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 levles 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 off PSA failure has, as yet, been shown to be a surrogate for clinical progression or survival.

ASTRO Consensus Definition

- 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.

MACK ROACH III et al, IJROBP, Vol. 65, No. 4, pp. 965–974, 2006

ASTRO Consensus Definition
Pitfalls

- 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 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

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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.

MACK ROACH III et al, IJROBP, Vol. 65, No. 4, pp. 965–974, 2006

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.