VALUE AND ROLE OF PSA AS A TUMOR MARKER OF RESPONSE/RELAPSE

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DISCLOSURE SLIDE

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The Discovery of PSA

• In 1960, Flocks was the first to experiment with antigens in the prostate

• In 1971, Hara characterized γ-seminoproteina in the semen fluid. Although this antigen was later shown to be similar to PSA, the original publications were in Japanese and consequently not available to the English-speaking scientific community.

• In 1980, PSA was first measured quantitatively in the blood by Papsidero, and Stamey carried out the initial work on the clinical use of PSA as a marker of prostate cancer.

Model of PSA biosynthesis in prostate cancer

In PCa, loss of basal cells, basement membrane, and normal lumen architecture results in a decrease in the luminal processing of proPSA to active PSA, and active PSA to inactive PSA, with relative increases in bound PSA and proPSA in the serum.

Balk SP, J Clin Oncol. 2003
The use of PSA as a serum marker

- PSA is a sensitive and specific serum marker for prostate tissue.
- The absolute value of serum PSA is useful for determining the extent of prostate cancer and assessing the response to prostate cancer treatment.
Monitoring serum PSA after treatment of localized stage prostate cancer

Routine monitoring of PSA in patients with prostate cancer treated with localized therapies (radical prostatectomy, radiation therapy) is recommended.

PSA assessments

- **AUA**: no recommendation about the timing
- **NCCN**: every 6–12 months for the first 5 years after therapy, then annually
- **EAU**: 3, 6, and 12 months after treatment, then every 6 months through the third year, then annually
Definition of biochemical progression
After radical prostatectomy

• Biochemical recurrence is defined as a serum PSA ≥0.2 ng/mL, which is confirmed by a second determination with a PSA ≥0.2 ng/mL, according to AUA and EAU guidelines.

• If the serum PSA never falls to undetectable levels or is rising rapidly, systemic disease is more likely than residual disease in the prostatic bed (Partin AW, Urology. 1994).

• In contrast, if the PSA gradually rises after remaining undetectable for two or more years, an isolated local recurrence in the prostatic bed is more likely (Pound CR, JAMA. 1999).
Management of Rising or persistently elevated serum PSA following radical prostatectomy

- Evidence of metastatic disease
  - YES: Consideration of systemic therapy (ADT)
  - NO: Candidate for salvage therapy?
    - YES: Salvage RT
    - NO: Consideration of systemic therapy (ADT)
When is the Timing of salvage RT?

For men in whom a PSA recurrence has been documented and who are candidates for salvage therapy, **salvage RT should be initiated promptly.**

However, there are no randomized trials defining the optimal timing.
When is the Timing of salvage RT?

- 1106 patients treated with salvage-RT at the Mayo Clinic
- Patients with the pre-salvage-RT PSA ≤0.5 ng/mL were compared with patients with PSA >0.5 ng/mL.
- There was a significantly lower incidence of biochemical relapse at 10 years (60 versus 68 percent), distant metastases (13 versus 25 percent), and cancer-specific mortality (6 versus 13 percent).

When is the Timing of salvage RT?

Information from the pre-salvage-RT PSA was combined with the surgical Gleason score, presence or absence of extraprostatic extension, status of surgical margins, presence or absence of seminal vesicle invasion, prostate bed RT dose, and use of neoadjuvant or concurrent ADT to generate a nomogram that can be used to predict the likelihood of 5- and 10-year freedom from biochemical failure.

Definition of biochemical progression
After radiation therapy

- Phoenix criteria by a second consensus conference was held by ASTRO in 2005 (Roach M 3rd, Int J Radiat Oncol Biol Phys. 2006)

- PSA failure was defined as follows:
  - A PSA rise of 2 ng/mL or more above the nadir PSA is considered the standard definition for biochemical failure after external beam RT, regardless of whether or not a patient receives androgen deprivation therapy.
  - Although an increase of 2 ng/mL or more is defined as a biochemical relapse, repeat confirmation is generally carried out to rule out a PSA bounce.
  - The Phoenix criteria were initially developed for external beam radiation therapy only. However, the same definition is generally used for patients treated with brachytherapy.
Can be PSA Predict factor of radiation therapy success?

- The decline in serum PSA following RT is gradual and the mean time for the PSA to reach its nadir is 18 months or longer.
- The nadir of the serum PSA concentration is a strong indicator of treatment success following RT.

PSA bounce

- Serum PSA levels typically fall after RT and can then rise transiently, at a median of 12 to 18 months after treatment.
- PSA bounce can occur in the absence of recurrent disease and does not necessarily signify a treatment failure or constitute an indication for therapeutic intervention.
- There are no definitive methods to distinguish a PSA bounce from recurrent cancer.
PSA-only recurrence

**PSA**

PSA is a specific tumor marker following local therapy, the absence of a rise in PSA can provide significant psychological reassurance.

If PSA rise

Is a biochemical recurrence alone necessarily an indication for therapy?
PSA-only recurrence

- Patients with PSA recurrence after RP or primary RT have different risks of subsequent PCa-specific mortality.

- For both groups, men with a PSA doubling time (PSA DT) of <3 mo, stage T3b or higher, Gleason score 8–10, and time to BCR of <3 yr represent a subgroup with a high risk of developing metastases and dying from PCa.

Cornford P, Eur Urol. 2017
Management of PSA relapse

EAU-ESTRO-SIOG Guidelines second-line therapy after treatment with curative intent

<table>
<thead>
<tr>
<th>Local salvage treatment</th>
<th>LE</th>
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<tbody>
<tr>
<td><strong>BCR after RP</strong></td>
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<tr>
<td>Offer patients with a PSA rise from the undetectable range and favourable prognostic</td>
<td>3</td>
<td>B</td>
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<td>factors (pT3a or lower, time to BCR &gt;3 yr, PSA DT &gt;12 mo, Gleason score ≤7) surveillance</td>
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<td>and possibly delayed salvage radiotherapy.</td>
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<td>Treat patients with a PSA rise from the undetectable range with salvage RT. The total</td>
<td>2</td>
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<td>dose of salvage RT should be at least 66 Gy and should be given early (PSA &lt;0.5 ng/ml).</td>
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<tr>
<td><strong>BCR after RT</strong></td>
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<td>Treat highly selected patients with localised PCa and a histologically proven local</td>
<td>3</td>
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<td>recurrence with salvage RP.</td>
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<tr>
<td>Due to the increased rate of side effects, perform salvage RP in experienced centres.</td>
<td>3</td>
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<td>Offer or discuss high-intensity focused ultrasound, cryosurgical ablation, and salvage</td>
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<td>B</td>
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<tr>
<td>brachytherapy with patients without evidence of metastasis and with histologically</td>
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<td>proven local recurrence. Inform patients about the experimental nature of these</td>
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<td>approaches.</td>
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<td><strong>Systemic salvage treatment</strong></td>
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<tr>
<td>Do not routinely offer ADT to asymptomatic men with BCR.</td>
<td>3</td>
<td>A</td>
</tr>
<tr>
<td>Do not offer ADT to patients with a PSA DT &gt;12 mo.</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>If salvage ADT (after primary RT) is started, offer intermittent therapy to responding</td>
<td>1b</td>
<td>A</td>
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Cornford P, Eur Urol. 2017
Risk of metastases after PSA relapse

- The prolonged natural history following biochemical recurrence is illustrated by a series of 1973 men treated with radical prostatectomy at Johns Hopkins between 1981 and 2010 who developed a biochemical recurrence (PSA ≥0.2 ng/mL) following radical prostatectomy.

- Multivariate analysis found that independent factors associated with the development of metastases were the PSA doubling time (<3 versus 3 to 8.9 versus 9 to 14.9 versus ≥15 months) and the Gleason score from the radical prostatectomy specimen (≤6 versus 7 versus 8 to 10).

Antonarakis ES, BJU Int. 2012
A retrospective analysis of 2694 men with localized prostate cancer treated with external beam RT illustrate the natural history after treatment with external beam RT.

With a median follow-up of 83 months, 609 men experienced biochemical failure, based upon the Phoenix criteria.

Following biochemical failure, the median time to the development of metastases was 5.4 years, and the median time to prostate cancer-specific mortality was 10.5 years.

Factors associated with a worse prognosis included a higher initial clinical tumor stage, shorter PSA doubling time, Gleason score, and a shorter interval from initial treatment to biochemical recurrence.

Zumsteg ZS, Eur Urol. 2015
HT following biochemical recurrence

Role of Hormonal Treatment in Prostate Cancer Patients with Nonmetastatic Disease Recurrence After Local Curative Treatment: A Systematic Review

- Early HT cannot be recommended as the standard of care in the setting of biochemical or local disease recurrence.
- Early HT should be reserved for those at highest risk of disease progression, defined mainly by a short PSA DT at relapse (<6–12 mo) or a high initial Gleason score (>7), and a long life expectancy.

van den Bergh R.C., Eur Urol 2016
PSA Metrics in Advanced Prostate Cancer

PSA level as a surrogate end point for survival in Advanced Prostate Cancer

A PSA response defined as a decrease to ≤1 ng/ml and to between 1 and 10 ng/ml was associated with a hazard ratio of 0.30 and 0.61 for overall survival, respectively, as compared to the non-responders (PSA>10 ng/ml).

Collette L., Eur Urol 2003
PSA Nadir and Time-to-Nadir during ADT with metastatic prostate cancer

PSA nadir <0.2 ng ml⁻¹ and longer TTN (>9 months) during initial hormone therapy are the most important early predictors for survival in prostate cancer patients with bone metastasis.

Sasaki T, Prostate Cancer Prostatic Dis. 2011
Castration-Resistant Prostate Cancer

EAU Guidelines on prostate cancer

CRPC is defined as castrate serum testosterone<50 ng/dl or 1.7 nmol/l plus one of the following types of progression

Biochemical progression:
Three consecutive rises in PSA 1 week apart, resulting in two 50% increases over the nadir, and PSA >2 ng/ml

Radiologic progression:
The appearance of new lesions: either two or more new bone lesions on bone scan or a soft tissue lesion using the Response Evaluation Criteria in Solid Tumours
Significance of PSA in M0 CRPC patients

In men with CRPC and no detectable clinical metastases, Baseline PSA level, PSA velocity, and PSA DT have been associated with time to first bone metastasis, bone metastasis-free survival, and OS.
When is the Timing of evaluation for metastatic disease?

RADAR group suggestion
A consensus statement by the Prostate Cancer Radiographic Assessments for Detection of Advanced Recurrence

- asymptomatic
  - PSA reached 2 ng/ml
    - bone scan
      - repeated when PSA reached 5 ng/ml

Crawford E.D., Urology 2014
PSA Doubling Time (PSADT) in CRPC Patients

For patients who have progressed to CRPC after ADT, more rapid PSADT before docetaxel chemotherapy is a significant independent risk factor for death.


Early PSA rise after chemotherapy

**PSA flare:**
PSA rise that occurs after initiation of taxane therapy.
PSA flare occurs in about 15% of mCRPC patients receiving Docetaxel

Should we discontinue treatment or not?

Retrospective studies showed flare is not associated with adverse outcomes and can therefore be disregarded

*Nelius T., Prostate 2009*
PSA flare in patients treated with Cabazitaxel

PFS and OS in patients with PSA flare were not significantly different from those in patients with immediate PSA decreases.

Prostate cancer without PSA rise

• Neuroendocrine differentiation (NED) has been observed in prostate cancer.

• NEPC may not be associated with significant serum elevation of PSA levels as Pca.

• NEPC patients present with distant metastasis when they are diagnosed.


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<tr>
<th>Neuroendocrine markers</th>
<th>Commonly used in clinical practice</th>
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<td>Chromogranin</td>
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<td>Synaptophysin</td>
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<td>Neuron specific enolase</td>
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<td>CD56</td>
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