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هفت سین ایرانی

GCOC 6

Panel subject:
PROSTATE CANCER

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Guilan univ. of medical sciences

- **Case 1**

- A 63 year old man who is a retired truck driver has come to you with the complaint of a moderate to severe pain in his left hip.

- He tells that has had this pain since 1 year ago, firstly was mild, but he did not care, later pain exacerbated that he can't sit easily.

- Also he complains of his weak urinary stream and frequency which has worsened recently (recent 3 months), no hematuria or dysuria.

- PMH: under controlled DM2 and mild HTN since 6 years ago
- FH: -
- HH: just smokes sometimes since youth, no opium and alchohol

- **What further Qs do you ask and why?**

- Other symptoms such as: WL, cough, …

- **What do you do now?**

- **Ph/E?**

Alert and conscious, not pale,

no LAPs, Lung and spines: Nl

AP: Nl.

Wt: 88 Kg, Ht: 181 cm

Ext: tenderness in Ant. Left hip with LROM, he can't sit easily.

- DD?

What do you do now?

- **Can we start treatment now?**

- **Or further W/U needed, then make correct decision?**

- CBC, BUN/Cr, LFT: Nl,
- ESR, LDH, Ca/P: Nl, UA: Nl
- Total PSA: 123, Testosteron?
- Hip localised CT without contarst: Lt femur head and neck lesions impending to frature.

- **Refer to expert urologist**

- **TR: a palpable mass with ECE**

- **Now what should you do?**

- **Can we start treatment now?**

- Imaging (APC CT, mpMRI, WBS) when?

- **NO, Biopsy needed.**
- **TRUS**
- **Adenocarcinoma, 10/16 +, GS: 9 (5+4)**

- APC CT: just 65*57*51 mm prostate gland and Lt hip enhanced lesion
- PMRI?
- WBS: just Lt hip uptake

PRINCIPLES OF GENETICS AND MOLECULAR/BIOMARKER ANALYSIS

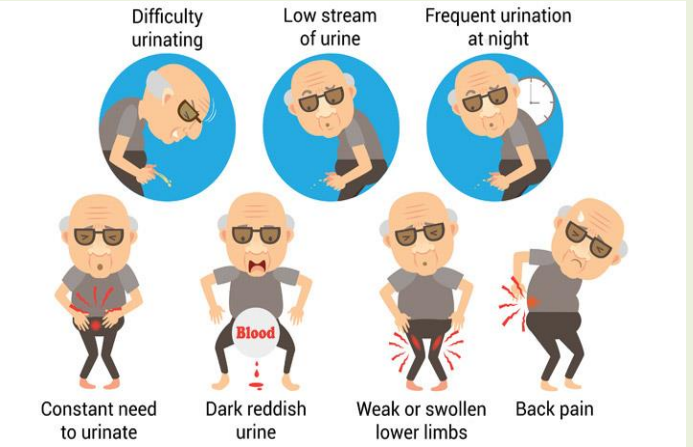
Germline testing is recommended *in patients with a personal history of prostate cancer* in the following scenarios:

- By Prostate Cancer Stage or Risk Group (diagnosed at any age)
  - Metastatic, regional (node positive), very-high risk localized, high-risk localized prostate cancer
- By Family History[a] and/or Ancestry
  - ≥1 first-, second-, or third-degree relative with:
    - ◊ breast cancer at age ≤50 y
    - ◊ colorectal or endometrial cancer at age ≤50 y
    - ◊ male breast cancer at any age
    - ◊ ovarian cancer at any age
    - ◊ exocrine pancreatic cancer at any age
    - ◊ metastatic, regional, very-high-risk, high-risk prostate cancer at any age
  - ≥1 first-degree relative (father or brother) with:
    - ◊ prostate cancer[b] at age ≤60 y
  - ≥2 first-, second-, or third-degree relatives with:
    - ◊ breast cancer at any age
    - ◊ prostate cancer[b] at any age
  - ≥3 first- or second-degree relatives with:
    - ◊ Lynch syndrome-related cancers, especially if diagnosed <50 y: colorectal, endometrial, gastric, ovarian, exocrine pancreas, upper tract urothelial, glioblastoma, biliary tract, and small intestinal cancer
  - A known family history of familial cancer risk mutation (pathogenic/likely pathogenic variants), especially in: *BRCA1, BRCA2, ATM, PALB2, CHEK2, MLH1, MSH2, MSH6, PMS2, EPCAM*
  - Ashkenazi Jewish ancestry
- Personal history of breast cancer

Germline testing may be considered *in patients with a personal history of prostate cancer* in the following scenarios:

- By Prostate Cancer Tumor Characteristics (diagnosed at any age)
  - ◊ intermediate-risk prostate cancer with intraductal/cribriform histology[c]
- By prostate cancer[b] AND a prior personal history of any of the following cancers:
  - ◊ exocrine pancreatic, colorectal, gastric, melanoma, pancreatic, upper tract urothelial, glioblastoma, biliary tract, and small intestinal

ADT for ADT naive M1 disease



- ADT is gold standard.
- Continuous or intermittent ADT?
- What options do we have for ADT?
  (Orchiectomy , abiraterone , docetaxel)
- How to prevent testosterone flare in weight bearing bones? (at least 1 week use of first generation antiandrogen)

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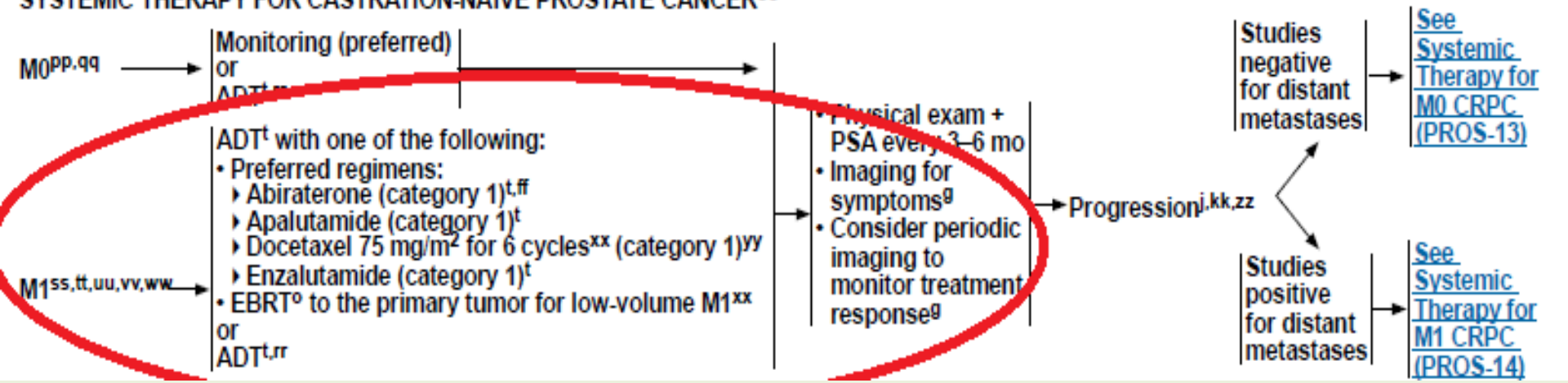
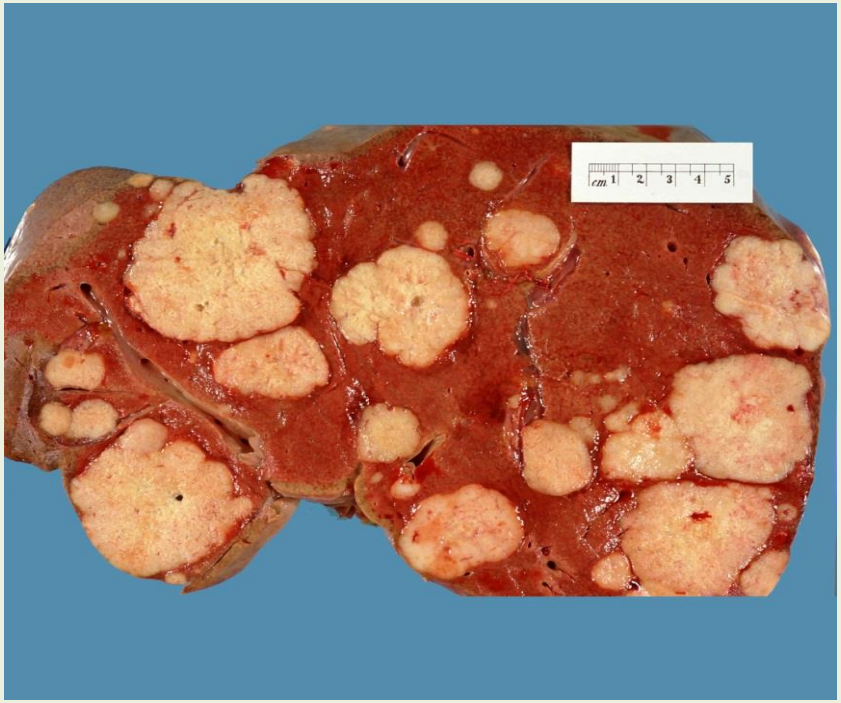
SYSTEMIC THERAPY FOR CASTRATION-NAÏVE PROSTATE CANCER[oo]



Visceral Metastases

- Two randomized phase 3 studies evaluated docetaxel-based regimens in symptomatic PC patiens:

- TAX 327
- SWOG 9916



- Docetaxel can be offered to men without metastatic prostate cancer or to men with low-volume metastatic prostate cancer?

- **High volume disease defined as:**

1. More than 3 bone metastases including one extra-axial bone lesion or

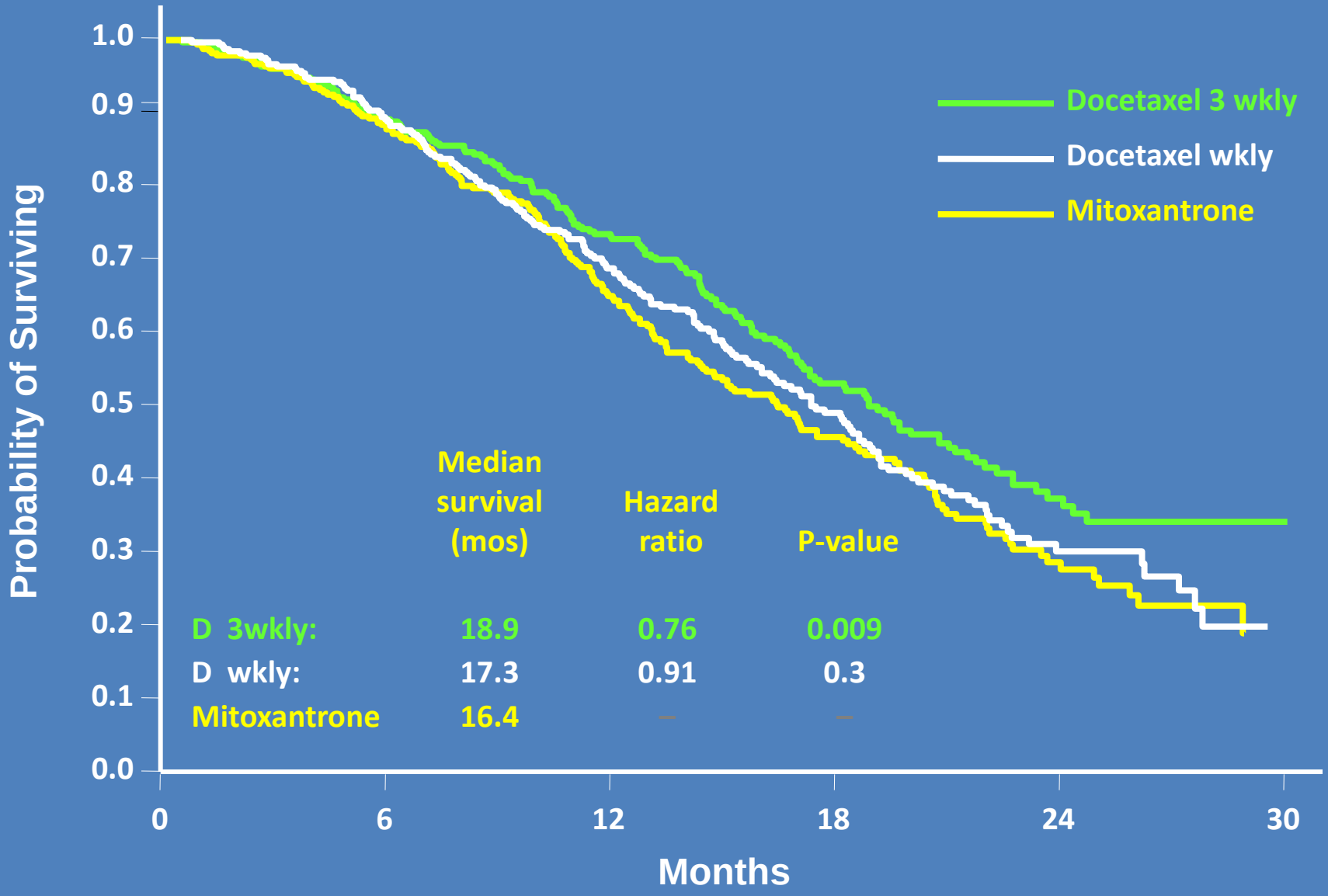
2. visceral metastases

- **Visceral Metastases**

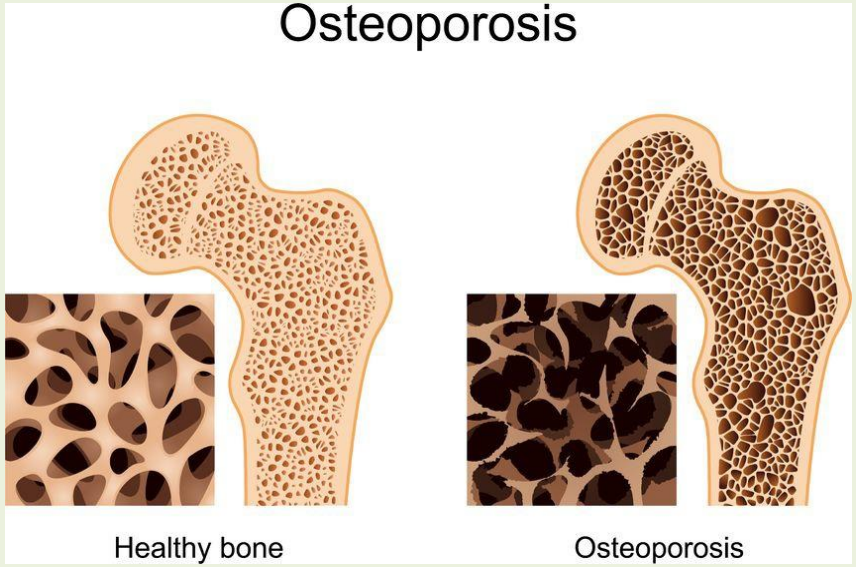
- Every 3 week docetaxel 75 mg/m2 IV with prednisone 10 mg/day P.O for 6-10 courses are category 1 for patients with symptomatic CRPC with visceral metastatic.

- Men with high-volume, ADT-naive, metastatic disease should be considered for ADT and docetaxel plus prednisone based on (CHAARTED) trial.

TAX 327: Survival Advantage Only Shown for Q3W Docetaxel



ADT side effects



If PSA rises again?

(e.g: PSA rises to 11, 5 years after Tx.)

Secondary hormone therapy in CRPC

- Mechanism of CRPC
- LHRH agonist or antagonist + …

1. Enzalotimide
2. Abiraterone + prednisolone
3. Ketoconazole , DES , flutamide, prednisolone …

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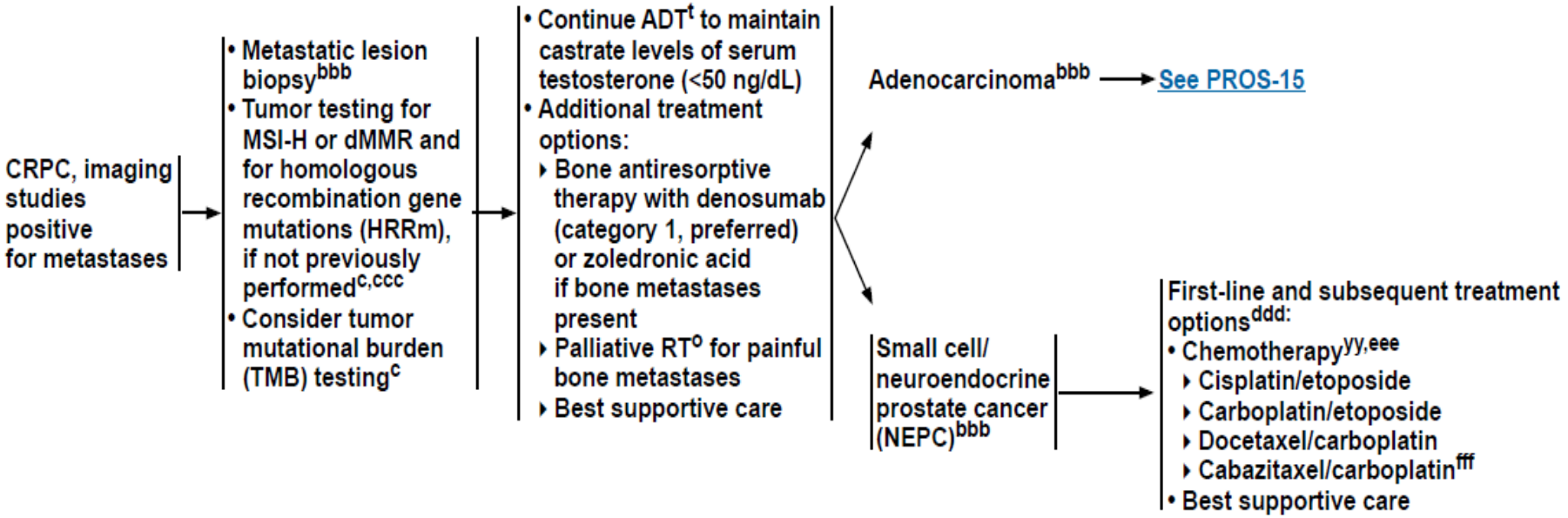
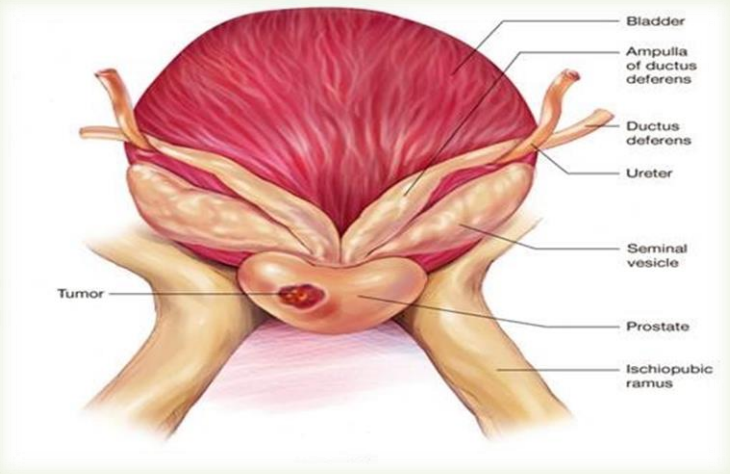
SYSTEMIC THERAPY FOR M1 CRPC[aaa]



No Visceral Metastases

- **Abiraterone acetate** with prednisone and **enzalutamide** (MDV3100, Xtandi) are category 1 for patients with asymptomatic, chemotherapy-naive, metastatic CRPC.



For symptomatic M1 CRPC?

SYSTEMIC THERAPY FOR M1 CRPC: ADENOCARCINOMA[dd,ggg,hhh]

No prior docetaxel/no prior novel hormone therapy[iii]

- Preferred regimens
  - Abiraterone[t,jjj] (category 1[kkk])
  - Docetaxel[yy,lll] (category 1)
  - Enzalutamide[t] (category 1)
- Useful in certain circumstances
  - Sipuleucel-T[yy,mmm] (category 1)
  - Radium-223[nnn] for symptomatic bone metastases (category 1)
- Other recommended regimens
  - Other secondary hormone therapy[t]

Prior novel hormone therapy/No prior docetaxel[iii,ooo]

- Preferred regimens
  - Docetaxel (category 1)[yy]
  - Sipuleucel-T[yy,mmm]
- Useful in certain circumstances
  - Olaparib for HRRm (category 1)[ppp]
  - Cabazitaxel/carboplatin[yy,fff]
  - Pembrolizumab for MSI-H, dMMR, or TMB ≥10 mut/Mb[yy]
  - Radium-223[nnn] for symptomatic bone metastases (category 1)
  - Rucaparib for BRCAm[qqq]
- Other recommended regimens
  - Abiraterone[t,jjj]
  - Abiraterone + dexamethasone[iii,qqq]
  - Enzalutamide[t]
  - Other secondary hormone therapy[t]

Prior docetaxel/no prior novel hormone therapy[iii]

- Preferred regimens
  - Abiraterone[t,jjj] (category 1)
  - Cabazitaxel[yy]
  - Enzalutamide[t] (category 1)
- Useful in certain circumstances
  - Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[yy]
  - Cabazitaxel/carboplatin[yy,fff]
  - Pembrolizumab for MSI-H, dMMR, or TMB ≥10 mut/Mb[yy]
  - Radium-223[nnn] for symptomatic bone metastases (category 1
- Other recommended regimens
  - Sipuleucel-T[yy,mmm]
  - Other secondary hormone therapy[t]

Prior docetaxel and prior novel hormone therapy[iii,ooo]

(All systemic therapies are category 2B if visceral metastases are present)

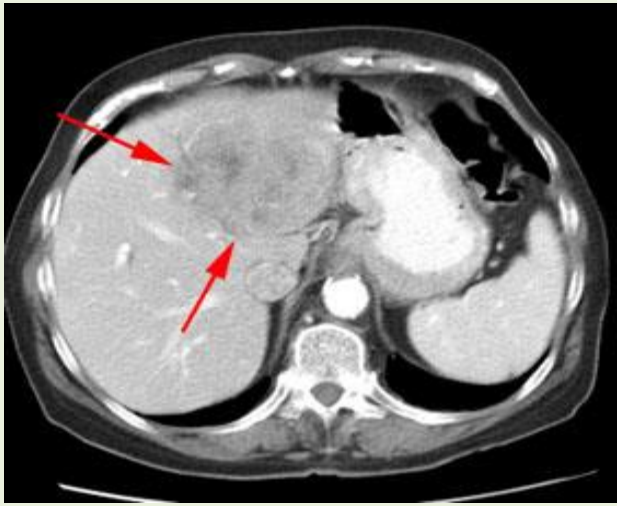
- Preferred regimens
  - Cabazitaxel[yy] (category 1[kkk])
  - Docetaxel rechallenge[yy]
- Useful in certain circumstances
  - Olaparib for HRRm (category 1[kkk])[ppp]
  - Cabazitaxel/carboplatin[yy,fff]
  - Pembrolizumab for MSI-H, dMMR, or TMB ≥10 mut/Mb[yy]
  - Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[yy]
  - Radium-223[nnn] for symptomatic bone metastases (category 1[kkk])
  - Rucaparib for BRCAm[qqq]
- Other recommended regimens
  - Abiraterone[t,jjj]
  - Enzalutamide[t]
  - Other secondary hormone therapy[t]

- **In visceral metastases of prostate cancer:**

- PSA rise alone does not define as docetaxel failure.

- Enzalotamide is another category 1.

- Abiraterone acetate is category 1.



- Radium-223 alone no.

- Mitoxantrone for palliation.

- **Progression Following Docetaxel**

- Enzalotamide is category 1.

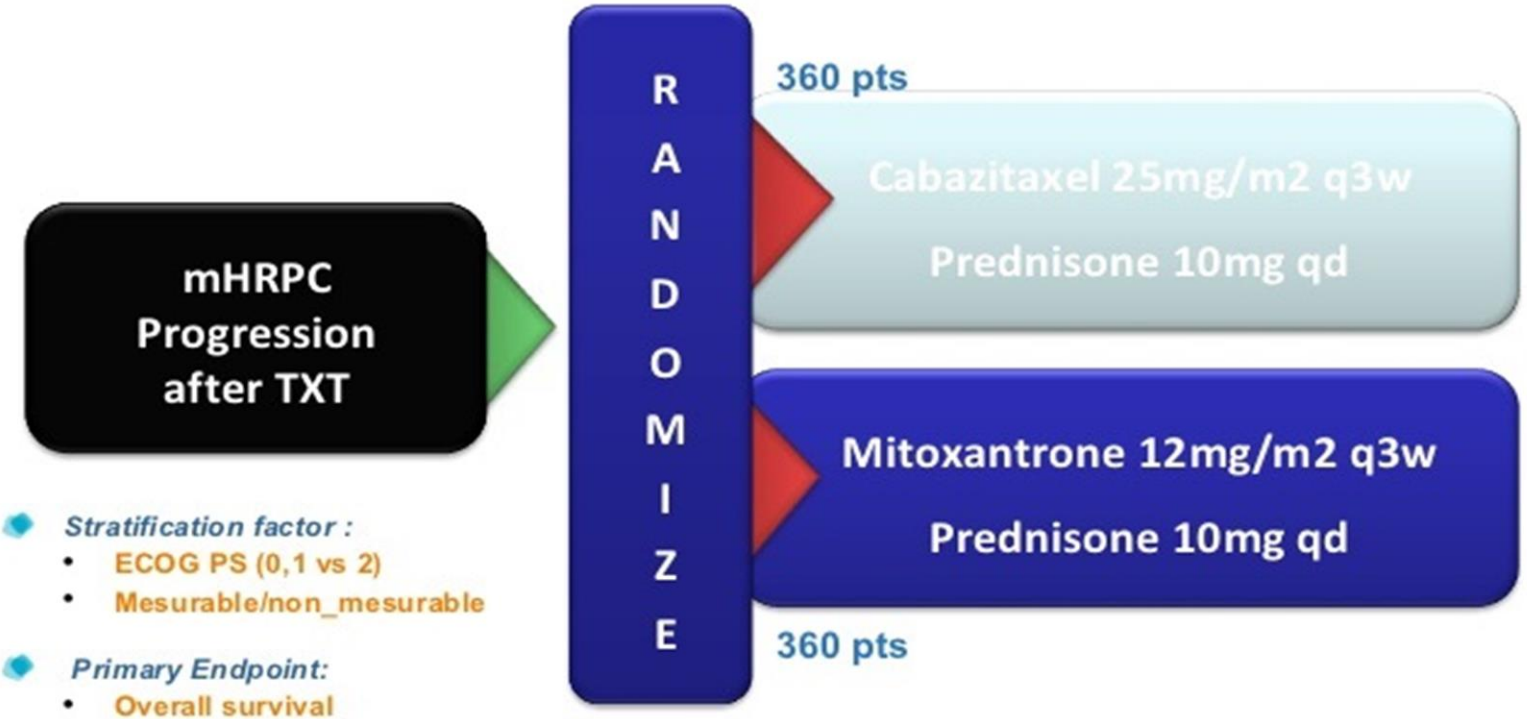
- Abiraterone acetate is category 1.

- Cabazitaxel with prednisone is category 1.

- Docetaxel rechalleng is category 2A.

Cabazitaxel in Second-line CRPC
TROPIC Study

2010

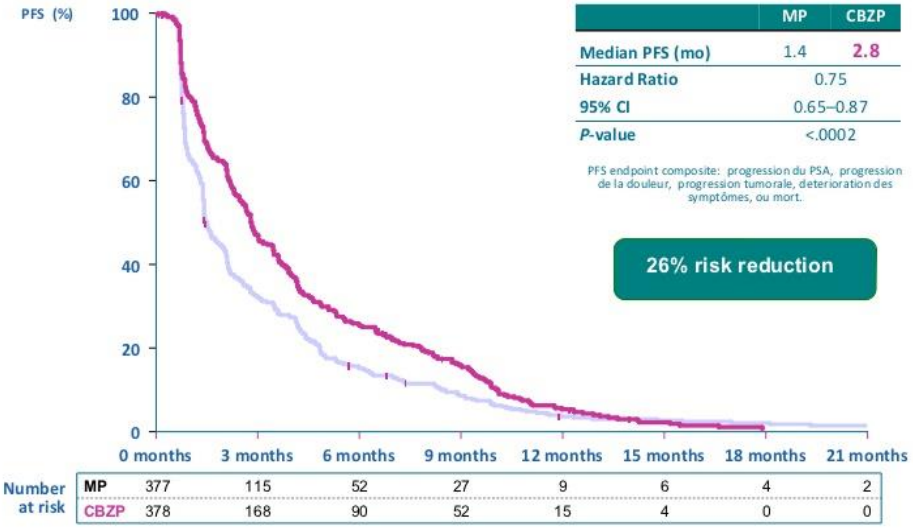


- *Stratification factor :*
  - ECOG PS (0,1 vs 2)
  - Mesurable/non_mesurable
- *Primary Endpoint:*
  - Overall survival
- *Secondary Endpoint:*
  - PSA response, PSA progression, PFS, RR, Pain progression, Safety, PK of cabazitaxel

Enrollment closed: 745/720 pts

Hypothesis: Reduction of 25% in the risk of death or median OS=10.67 months for cabazitaxel vs 8 months
511 events, duration 36 months

Progression-free survival

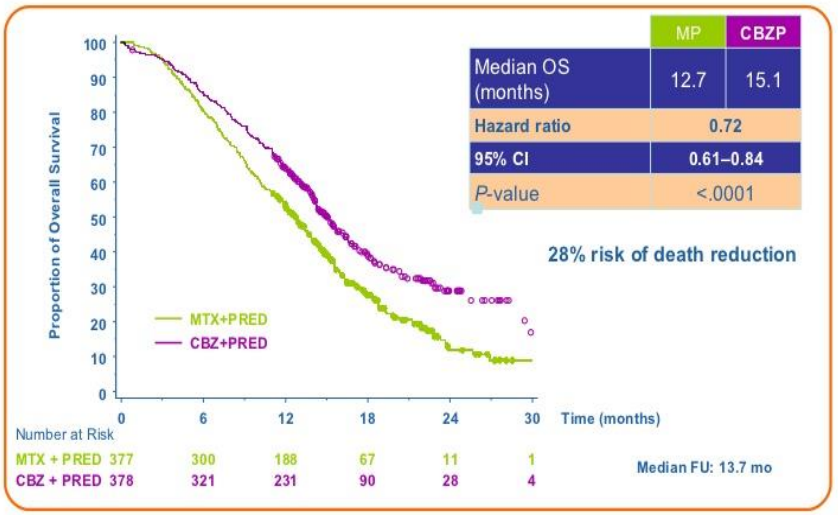


	MP	CBZP
Median PFS (mo)	1.4	2.8
Hazard Ratio	0.75	
95% CI	0.65–0.87	
P-value	<.0002	

PFS endpoint composite: progression du PSA, progression de la douleur, progression tumorale, deterioration des symptômes, ou mort.

26% risk reduction

Cabazitaxel vs Mitoxantrone: Overall Survival



	MP	CBZP
Median OS (months)	12.7	15.1
Hazard ratio	0.72	
95% CI	0.61–0.84	
P-value	<.0001	

28% risk of death reduction

Median FU: 13.7 mo

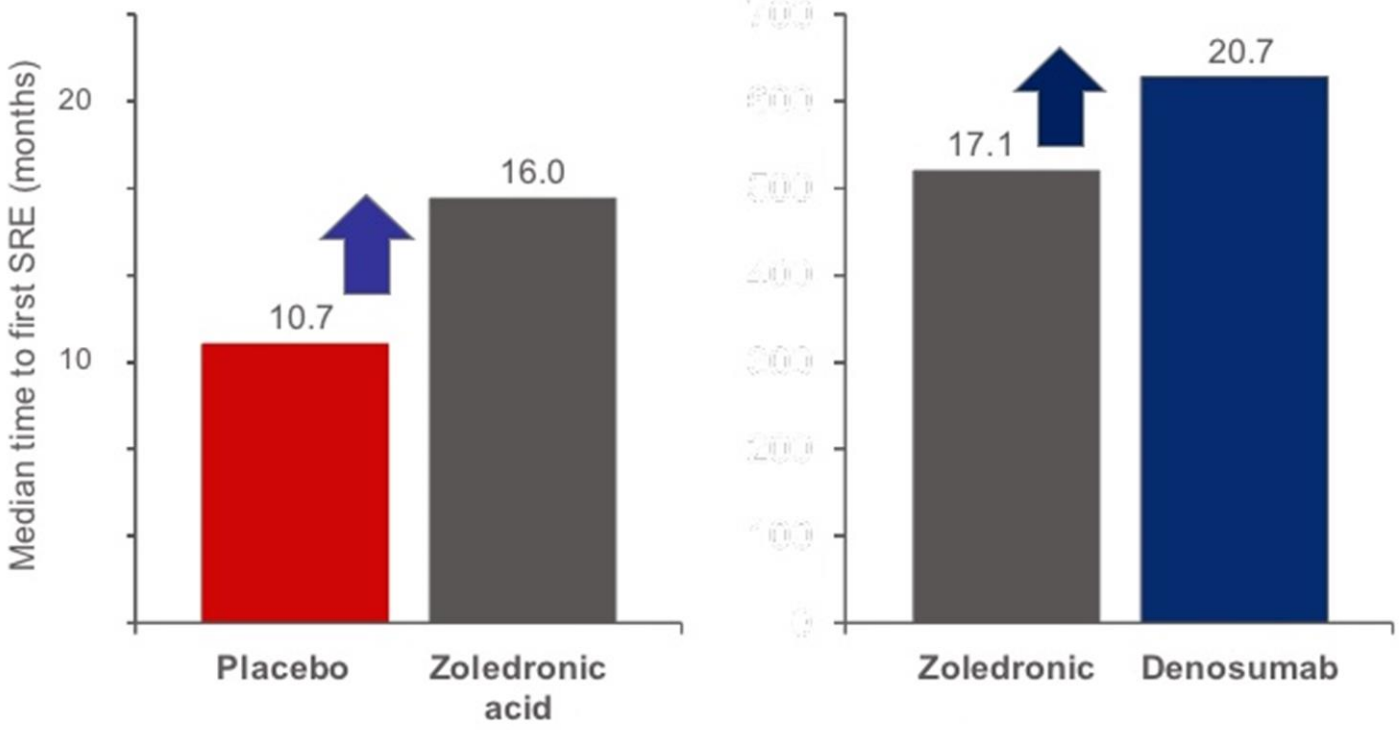
De Bono et al. Lancet 2010

A decade of research in prostate cancer

2004-2009:
No significant result

2010:
- Sipuleucel-T
- Cabazitaxel
- Denosumab
- Abiraterone

2000-2010: A decade of progress in preventing SRE in men with prostate cancer



Denosumab (120 mg Q4W) is not approved for use in patients with advanced cancer to delay SREs. Denosumab is investigational in that setting.

Saad, et al. J Natl Cancer Inst 2004;96:879-82;
Fizazi, et al. J Clin Oncol 2010;28 (suppl 18) LBA4507.

- If mCRPC fails to respond to ADT, docetaxel, Abiraterone, enzalotamide what are the other options?

- 1- Olaparib
- 2- Rucaprib
- 3- Sipuleucel-T
- 4- Pembrolizumab

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Comment > Future Oncol. 2021 May;17(14):1699-1707. doi: 10.2217/fon-2020-1291. Epub 2021 Feb 8.

Darolutamide and survival in nonmetastatic, castration-resistant prostate cancer: a patient perspective of the ARAMIS trial

K Fizazi [1], Ian Blue [2], Joel T Nowak [2 3]

Affiliations + expand

PMID: 33554636 DOI: 10.2217/fon-2020-1291

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- **Case 2**

- A 59 year old man who is an experienced and skilled carpenter has come to you with the complaint of weak urinary stream and frequency which has worsened recently (recent 4 months) and mild to mod. dysuria, no hematuria.

- PMH: -, FH: -, HH: -, Ph/E: Nl ***(TR?)***

- CBC, BUN/Cr, LFT: Nl, ESR, LDH, Ca/P: Nl, UA: Nl, Total PSA: 8.6, Testosteron?

- Imaging: just PMRI +/- GAD done

- **Core biopsy under TRUS: Adenocarcinoma, 5/15 +, GS: 6, T2a**

- **What do you do now?**

INITIAL RISK STRATIFICATION AND STAGING WORKUP FOR CLINICALLY LOCALIZED DISEASE[d]

Risk Group	Clinical/Pathologic Features See Staging (ST-1)			Additional Evaluation[g,h]	Initial Therapy
Very low[e]	Has all of the following: • cT1c • Grade Group 1 • PSA <10 ng/mL • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core • PSA density <0.15 ng/mL/g			• Consider confirmatory mpMRI ± prostate biopsy if MRI not performed initially. All patients should undergo a confirmatory prostate biopsy within 1-2 years of their diagnostic biopsy.	See PROS-3
Low[e]	Has all of the following but does not qualify for very low risk: • cT1–cT2a • Grade Group 1 • PSA <10 ng/mL			• Consider confirmatory mpMRI ± prostate biopsy and/or molecular tumor analysis if MRI not performed inititally to establish candidacy for active surveillance. All patients should undergo a confirmatory prostate biopsy within 1-2 years of their diagnostic biopsy.	See PROS-4
Intermediate[e]	Has all of the following: • No high-risk group features • No very-high-risk group features • Has one or more intermediate risk factors (IRFs): ▸ cT2b–cT2c ▸ Grade Group 2 or 3 ▸ PSA 10–20 ng/mL	Favorable intermediate	Has all of the following: • 1 IRF • Grade Group 1 or 2 • <50% biopsy cores positive (eg, <6 of 12 cores)[f]	• Consider confirmatory mpMRI ± prostate biopsy and/or molecular tumor analysis if MRI not performed initially for those considering active surveillance. All patients should undergo a confirmatory prostate biopsy within 1-2 years of their diagnostic biopsy.	See PROS-5
		Unfavorable intermediate	Has one or more of the following: • 2 or 3 IRFs • Grade Group 3 • ≥ 50% biopsy cores positive (eg, ≥ 6 of 12 cores)[f]	Bone and soft tissue imaging[i,j] • If regional or distant metastases are found, see PROS-8 or PROS-12	See PROS-6
High	Has no very-high-risk features and has exactly one high-risk feature: • cT3a OR • Grade Group 4 or Grade Group 5 OR • PSA >20 ng/mL			Bone and soft tissue imaging[i,j] • If regional or distant metastases are found, see PROS-8 or PROS-12	See PROS-7
Very high	Has at least one of the following: • cT3b–cT4 • Primary Gleason pattern 5 • 2 or 3 high-risk features • >4 cores with Grade Group 4 or 5			Bone and soft tissue imaging[i,j] • If regional or distant metastases are found, see PROS-8 or PROS-12	See PROS-7

See Footnotes for Initial Risk Stratification and Staging Workup for Clinically Localized Disease (PROS-2A).

LOW-RISK GROUP

EXPECTED PATIENT SURVIVAL[k]	INITIAL THERAPY	ADJUVANT THERAPY
≥10 y	Active surveillance (preferred for most patients)[m,v] • Consider confirmatory mpMRI +/- prostate biopsy and/or molecular tumor analysis[w] if MRI not performed initially[n] • All patients should undergo a confirmatory prostate biopsy within 1-2 years of their diagnostic biopsy[n] • PSA no more often than every 6 mo unless clinically indicated • DRE no more often than every 12 mo unless clinically indicated • Repeat prostate biopsy no more often than every 12 mo unless clinically indicated[x] • Repeat mpMRI no more often than every 12 mo unless clinically indicated	Progressive disease[u] See Initial Risk Stratification and Staging Workup for Clinically Localized Disease (PROS-2)
	EBRT[o] or brachytherapy[o]	See Monitoring for Initial Definitive Therapy (PROS-9)
	RP[p] → Adverse feature(s):[r,s] EBRT[o] ± ADT[t] or Monitoring, with consideration of early RT for a detectable and rising PSA or PSA >0.1 ng/mL (See PROS-9)	
	RP[p] → No adverse features	
<10 y[e]	Observation[q]	See Monitoring (PROS-9)

- **We do RP for him. After 5 years of RP we have PSA rise. Now what should we do?**

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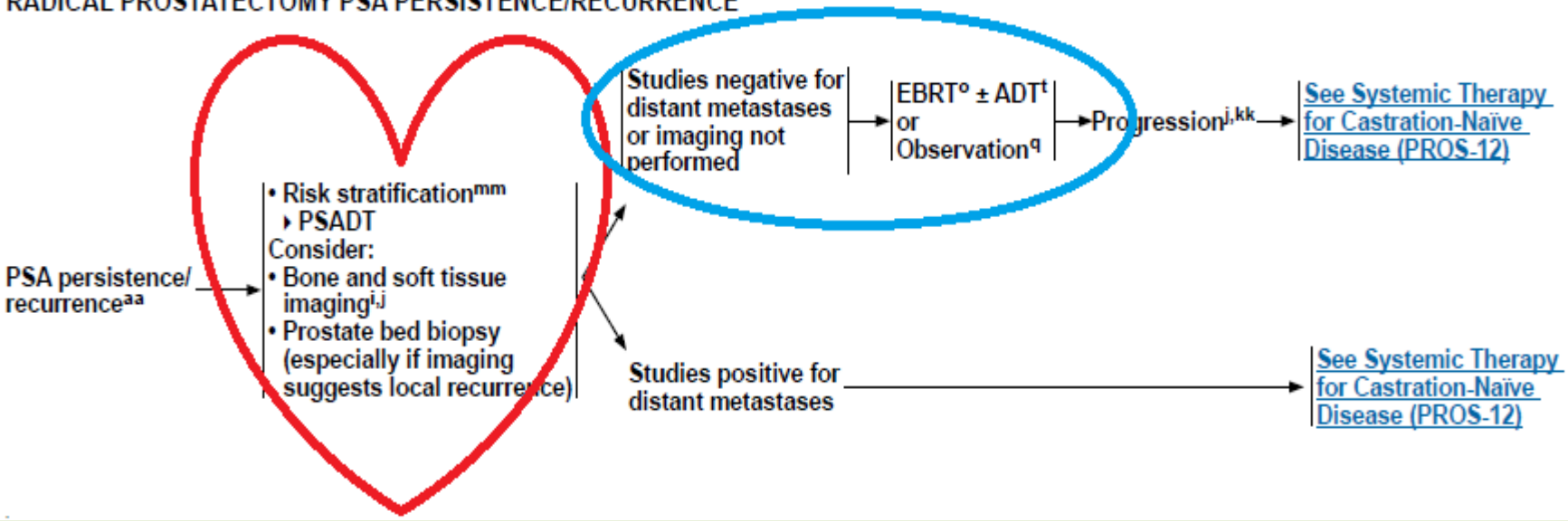
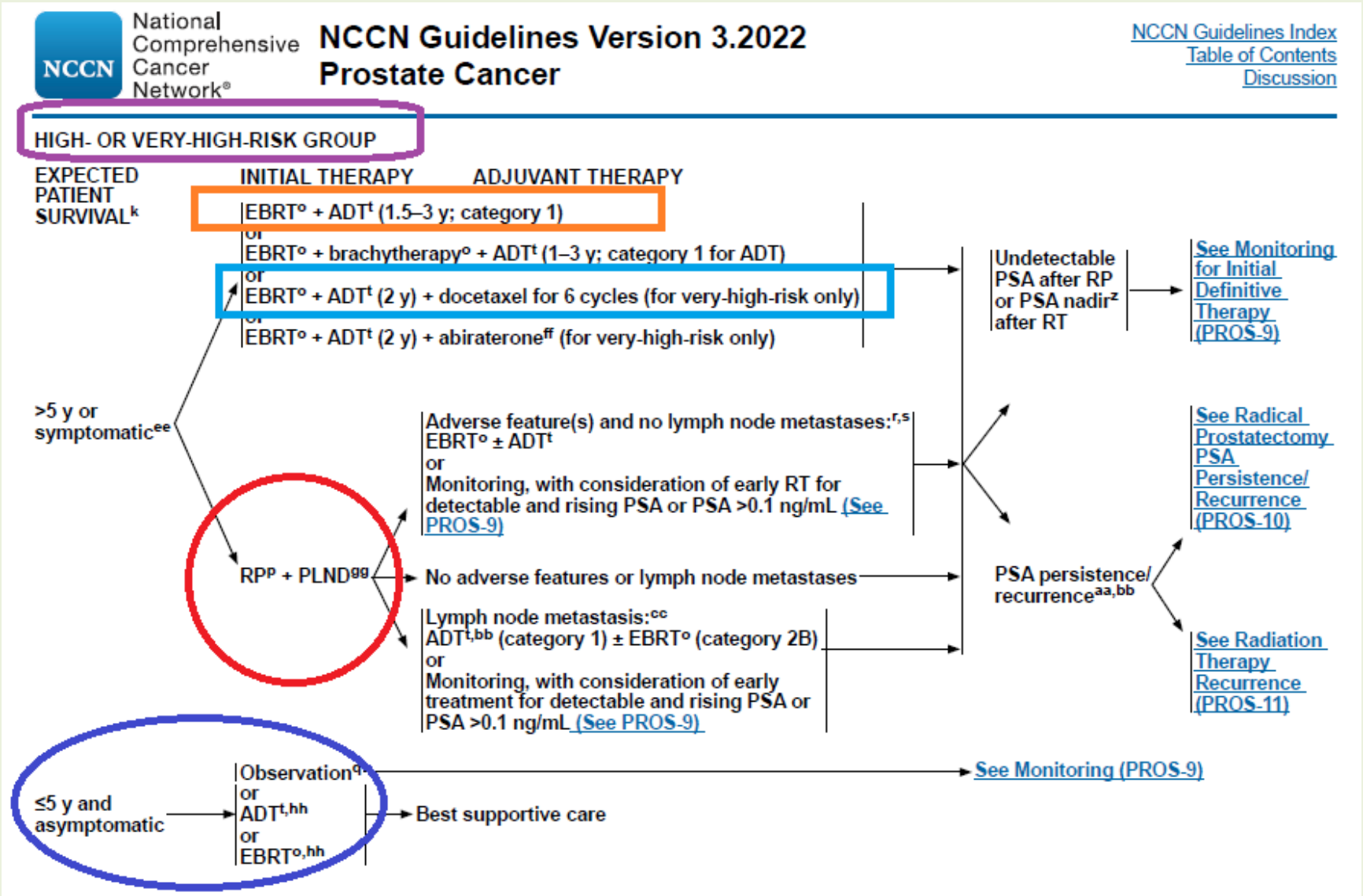
RADICAL PROSTATECTOMY PSA PERSISTENCE/RECURRENCE

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HIGH- OR VERY-HIGH-RISK GROUP
EXPECTED PATIENT SURVIVAL[k]
INITIAL THERAPY
ADJUVANT THERAPY
EBRT[o] + ADT[t] (1.5–3 y; category 1)
or
EBRT[o] + brachytherapy[o] + ADT[t] (1–3 y; category 1 for ADT)
or
EBRT[o] + ADT[t] (2 y) + docetaxel for 6 cycles (for very-high-risk only)
or
EBRT[o] + ADT[t] (2 y) + abiraterone[ff] (for very-high-risk only)
Undetectable PSA after RP or PSA nadir[z] after RT
See Monitoring for Initial Definitive Therapy (PROS-9)
>5 y or symptomatic[ee]
Adverse feature(s) and no lymph node metastases:[r,s]
EBRT[o] ± ADT[t]
or
Monitoring, with consideration of early RT for detectable and rising PSA or PSA >0.1 ng/mL (See PROS-9)
See Radical Prostatectomy
PSA Persistence/ Recurrence (PROS-10)
RP[p] + PLND[gg]
No adverse features or lymph node metastases
PSA persistence/ recurrence[aa,bb]
Lymph node metastasis:[cc]
ADT[t,bb] (category 1) ± EBRT[o] (category 2B)
or
Monitoring, with consideration of early treatment for detectable and rising PSA or PSA >0.1 ng/mL (See PROS-9)
See Radiation Therapy Recurrence (PROS-11)
≤5 y and asymptomatic
Observation[q]
or
ADT[t,hh]
or
EBRT[o,hh]
Best supportive care
See Monitoring (PROS-9)

Thank you for your attention