BIO CHEMICAL RECURRENCE IN PROSTATE CANCER

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Pre PSA era

Recurrences after definitive therapy defined by:

- Clinically palpable pelvic mass
- Metastatic disease
- Radiological studies
Post Tmt. PSA

- PSA is widely used for screening, diagnosing, determining prognosis, and selecting the appropriate treatment for men with prostate cancer.
- After treatment, PSA is used to determine the effectiveness of treatment.
- Biochemical recurrences can now be detected many years before development of clinically evident disease.
Biochemical recurrence

- BCR is defined by a rise in serum PSA level or persistently detectable PSA level following definitive Rx.
- First evidence of treatment failure
- Occurs commonly in isolation without any objective clinical findings.
- BCR definitions vary depending on the primary treatment modality
Biochemical recurrence

- Incidence varies from 30 – 40% of patients who receive localized therapy.
- Management represents a diagnostic and therapeutic dilemma.
- The benefits of further therapy must be balanced against the potential for tmt. related sequelae over a period of time.
- Therefore it is difficult to select when to treat these pts.
PSA estimation

- Standard assays
- Ultra sensitive PSA measurements detecting levels of 0.0001 to 0.04 ng/ml. providing a lead time of detection of 1 to 2 years over standard assays.
- It is important to mention type of assay and the minimal detectable level
- Serial PSA measurements must be performed by the same lab for consistency
Post RT PSA values

- Unlike surgery, prostate gland is left in situ after RT
- Decrease in PSA depends on effect of RT both on normal and cancerous prostate tissue
- PSA levels decrease slowly unlike surgery
- PSA nadir values achieved as late as 18 months post RT
- Also depends on type of RT: EXRT vs BT
PSA bounce

- Transient increase of PSA during radiation therapy
- PSA fluctuations are common during the follow up period post RT.
- 35% of patients have PSA bounce upto a mean period of 18 months post RT.
- Important to note that PSA levels may rise above nadir levels but ALSO fall to or below nadir levels.
PSA values after tmt.

- Reports from the early 1990s tended to emphasize the need for normal values (4.0 ng/mL) or other threshold values such as 2 or 1 ng/mL.
- This lack of standardization made it impossible to compare the results from different institutions.
ASTRO consensus defn.

- Need for a standard definition that allowed radiotherapy series from different institutions to be compared.
- To be useful and relevant to everyday clinical practice
- In 1994 the Board of ASTRO formed a committee to develop a standard definition for PSA failure after external beam radiotherapy (EBRT).
- Thus was born the ASTRO Consensus Definition
ASTRO Consensus Definition

- PSA failure: occurring after three consecutive PSA rises after a nadir

- Date of failure: the point halfway between the nadir date and the first rise or any rise great enough to provoke initiation of salvage therapy.

- PSA determinations be obtained at 3 to 4 month intervals during the first 2 years after the completion of radiation therapy, and every 6 months thereafter.
ASTRO Consensus Definition

- Biochemical failure is not justification to initiate additional treatment. *It is not equivalent to clinical failure.*
- It is an appropriate early endpoint for clinical trials.
- No definition of PSA failure has, as yet, been shown to be a surrogate for clinical progression or survival.
These conclusions reflected the desire for recommendations about therapeutic interventions to be evidence based.

They also left open the possibility that “PSA failure” might in some cases be a clinically irrelevant endpoint.
Backdating seriously biases the Kaplan-Meier estimates of event-free survival.

Definition was not linked to clinical progression, survival, or therapeutic interventions.

Not developed using data of hormonal therapy or brachytherapy, but this definition came to be applied in both of these settings as well.

Also applied to patients treated with nonradiation-based approaches such as radical prostatectomy and cryosurgery.

Phoenix consensus

- To address the shortcomings of the ASTRO Consensus definition, a second Consensus Conference was held on January 2005 in Phoenix, Arizona to formally consider replacing or revising the ASTRO Consensus definition.

- This conference was jointly sponsored by ASTRO and the Radiation Therapy Oncology Group (RTOG).

- The definitions proposed are to define success or failure in the context of a population, not an individual.
Caution for interpretation

- Defining PSA/biochemical success for an individual vs. a population are separate questions

- Individual: guided by clinical judgment.

- Population: a computer program can be written to calculate automatically the disease-free status for a large number of patients.

Phoenix consensus

- recommended that a rise by 2 ng/mL or more above the nadir PSA (defined as the lowest PSA achieved) be considered as the current standard definition for biochemical failure after radiotherapy with or without short-term hormonal therapy

- Also called **nadir +2 definition**.

- The date of failure was “at call” and not backdated.
Natural history of progression

- Indolent course of disease after BCR
- Median time to progression was 8 years and death approx. 5 years later. (RP gp.)*
- PSADT, Gleason's score and time to PSA recurrence were significant predictors of clinical failure
- Shorter PSADT (< 6 months) and higher PSAV associated with progression to systemic disease

*(Pound et al : JAMA 1999;281:1591-7)*
Diagnostic evaluation of BCR

- DRE: usually inconclusive
- Biopsy.
- Bone Scan. (higher +ve if PSA is high)
- PET scan
Conclusions

- BCR after local therapy occurs in approx. 40% of pts.
- Risks and benefits of further therapies to be assessed
- Time to recurrence, PSADT, PSA kinetics, Gleasons score may help in deciding therapies.
- ASTRO AND Phoenix definitions yet to be fully validated in clinical settings.