Βιοχημική υποτροπή σε ασθενή με καρκίνο του προστάτη:

Θα νικήσουμε τον καρκίνο, θα χάσουμε τον ασθενή!

Διονύσης Μητρόπουλος
Καθηγητής Ουρολογίας
Ιατρική Σχολή Πανεπιστημίου

Επιθετικοί θεραπευτικοί χειρισμοί σε ασθενείς με καρκίνο του προστάτη και ιοχημική υποτροπή:

Θα νικήσουμε (:) τον

Βιοχημική υποτροπή μετά από τί;

- Ριζική προστατεκτομή
- Ακτινοθεραπεία
- Ανδρογονικό αποκλεισμό
  - ✓ παρουσία μεταστάσεων
  - ✓ απουσία μεταστάσεων

Βιοχημική υποτροπή μετά από ριζική προστατεκτομή

Ορισμός (EAU guidelines 2012):
PSA > 0.2 ng/ml επιβεβαιωμένο σε δύο συνεχείς μετρήσεις

1&5 Treatment of PSA-only recurrences

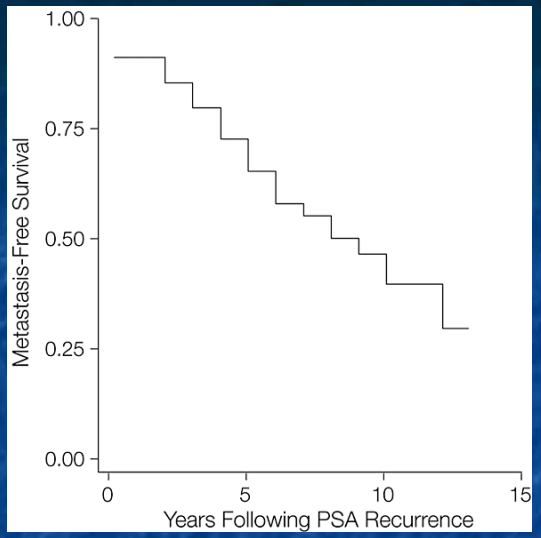
The timing and mode of treatment of PSA-only recurrence after RP or radiation therapy remains controversial.

After RRP observation, the therapeutic options are:

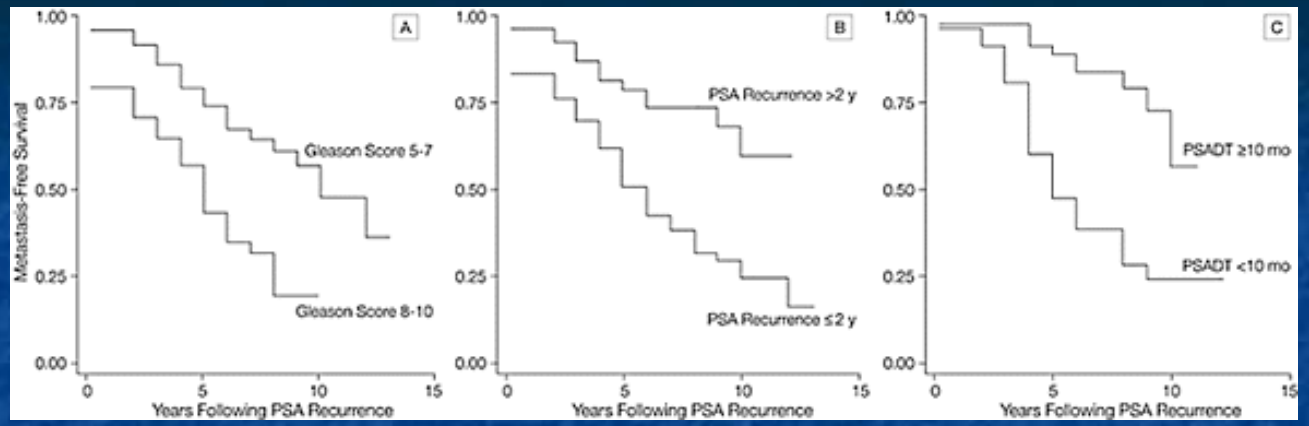
- radiation therapy to the prostatic bed;
- (complete) androgen blockade (CAB);
- intermittent androgen deprivation (IAD);
- combination of antiandrogens with 5-α-reductase inhibitors;
- early chemohormonal approaches.

Η υποτροπή του PSA μπορεί να προηγηθεί των μεταστάσεων γιά χρόνια

Οι ασθενείς με υποτροπή του PSA μετά από ριζική προστατεκτομή έχουν μιά μακρά πορεία μέχρι να σημειωθεί θάνατος λόγω της νόσου



Actuarial Likelihood of Metastasis-Free Survival in 304 Men With Prostate-Specific Antigen (PSA) Elevation After Radical Prostectomy.



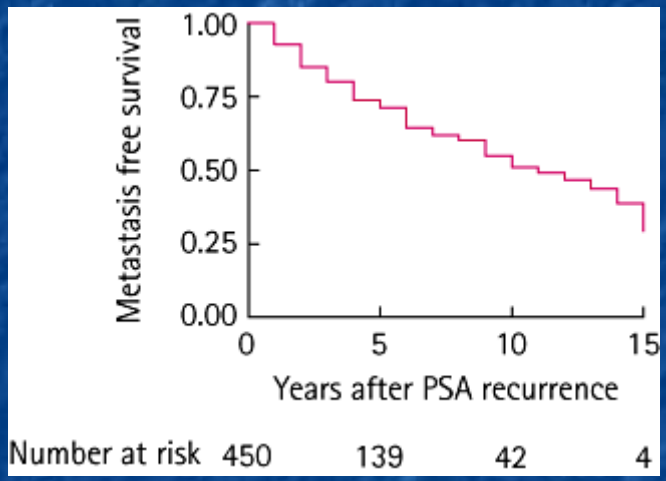
Actuarial Likelihood of Metastasis-Free Survival in 304 Men With Prostate-Specific (PSA) Antigen Elevation After Radical Prostatectomy A, Based on Gleason scores in the radical prostatectomy specimen (P<.001).

Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC: Natural history of progression after PSA elevation after radical prostatectomy JAMA 1999; 281:1591

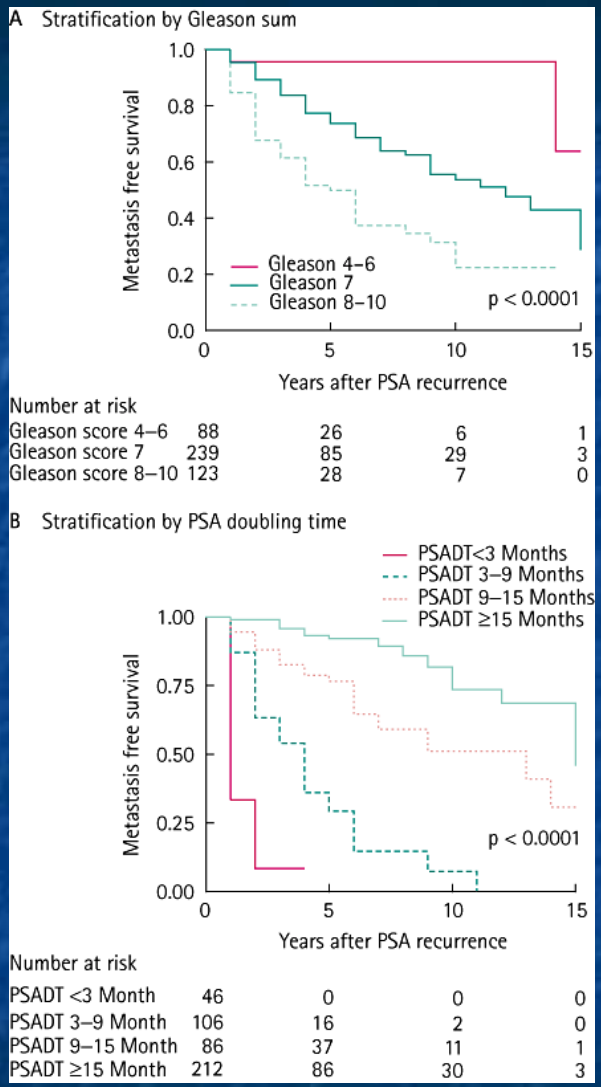
BJUI

The natural history of metastatic progression in men with prostate-specific antigen recurrence after radical prostatectomy: long-term follow-up

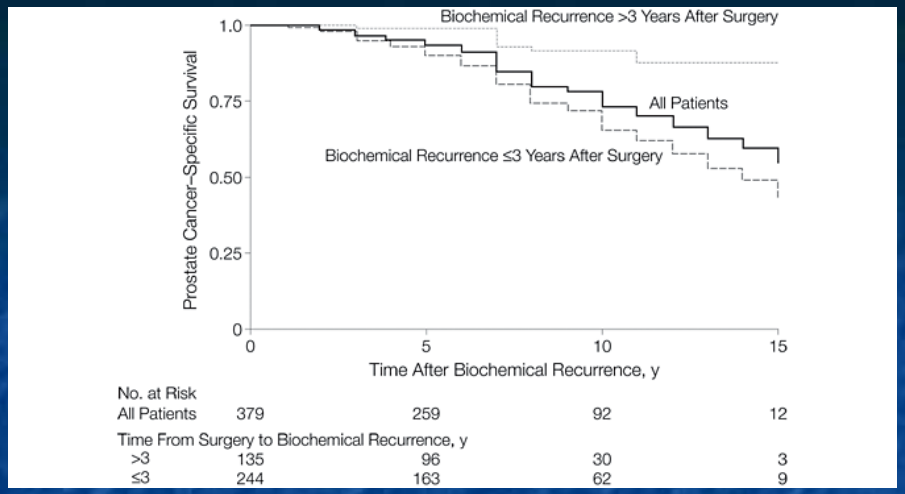
Emmanuel S. Antonarakis, Zhaoyong Feng*, Bruce J. Trock*, Elizabeth B. Humphreys*, Michael A. Carducci, Alan W. Partin*, Patrick C. Walsh* and Mario A. Eisenberger



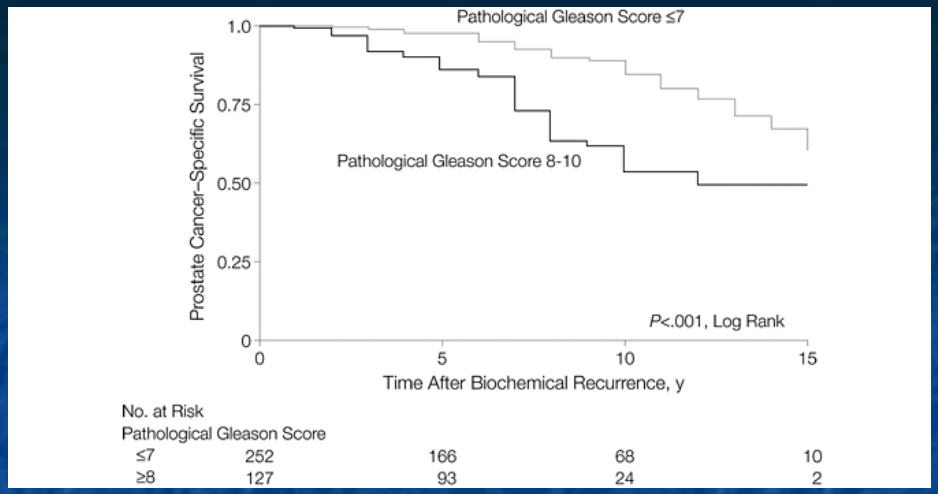
The natural history of metastatic progression in men with prostate-specific antigen recurrence after radical prostatectomy: long-term follow-up



Kaplan–Meier estimates of MFS, stratified by (a) pathological Gleason sum and (b) PSA doubling time.



Fifteen-Year Actuarial Kaplan-Meier Prostate Cancer-Specific Survival Curves by Time of Recurrence Biochemical recurrence stratified by all comers vs early biochemical recurrence (within 3 years following surgery) vs late biochemical recurrence (>3 years following surgery).



Fifteen-Year Actuarial Kaplan-Meier Prostate Cancer-Specific Survival Curves by Gleason Score Biochemical recurrence segregated by pathological Gleason score among patients who experienced a biochemical recurrence.

On multivariable analysis, pathological Gleason score (hazard ratio [HR], 2.33; 95% CI, 1.38-3.95; P = .002), time from surgery to biochemical recurrence (HR, 2.55; 95% CI, 1.15-5.62; P = .02), and PSADT as a continuous variable (HR, 0.86; 95% CI, 0.81-0.91; P<.001) were the only significant independent risk factors for time to prostate cancer-specific mortality following biochemical recurrence.

Freedland SJ, Humphreys EB, Mangold LA, Eisenberger M, Dorey FJ, Walsh PC et al. Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. JAMA 2005; 294:433

EUROPEAN UROLOGY 51 (2007) 1175–1184

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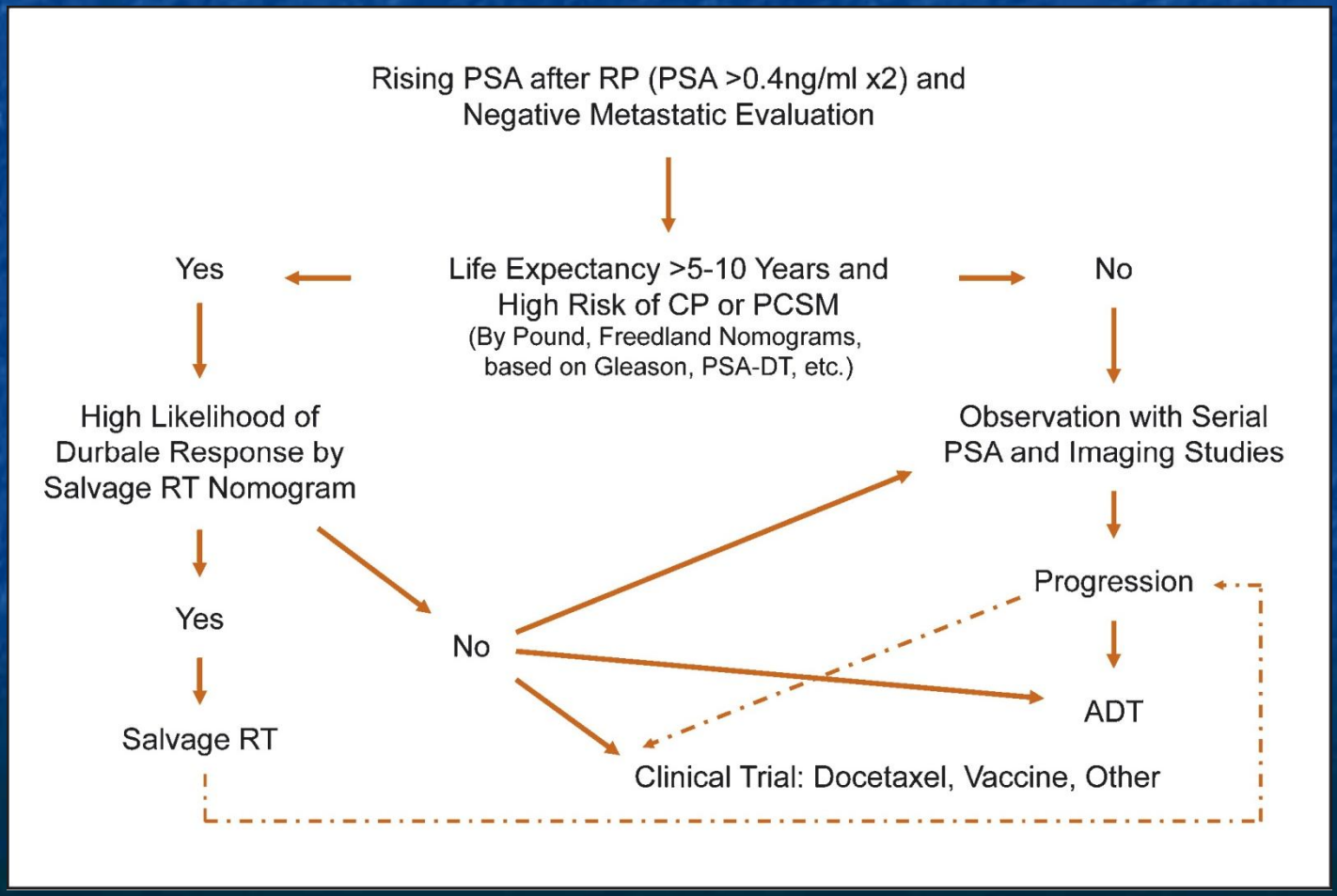
journal homepage: www.europeanurology.com

European Association of Urology

Review – Prostate Cancer

Natural History of Biochemical Recurrence after Radical Prostatectomy: Risk Assessment for Secondary Therapy

Matthew N. Simmons, Andrew J. Stephenson, Eric A. Klein **



Guidelines on

Prostate Cancer

A. Heidenreich (chairman), P.J. Bastian, J. Bellmunt, M. Bolla, S. Joniau, M.D. Mason, V. Matveev, N. Mottet, T.H. van der Kwast, T. Wiegel, F. Zattoni

18.5.4 *Management of PSA relapse after RP*

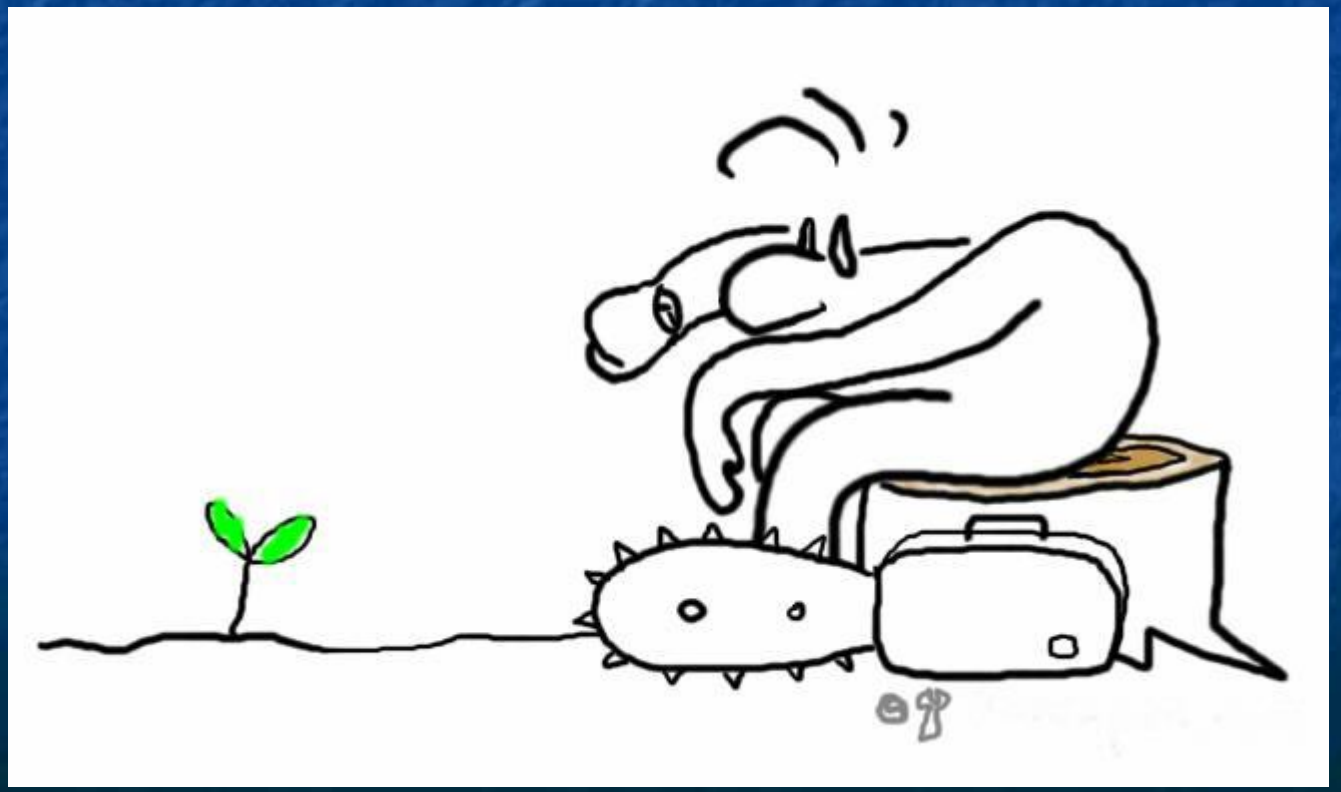
Recommendations	GR
Local recurrences are best treated by salvage radiation therapy with 64-66 Gy at a PSA serum level < 0.5 ng/mL.	B
For patients with presumed local recurrence who are too unfit or unwilling to undergo radiation therapy, expectant management can be offered.	B
PSA recurrence indicative of systemic relapse is best treated by early ADT resulting in decreased frequency of clinical metastases.	B
Luteinising hormone releasing hormone (LHRH) analogues/antagonists/orchiectomy or bicalutamide, 150 mg/day, can both be used when there is an indication for hormonal therapy.	A

It has been suggested that men with slowly progressing disease, even though still at risk of systemic progression, may not benefit from salvage radiotherapy because they have a low risk of development of lethal PCa. Certainly, longer follow-up is needed to answer this question. However, more data are required from prospective randomised trials.

Although patients with post-operative PSA recurrence often undergo ADT before evidence of metastatic disease, the benefit of this approach is uncertain.
Evidence from well-designed, prospective, randomised studies is needed before the use of early hormonal therapy can be advocated in clinical practice.

Radiation therapy after radical prostatectomy: patience is a virtue !

KM Slawin, Rev Urol 2002



Βιοχημική υποτροπή μετά από ακτινοθεραπεία

Ορισμός (EAU guidelines 2012):
PSA > +2 ng/ml της τιμής ναδίρ

18.6 Management of PSA failures after radiation therapy

In a recent review of the data of the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) comprising 2336 patients with PCa, Grossfeld et al. (98) demonstrated that 92% of patients initially irradiated received ADT for secondary treatment of PSA progression. In the absence of salvage procedures, the mean time interval from biochemical to clinical progression is approximately 3 years. Therapeutic options in these patients are ADT or local procedures, such as salvage RP, cryotherapy and interstitial radiation therapy

18.6.6 *Guidelines for the management of PSA relapse after radiation therapy*

Recommendations	GR
Local recurrences may be treated by salvage RP in carefully selected patients, who presumably demonstrate organ-confined disease, i.e. PSA <1.0 ng/mL, PSA DT > 12 months, low-dose-radiation brachytherapy, biopsy Gleason score < 7.	B
Cryosurgical ablation of the prostate and interstitial brachytherapy are alternative procedures in patients not suitable for surgery.	B
High-intensity-focused ultrasound may be an alternative option. However, patients must be informed about the experimental nature of this treatment modality due to the short follow-up periods reported.	
In patients with presumed systemic relapse, ADT may be offered.	B

18.6.1.1 Summary of salvage RP

In general, salvage RP should be considered only in patients with a low co-morbidity, a life expectancy of at least 10 years, an organ-confined PCa < T2, Gleason grade < 7, and pre-surgical PSA < 10 ng/mL. In all other patients, accurate pre-surgical staging is not easily defined after radiation therapy, increasing the risk not only for anterior and total extirpation procedures, but also for associated complications and decreased long-term disease-specific survival.

18.6.2 Salvage cryosurgical ablation of the prostate (CSAP) for radiation failures

Salvage cryosurgery has been proposed as an alternative to salvage RP because it has the potential to have less morbidity but equal efficacy. However, there have only been a very few studies, with disappointing results.

18.6.3 Salvage brachytherapy for radiation failures

The experience with salvage brachytherapy for radiation failures is very limited. In conclusion, freedom from biochemical failure after salvage iodine-125 implantation for locally recurrent Pca after radiotherapy is limited, and both genitourinary and gastrointestinal toxicity occur frequently.

18.6.5 High-intensity focused ultrasound (HIFU)

The experience of HIFU for the treatment of locally recurrent PCa after radiation therapy is limited to a few retrospective studies. Urinary incontinence and the development of rectourethral fistula are the most significant complications of salvage HIFU therapy

18.6.4 Observation

Patients with signs of local recurrence only (i.e. low-risk patients with late recurrence and a slow PSA rise), who are not opting for second-line curative options, are best managed by observation alone. A retrospective cohort analysis of hormonal therapy versus watchful waiting (WW) in 248 men with PSA failure after radiotherapy showed no advantage for hormonal therapy in the subgroup of men with a PSA DT of > 12 months after radiotherapy. The 5-year metastasis-free survival rate was 88% with hormonal therapy versus 92% with WW (p = 0.74)

(Pinover WH, Horwitz EM, Hanlon AL, et al. Validation of a treatment policy for patients with prostate specific antigen failure after three-dimensional conformal prostate radiation therapy. Cancer 2003 Feb;97(4):1127-33)

Βιοχημική υποτροπή μετά από ορμονικό αποκλεισμό

Ορισμός (EAU guidelines 2012):

Table 22: Definition of CRPC

Castrate serum levels of testosterone (testosterone < 50 ng/dL or < 1.7 nmol/L)
Three consecutive rises of PSA, 1 week apart, resulting in two 50% increases over the nadir, with a PSA > 2 ng/mL
Anti-androgen withdrawal for at least 4 weeks for flutamide and for at least 6 weeks for bicalutamide*
PSA progression, despite consecutive hormonal manipulations†

* *Either anti-androgen withdrawal or one secondary hormonal manipulation should have been done in order to fulfil the criteria for CRPC if patients have been treated with antiandrogens in the context of maximum androgen blockade or step up therapy following PSA progression after failure of LHRH treatment.*

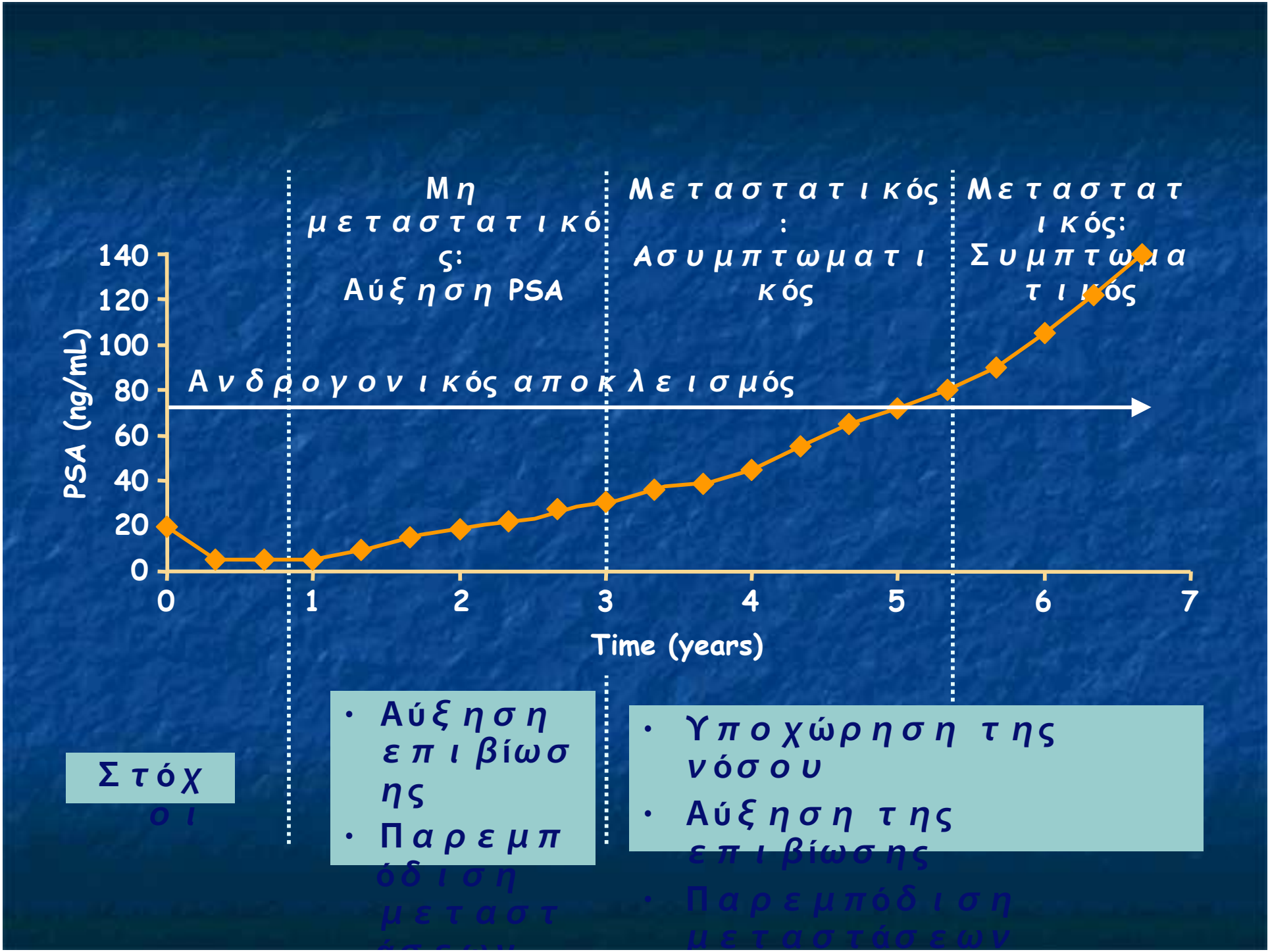
† *Progression of osseous lesions: progression or appearance of two or more lesions on bone scan or soft tissue lesions using RECIST (Response Evaluation Criteria in Solid Tumours) and with nodes ≥ 2 cm in diameter.*

19.2 Definition of relapsing prostate cancer after castration

The previously term, 'hormone-refractory prostate cancer' referred to a very heterogeneous disease. It included different patient cohorts with significantly different median survival times (Table 21).

Table 21: Estimated natural mean survival of patients with HRPC presenting with different clinical scenarios

Patient characteristics	Estimated mean survival
Asymptomatic PSA	
No metastases	20-36 months
Minimal metastases	18-27 months
Extensive metastases	9-12 months
Symptomatic PSA	
Minimal metastases	14-16 months
Extensive metastases	9-12 months


Μη μεταστατικός: Αύξηση PSA
Μεταστατικός: Ασυμπτωματικός
Μεταστατικός: Συμπτωματικός
Ανδρογονικός αποκλεισμός
PSA (ng/mL)
140
120
100
80
60
40
20
0
0
1
2
3
4
5
6
7
Time (years)
Στόχοι
• Αύξηση επιβίωσης
• Παρεμπόδιση μεταστ
• Υποχώρηση της νόσου
• Αύξηση της επιβίωσης
• Παρεμπόδιση μεταστάσεων

PSA: Promoting Stress and Anxiety

ELSEVIER

SPECIAL COMMUNICATION
CME ARTICLE

PSAdynia AND OTHER PSA-RELATED SYNDROMES: A NEW EPIDEMIC—A CASE HISTORY AND TAXONOMY

LAURENCE H. KLOTZ

UROLOGY *50* (6), *1997*

1. PSADYNIA [p-s-a-dineea]

A state of emotional or physical distress due to an elevated prostate-specific antigen (PSA) level. This condition usually occurs in the PSA-affected individual (proband); however, it is highly contagious and may infect his spouse or immediate family. Frequently an entire extended family may suffer from the condition, concurrently or asynchronously. The acute phase is common and more easily treated; the chronic phase may persist for years. It is often an exasperating condition for both the affected individuals and the treating physician. PSAdynia clearly has an adverse effect on quality of life; some have suggested that longevity may be affected, but this remains unproven.

There are two distinct subtypes of PSAdynia: (1) PSAdyniaPIB (PSAdynia: Prostate Is Benign) and (2) PSAdyniaCAP (PSAdynia: Cancer of the Prostate). The taxonomy is further divided as follows:

1. PSAdyniaBiP (PSAdynia: Benign Prostate).
   - 1.1 PSAdyniaBiP:0 (Biopsy pending)
   - 1.2 PSAdyniaBiP:1 (1st biopsy negative)
   - 1.3 PSAdyniaBiP:2 (2nd biopsy negative)
   - 1.N PSAdyniaPIB:N (Nth biopsy negative)
2. PSAdyniaCAP (PSAdynia: Cancer of the Prostate).
   - 2.1 PSAdyniaCAP:WW (High PSA on a watchful waiting protocol)
   - 2.2 PSAdyniaCAP:XRT (Rising PSA after radiation)
   - 2.3 PSAdyniaCAP:RP (Rising PSA after prostatectomy). The main distinguishing feature of PSAdyniaCAP:RP is the minimal level of PSA (ie, >0.0001 ng/mL) which has been reported to induce the clinical features of PSAdynia.
   - 2.4 PSAdyniaCAP:AA (Rising PSA after androgen ablation)

8. PSADIC [p-sadic]

Restricted to health practitioners (particularly urologists) who have an interest in prostate cancer. A sense that the entire spectrum of intellectual development in their field has been reduced to various aspects of PSA. Case reports only to date; but concerns exist that this may be the "tip of the iceberg." Recommended treatment: Attendance at a 3-day seminar on urolithiasis or erectile dysfunction.

CONCLUSIONS

This condition has reached epidemic proportions. Only a concerted effort by the scientific community to better understand the protean clinical manifestations, natural history, and mode of contagion of PSAdynia will lead to improved treatment and quality of life.

Η αποτελεσματικότητα της όποιας επικουρικής θεραπείας θα πρέπει να «ζυγίζεται» σε σχέση:

- με τις παρενέργειες
- την επίδραση στη ποιότητα ζωής (QoL)

- την σχέση κόστους-αποτελεσματικότητας ;


PUMA
The Cat That Came Back
Can Nokia Grow Again?
Why We Should Thank China
FORTUNE
[SPECIAL INVESTIGATION]
WHY WE'RE LOSING THE WAR ON CANCER
(AND HOW TO WIN IT)
By Clifton Leaf
EUROPE EDITION