recommended for high-risk to very high-risk patients & for intermediate-risk patients w/ >10% probability of pelvic LN involvement in nomogram
- Imaging may be considered in symptomatic very low-, low- & intermediate-risk patients
- Bone imaging should be performed for any patient w/ symptoms consistent w/ bone metastases

Plain Film Radiography

- May be used to assess for presence of bone pathologies in symptomatic patients

Ultrasonography

- TRUS may be used to assess the prostate gland if PSA levels & DRE results are inconclusive
- Also used as a guide during transrectal prostate biopsies
- Considered in patients w/ suspected recurrence after surgery

Computed Tomography (CT) Scan

- May be used to assess for presence of bone pathologies, gross extracapsular disease, nodal metastatic disease, &/or visceral metastatic disease
- May be used for pelvic &/or abdominal examination as part of initial evaluation & for follow-up evaluation for recurrence or progression
- May be used for lymph node staging in asymptomatic patients at intermediate-high risk (PSA level >10 ng/mL, Gleason score >8, or clinical stage >T3)

Magnetic Resonance Imaging (MRI)

- mpMRI by diffusion-weighted imaging or H1-spectroscopy may be done to assess if repeat prostate biopsy is needed in patients w/ negative results in TRUS
  - Detects large & poorly differentiated tumors & extracapsular extension, used for staging of pelvic lymph nodes, & detects bone metastases (98-100% sensitivity & specificity)
- May be used for pelvic &/or abdominal examination as part of initial evaluation & for follow-up evaluation for recurrence or progression
- Sensitivity at >2 cc: 67-75% for Gleason <6; 97% for Gleason 7; 100% for Gleason >8
- mpMRI is preferred over CT for abdominal/pelvic staging
- Positive results may suggest repeat prostate biopsy

Radionuclide Bone Scan

- A conventional technetium-99m-methylene diphosphonate (MDP) bone scan is used to assess for possible bone involvement
- May be performed for symptomatic patients w/ PSA results of >10 ng/mL, Gleason score >8, long life expectancy, higher T stage & those w/ decreasing PSA doubling time (PSADT)
- May be considered in patients w/ increasing PSA or positive DRE post-radiotherapy who may benefit from additional local or systemic therapy
- Recommended for patients at high- to very-high risk & in patients at intermediate risk w/ T2 & PSA of >10 ng/mL

Positron Emission Tomography (PET)/CT Scan & PET/MRI

- F-18 sodium fluoride, C-11 choline, & F-18 fluciclovine PET/CT or PET/MRI may be considered after bone scan for further evaluation of the bones w/ equivocal bone scan results
- Gallium-68 prostate-specific membrane antigen (^{68}Ga-PSMA) PET/CT scan demonstrates high sensitivity w/ histopathological diagnosis, & has better sensitivity & specificity compared to CT or bone scan for the detection of recurrences at lower PSA levels
  - Can be utilized in staging prostate cancer
- Consider C-11 choline or F-18 fluciclovine PET/CT or PET/MRI for soft tissue & bone evaluation if other work-ups did not show any evidence of metastasis

2 DIAGNOSIS (CONT'D)

Other Biomarker Tests

- Have been associated w/ prostate cancer diagnosis but are not routinely performed
- Biomarkers other than PSA that are used for prostate cancer include apoptosis markers (eg Bcl-2, Bax), proliferation rate markers (eg Ki67), p53 mutation/expression, p27, E-cadherin, DNA plody, p16
- Other biomarker tests recommended by the National Comprehensive Cancer Network (NCCN) include percent free PSA (%f PSA), Prostate Health Index (PHI), four kallikrein (4K) score®, prostate cancer antigen 3 (PCA3), ConfirmMDx & ExoDx *Prostate*(*IntelliScore*) (EPI) test
- Tests that are currently being studied include Mi-Prostate Score (MiPS) & SelectMDx
- An increase in serum acid phosphatase levels may indicate poor prognosis in patients w/ localized & disseminated disease

SCREENING RECOMMENDATIONS

- 45-75 years of age at average risk for prostate cancer
- 40-75 years of age at high risk for developing prostate cancer: African descent, germline mutations, w/ 1st- or 2nd-degree relatives diagnosed w/ metastatic prostate, ovarian, breast (female at ≤45 years of age), colorectal, endometrial (≤50 years of age) or pancreatic cancer, ≥2 1st- or 2nd-degree relatives diagnosed w/ prostate, breast, colorectal or endometrial cancer at any age
- Very healthy >75-year-old individuals w/ minimal or no comorbidities
- W/ previous PSA level of >1 g/mL at 40 years old or >2 ng/mL taken at 60 years old
- W/ initial screening which includes PSA & DRE
- W/ negative results but at risk for prostate cancer, repeat screening should be done depending on the PSA & DRE results:
  - PSA <1 ng/mL w/ normal DRE = 2- to 4-year intervals
  - PSA 1-3 ng/mL w/ normal DRE = 1- to 2-year intervals
  - PSA >3 ng/mL in 40-75 years old &/or very suspicious DRE & PSA ≥4 ng/mL in >75 years old or very suspicious DRE = PSA, DRE if not done, mpMRI; consider biomarkers
  - PSA <4 ng/mL w/ normal DRE & no other indications for biopsy = 1- to 4-year intervals

ALTERNATIVE DIAGNOSIS

- Benign prostatic hypertrophy
- Prostatitis
- Prostatic calculi
- Sarcoma
- Small cell carcinoma
- Transitional cell carcinomas
- Neuroendocrine tumors

3 STAGING

- Determines the extent of cancer upon diagnosis
- Important factor in the choice of treatment & provides information about the prognosis of the disease

Tumor, Nodes & Metastasis (TNM) System

- Developed by the American Joint Committee on Cancer (AJCC) & Union Internationale Contre le Cancer (UICC)

Clinical T (cT)

T - Primary Tumor		
TX		Primary tumor cannot be assessed
T0		Negative evidence of primary tumor
T1		Clinically inapparent & not palpable tumor
	T1a	Tumor incidental histological finding in ≤5% of resected tissue
	T1b	Tumor incidental histological finding in >5% of resected tissue
	T1c	Tumor that is not palpable identified by needle biopsy found in one or both sides
T2		Tumor confined within the prostate is palpable
	T2a	Tumor involves half of one lobe or less
	T2b	Tumor involves greater than half of one lobe but not both lobes
	T2c	Tumor involves both lobes
T3		Not fixed extraprostatic tumor or does not invade adjacent structures
	T3a	Unilateral or bilateral extracapsular extension
	T3b	Tumor invades the seminal vesicle(s)
T4		Fixed tumor or invades adjacent structures other than the seminal vesicles (ie external sphincter, bladder, rectum, levator muscles, &/or pelvic wall)

Pathological T (pT)

T - Primary Tumor		
T2		Confined in the organ
T3		Positive extension extraprostatically
	T3a	Unilateral or bilateral extraprostatic extension
	T3b	Tumor invades seminal vesicle(s)
T4		Fixed tumor or invades adjacent structures other than the seminal vesicles (ie external sphincter, rectum, bladder, levator muscles, &/or pelvic wall)
N - Regional Lymph Nodes		
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Regional lymph node metastasis present
M - Distant metastasis[1]		
M0		No distant metastasis
M1		Distant metastasis
	M1a	Non-regional lymph node(s)
	M1b	Bone(s)a
	M1c	Other site(s) w/ or without bone disease

[1]*The most advanced category (M1c) should be used when >1 metastasis site is present*

Adapted from: TNM Staging System for Prostate Cancer (8th ed., 2017) in National Comprehensive Cancer Network. NCCN guidelines: prostate cancer version 2.2021. NCCN. Feb 2021; European Association of Urology (EAU)-European Association of Nuclear Medicine (EANM)-European Society for Radiotherapy & Oncology (ESTRO)-European Society of Urogenital Radiology (ESUR)-International Society of Geriatric Oncology (SIOG) guidelines on prostate cancer-2020 update. 2021.

Staging

- Should be based on the PSA level, tumor grade & positive prostate biopsies

Stage	Tumor	Node	Metastasis	PSA (ng/mL)	Grade Group
I	cT1a-c	N0	M0	PSA <10	1
	cT2a	N0	M0	PSA <10	1
	pT2	N0	M0	PSA <10	1
IIA	cT1a-c	N0	M0	PSA ≥10<20	1
	cT2a	N0	M0	PSA ≥10<20	1
	pT2	N0	M0	PSA ≥10<20	1
	cT2b	N0	M0	PSA <20	1
	cT2c	N0	M0	PSA <20	1
IIB	T1-2	N0	M0	PSA <20	2
IIC	T1-2	N0	M0	PSA <20	3
	T1-2	N0	M0	PSA <20	4
IIIA	T1-2	N0	M0	PSA ≥20	1-4
IIIB	T3-T4	N0	M0	Any PSA	1-4
IIIC	Any T	N0	M0	Any PSA	5
IVA	Any T	N1	M0	Any PSA	Any
IVB	Any T	Any N	M1	Any PSA	Any

Adapted from: National Comprehensive Cancer Network. NCCN guidelines: prostate cancer version 2.2021. NCCN. Feb 2021; American Cancer Society. Prostate cancer staging. Aug 2019.

3 STAGING (CONT'D)

Risk Stratification

- Based on the PSA level, biopsy, Gleason score & TNM classification
- Helps in decision making for the management of patients diagnosed w/ prostate cancer

Risk Group	Clinical Stage		PSA		Grade Group or Gleason Pattern		Others
Clinically Localized							
Very Low	T1c	&	<10 ng/mL	&	Grade group 1	&	<3 prostate biopsy fragments/cores positive, w/ ≤50% cancer in each fragment/core & PSA density <0.15 ng/mL/g
Low	T1-T2a	&	<10 ng/mL	&	Grade group 1		
Intermediate	T2b-T2c	or	10-20 ng/mL	or	Grade group 2-3		
Intermediate - Favorable	T2b-T2c	or	10-20 ng/mL	or	Grade group 1 or 2	&	1 intermediate risk factor (IRF) & percentage of positive biopsy cores <50%
Intermediate - Unfavorable	T2b-T2c	or	10-20 ng/mL	or	Grade group 3	&/or	2 or 3 IRF &/or percentage of positive biopsy cores ≥50%
High	T3a	or	>20 ng/mL	or	Grade group 4 or 5		Exactly 1 high-risk feature
Locally Advanced							
Very High	T3b-T4	or	Any	or	Primary Gleason pattern 5 **or** Grade group 4 or 5 in >4 cores		2 or 3 high-risk features
Regional	Any T, N1, M0						
Metastatic	Any T, any N, M1						

Adapted from: National Comprehensive Cancer Network. NCCN guidelines: prostate cancer version 2.2021. NCCN. Feb 2021; EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer-2020 update. 2021; European Society for Medical Oncology. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment & follow-up. Jun 2020.

Cancer of the Prostate Risk Assessment (CAPRA)

- A straightforward scoring system (0-10) that predicts likelihood of metastasis, cancer-specific mortality, & overall survival
- Based on the patient's age, PSA levels, Gleason score, clinical stage, & percent of malignant biopsy cores
- Also predicts disease recurrence after radical prostatectomy

4 ASSESSMENT

- Key determinant of primary treatment for patients diagnosed w/ prostate cancer include life expectancy estimation, family history & risk for germline mutations

Life Expectancy Estimation

- A key determinant of primary treatment for prostate cancer when considering observation or active surveillance
- Done using life tables such as the Memorial Sloan Kettering Male Life Expectancy tool, the Minnesota Metropolitan Life Insurance Tables, the Social Security Administration Life Insurance Tables, or the WHO's Life Tables by Country, & computed based on patient's health status

Family History

- Criteria that signify strong family history of prostate cancer & should prompt genetic testing include:
  - Brother, father or >1 family member ≤60 years old diagnosed or who passed away due to prostate cancer
  - Ashkenazi Jewish ancestral lineage: Associated w/ germline mutations in *BRCA2* or *BRCA1*
  - ≥3 cancers of the following carcinomas present on the same side of the family, especially if diagnosed ≤50 years of age: Breast, bile duct, colorectal, endometrial, gastric, renal, ovarian, melanoma, pancreatic, prostate, urothelial, small intestines

4 ASSESSMENT (CONT'D)

Genetic Testing

Germline Testing

- Recommended for prostate cancer patients w/ any of the following: Family history of prostate cancer, high-risk, very high-risk, regional or metastatic prostate cancer, intermediate-risk prostate cancer w/ intraductal/cribriform histology, or Ashkenazi Jewish ancestry
- Should include *MLH1*, *MSH2*, *MSH6*, *PMS2*, *BRCA2*, *BRCA1*, *ATM*, *PALB2* & *CHEK2*
  - Cancer predisposition next-generation sequencing (NGS) panel testing which includes above genetic mutations except for *PALB2* may be considered
- Recommended for very low-, low- & intermediate-risk groups if patient has strong family history of prostate cancer or w/ intraductal/cribriform histology
- Genetic counseling is needed before germline testing

Molecular Assays

- Provide a more personalized or precise approach to treatment
- Available tumor-based molecular assays include Decipher, Oncotype DX Prostate, Prolaris & ProMark
- Recommended somatic tests for the following patients:
  - Regional or metastatic prostate cancer: Tumor testing for somatic homologous recombination gene mutations (HRRm) which includes *MLH1, MSH2, MSH6, PMS2, BRCA2, BRCA1, ATM, CHEK2* & microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR) (to check for Lynch syndrome)
    - Cancer predisposition NGS panel testing which includes *BRCA2, BRCA1, ATM, CHEK2, PALB2, MLH1, MSH2, MSH6, PMS2* should be considered
  - Low- & favorable intermediate-risk prostate cancer w/ life expectancy ≥10 years: Decipher, Oncotype DX Prostate, Prolaris, & ProMark
  - Unfavorable intermediate- & high-risk prostate cancer w/ life expectancy ≥10 years: Decipher & Prolaris tumor-based molecular assays
  - PSA resistance/recurrence after radical prostatectomy: Decipher molecular assay to be used during counseling for risk stratification
- For post-prostatectomy patients, Decipher molecular assay is recommended if not previously done to test for adverse features
- For patients w/ history of Abiraterone/Enzalutamide therapy for metastatic CRPC, androgen receptor splice variant 7 (AR-V7) testing in circulating tumor cells may be considered to help w/ treatment decision making
- Tumor testing for MSI-H or dMMR is recommended for patients w/ mCRPC & can be considered in those w/ regional or castration-naive metastatic prostate cancer
- Decipher molecular assay is recommended post-prostatectomy to decide on adjuvant treatment if adverse factors are present

Gleason Score

- Useful in determining tumor grade, prognostic risk & management strategies

Gleason Score	Definition
Gleason X	Gleason score cannot be assessed
Gleason <6	Well differentiated (slight anaplasia)
Gleason 7	Moderately differentiated (moderate anaplasia)
Gleason 8-10	Poorly differentiated/undifferentiated (marked anaplasia)

Grade Group

- New histologic grading system developed by the International Society of Urological Pathology (ISUP) that assigns grade groups based on the Gleason score & thereby provides better management strategies

Grade Group	Gleason Score	Risk Group	Description
1	≤6 (≤3+3)	Very low	Only individual, discrete, well-formed glands
2	7 (3+4)	Intermediate	Predominantly well-formed glands w/ lesser component of poorly formed/fused/cribriform/glomeruloid glands
3	7 (4+3)	Intermediate	Predominantly poorly formed/fused/cribriform/glomeruloid glands w/ lesser component of well-formed glands
4	8 (4+4, 3+5, 5+3)	High	Only poorly formed/fused/cribriform/glomeruloid glands *or* Predominantly well-formed glands & lesser component lacking glands *or* Predominantly lacking glands w/ lesser component of well-formed glands
5	9 (4+5, 5+4) or 10 (5+5)	Very high	Lack of gland formation w/ or without poorly formed/fused/cribriform glands

A OBSERVATION & ACTIVE SURVEILLANCE

Observation/Watchful Waiting

- Based on the premise that it may be more beneficial to provide palliative therapy at the time when local or metastatic progression occurs, thereby maintaining quality of life
  - Also prompts a change in diagnostic tests when symptoms suggest disease progression
- Management option for:
  - Patients who prefer not to undergo treatments
  - Elderly men or immunocompromised patients w/ comorbidities &/or poor prognostic features
  - Patients who will not benefit but will only incur harm from definitive treatments
- Preferred for patients w/ low-risk prostate cancer w/ life expectancy of <10 years
- Recommended for patients w/ non-metastatic castration-resistant prostate cancer (CRPC), w/ continued androgen deprivation therapy
- Includes monitoring of PSA & DRE every 6 months

Advantage

- Potential harm from different unnecessary therapies & early initiation &/or continuous ADT may be avoided

Disadvantage

- Increases the risk for urinary retention & pathologic fracture without prior symptoms or increasing PSA

Active Surveillance

- Watchful waiting while actively monitoring the disease course to be able to intervene when the disease progresses, delaying the potential side effects of treatments
- Recommended for patients w/ very low-risk prostate cancer w/ life expectancy of 10-20 years
  - Preferred in patients w/ very low-risk prostate cancer w/ life expectancy of >20 years
- Recommended for patients w/ low-risk prostate cancer w/ life expectancy of ≥10 years
- Considered for patients w/ favorable intermediate-risk prostate cancer
- Criteria for the use of active surveillance include: Clinical stage T1c or T2a, grade group 1, <3 positive cores w/ ≤50% cancer involvement in any core, PSA <10 ng/mL, PSA density <0.15 ng/mL/g
  - Decision to use active surveillance should not be based solely on above criteria
- Treatment option for those w/ low-risk localized disease & candidates for radical prostatectomy or radiotherapy
  - May also be suggested to asymptomatic patients, elderly men, & those w/ comorbidities
- Presence of any of the following pathology should prompt exclusion for active surveillance: Predominant ductal carcinoma, sarcomatoid carcinoma, small cell carcinoma, extraprostatic extension (EPE) or lymphovascular invasion (LVI) in needle biopsy, perineal invasion

Inclusions

- Initial: mpMRI &/or prostate biopsy if not performed previously
- 1st year: Monitoring of PSA every 6 months & DRE, prostate biopsy & mpMRI every 12 months
  - Repeat needle biopsy within 6 months from initial diagnosis is indicated for patients w/ <10 cores
  - Repeat biopsy may not be performed if the life expectancy is <10 years
- 2nd-4th year: PSA monitoring every 3-6 months & DRE every 6-12 months
- 5th year & yearly thereafter: PSA every 6 months & DRE every 12 months
- PSA kinetics (doubling time & velocity) should be monitored all throughout active surveillance duration

Advantages

- Eligible patients may avoid or delay treatment
- Potential harm from different treatment modalities may be avoided
- Patient may go back to their normal activities & may retain present quality of life
- Smaller/undiagnosed malignancies will remain therapy-naive, thereby preventing future treatment resistance
- Expenses may be reserved for more definitive treatments

Disadvantages

- Chance for early treatment & cure may be missed
- High propensity for disease progression & metastasis
- Tumor size may increase, making surgery & medical management more difficult
- Preservation of function may be more difficult for more aggressive & bigger tumors
- Increased anxiety due to untreated malignancy & uncertainty of disease progression
- Intermittent monitoring w/ diagnostics & clinic visits are required

B RADIATION THERAPY

Interstitial Prostate Brachytherapy
- Implantation of small radioactive sources into the prostate gland
- Recommended initial therapeutic strategy for patients w/ very low-risk prostate cancer w/ life expectancy of >20 years & low-risk prostate cancer w/ life expectancy of ≥10 years not suitable for active surveillance
  - Difficult to perform in patients w/ very small or very large prostates, bladder outlet obstruction symptoms, or previous transurethral resection of the prostate (TURP)
- Recommended for patients w/ favorable intermediate-risk prostate cancer w/ life expectancy of ≥5 years
- Recommended for patients w/ unfavorable intermediate- to very high-risk prostate cancer when given in combination w/ EBRT & ADT
  - Showed improved biochemical control when given together w/ ADT & EBRT (45-50 Gy), but w/ more side effects
- Recommended doses:
  - 120 Gy (palladium)
  - 140 Gy (^{125}I) w/ postoperative dosimetry

Low Dose-Rate Brachytherapy
- Uses permanent low-energy seeds (Iodine-125, Palladium-103, Cesium-131) for implantation that delivers adequate doses
- Recommended for patients w/ the following:
  - Stage T1b-T2a N0 M0
  - ISUP grade 1 w/ ≤50% biopsy cores involved or ISUP grade 2 w/ ≤33% biopsy cores involved
  - ≤10 ng/mL initial PSA level
  - <50 cm^3 prostate volume International Prostatic Symptom Score (IPSS) ≤12 & urinary flow test result of >15 mL/min
- May be given to low-risk patients without recent TURP
- May be given to patients w/ intermediate- to high-risk together w/ EBRT
- Recommended dose:
  - Iodine-125: 145 Gy (110 Gy w/ 40-50 Gy EBRT)
  - Palladium-103: 125 Gy (90-100 Gy w/ 40-50 Gy EBRT)

High Dose-Rate Brachytherapy
- Uses temporary radioactive sources (eg Iridium-192) inserted into different locations in the prostate gland
- Recommended dose:
  - Monotherapy: 13.5 Gy x 2 fractions
  - W/ EBRT: 9.5-11.5 Gy x 2 fractions; 5.5-7.5 Gy x 3 fractions; 4-6 Gy x 4 fractions

External Beam Radiotherapy (EBRT)
- Recommended initial therapeutic strategy for patients w/ very low- to high-risk prostate cancer
- Limited radiation fields are preferred over extended field radiotherapy for localized & locally advanced prostate cancer
- May be given w/ or without ADT or w/ brachytherapy w/ or without ADT in patients w/ unfavorable intermediate risk
- Recommended to be given concomitantly w/ ADT as initial therapy in patients w/ high or very high risk
- Localization of prostate w/ image-guided radiation therapy (IGRT) is necessary w/ either 3-dimensional conformal radiation therapy (3D-CRT) or intensity-modulated radiation therapy (IMRT) for reducing target margin & ensuring treatment accuracy
  - Dose-escalated IMRT w/ IGRT is the best available approach due to low toxicity
- Recommended dose for patients w/ low-risk prostate cancer is 75.6-79.2 Gy; intermediate- to high-risk & metastatic prostate cancer is 81.0 Gy

Stereotactic Body Radiotherapy (SBRT)
- Uses high conformal, high-dose radiation delivered precisely using imaging techniques
- May be considered in patients w/ limited metastatic disease to the vertebra or paravertebral regions when ablation is to be achieved, oligometastatic progression to achieve progression-free survival, & in symptomatic patients w/ lesions in or immediately adjacent to a previously irradiated treatment field
- May be considered as an alternative to conventionally fractionated regimens or to EBRT in unfavorable intermediate- or high-risk patients when combined w/ ADT when EBRT is medically challenging

Proton Beam Therapy
- Delivers less radiation to surrounding normal tissues thereby decreasing long-term treatment morbidity
- Further studies are needed to prove the efficacy of proton therapy against prostate cancer & its superiority to photon-based radiation therapy

Radiopharmaceutical Therapy
- Eg Radium-223 dichloride, ß-emitting agents (Strontium-89, Samarium-153)
- Option for palliative treatment of patients w/ metastatic disease

Beta-Emitting Radioactive Agents
- Eg Strontium-89 (Sr-89, 89Sr), Samarium-153 (Sm-153, 153Sm)
- Used for palliative treatment of painful bone or widespread metastases that are not eligible for chemotherapy

Radium-223 dichloride
- An alpha particle-emitting radioactive agent used for metastatic CRPC w/ symptomatic bone metastases but without visceral involvement
  - Studies have shown that patients given Radium-223 had better overall survival & time to appearance of symptomatic bone events than those given placebo

C SURGERY

Orchiectomy

- Surgical option of ADT (*Please refer to the discussion of orchiectomy in the next page*)

Radical Prostatectomy

- Removal of the prostate gland as a whole, including the seminal vesicles, ampulla of the vas deferens, & lymph nodes w/ preservation of function (continence, potency)
- First-line treatment for patients w/ tumors confined to the prostate gland, w/ very low- to intermediate-risk disease, & life expectancy of ≥10 years
  - Treatment option for patients w/ high- to very high-risk disease & a salvage therapy option for patients w/ biochemical recurrence after EBRT, brachytherapy or cryotherapy if w/ no metastases, ISUP grade 4-5 or PSA >20 ng/mL
- High cure rate for patients w/ purely localized disease

Pelvic Lymph Node Dissection (PLND)

- Recommended for patients w/ high-risk or locally advanced disease w/ nodal metastases, done concurrently w/ radical prostatectomy
- Extended PLND, which involves the removal of the lymph nodes in the area of the external iliac artery & vein, veins within the obturator fossa, & medial & lateral nodes of the internal iliac artery, is preferred due to its completeness of disease staging & is therapeutically more advantageous in patients w/ microscopic metastases compared to PLND alone
  - May be done in patients w/ intermediate risk w/ >5% estimated risk of lymph node involvement

Cryosurgery (Cryotherapy/Cryoablation)

- Minimally invasive surgical procedure that involves freezing & destruction of tumor tissues
- Treatment option for patients w/:
  - High-risk prostate cancer following radiation therapy
  - Low- to intermediate-risk prostate cancer not a candidate for prostatectomy due to comorbidities
  - Relative contraindications to radiotherapy
- Prostate volume should be <40 mL at the time of therapy
- Lower risk of damage to nearby structures & complication secondary to radical treatment
- Studies reported a range of 52%-92% biochemical disease-free survival within 5-7 years, depending on criteria used
  - Discussion w/ patient should be made regarding the lack of long-term efficacy comparative outcome data

Other Ablative Techniques

- Eg high-intensity focused ultrasound (HIFU), radiofrequency ablation & electroporation
- HIFU is a minimally invasive procedure that uses focused ultrasound waves emitted from a transducer to cause thermal damage to malignant tissues
  - Alternative treatment to localized prostate cancer w/ disease recurrence after radiotherapy
  - May be applicable for low- to intermediate-risk patients but further studies are needed to conclude use

D ANDROGEN DEPRIVATION THERAPY (ADT)

- Treatment option for patients w/ disease progression despite surgical treatments & radiotherapy, or for symptomatic control of symptoms in patients who are against, w/ contraindications, or cannot tolerate surgical procedures
- Recommended as 1st-line therapy in high- to very high-risk & metastatic prostate cancer & as adjuvant therapy for patients w/ low- to intermediate-risk prostate cancer
- May be offered to intermediate- to high-risk & locally advanced prostate cancer patients prior to, during, or after EBRT or in combination w/ radical radiotherapy
  - Long-term ADT (18-36 months duration) is recommended for high-risk to very high-risk disease
  - Short-term ADT (4-6 months duration) is recommended for intermediate-risk disease
- Treatment option for patients w/ disease progression after observation who require treatment or w/ life expectancy of ≤5 years
- PSA levels should be measured every 3 months for patients under intermittent ADT
  - Restart ADT if PSA measurements reach >10 ng/mL or if patients becomes symptomatic
- Bone mineral density (BMD), serum calcium & vitamin D levels should be assessed every 2 years
- Advise patients on ADT to have a healthy weight & diet, stop smoking, lessen alcohol intake, meet recommended levels of calcium & vitamin D, & have an annual screening for diabetes & dyslipidemia

D ANDROGEN DEPRIVATION THERAPY (ADT) (CONT'D)

Treatment Strategies for ADT

- Luteinizing hormone-releasing hormone (LHRH) analogs (medical castration) & bilateral orchiectomy (surgical castration) are equally effective

Recommended ADT Options for Clinically Localized Prostate Cancer

- LHRH agonist monotherapy
- LHRH agonist w/ 1st-generation anti-androgen
- LHRH antagonist

Recommended ADT Options for Regional Prostate Cancer

- Orchiectomy w/ or without Abiraterone
- LHRH agonist monotherapy
- LHRH agonist w/ 1st-generation anti-androgen *or* Abiraterone
- LHRH antagonist w/ or without Abiraterone

Recommended ADT Options for Castration-naive Prostate Cancer without Metastasis

- If w/ PSA persistence or recurrence after radical prostatectomy: EBRT w/ or without neoadjuvant/concurrent &/or adjuvant ADT
- If w/ PSA persistence or recurrence after EBRT, TRUS-biopsy negative, or w/ disease progression after salvage EBRT:
  - Orchiectomy
  - LHRH agonist monotherapy
  - LHRH agonist w/ 1st-generation anti-androgen
  - LHRH antagonist

Recommended ADT Options for Castration-naive Metastatic Prostate Cancer

- Orchiectomy w/ or without Docetaxel
- Orchiectomy w/ Abiraterone, Apalutamide or Enzalutamide
- LHRH agonist monotherapy w/ or without Docetaxel
- LHRH agonist w/ 1st-generation anti-androgen w/ or without Docetaxel
- LHRH agonist w/ Abiraterone, Apalutamide or Enzalutamide
- LHRH antagonist w/ or without Docetaxel
- LHRH antagonist w/ Abiraterone, Apalutamide or Enzalutamide

Orchiectomy

- Also called surgical castration, total or subcapsular pulpectomy, where one or both testicles (bilateral orchiectomy) are removed
- Surgical option of ADT, to be done w/ or without Abiraterone therapy
- Recommended castration method for patients w/ intermediate- to very high-risk prostate cancer & those w/ treatment-naive locally advanced & metastatic prostate cancer
- Treatment option for patients w/ disease progression after observation of localized disease who require treatment or w/ life expectancy of ≤5 years

Luteinizing Hormone-Releasing Hormone (LHRH) Analogs

- Efficacy for castration is the same as orchiectomy
- First-line agents used for ADT in prostate cancer
- Treatment option for patients w/ disease progression after observation of localized disease who require treatment or w/ life expectancy of ≤5 years

LHRH Agonists

- Eg Goserelin, Histrelin, Leuprorelin (Leuprolide), Triptorelin
- Mechanism of action: Stimulates luteinizing hormone-releasing hormone receptors, inducing a transient LH & FSH surge, leading to androgen release inhibition
- Induces the flare-up phenomenon, a sudden increase in testosterone, which may lead to increased bone pain, urethral obstruction, renal failure, spinal cord compression
- Efficacy of Leuprorelin may be affected by handling errors during preparation & administration
  - Based on the recommendation by the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA), Leuprorelin-containing depot medicinal products using dual-chamber prefilled syringe device are preferred over vial-ampoule presentation, due to fewer reported medication errors w/ dual devices compared to products w/ complex reconstitution steps for preparation & administration

LHRH Antagonists

- Eg Degarelix, Relugolix
- Mechanism of action: Rapidly & directly inhibits androgen release thereby suppressing testicular androgen activity without the flare-up phenomenon

D ANDROGEN DEPRIVATION THERAPY (ADT) (CONT'D)

Secondary Hormone Therapy

- Second-generation anti-androgens, eg Abiraterone acetate, Apalutamide, Darolutamide, Enzalutamide given in combination w/ ADT for patients w/ castration-sensitive prostate cancer or as monotherapy in CRPC
- Recommended for patients w/ progressive disease despite medical & surgical castration

Abiraterone acetate

- May be used for patients w/ metastatic, high-risk, castration-sensitive prostate cancer together w/ LHRH analogs or orchiectomy, & metastatic CRPC pre- or post-Docetaxel therapy
- Fine-particle formulation can be used instead of the standard form
- Administered together w/ Prednisone; fine-particle Abiraterone is given w/ Methylprednisolone
  - Combination should not be given w/ anti-androgen
  - May consider switching Prednisone to Dexamethasone 1 mg/day for patients w/ disease progression on either formulation of Abiraterone
- Increased median survival, provided pain palliation, showed PSA level decrease, & delayed radiographic progression in studies done to prove the efficacy of Abiraterone in patients w/ metastatic CRPC who were given Docetaxel-containing regimens
- Studies showed that addition of Abiraterone to ADT in patients w/ high-risk metastatic prostate cancer improved overall survival compared w/ ADT alone
- Mechanism of action: Inhibits the enzyme CYP17 in turn suppressing testosterone production

Apalutamide

- Treatment option for patients w/ non-metastatic CRPC if PSADT is ≤10 months & metastatic, castration-sensitive prostate cancer
- Mechanism of action: Acts as an androgen receptor inhibitor thereby inhibiting AR nuclear translocation, DNA binding & androgen receptor-mediated transcription

Darolutamide

- Treatment option for patients w/ non-metastatic CRPC if PSADT is ≤10 months
- Mechanism of action: Competitively inhibits androgen binding to androgen receptors thereby inhibiting nuclear translocation & DNA interaction

Enzalutamide

- May be used for patients w/ both metastatic & non-metastatic CRPC if PSADT is ≤10 months & metastatic, castration-sensitive prostate cancer
  - Treatment option for patients w/ metastatic CRPC pre- or post-Docetaxel
  - Compared w/ placebo, treatment w/ Enzalutamide showed significant lower risk of metastasis or death in patients w/ non-metastatic CRPC w/ a rapidly increasing level of PSA
- Mechanism of action: Potent competitive inhibitor of androgen binding to androgen receptors, inhibits nuclear translocation of activated receptors & the association of the activated androgen receptor w/ DNA despite androgen receptor over-expression & prostate cancer cell resistance to anti-androgens

Other Secondary Hormone Therapy

Adrenal/Paracrine Androgen Synthesis Inhibitors

- Eg Ketoconazole
- Treatment option for patients w/ CRPC w/ or without visceral metastases
- Not to be used if positive for disease progression after Abiraterone therapy
- Mechanism of action: Anti-androgenic properties that block androgen production

Anti-Androgen Therapy

- Eg Steroidal (Cyproterone acetate, Megestrol acetate, Medroxyprogesterone acetate); Non-steroidal or 1st generation anti-androgens (Bicalutamide, Flutamide, Nilutamide)
- Treatment option for patients w/ advanced disease, metastatic, or non-metastatic CRPC
  - May be given concomitantly w/ LHRH analogs or orchiectomy for better androgen blockade (combined androgen blockade)
  - May be offered to patients w/ metastatic disease who prefer their sexual function restored even w/ more side effects
- Bicalutamide monotherapy may also help prevent non-metastatic bone fractures w/ its bone-protective properties, though monotherapy use is rare
- Mechanism of action: Blocks androgen receptors, thereby reducing the effect of endogenous hormones

Estrogens

- Eg Diethylstilbestrol (DES)
- Studies have shown that oral estrogen therapy has the same efficacy for castration as bilateral orchiectomy
- Mechanism of action: Inactivates androgens, down-regulates LHRH secretion, Leydig cell function direct suppression

Not all products are available or approved for above use in all countries.
Specific prescribing information may be found in the latest MIMS.

D ANDROGEN DEPRIVATION THERAPY (ADT) (CONT'D)

Docetaxel

- Systemic treatment added to ADT for patients w/ metastatic, castration-sensitive prostate cancer
- Studies showed that addition of Docetaxel to ADT in patients w/ metastasis significantly improved overall survival compared w/ ADT alone
- Mechanism of action: Promotes the assembly of microtubules from tubulin dimers, & inhibits the depolymerization of tubulin which stabilizes microtubules in the cell, resulting in inhibition of DNA, RNA, & protein synthesis

E SYSTEMIC THERAPY

Chemotherapy

- Eg Cabazitaxel, Carboplatin, Docetaxel, Doxorubicin, Etoposide, Estramustine, Mitoxantrone, Paclitaxel, Vinblastine, Vinorelbine
- Recommended for patients w/ progressive disease despite medical & surgical castration (both hormone-resistant &/or castration-resistant metastatic prostate cancer)

Cabazitaxel

- Alternative treatment to those intolerant or unresponsive to Docetaxel therapy in patients w/ symptomatic metastatic CRPC
- Patients given Cabazitaxel exhibited improvement in PFS, PSA response rate & overall survival in several studies
- Given w/ concomitant steroids (daily Prednisone or Dexamethasone on day of chemotherapy)

Docetaxel

- Recommended 1st-line treatment for men w/ symptomatic metastatic CRPC
- Proven to improve PSA response & time to recurrence & clinical progression
- Should be reserved for prostate cancer patients w/ confirmed metastatic disease

Mitoxantrone

- May be used for palliative therapy of the pain caused by bone metastasis of CRPC in patients who cannot tolerate other therapies
- Given concomitantly w/ corticosteroids

Olaparib

- A poly-ADP ribose polymerase (PARP) inhibitor used as a treatment option for patients w/ mCRPC & a pathogenic mutation (germline &/or somatic) in a homologous recombination repair (HRRm) gene (*BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D* or *RAD54L*), w/ history of androgen receptor-directed therapy

Rucaparib

- A PARP inhibitor used as a treatment option for patients w/ mCRPC & a pathogenic *BRCA1* or *BRCA2* mutation (germline &/or somatic) w/ history of androgen receptor-directed therapy & a taxane-based chemotherapy

Immunotherapy

Pembrolizumab

- Anti-PD1 antibody used for patients w/ unresectable or metastatic MSI-H or dMMR solid tumors that have progressed on prior treatment & w/ no satisfactory alternative treatment options

Sipuleucel-T

- Cancer vaccine produced from the combination of autologous antigen-presenting blood mononuclear cells & recombinant human fusion protein
- Studies have shown that Sipuleucel-T may help extend mean survival w/ reduction in mortality risk
- May be given to metastatic CRPC patients w/ Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, life expectancy of >6 months, absent hepatic metastasis, & minimal or absent symptoms
- Not recommended for patients w/ small cell/neuroendocrine prostate cancer

F FOLLOW-UP

Local Recurrence
- Initial PSA levels of ≥0.2 ng/mL & subsequent confirmatory levels of ≥0.2 ng/mL signify biochemical recurrence
  - Biochemical recurrence can be categorized as either:
    - PSA level that fails to fall to undetectable levels post-radical prostatectomy
    - PSA level undetectable post-radical prostatectomy but w/ ≥2 subsequent laboratory results w/ detectable PSA level
  - Persistent or low PSA levels due to slow PSA metabolism or residual benign tissue
- Endorectal ultrasound may be considered to rule out recurrence after radical prostatectomy

Follow-up Examinations

PSA Monitoring
- PSA levels should be significantly lower after radical prostatectomy, radiation therapy, cryotherapy & other treatments
- Should be done every 3-6 months x 5 years then every 6-12 months x 5 years, then annually
- Asymptomatic patients do not require further imaging if PSA is stable

Digital Rectal Exam
- Timing of DRE after EBRT or radical prostatectomy: Annual

Bone Scan
- May be done if w/ symptoms or PSA levels rise after local therapy
- Should be performed every 6-12 months to monitor ADT & 8-12 week-interval for patients w/ CRPC
- Bone densitometry measurement by dual-energy x-ray absorptiometry (DEXA) scans should be obtained regularly especially in patients at high risk for skeletal side effects & for monitoring of treatment response to Denosumab or bisphosphonates

CT Scan/MRI
- May be considered if the following occurs after radical prostatectomy:
  - PSA levels still detectable (PSA persistence)
  - Previously undetectable PSA is suddenly detected (PSA recurrence)
  - Recorded PSA increases in >2 PSA level examinations
  - Increasing PSA or positive DRE after radical prostatectomy
- Spinal MRI to detect cord compression is recommended in CRPC patients w/ vertebral metastases & neurological symptoms
- For patients without any evidence of metastases, the following imaging studies may be considered:
  - For further soft tissue & bone evaluation: C-11 choline PET/CT, PET/MRI, F-18 fluciclovine PET/CT or PET/MRI
  - For further bone evaluation: F-18 sodium fluoride PET/CT or PET/MRI

PET/CT Scan & PET/MRI
- Has comparable sensitivity & specificity w/ other FDA-approved imaging agents in detecting recurrences at lower PSA levels
  - PSA level cut-off of Choline PET/CT is between 1-2 ng/mL & PSMA PET/CT is <1 ng/mL
- Has good sensitivity in prostate cancer restaging
- Useful in identifying CRPC & in predicting response to therapy

Salvage Treatments
- Local salvage therapy options include salvage radical prostatectomy, HIFU, cryoablation & brachytherapy
  - Considered in patients w/ low comorbidity, life expectancy of at least 10 years, a presalvage therapy PSA level <10 ng/mL, initial ISUP ≤3 initial clinical stage of T1/T2 & no lymph node involvement
- Salvage radiotherapy is a treatment option for patients w/ increasing PSA levels after radical prostatectomy & no presence of distant metastasis; should be given once biochemical recurrence has been confirmed
  - May consider hormone therapy if PSA is 0.20 ng/mL postoperatively
  - Recommended doses for adjuvant/salvage post-prostatectomy RT are 64-72 Gy
- Salvage brachytherapy (permanent low dose-rate or temporary high dose-rate) may be considered in patients w/ confirmed local recurrence after EBRT or brachytherapy
- Primary salvage or adjuvant radiotherapy may be considered in patients w/ PSA recurrence post-radical prostatectomy if without distant metastases
  - Patients w/ pathological T3 colorectal cancer, positive margin/s or seminal vesicle involvement may be given adjuvant radiotherapy, usually given within 1 year post-radical prostatectomy & after recovery from operative side effects
  - Patients w/ previously undetectable PSA that became detectable on 2 measurements or w/ persistently detectable PSA post-radical prostatectomy may be given salvage radiotherapy
- Salvage radical prostatectomy may be used for patients w/ local recurrence after radiotherapy or cryotherapy
- Salvage ADT alone may be considered in patients w/ proven or high suspicion of metastasis, symptomatic local disease, or biochemical relapse w/ rapid PSA doubling time
- Salvage cryoablation of the prostate may be an alternative to salvage radical prostatectomy
- Salvage HIFU may be used as an alternative option for radiation-recurrent prostate cancer

G CASTRATION-RESISTANT PROSTATE CANCER (CRPC)

- Also known as castration-recurrent prostate cancer
- Recurrence or disease progression (clinical, radiographical or biochemical) despite medical or surgical castration
- Criteria for defining CRPC:
  - PSA progression (PSA level >2 ng/mL, listed 3 consecutive increases 1 week apart, resulting in 25% increase over the nadir value)
  - Serum testosterone levels <50 ng/dL or <1.7 nmol/L
  - Anti-androgen withdrawal of >4-6 weeks
  - Radiological progression (new lesions, either ≥2 new bone lesions on bone scan or soft tissue lesion)

CRPC without Metastasis (M0)

- May consider observation w/ ADT if PSADT >10 months
- Offer Apalutamide, Darolutamide or Enzalutamide w/ ADT if PSADT ≤10 months

CRPC w/ Metastasis (M1)

- Patients w/ metastatic CRPC (mCRPC) should continue ADT w/ additional secondary hormone therapies, chemotherapies or immunotherapies

Secondary Hormone Therapy for CRPC without Metastasis (M0) & Metastatic CRPC (M1)

Second-Generation Anti-androgen

- Apalutamide (for M0 & PSADT ≤10 months)
- Darolutamide (for M0 & PSADT ≤10 months)
- Enzalutamide (for M0 & PSADT ≤10 months or M1)

Androgen Metabolism Inhibitor

- Abiraterone w/ Prednisone (for M1 only)
- Fine-particle Abiraterone w/ Methylprednisolone (for M1 only)

Other Secondary Hormone Therapy (for M0 or M1)

- Ketoconazole w/ or without Hydrocortisone
- 1st generation anti-androgen (Nilutamide, Flutamide or Bicalutamide)
- Corticosteroids (Hydrocortisone, Prednisone or Dexamethasone)
- Estrogen w/ DES
- Anti-androgen withdrawal

Systemic Therapy for Metastatic CRPC

Chemotherapy

- Docetaxel w/ Prednisone or Dexamethasone
- Cabazitaxel/Carboplatin w/ Prednisone or Dexamethasone
- Mitoxantrone w/ Prednisone

Immunotherapy

- Sipuleucel-T
- Pembrolizumab

Aggressive Variant Prostate Cancer

- Prostate cancer may be classified as aggressive variant if at least 1 of the following criteria are met:
  - Small cell/neuroendocrine prostate carcinoma histology
  - Exclusive visceral metastases
  - Predominant lytic bone metastases
  - Bulky (>5 cm) lymphadenopathy or Gleason score ≥8 at diagnosis
  - PSA <10 ng/mL w/ ≥20 bone metastases
  - ≥2 times elevated lactate dehydrogenase (LDH) or carcinoembryonic antigen (CEA)
  - <6 months interval response to ADT
- Contains defects in at least 2 of 3 tumor suppressors: Tumor protein 53 (TP53), retinoblastoma protein 1 (RB1), & phosphatase & tensin homolog (PTEN)

Small cell/neuroendocrine Prostate Carcinoma

- Characterized by small, blue neuroendocrine cells which do not secrete PSA but express neuroendocrine markers [chromogranin A, synaptophysin & neuron-specific enolase (NSE)]
- Metastasizes to visceral organs & responds temporarily to chemotherapy

H TREATMENT STRATEGY FOR ADENOCARCINOMA-TYPE METASTATIC CRPC

- Novel hormone therapy includes Abiraterone, Apalutamide, Darolutamide, or Enzalutamide received for metastatic castration-naive prostate cancer, M0 CRPC, or previous lines of treatment for M1 CRPC

Recommended Options for Patients without Prior Docetaxel & Novel Hormone Therapy Use

- Preferred treatment options include Abiraterone, Docetaxel & Enzalutamide
- Regimens that can be used depending on patient's status include:
  - Recommended only for asymptomatic or minimally symptomatic patients, no liver metastases, w/ life expectancy >6 months, & ECOG performance status 0–1: Sipuleucel-T
  - Symptomatic bone metastases: Radium-223
- Other recommended therapies include other secondary hormone therapy

Recommended Options for Patients Previously Given Novel Hormone Therapy but No Prior Use of Docetaxel

- Preferred regimens include Docetaxel & Sipuleucel-T
- Regimens that can be used depending on patient's status include:
  - *BRCA* mutation-positive: Rucaparib
  - Fit patients w/ aggressive variant prostate cancer (eg visceral metastases, low PSA & bulky disease, high LDH, high CEA, lytic bone metastases, neuroendocrine prostate cancer histology) or unfavorable genomics (defects in at least 2 of PTEN, *TP53* & *RB1*): Cabazitaxel/Carboplatin
  - HRRm positive: Olaparib
  - MSI-H or dMMR positive: Pembrolizumab
  - Symptomatic bone metastases: Radium-223
- Other recommended therapies include Abiraterone w/ or without Dexamethasone, Enzalutamide & other secondary hormone therapy

Recommended Options for Patients Previously Given Docetaxel but No Prior Novel Hormone Therapy Use

- Preferred regimens include Abiraterone, Cabazitaxel & Enzalutamide
- Regimens that can be used depending on patient's status include:
  - Fit patients w/ aggressive variant prostate cancer (eg visceral metastases, low PSA & bulky disease, high LDH, high CEA, lytic bone metastases, neuroendocrine prostate cancer histology) or unfavorable genomics (defects in at least 2 of PTEN, *TP53* & *RB1*): Cabazitaxel/Carboplatin
  - MSI-H or dMMR positive: Pembrolizumab
  - Symptomatic bone metastases: Radium-223
  - Symptomatic patients w/ visceral metastases intolerant to other therapies: Mitoxantrone
- Other recommended therapies include Sipuleucel-T & other secondary hormone therapy

Recommended Options for Patients Previously Given Docetaxel & Novel Hormone Therapy

- Preferred regimens include Cabazitaxel & Docetaxel rechallenge
  - Docetaxel rechallenge to be given after progression on novel hormone therapy in castration-naive patients negative for disease progression on prior Docetaxel therapy
- Regimens that can be used depending on patient's status include Cabazitaxel/Carboplatin, Mitoxantrone Olaparib, Pembrolizumab, Radium-223 & Rucaparib, depending on the characteristics mentioned in patients previously given novel hormone therapy or Docetaxel
- Other recommended therapies include Abiraterone, Enzalutamide & other secondary hormone therapy

I PALLIATIVE THERAPY

Pharmacological Therapy

- Palliative ADT can be given to patients who are high-risk, very high-risk, regional or metastatic prostate cancer w/ a life expectancy of ≤5 years & men w/ disease progression during observation
- Mitoxantrone may be used for patients w/ symptomatic metastatic CRPC who have contraindications to Cabazitaxel or Radium-223 therapy
- Denosumab & bisphosphonates (Eg Alendronate, Pamidronate, Zoledronic acid) may be suggested in patients w/ metastatic CRPC w/ bone metastasis to help prevent bone fractures, metastases, & other skeletal complications
- May use analgesics for painful bone metastases & corticosteroids if w/ spinal cord compression

Radiation Therapy

- Single fraction EBRT is recommended for palliation of uncomplicated, painful bone metastasis
- Recommended dose:
  - Non-vertebral metastases: 800 cGy x 1 fraction
  - Widespread bone metastases: Sr-89 or Sm-153 w/ or without focal EBRT

Referral

- Refer patient & his family to facilities that can provide palliative care services that can assist both the patient & his family while dealing w/ prostate cancer
- Referral to pain clinics or palliative care team may also help in the symptomatic management of prostate cancer patients

Not all products are available or approved for above use in all countries.
Specific prescribing information may be found in the latest MIMS.

Dosage Guidelines

ANTIFUNGAL		
Drug	**Dosage**	**Remarks**
Ketoconazole	400 mg PO 8 hrly May be increased to 1200 mg/day	**Adverse Reactions** • GI effects (N/V, diarrhea, elevated liver function tests (LFTs), hepatitis); Other effects (pruritus, testosterone & adrenal steroid synthesis inhibition, gynecomastia, allergic reactions) **Special Instructions** • Use w/ caution in patients w/ adrenal insufficiency • Contraindicated in patients w/ liver disease, in recovery phase of hepatitis, & hepatic impairment • Monitor LFTs during treatment

CANCER HORMONE THERAPY		
Drug	**Dosage**	**Remarks**
Anti-androgen Preparations		
Apalutamide	**Metastatic castration-sensitive prostate cancer:** 240 mg PO 24 hrly **Nonmetastatic CRPC:** 240 mg PO 24 hrly	**Adverse Reactions** • Musculoskeletal effects (falls, fractures, arthralgia); CV effects (QT prolongation, ischemic heart disease, heart failure); Metabolic effects (hypercholesterolemia, hypertriglyceridemia, hyperkalemia, hyperglycemia); GI effects (diarrhea, nausea); Dermatologic effects (rash, pruritus); Hematologic effects (anemia, leukopenia, lymphopenia); Other effects (fatigue, peripheral edema, decreased wt) **Special Instructions** • Use w/ caution in patients w/ history of seizures or predisposing factors for seizure, risk of falls or fractures, recent CV disease & QT prolongation, severe renal or hepatic impairment
Bicalutamide	**Advanced prostate cancer in combination w/ LHRH analog therapy or surgical castration:** 50 mg PO 24 hrly **Locally advanced prostate cancer at high risk for disease progression:** 150 mg PO 24 hrly	**Adverse Reactions** • Dermatologic effects (pruritus, alopecia, hair regrowth, dry skin); GI effects (nausea, diarrhea, hepatic changes); Other effects (gynecomastia, breast tenderness/pain, wt gain, decreased libido, impotence, asthenia, anemia, hot flushes) **Special Instructions** • When used for the treatment of locally advanced PC at high risk for disease progression, therapy should be taken continuously for at least 2 yr or until disease progression • Use w/ caution in patients w/ moderate to severe hepatic impairment, hereditary galactose intolerance, Lapp lactase deficiency, glucose-galactose malabsorption

Dosage Guidelines

CANCER HORMONE THERAPY (CONT'D)		
Drug	**Dosage**	**Remarks**
Anti-androgen Preparations (Cont'd)		
Cyproterone acetate	**Anti-androgen treatment:** **Initial dose:** 100 mg PO 12 hrly x 5-7 days **Maintenance dose[1]:** 100 mg PO 12 hrly for 3-4 wk **Inoperable prostatic carcinoma without orchiectomy:** 100 mg PO 8-12 hrly	**Adverse Reactions** • GU effect (inhibition of spermatogenesis); Other effects (tiredness, diminished vitality, depressive mood, restlessness, wt change, breast tension, gynecomastia) • W/ high doses: Liver function disturbances, shortness of breath sensation, reduced adrenal cortex function **Special Instructions** • Should be taken w/ food • Use w/ caution in patients w/ sickle cell anemia, severe diabetes w/ vascular changes or history of thromboembolic processes, liver function impairment; regular liver function, adrenocortical function & RBC count monitoring is advised • Should not be given before the conclusion of puberty • Contraindicated in patients w/ liver diseases or existing liver tumors, history of jaundice, Dubin-Johnson syndrome, Rotor syndrome, severe chronic depression, previous or existing thromboembolic processes, severe diabetes w/ vascular changes, sickle-cell anemia
Darolutamide	**CRPC:** 600 mg PO 12 hrly	**Adverse Reactions** • CV effects (ischemic heart disease, heart failure); Other effects (fatigue, asthenia, pain in extremity, rash, decreased neutrophil count, increased AST, increased bilirubin) **Special Instructions** • Swallow tablets whole w/ food • Use w/ caution in patients w/ severe renal impairment, moderate hepatic impairment, significant CV disease • Contraception is advised during & for 1 wk after treatment
Enzalutamide	**Metastatic castration-sensitive prostate cancer:** 160 mg PO 24 hrly **CRPC:** 160 mg PO 24 hrly	**Adverse Reactions** • CNS effects (headache, memory impairment, cognitive disorder, anxiety); Dermatologic effects (pruritus, dryness); Other effects (hot flushes, visual hallucinations, fractures, hypertension, fatigue) **Special Instructions** • Use w/ caution in patients w/ history of seizures, renal & hepatic impairment, recent CV disease, fructose intolerance, & for those undergoing anticoagulant treatment • Contraception is advised during & for 3 mth after treatment
Flutamide	250 mg PO 8 hrly	**Adverse Reactions** • GI effects (N/V, diarrhea, increased appetite, transient abnormal liver function); Neurologic effect (insomnia); GU effects (reduced sperm count, decreased libido, impotence); Other effects (gynecomastia, breast tenderness, galactorrhea, tiredness, chest pain, hair growth changes) **Special Instructions** • Use w/ caution in patients w/ liver injury or jaundice, serum transaminase >2-3 x upper limit of normal (ULN); perform periodic LFTs

[1]Given together w/ a GnRH agonist. Please see the latest MIMS for specific formulations.

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Dosage Guidelines

CANCER HORMONE THERAPY (CONT'D)		
Drug	**Dosage**	**Remarks**
Anti-androgen Preparations (Cont'd)		
Nilutamide	**Initial dose:** 300 mg PO 24 hrly **or** 150 mg PO 12 hrly x 4 wk **Maintenance dose:** 150 mg PO 24 hrly	**Adverse Reactions** • CNS effects (headache, memory impairment, cognitive disorder, anxiety); Dermatologic effects (pruritus, dryness); Other effects (hot flushes, visual hallucinations, fractures, hypertension) **Special Instructions** • Use w/ caution in patients w/ anti-androgen withdrawal syndrome, QT prolongation history, risk for torsades de pointes, Japanese ethnicity • Monitor hepatic & pulmonary function prior to & during treatment • Contraindicated in patients w/ severe hepatic impairment, respiratory insufficiency, & those w/ treatment failure w/ previous hormonal treatment
Gonadotropin Releasing Hormone Analogues		
Buserelin acetate	**Day 1-7:** 500 mcg SC 8 hrly **Day 8**: Maintain on 100 mcg/spray 1 spray into each nostrils 4 hrly	**Adverse Reactions** • Neurologic effects (depressive moods, dizziness, headache); GI effects (N/V, diarrhea); GU effect (obstructed micturition); Dermatologic effect (skin reddening); Resp effects (thrombosis w/ pulmonary embolism, dyspnea); Musculoskeletal effects (bone pain, weakness); Other effects (loss of libido, breast enlargement, hot flushes, urticaria) **Special Instructions** • Contraindicated in patients who recently underwent orchiectomy • Use w/ caution in patients w/ hypertension, diabetes, depression & those w/ increased risk of osteoporosis
Goserelin acetate	3.6 mg SC every 4 wk **or** 10.8 mg SC every 12 wk	**Adverse Reactions** • Musculoskeletal effects (arthralgia, paresthesias, increase in bone pain, decreased bone mineral density); GU effect (ureteric obstruction); Dermatologic effects (rashes, burning at inj site, sweating); CV effect (BP changes); Other effects (hot flushes, decreased libido, breast swelling/ tenderness) **Special Instructions** • Use w/ caution in patients w/ increased risk for urinary obstruction & spinal cord compression, preexisting DM, reduced glucose tolerance during LHRH treatment

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Dosage Guidelines

CANCER HORMONE THERAPY (CONT'D)		
Drug	**Dosage**	**Remarks**
Gonadotropin Releasing Hormone Analogues (Cont'd)		
Histrelin acetate	**Implant:** 50 mg SC for 12 mth	**Adverse Reactions** • CNS effects (insomnia, decreased libido, headache); GI effect (constipation); GU effects (hematuria, urethral/bladder outlet obstruction, transient increase in serum testosterone, erectile dysfunction, testicular atrophy, renal impairment); Dermatologic effect (implant site reaction); Musculoskeletal effect (decreased bone density); Other effects (hot flushes, fatigue, increased wt, gynecomastia) **Special Instructions** • Insert implant in the inner aspect of the upper arm • Contraindicated in patients w/ hypersensitivity to GnRH, GnRH agonist analogs, or synthetic LHRH or LHRH agonist analog • Use w/ caution in patients w/ metastatic vertebral lesions &/or urinary tract obstruction • Avoid wetting inserted arm 24 hr after implantation, & heavy lifting or strenuous exertion using the implanted arm for 7 days
Leuprorelin (Leuprolide)	3.75-7.5 mg SC/IM 4 wkly **or** 11.25-22.5 mg SC/IM 3 mthly **Hormone-dependent advanced prostate cancer:** 30-45 mg SC 6 mthly (interval of 168-182 days)	**Adverse Reactions** • GI effects (N/V); Musculoskeletal effects (transient increase in bone pain, weakness/paresthesia of the lower limbs); GU effects (worsening of preexisting hematuria or urinary obstruction, impotence, testicular atrophy); CNS effects (headache, insomnia, dizziness, diaphoresis); Other effects (hot flushes, limb edema, erythema, fatigue, inj site burning, decrease in libido, gynecomastia) **Special Instructions** • Use w/ caution in patients w/ urinary obstruction &/or metastatic vertebral lesions • Follow the correct preparation & administration steps to avoid medication errors • Should only be administered by a trained healthcare professional • Monitor testosterone & PSA levels
Triptorelin	3.75 mg IM 4 wkly **Locally advanced or metastatic, hormone-dependent prostate cancer:** 11.25 mg IM 3 mthly	**Adverse Reactions** • Musculoskeletal effects (paresthesia in lower limbs, back pain, musculoskeletal pain, pain in extremity); Dermatologic effects (inflammation, edema, inj site reaction, erythema); CNS effects (headache, dizziness); Other effects (loss of libido, hot flushes, hyperhidrosis, erectile dysfunction, fatigue, urinary symptoms, nausea) **Special Instructions** • Use w/ caution in patients w/ additional risk factors for osteoporosis, known depression, high risk for metabolic or CV disease, & in patients currently on anticoagulant treatment • Close monitoring is advised if Triptorelin is given in combination w/ drugs that modify the secretion of pituitary gonadotropins

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Dosage Guidelines

CANCER HORMONE THERAPY (CONT'D)

Drug	Dosage	Remarks
Other Hormone Antagonists & Related Agents		
Abiraterone acetate[1]	**Metastatic CRPC:** 1000 mg PO 24 hrly in combination w/ Prednisone 5 mg PO 12 hrly or Methylprednisolone 4 mg PO 12 hrly **High-risk metastatic hormone-sensitive prostate cancer:** 1000 mg PO 24 hrly in combination w/ Prednisone 5 mg PO 24 hrly	**Adverse Reactions** • CV effect (hypertension); Metabolic effects (hypokalemia, hypertriglyceridemia, increased ALT); GU effect (UTI); GI effects (diarrhea, vomiting); Other effects (peripheral edema, fluid retention, headache, upper resp tract infection, arthralgia) **Special Instructions** • Should be taken on an empty stomach • Use w/ caution in patients w/ HTN, hypokalemia & fluid retention (eg heart failure) due to excess mineralocorticoid, hepatotoxicity, corticosteroid withdrawal in stressful situations • Contraindicated in patients w/ severe hepatic impairment • Monitor blood pressure, liver function & serum potassium
Degarelix	**Initial dose:** 120 mg x 2 doses SC **Maintenance dose:** 80 mg SC mthly	**Adverse Reactions** • GI effects (diarrhea, nausea, increased liver transaminases); CNS effects (dizziness, insomnia, headache); GU effects (testicular atrophy, erectile dysfunction); Dermatologic effects (inj site reaction, rash, hyperhidrosis); Other effects (hot flushes, anemia, increased wt, musculoskeletal pain, chills, pyrexia, fatigue, flu-like illness) **Special Instructions** • Use w/ caution in patients w/ history of corrected QT interval >450 millisec, torsades de pointes, severe untreated asthma, anaphylactic reactions/urticaria/ angioedema, decreased bone density, glucose tolerance, renal & hepatic impairment
Relugolix	**Loading dose:** 360 mg PO on day 1 **Maintenance dose:** 120 mg PO 24 hrly at the same time each day	**Adverse Reactions** • GI effects (constipation, diarrhea); Metabolic effects (increased glucose, increased triglycerides, increased AST, increased ALT); Other effects (hot flush, musculoskeletal pain, decreased Hb) **Special Instructions** • Use w/ caution in patients taking p-gp inhibitors & strong CYP3 inducers
Progestogen		
Megestrol acetate	120 mg PO 24 hrly w/ Diethylstilbestrol 0.1 mg PO	**Adverse Reactions** • GI effects (N/V, diarrhea); Dermatologic effects (hypersensitivity reactions, skin rash, urticaria); Metabolic effect (hyperglycemia); CV effects (thromboembolic phenomena, fluid retention/edema); Other effects (tumor flare, dyspnea, wt gain, carpal tunnel syndrome, alopecia) **Special Instructions** • Should be taken w/ food • Use w/ caution in patients w/ history of thrombophlebitis

[1]Given in combination w/ corticosteroids. Please see the latest MIMS for specific formulations.

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Dosage Guidelines

CYTOTOXIC CHEMOTHERAPY		
Drug	**Dosage**	**Remarks**
Cytotoxic Antibiotics, Anthracyclines & Related Substances		
Doxorubicin	60-75 mg/m^2 IV every 21 days **or** 20-25 mg/m^2 IV 24 hrly x 3 days, repeated every 3-4 wk **Combination therapy:** 40-60 mg/m^2 IV 3-4 wkly **Max dose:** 500 mg/m^2	**Adverse Reactions** • GI effects (N/V, diarrhea); CV effects (CHF, ventricular tachycardia, AV block, bundle branch block, bradycardia, thromboembolism, asymptomatic drops in LVEF); Hematologic effects (secondary leukemia, acute lymphocytic & myelogenous leukemia, leukopenia, neutropenia, anemia, thrombocytopenia); CNS effect (anorexia); Other effects (infections, conjunctivitis, keratitis, pneumonia, hyperuricemia, chemical cystitis, embolism, inj site reaction) **Special Instructions** • Contraindicated in patients w/ persistent myelosuppression, severe hepatic impairment, cardiomyopathy, recent MI, severe arrhythmias, previous treatments w/ Epirubicin at maximum dose &/or other anthracyclines & anthracenediones • Use w/ caution in patients w/ hepatic impairment, phlebosclerosis, tumor lysis syndrome, catheterization problems, acute toxicities, generalized infections • Monitor CBC, cardiac, hepatic & renal function • Total cumulative dose for Doxorubicin should be <550 mg/m^2 (perform baseline echocardiogram) & Epirubicin 900-1000 mg/m^2
Epirubicin	**Initial dose:** 60-120 mg/m^2 body surface IV **Maximum dose:** 135 mg/m^2 IV on day 1 or in divided doses on day 1-3 3-4 wkly **Combination therapy:** **Max dose:** 120 mg/m^2 IV on day 1 3-4 wkly	
Mitoxantrone HCl	**Analgesic treatment of hormone-refractory prostate cancer:** 12 mg/m^2 as short-term IV infusion in combination w/ Prednisone 10 mg PO at 21-day intervals	**Adverse Reactions** • GI effects (N/V, stomatitis, diarrhea, abdominal pain, constipation, anorexia, mucositis, altered taste); CV effects (asymptomatic decrease in left ventricular ejection fraction (LVEF), transient ECG changes, arrhythmia); Resp effect (rhinitis); Musculoskeletal effect (cramps); CNS effects (somnolence, confusion, anxiety, mild paresthesia); Hematologic effects (transient leukopenia, thrombocytopenia, anemia); Ophthalmologic effects (reversible blue scleral discoloration, conjunctivitis); Other effects (neuritis, alopecia, urine discoloration, blue green nail/skin discoloration) **Special Instructions** • Contraindicated in patients w/ severe bone marrow suppression • Use w/ caution in patients w/ history of anthracycline treatment, myelosuppression, cardiac pathologies such as cardiac insufficiency & decreased LVEF, severe hepatic insufficiency, edema, ascites, pleural effusion • Administration of live vaccines should be avoided

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Dosage Guidelines

CYTOTOXIC CHEMOTHERAPY (CONT'D)		
Drug	**Dosage**	**Remarks**
Other Antineoplastic Agent		
Estramustine phosphate	**Initial dose:** 560-840 mg PO in divided doses Adjusted to 140-1400 mg/day PO according to response & tolerance	**Adverse Reactions** • GI effects (N/V, diarrhea, impaired liver function); CV effects (thromboembolism, ischemic heart disease, CHF, HTN, MI); Other effects (fluid retention, edema, skin rashes, gynecomastia, impotence) **Special Instructions** • Discontinue if no effect is seen after 4-6 wk • Should be taken on an empty stomach, at least 1 hr before or 2 hr after meals; not to be taken w/ milk, milk products, or drugs containing calcium, magnesium or aluminum (eg antacids) • Contraindicated in patients w/ severe liver disease, severe cardiovascular disease (ischemic, thromboembolic, or complications related to fluid retention • Use w/ caution in patients w/ history of thrombophlebitis, thrombosis/thromboembolic disorders; cerebral vascular/CAD, diabetes, HTN, exacerbation of preexisting or incipient peripheral edema, CHD, epilepsy, migraine, metabolic bone diseases, renal & hepatic insufficiency, patients at risk of hypercalcemia • Administration of live or live-attenuated vaccines should be avoided
Platinum-Containing Antineoplastic Agent		
Cisplatin	50-120 mg/m^2 IV every 4 wk **or** 15-20 mg/m^2 IV infusion 24 hrly x 5 days **or** 25-35 mg/m^2 IV once wkly every 2 wk	**Adverse Reactions** • GU effects (mild reversible renal function impairment, microhematuria); Hematologic effects (leukopenia, thrombocytopenia, anemia, severe bone marrow depression); Other effects (GI & auditory disturbances, hyperuricemia, immunosuppression, peripheral neuropathy w/ paresthesia) • Side-effects are dose-dependent **Special Instructions** • Contraindicated in patients w/ bone marrow depression, severe renal impairment, dehydration, chickenpox, herpes zoster, gout, urate calculi, recent infections, & Cisplatin-induced peripheral neuropathy • Use w/ caution in patients w/ mild, renal, hematopoietic system & hearing impairment • Monitoring of renal function, blood count, auditory function, liver enzymes & plasma & electrolytes prior to & during treatment are advised
Taxanes		
Cabazitaxel[1]	**Hormone-refractory prostate cancer:** 25 mg/m^2 as a 1-hr IV infusion every 3 wk	**Adverse Reactions** • GI effects (diarrhea, N/V, constipation, abdominal pain, anorexia, dysgeusia); Hematologic effects (leukopenia, thrombocytopenia, anemia, neutropenia, febrile neutropenia); Resp effects (dyspnea, cough); Other effects (pyrexia, fatigue, hematuria, back pain, arthralgia) **Special Instructions** • Contraindicated in patients w/ neutrophil count <1,500/mm^3, hepatic impairment, & concomitant vaccination w/ yellow fever vaccine • Use w/ caution in patients w/ Hb <10 g/dL, risk of neutropenia, nausea, vomiting, diarrhea, dehydration, renal failure, cardiac arrhythmias, liver disease, epilepsy, & those currently on CYP3A4 inhibitors/inducers • Monitor for hypersensitivity reactions & peripheral neuropathy

[1]Given in combination w/ corticosteroids. Please see the latest MIMS for specific formulations.

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Dosage Guidelines

CYTOTOXIC CHEMOTHERAPY (CONT'D)		
Drug	**Dosage**	**Remarks**
Taxanes (Cont'd)		
Docetaxel[1]	75 mg/m^2 IV as a 1-hr infusion given 3 wkly	**Adverse Reactions** • GI effects (diarrhea, dysgeusia, stomatitis, nausea); Hematologic effects (febrile neutropenia, anemia); CNS effects (peripheral sensory neuropathy, anorexia); Dermatologic effects (rash, eruptions, alopecia, nail disorders); Other effects (infections, myalgia, fluid retention, asthenia, bone marrow suppression, hypotension, infusion site reaction, increased serum transaminases) **Special Instructions** • Contraindicated in patients w/ baseline neutrophil count of <1,500 cell/mm^3, severe liver impairment • Use w/ caution in patients w/ neutropenia, fluid retention, liver/ renal impairment, peripheral neurotoxicity, skin reactions
Therapeutic Radiopharmaceuticals		
Radium RA 223 dichloride	**CRPC w/ symptomatic bone metastases & no known visceral metastatic disease:** 50 kBq/kg body wt IV at 4-wk intervals x 6 doses	**Adverse Reactions** • GI effects (N/V, diarrhea); Hematologic effects (thrombocytopenia, neutropenia, pancytopenia, leukopenia); Other effect (inj site reactions) **Special Instructions** • Use w/ caution in patients w/ bone marrow suppression, Crohn's disease & ulcerative colitis, acute inflammatory bowel disease, increased cancer risk, hereditary defects • Obtain baseline hematologic values & orthopedic stabilization in patients at risk for fracture prior to every dose • Advise patient to use effective contraceptive methods during & up to 6 mth after treatment
Strontium-89 (Strontium chloride, ^{89}Sr)	148 MBq IV **or** 1.5-2.2 MBq/kg IV **Max dose:** 2.2 MBq/kg/dose IV	**Adverse Reactions** • Hematologic effects (thrombocytopenia, leukopenia); Other effects (hot flushes, transient increased pain 36-72 hr post-inj) **Special Instructions** • Use w/ caution in patients w/ previous extensive bone radiation, other bone seeking isotope inj, X-ray, chemotherapy; compromised bone marrow function; renal impairment, short life expectancy, local beam therapy • Monitor CBCs (especially platelets) pre- & ≥8 wk post-treatment • Contraindicated in patients w/ severely compromised bone marrow unless benefit > risk • Should not be administered rapidly (<30 sec) • Repeat administrations should not be performed within 3 mth of the previous inj

[1]Given in combination w/ corticosteroids. Please see the latest MIMS for specific formulations.

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Dosage Guidelines

OESTROGENS, PROGESTERONES & RELATED SYNTHETIC DRUGS

Drug	Dosage	Remarks
Conjugated estrogens	**Advanced androgen-dependent prostate carcinoma (palliative therapy):** 1.25-2.5 mg PO 8 hrly	**Adverse Reactions** • GI effects (abdominal pain, diarrhea, dyspepsia, flatulence, nausea); CNS effects (headache, dizziness, insomnia, depression); Resp effects (increased cough, pharyngitis, rhinitis, sinusitis, infection); Musculoskeletal effects (arthralgia, back pain, leg cramps, myalgia); Other effects (asthenia, flu syndrome, breast pain, pruritus) **Special Instructions** • Should be taken w/ food to reduce nausea • Use w/ caution in patients w/ hypertension, impaired hepatic function, hypertriglyceridemia, cholestatic jaundice, hypothyroidism, fluid retention, epilepsy, migraine, DM, porphyria, hypoparathyroidism, asthma, SLE & hepatic hemangiomas • Contraindicated in patients w/ history of, known or suspected breast cancer; in patients w/ hepatocellular cancer, stroke, thromboembolic disease
Diethylstilbestrol	1-3 mg PO 24 hrly	**Adverse Reactions** • GI effect (GI disturbances); CNS effect; CV effect; Other effects (jaundice, impotence, feminization, gynecomastia, hypercalcemia, chloasma, keratoconus, contact lenses intolerance, altered carbohydrate metabolism, loss of diabetic control) **Special Instructions** • Use w/ caution in patients w/ renal & hepatic impairment • Contraindicated in patients w/ thromboembolic disease & porphyria
Medroxyprogesterone acetate[1]	100-500 mg PO 24 hrly	**Adverse Reactions** • GI effects (changes in appetite, GI disturbances, liver enzyme changes); Dermatologic effects (chloasma, rashes, acne, hair loss, hirsutism); CNS effects (drowsiness, insomnia, headache, mental depression); Other effects (fever, breast changes, fluid retention, fatigue, changes in libido, jaundice, changes in serum lipid profile) **Special Instructions** • Should be taken w/ food • Use w/ caution in patients w/ cardiovascular or renal impairment, DM, asthma, epilepsy, migraine, depression & other conditions aggravated by fluid retention • Contraindicated in patients w/ thrombophlebitis, thromboembolic disturbances, hepatic insufficiency, hormone-dependent carcinoma

[1]Combination w/ other estrogens, progesterones & related synthetic drugs are available. Please see the latest MIMS for specific formulations.

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Dosage Guidelines

TARGETED CANCER THERAPY		
Drug	**Dosage**	**Remarks**
Monoclonal Antibody		
Pembrolizumab	**MSI-H/MMR mutation-positive:** 200 mg by IV infusion over 30 min 3 wkly until disease progression, unacceptable toxicity, or up to 24 mth in patients without disease progression	**Adverse Reactions** • GI effects (nausea, constipation, decreased appetite, diarrhea); Resp effects (cough, pneumonitis, dyspnea, pneumonia); Dermatologic effects (pruritus, rash, cellulitis); Other effects (fatigue, arthralgia, renal failure, pain) **Special Instructions** • Withhold treatment if any of the following occurs: Moderate pneumonitis, moderate or severe immune-mediated colitis, moderate hypophysitis, severe hyperglycemia, moderate immune-mediated nephritis • Discontinue if life-threatening adverse events of pneumonitis, colitis, hypophysitis, hyperthyroidism, nephritis, infusion reactions, severe liver enzyme elevations occur • Monitor liver enzymes, serum creatinine, & thyroid & renal function
Protein Kinase Inhibitors		
Olaparib	**Homologous recombination repair gene mutation-associated mCRPC previously treated w/ androgen receptor-directed therapy:** 300 mg PO 12 hrly until disease progression, unacceptable toxicity *Cycled every 28 days*	**Adverse Reactions** • GI effects (dysgeusia, N/V, diarrhea, dyspepsia, stomatitis, upper abdominal pain); Hematologic effects (anemia, neutropenia, lymphopenia, mean corpuscular volume elevation, thrombocytopenia); Other effects (increased creatinine, decreased appetite, headache, dizziness, fatigue) **Special Instructions** • Should be taken on an empty stomach • Start treatment not later than 8 wk after completion of final dose of the platinum-containing regimen • Interrupt treatment if severe hematological toxicity or blood transfusion dependence develops, or if new or worsening resp symptoms or a radiological abnormality occurs; discontinue treatment if pneumonitis is confirmed • Use w/ caution in patients w/ myelodysplastic syndrome/acute myeloid leukemia, moderate to severe renal impairment, hepatic impairment • Avoid co-administration w/ strong CYP3A inducers or inhibitors
Rucaparib	***BRCA* mutation-associated mCRPC previously treated w/ androgen receptor-directed therapy & a taxane-based chemotherapy:** 600 mg PO 12 hrly until disease progression or unacceptable toxicity	**Adverse Reactions** • GI effects (N/V, constipation, abdominal pain); Resp effects (acute resp distress syndrome, pneumonia); CV effects (QT prolongation, cardiac failure); Hematologic effects (anemia, thrombocytopenia, leukopenia, neutropenia); Metabolic effect (dyslipidemia, increased serum creatinine, increased ALT, AST & alkaline phosphatase); Other effects (rash, asthenia, fatigue, balance disorder, decreased appetite, decreased wt) **Special Instructions** • Contraindicated in patients w/ leukemia, myelodysplastic syndrome • Monitor CBC

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Dosage Guidelines

Palliative Therapy

AGENTS AFFECTING BONE METABOLISM		
Drug	**Dosage**	**Remarks**
Denosumab	120 mg SC into thigh, abdomen or upper arm 4 wkly	**Adverse Reactions** • Dermatologic effects (alopecia, hyperhidrosis); Musculoskeletal effects (musculoskeletal pain, osteonecrosis of the jaw); Metabolic effects (hypocalcemia, hypophosphatemia); Other effects (dyspnea, diarrhea, new primary malignancy, tooth extraction) **Special Instructions** • Hypocalcemia should be corrected prior to initiating therapy • Contraindicated in patients w/ hypocalcemia
Zoledronic acid	4 mg IV infusion as a single dose over not <15 min every 3-4 wk	**Adverse Reactions** • CV effects (hypotension, hypertension, bradycardia, atrial fibrillation, peripheral edema, chest pain); CNS effects (insomnia, somnolence, anxiety, depression, confusion, agitation, headache, dizziness, vertigo, asthenia, paresthesia, taste disturbance, hypoesthesia, hyperesthesia, tremor, hallucination); GI effects (abdominal pain, N/V, anorexia, dyspepsia, constipation, diarrhea, stomatitis, sore throat, decreased/increased wt, dehydration, decreased appetite, dry mouth); Hematologic effects (anemia, neutropenia, granulocytopenia, thrombocytopenia, leukopenia, pancytopenia); Musculoskeletal effects (myalgia, bone pain, back pain, arthralgia, muscle cramps); Other effects (hypophosphatemia, hypomagnesemia, hyperkalemia, hypokalemia, hypernatremia, increased creatinine, hypocalcemia, fever & flu-like syndrome, progression of cancer, fatigue, chills, weakness, uveitis, conjunctivitis) **Special Instructions** • Use w/ caution in patients w/ renal & hepatic impairment, asthma • Evaluate serum creatinine concentration prior to therapy • Monitor serum levels of Ca, phosphate & Mg after initiating therapy; hydration & electrolyte levels • Discontinue use if ocular disturbances occur

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