Βιοχημική υποτροπή σε ασθενή με καρκίνο του προστάτη:

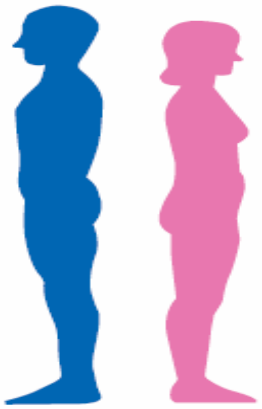
Ανδρέας Σκολαρίκος
Επίκουρος Καθηγητής Ουρολογίας
Ιατρική Σχολή Πανεπιστημίου Αθηνών


Ογκολόγοι
Ακτινοθεραπευτές
Ουρολόγοι

Νέες Περιπτώσεις και Θάνατοι *2010*

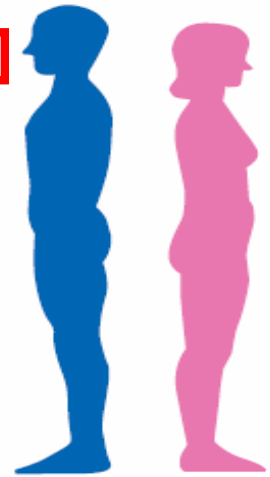
Estimated New Cases*

Males			Females		
Prostate	217,730	28%	Breast	207,090	28%
Lung & bronchus	116,750	15%	Lung & bronchus	105,770	14%
Colon & rectum	72,090	9%	Colon & rectum	70,480	10%
Urinary bladder	52,760	7%	Uterine corpus	43,470	6%
Melanoma of the skin	38,870	5%	Thyroid	33,930	5%
Non-Hodgkin lymphoma	35,380	4%	Non-Hodgkin lymphoma	30,160	4%
Kidney & renal pelvis	35,370	4%	Melanoma of the skin	29,260	4%
Oral cavity & pharynx	25,420	3%	Kidney & renal pelvis	22,870	3%
Leukemia	24,690	3%	Ovary	21,880	3%
Pancreas	21,370	3%	Pancreas	21,770	3%
All Sites	**789,620**	**100%**	**All Sites**	**739,940**	**100%**



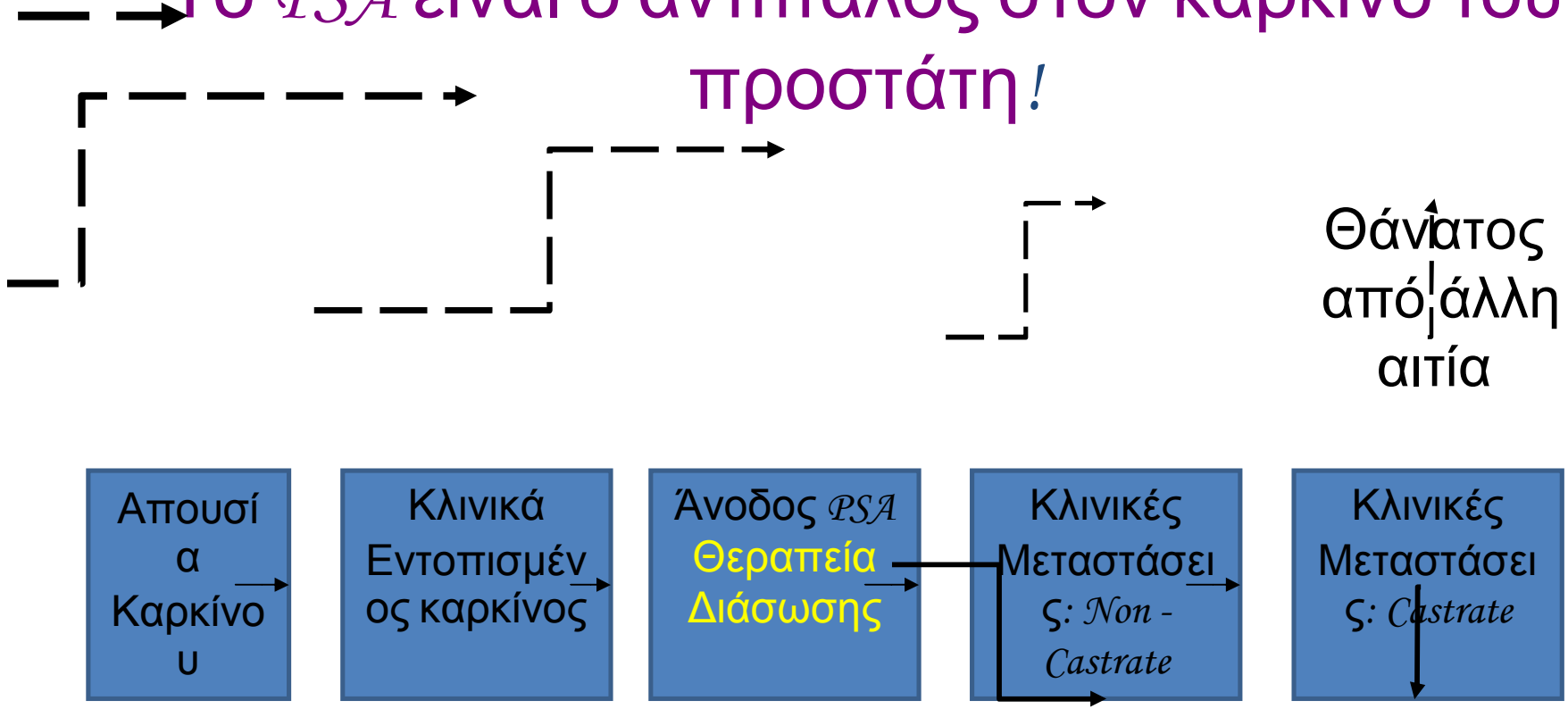
Estimated Deaths

Males			Females		
Lung & bronchus	86,220	29%	Lung & bronchus	71,080	26%
Prostate	32,050	11%	Breast	39,840	15%
Colon & rectum	26,580	9%	Colon & rectum	24,790	9%
Pancreas	18,770	6%	Pancreas	18,030	7%
Liver & intrahepatic bile duct	12,720	4%	Ovary	13,850	5%
Leukemia	12,660	4%	Non-Hodgkin lymphoma	9,500	4%
Esophagus	11,650	4%	Leukemia	9,180	3%
Non-Hodgkin lymphoma	10,710	4%	Uterine Corpus	7,950	3%
Urinary bladder	10,410	3%	Liver & intrahepatic bile duct	6,190	2%
Kidney & renal pelvis	8,210	3%	Brain & other nervous system	5,720	2%
All Sites	**299,200**	**100%**	**All Sites**	**270,290**	**100%**



Jemal, A., Siegel, R., Xu, J., Ward, E., CA Cancer J Clin 2010;60;277-300; Cancer

Το *PSA* είναι ο αντίπαλος στον καρκίνο του προστάτη!



Μοντέλο Προόδου του Καρκίνου του Προστάτη

Βιοχημική υποτροπή μετά από τί;

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

Βιοχημική υποτροπή

- Θεραπεία : Ναι ή Όχι ;
- Τοπική ή Συστηματική Θεραπεία;

Βιοχημική υποτροπή

- Φυσική Πορεία της νόσου επί βιοχημικής υποτροπής

- Οι διαγνωστικές και θεραπευτικές παρεμβάσεις έχουν θέση μόνο επί θετικού θεραπευτικού αποτελέσματος

Πως ορίζεται το τελευταίο;

- *OS, CSS, FFBF, QOL, Delay of complications;*
- Ποιος είναι ο ρόλος της ηλικίας ή του προσδόκιμου επιβίωσης κατά την υποτροπή;
- Ποιος είναι ο ρόλος των επιπλοκών της θεραπείας;

Βιοχημική Υποτροπή - Ορισμοί

- ***RP:*** *PSA > 0.2 ng/ml* επιβεβαιωμένο σε δύο συνεχείς μετρήσεις *(EAU guidelines 2012)*
- ***RT:*** *3* **διαδοχικές αυξήσεις** του *PSA* πάνω από το ***nadir*** *(ASTRO ,AUA)* ή αύξηση *PSA* ***2ng/ml*** **ή περισσότερο** πάνω από το ***nadir*** *(RTOG-ASTRO Phoenix Conference, EAU)*
- ***CRPC:*** Επίπεδα τεστοστερόνης ευνουχισμού *(<50ng/dl* ή *1.7nmol/L),* **τρείς συνεχόμενες αυξήσεις του *PSA,*** ανά εβδομάδα, με δύο αυξήσεις *>50%* από το ναδίρ, με *PSA>2ng/ml,* Απόσυρση των αντιανδρογόνων για τουλάχιστον *4* εβδομάδες για τη φλουταμίδη και *6* εβδομάδες για την βικαλουταμίδη, Πρόοδο του *PSA* παρόλο τους συνεχιζόμενους ορμονικούς χειρισμούς

Μεταστατική νόσος ή Τοπική υποτροπή;

- *80%* **για M+**
- **Υποτροπή** < *1***έτος**
- *PSADT 4-6mt*
- *GS 8-10*
- *pT3b, pTxpN1*

- *EAU Guidelines 2012*

80% **τοπική**

Υποτροπή >*3***έτη**

PSADT >11mt

GS <6

*pT3***α**,*pN0*

RP

Outline Level
– Fifth Outline Level

EAU Guidelines 2012

Μεταστατική νόσος ή βιοχημική υποτροπή;

- **Τοπική**
- Θετική βιοψία προστάτη *18* μήνες μετά την ακτινοβόληση +
- Συνοδός αύξηση του *PSA (*καθυστερημένη και αργά αυξανόμενη*)* αν και η βιοψία ενδείκνυται μόνο όταν έπεται *salvage* τοπική θεραπεία +
- Απουσία μεταστατικής νόσου σε *CT, MRI* ή σπινθηρογράφημα οστών

el

RT · *EAU Guidelines 2012*

Outline

Level

Μεταστατική Νόσος

Πρώιμη ή Καθυστερημένη ορμονική θεραπεία;

- *VACURG:* κανένα πλεονέκτημα *OS*
- *MRC :* καθυστέρηση εμφάνισης μεταστάσεων, μείωση οστικών επιπλοκών (≥T*3*, ασυμπτωματική μεταστατική νόσος)
- ***Cochrane:*** Αυξάνει *10y OS, CSS, PFS (VACURG -1 , VACURG-II, MRC, ECOG* σε ασθενείς με ιστολογική λεμφαδενική συμμετοχή μετά *RP)*

EAU οδηγίες

18.7 Guidelines for second-line therapy after treatment with curative intent

Recommendations	GR
Presumed local failure after radical prostatectomy	
Patients with presumed local failure only may be candidates for salvage radiotherapy. This should be given with at least 64 Gy and preferably before PSA has risen above 0.5 ng/mL.	B
Other patients are best offered a period of watchful waiting (active monitoring), with possible hormonal therapy later on.	
Presumed local failure after radiotherapy	
Selected patients may be candidates for salvage RP and patients should be informed about the higher risk of complications, e.g. incontinence and erectile dysfunction.	C
Salvage RP should only be performed in experienced centres.	
Other patients are best offered a period of watchful waiting (active monitoring), with possible hormonal therapy later on.	
Presumed distant failure	
There is some evidence that early hormonal therapy may be of benefit in +/- local failure, delaying progression, and possibly achieving a survival benefit in comparison with delayed therapy. The results are not without controversy.	B
Local therapy is not recommended except for palliative reasons.	

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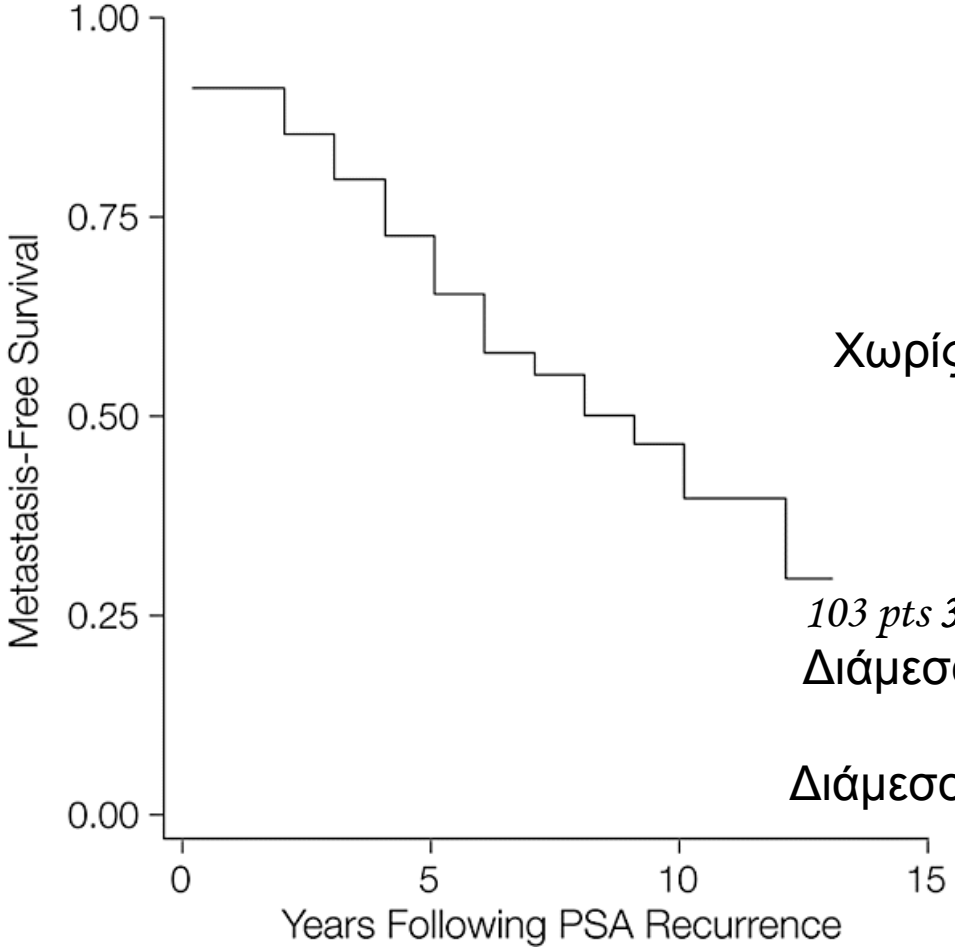
Local therapy is not recommended except for palliative reasons.	

- Βιοχημική υποτροπή μετά από Ριζική Προστατεκτομή

Φυσική Πορεία της Βιοχημικής Υποτροπής

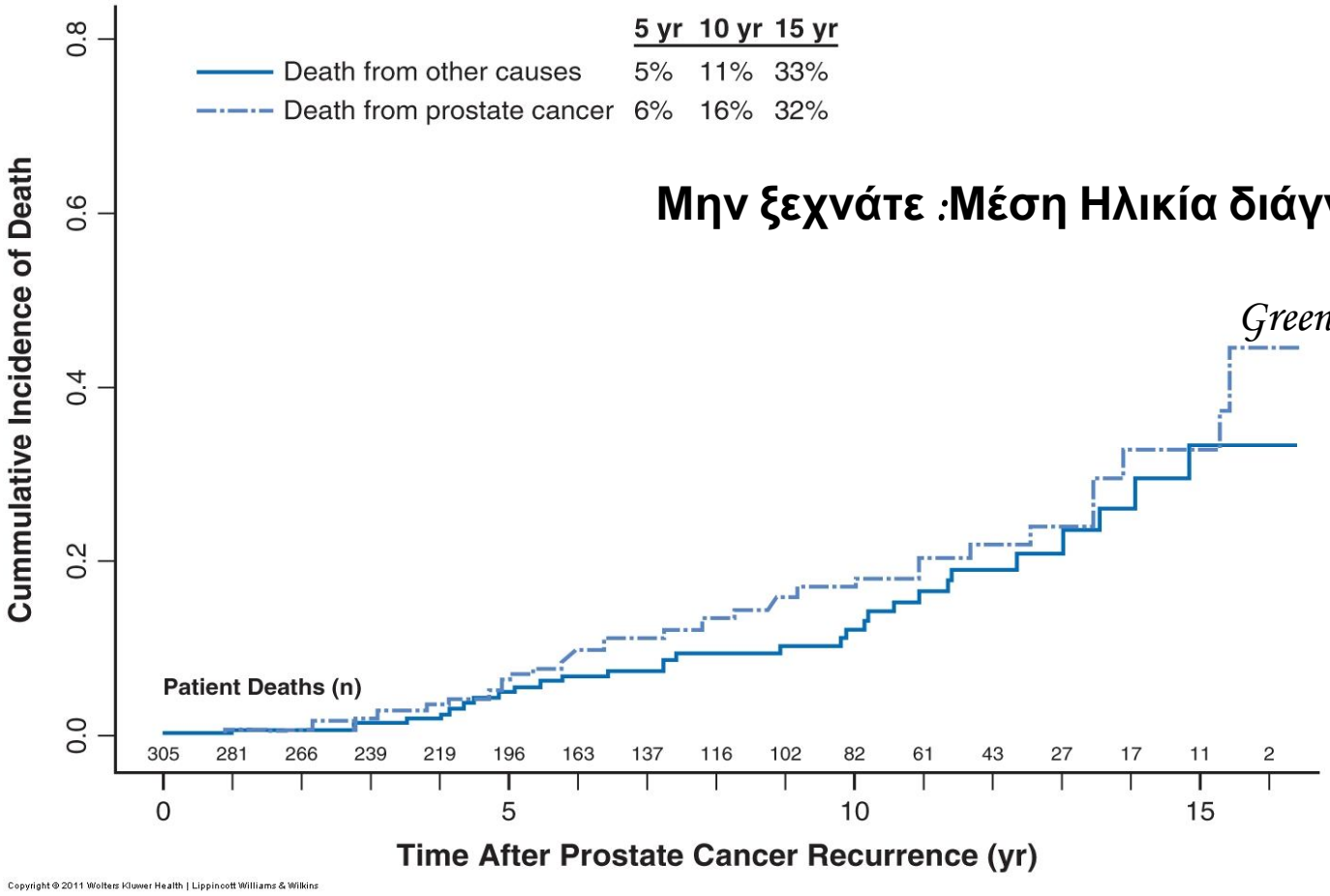


304/379pts
Χωρίς *neoadjuvant* ή ορμονική θεραπεία έως τη μετάσταση
Λίγοι με *Salvage* Ακτινοθεραπεία

103 pts ***34%*** ανέπτυξαν μεταστάσεις στα *15*-χρόνια
Διάμεσος χρόνος από *BCR* έως την μετάσταση *8* **χρόνια**
Διάμεσος χρόνος από μετάσταση έως το θάνατο *5* **χρόνια**

Pound JAMA 1999; 281:1591
Freeland JAMA 2005;294:433

Φυσική Πορεία της Βιοχημικής Υποτροπής



Μην ξεχνάτε :Μέση Ηλικία διάγνωσης τα *65* έτη

Greene Urology 2005

Scardino Urology 2005;66:83-94

Φυσική Πορεία της Βιοχημικής Υποτροπής

- Ισχύει το ίδιο και για την Ευρώπη;

- *Time trends of biochemical recurrence (BCR) following radical prostatectomy (RP) among 1574 BCR patients*

- Αμβούργο

Abstract 639 AUA 2011

Φυσική Πορεία της Βιοχημικής Υποτροπής

- Χρόνος έως *BCR* ***1.8*** **χρόνια** *(2.1 Pound John Hopkins , 2.4 Hull MSKCC)*
- Χρόνος από *BCR* έως τη Μετάσταση ***4.7 years*** *(8 Pound)*
- Χρόνος από *BCR* έως το θάνατο ***6*** **χρόνια** *(13 Pound)*
- *92%* και *81%* των *BCR* ήταν ελεύθεροι μεταστάσεων στα *5* και *10* χρόνια, αντίστοιχα

Abstract 639 AUA 2011

Φυσική Πορεία της Βιοχημικής Υποτροπής

Τι προκαλεί τη διαφορά;

- Μεγαλύτερο δείγμα *(German 1574, Pound 304, Hull 147);*
- ↑↑↑↑ χρήση *ADT, RT,* Υποστηρικτικής θεραπείας *(*π.χ. *biophosponates)* στις ΗΠΑ;

Impact of Biochemical Recurrence in Prostate Cancer Among US Veterans

Edward M. Uchio, MD; Mihaela Aslan, PhD; Carolyn K. Wells, MPH; Juan Calderone, MD; John Concato, MD, MS, MPH

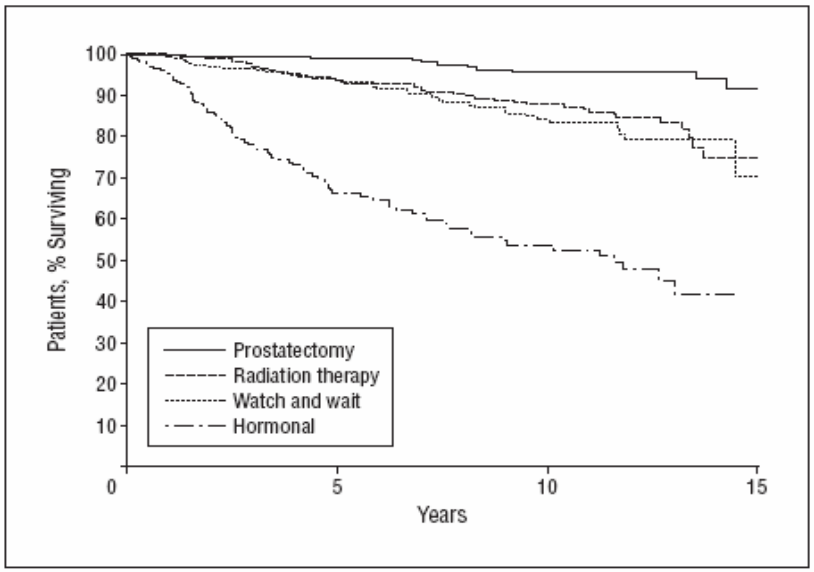
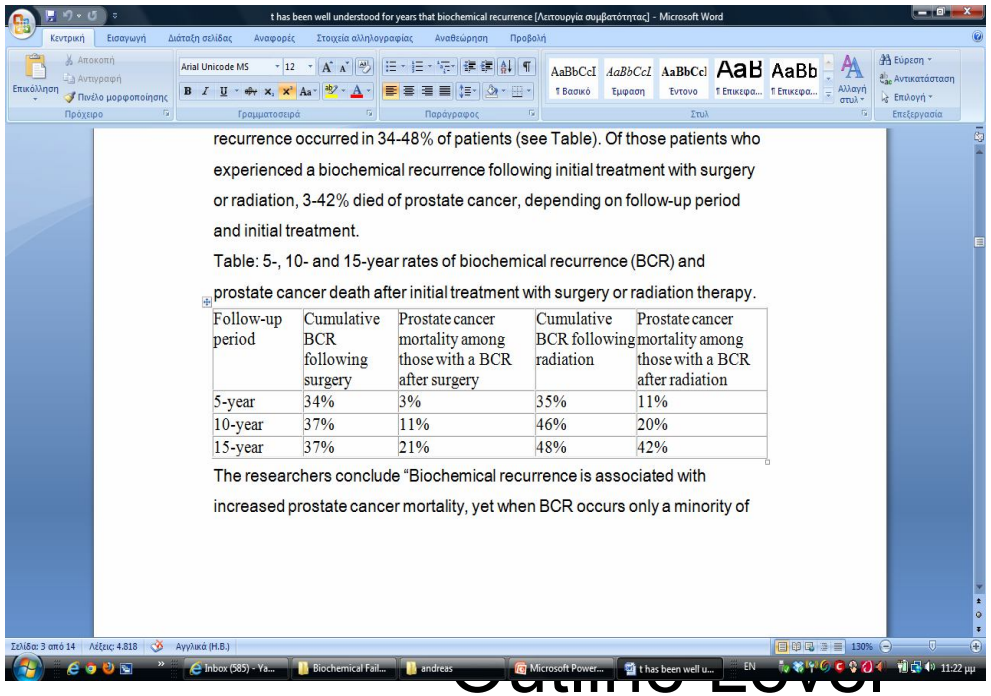


Figure 1. Prostate cancer mortality based on treatment received (N=1156 patients).



recurrence occurred in 34-48% of patients (see Table). Of those patients who experienced a biochemical recurrence following initial treatment with surgery or radiation, 3-42% died of prostate cancer, depending on follow-up period and initial treatment.

Table: 5-, 10- and 15-year rates of biochemical recurrence (BCR) and prostate cancer death after initial treatment with surgery or radiation therapy.

Follow-up period	Cumulative BCR following surgery	Prostate cancer mortality among those with a BCR after surgery	Cumulative BCR following radiation	Prostate cancer mortality among those with a BCR after radiation
5-year	34%	3%	35%	11%
10-year	37%	11%	46%	20%
15-year	37%	21%	48%	42%

The researchers conclude "Biochemical recurrence is associated with increased prostate cancer mortality, yet when BCR occurs only a minority of

- Click to edit the Outline Level
  - Fifth Outline Level

1156 Ασθενείς

Uchio Archives of Internal Medicine. 2010;170:1390-1395.

Impact of Biochemical Recurrence in Prostate Cancer Among US Veterans

Edward M. Uchio, MD; Mihaela Aslan, PhD; Carolyn K. Wells, MPH; Juan Calderone, MD; John Concato, MD, MS, MPH

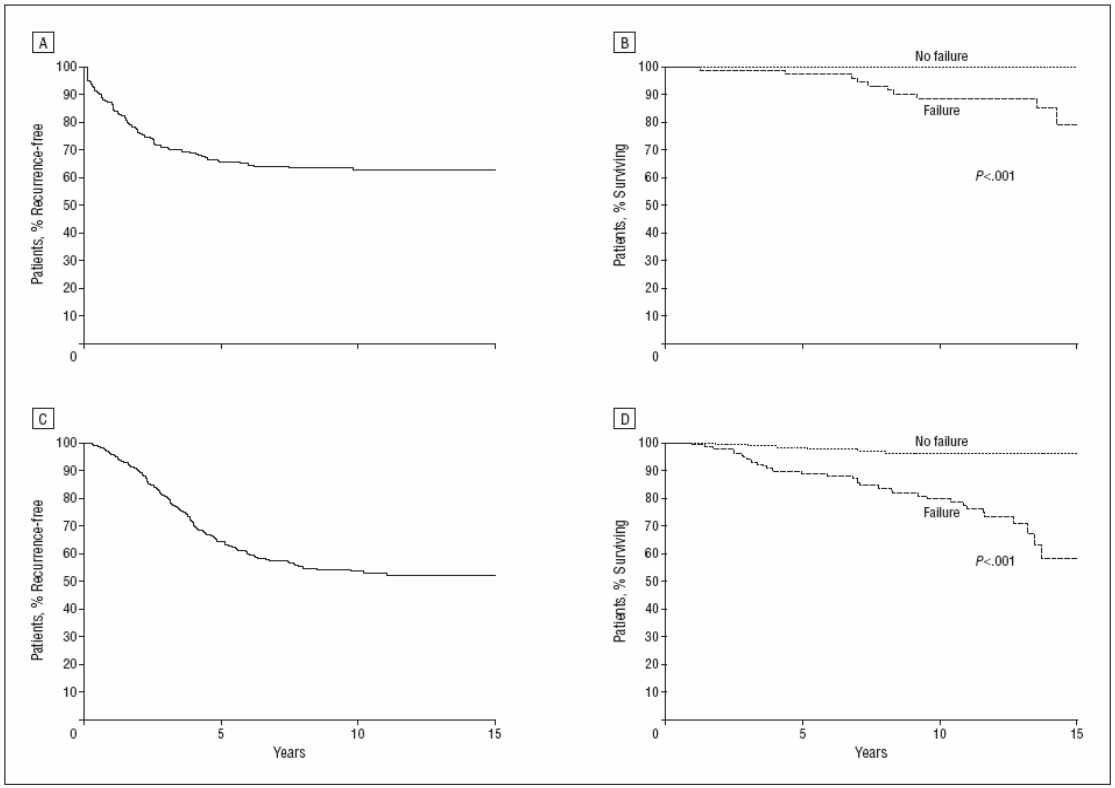
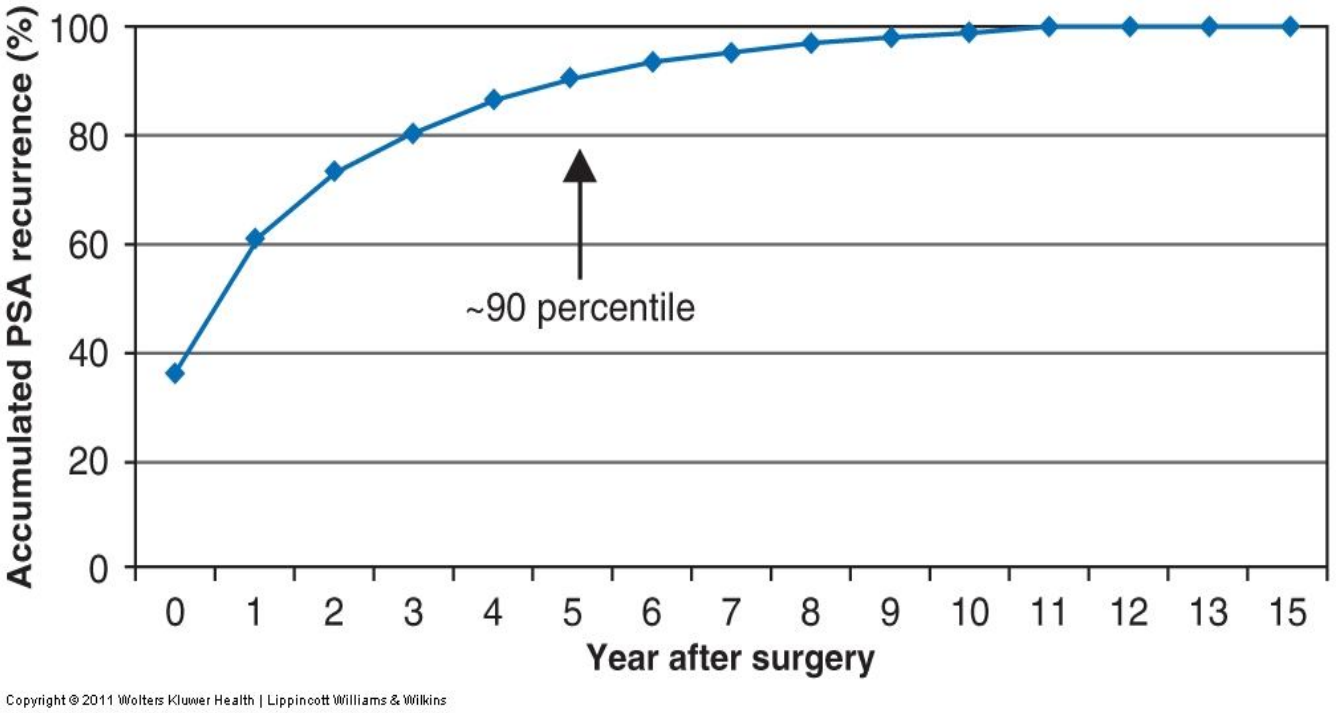


Figure 2. Kaplan-Meier curves. A, Time to biochemical recurrence (BCR) among men receiving prostatectomy (n=225); B, time to prostate cancer mortality based on BCR ("treatment failure" [n=81] vs "no treatment failure" [n=144]) among men receiving prostatectomy; C, time to BCR among men receiving radiation therapy (n=398); and D, time to prostate cancer mortality based on BCR ("treatment failure" [n=161] vs "no treatment failure" [n=237]) among men receiving radiation therapy.

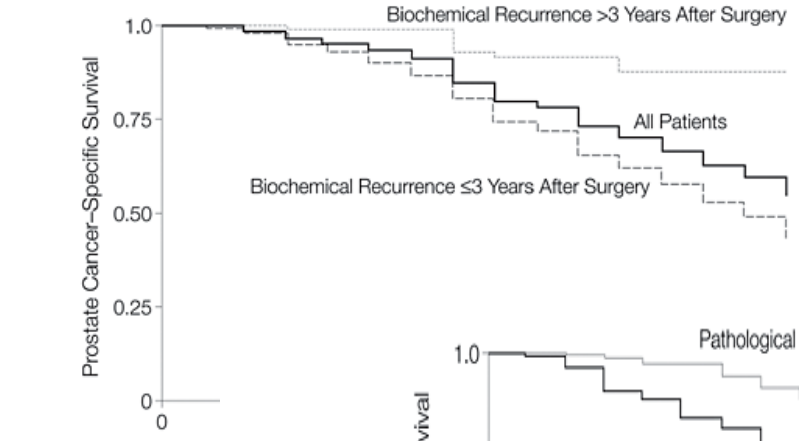
Φυσική Πορεία της Βιοχημικής Υποτροπής



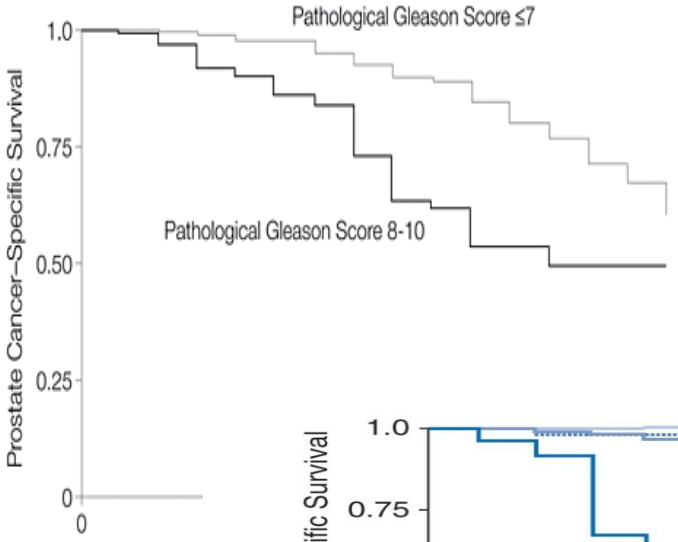
Οι ασθενείς με υποτροπή ≤*5* χρόνια είχαν μεγαλύτερη πιθανότητα να πεθάνουν από τη νόσο

Duke Prostate Cancer database N=4,561
Caire Urology 2009;74:643-647

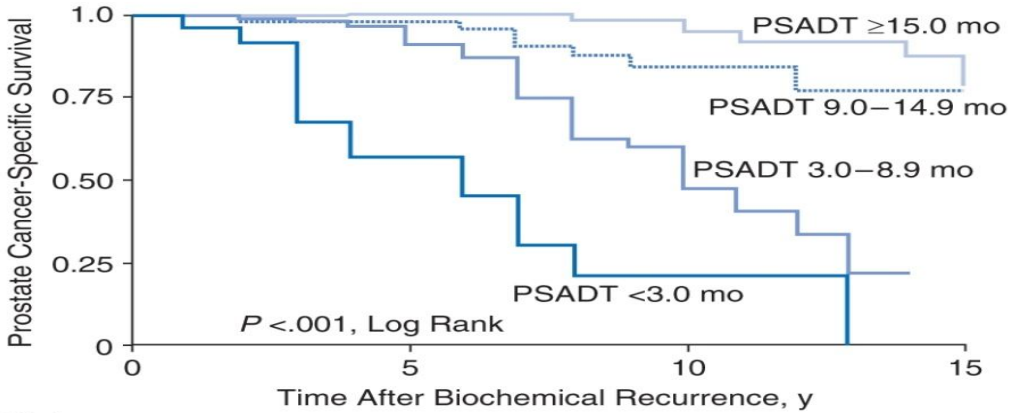
Δεν είναι όλοι οι ασθενείς ίδιοι



No. at Risk
All Patients 379
Time From Surgery to Bio
>3 135
≤3 244



No. at Risk
Pathological Gleason Score
≤7 252
≥8 127

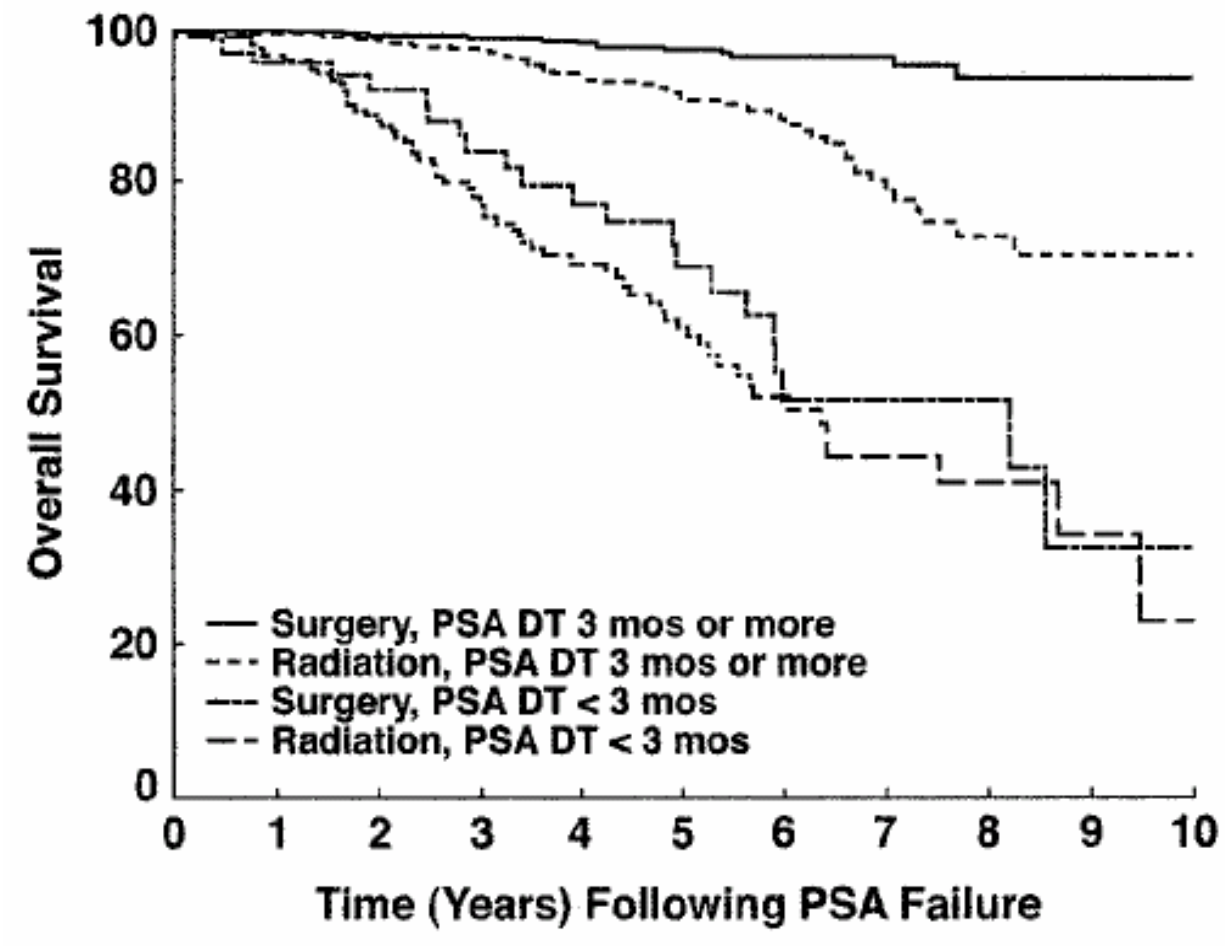


No. at Risk

PSADT, mo				
<3.0	23	10	2	0
3.0–8.9	119	85	19	0
9.0–14.9	79	51	19	3
≤15	158	113	52	9

Pound JAMA 1999; 281:1591
Freeland JAMA 2005;294:433

Δεν είναι όλοι οι ασθενείς ίδιοι

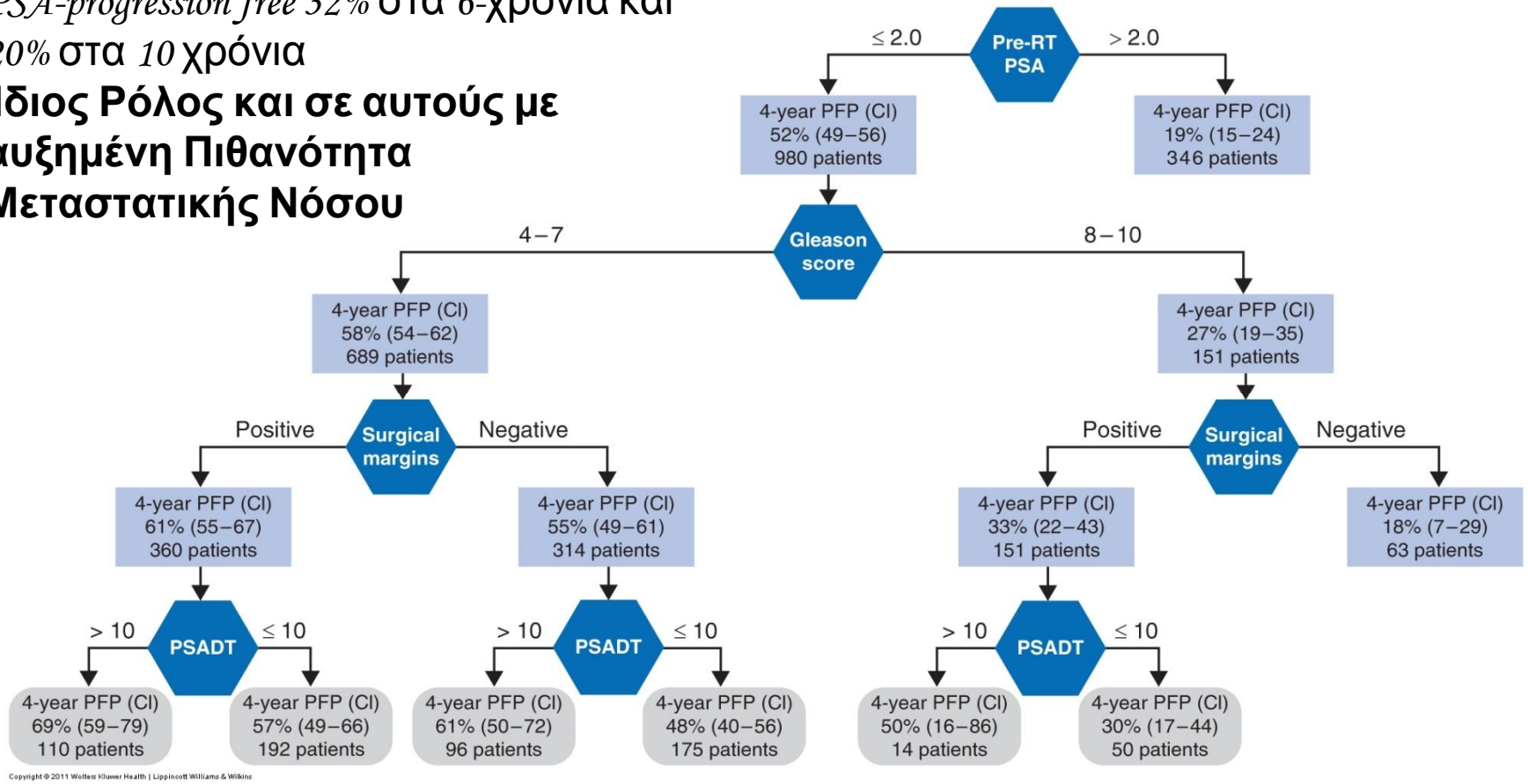


D'Amico J Urol 2004

Salvage Ακτινοθεραπεία

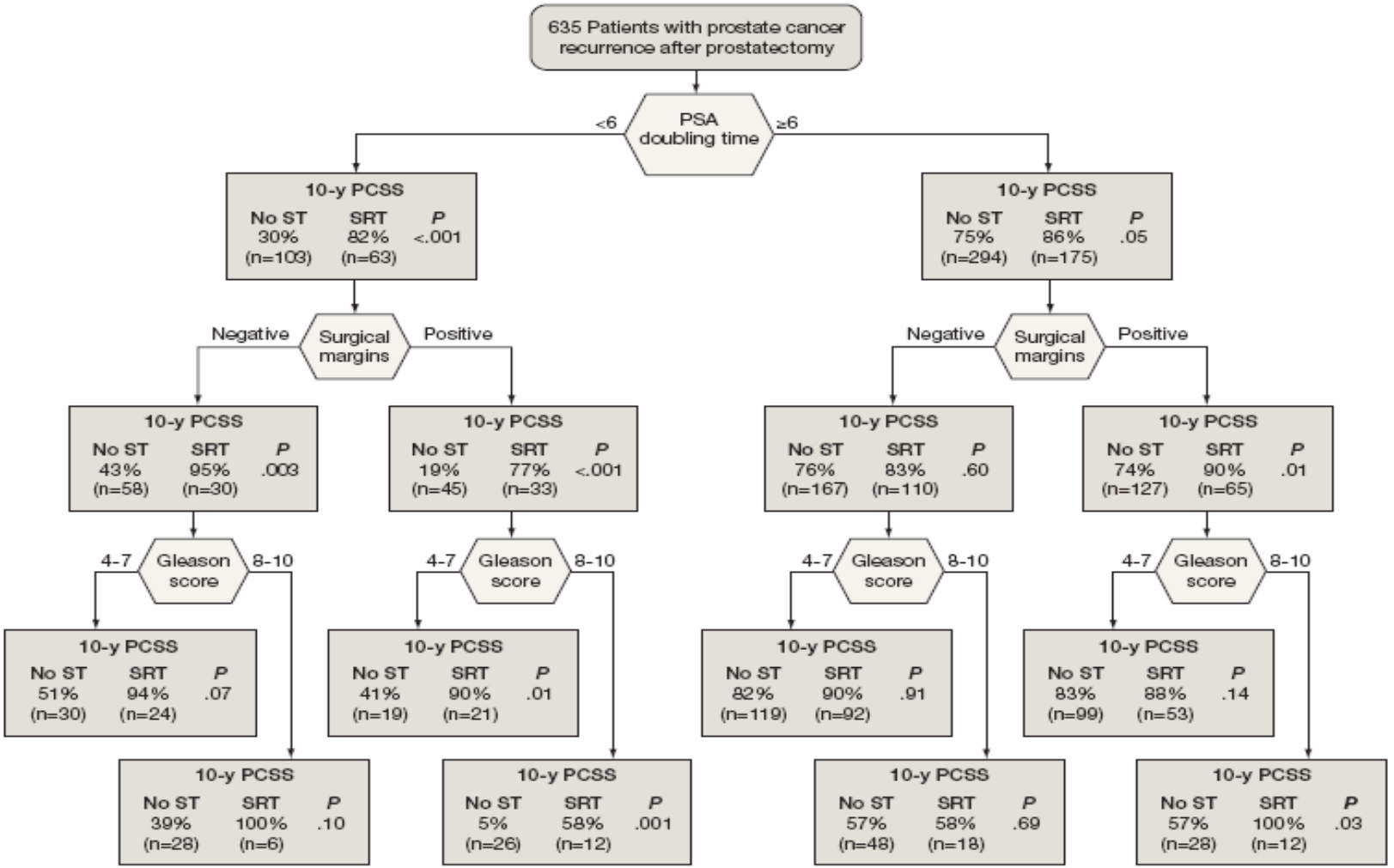
PSA-progression free 32% στα *6*-χρόνια και *20%* στα *10* χρόνια

Ίδιος Ρόλος και σε αυτούς με αυξημένη Πιθανότητα Μεταστατικής Νόσου



Stephenson J Clin Oncol 2007 ;25:2035

Figure 2. Kaplan-Meier Prostate Cancer–Specific Survival (PCSS) Estimates at 10 Years



Survival rates are following recurrence in men who received no salvage therapy (ST) vs salvage radiotherapy (SRT; with or without hormonal therapy), stratified by prostate-specific antigen doubling time, surgical margin status, and postoperative Gleason score.

ΑΚΘ Διάσωσης καλύτερη σε *CSS* σε ασθενείς με

·*PSA DT<6mt*

·Αντιμετώπιση εντός *2* ετών από την ΒΥ

Trock J Clin Oncol 2008 ;23:2760

Salvage Ακτινοθεραπεία

ADT + SRT

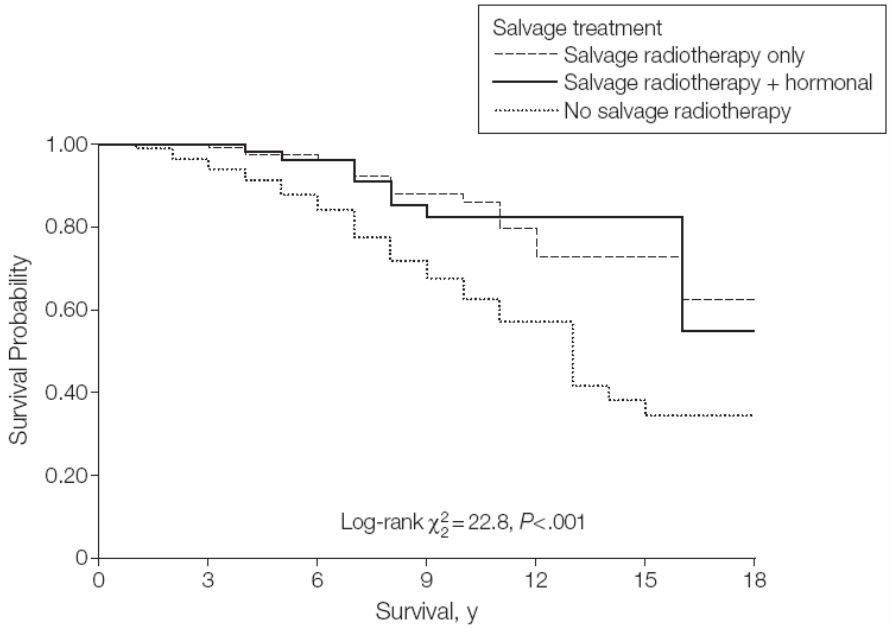
RTOG 9061

RTOG 0534

FNCLCC-GETUG 16/0504

RADICALS

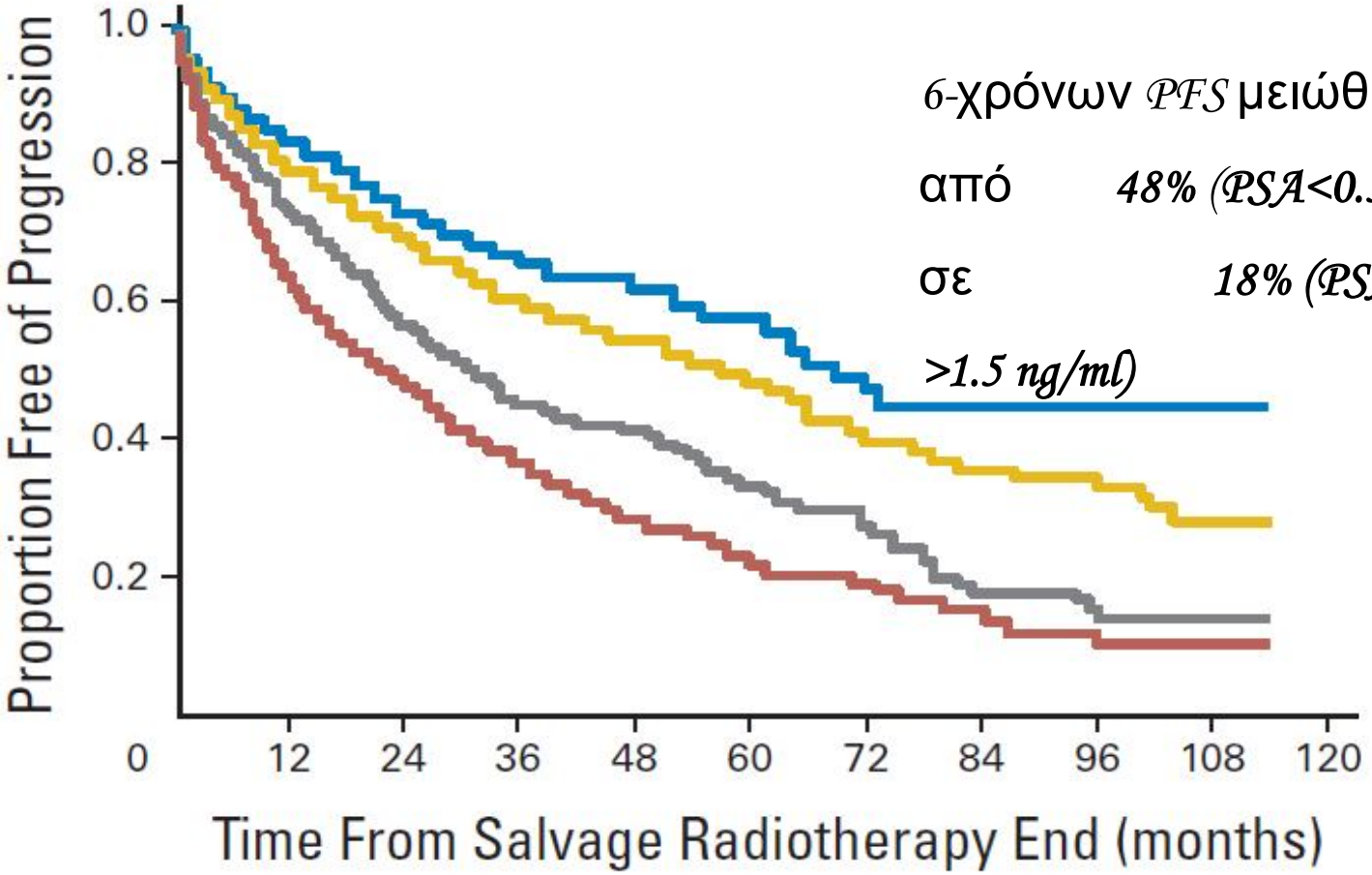
Figure 1. Prostate Cancer–Specific Survival Following Recurrence After Radical Prostatectomy (1982-2004)



No. at risk							
Salvage radiotherapy only	160	124	83	52	33	10	1
Salvage radiotherapy + hormonal	78	64	41	26	13	8	2
No salvage radiotherapy	397	295	198	86	28	9	1

Trock J Clin Oncol 2008 ;23:2760

Salvage Ακτινοθεραπεία



6-χρόνων *PFS* μειώθηκε

από *48% (PSA<0.5 ng)*

σε *18% (PSA >1.5 ng/ml)*

Τα αποτελέσματα των μελετών με *ART* συνηγορούν υπέρ της γρήγορης αντιμετώπισης επί ανόδου του *PSA*

Stephenson J Clin Oncol 2007 ;25:2035

TABLE 13E.6

SALVAGE RADIOTHERAPY: DOSE ESCALATION

First Author (Year)	N	Dose (*n*)	FFBF % (yr)	*p*
Anscher (2000) (88)	89	≤65 Gy (36)	0 yr (Median)	<0.001
		>65 Gy (53)	2.2 yr (Median)	
Macdonald (2003) (93)	60	≤64.8 Gy (22)	28 (5)	0.026
		>64.8 Gy (38)	59 (5)	
King (2008) (100)	122	~60 Gy (38)	23 (5)	<0.0001
		~70 Gy (84)	66 (5)	
Bernard (2010) (102)	364	<64.8 Gy (154)	43(5)	0.08[a]
		64.8–66.6 Gy (124)	54 (5)	0.02[b]
		>66.6 Gy (86)	61 (5)	

[a]<64.8 Gy vs. 64.8–66.6 Gy.
[b]<64.8 Gy vs. >66.6 Gy.

Spiotto et al. (115) showed a benefit when the pelvic lymph nodes were included in patients with high risk features (5-year

Hypofractionation has also been shown to be alternative to regular fractionation with exceller (116,117); however, longer follow-up is required.

Androgen Deprivation Therapy in the Setting

Retrospective data suggest that ADT in combinatic improves outcome, but these studies are far from (50,94,118–121). In contrast, Trock et al. (51) c that the addition of ADT significantly altered ca mortality. The use of ADT with SRT is a contemp tion that is the centerpiece of several randomized t

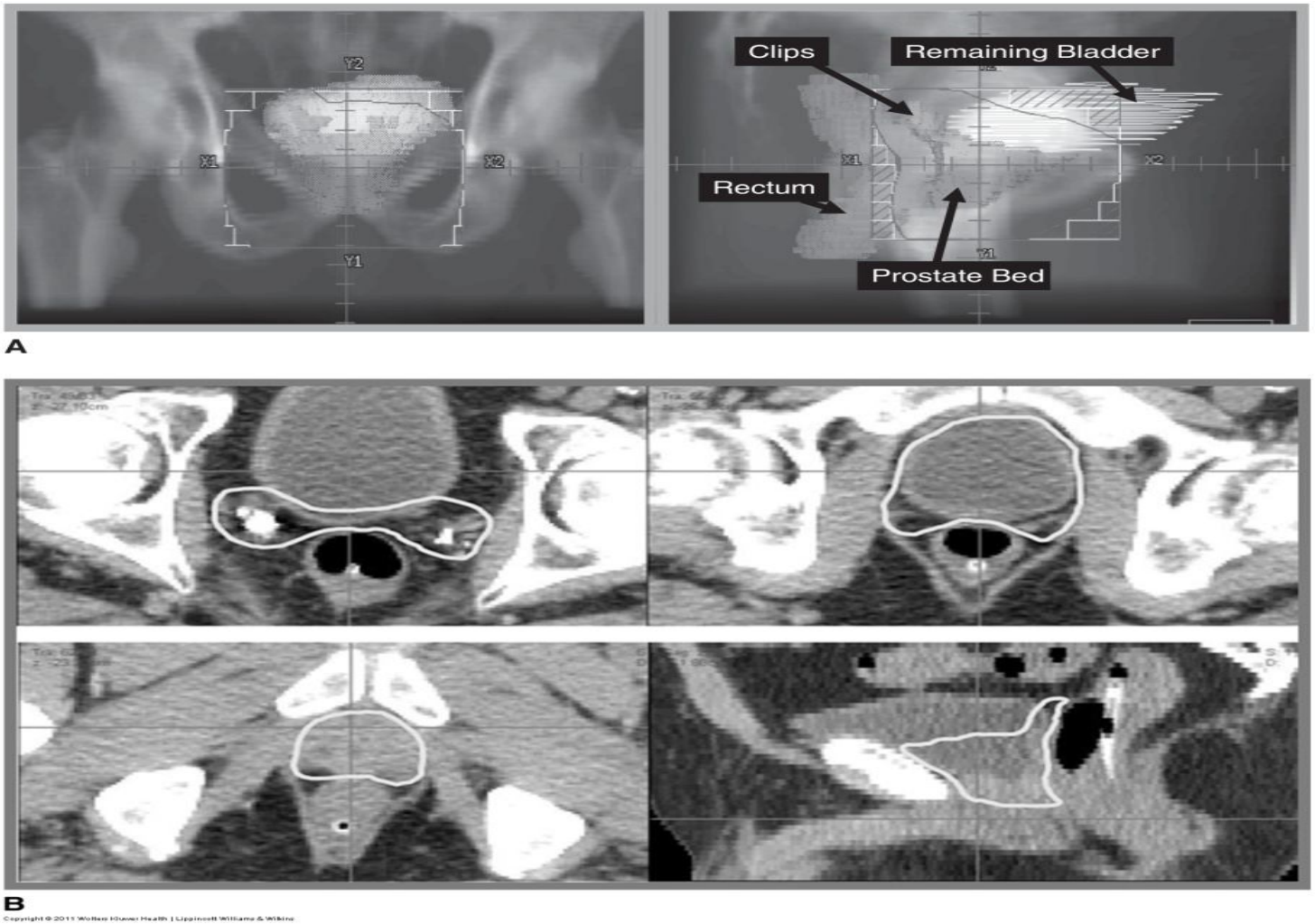
RTOG 9601, which compares radiotherapy alo therapy plus long-term ADT using 150 mg/day of b for 2 years is closed to accrual and will be reporte aforementioned RTOG 0534 compares radiothe prostate bed alone to prostate bed plus short term A 6 months to prostate bed and the pelvic lymph node term ADT. FNCLCC-GETUG 16/0504 compares RT + 6 months of ADT and the RADICALS tri short- and long-term ADT, along with adjuvant ve

ADJUVANT VERSUS SALV RADIOTHERAPY

The optimal timing of radiotherapy for patients wi

Pollack Genit Oncol 2011;238

3DCRT IMRT



Lymph Node treatment ? RTOG 0534

Pollack Genit Oncol 2011;238

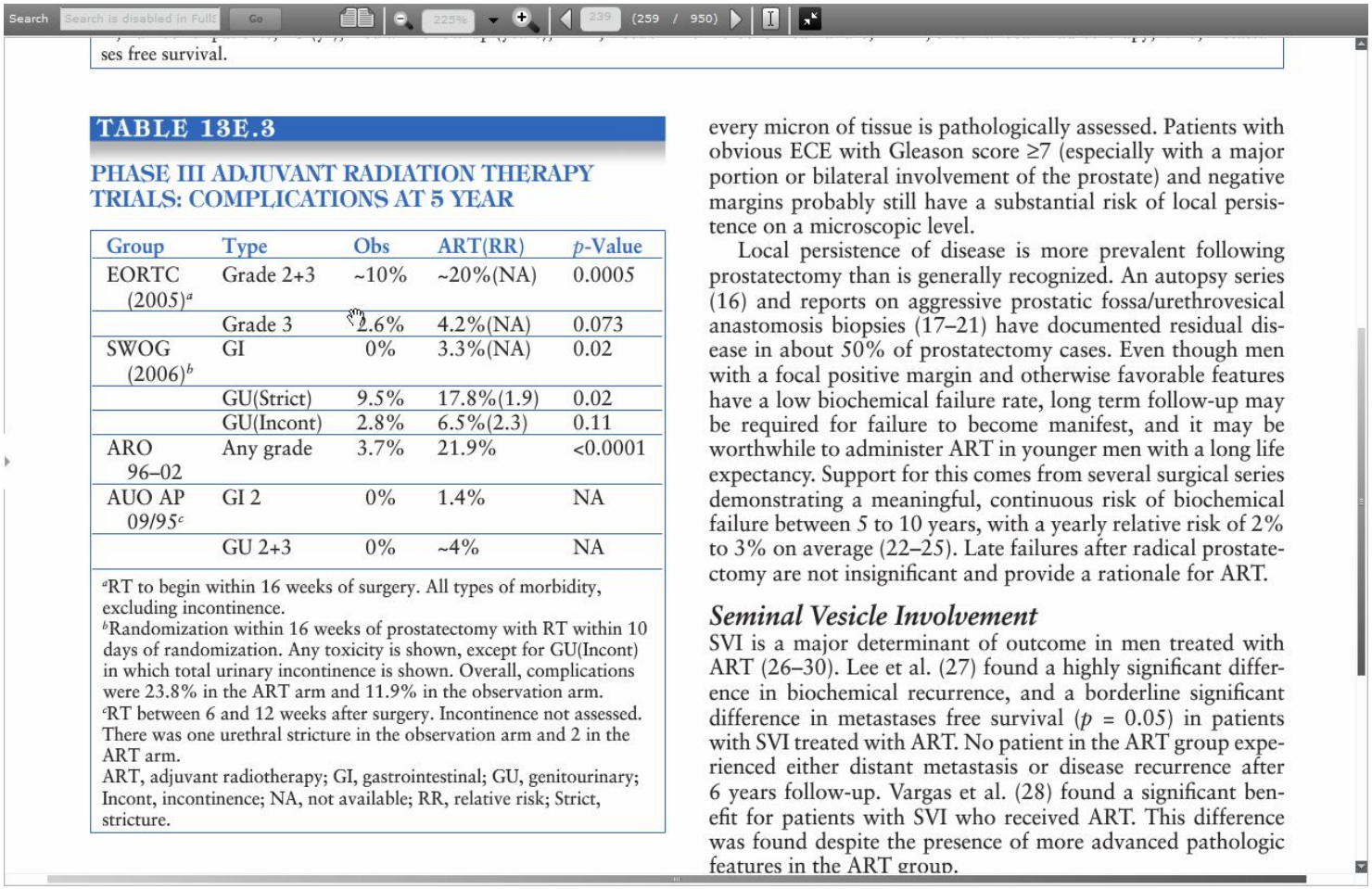
Επικουρική ΑΚΘ *vs.* Παρακολούθηση

3 προοπτικά τυχαιοποιημένες μελέτες – *LEVEL 1b*

Study	*N*	*Median FU*	*Biochemical PFS*	*Mets*	*Death (%)*
EORTC 22911 *Bolla et al*	*Van Popel 2011 EAU Vienna* *FU>10years MF NS OS NS*				
SWOG 8794 *Thompson et al*	*Thompson et al J Urol 2009* *12.6 years MF p<0.016 OS p<0.023*				
ARO 96-02 *Wiegel et al*	*388*	*4.5 yr*	*72 vs 54%**** *p=0.0015*	*2 vs 3.1%*	*3.4 vs 5%*

Bolla M et al Lancet 2005
Thompson IM et al JAMA 2006
Wiegel T et al J Clin Oncol 2009

Adjuvant Ακτινοθεραπεία



ses free survival.

TABLE 13E.3

PHASE III ADJUVANT RADIATION THERAPY TRIALS: COMPLICATIONS AT 5 YEAR

Group	Type	Obs	ART(RR)	*p*-Value
EORTC (2005)[a]	Grade 2+3	~10%	~20%(NA)	0.0005
	Grade 3	2.6%	4.2%(NA)	0.073
SWOG (2006)[b]	GI	0%	3.3%(NA)	0.02
	GU(Strict)	9.5%	17.8%(1.9)	0.02
	GU(Incont)	2.8%	6.5%(2.3)	0.11
ARO 96–02	Any grade	3.7%	21.9%	<0.0001
AUO AP 09/95[c]	GI 2	0%	1.4%	NA
	GU 2+3	0%	~4%	NA

[a]RT to begin within 16 weeks of surgery. All types of morbidity, excluding incontinence.
[b]Randomization within 16 weeks of prostatectomy with RT within 10 days of randomization. Any toxicity is shown, except for GU(Incont) in which total urinary incontinence is shown. Overall, complications were 23.8% in the ART arm and 11.9% in the observation arm.
[c]RT between 6 and 12 weeks after surgery. Incontinence not assessed. There was one urethral stricture in the observation arm and 2 in the ART arm.
ART, adjuvant radiotherapy; GI, gastrointestinal; GU, genitourinary; Incont, incontinence; NA, not available; RR, relative risk; Strict, stricture.

every micron of tissue is pathologically assessed. Patients with obvious ECE with Gleason score ≥7 (especially with a major portion or bilateral involvement of the prostate) and negative margins probably still have a substantial risk of local persistence on a microscopic level.

Local persistence of disease is more prevalent following prostatectomy than is generally recognized. An autopsy series (16) and reports on aggressive prostatic fossa/urethrovesical anastomosis biopsies (17–21) have documented residual disease in about 50% of prostatectomy cases. Even though men with a focal positive margin and otherwise favorable features have a low biochemical failure rate, long term follow-up may be required for failure to become manifest, and it may be worthwhile to administer ART in younger men with a long life expectancy. Support for this comes from several surgical series demonstrating a meaningful, continuous risk of biochemical failure between 5 to 10 years, with a yearly relative risk of 2% to 3% on average (22–25). Late failures after radical prostatectomy are not insignificant and provide a rationale for ART.

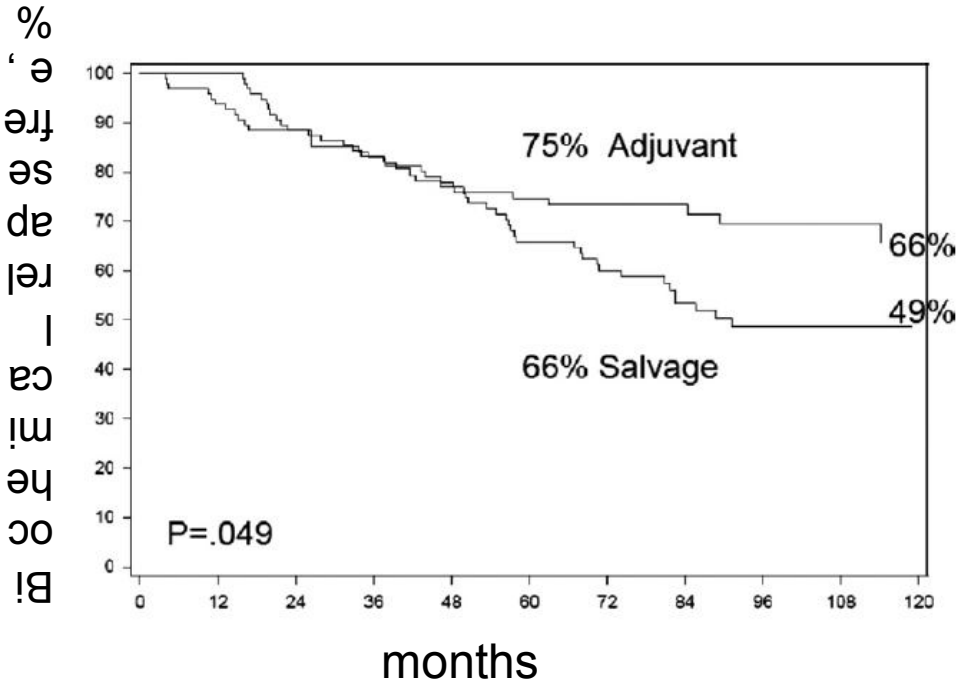
Seminal Vesicle Involvement

SVI is a major determinant of outcome in men treated with ART (26–30). Lee et al. (27) found a highly significant difference in biochemical recurrence, and a borderline significant difference in metastases free survival ($p = 0.05$) in patients with SVI treated with ART. No patient in the ART group experienced either distant metastasis or disease recurrence after 6 years follow-up. Vargas et al. (28) found a significant benefit for patients with SVI who received ART. This difference was found despite the presence of more advanced pathologic features in the ART group.

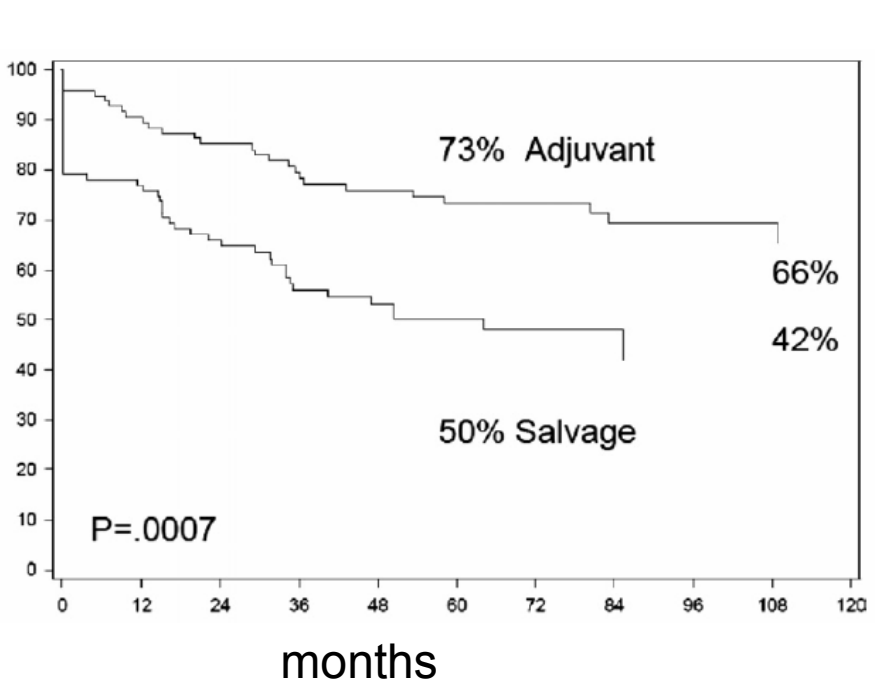
Pollack Genit Oncol 2011;238

Επικουρική ΑΚΘ *vs.* ΑΚΘ Διάσωσης

From date of surgery



From end of RT



Πολυκεντρική μελέτη *2299 pts*

Trabulsi et al. Urology 2008

EUROPEAN UROLOGY 52 (2007) 1175–1184

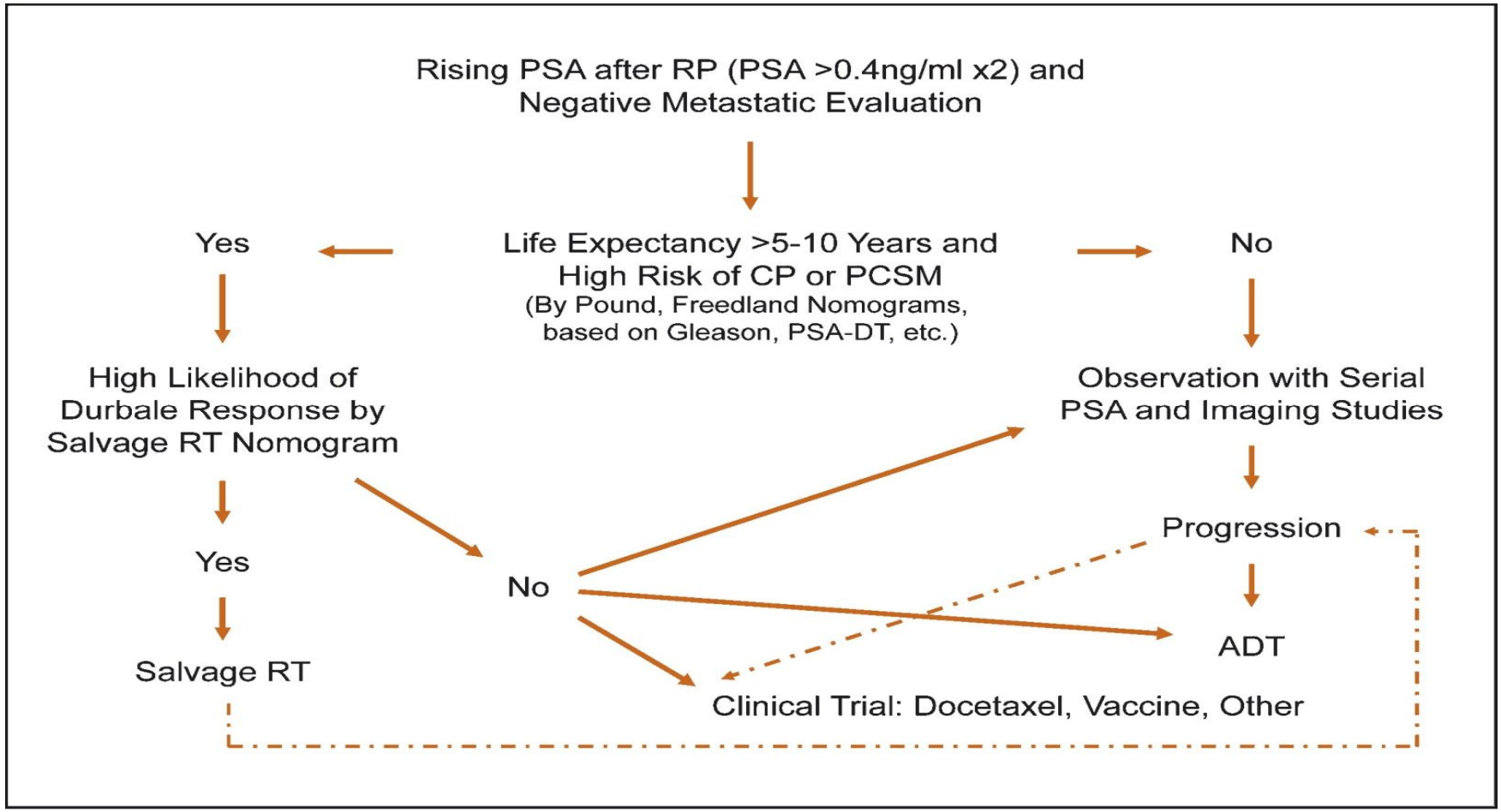
available at www.sciencedirect.com
journal homepage: www.europeanurology.com

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 *



ΕΑΟ οδηγίες

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

- Βιοχημική υποτροπή μετά από Ακτινοβολία

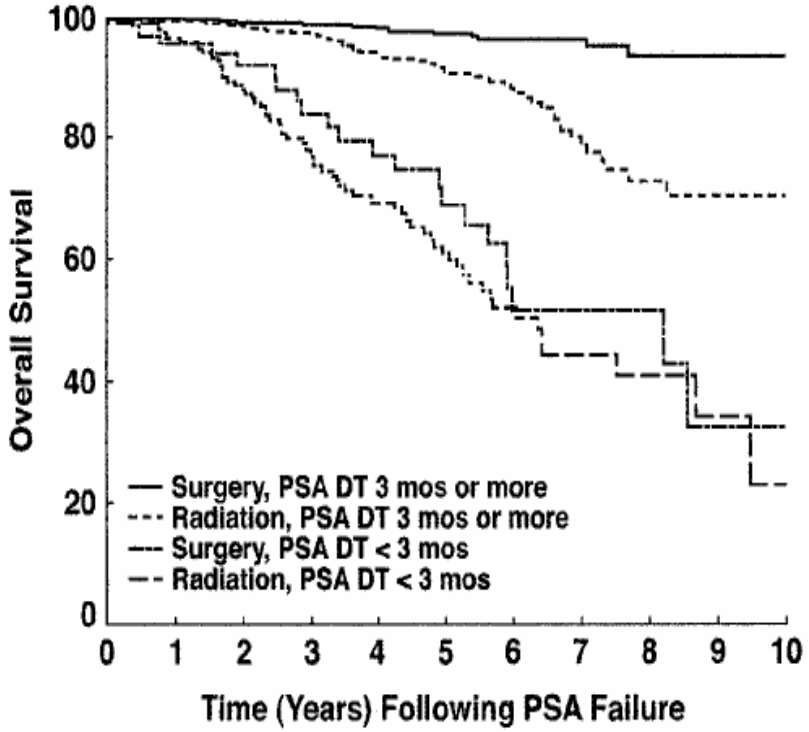
Φυσική Πορεία της Βιοχημικής Υποτροπής

- Όταν δεν εφαρμόζονται θεραπείες διάσωσης ο μέσος χρόνος από τη βιοχημική υποτροπή έως την κλινική πρόοδο της νόσου είναι τα *3* χρόνια. EAU guidelines 2012

Δεν είναι όλοι οι ασθενείς ίδιοι

- **ΚΑΛΥΤΕΡΟΙ ΥΠΟΨΗΦΙΟΙ**
  - *PSA <10ng/ml*
  - *PSADT>10*
  - *GS<7-8*
  - *cT1c/T2*
  - Προσδόκιμο επιβίωσης *>1*
  - Χαμηλή συνοσηρότητα

- Click to edit the



- Fifth Outline Level

D'Amico J Urol 2004

ΘΕΡΑΠΕΥΤΙΚΕΣ ΕΠΙΛΟΓΕΣ

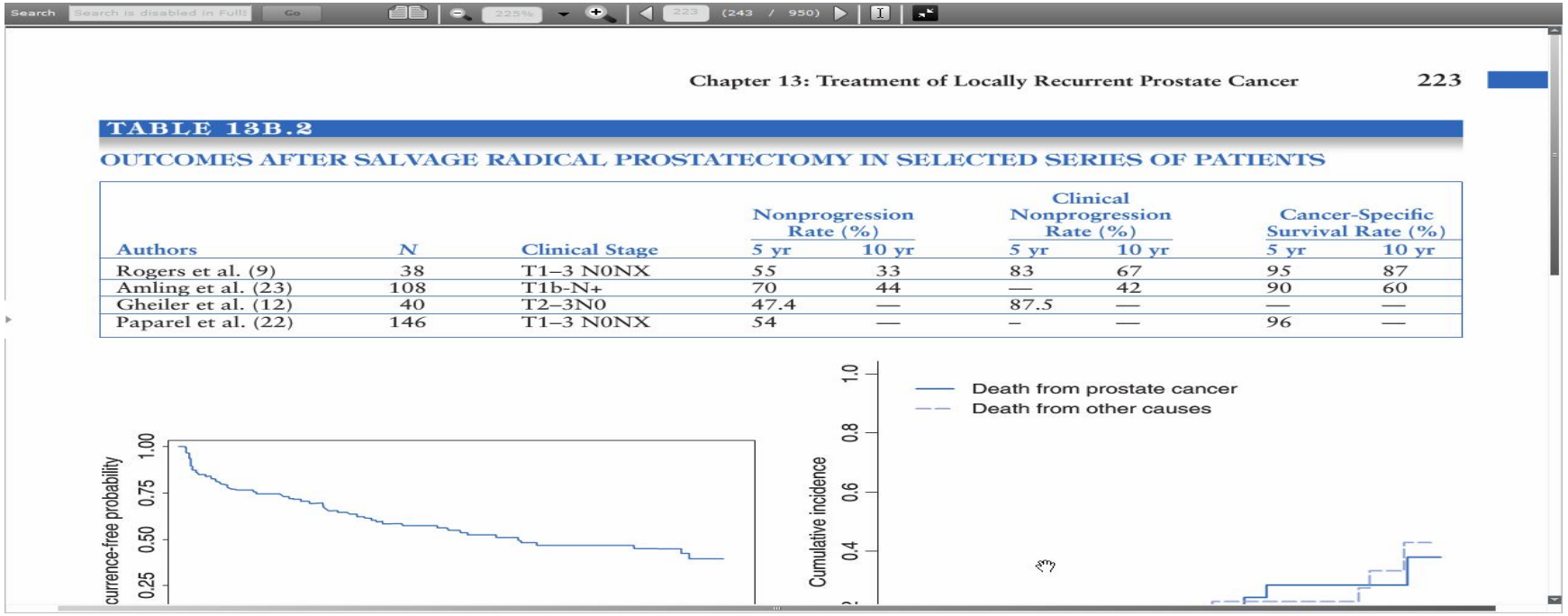
- *(Observation)*
- *Salvage RP*
- *Salvage Cryo*
- *Salvage BRT*
- *Salvage HIFU*

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)

Salvage RP



Chapter 13: Treatment of Locally Recurrent Prostate Cancer 223

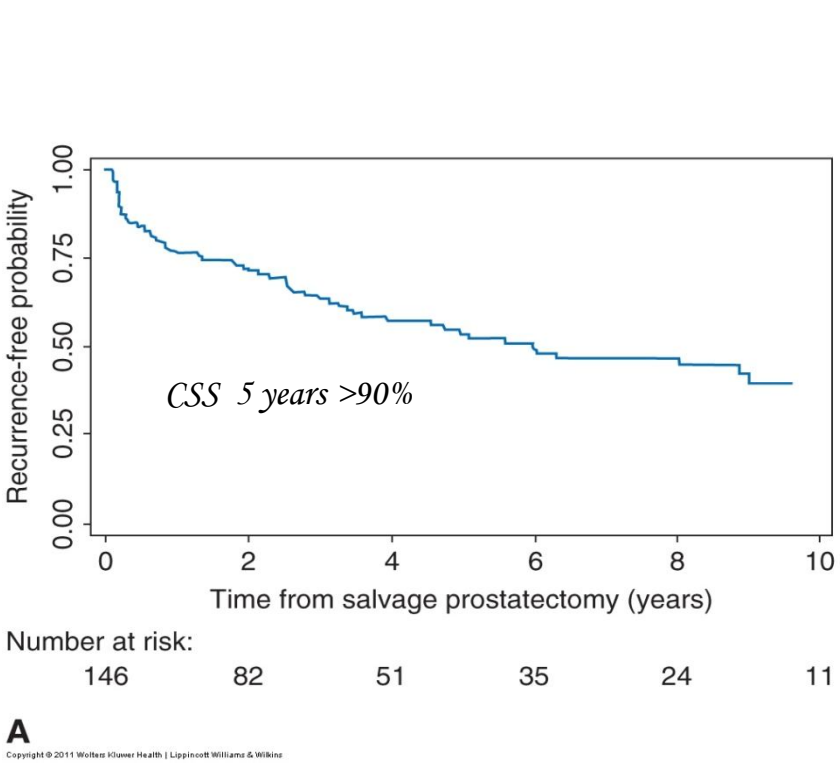
TABLE 13B.2

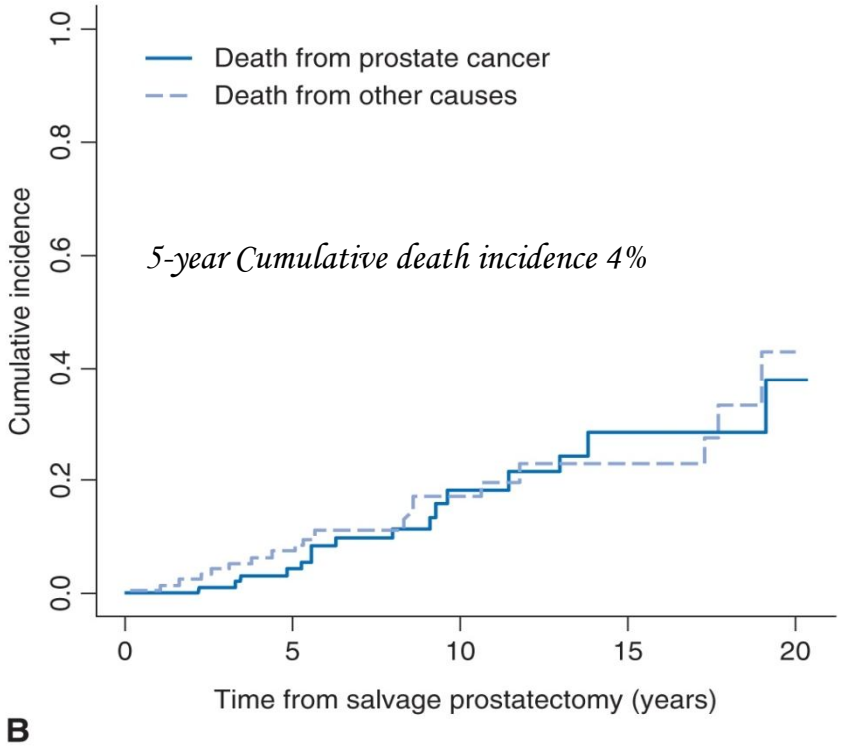
OUTCOMES AFTER SALVAGE RADICAL PROSTATECTOMY IN SELECTED SERIES OF PATIENTS

Authors	N	Clinical Stage	Nonprogression Rate (%)		Clinical Nonprogression Rate (%)		Cancer-Specific Survival Rate (%)	
			5 yr	10 yr	5 yr	10 yr	5 yr	10 yr
Rogers et al. (9)	38	T1–3 N0NX	55	33	83	67	95	87
Amling et al. (23)	108	T1b-N+	70	44	—	42	90	60
Gheiler et al. (12)	40	T2–3N0	47.4	—	87.5	—	—	—
Paparel et al. (22)	146	T1–3 N0NX	54	—	–	—	96	—

Η *RP* διάσωσης και η *standard RP* όταν συγκρίνονται κατά στάδια έχουν παρόμοια ογκολογικά αποτελέσματα

Salvage RP





Το *PSA* πριν τη *RP* διάσωσης και το *Gleason score* της βιοψίας σχετίζονται σημαντικά με το **θάνατο από το** *CaP*

Paparel, Scardino Eur Urol 2009;55:404-410

Salvage RP

Organ-confined Pca και *NSM*

- *Gleason score* βιοψίας πριν την *SRP*
- *<50%* του υλικού θετικό στη βιοψία
- *PSA DT >12* μήνες
- Βραχυθεραπεία χαμηλής δόσης

Axel Heidenreich[a,b,*], Stephanie Richter[a,b], David Thüer[b], David Pfister[a,b] EUROPEAN UROLOGY 57 (2010) 437–445

Salvage RP

TABLE 13B.1

COMPLICATIONS OF SALVAGE RADICAL PROSTATECTOMY

Author	Year	No. of Patients	EBL (mL)	Strictures (%)	Rectal Injuries (%)	Other (%)[a]	Incontinence (%)[b] Mild	Incontinence (%)[b] Severe
Thompson et al. (13)	1988	5	—	0	0	20	20	60
Link and Freiha (14)	1991	14	1,000	7	0	—	3.6	—
Moul and Paulson (15)	1991	4	800	—	—	100	0	—
Ahlering et al. (16)	1992	11	—	—	0	—	64	—
Pontes et al. (17)	1992	35	—	11.5	6	9	28	17
Stein et al. (18)	1992	11	1,100	18	0	27	64	—
Zincke (19)	1992	32	—	19	6.3	25	26.7	—
Brenner et al. (20)	1994	10	1,650	10	0	20	10	10
Rogers et al. (9)	1995	40	910	27.5	15	20	58	—
Gheiler et al. (12)	1998	30	1,100	13	7	17	23	26
Stephenson et al. (21)	2004	100	1,000	30	7	—	38	23

[a]Other major operative complications include postoperative hemorrhage, ureteral injury, and prolonged anastomotic leakage.
[b]Mild incontinence indicates stress incontinence requiring fewer than two pads per day, and severe incontinence implies greater than two pads per day.
EBL, estimated blood loss.

Θεραπείες Διάσωσης σε Β.Υ. μετά από ΑΚΘ «ΟΓΚΟΛΟΓΙΚΑ ΑΠΟΤΕΛΕΣΜΑΤΑ»

	Nb pt	FU (mt)	bDFS % @ 5years	bDFS % @ 10 years
Salvage RP	*40-138*	*35-92*	*47-71*	*30-43*
Salvage CRYO	*18-279*	*12-39*	*44-73*	
Salvage BRT	*13-49*	*19-64*	*34-87*	
Salvage HIFU	*32-167 (3)*	*7-14*	*53 (3)*	

Θεραπείες Διάσωσης σε Β.Υ. Μετά από ΑΚΘ «ΕΠΙΠΛΟΚΕΣ»

	Ακράτεια %	Στένωμα %	Συρίγγιο/κάκωση ορθού %	Στυτική Δυσλειτουργία %
Salvage RP	20-68	9-32	0-15	72-84
Salvage CRYO 3rd	4-40	0-20	0-2	86
Salvage BRT	GU (G 3-4) 14-47		GI (G 3-4) 2-24	NA
Salvage HIFU	7-50	8-36	3-7	72

EAU οδηγίες

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 < 10 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

- Βιοχημική υποτροπή μετά από Ορμονικό χειρισμό

Φυσική Πορεία της Βιοχημικής Υποτροπής

Δεν είναι όλοι οι ασθενείς ίδιοι

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

PSA σαν δείκτης ανταπόκρισης στη θεραπεία

Κατά

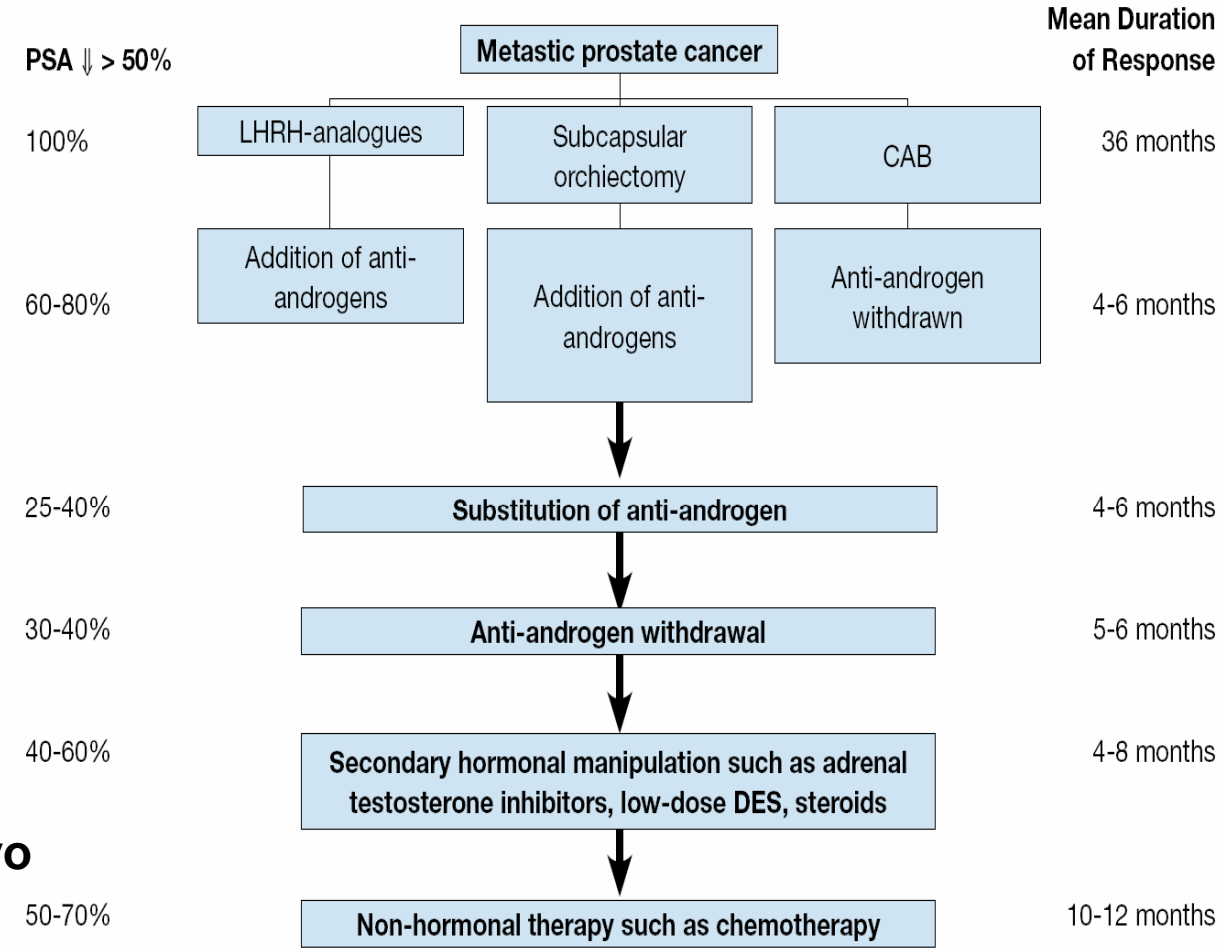
- Καμία συμφωνία στο μέγεθος και τη διάρκεια της μείωσης της τιμής του
- Μελέτες με εμβόλια *(Provenge, Tricom)* δεν είχαν καμία μεταβολή στο *PSA* αλλά κατέδειξαν σημαντική αύξηση της *OS*
- Το *PSA* επηρεάζεται παροδικά από τα φάρμακα
- Δεν συνδέεται με το *QOL* και την ανακούφιση από τα συμπτώματα

PSA σαν δείκτης ανταπόκρισης στη θεραπεία

Υπέρ

- Μείωση ≥*50% PSA* μετά τη θεραπεία συνδυάζεται με *>25* μήνες αύξηση στην επιβίωση
- Μείωση ≥ *30%* ευόδωσαν την επιβίωση *(*πάνω από *15* μήνες επιπλέον επιβίωση*) (TAX 32-docetaxel, SWOG99-16)*
- Έλλειψη άλλων δεικτών

Figure 1: Flowsheet of the potential therapeutic options after PSA progression following initial hormonal therapy



LHRH = luteinising hormone releasing hormone; CAB = complete androgen blockade; DES = diethylstilboesterol.

Abiraterone *1* **χρόνο ανταπόκριση**
5 μήνες *OS*
10% επιπλοκές
13% σε *placebo*

agent (9,10).

hydrocortisone alone (5) (Table 14D.1). This study included

TABLE 14D.1

LANDMARK PHASE III TRIALS IN CRPC

Treatment Arms	No.	≥ 50% PSA Response (%)	Measurable Response (%)	Median PFS (mo)	Median OS (mo)	Progression Free Survival (months)	References
Mitoxantrone + prednisone vs. prednisone	80 81	33 22 $p = 0.11$	NR	NR	<12 mo <12 mo $p = 0.27$	43 (wk)	Tannock (6)
Mitoxantrone + hydrocortisone vs. hydrocortisone	119 123	38 22 $p = 0.008$	7 4 $p = 0.375$	3.7[a] 2.3[a] $p = 0.02$	12.3 12.6 $p = 0.77$	$p < 0.0001$	Kantoff (5)
Docetaxel + estramustine q3 wk vs. mitoxantrone + prednisone	386 384	50 27 $p = 0.008$	17 11 $p = 0.3$	6.3 3.2 $p = 0.001$	17.5 15.6 $p = 0.02$	18 (wk)	Petrylak (15)
Docetaxel q3 wk + prednisone q3 wk vs. docetaxel weekly + prednisone vs. mitoxantrone + prednisone	335 334 337	45 48 $p = 0.001$[b] 32 $p < 0.001$[b]	12 8 $p = 0.11$[b] 7 $p = 0.59$[b]	NR	18.9 17.4 $p = 0.009$[b] 16.5 $p = 0.36$[b]	3.7	Tannock (16)
Satraplatin + prednisone vs. placebo + prednisone	638 315	25.4 12.4 $p < 0.001$	8 0.7 $p = 0.002$	11.1 wk 9.7 wk $p < 0.001$	61.3 wk 61.4 wk $p = 0.8$	$p = 0.25$	Stanberg (56)
Cabazitaxel + prednisone vs. mitoxantrone + prednisone	377 378	39.2 17.8 $p = 0.002$	14.4 4.4 $p = 0.005$	2.8 1.4 $p < 0.001$	15.1 12.7 $p < 0.001$	2.3	De Bono (31)
Docetaxel + prednisone + bevacizumab vs. docetaxel + prednisone	524 526	69.5 57.9 $p = 0.0002$	53.2 42.1 $p = 0.01$	9.9 7.5 $p < 0.0001$	22.6 21.5 $p = 0.18$	$p < 0.0001$	Kelly (71)
Sipuleucel-T vs. placebo	341 171	NR	NR	NR	25.8 21.7 $p = 0.017$	3	Kantoff (106)

[a]Median time to progression
[b](vs. mitoxantrone)

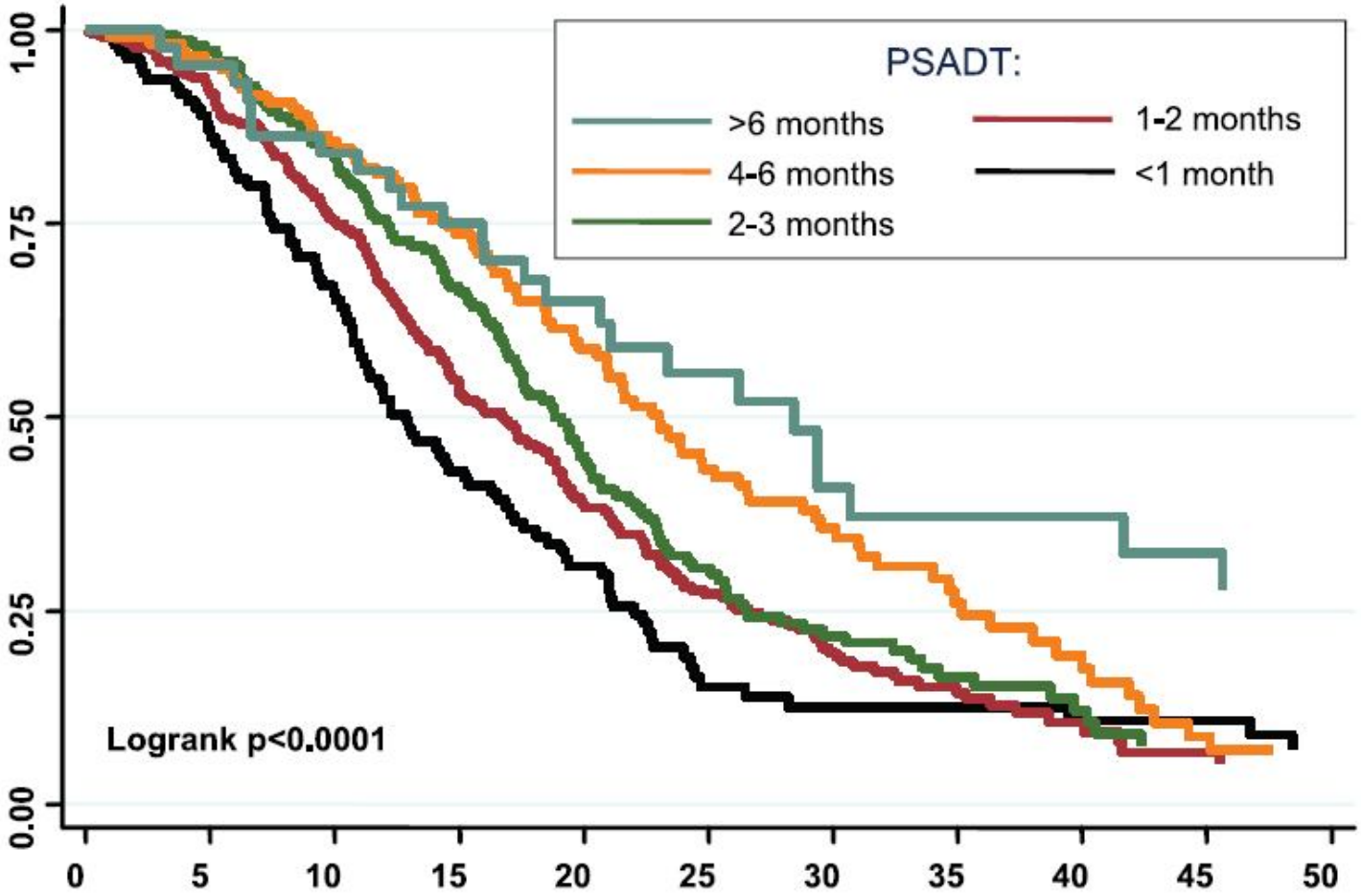
CRPC

- *Estramustine*
- *Mitoxantrone*
- *Docetaxel*
- *Cabazitaxel*

} ***Survival advantage***

- Η διάμεση επιβίωση επί μεταστατικού *CRPC* είναι ακόμη μόνο *2-3* χρόνια

*TAX 327:*βραχύς *PSA- DT* πριν την έναρξη της ΧΜΘ προβλέπει την *OS*



Armstrong et al, Clin Canc Res 2007, 13: 6396-6403

ΕΑΟ οδηγίες

19.10 Summary of treatment after hormonal therapy

(Until results from randomised controlled trials on novel agents MDV3100 and abiraterone become available, there are no significant changes in the treatment of prostate cancer after hormonal therapy [27]).

Recommendations	GR
It is recommended to stop anti-androgen therapy once PSA progression is documented.	B
No clear-cut recommendation can be made for the most effective drug for secondary hormonal.	
manipulations because data from randomised trials are scarce.	C

Comment: Four to six weeks after discontinuation of flutamide or bicalutamide, an eventual anti-androgen withdrawal effect will be apparent.

EAU οδηγίες

19.8.1 ***Timing of chemotherapy in metastatic CRPC***

The timing of chemotherapy varies in metastatic CRPC. It is advisable to start it immediately in symptomatic patients, if possible every 3 weeks, as this schedule is associated with an improvement in survival. However, a weekly regimen will result in the same symptom improvement and must be considered in patients unable to receive the optimal regimen (LE: 1b), as it is more effective than best supportive care (93). In asymptomatic patients, timing is not so clear and must be discussed individually.

Several poor prognostic factors have been described, such as a PSA level > 114 ng/mL, PSA doubling time (PSA-DT) < 55 days, or the presence of visceral metastases (94). A better risk group definition has been recently presented, based on the TAX 327 study cohort. The predictive factors were visceral metastases, pain, anaemia (Hb < 13 g/dL), bone scan progression, and prior estramustine before docetaxel. Patients were categorised into three risk groups: good risk (0–1 factor), intermediate (2 factors) and high risk (3–4 factors), leading to three different median OS: 25.7, 18.7 and 12.8 months, respectively (46) . In addition, two independent studies have suggested that improved survival can be predicted by C-reactive protein (CRP) levels < 8 mg/L (hazard ratio [HR], 2.96) (95,96). Age by itself is not a contraindication to docetaxel (97).

Currently, the only indication for chemotherapy in CRPC non-metastatic patients is inside clinical trials and patients should be advised to participate.

Ποικίλει στον *CRPC*

- Σε μη-μεταστατικούς ασθενείς μόνο εντός κλινικών μελετών
- Σε μεταστατικούς μη- συμπτωματικούς ασθενείς*;*
- Σε μεταστατικούς συμπτωματικούς ασθενείς *:* Άμεσα- βελτίωση της επιβίωσης