



# **Prostate Cancer: 2010 Guidelines Update**

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# 2010 NCCN Guidelines Update

## Castration-Recurrent CaP

- Chemotherapy Simplified
  - Docetaxel 1st line regimen
  - No best second line regimen
- Sipuleucel-T (Provenge®)
  - Asymptomatic or minimally symptomatic
  - ECOG 0-1



**When should active surveillance be the only recommendation for a 65 yo man with clinically localized CaP?**

- A. When CaP is low risk and health is excellent
- B. When CaP is low risk and health is average
- C. When CaP is very low risk and health is excellent
- D. When CaP is very low risk and health is average
- E. He should be treated no matter what!



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# PSA and Prostate Cancer

- 1980s: 16% diagnosed with metastatic CaP
- 2002: 4% diagnosed with metastatic CaP
- CaP mortality rate declined 33% from 1993 to 2003
- Tyrol PSA-based screening study (Bartsch G, BJU Int, 2008) shows 54% decline in CaP-specific mortality and 10 yr PSA lead-time

# March 26, 2009 CaP Explosion

NEJM 360:1310-19 and 1320-28

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Screening and Prostate-Cancer Mortality in a Randomized European Study

Fritz H. Schröder, M.D., Jonas Hugosson, M.D., Monique J. Roobol, Ph.D.,  
Teuvo L.J. Tammela, M.D., Stefano Ciatto, M.D., Vera Nelen, M.D.,  
Maciej Kwiatkowski, M.D., Marcos Lujan, M.D., Hans Lilja, M.D.,  
Marco Zappa, Ph.D., Louis J. Denis, M.D., Franz Recker, M.D.,  
Antonio Berenguer, M.D., Liisa Mänttinen, Ph.D., Chris H. Bangma, M.D.,  
Gunnar Aus, M.D., Arnauld Villers, M.D., Xavier Rebillard, M.D.,  
Theodorus van der Kwast, M.D., Bert G. Blijenberg, Ph.D., Sue M. Moss, Ph.D.,  
Harry J. de Koning, M.D., and Anssi Auvinen, M.D., for the ERSPC Investigators\*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Mortality Results from a Randomized Prostate-Cancer Screening Trial

Gerald L. Andriole, M.D., E. David Crawford, M.D., Robert L. Grubb III, M.D.,  
Saundra S. Buys, M.D., David Chia, Ph.D., Timothy R. Church, Ph.D.,  
Mona N. Fouad, M.D., Edward P. Gelmann, M.D., Paul A. Kvale, M.D.,  
Douglas J. Reding, M.D., Joel L. Weissfeld, M.D., Lance A. Yokochi, M.D.,  
Barbara O'Brien, M.P.H., Jonathan D. Clapp, B.S., Joshua M. Rathmell, M.S.,  
Thomas L. Riley, B.S., Richard B. Hayes, Ph.D., Barnett S. Kramer, M.D.,  
Grant Izmirlian, Ph.D., Anthony B. Miller, M.B., Paul F. Pinsky, Ph.D.,  
Philip C. Prorok, Ph.D., John K. Gohagan, Ph.D., and Christine D. Berg, M.D.,  
for the PLCO Project Team\*

## Need to Treat to Prevent 1 Death:

- 28 screen-detected CaP (Schroder, NEJM, 2009)
- 100 low risk CaP (Klotz, J Clin Oncol, 2005)
- No survival benefit (Andriole, NEJM, 2009)

## 2010 Guideline Updates

1. Defined new risk category: very low risk CaP
2. Active surveillance only recommendation for men with
  - a. low risk CaP and L Exp < 10 yrs
  - b. very low risk CaP and L Exp < 20 yrs
3. Active surveillance program defined
4. Daily IGRT required for high dose XRT ( $\geq 78$ Gy)
5. External beam radiation failure work-up and treatment clarified
6. Chemotherapy algorithms simplified
7. Immunotherapy for castration-recurrent CaP



# **Preoperative Criteria** associated with **Clinically Insignificant Disease in the Radical Prostatectomy Specimen**

- Gleason Sum <7
- PSA <10
- No. positive biopsy cores <3
- CaP <50% in any biopsy
- PSAD <0.15

Epstein, JAMA, 1994

## 2010 NCCN Concerns

- High prevalence of CaP upon autopsy (Sakr, In Vivo, 1994)
- High frequency of CaP upon biopsy even when PSA and DRE normal (Thompson, NEJM, 2004)
- Mortality about 1/6 incidence (Jemal, CA Cancer J Clin, 2009)
- 23-42% of US screen-detected CaP over-treated

# 2010 Guideline Updates

## 1. Very low risk CaP

### Low Risk

- T1-T2a
- GS 2-6
- PSA<10

### Very Low Risk

- T1c
- GS 2-6
- PSA<10
- <3 cores positive
- <50% CaP in any core
- PSAD<0.15

## 2010 Guideline Updates

2. Active surveillance only recommendation for men with:

- a. Low risk CaP and L Exp < 10 yrs
- b. Very low risk CaP and L Exp < 20 yrs

## 2010 Guideline Updates

### 3. Active surveillance program clarified

- a. PSA as often as every 6 mo
- b. DRE as often as every 12 mo
- c. Prostate biopsy as often as every 12 mo when L Exp > 10 yrs
- d. Uncertain what the progression criteria should be to warrant treatment

# Best Argument for Immediate Treatment

- Randomized, controlled trial of RP vs. EM
- RP decreased absolute risk for
  - Local progression by 25%
  - Distant metastasis by 10%
  - Overall mortality by 5%
- Men < 65 yrs experienced greatest survival advantage
- Most diagnosed before the PSA era

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  - Local progression by 25%
  - Distant metastasis by 10%
  - Overall mortality by 5% **but was only 14.9% vs 9.6%**
- Men < 65 yo experienced greatest survival advantage **but found in a statistically improper subset analysis**
- Most diagnosed before the PSA era **so not applicable to US or today**

## 2009 NCCN: Active Surveillance or Immediate Active Treatment?

- The **risks** of AS include
  - chance of missed opportunity for cure
  - nerve-sparing may be more difficult
  - anxiety
- The **benefits** of AS include
  - avoidance of treatment-related side effects from a treatment that was unnecessary



# North American AS Experience

Center	Toronto <sup>1</sup>	Johns Hopkins <sup>2</sup>	UCSF <sup>3</sup>
No. Patients	450	407	531
Age (yr)	70	66	63
F/U (mo)	82	41	43
OS	68%	98%	98%
CSS	97%	100%	100%
<b>Treatment</b>	<b>30%</b>	<b>25%</b>	<b>24%</b>
GS↑	8%	19%	38%
PSA	14% (DT<3 yrs)	-	26% (PSAV>0.75)
Nodule	1%	-	-
<b>Anxiety</b>	<b>3%</b>	<b>7%</b>	<b>8%</b>

16% {

1. Klotz, J Clin Oncol, 2010; 2. Carter, J Urol, 2007; Sheridan, J Urol, 2008;  
3. Dall'Era, Cancer, 2008



**How does one estimate life expectancy with enough accuracy to guide treatment decision making in prostate cancer?**

- A. Ask the patient
- B. Use the Minnesota Metropolitan Life Insurance tables
- C. Use the Social Security Administration tables
- D. Adjust for overall health status
- E. All of the above



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# Life Expectancy Estimation

- LExp can be estimated using the Minnesota Metropolitan Life Insurance Tables or the Social Security Administration LExp Tables.
- LExp can be adjusted for individual patients by adding or subtracting 50% based upon whether one believes the patient is in the healthiest quartile or the unhealthiest quartile, respectively.
  - SSA LExp for 65-year old American man = 16 yrs
  - If upper quartile of health, LExp = 24 yrs
  - If lower quartile of health, LExp = 8 yrs
- 2007 NCCN Guidelines, for the first time, included “Principles of Life Expectancy Estimation.”

# Time to Death from Prostate Cancer

- Gleason score
  - 2-6 favorable
  - 7-10 unfavorable
- Tumor volume
  - < 4 cc favorable
  - $\geq$  4 cc unfavorable (nodule, PSA/3, >3 biopsies, >50% of a biopsy)
- Aggressiveness
  - Low if both favorable
  - High if both unfavorable
  - Intermediate if only 1 favorable
- Time to symptomatic metastases by aggressiveness
  - Low 12 yrs
  - Intermediate 10 yrs
  - High 8 yrs
- Time to death
  - Time to symptoms + 3 yrs for remission due to ADT + 10 yr PSA early detection lead time [if applicable]

McNeal, Human Pathol, 1992; Bartsch G, BJU Int, 2008



## Case

65 yo man presents with PSA 7.2, clinical stage T1c, and Gleason score 3+3=6 prostate cancer in 10% of 1 of 12 biopsies. Health is **excellent**. The best choice for treatment is:

1. 3D Conformal Radiation
2. Interstitial Implant (seeds)
3. Prostatectomy
4. Cryotherapy
5. Active Surveillance

- CaP-limited LExp is 12 (low aggressiveness) + 3 (ADT) + 10 (PSA lead time) = 25 yrs
- LExp by age = 16.4 yrs
  - Excellent health = 24.6 yrs
  - Average health = 16.4 yrs
  - Poor health = 8.2 yrs
- Chance of CaP death
  - Excellent health = 50%
  - Average health = 10%
  - Poor health = 0%
- Chance of cure of CaP by Partin Tables 83%
- Chance of CaP death after RP
  - Excellent health = 7%
  - Average health = 2%
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**When is active surveillance an appropriate option in men with clinically localized prostate cancer?**

- A. When CaP is poorly differentiated
- B. When CaP is palpable
- C. When PSA exceeds 20
- D. When PSA doubling time exceeds 5 yrs



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# Radiation

- 3D conformal and **IMRT** (intensity modulated RT) and **IGRT** (image guided RT) techniques **required (2009)**
- Patients with high-risk CaP **require pelvic lymph node irradiation** and neoadjuvant + concomitant + adjuvant **androgen deprivation therapy** for 2 or 3 y **(2009)**
- **Daily IGRT** **required** for high dose XRT ( $\geq 78\text{Gy}$ ) **(2010)**

# External Beam Radiation Failure

- More aggressive evaluation, which may include endorectal MRI, MR Spectroscopy, repeat biopsy, PSADT
- No salvage prostatectomy, cryosurgery, or brachytherapy if can't document recurrence with biopsy

## 5 Take Home Messages

- Estimate Life Expectancy
- Risk stratify using Stage, Gleason Sum and PSA
- AS should be the first option discussed against which the benefits (potential and need for cure) and risks (mortality, urinary incontinence and impotence) of treatment should be compared
- AS should be recommended for very low and low-risk CaP when L Exp is <20 and <10 yrs, respectively
- Sipuleucel-T (Provenge®) is a new option for castration-recurrent CaP