BPH with persistently elevated PSA
PSA in BPH: present status

- AUA & EAU BPH guideline:
  - PSA: recommended test
    - AUA practice guideline committee. J Urol 2003;170:530

- Korean survey on 250 urologists:
  - Use of PSA in the diagnosis of BPH: 96.4%
    - 2nd prostate academy. 2007
Consensus on men with elevated PSA (≥4ng/ml)

Systematic prostate biopsy: 8-12 cores at least + additional targeted cores if needed

Follow-up PSA (fPSA)

- elevated PSA
  - Consider repeat biopsy

- negative
  - Biopsy
    - negative
      - Follow-up PSA (fPSA)

Repeat biopsy

- When?
- Whom?
- How?
- How many times?
- Symptomatic BPH →

Treat BPH or keep on doing biopsy forever?
Repeat biopsy: When?

- No consensus
- 6 to 12 months after 1st biopsy generally considered adequate
Repeat biopsy: Whom?

- Use of PSA kinetics
  - PSA velocity: 0.75ng/ml/yr, 1ng/ml/yr…

- Use of PSA surrogates
  - Free-to-total PSA
  - PSA density
  - PSA-TZ density…

- Palpable suspicious nodule or abnormal lesion on TRUS
  - Notwithstanding normal or stable PSA
Repeat biopsy: How?

- Repeat the 1st biopsy technique if adequate
- Change of biopsy technique:
  - Saturation biopsy (~24 cores)
  - Transitional zone sampling
  - Perineal biopsy
  - Vienna nomogram
  - ...

Repeat biopsy: How many times?

- No consensus
- Second biopsy: 10-35% detection rate
- Biopsies subsequent to 2 first biopsies: <10% detection rate and of lower grade, stage and volume

Djavan et al. J Urol 2001;166:1679

- >90% of CaP are detected by first 2 sextant biopsies

Roehl et al. J Urol 2002;167:2435
Symptomatic BPH

- In BPH patients with little improvement with α-blocker and 1 or multiple negative prostate biopsy, persistent PSA elevation may interfere proper treatment.

  → Medical or surgical challenge, could it interfere, be harmless or even help diagnose CaP?

- 5ARI
- Surgery
Finasteride challenge

  - RCT evaluating the effect of finasteride on the risk of AUR and the need for surgery in men with BPH for 4 years (3040 men)
  - PSA <10ng/ml
  - Prerandomization BX in 731 men with PSA $\geq$ 4ng/ml → 717 (98%) men with negative biopsy enrolled (at least 4 cores)
  - Protocol amendment to include end-of-study biopsy in men with baseline PSA $\geq$ 4ng/ml after publication of results emphasizing the importance of repeat biopsies for men with elevated PSA.
PLESS: results

- Finasteride decreased prostate volume by 25-30%
- Finasteride decreased PSA by 50%
  - multiplied f/u PSA by 2 in finasteride group

# PLESS: results

<table>
<thead>
<tr>
<th></th>
<th>Finasteride (1523)</th>
<th>Placebo (1511)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients biopsied</td>
<td>Cancers detected</td>
</tr>
<tr>
<td>Surgery for BPH</td>
<td>65</td>
<td>4</td>
</tr>
<tr>
<td>PSA elevation</td>
<td>95</td>
<td>26</td>
</tr>
<tr>
<td>DRE</td>
<td>33</td>
<td>10</td>
</tr>
<tr>
<td>Other clinical</td>
<td>28</td>
<td>7</td>
</tr>
<tr>
<td>End-of-study biopsy (baseline PSA ≥ 4ng/ml)</td>
<td>169</td>
<td>25</td>
</tr>
<tr>
<td>Totals</td>
<td>390</td>
<td>72</td>
</tr>
</tbody>
</table>

Andriole et al. Urology 1998;52:195
PLESS: results

- With PSA limit of 4.0 (2.0 for finasteride), higher specificity ($p<0.0001$) and likelihood ratio ($p<0.05$) for finasteride than for placebo

$\text{Finasteride, AUC}=0.84$
$\text{Placebo, AUC}=0.79$
$P=0.07$

→ Usefulness of PSA for prostate cancer detection is preserved by multiplying PSA by 2 in finasteride group
Finasteride challenge

- Finasteride for 1 year in 38 men with PSA > 4ng/ml and ≥ 2 negative prostate biopsy
- Cancer detection rate at 1 year rebiopsy:
  - PSA decrease ≥ 50%: 0/10 (0%)
  - PSA decrease 33-50%: 6/19 (32%)
  - PSA decrease < 33%: 5/9 (56%)

Kaplan et al. Urology 2002;60:464
Finasteride challenge

- Finasteride for 6 months in 23 men with PSA > 4ng/ml and at least 1 negative 12 core prostate biopsy
- Cancer at 6 M rebiopsy: 6 (26%)
  - Benign: 44% decrease in PSAD
  - CaP: 5% decrease in PSAD

Handel et al. Urology 2006;68:1220
Finasteride challenge: PCPT

- Randomized placebo-controlled trial to determine if finasteride would reduce CaP prevalence after 7 years of Tx
- 18882 men enrolled
Better sensitivity and AUC for detecting CaP by PSA in finasteride group than in control

TURP after repeated negative prostate biopsies

- Rationale: pure TZ cancer incidence: 0-28% (generally <5%)
- Several series of TURP after repeated negative needle biopsies in patients with significant BOO and rising PSA
  ⇒ effectiveness of TURP for both treatment of BOO and diagnosis of PC?
<table>
<thead>
<tr>
<th>Authors</th>
<th>No Pts</th>
<th>Prev Bx times &amp; method</th>
<th>Tx</th>
<th>Reason for Tx</th>
<th>No PC (%)</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kitamura et al. 2002</td>
<td>18</td>
<td>Sext + perin TZ Bx</td>
<td>TURP</td>
<td>Relief of BOO</td>
<td>5 (28)</td>
<td>All low GS (2-5), low volume</td>
</tr>
<tr>
<td>Zigeuner et al. 2003</td>
<td>445</td>
<td>1.8 (1-8)</td>
<td>TURP, OP</td>
<td>Medical Tx failure</td>
<td>35 (7.9)</td>
<td>DRE(-): 5.5%; DRE (+):16.5%</td>
</tr>
<tr>
<td>Radhakrishnan et al. 2004</td>
<td>14</td>
<td>Sext x 2</td>
<td>TURP</td>
<td>Diagnostic for rising PSA?</td>
<td>3 (21)</td>
<td>All signif. PC</td>
</tr>
<tr>
<td>Startsev et al. 2005</td>
<td>49</td>
<td>Sext x 1</td>
<td>Imm. TURP</td>
<td>Severe LUTS</td>
<td>12 (24.5)</td>
<td></td>
</tr>
<tr>
<td>Puppo et al. 2006</td>
<td>14</td>
<td>≥3, 41.5 cores</td>
<td>TURP + TR Bx</td>
<td>Diagnostic</td>
<td>8 (57)</td>
<td>All signif. PC</td>
</tr>
<tr>
<td>Van Renterghem et al. 2007</td>
<td>82</td>
<td>≥2, one 12 core biopsy</td>
<td>TURP</td>
<td>Minor LUTS, but BOO on UDS</td>
<td>8 (9.8)</td>
<td>74: PSA 8.8 → 1.1 1st year, 1.3 2nd year after op.</td>
</tr>
</tbody>
</table>
Post TURP prostatectomy

- Longer operative time and higher complication rates in both open RRP and LRP
- May be associated with higher margin(+) rate
- Higher risk of anastomotic leakage due to bladder neck fibrosis

- wait at least 2 months after TURP
- explain to the patient about higher risk
- avoid transperitoneal approach in LRP
Conclusions

- BPH patients with persistently elevated PSA after 1st negative biopsy should be offered at least 1 repeat biopsy.
- Benefit of more than 2 biopsies is controversial in these patients.
- Use of 5ARI does not lower and may even strengthen the usefulness of PSA in detecting CaP in these patients.
Conclusions

- TURP benefits patients with severe LUTS after negative biopsy by relieving BOO and diagnosing a few additional CaP.
- However, diagnostic TURP after negative biopsies is not fully justified (low positive rate, clinically insignificant cancer, surgical morbidity of radical prostatectomy after TURP).