

Medical Management of Prostate Cancer

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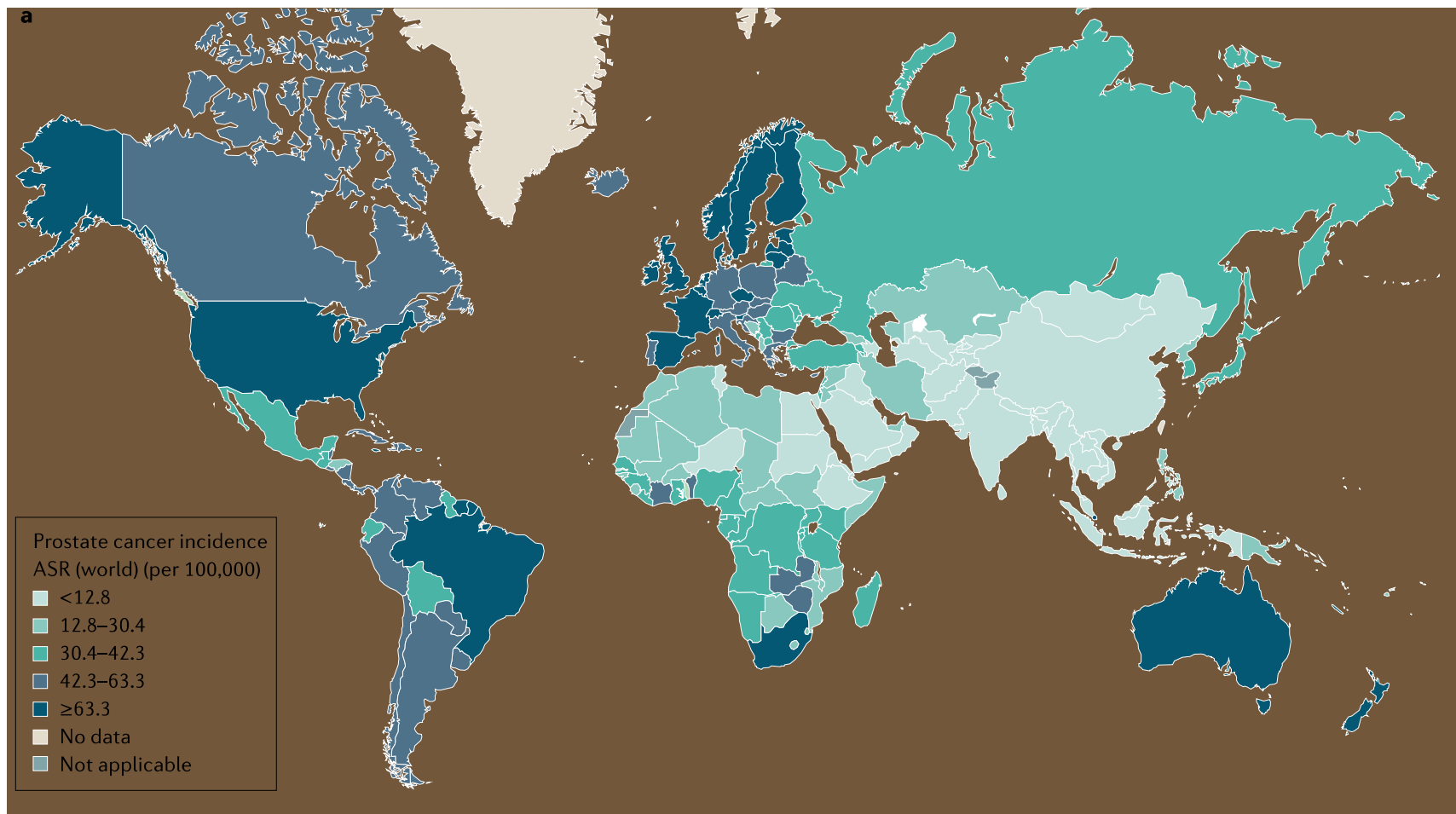
Editorial Board: Expert Review Anticancer Therapy, Kidney Cancer, Cure

Reviewer: NEJM, JCO, Science, Lancet, Lancet Oncology, JAMA et al.

Prostate Cancer Management

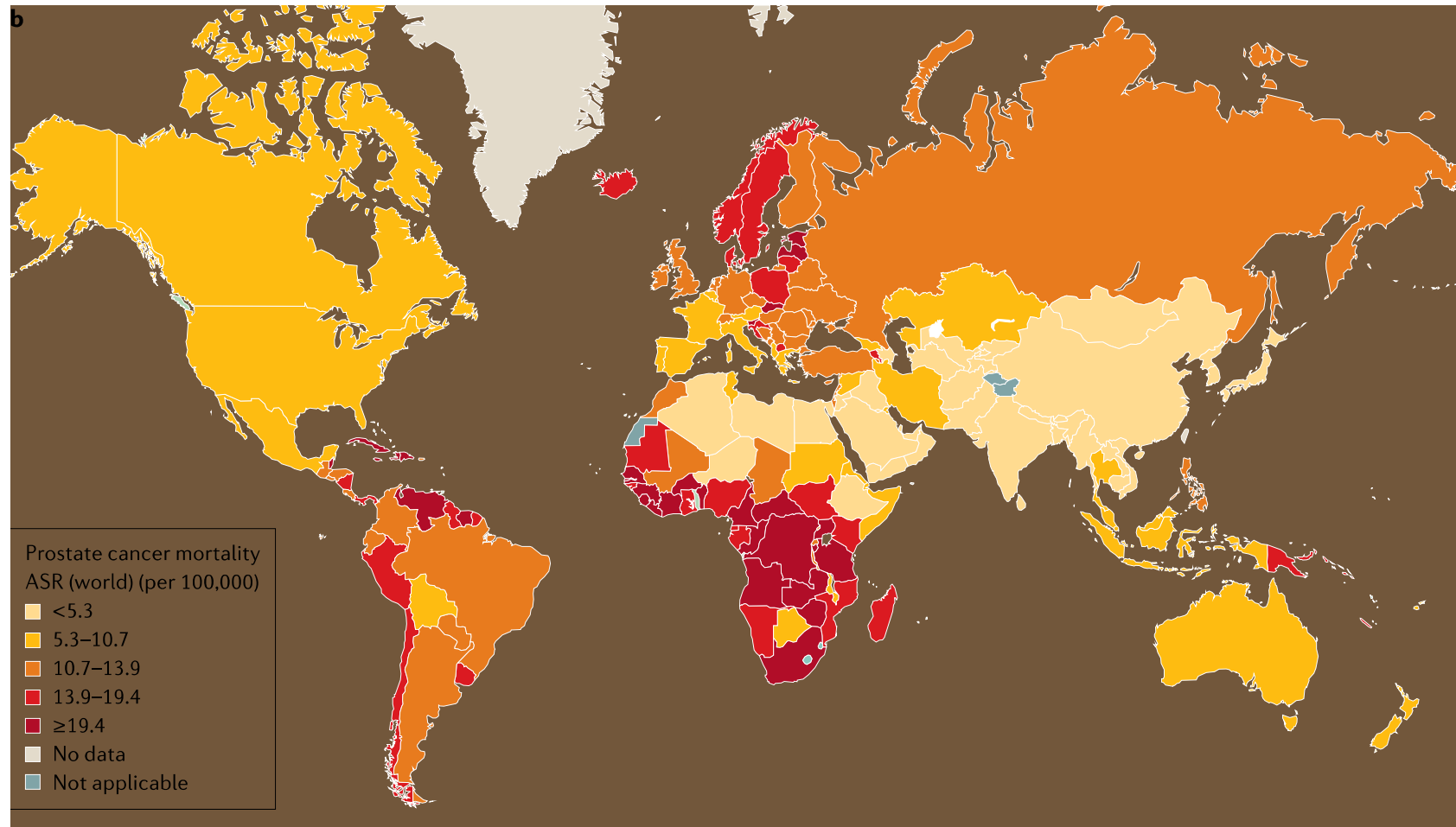
- Overview
- Prostate cancer screening
current status
- Stage Migration
- Therapeutics
- Conclusions

PROSTATE CANCER Worldwide Incidence



Rebello, R.J., Oing, C., Knudsen, K.E. *et al.* Prostate cancer. *Nat Rev Dis Primers* **7**, 9 (2021). <https://doi.org/10.1038/s41572-020-00243-0>

PROSTATE CANCER Worldwide Mortality



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Prostate Cancer

- 240,000 new cases in 2019
- 36,000 deaths in 2019
- Data base for making treatment recommendations remarkably limited

“Inability to recruit to Prostate Cancer Clinical Trials limits our ability to advance our understanding of the leading cancer and second leading cause of cancer death in men.”

Table 5
Comparison between breast and prostate cancer

	ACS 2003 estimates of cancer incidence and death [47]		Number of NIH trials [48]		
	Number of new patients diagnosed	Number of patients dying of disease	FY97-FY01		
			Active trials (alive)	New trials activated (born)	Total patient accrual
Breast	211,300	39,800	107	65	34,757
Prostate	220,900	28,900	83	51	8,309

Risk Factors

■ Male Sex

Parkin DM, et al. *CA Cancer J Clin*. 1999;49:33-64.

Oesterling J, et al. *Cancer: Principles & Practice of Oncology*. 1997;1322-1386.

Kassabian VS, et al. *The American Cancer Society Textbook of Clinical Oncology*. 2nd ed. 1995;311-329.

Risk Factors

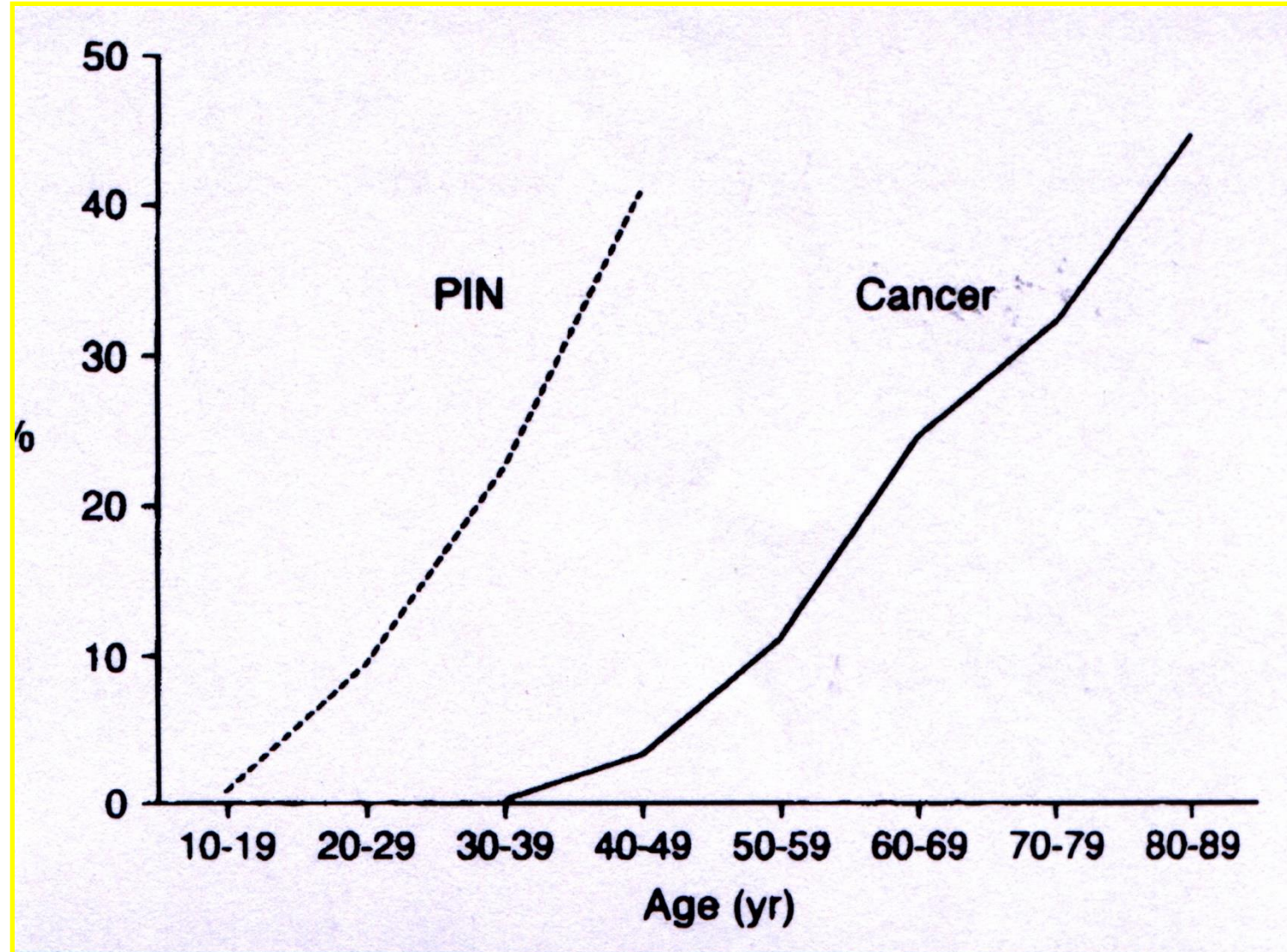
- Male Sex
- Age

Parkin DM, et al. *CA Cancer J Clin*. 1999;49:33-64.

Oesterling J, et al. *Cancer: Principles & Practice of Oncology*. 1997;1322-1386.

Kassabian VS, et al. *The American Cancer Society Textbook of Clinical Oncology*. 2nd ed. 1995;311-329.

PIN and CaP increase with Age



Risk Factors

- Male Sex
- Age
- Diet

Parkin DM, et al. *CA Cancer J Clin*. 1999;49:33-64.

Oesterling J, et al. *Cancer: Principles & Practice of Oncology*. 1997;1322-1386.

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Dietary Factors

- Increase Risk

- Fat

- Decrease Risk

- Soy (isoflavones)
 - Vitamin E
 - Selenium
 - Vitamin D
 - Lycopene

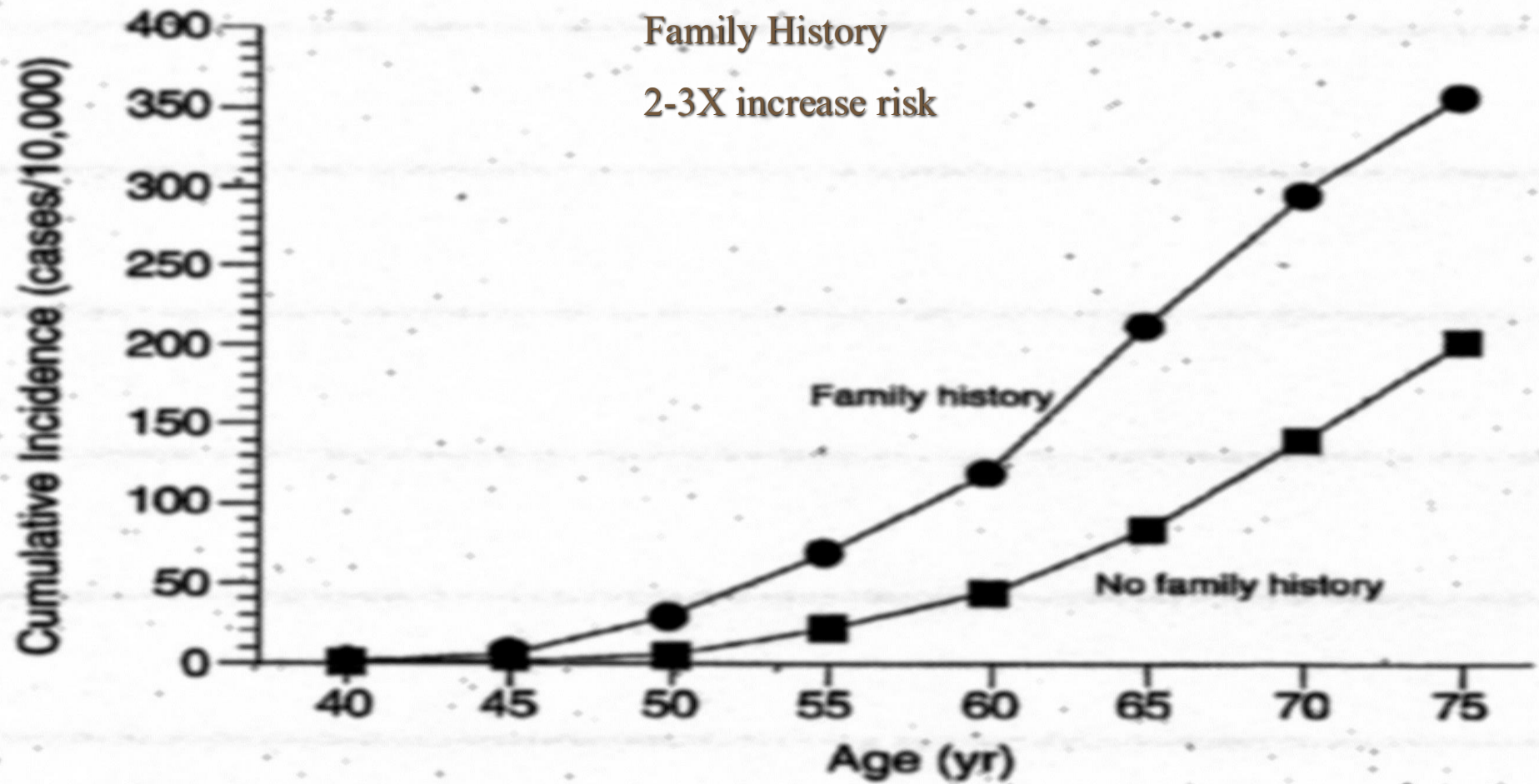
Risk Factors

- Male Sex
- Age
- Diet
- Family history

Parkin DM, et al. *CA Cancer J Clin*. 1999;49:33-64.

Oesterling J, et al. *Cancer: Principles & Practice of Oncology*. 1997;1322-1386.

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Risk Factors

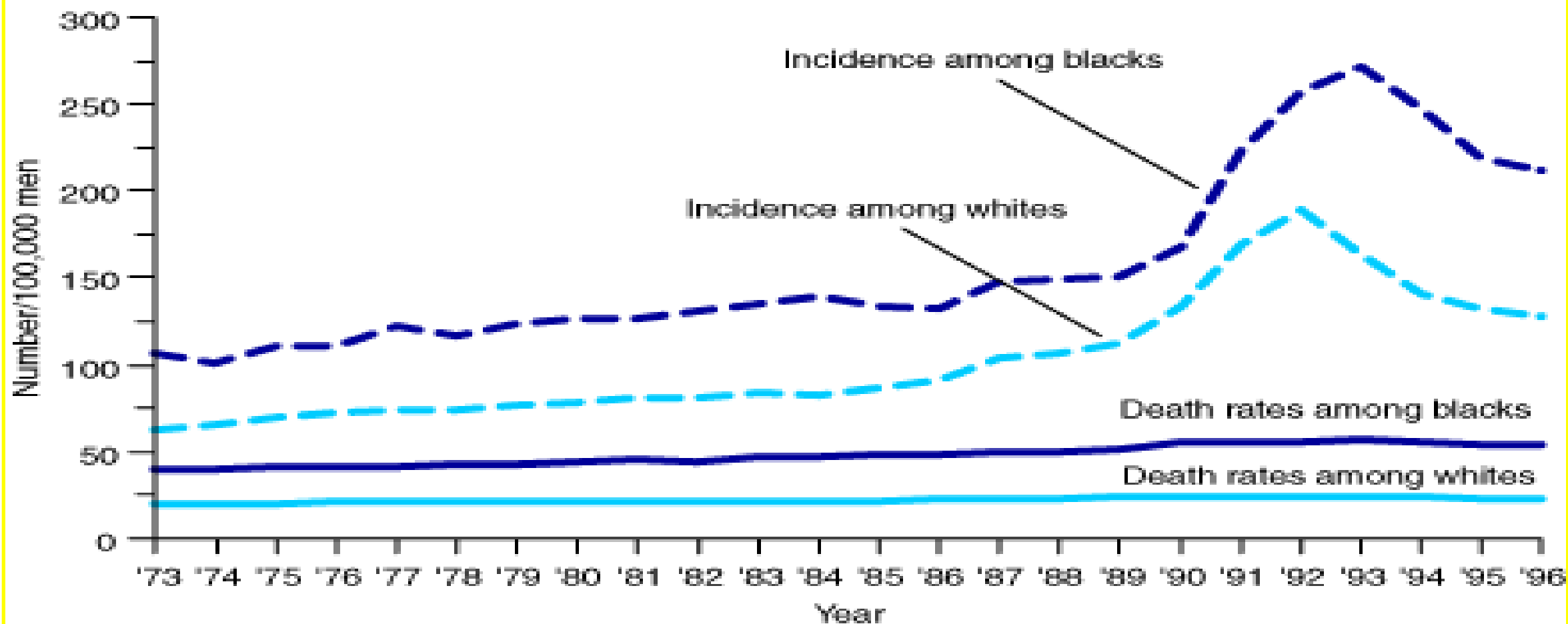
- Male Sex
- Age
- Diet
- Family history
- Race

Parkin DM, et al. *CA Cancer J Clin.* 1999;49:33-64.

Oesterling J, et al. *Cancer: Principles & Practice of Oncology*. 5th ed. 1997;1322-1386.

Kassabian VS, et al. *The American Cancer Society Textbook of Clinical Oncology*. 2nd ed. 1995;311-329.

Prostate Cancer (Invasive): Incidence and Death Rates, by Race, United States, 1990–1996*



*Rate is age-adjusted to 1970 U.S. population.

Source: National Cancer Institute, *SEER Cancer Statistics Review, 1973–1996*.

Risk Factors

- Male Sex
- Age
- Diet
- Family history
- Race
- Androgen levels

Parkin DM, et al. *CA Cancer J Clin*. 1999;49:33-64.

Oesterling J, et al. *Cancer: Principles & Practice of Oncology*. 5th ed. 1997;1322-1386.

Kassabian VS, et al. *The American Cancer Society Textbook of Clinical Oncology*. 2nd ed. 1995;311-329.

Androgen Hypothesis

- Huggins and Hodges 1941.
- Androgens necessary for the development of the prostate gland.
- Higher levels of androgen in the physiologic range increase risk of Prostate Cancer.

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Epimedium Sagittum, Also known as Horny Goat Weed (20:1) 300 mg. Although this herb has a history of traditional use for disorders of the kidneys, joints, liver, back and knees, its principle use is as an aphrodisiac. According to one herbal author, Horny Goat Weed has testosterone-like effects. It stimulates sexual activity in both men and

Prostate Cancer Screening



CaP Screening Recommendations

Country/region	Recommendation			
	Without additional risk factors	Family history of any cancer	BRCA2 germline mutation carrier	African American ancestry
USA (USPSTF, AUA)	From age 55 to 69 years and if >10 years LE; stop at age 70 years	Individual decision-making before age 55 years	N/A	Individual decision-making before age 55 years
Canada (CUA)	From age 50 to 70 years and if >10 years LE	From age 45 years if >10 years LE	N/A	N/A
Europe (EAU, ESTRO, SIOG)	From age 50 years and only if >10 years LE	From age 45 years if >10 years LE	From age 40 years	From age 45 years if >10 years LE
Japan (JUA)	From age 50 years	From age 40 years	N/A	N/A

Based on shared decision-making with their clinician, patients can take a PSA test to screen for prostate cancer. LE, life expectancy, N/A, not assessed.

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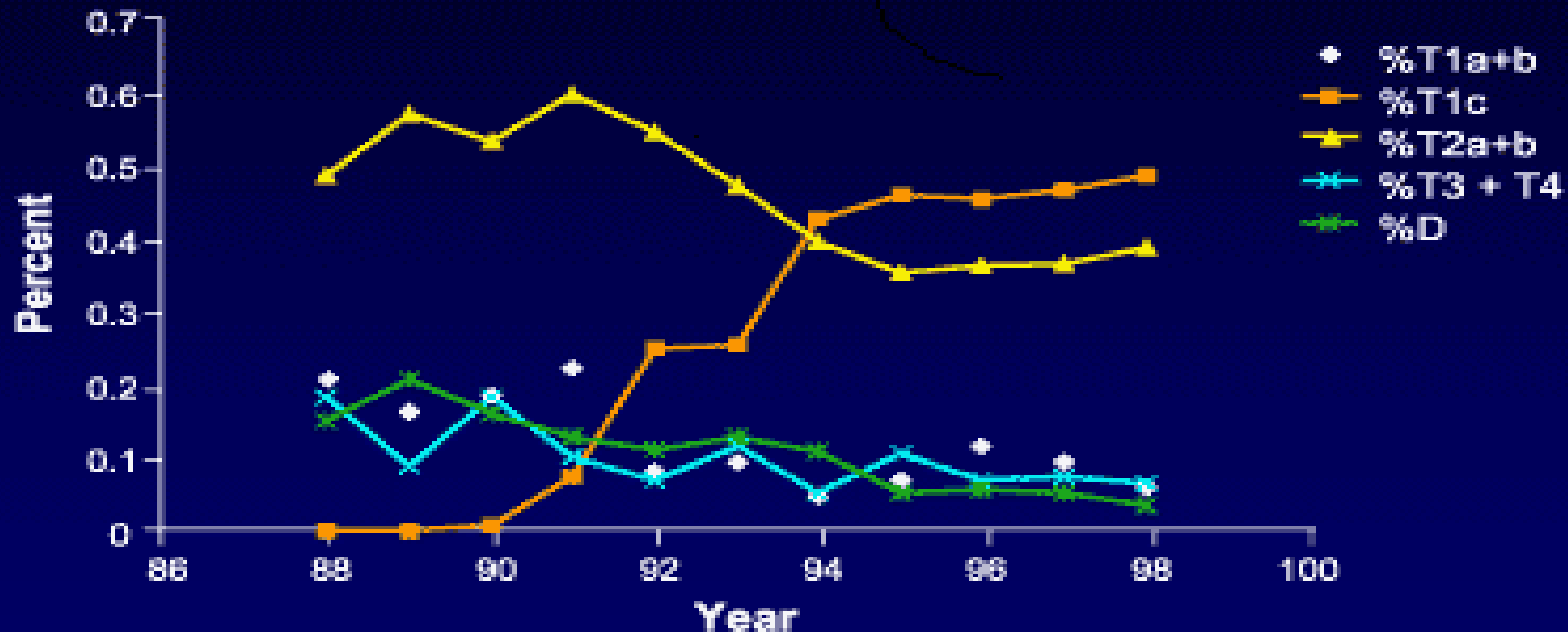
Prevalance of Prostate Cancer at Autopsy

Age (Years)	U.S. Population	Prevalence of Latent Ca P (%)	Number with Ca P
50-59	10,632,000	22.1	2,349,672
60-69	9,710,000	36.1	3,505,310
70-79	5,849,000	37.8	2,210,922
≥ 80	2,155,000	53.7	1,157,235
Total	-	--	9,223,139

Improving accuracy of PSA

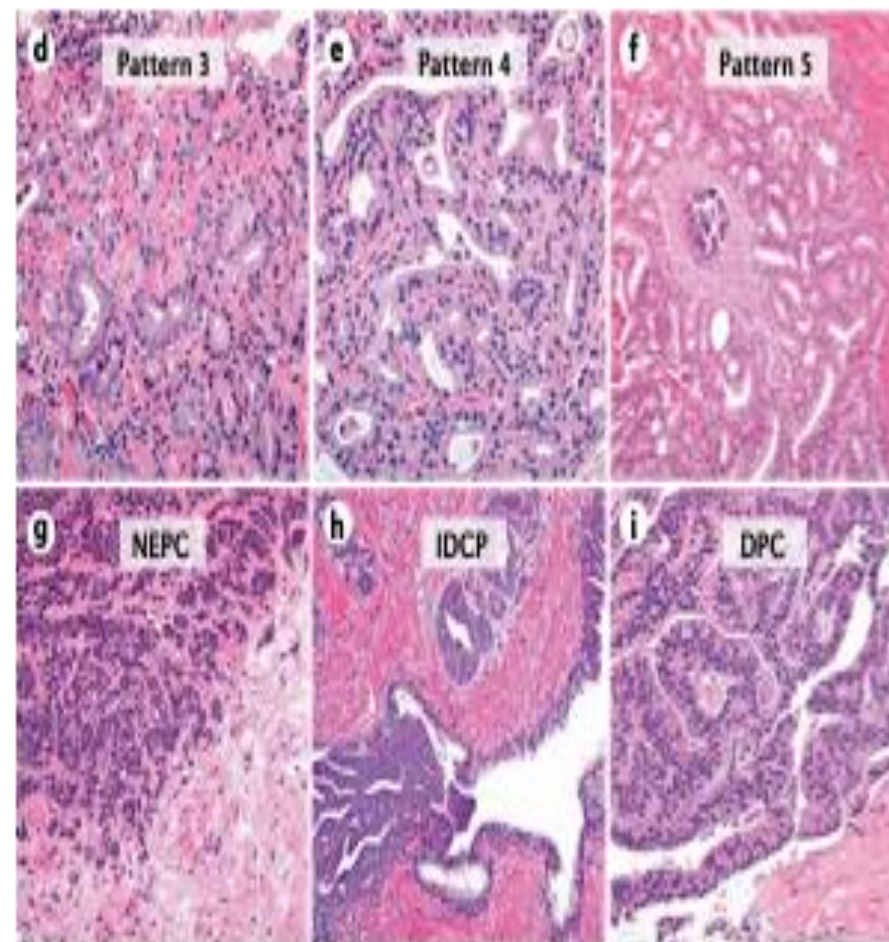
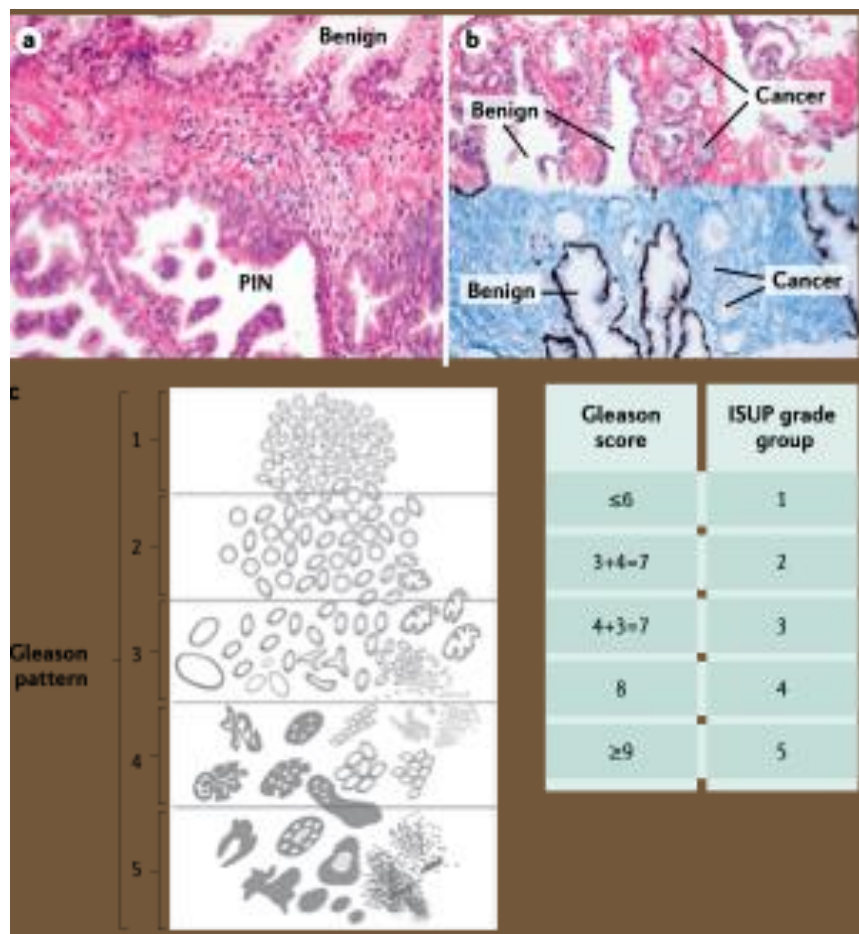
- PSA density
 - Serum PSA level/prostate volume
- PSA velocity
 - Change in serum PSA over time
- Age-adjusted PSA
 - Different normal cutoff levels for different age groups
- Prostate-specific-membrane antigen (PSMA)
- Free-to-total PSA
 - Measurement of free and complexed circulating PSA

PSA Stage Migration at WRAMC



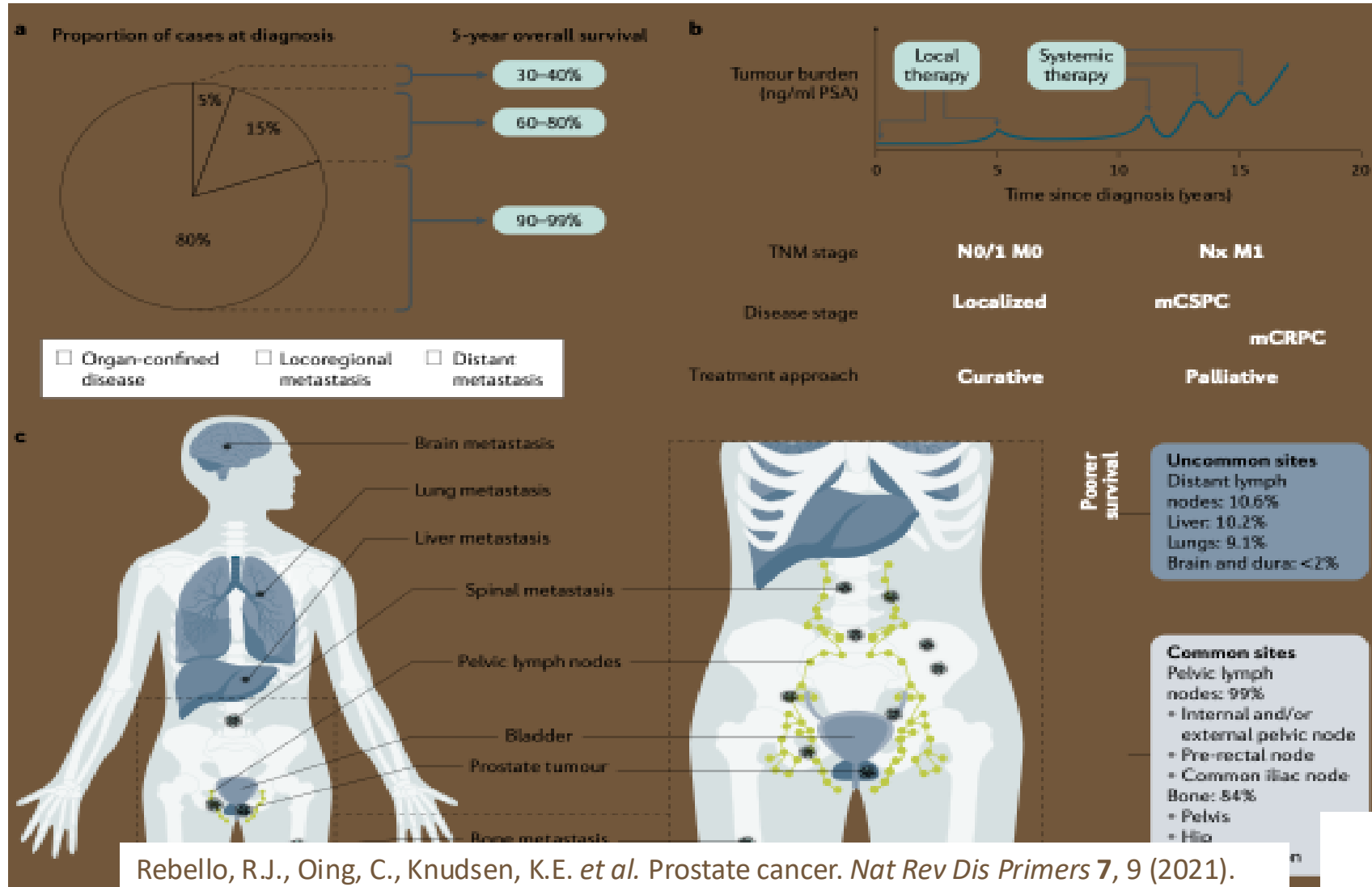
WRAMC = Walter Reed Army Medical Center.

Prostate Cancer Histology



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Prostate Cancer Natural History



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Signs and Symptoms

Early Disease

- Peripheral zone: none
- Transition zone:
 - Urinary hesitancy, frequency, urgency
 - Decreased force of urine stream
 - Nocturia

Progressive Disease

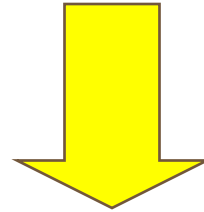
- Hematospermia
- Decreased ejaculate volume
- Impotence

Advanced Disease

- Bone pain

Staging- Characterizing the Primary Tumor

- Clinical Stage
- Gleason Histologic Grade
- PSA



Risk stratify on chance of
extraprostatic disease

GOAL is to find those who can be cured with local therapy: Radiation
or Surgery !!!!!

Multifactor Staging Risk Groups

Group	PSA	Gleason Score	Stage
Low Risk	<10	1-6	T1c/T2a
Inter. Risk	10-20	7	T2b
High Risk	>20	8-10	T2c

Who should be treated and who should not ?

Clinical Case - 2

63 YO HM recently diagnosed with prostate cancer on rising PSA found on routine screening. (PSA = 8)

Stage T1c

Biopsy: Gleason 7 (3+4) adenocarcinoma

DRE: NO palpable nodules, diffuse enlarge

CT Abd/Pelvis: No evidence of extraprostatic disease

Bone Scan: No evidence of bone metastasis

Co-morbid life expectancy: Normal

Multifactor Staging Risk Groups

Group	PSA	Gleason Score	Stage
Low Risk	<10	1-6	T1c/T2a
Inter. Risk	10-20	7	T2b
High Risk	>20	8-10	T2c

Clinical Case - 4

Based on risk stratification:

PSA < 10 = Favorable

Normal DRE = Favorable

Gleason 7 = Intermediate

Therapy Options for Organ-Confined Prostate Cancer (Low/Inter Risk)

- Radical prostatectomy
- External beam radiotherapy
 - Conformal techniques
 - IMRT
 - Proton Therapy
- Brachytherapy (Iodine, palladium)
- Cryotherapy
- Observation/Expectant Management

Radical Prostatectomy

- Improvements in surgical techniques have decreased blood loss, urinary complications and hospital stay
- Nerve sparing
- Laparoscopic prostatectomy

Radiation Therapy

- Conformal therapy
 - Dose = more is better (>72 GY)
- Brachytherapy
 - Best results in early stage disease (Stage 1 and 2)

Therapy options for “High Risk” Prostate Cancer

● Androgen Ablation and XRT

–2-4 months LHRH agonist $\Rightarrow$ XRT to >72 GY $\Rightarrow$ LHRH agonist x 1-3 years

–80% 5 year survival
2002

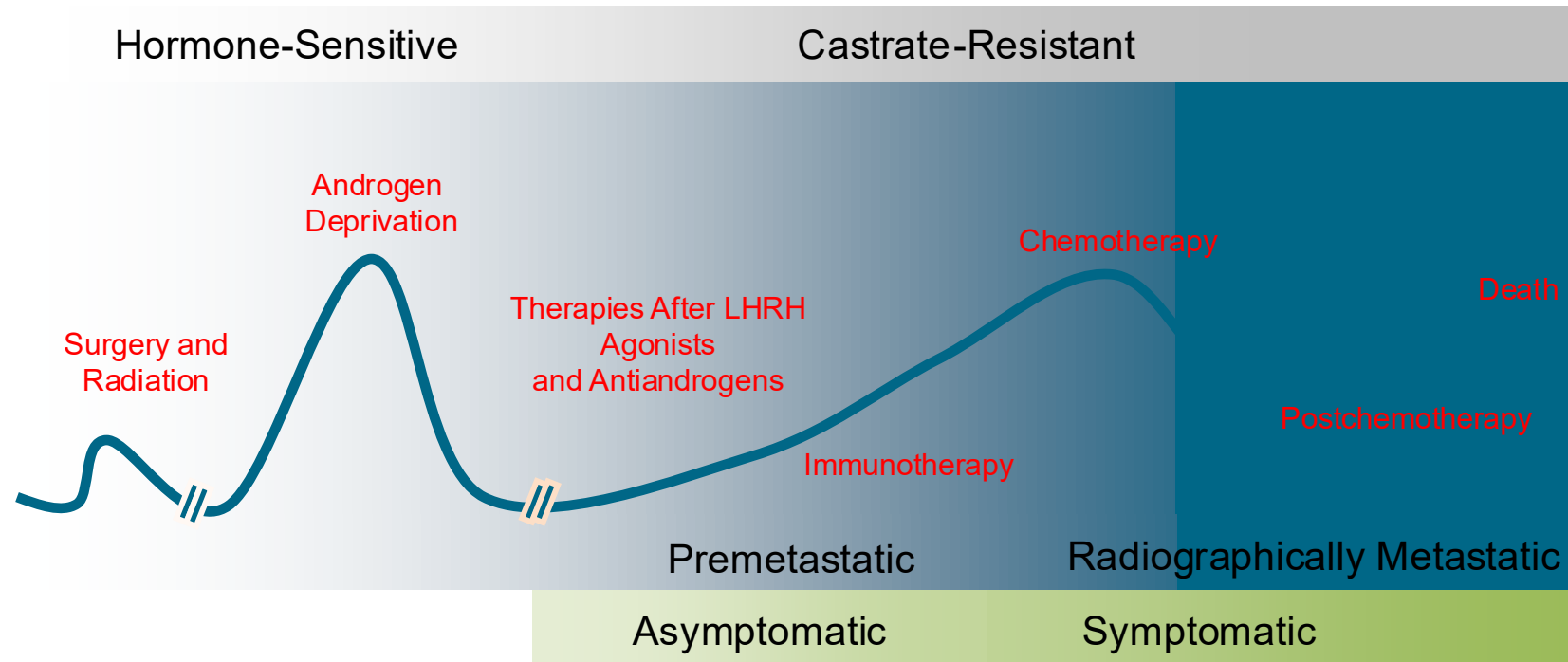
Hanks et al. ASCO

● RRP + Bilateral Pelvic LN Dissection

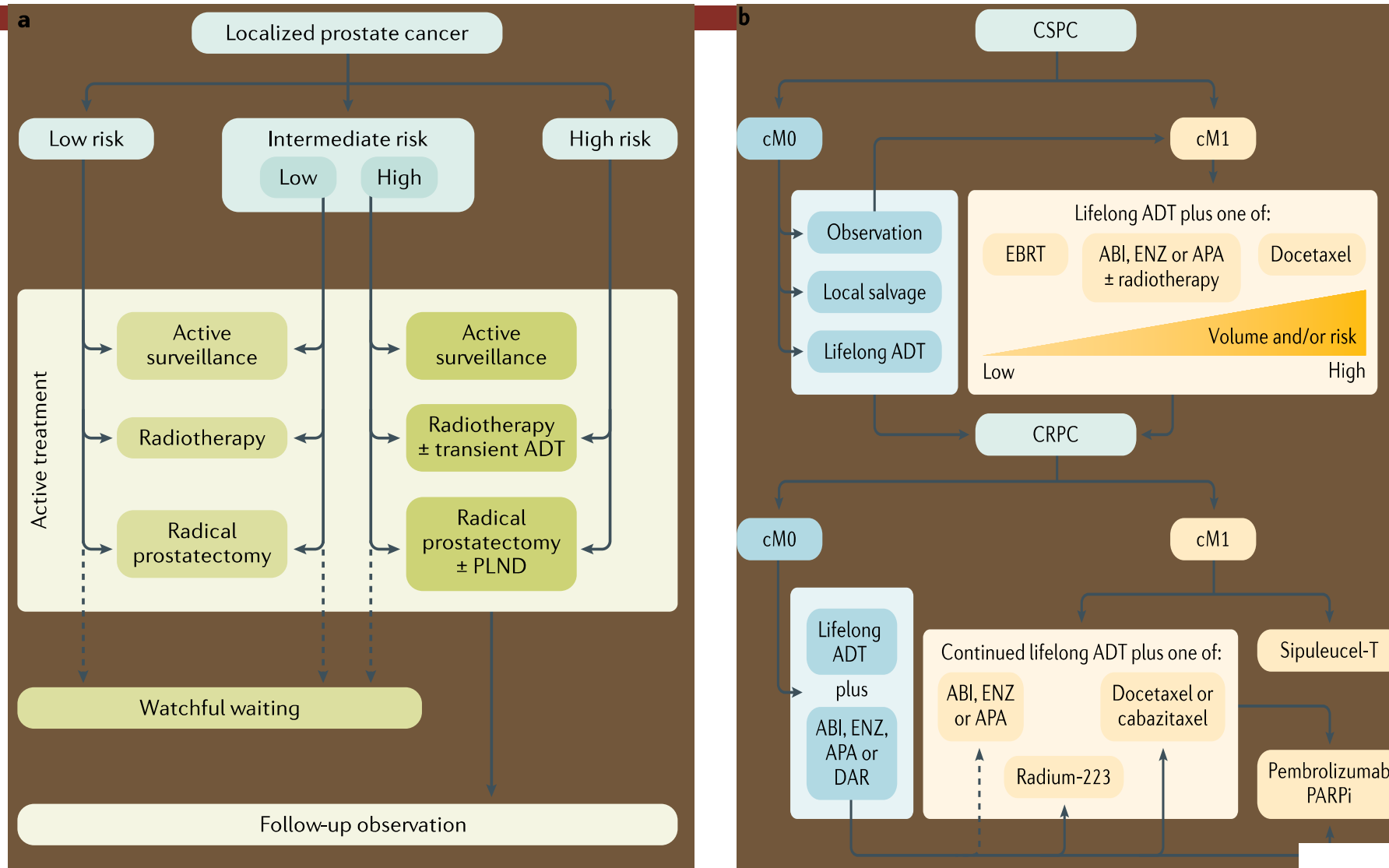
–If LN (+) then androgen ablation
NEJM 1999

Messing et al.

Natural History of Prostate Cancer

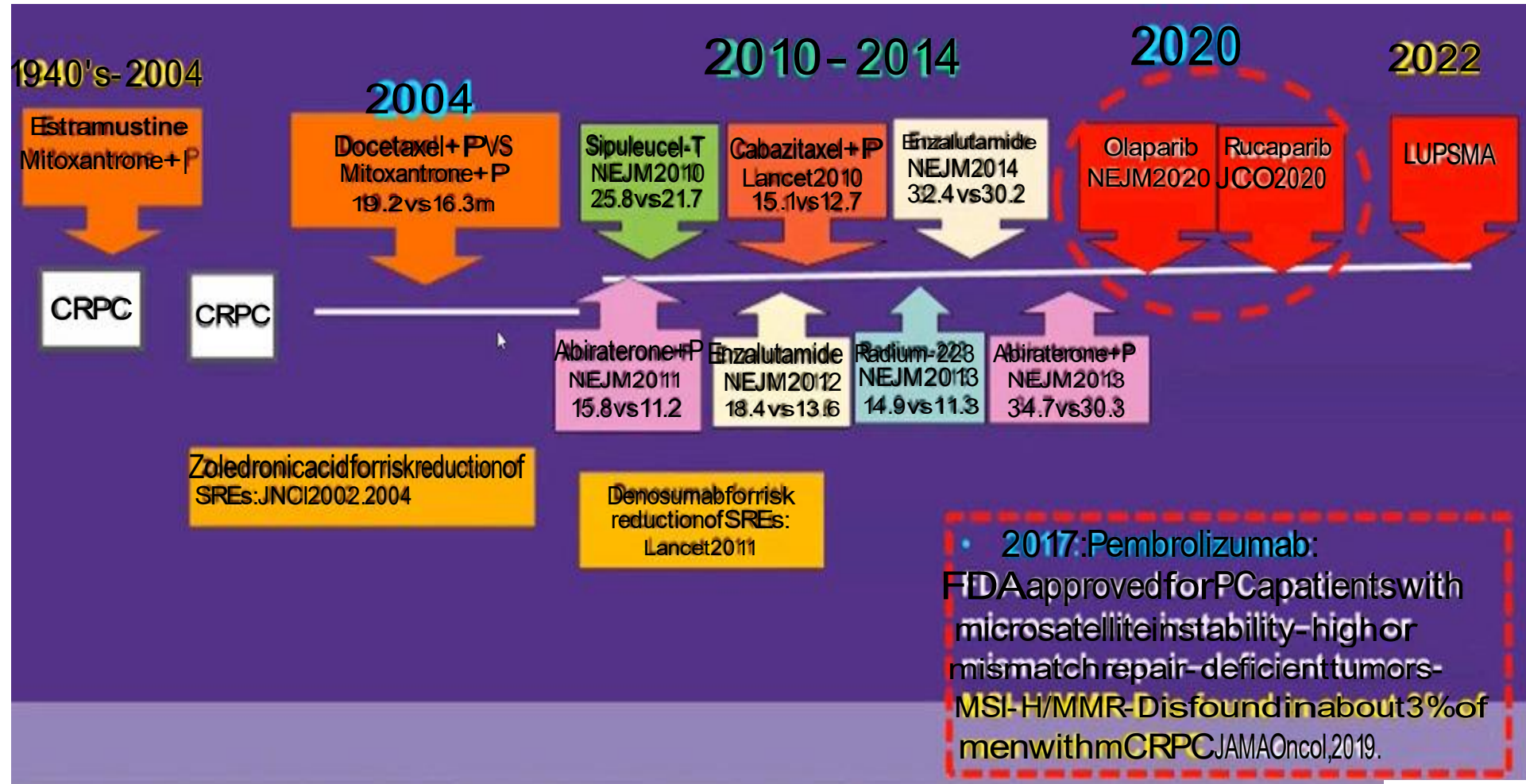


Treatment of Prostate Cancer



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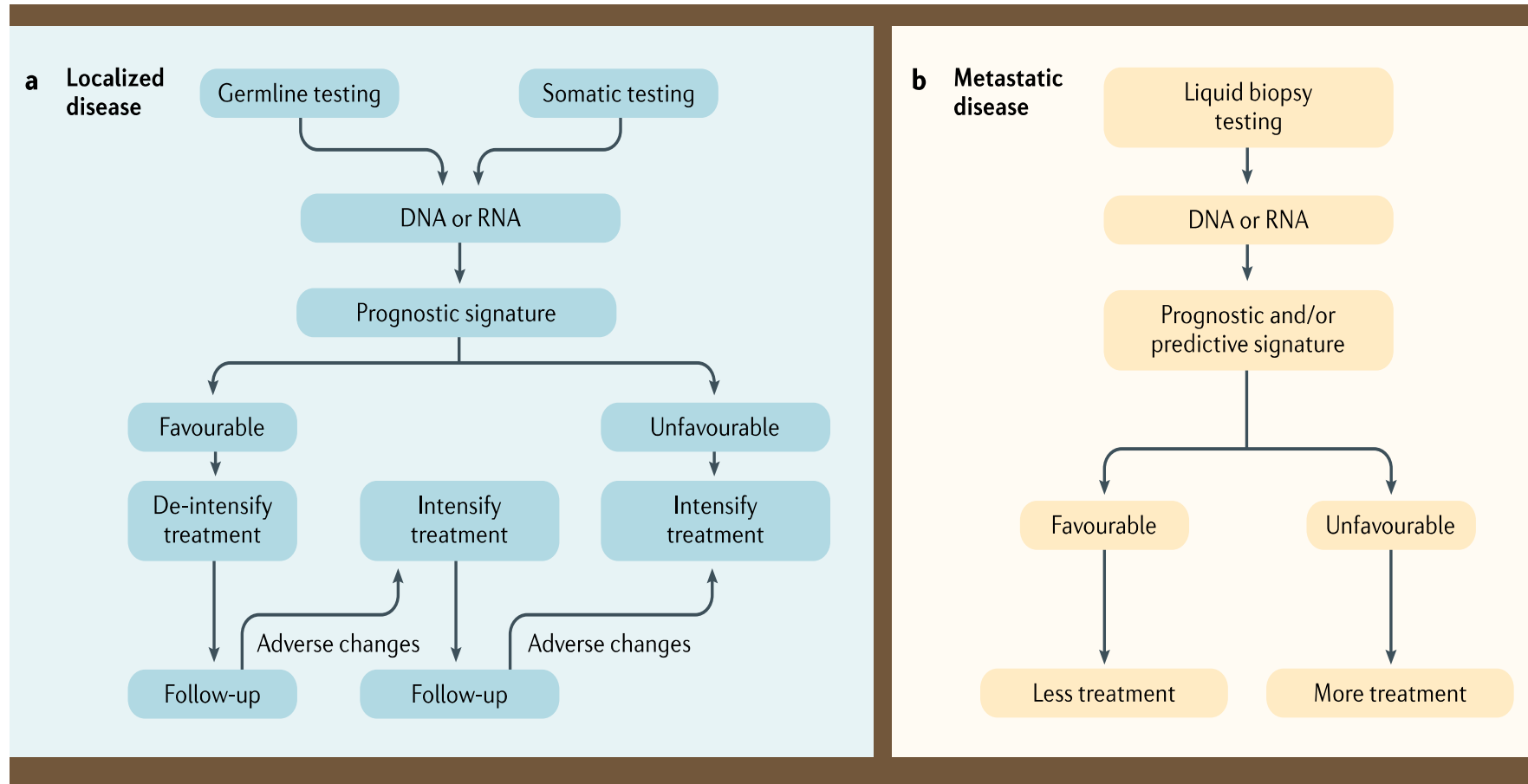
Evolution of Prostate Cancer Treatment



Prostate Cancer Treatment Survival Impact

Agent	Indication	Route Schedule	Cortico-steroids	Symptoms	Contra-indications	PSA Response	Median OS Benefit, Mos
Sipuleucel-T	pre/post docetaxel	IV every 2 wk x 3	no	asymptomatic, minimally sx	narcotics for pain, liver mets	no	4.1
Abiraterone	pre/post docetaxel	oral, empty stomach	yes*	not specified	severe liver dysfx, low K, heart failure	yes	Post-doc: 4.6 Pre-doc: 4.4
Enzalutamide	pre/post docetaxel	oral	no	not specified	seizures	yes	Post-doc: 4.8 Pre-doc: 4.0
Docetaxel	mCRPC	IV every 3 wk	yes*	not specified	moderate liver dysfx, cytopenias	yes	2.4
Cabazitaxel	post docetaxel	IV every 3 wk	yes*	not specified	moderate liver dysfx, cytopenias	yes	2.4
Radium-223	post docetaxel or not fit for doc	IV, every 4 wks for 6 doses	not required	symptomatic bone metastases	visceral mets	NR	3.6

Treatment of Prostate Cancer



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Treatment and Toxicity

Treatment	Short-term symptoms	Long-term symptoms
None or watchful waiting or active surveillance	Blood in urine (haematuria) or semen; difficulty urinating and/or full bladder (dysuria); unexplained weight loss; erectile dysfunction	Skeletal-related events (bone pain, pathological fractures, hypercalcaemia and spinal cord compression); weight loss; death
Surgery	Erectile dysfunction; urinary incontinence	Erectile dysfunction; urinary incontinence
Radiotherapy (external beam or brachytherapy)	Bowel irritability and/or mucus or blood in stools, diarrhoea, discomfort; urinary irritability and/or urgency, haematuria and urinary retention; secondary malignancy	Chronic bowel irritability; erectile dysfunction; chronic urinary irritability
Androgen deprivation therapy (LHRH analogues or surgical castration)	Cognitive dysfunction; bone pain (flair phenomenon); reduced libido and/or impotence; hot flushes; asthenia; fatigue; gynaecomastia	Loss of muscle mass and/or sarcopenia; osteopenia and/or osteoporosis; weight gain; reduced libido and/or impotence; hot flushes; asthenia; fatigue
Second-generation androgen receptor-targeting agents	Enzalutamide: cognitive dysfunction; seizures; falls; pathological fractures; pruritus Abiraterone acetate: fluid retention; hypokalaemia; oedema; arterial hypertension; cardiovascular events; elevated liver enzymes	Cognitive dysfunction; falls; pathological osteopenia
Chemotherapy (taxanes)	Myelosuppression (neutropenia, thrombocytopenia and/or anaemia); neutropenic fever; diarrhoea; sensory polyneuropathy; nausea and/or vomiting; oedema; alopecia; rash; fatigue; asthenia; allergic reactions	Sensory polyneuropathy; oedema; skin irritability (sun, irradiation); radiation recall phenomenon; chronic fatigue

Table 1. Treatment and toxicity

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Androgen Deprivation Therapy

- Decrease serum testosterone by 95%
- Primary treatment for men with metastatic disease
- Response rate very high (>90%)
- Duration of response in men with bone metastases is 18 months.
- Duration poorly defined in men with earlier disease

Hormonal Therapy: Side Effects

- Impaired libido
- Hot flushes
- Muscle wasting
- Fatigue
- Gynecomastia
- Weight gain
- Depression
- Osteoporosis
- Anemia

TREATMENT GUIDELINES

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NCCN Guidelines Version 2.2025 Prostate Cancer

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SYSTEMIC THERAPY FOR M1 CRPC: ADENOCARCINOMA^{f,fff,ggg,hhh,iii}

No prior docetaxel/no prior novel hormone therapy ⁱⁱⁱ	Progression on prior novel hormone therapy/no prior docetaxel ⁱⁱⁱ
• Preferred regimens ▶ Abiraterone^{z,kkk} (category 1 if no visceral metastases) ▶ Docetaxel^{ddd} (category 1) ▶ Enzalutamide^z (category 1) • Useful in certain circumstances ▶ Niraparib/abiraterone^{z,iii,mmm} for <i>BRCA</i> mutation (category 1) ▶ Olaparib/abiraterone^{z,kkk,iii} for <i>BRCA</i> mutation (category 1) ▶ Pembrolizumab for MSI-high (MSI-H)/dMMR^{ddd} (category 2B) ▶ Radium-223^{s,nnn} for symptomatic bone metastases (category 1) ▶ Sipuleucel-T^{ddd,ooo} (category 1) ▶ Talazoparib/enzalutamide for HRR mutation^{z,iii} (category 1) • Other recommended regimens ▶ Other secondary hormone therapy^z	• Preferred regimens ▶ Docetaxel (category 1)^{ddd} ▶ Olaparib for <i>BRCA</i> mutationⁱⁱⁱ (category 1) ▶ Rucaparib for <i>BRCA</i> mutationⁱⁱⁱ (category 1) • Useful in certain circumstances ▶ Cabazitaxel/carboplatin^{ddd} ▶ Lutetium Lu 177 vipivotide tetraxetan (Lu-177–PSMA-617) for PSMA-positive metastases^{ppp} ▶ Niraparib/abiraterone^{z,iii,mmm} for <i>BRCA</i> mutation (category 2B) ▶ Olaparib for HRR mutation other than <i>BRCA1/2</i>ⁱⁱⁱ ▶ Pembrolizumab for MSI-H/dMMR or TMB ≥10 mut/Mb^{ddd} (category 2B) ▶ Radium-223^{s,nnn} for symptomatic bone metastases (category 1) ▶ Sipuleucel-T^{ddd,ooo} ▶ Talazoparib/enzalutamide for HRR mutation^{z,iii} (category 2B) • Other recommended regimens ▶ Other secondary hormone therapy^z
Progression on prior docetaxel/no prior novel hormone therapy ⁱⁱⁱ	Progression on prior docetaxel and a novel hormone therapy ⁱⁱⁱ
• Preferred regimens ▶ Abiraterone^{z,kkk} (category 1) ▶ Cabazitaxel^{ddd} ▶ Enzalutamide^z (category 1) • Useful in certain circumstances ▶ Cabazitaxel/carboplatin^{ddd} ▶ Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies^{ddd} ▶ Niraparib/abiraterone^{z,iii,mmm} for <i>BRCA</i> mutation ▶ Olaparib/abiraterone^{z,kkk,iii} for <i>BRCA</i> mutation ▶ Pembrolizumab for MSI-H/dMMR^{ddd} (category 2B) ▶ Radium-223^{s,nnn} for symptomatic bone metastases (category 1) ▶ Sipuleucel-T^{ddd,ooo} ▶ Talazoparib/enzalutamide for HRR mutation^{z,iii} • Other recommended regimens ▶ Other secondary hormone therapy^z	• Preferred regimens ▶ Cabazitaxel^{ddd} (category 1) ▶ Docetaxel rechallenge^{ddd} • Useful in certain circumstances ▶ Cabazitaxel/carboplatin^{ddd} ▶ Lu-177–PSMA-617 for PSMA-positive metastases^{ppp} (category 1) ▶ Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies^{ddd} ▶ Olaparib for HRR mutationⁱⁱⁱ (category 1 for <i>BRCA</i> mutation) ▶ Pembrolizumab for MSI-H/dMMR, or TMB ≥10 mut/Mb^{ddd} ▶ Radium-223^{s,nnn} for symptomatic bone metastases (category 1) ▶ Rucaparib for <i>BRCA</i> mutationⁱⁱⁱ • Other recommended regimens ▶ Other secondary hormone therapy^z

[Footnotes for Systemic Therapy for M1 CRPC: Adenocarcinoma \(PROS-16A\).](#)

Note: All recommendations are category 2A unless otherwise indicated.

A New Vision for Cancer Care

– Coming 2025

