VALUE OF PSA AS TUMOUR MARKER OF RELAPSE AND RESPONSE

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Prostate Specific Antigen (PSA) has a role in:

**Detection**
- Healthy man
- Man with prostate cancer
- Missed cases

**Risk stratification**
- PSA suggests cancer where there is none
- PSA misses these two cases
- PSA finds these three cases

**Monitoring**

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>PSA</th>
<th>Gleason Score</th>
<th>Clinical Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>&lt;10 ng/ml</td>
<td>&lt;6 AND</td>
<td>T1-T2a</td>
</tr>
<tr>
<td>Intermediate</td>
<td>10-20 ng/ml</td>
<td>7 OR</td>
<td>T2b-T2c</td>
</tr>
<tr>
<td>High risk</td>
<td>&gt;20 ng/ml</td>
<td>8-10 OR</td>
<td>T3-T4</td>
</tr>
</tbody>
</table>

B

Maximum PSA change %

Docetaxel experienced

Docetaxel naive
Monitoring primary treatment

- Most PrCa cases are diagnosed in early stages when cure is possible.
- Recurrence occurs in approx 20-30% after primary treatment.

- Patients are followed up to:
  - Assess immediate and long term oncologic results
  - Side effects, complications, functional outcome
  - Discuss management if relapse

- PSA and DRE. No images are required…. unless suspicion of relapse *(biochemical, clinical…)*

- PSA rise usually precedes clinical recurrence.
- A single elevated single PSA level should be **confirmed** before starting second line therapy solely based on PSA.

*EAU guidelines, 2015*
*NCCN guidelines, v1.2016*
*NICE guidelines, 2014*
Monitoring primary treatment

- **NCCN guidelines**
  - PSA every 6-12 months for 5 years, then annually.
    DRE annually but may be omitted if undetectable PSA

- **NICE guidelines**
  - PSA 6 weeks after treatment, every 6 months for 2 years, and once a year thereafter.
    DRE no needed while the PSA remains at baseline levels.

- **EAU guidelines**
  - PSA may be the only test in cases with favourable pathology (<T3a, pN0, Gleason <8).
    Recurrence without PSA rise has only been proven for “undifferentiated” tumours.

- **No images** are required unless biochemical failure or recurrence is suspected
- PSA is expected to be **undetectable 6 weeks after surgery**. Persistent elevated PSA after 6 weeks may be due to residual cancer.

- PSA levels **fall slowly after RT** compared to RP (months/years). A **PSA nadir <0.5ng/mL** has been associated with favourable outcome after RT.
Definition of Biochemical Recurrence

PSA level for definition of treatment failure differs between RP and RT

- After Radical Prostatectomy:
  - PSA $\geq 0.2$ ng/mL with a second confirmatory level over 0.2ng/mL Measured 6-8 weeks after surgery (or later)

- After Radiotherapy:
  - Rise of 2 ng/mL above the post-treatment PSA nadir

Time from RP to biochemical recurrence is a significant risk factor for specific mortality.

Biochemical recurrence stratified by all comers vs early biochemical recurrence (within 3 years following surgery) vs late biochemical recurrence (>3 years following surgery).

Table 3. Estimate of the Risk of Prostate Cancer-Specific Survival After Biochemical Recurrence Following Radical Prostatectomy

<table>
<thead>
<tr>
<th>Time After Surgery</th>
<th>Recurrence &gt;3 y</th>
<th>Recurrence ≤3 y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gleason Score &lt;8</td>
<td>Gleason Score ≥8</td>
</tr>
<tr>
<td>5-y Estimate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥15.0</td>
<td>100 (98 to 100)</td>
<td>99 (96 to 99)</td>
</tr>
<tr>
<td>9.0-14.9</td>
<td>99 (70 to 100)</td>
<td>98 (75 to 100)</td>
</tr>
<tr>
<td>3.0-8.9</td>
<td>97 (81 to 100)</td>
<td>94 (74 to 99)</td>
</tr>
<tr>
<td>&lt;3.0</td>
<td>92 (70 to 98)</td>
<td>83 (62 to 96)</td>
</tr>
<tr>
<td>10-y Estimate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥15.0</td>
<td>98 (96 to 100)</td>
<td>96 (93 to 98)</td>
</tr>
<tr>
<td>9.0-14.9</td>
<td>95 (75 to 99)</td>
<td>90 (68 to 98)</td>
</tr>
<tr>
<td>3.0-8.9</td>
<td>84 (62 to 94)</td>
<td>68 (37 to 89)</td>
</tr>
<tr>
<td>&lt;3.0</td>
<td>59 (29 to 83)</td>
<td>30 (10 to 63)</td>
</tr>
</tbody>
</table>

Stephen J. Freedland et al. JAMA 2005
PSA doubling time - PSDT

- A measure of the exponential increase in PSA over time
- No standardisation of calculation
  - Number of PSA values used
  - Interval between PSA measures
    (p.e. 3 values in a 6 months period, 3 values from nadir to BR)
- Several calculation tools available online
Fifteen-year actuarial Kaplan-Meier prostate cancer–specific and all-cause estimated risk of death among patients with a prostate-specific antigen (PSA) recurrence after radical prostatectomy

A) All patients with PSA recurrence
(B) patients with a PSADT <3 months (lines superimposed)
(C) patients with a PSADT 3.0-8.9 months
(D) patients with a PSADT <9.0 -14.9 months
(E) patients with a PSADT ≥ 15 months

Stephen J. Freedland et al. JCO 2007;25:1765-1771
The natural history of metastatic progression in men with prostate-specific antigen recurrence after radical prostatectomy: long-term follow-up

Emmanuel S. Antonarakis, Zhaoyong Feng*, Bruce J. Trock*, Elizabeth B. Humphreys*, Michael A. Carducci, Alan W. Partin*, Patrick C. Walsh* and Mario A. Eisenberger

Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, and *Brady Urological Institute, Johns Hopkins University, Baltimore, MD, USA

### TABLE 3 MFS after PSA recurrence according to pathological Gleason score and PSA doubling time

<table>
<thead>
<tr>
<th>Pathological Gleason score 8–10</th>
<th>Pathological Gleason score 7</th>
<th>Pathological Gleason score 4–6</th>
<th>PSADT &lt;3 months</th>
<th>PSADT 3–9 months</th>
<th>PSADT 9–15 months</th>
<th>PSADT ≥15 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 122)</td>
<td>(n = 238)</td>
<td>(n = 88)</td>
<td>(n = 46)</td>
<td>(n = 106)</td>
<td>(n = 89)</td>
<td>(n = 152)</td>
</tr>
<tr>
<td>Median MFS, years (95% CI)</td>
<td>3 (3, 6)</td>
<td>11 (6, 17)</td>
<td>&gt;15 (4, &gt;15)</td>
<td>4 (2, 6)</td>
<td>13 (6, &gt;15)</td>
<td>15 (5, &gt;17)</td>
</tr>
<tr>
<td>Metastasis-free rate at 5 years, % (95% CI)</td>
<td>43 (32, 54)</td>
<td>71 (63, 78)</td>
<td>94 (66,98)</td>
<td>5 (1, 21)*</td>
<td>27 (16,39)</td>
<td>77 (63,88)</td>
</tr>
<tr>
<td>Metastasis-free rate at 10 years, % (95% CI)</td>
<td>19 (9, 33)</td>
<td>52 (41, 62)</td>
<td>94 (66,98)</td>
<td>N/A</td>
<td>7 (1,22)</td>
<td>51 (34,68)</td>
</tr>
</tbody>
</table>

*Last subject censored at 4 years. In each subgroup, the median MFS as well as the 5- and 10-year probabilities of MFS from the time of PSA recurrence are shown. n, number of men in each subgroup; N/A, not applicable.
Metastasis and Survival after Biochemical Recurrence post RP

LOW RISK:
PSA recurrence >3 years
PSADT >12 months
≤T3a
Gleason ≤7

HIGH RISK:
PSA recurrence <3 years
PSADT <3 months
T3b
Gleason ≥8
Metastasis and Survival after Biochemical Relapse post RT

LOW RISK:
PSA recurrence >3 years
PSADT >15 months
≤T3a
Gleason ≤7

HIGH RISK:
PSA recurrence <3 years
PSADT <3 months
T3b-T4
Gleason ≥8

Zumsteg et al, Eu Urol, 2015
Nomogram Predicting Prostate Cancer-specific Mortality for Men with Biochemical Recurrence After Radical Prostatectomy


EUROPEAN UROLOGY 67 (2015) 1160–1167

Points
- Age at Diagnosis:
  - 65 70 75 80
- Time to BCR, mo:
  - 4 6 8 10 12 14 16 18
- PSADT, mo:
  - 25 15 13 11 9 7 5 3 1
- PSA at BCR:
  - 0.2 0.4 0.6 0.8 1 2 3 4 5 6 7 8 9 10 15 20+
- Preoperative PSA:
  - 40 50 60 70 80 90 100
- Pathological Gleason Score:
  - 6 3+4 9
- Extraprostatic Extension:
  - ABSENT PRESENT
- Surgical Margins:
  - NEGATIVE POSITIVE
- Seminal Vesicle Invasion:
  - ABSENT PRESENT
- Lymph Nodes:
  - NEGATIVE

Total Points:
- 0 50 100 150 200 250 300 350 400 450

5-yr Prostate Cancer-specific Cumulative Incidence:
- 0.001 0.01 0.05 0.1 0.2 0.3 0.5 0.7 0.9

10-yr Prostate Cancer-specific Cumulative Incidence:
- 0.01 0.05 0.1 0.2 0.3 0.5 0.7 0.9

15-yr Prostate Cancer-specific Cumulative Incidence:
- 0.01 0.05 0.1 0.2 0.3 0.5 0.7 0.9
Management of Biochemical Failure

The best timing to start ADT remains unclear:

- PSADT, life expectancy, symptoms,…
  - Short PSADT and long life expectancy should consider ADT earlier
  - but men with PSADT <12 monts who are old are candidates for observation

- Discuss Intermittent ADT with patients
**Metastatic Castration Resistant Prostate Cancer (mCRPC)**

**Definition:**
- Castrate serum levels of testosterone (testosterone <50ng/dl or <1.7nmol/l)
- Three consecutive rises of PSA, 1 week apart, resulting in a 50% increase over the nadir with PSA >2.0ng/ml
  - If MAB: Antiandrogen withdrawal for at least 4 weeks (flutamide) or 6 weeks (bicalutamide)
- Radiographic progression (RECIST 1.1 and PCWG3 criteria)

**Prognosis and treatment decisions in clinical practice are based on:**
- Symptoms: tumour-related pain and asthenia
- Number and site of metastases
- Performance Status
- Tumour markers: **PSA level & PSA doubling time (PSADT)**
- Other biochemical parameters related to tumour-burden: Alkaline Phosphatase (AP), Lactate Dehydrogenase (LDH), Albumin

**There are not reliable and validated predictive markers of treatment benefit to help “precision medicine” in mCRPC….yet**
Monitoring mCRPC

- PSA should be **assessed by cycle** (3 or 4 weeks)

- PSA outcomes should be interpreted **within the context of a drug’s mechanism of action** and the anticipated timing of a potential favorable/unfavorable effect on PSA should be considered
  - Recognize that a favourable effect on PSA may be delayed for ≥12 weeks, even for a cytotoxic drug.
  - Ignore early rises (before 12 weeks) in determining PSA response
  - Monitor PSA by cycle but plan to continue through early rises for **a minimum of 12 weeks unless other evidence of progression**

- **Rising PSA is typically the first sign of tumour regrowth**, followed by worsening of the disease by imaging and the development of clinical symptoms.

- **An isolated PSA rise after an initial decline should not prompt treatment discontinuation**. Wait until **radiographic or clinical progression**
Outcome measure for clinical trials

For Control/Relieve/eliminate endpoints (response)

- Record the *% change from baseline at 8-9 or 12 weeks* depending on trial design.
  
  Separately, the **maximal change** (rise or fall) at any time (waterfall plot)

- Localized disease: report the % the proportion of patients who have undergone RP and achieved a nadir < 0.2 ng/mL and the % of primary RT treated patients who achieved a nadir less than 0.5 ng/ml

*Scher, JCO, 2016*
For delay/prevent endpoints (progression)

- After decline from baseline: record the time from start of therapy to first PSA increase that is $\geq 25\%$ and $\geq 2\text{ng/mL}$ above the nadir and which is confirmed by a second value $\geq 3\text{-}4$ weeks later.

- Recording the duration of PSA decline is of little value

- No decline from baseline: PSA progression $\geq 25\%$ and $\geq 2\text{ng/mL}$ increase from baseline beyond 12 weeks.

Scher, JCO, 2016
PSA progression may **not indicate a need to stop treatment**
Therapy may be continued if **progression by PSA or imaging is slow** and the disease-related **symptoms** that were present at baseline remain **controlled**: **No Longer Clinical Benefit**