

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

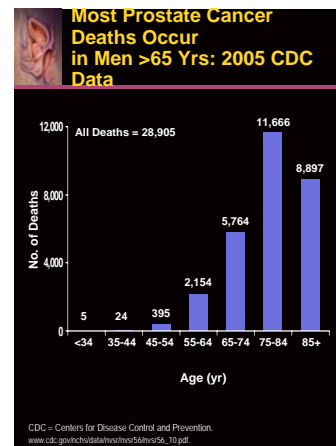
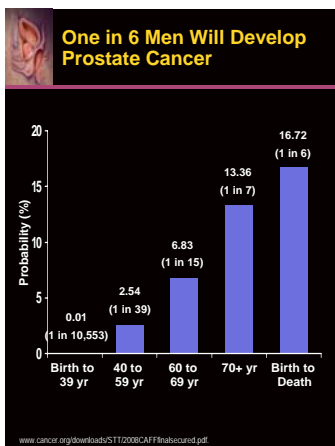
- Prostate Cancer Facts
- Diagnosis and Staging
- Historical Perspective on Therapy (1940-1990s)
- Timing of ADT and ADT as Adjuvant Therapy
- LHRH Analogs
- Alternative Strategies to Classic Androgen Deprivation

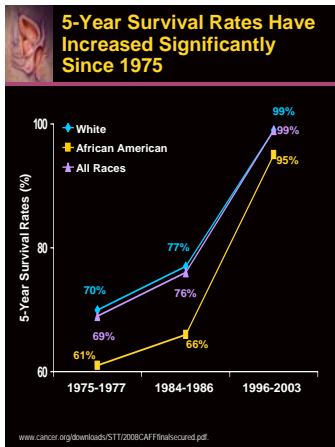
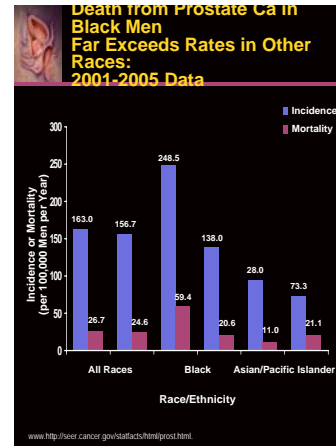
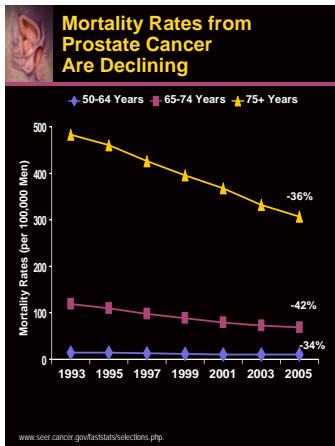
LHRH = luteinizing hormone-releasing hormone.

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/2008CAFFFinalscored.pdf
2. www.http://seer.cancer.gov/statfacts/html/prost.htm





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- ◆ 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

ADT = androgen deprivation therapy; LHRH = luteinizing hormone-releasing hormone

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

Chang SS, Amin MB. CA Cancer J Clin. 2008;58:54-59.

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

Chang SS, Amin MB. CA Cancer J Clin. 2008;58:54-59.

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 | N0 N1 Any N | M0 M1 | Any GS Any GS Any GS |

AJCC Cancer Staging Manual (6th ed.), 2002.

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;suppl 6:S10-S17.
2. Terris MK, et al. www.emedicine.medscape.com/article/151114.

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, DXA = dual-energy x-ray absorptiometry.
Terris MK, et al. www.emedicine.medscape.com/article/151114.

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Testosterone Production in the Hypothalamic-Pituitary-Gonadal Axis

GnRH = gonadotropin-releasing hormone; LH = luteinizing 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.
Tennis MK, et al. <http://emedicine.medscape.com/article/464114>.

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)

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

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. Lopez H. *Rev Urol*. 2005;7(suppl 5):S3-S12. 2. Hokenstedt BA, Pienta KJ. *CA Cancer J Clin*. 2002;52:154-176.

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

| | |
|--------------|-----|
| LHRH Agonist | 78% |
| Orchiectomy | 22% |

Cassileth B, et al. *J Urol* 1999;161:62-67.

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

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Clinical Benefit of Primary ADT in Metastatic Disease

| Nesbit and Baum, 1950 ¹ | | | |
|------------------------------------|------|-------------|-------------------|
| 5-Year Survival | | | |
| Controls | DES | Orchiectomy | Orchiectomy + DES |
| 6.0% | 9.7% | 21.6% | 20.0% |

| Eisenberger et al, 1998 ² | | | |
|--------------------------------------|---------------------|---------------------------------|---------|
| 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 <4.0 ng/mL | 61.5% | 74% | <0.001 |

1. Nesbit RM, Baum WC. *JAMA* 1960;183:1317-1320.
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. Coia JE, Crawford ED. *J Urol* 1999;161:1991-1998. 2. Hellebrandt 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

- ❖ EOCG/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

EOCG = 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. Nishii RM, et al. *Urology*. 2008;71:1036-1042. 2. Cox RL, Crawford ED. *J Urol*. 1995;154:1991-1998. 3. MRC. *Br J Urol*. 1997;79:235-246. 4. Hollensen BA, Pienta KJ. *CA Cancer J Clin*. 2002;52:154-179. 5. Messing EM, et al. *N Engl J Med*. 1999;341:1781-1788. 6. Studer U, et al. *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 6):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. Hollensen BA, Pienta KJ. *CA Cancer J Clin*. 2002;52:154-179.
2. Galsbo TA, et al. *Rev Urol*. 2007;9:163-180.

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LHRH = luteinizing hormone-releasing hormone.

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*. 2006;7(suppl 9):S3-S12.
2. Schulz AV. *BJU Int*. 2007;100(suppl 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. Loper H. *Rev Urol* 2005;(suppl 5):S3-S12.
2. Schally AV. *BJU Int* 2007;100(Suppl 2):4.

LHRH Analogs Offer Several Therapeutic Options

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

Physicians' Desk Reference 2008 62nd ed. Montvale, NJ: Thomson PDR; 2007.

How Do the LHRH Analogs Compare?

| INJECTIONS ¹ | IMPLANT ^{2,3} |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> 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 <ul style="list-style-type: none"> Inserted using disposable syringe May require local anesthetic Initial testosterone flare Achieve castrate levels after 2 to 4 wk; maintained throughout dosing interval | <ul style="list-style-type: none"> 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 <ul style="list-style-type: none"> Incision needed for placement through cannula in insertion tool Requires local anesthetic Removed at end of dosing interval Initial testosterone flare Achieve castrate levels by wk 4; maintained throughout dosing interval |

1. Loper H. *Rev Urol* 2005;(suppl 5):S3-S12. 2. Dineen MK, et al. *J Clin Pharmacol* 2005;45:1245-1249. 3. Cnaan B, et al. *J Urol* 2000;163:838-844.

Histrelin Implant Achieves Chemical Castration by Week 4

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

Chemical Castration Level (Testosterone <50 ng/dL)

Dineen MK, et al. *J Clin Pharmacol* 2005; 45:1245-1249.

Histrelin Implant Maintains Chemical Castration for 52 Weeks

Data from a Phase 3 Trial (N=138)

Chemical Castration Level (Testosterone <50 ng/dL)

Schlegel PN. *J Urol* 2006;175:1353-1358.

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.

1. Gelber GS, et al. *Urology* 2000; 55:97-101. 2. Loprinzi CL, et al. *N Engl J Med* 1994; 331:343-352. 3. Smith JA, et al. *J Urol* 1994; 152:130-134. 4. Guise TA, et al. *Rev Urol* 2007;9:163-180. 5. Michelson MD, et al. *Cancer* 2008;104:581-591.

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, CTBL = cancer treatment-induced bone loss.
DEXA = dual energy x-ray absorptiometry.
Gabe TA, et al. *Rev Urol* 2007;9:163-169.

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^{2,4}
 - Biodegradable product⁴
 - Effects not reversible in short term⁴

1. Hollstedt BA, Pienta KJ. *CA Cancer J Clin* 2002;52:154-179. 2. Chertin B, et al. *J Urol* 2000;163:838-844. 3. Dinesh KK, et al. *J Clin Pharmacol* 2005;45:1245-1249. 4. Schlegel PN, et al. *J Urol* 2006;175:1353-1358.

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

Schlegel PN, et al. *J Urol* 2006;175:1353-1358.

Considerations of Once-Yearly Implant vs. Multiple Injections or Implants (cont'd)

- ❖ Benefits to the office
- ❖ One implant/patient/year: reduces administrative burden by at least 2/3
- ❖ Opens up patient scheduling for new and established patients
- ❖ Enhances compliance and quality of care for patients
- ❖ Allows clinician to focus on patient needs during follow-up visits

Schlegel PN, et al. *J Urol* 2006;175:1353-1358.

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

1. Hollstedt BA, Pienta KJ. *CA Cancer J Clin* 2002;52:154-179. 2. Schlegel PN, et al. *J Urol* 2006;175:1353-1358.

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

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- ❖ 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
- ❖ AJA Panel recommendations for biochemical recurrence (2007)^{1,2}
 - After RRP: first value >0.2 ng/mL with confirmed PSA value >0.2 ng/mL
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2. Clark NW, *Eur Urol Suppl*. 2008;7:410-415.

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- ❖ 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

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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.
Hasknell BA, Pienta KJ. *CA Cancer J Clin*. 2002;52:154-179; Crawford ED, et al. *N Engl J Med*. 1999;7:419-424.

CAB vs. Castration: Meta-Analyses

PCTCG: overall¹ n=8215
PCTCG: nilutamide¹ n=1751
PCTCG: flutamide¹ n=4816
PCTCG: flutamide + nilutamide¹ n=2024
PCTCG: CPA¹ n=1661
Caubet: NSAA PCTCG² n=3732
Caubet: NSAA (PH)² n=1978
Caubet: NSAA (LH)² n=2357
Niotz: NSAA³ n=1015
Debrayne: nilutamide⁴ n=1151
Bennett: flutamide⁵ n=4128

0.5 CAB Better (0.4B Worse) 0.5
Hazard Ratio and 95% Confidence Limits

PCTCG = Prostate Cancer Trialists' Collaborative Group; CPA = cyproterone acetate; NSAA = nonsteroidal anti-androgen; PH = proportional hazards; LH = log hazard ratio.
1. Prostate Cancer Trialists' Collaborative Group. *Lancet*. 2000;355:1491-1498. 2. Caubet JF, et al. *Urology*. 1997;49:37-42.
3. Klotz LH, Neuman T. *Can J Urol*. 1996;3(Suppl. 1):102-105. 4. Debrayne FM, et al. *Eur Urol*. 1996;30(Suppl. 2):245.
5. Abatecola V, Bennett CL, et al. *Prostate Cancer Prostate Dis*. 1999;2:4-8.



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


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



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, ketoconazole/hydrocortisone
 - FDA-approved chemotherapy: docetaxel (survival benefit), mitoxantrone (palliative benefit)
 - Palliation using EBRT, analgesics

Terris MK, et al. Available at: <http://medicine.medscape.com/article/64114>.



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