

When PSA fails

Urology Grand Rounds
Alexandra Perks

Rising PSA after Radical Prostatectomy

- Issues
- Natural History
- Local vs Metastatic
- Treatment options

- 10 000 men / year in Canada
- 4000 RRP
- 15-year PSA failure rate ~ 25%

PSA Principles

PSA half-life (2.2 +/- 0.8 days)

Serum PSA undetectable by 21 to 30 days

Ddx detectable PSA after RRP

- False positive
- Residual benign prostate
 - 27% RRP specimens benign glands at margin
 - Ectopic prostatic tissue
- Tumor recurrence
 1. Local recurrence
 2. Metastatic

Case:

- 5 years after RRP → PSA = 0.4
- Mucosal nodule on DRE
- GI removed it
- Path = submucosal nodule in rectum of Gleason 3+3 = 6 CaP, negative margins
- PSA became undetectable

Issues

1. Not all pts have impending mets and DS-death
2. Difficult to localize recurrent disease
3. Rising PSA a “surrogate” outcome measure for CaP?
4. No RCTs using AWT for a rising PSA after RRP

Defining Biochemical Recurrence

Mayo Clinic series – Amling, J Urol 2001
2,782 RRP cases between 1987–1993

“PSA > 0.4 ng/ml - best level to consider treatment”

	<u>% pts in whom PSA rose within 3 yrs</u>	
0.2 ng/ml	49%	
0.3 ng/ml	62%	→ 1/3 did not rise
0.4 ng/ml	72%	

Natural History

~ 80% of PSA recurrences occur within 3 - 5 years

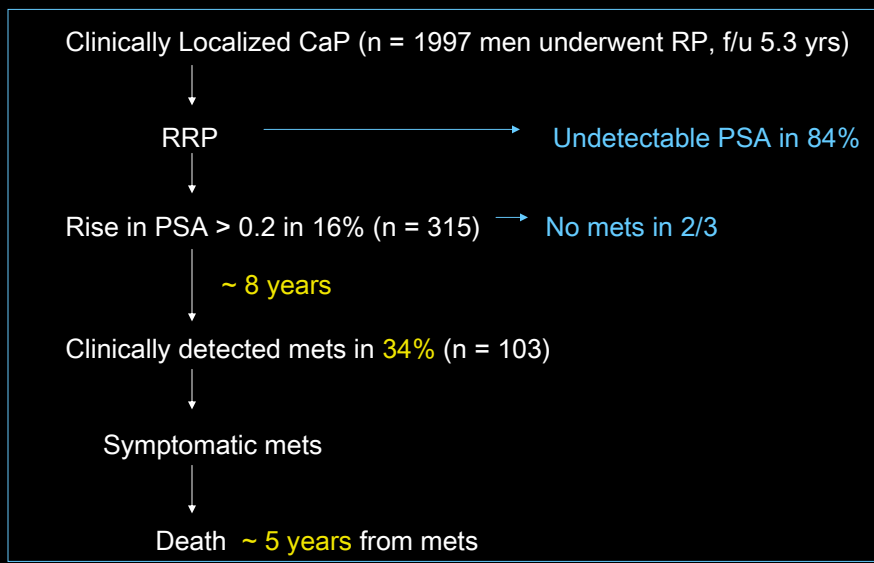
Table 89-4. YEAR OF FAILURE OF 175 PATIENTS WITH RECURRENT PROSTATE CANCER AFTER RADICAL PROSTATECTOMY

Year	Number of Failures at End of Each Year	Percentage of Failures
1	91	52
2	28	16
3	20	11.4
4	16	9.1
5	11	6.3
6	4	2.3
7	3	1.7
8	1	0.6
9	1	0.6
≥10	0	0

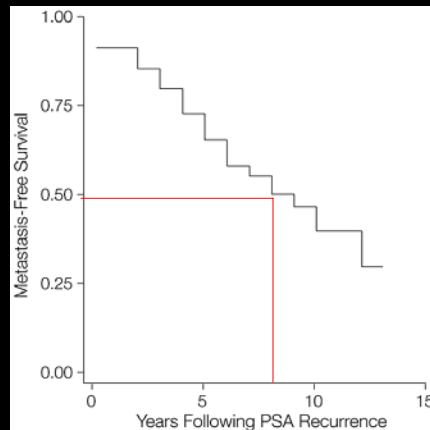
Modified from Hull GW, Rabbani F, Abbas F, et al: Cancer control with radical prostatectomy alone in 1000 consecutive patients. *J Urol* 2002;167:528-534.

Natural History of Progression After PSA Elevation Following Radical Prostatectomy.

JAMA 1999; CR Pound, AW Partin, MA Eisenberger, DW Chan, JD Pearson, PC Walsh

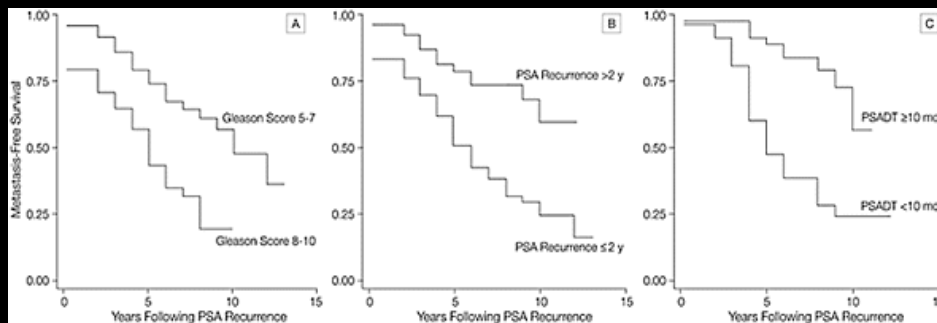


Likelihood of Mets-Free Survival in 304 Men With PSA Elevation After RRP



Pound JAMA 1999 – median time to metastases = 8 years
 Partin J Urol 2003 – median time to metastases = 7.5 years

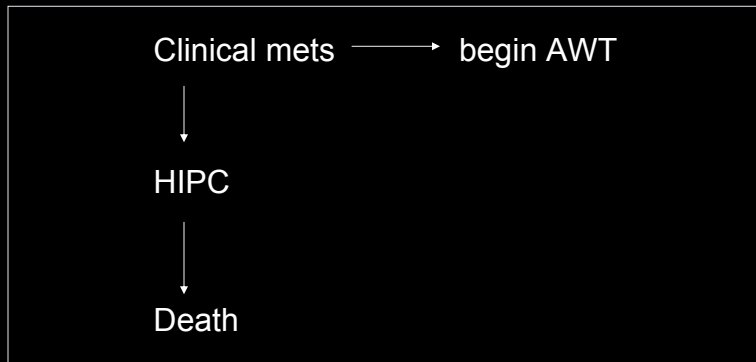
Risk factors for progression to metastases



- | | |
|------------------------------------|-------------------------|
| 1. Gleason | 8-10 |
| 2. Time to biochemical progression | < 2yrs |
| 3. PSA doubling time | <10-12 months |

Pound, JAMA 1999
 Partin, J Urol 2003
 Roberts, Mayo Clin Proc 2001 – multivariate analysis

Natural history of metastatic disease

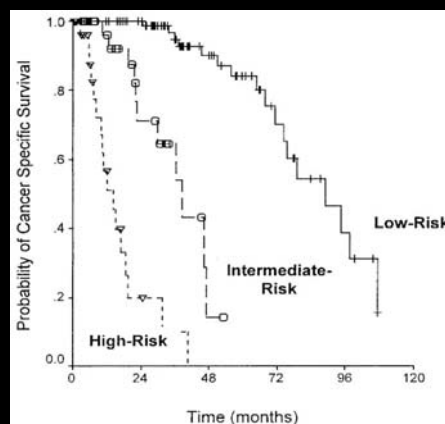


* Median time to death ~ 5 years

Pound JAMA 1999 – median time to death = 5 years
Partin J Urol 2003 – median time to death = 6.5 years

Risk factors for shortened survival once pt had HIPC

- | | |
|-----------------------------------|-------------|
| 1. PSA DT | < 6 months |
| 2. PSA nadir on AWT | > 0.5 ng/ml |
| 3. Time to PSA progression on AWT | < 7 months |



- Shulman, J Urol 2004

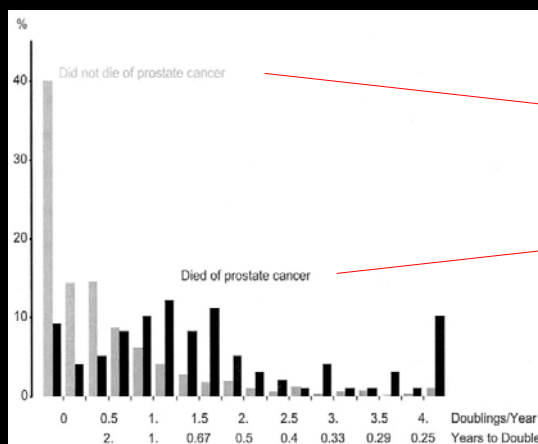
Natural History

- 10 year BCR-free 47% to 73%
- 10 year mets-free survival 80% to 85%
- Cause-specific survival 90%
- Overall survival rate at 10 yrs was equal in pts with and without BCR

Overall survival at 10 yrs 88% with BCR
93% without BCR

- Jhaveri, Urology 1999

Risk factor for mortality



Pts who did not die of CaP had no increase in PSA (40%) or **PSA DT > 1 yr (44%)**

Pts who died of CaP median **PSA DT = 0.8 yrs**

- Albertson, J Urol 2004

- 1,136 men treated with RRP or EXRT +/- AWT

Calculating PSADT:

$$\text{PSADT} = [\log(2) \times t] \div [\log(\text{final PSA}) - \log(\text{initial PSA})]$$

Palm program at www.mskcc.org

Differentiating benign tissue from CaP

- “Benign prostate, PSA usually rises and then levels off, whereas, cancer causes steady, continuing rise”
- “Even if post-op TRUSBx documents benign tissue, PSA kinetics suggest that it is highly unlikely that a detectable PSA is due only to benign tissue, but that malignant tissue coexists”

Foster, 1995

Ravery, Semin Urol Onc 1999

Scardino, Urol Clin NA 2003

Local vs Distant Metastases

Local recurrence	Distant mets +/- local recurrence
4%	8%
1.7%	5.6%

- *Partin 1994* - 1,058 men RRP for localized CaP, 10 yr f/u
- *Han 2001* - 2,404 men, 15-yr John Hopkins experience
 - 17% PSA recurrence rate
 - 9.7% PSA-only recurrence

Differentiating local relapse from mets

DRE	
TRUS +/- Bx	Minimal role post-RRP
CT	Minimum PSA ~ 10-20. Minimum size > 2 cm.
PET scan	Cannot differentiate CaP from BPH, scar from local recurrence
Endorectal MRI	Under investigation
ProstaScint	Approved by FDA 1998
Bone scan	< 5% positive when PSA < 40 – 45 ng/mL

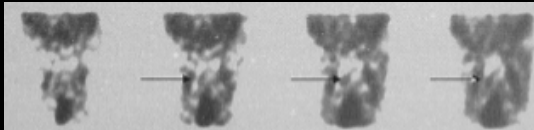
THE ROLE OF ¹¹¹INDIUM-CAPROMAB PENDETIDE IMAGING FOR ASSESSING BIOCHEMICAL FAILURE AFTER RADICAL PROSTATECTOMY

SIMON WILKINSON* AND GERALD CHODAK

From the Weiss Memorial Hospital, University of Chicago, Chicago, Illinois

THE JOURNAL OF UROLOGY® July 2004

- Abnormal ProstaScint in 85.7% (36 pts)
- Median PSA 1.2 ng/ml
- 15 pts with uptake in fossa had salvage XRT
- 30 month f/u
- **7 of 15 (47%) achieved durable response**



Clinicopathologic features of local and metastatic disease after RRP

Local recurrence

PSA DT > 6 months
PSA recurrence > 2 yrs
+ve surgical margins?

Metastases

PSA DT < 6-10 months
PSA recurrence < 1 - 2 yrs
Gleason 8 – 10
LN involvement
SV involvement

- Scardino 2003 - review
- Foster 1993, Roberts 2001, Patel 1997, Pound 1999, 1997, Amling 2000

Does margin status predict local recurrence?

Positive margins not essential for local recurrence

~ 30% had negative margins, 15% - 48% organ-confined

Margin status predictive on multivariate analysis

Most predictive factor of local recurrence ($p < 0.02$)

Negative margins a/w progression after salvage XRT ($p < 0.001$)

- Kupelian Urol 1996

- Stephensen JAMA 2004

Treatment options

1. Expectant management / observe
2. Salvage XRT to prostatic bed
3. Early androgen withdrawal therapy

Salvage XRT

ASTRO consensus statement for PSA recurrence after RRP (1999):

1. Start salvage XRT before PSA 1.5 ng/ml
2. Radiation dose > 64 Gy
3. No standard role for NHT or adjuvant HT (no RCT)

Forman, J Urol 1997: 64% 5-yr disease-free survival
83% PSA < 2 ng/ml
33% PSA > 2 ng/ml $p = 0.001$

Salvage XRT

Stephensen JAMA 2004

501 pts salvage radiotherapy for increasing PSA after RP, f/u 45 mo

4-year progression-free survival = 45%

No adverse features:

4-year progression-free survival = 77%

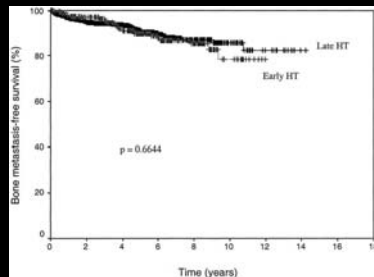
<u>Predictors of progression</u>	<u>Hazard ratio (95% CI)</u>
Gleason 8 -10	2.6 (1.7-4.1)
Pre-radiotherapy PSA > 2.0	2.3 (1.7-3.2)
Negative surgical margins	1.9 (1.4-2.5)
PSA DT < 10 months	1.7 (1.2-2.2)
SV invasion	1.4 (1.1-1.9)

Early Androgen Withdrawal Therapy

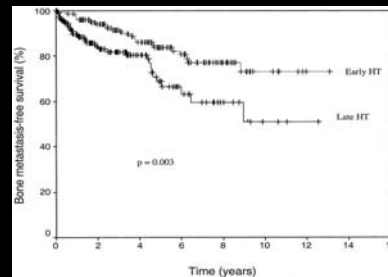
Early vs Delayed Hormonal Therapy for PSA Only
Recurrence After RRP. Moul et al, 2004

The Journal of Urology

1352 pts BCR after RRP (27%) ← Early HT (PSA < 10), n = 307
Late HT (PSA > 10) or no HT, n = 1045



Overall (n = 1352)
HR = 1.02, p = 0.95



Gleason > 7 or PSA-DT ≤ 12 mo
HR = 2.2, p = 0.005

An Approach

- Take a risk stratified approach to PSA recurrence
- Consider
 - Natural history, risk of local recurrence, risk of future metastases and CaP-specific mortality
 - Side effects of hormone therapy and salvage XRT
 - Pt's health, life expectancy, QOL, wishes

Other options

1. AA monotherapy (bicalutamide 150 mg)

1453 men M0 PCa, bicalutamide vs castration
Equivalent time to progression and survival
QOL favorable for bicalutamide

- *Iverson J Urol 2000*

2. Step-up HT regimens

Experimental at this time

3. Intermittent hormone therapy

PR-7: Intermittent vs continuous HT for PSA > 3

Remember...

Metastatic CaP without rising PSA

2.3% - 2.6%

- *Leibman 1995, Oefelein 1995*

Small cell carcinoma

Histological dedifferentiation

Local or metastatic to bone (lytic), brain, lung, viscera

Tx: Chemotherapy (not HT)