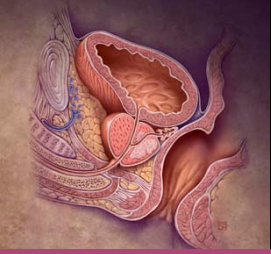




Advanced Prostate Cancer

Understanding Therapy Options



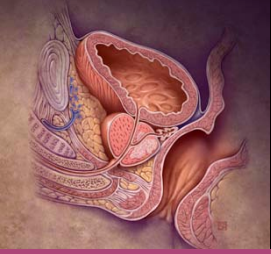
Learning Objectives

- ❖ Describe the epidemiology of advanced prostate cancer in the US
- ❖ Define the diagnostic criteria for advanced prostate cancer
- ❖ List the current treatment options available for advanced prostate cancer, including rationale, side effects, and appropriate monitoring
- ❖ Describe strategies for managing side effects
- ❖ Delineate the prognosis for patients with advanced prostate cancer



Agenda

- ❖ Prostate Cancer Facts
- ❖ Diagnosis and Staging
- ❖ Historical Perspective on Therapy (1940-1990s)
- ❖ Timing of ADT and ADT as Adjuvant Therapy
- ❖ LHRH Analogs
- ❖ Alternative Strategies to Classic Androgen Deprivation



Prostate Cancer Is a Significant Disease

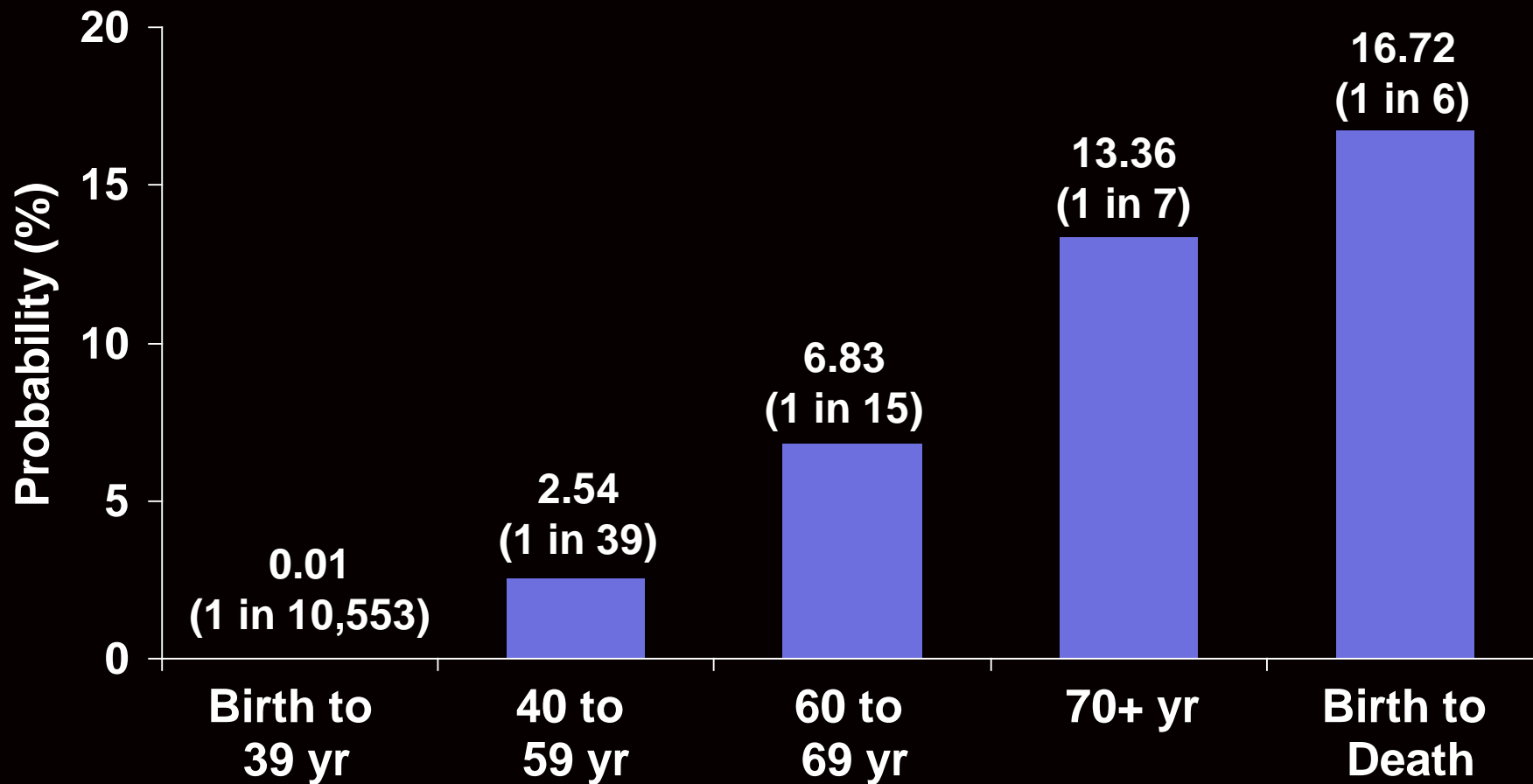
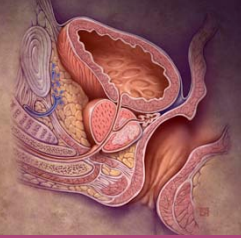
- ❖ 2008 estimates¹
 - 186,320 new cases (25% of all new cancer cases)
 - 28,660 deaths (10% of all cancer deaths)
- ❖ 2001-2005 SEER statistics²
 - Median age at diagnosis = 68 yr
 - Median age at death = 80 yr
- ❖ 5-year relative survival rate = 98.9%²
 - 99.5% for white men
 - 95.4% for black men

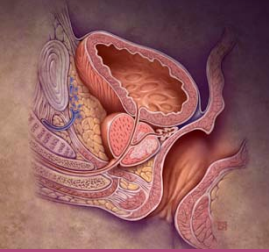
SEER = Surveillance Epidemiology and End Results.

1. www.cancer.org/downloads/STT/2008CAFFfinalsecured.pdf.

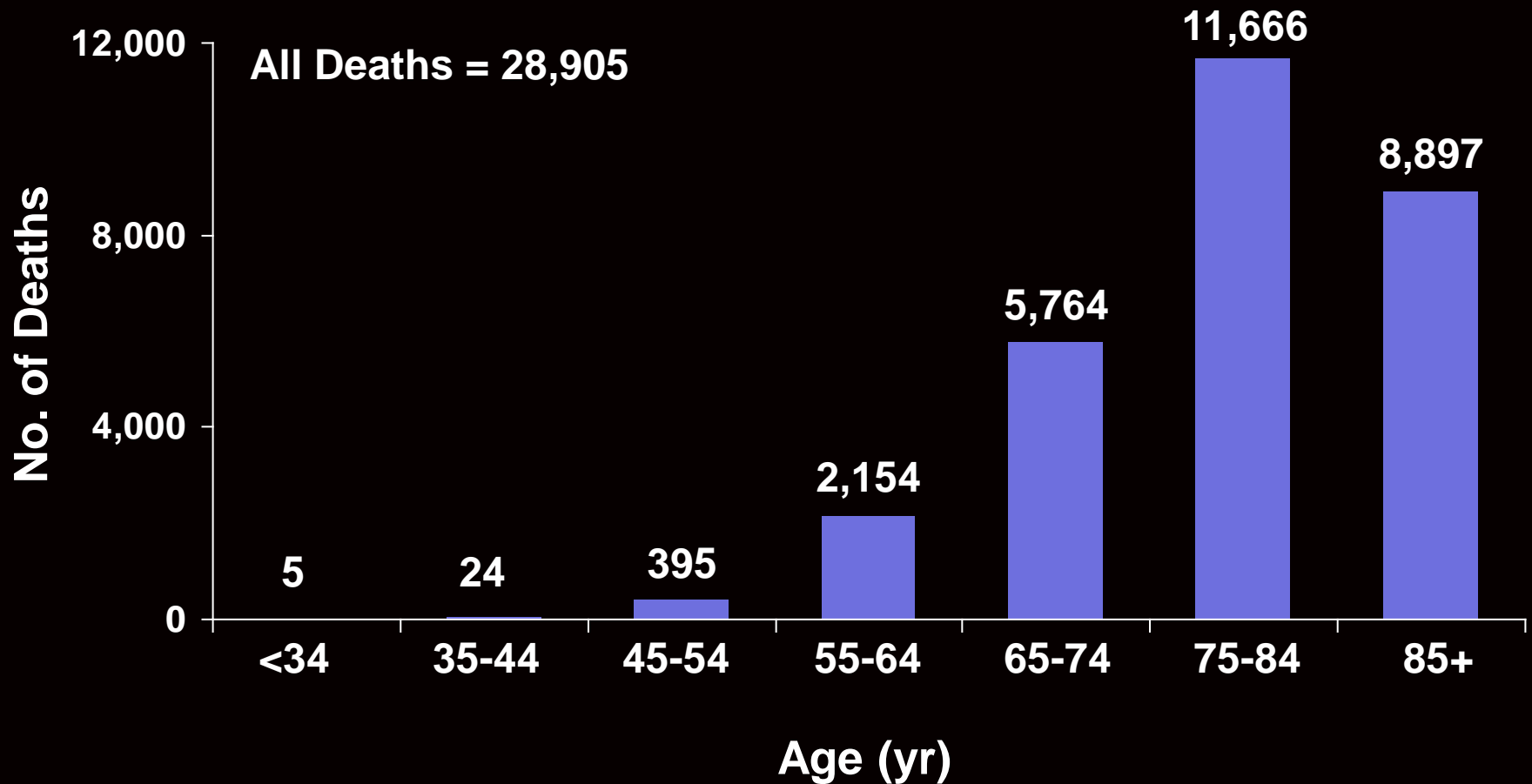
2. [www.http://seer.cancer.gov/statfacts/html/prost.html](http://seer.cancer.gov/statfacts/html/prost.html).

One in 6 Men Will Develop Prostate Cancer





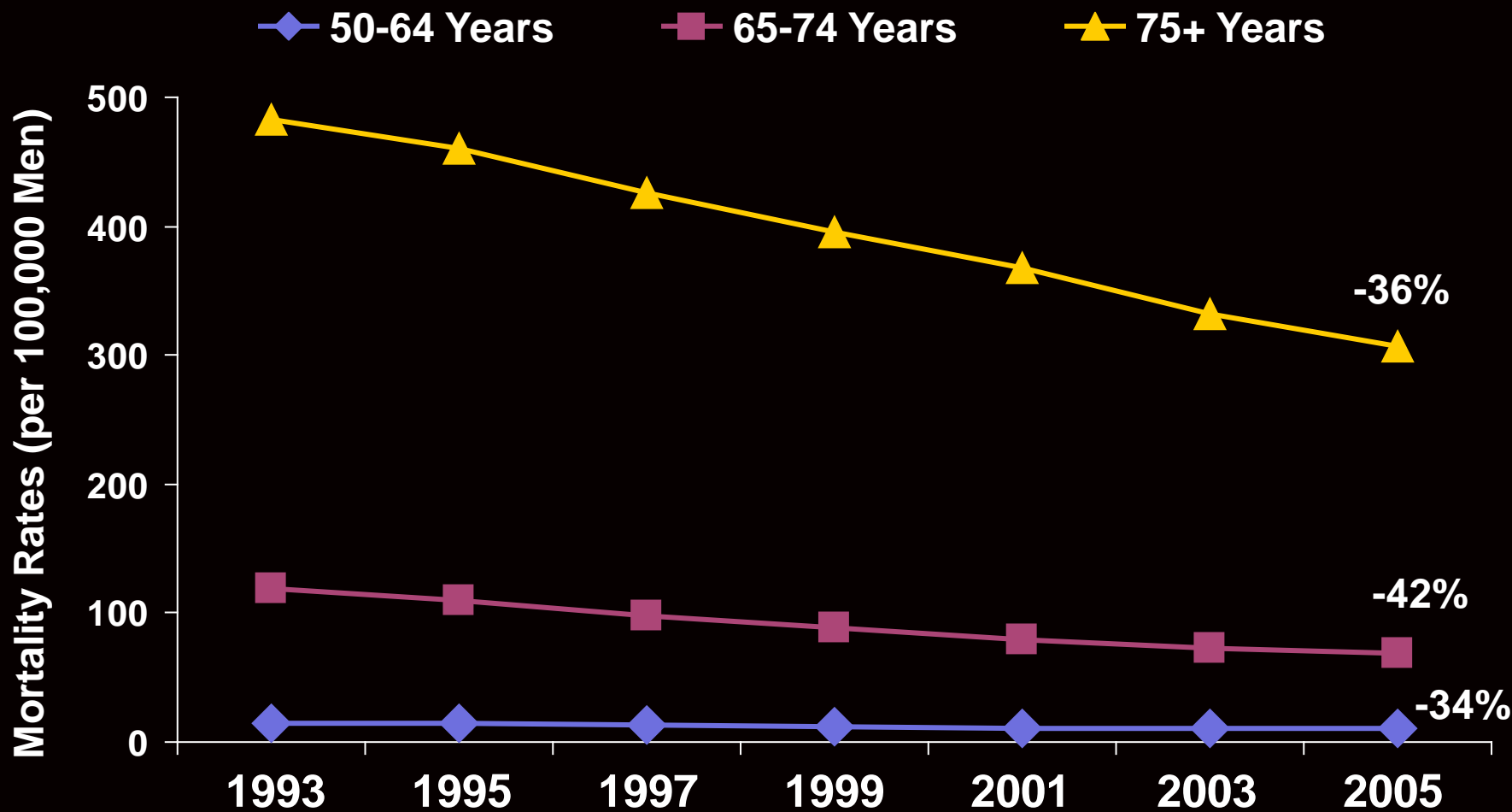
Most Prostate Cancer Deaths Occur in Men >65 Yrs: 2005 CDC Data



CDC = Centers for Disease Control and Prevention.

www.cdc.gov/nchs/data/nvsr/nvsr56/nvsr56_10.pdf

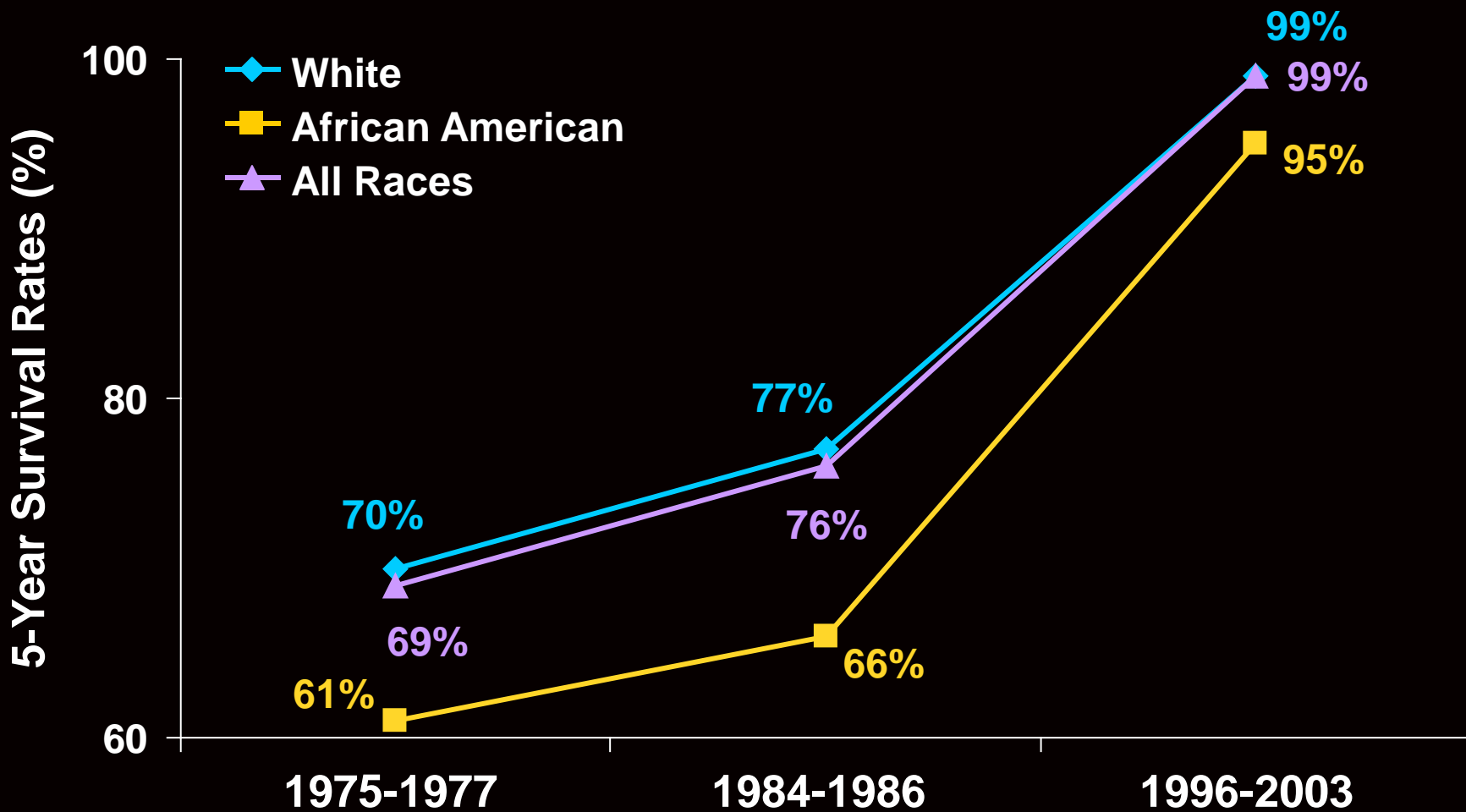
Mortality Rates from Prostate Cancer Are Declining

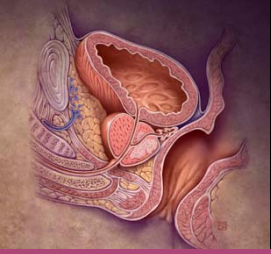


Death from Prostate Ca in Black Men Far Exceeds Rates in Other Races: 2001-2005 Data



5-Year Survival Rates Have Increased Significantly Since 1975



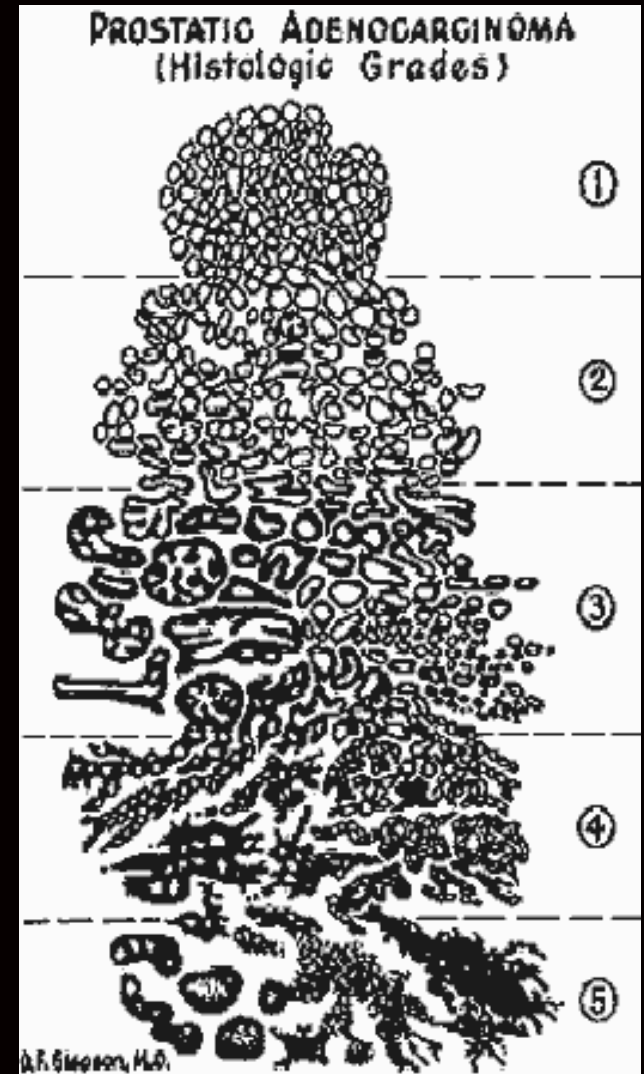


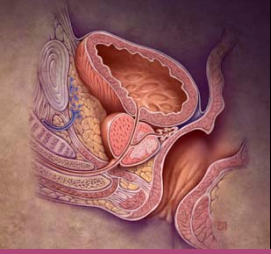
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How Is Prostate Cancer Graded? The Gleason System

- ❖ Gleason grade or pattern of cancer growth appearance (scale: 1 to 5)
 - 1 = Cancerous tissue resembles normal prostate tissue
 - 2 to 4 = Cancerous tissue looks less and less like normal prostate tissue
 - 5 = Tissue lacks normal prostate tissue characteristics; spread haphazardly throughout the prostate
- ❖ Gleason score (range: 2 to 10)
 - 2 to 4 = low grade
 - 5 to 7 = intermediate grade
 - 8 to 10 = high grade
 - The higher the score, the more likely the cancer is to grow and spread rapidly





What Information Is Used to Determine the Clinical Stage of Prostate Cancer?

- ❖ Clinical staging provides information for determining prognosis and treatment options
- ❖ All or any combination of these modalities can be used:
 - PSA level
 - Digital rectal examination
 - Gleason score
 - Bone scan results
 - Abdominal and pelvic CT results
 - MRI scan results
 - Surgical specimen (prostate and surrounding tissues)
 - Lymph node biopsies

PSA = prostate serum antigen; CT = computed tomography; MRI = magnetic resonance imaging.



How Is Prostate Cancer Staged? The AJCC Anatomic-based System

Primary Tumor (cT) (clinical)

Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor neither palpable nor visible by imaging
T2	Tumor confined within prostate
T3	Tumor extends through prostate capsule
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles*

Regional Lymph Nodes (N)

Nx	Regional lymph nodes were not assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)

Distant Metastasis (M)

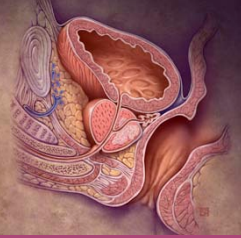
Mx	Distant metastasis cannot be assessed (not evaluated by any modality)
M0	No distant metastasis
M1	Distant metastasis

AJCC = American Joint Committee on Cancer.

*Bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall.

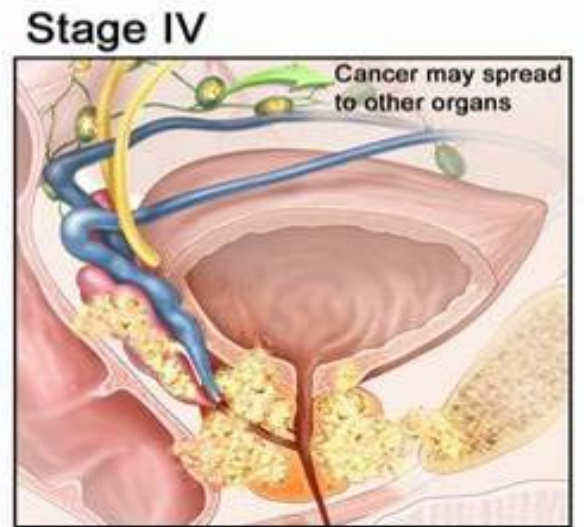
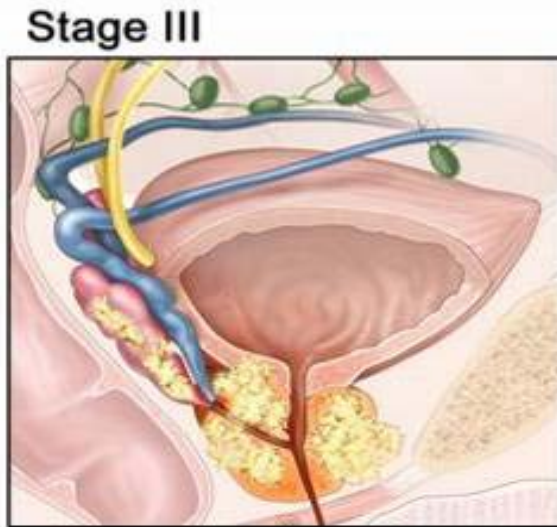
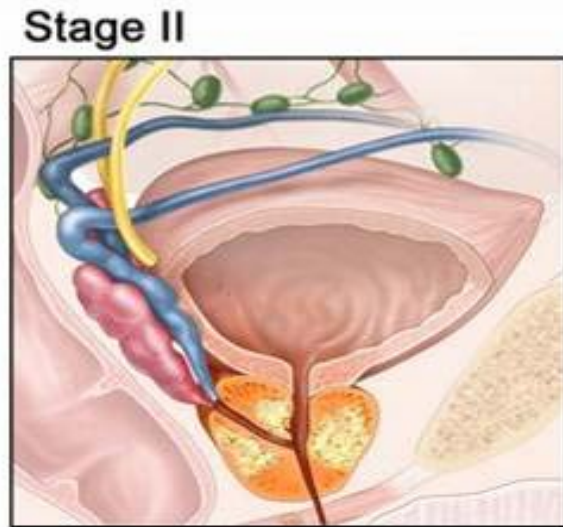
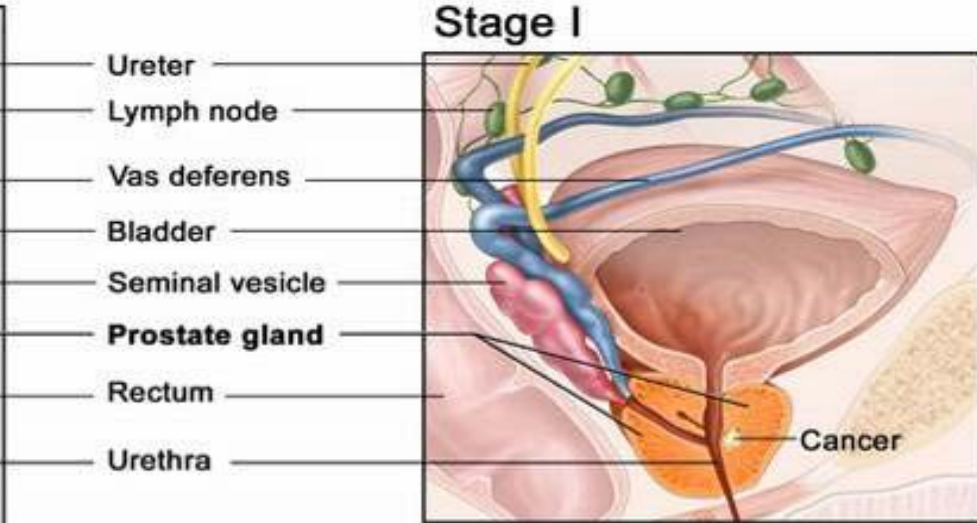
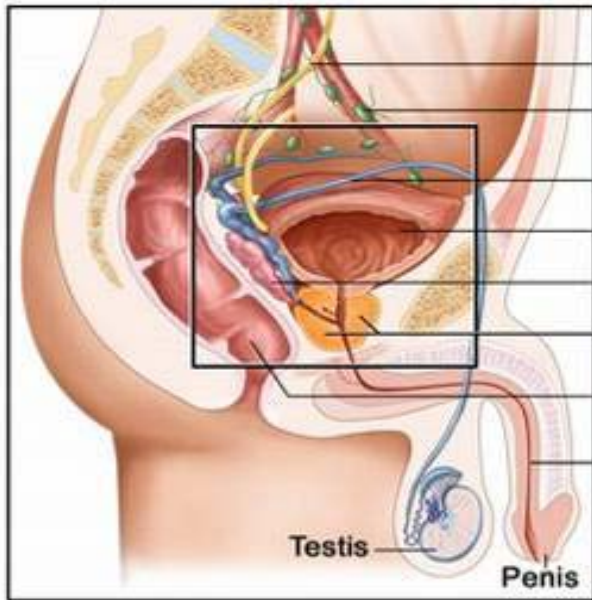
AJCC Cancer Staging Manual (6th ed.). Staging Forms. Springer-Verlag, 2002.

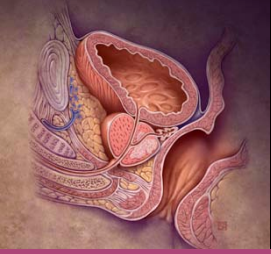
AJCC System Is Used to Determine Prostate Cancer Stage



	Primary Tumor (cT)	Regional Lymph Nodes (N)	Metastasis (M)	Gleason Score
Stage I	T1	N0	M0	GS1
Stage II	T1-2	N0	M0	GS2, 3-4
Stage III	T3	N0	M0	Any GS
Stage IV	T4 Any T Any T	N0 N1 Any N	M0 M0 M1	Any GS Any GS Any GS

AJCC System Stages of Prostate Cancer



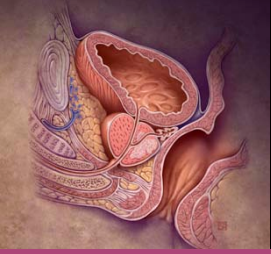


What Is Advanced Prostate Cancer?

- ❖ Locally advanced tumors (clinical T3/T4, N0, M0)^{1,2}
- ❖ Metastatic disease¹
- ❖ Recurrence after local therapy
 - Biochemical relapse (PSA rise)¹
 - Radiographic evidence of disease²

1. Moul JW. *Rev Urol*. 2004;6(suppl 8):S10-S17.

2. Terris MK, et al. www.emedicine.medscape.com/article/45r114.



How Is Advanced Prostate Cancer Evaluated and Monitored?

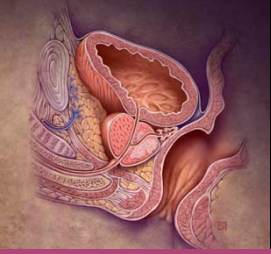
❖ Laboratory studies

- Serum PSA levels
- Testosterone levels
- CBC, blood chemistries, urinalysis
- CMP

❖ Radiologic studies

- Chest x-ray
- CT: abdomen and pelvis
- Bone scan
- DXA (DEXA scan)
- ProstaScint® (?)

CBC = complete blood count, CMP = cardiometabolic profile, CT = computed tomography, DEXA = dual-energy x-ray absorptiometry.

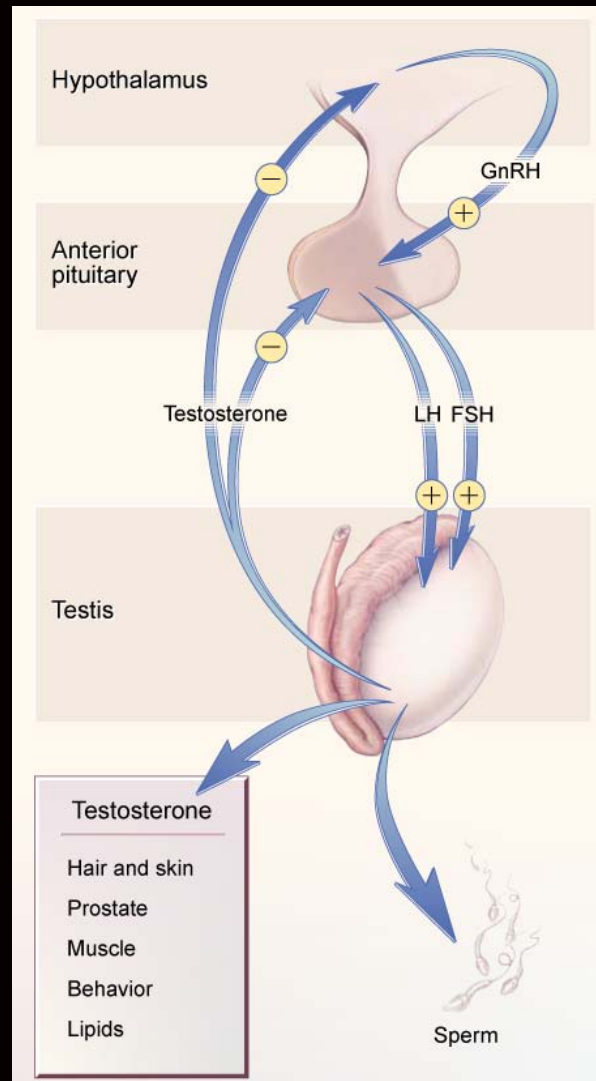


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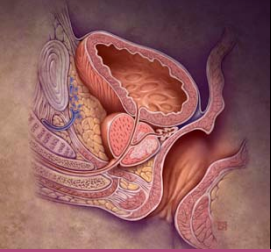


Testosterone Production in the Hypothalamic-Pituitary-Gonadal Axis



GnRH = gonadotropin-releasing hormone; LH = leutinizing hormone; FSH = follicle-stimulating hormone.

Bagatell CJ, Bremner WJ. *N Engl J Med.* 1996;334:707-715.

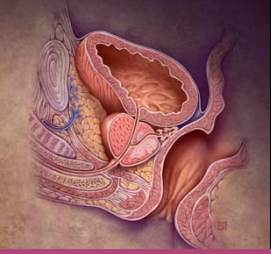


What Are the Options for the Clinical Management of Advanced Prostate Ca?

- ❖ External beam radiation therapy (EBRT)
 - May be curative in locally advanced (cT3) disease
 - Used for palliation in metastatic disease
 - Efficacy improved in combination with ADT
- ❖ ADT
 - Produces significant responses
 - Limited curative potential
- ❖ CAB (ADT + oral anti-androgen)

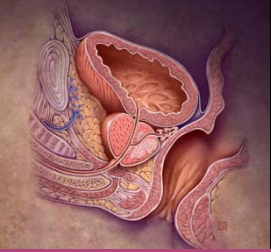
EBRT = external beam radiation therapy; CAB = combined androgen blockade.

Terris MK, et al. <http://emedicine.medscape.com/article/454114>.



What Is the Rationale for Hormonal Therapy for Advanced Prostate Ca?

- ❖ High-risk localized disease
 - PSA >20 ng/mL or
 - Gleason score >8 or
 - AJCC stage >T2c (involves both lobes) or T3 (extends through capsule)
- ❖ Metastatic disease
- ❖ Biochemical relapse (PSA rise)



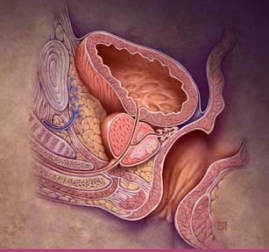
How Is Biochemical Recurrence Defined?

- ❖ Literature review: 1991-2004¹
 - 436 articles on treatment outcomes in cT1-2N0M0 disease
 - 166 different definitions of recurrence¹
 - 53 different definitions after RRP
 - 99 different definitions after EBRT
- ❖ AUA Panel recommendations for biochemical recurrence (2007)^{1,2}
 - After RRP: first value >0.2 ng/mL with confirmed PSA value >0.2 ng/mL
 - After EBRT: nadir PSA level $+2$ ng/mL (ASTRO criteria)

RRP = radical retropubic prostatectomy, AUA = American Urologic Association, ASTRO = American Society for Therapeutic Radiology and Oncology.

1. Cookson M, et al. *J Urol.* ;177:540-545.

2. Clark NW. *Eur Urol Suppl.* 2008;7:410:415.



How Is Biochemical Recurrence Defined? (cont'd)

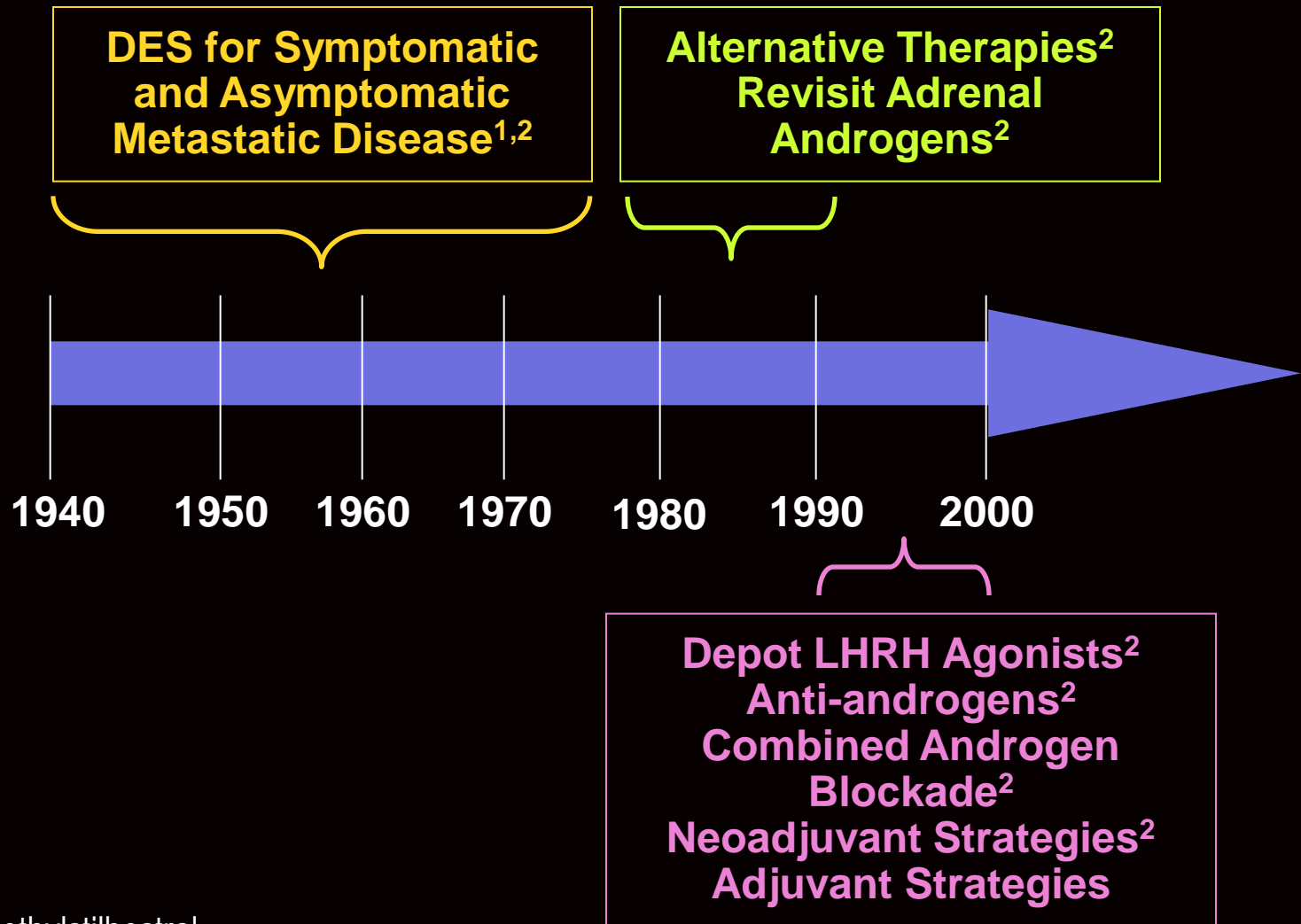
- ❖ Treatment other than RRP or EBRT: nadir PSA level <0.5 ng/mL¹
- ❖ PSA bounce after radiation: PSA increases after 12 to 18 mo but returns to nadir²
- ❖ Ultrasensitive PSA¹

RRP = radical retropubic prostatectomy, AUA = American Urologic Association, ASTRO = American Society for Therapeutic Radiology and Oncology.

1. Cookson M, et al. *J Urol.* ;177:540-545.

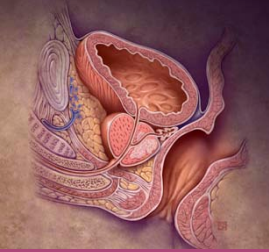
2. Clark NW. *Eur Urol Suppl.* 2008;7:410-415.

Hormonal Therapy Has Been Used Since the 1940s



DES = diethylstilbestrol.

1. Lepor H. *Rev Urol.* 2005;7(suppl 5):S3-S12; 2. Hellerstedt BA, Pienta KJ. *CA Cancer J Clin* 2002;52:154-179.



The 1990s Ushered in New Agents and Strategies

- ❖ Defining advanced prostate cancer (PCa)¹
- ❖ Hormonal therapeutic options²
 - LHRH agents: eliminates need for surgical castration
 - Anti-androgens: address risk for relapse
 - Combined androgen blockade (CAB)
- ❖ Adjuvant strategies²
- ❖ Timing of therapy: immediate vs. delayed^{1,2}

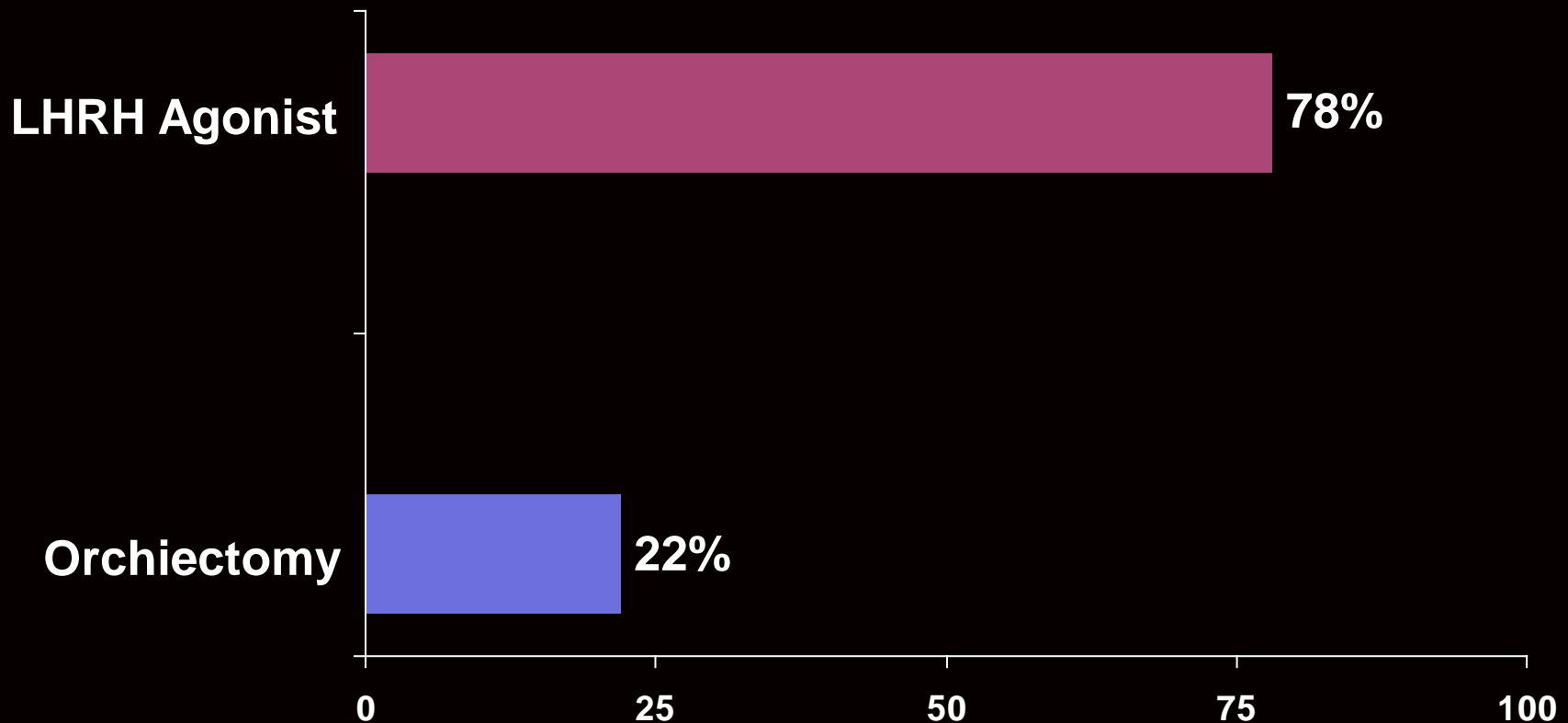
1. Moul JW. *Rev Urol*. 2004;6(suppl 8):S10-17

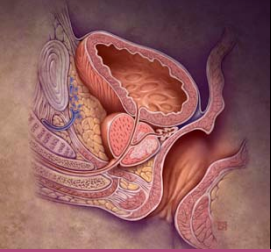
2. Hellerstedt BA, Pienta KJ. *CA Cancer J Clin* 2002;52:154-179.



Patients Prefer LHRH Analog Therapy to Orchiectomy

Treatment decisions made by 147 patients at 13 US and Canadian centers in consultation with physicians





What Is the Future of Hormonal Therapy?

❖ Historical perspective:¹

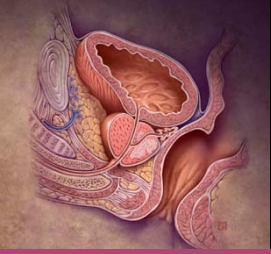
- The only beneficial systemic therapy
- Should be delayed until disease is symptomatic/metastatic
- Not curative
- Significant side effects

❖ What does the future hold?

- Should we be using hormonal therapy earlier?²
- Are there advantages to intermittent vs. combined androgen blockade?¹
- Can hormonal therapy improve survival?²

1. Hellerstedt BA, Pienta KJ. *CA Cancer J Clin* 2002;52:154-179.

2. Moul JW. *Rev Urol*. 2004;6(suppl 8):S10-S17.



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Clinical Benefit of Primary ADT in Metastatic Disease

Nesbit and Baum, 1950¹

5-Year Survival

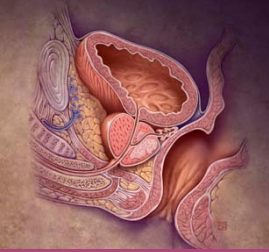
Controls	DES	Orchiectomy	Orchiectomy + DES
6.0%	9.7%	21.6%	20.0%

Eisenberger et al, 1998²

Outcome	Orchiectomy (n=685)	Orchiectomy + Flutamide (n=697)	P Value
Overall survival	29.9 mo	33.5 mo	0.16
Progression-free survival	18.6 mo	20.4 mo	0.26
PSA \leq 4.0 ng/mL	61.5%	74%	<0.001

1. Nesbit RM, Baum WC. *JAMA*. 1950;143:1317-1320.

2. Eisenberger MA, et al. *N Engl J Med*. 1998;339:1036-1042.



Early Initiation of ADT Improves Survival

- ❖ VACURG Study II (DES)^{1,2}
 - DES 0.25 mg, 1 mg, or 5 mg/day vs. placebo
 - DES 1 mg improved survival compared to DES 0.25 mg or 5 mg, or placebo
- ❖ MRC Study (Immediate vs. delayed therapy)³
 - Asymptomatic metastatic or T3 disease
 - Immediate therapy reduced incidence of spinal cord compression and need for TURP
 - Initial survival advantage decreased over time
- ❖ Adjuvant radiation studies showed survival benefit of hormonal therapy +EBRT²

VACURG = Veterans Administration Cooperative Urological Research Group; MRC = Medical Research Council; TURP = transurethral resection of the prostate.

1. Cox RL, Crawford ED. *J Urol*. 1995;154:1991-1998; 2. Hellerstedt BA, Pienta KJ. *CA Cancer J Clin* 2002;52:154-179; 3. MRC. *Br J Urol*. 1997;79:235-246.



Phase 3 Trials Confirmed Survival Benefit of Immediate vs. Delayed ADT

❖ ECOG/Intergroup D1 Study¹

- Node-positive patients after prostatectomy
- Median 7-year follow-up confirmed initial results
- Early treatment significantly reduced mortality vs. observation (15% vs. 35%; $P=0.02$)

❖ EORTC 30891²

- Locally advanced disease and no previous treatment²
- Lower cancer-related mortality with ADT if initial PSA <8 ng/mL vs. 50 ng/mL
- Also benefit if PSA doubling time <12 mo

ECOG = Eastern Cooperative Oncology Group; EORTC = European Organisation for Research and Treatment of Cancer.

1. Messing EM, et al. *N Engl J Med.* 1999;341:1781-1788; 2. Studer U, et al. *Eur Urol.* 2008;53:941-949.

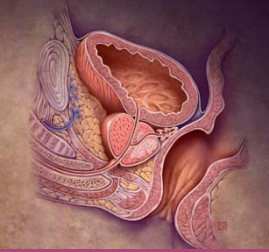


Which Patients Benefit from Early ADT?

- ❖ After radical prostatectomy¹⁻⁷
- ❖ For lymph node–positive disease^{5,6}
- ❖ In combination with EBRT for locally advanced disease and/or intermediate- to high-risk clinically localized disease⁵
- ❖ For symptomatic metastatic disease^{1,2,5}

**Results of most studies based on
>12 months of hormonal therapy**

1. Nesbit RM, Baum WC. *JAMA*. 1950;143:1317-1320; 2. Eisenberger MA, et al. *N Engl J Med*. 1998;339:1036-1042; 3. Cox RL, Crawford ED. *J Urol*. 1995;154:1991-1998; 4. MRC. *Br J Urol*. 1997;79:235-246; 5. Hellerstedt BA, Pienta KJ. *CA Cancer J Clin* 2002;52:154-179; 6. Messing EM, et al. *N Engl J Med*. 1999;341:1781-1788; 7. Studer U, *Eur Urol*. 2008;53:941-949.



Where Is Additional Level 1 Evidence of Survival Benefit of Early ADT Needed?

- ❖ Further evidence of improved survival in asymptomatic stage III or IV disease¹
- ❖ Controversial for use in biochemical failure after localized therapy (EBRT, cryotherapy, HIFU, radical prostatectomy)²
- ❖ Additional evidence of benefit as adjuvant therapy for:
 - Rapid PSA doubling time^{1,3}
 - Gleason score >7¹
 - Early biochemical recurrence¹
- ❖ No solid evidence of benefit as neoadjuvant therapy¹

HIFU = high-intensity focused ultrasound.

1. Moul JW. *Rev Urol*. 2004;6(suppl 8):S10-S17; 2. Bolla M, et al. *N Engl J Med*. 1997;337:295-300; 3. Tenenholz TC, et al. *Urol Oncol*. 2007;25:101-109.

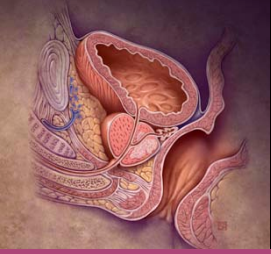


ADT Has Common Adverse Effects

Adverse Effect	Incidence
Impotence	50% to 100% ^{1,2}
Hot flashes	50% to 80% ^{1,2}
Anemia	Common ^{1,2}
Muscle wasting	Common ^{1,2}
Weakness	Common ¹
Osteopenia/Osteoporosis	1.8% to 3.3% per year ¹

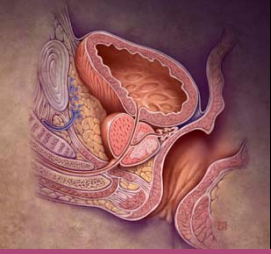
1. Hellerstedt BA, Pienta KJ. *CA Cancer J Clin* 2002;52:154-179.

2. Guise TA, et al. *Rev Urol*. 2007;9:163-180.



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LHRH Analogs: The Big Picture

❖ Advantages of LHRH analogs

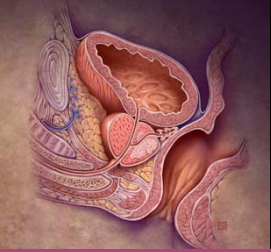
- Eliminate psychological and social impact of surgical castration^{1,2}
- Avoid serious cardiovascular, hepatic, mammatropic effects of DES^{1,2}
- Avoid hepatotoxicity of anti-androgens²

❖ Mechanism of action^{1,2}

- Desensitize GnRH receptors to shut down LH, FSH production
- Suppress testosterone production

1. Lepor H. *Rev Urol.* 2005;7(suppl 5):S3-S12.

2. Schally AV. *BJU Int.* 2007;100 Suppl 2:2-4.



LHRH Analogs: The Big Picture (*cont'd*)

- ❖ Developed by modifying 6th amino acid residue of GnRH¹
 - Longer half-life
 - Greater potency
- ❖ Depot formulations¹
 - Injections and implants
 - Extended-dosing intervals of 1, 3, 4, 6, and 12 months

1. Lepor H. *Rev Urol.* 2005;7(suppl 5):S3-S12.

2. Schally AV. *BJU Int.* 2007;100 Suppl 2:2-4.



LHRH Analogs Offer Several Therapeutic Options

Generic (Trade) Name	Dose (mg)	Formulation	Dosing Interval
Leuprolide acetate (Eligard [®])	7.5 22.5 30 45	SC injection	1 mo 3 mo 4 mo 6 mo
Leuprolide acetate (Lupron [®])	7.5 22.5 30	IM injection	1 mo 3 mo 4 mo
Goserelin acetate (Zoladex [®])	3.6 10.8	SC injection	1 mo 3 mo
Histrelin acetate (Vantas [®])	50	SC implant	1 yr



How Do the LHRH Analogs Compare?

INJECTIONS¹

- ❖ 3.6 to 45 mg in copolymer matrix or microspheres with diluent
- ❖ 1-, 3-, 4-, and 6-mo dosing intervals
- ❖ Inserted into abdominal wall below naval line
 - Inserted using disposable syringe
 - May require local anesthetic
- ❖ Initial testosterone flare
- ❖ Achieve castrate levels after 2 to 4 wk; maintained throughout dosing interval

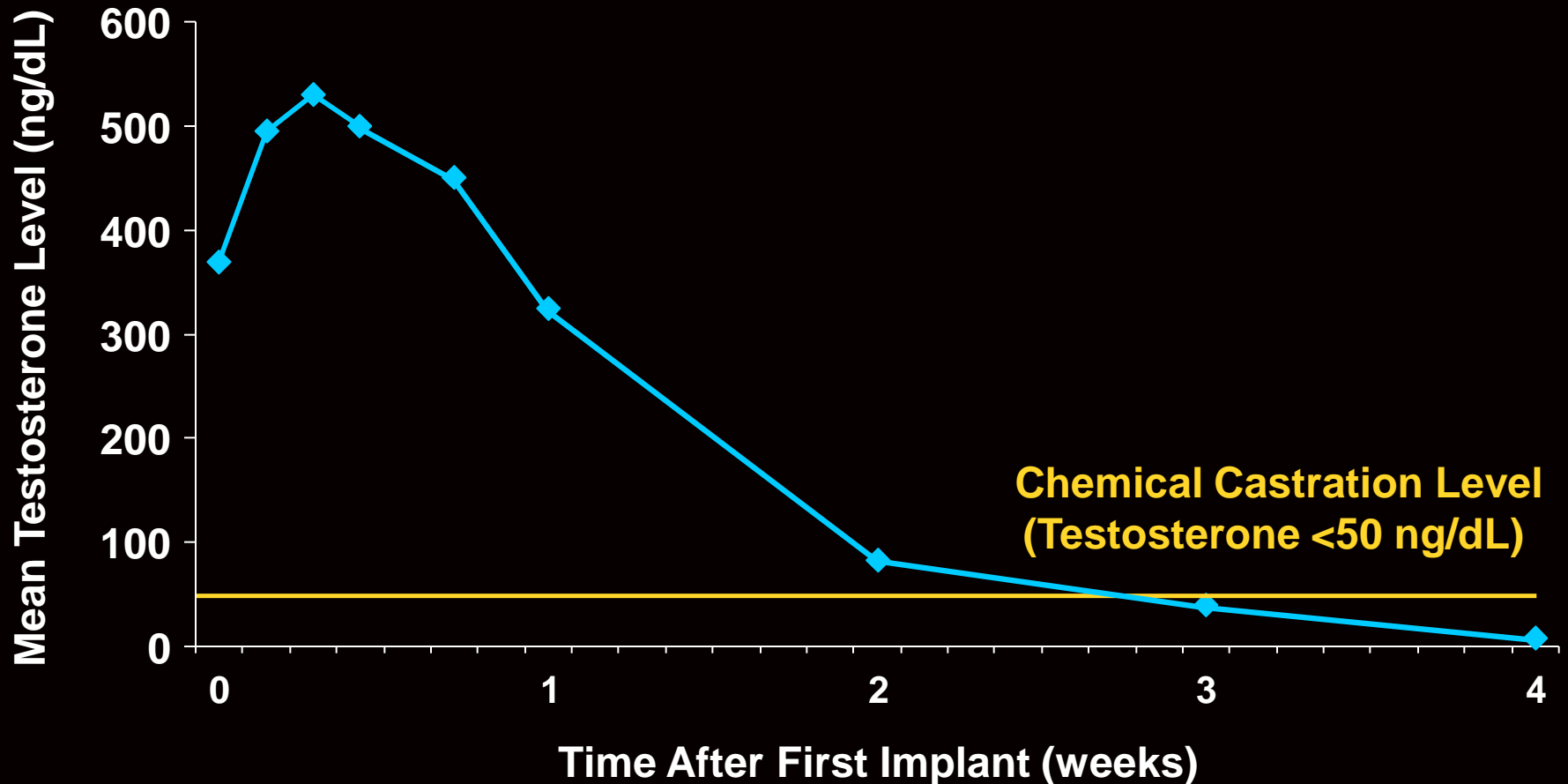
IMPLANT^{2,3}

- ❖ 50 mg in hydrogel reservoir, 3-cm long x 3-mm diameter nonbiodegradable device
- ❖ 12-mo dosing interval
- ❖ Inserted subcutaneously into inner aspect of nondominant upper arm
 - Incision needed for placement through cannula in insertion tool
 - Requires local anesthetic
 - Removed at end of dosing interval
- ❖ Initial testosterone flare
- ❖ Achieves castrate levels by wk 4; maintained throughout dosing interval



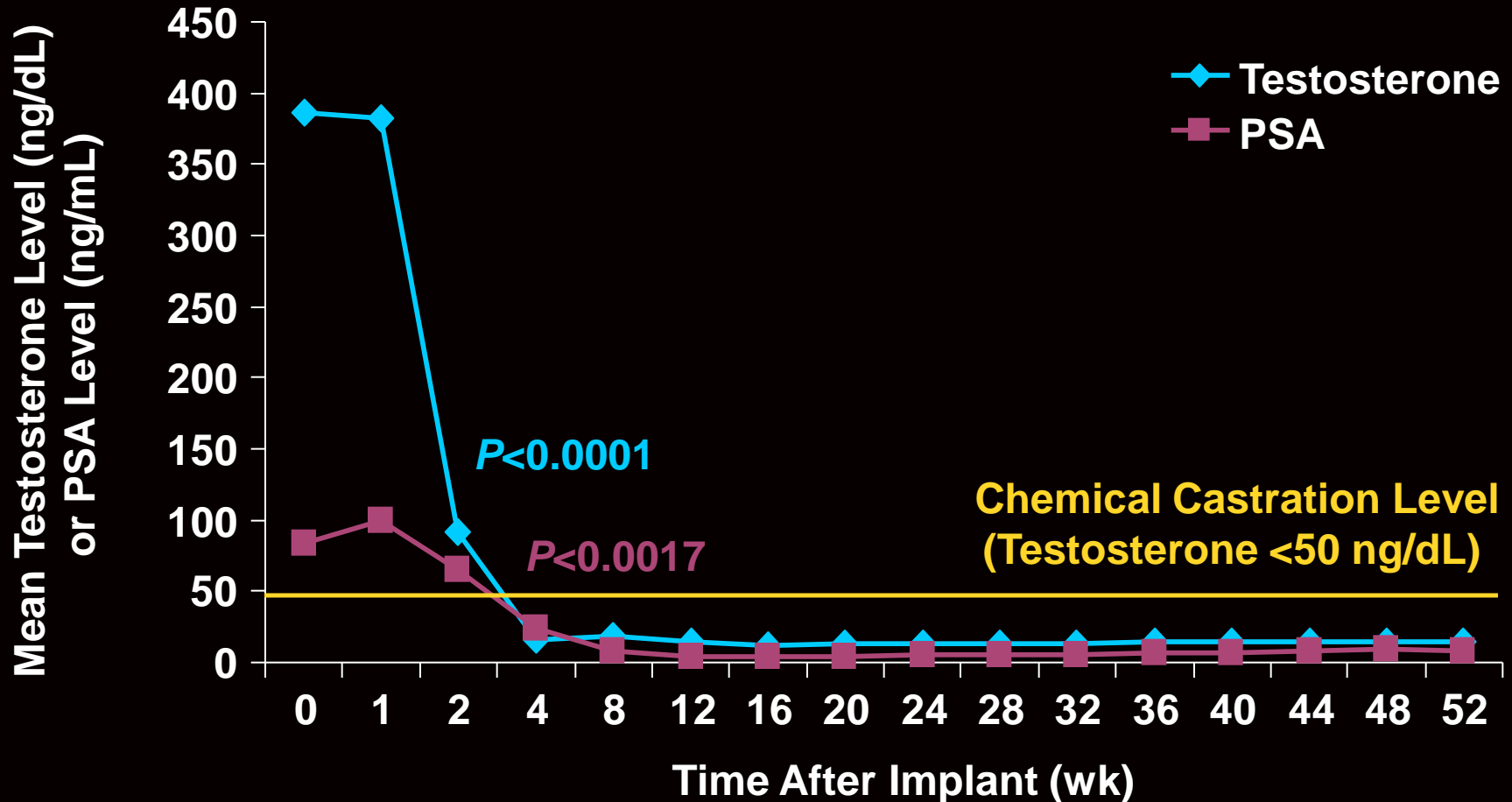
Histrelin Implant Achieves Chemical Castration by Week 4

Data from 17 Patients in a Phase 3 Trial (N=138)



Histrelin Implant Maintains Chemical Castration for 52 Weeks

Data from a Phase 3 Trial (N=138)





Strategies to Manage Adverse Effects of ADT

Side Effect	Strategies
Hot flashes	<ul style="list-style-type: none"> ❖ Estrogens¹ ❖ Megestrol acetate/progesterone^{2,3,5} ❖ Clonidine⁴ ❖ SERMs (in clinical trials)⁴ ❖ Antidepressants (SSRIs)^{4,5} ❖ Alternative therapies (soy, vitamin E)⁴
Anemia	<ul style="list-style-type: none"> ❖ Identify correctable causes in symptomatic patients ❖ Iron deficiency or vitamin B12/folate deficiency ❖ rHuEPO and blood transfusions⁵

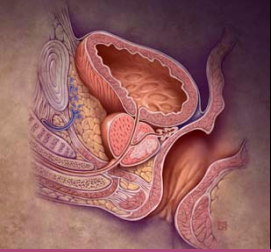
SERMs =selective estrogen receptor modulators , Hct = hematocrit, rHuEPO = recombinant human erythropoietin.



Strategies to Manage Adverse Effects of ADT (cont'd)

Side Effect	Strategies
Cardiovascular issues (weight gain, metabolic syndrome)	<ul style="list-style-type: none">❖ Regular exercise❖ Smoking cessation❖ Measure BMI❖ Monitor lipids and glucose❖ EKG
Osteopenia/ Osteoporosis	<ul style="list-style-type: none">❖ Daily calcium (800-1200 mg)❖ Regular exercise❖ Consider bis-phosphonates for osteoporosis❖ Baseline DEXA scan
Muscle atrophy	<ul style="list-style-type: none">❖ Exercise

BMI = body mass index, EKG = electrocardiogram, CTIBL = cancer treatment-induced bone loss; DEXA = dual energy x-ray absorptiometry.



Considerations in Selecting an LHRH Analog

- ❖ Similar efficacy and adverse event profiles among agents¹
- ❖ Patient and office considerations with short-term injectable LHRH analogs
 - Painful when administered²
 - Inconvenient²
 - Require frequent office visits³
 - May affect compliance³
 - Missed injections affect disease progression⁴
 - Patient commitment to long-term treatment³
 - Significant use of office staff time: cost effectiveness issue?⁴
 - Biodegradable product⁴
 - Effects not reversible in short term⁴



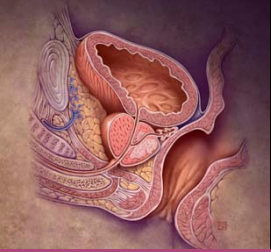
Considerations of Once-Yearly Implant vs. Multiple Injections or Implants

- ❖ Benefits to the patient
- ❖ Single annual procedure vs. multiple injections or implants
- ❖ Flexibility to seek consultative follow-up
 - Office visits not tied to getting an injection or timing of the injection
- ❖ Improved adherence and continuity of treatment
 - Testosterone levels remain low all year
 - Missing a visit does not affect or disrupt androgen suppression
- ❖ Device easily removed to allow cessation of LHRH treatment



Who May Benefit From Once-Yearly LHRH Therapy?

- ❖ Newly diagnosed patients¹
 - Locally advanced tumors (cT3/T4, N0, M0)
 - Metastatic disease
- ❖ Recurrence after local therapy¹
 - Biochemical recurrence (PSA rise)
 - Radiographic evidence of disease
- ❖ Not all patients will be candidates for once-yearly therapy (eg, end-stage disease)²



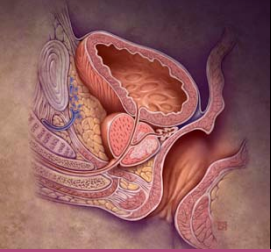
Summary of LHRH Analog Therapy

- ❖ Preferred by patients over orchiectomy
- ❖ Improves outcomes in advanced prostate cancer
- ❖ May improve outcomes in high-risk prostate cancer as adjuvant therapy or in cases of biochemical failure
- ❖ Options for LHRH analog therapy include:
 - Leuprolide 1-, 3-, 4-, and 6-month injections
 - Goserelin 1- and 3-month injections
 - Histrelin 12-month implant
- ❖ Implement lifestyle changes, medical and alternative therapies, and close monitoring to control or prevent untoward effects of ADT



Agenda

- ❖ Prostate Cancer Facts
- ❖ Diagnosis and Staging
- ❖ Historical Perspective on Therapy (1940-1990s)
- ❖ Timing of ADT and ADT as Adjuvant Therapy
- ❖ LHRH Analogs
- ❖ **Alternative Strategies to Classic Androgen Deprivation**



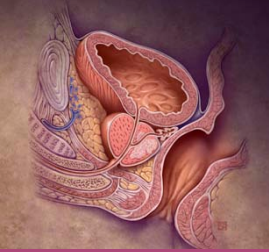
How Is Biochemical Recurrence Defined?

- ❖ Literature review: 1991-2004¹
 - 436 articles on treatment outcomes in cT1-2N0M0 disease
 - 166 different definitions of recurrence¹
 - 53 different definitions after RRP
 - 99 different definitions after EBRT
- ❖ AUA Panel recommendations for biochemical recurrence (2007)^{1,2}
 - After RRP: first value >0.2 ng/mL with confirmed PSA value >0.2 ng/mL
 - After EBRT: nadir PSA level $+2$ ng/mL (ASTRO criteria)

RRP = radical retropubic prostatectomy, AUA = American Urologic Association, ASTRO = American Society for Therapeutic Radiology and Oncology.

1. Cookson M, et al. *J Urol.* ;177:540-545.

2. Clark NW. *Eur Urol Suppl.* 2008;7:410:415.



How Is Biochemical Recurrence Defined? (cont'd)

- ❖ Treatment other than RRP or EBRT: nadir PSA level <0.5 ng/mL¹
- ❖ PSA bounce after radiation: PSA increases after 12 to 18 mo but returns to nadir²
- ❖ Ultrasensitive PSA¹

RRP = radical retropubic prostatectomy, AUA = American Urologic Association, ASTRO = American Society for Therapeutic Radiology and Oncology.

1. Cookson M, et al. *J Urol.* ;177:540-545.

2. Clark NW. *Eur Urol Suppl.* 2008;7:410-415.



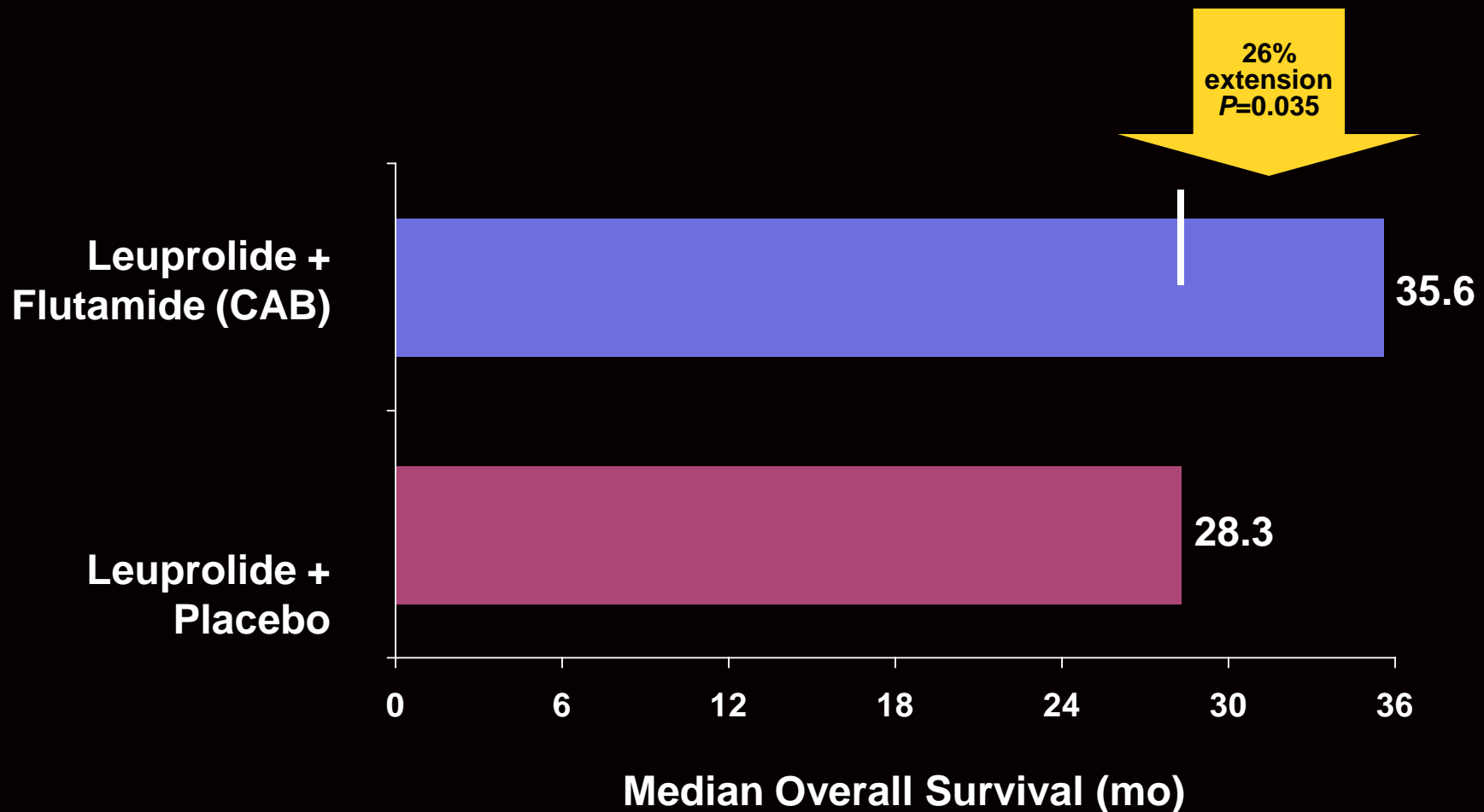
Independent Risk Factors Predicting Prostate Ca-Specific Death Post-RP

- ❖ Short time to biochemical recurrence
- ❖ Short PSA-DT
- ❖ High Gleason score

Variable	HR for PCSD	P Value
Time from RP to biochemical recurrence (<3 yr vs. >3 yr)	3.53	.002
PSA-DT (vs. >15 mo)		
<3.0 mo	27.48	<.001
3.0 to 8.9 mo	8.76	<.001
9.0 to 14.9 mo	2.44	.09
Pathologic Gleason score (>8 vs <8)	2.26	.002

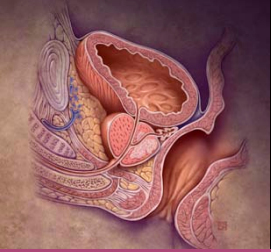
PCSD = prostate cancer-specific death, HR = hazard ratio, PSA-DT = PSA doubling time.
Freedland SJ, et al. *JAMA*. 2005;294:433-439.

NCI Trial: Combined Androgen Blockade (CAB) Extends Survival



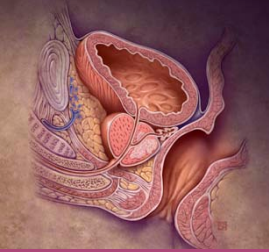
NCI = National Cancer Institute.

Hellerstedt BA, Pienta KJ. *CA Cancer J Clin.* 2002;52:154-179; Crawford ED, et al. *N Engl J Med.* 1989;7:419-424.



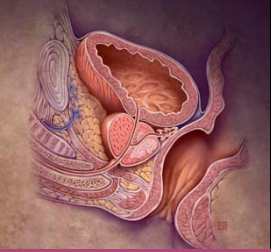
What About Intermittent Therapy?

- ❖ Proposed as an alternative to continuous ADT
 - Give patient a “break” from side effects of ADT
 - Potential to prolong androgen sensitivity
 - Possibly cost-efficient
- ❖ Definition of “intermittent”
 - Time of treatment after first cycle could be 6-15 months
 - Time off decreases with each consecutive cycle
- ❖ Evidence
 - Small trials
 - No Level I evidence
 - AUA does not support based on current evidence and await results from larger randomized trials



What to Do When Hormone Therapy Fails

- ❖ Progression despite castrate testosterone levels on LHRH therapy
- ❖ Diagnostics
 - Restage with bone scan and CT scan
 - PSA and testosterone levels (<50 ng/mL)
- ❖ Treatment options for androgen-independent prostate cancer
 - Continue LHRH analog therapy
 - Consider secondary hormonal manipulations: anti-androgen, ketaconazole/hydrocortisone
 - FDA-approved chemotherapy: docetaxel (survival benefit), mitoxantrone (palliative benefit)
 - Palliation using EBRT, analgesics



Conclusions

- ❖ Advanced prostate cancer affects >50,000 men annually
- ❖ Hormonal therapy remains the mainstay of treatment
- ❖ Earlier intervention with LHRH analogs improves survival in some patients
- ❖ Side effects of LHRH analogs may be significant and require monitoring
- ❖ Future strategies and therapies may reduce side effects and improve QoL