

When radical prostatectomy is not enough:

The evolving role of post-operative radiation therapy

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Learning objectives:

To review

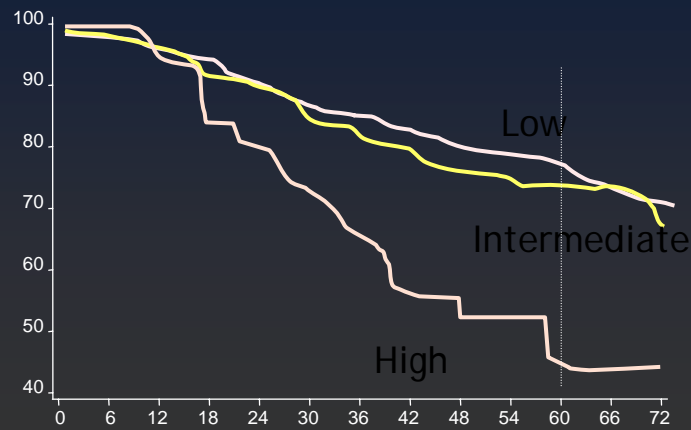
- Contemporary results achieved with RRP
- Local experience with post-operative radiation therapy a) adjuvant b) salvage
- Phase 3 data of the use of adjuvant post-operative radiation
- Salvage options
- [Current trials proposals]

To discuss

- a BC treatment algorithm



Canadian outcomes after RRP

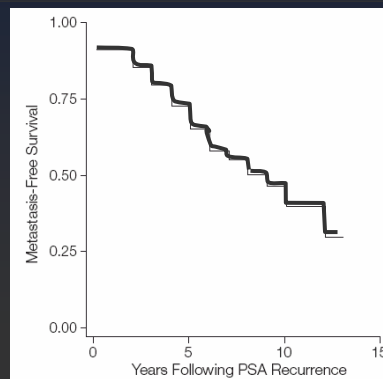


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Redrawn: Gleave 3 v 8 mo CUOG trial

Outcomes after PSA relapse - Pound

- ◆ single-surgeon case series, n= 1997
 - PSA relapse: PSA>0.2
- ◆ 304 relapses

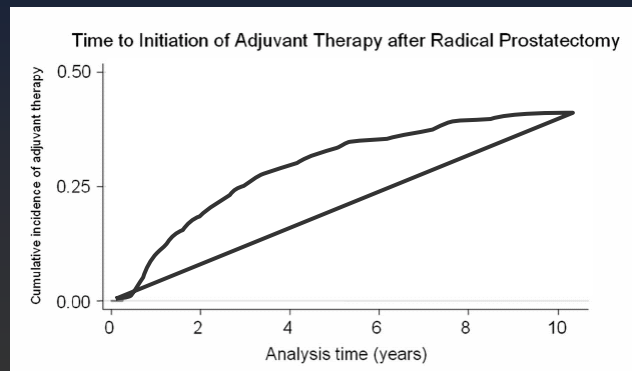


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Pound JAMA, May 5, 1999—Vol 281, No. 17

Use of secondary treatments

- ◆ 40% get secondary therapy eventually



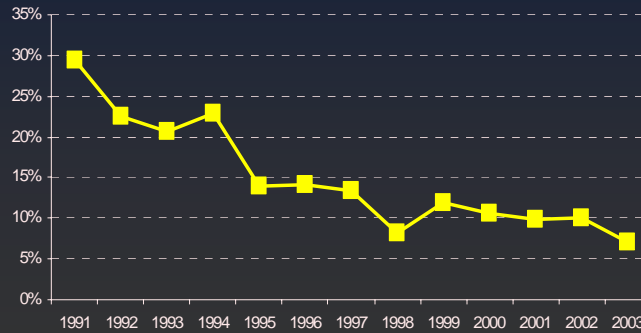
Use of secondary treatments

CAPSURE data

- ◆ Adjuvant
 - 6.5% of RRP patients
 - 13% where +ve margins
- ◆ Subsequently
 - 14%
 - ◆ 43% RT
 - ◆ 56% ADT

Use of secondary radiation

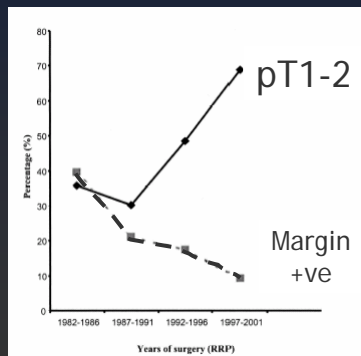
BCCA -declining use of post-op RT



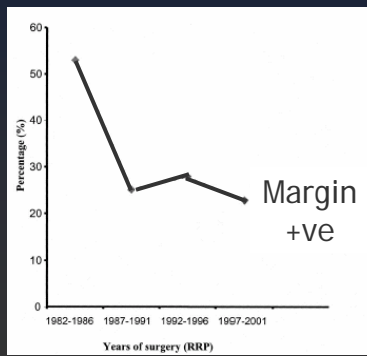
Grossfield et al., UROLOGY 60 (Supplement 3A), September 2002

Positive margin rates

◆ 24% from 3 month arm of 3 v 8 mo study



cT1-2



cT3



Han, Journal of Urology Vol. 171, 23-26, January 2004

What should we be doing for these men?

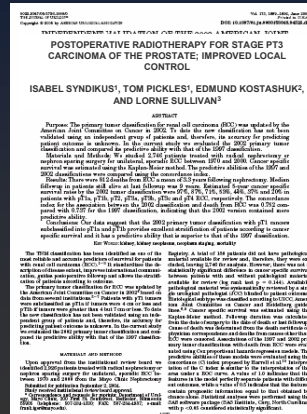


Published BC experience

Isabel Syndikus, Tom Pickles, Ed Kostashuk, And Lorne Sullivan

Prospective study

- 203 consecutive patients, clinical T2
 - ◆ 88 surgery only
 - ◆ 89 early adjuvant RT (mainly pT3)
 - ◆ 29 salvage RT
- Old fashioned RT
 - 50-55Gy in 16-20#



Journal of Urology, Volume 155(6), June 1996



BC experience

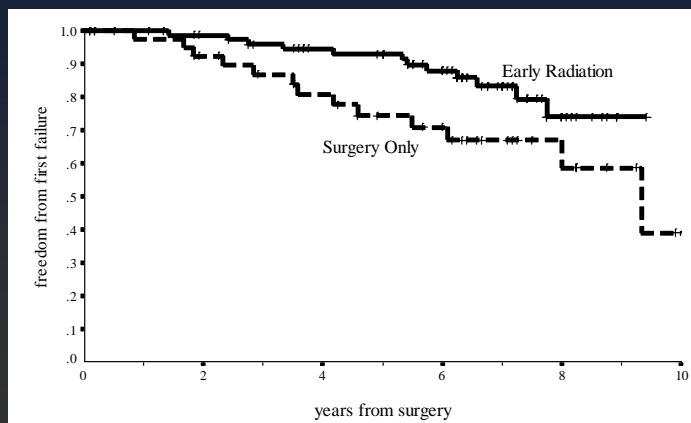
3 Groups followed prospectively
-baseline characteristics

	<u>Surgery only</u>	<u>Adjuvant</u>	<u>Salvage</u>
+ve margins	45%	90%	69%
SV +ve	7%	39%	12%
Ece	30%	60%	57%



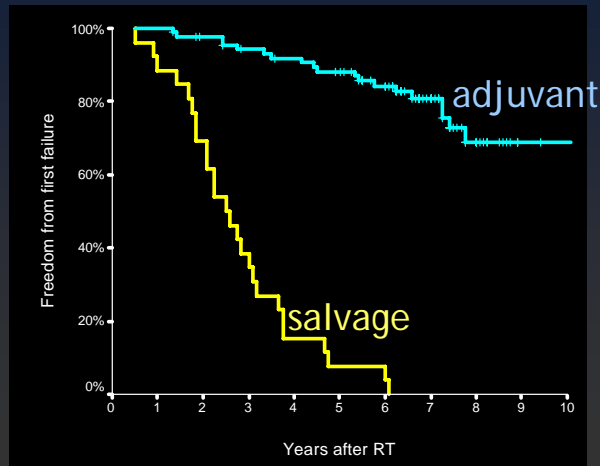
Syndikus et al, Journal of Urology, Volume 155(6), June 1996, pp 1983-1986

BC experience



Syndikus et al, Journal of Urology, Volume 155(6), June 1996, pp 1983-1986

BC experience salvage v adjuvant



Syndikus et al, Journal of Urology, Volume 155(6), June 1996, pp 1983-1986

Multivariate Analysis

Factor	p	Relative Risk
Post-op PSA	<0.001	1.13/ng/ml
Seminal vesicle	<0.001	3.13
Early Post-op RT	0.006	0.43
Lymph nodes	0.024	1.85
Positive margins	0.06	1.7
Extracapsular extension	ns	-
Pathological grade	ns	-



Syndikus et al, Journal of Urology, Volume 155(6), June 1996, pp 1983-1986

Multivariate Analysis

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Syndikus et al, Journal of Urology, Volume 155(6), June 1996, pp 1983-1986

Toxicity

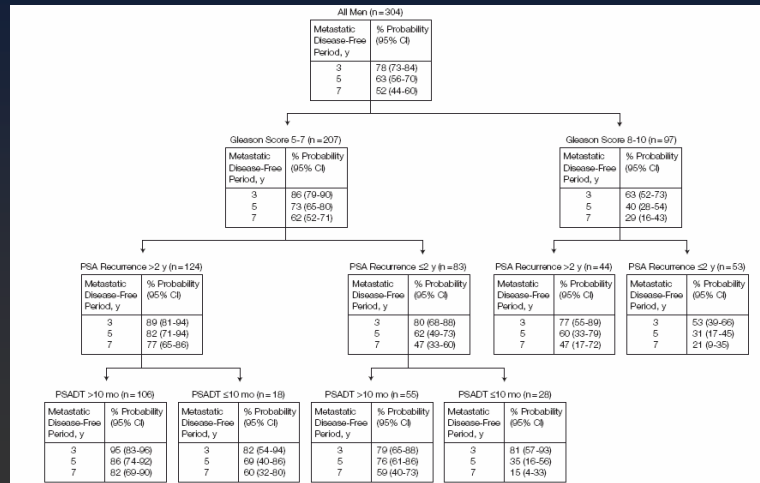
p=0.009 overall

	<u>Surgery only</u>	<u>Adjuvant</u>	<u>Salvage</u>
GU grade 2	27%	25%	27%
GU grade 3	15%	13%	15%
GU grade 4	0%	6%	12%
GI grade 2	2%	10%	4%
GI grade 3	0%	0%	0%
GI grade 4	1%	0%	0%
Impotent	59%	89%	



Syndikus et al, Journal of Urology, Volume 155(6), June 1996, pp 1983-1986

Pound algorithm for relapse



Kattan nomogram for relapse

Memorial Sloan-Kettering Cancer Center

Prostate Nomogram - Post-Radical Prostatectomy [Change Treatment Stage](#)

Pre-treatment PSA: 8
 Prostate Capsule Inv: Est.
 Pathology Gleason Sum: 7
 Surgical Margins Pos
 Seminal Vesicle Inv
 Lymph Node Involvement
 Neo-Adjuvant Hormones
 Neo-Adjuvant XRT

Results

2 yr Progression-Free Probability: **65%**
 5 yr Progression-Free Probability: **38%**
 7 yr Progression-Free Probability: **30%**

To learn more about Progression-Free Probability, [click here](#). Results are accurate to +/- 8%. Print your results and discuss them with your doctor.



www.nomograms.org

Adverse factors

- ◆ Pre-op Staging
 - PSA, Gleason, % +ve cores, T stage
- ◆ Post-op pathology
 - Nodal status
 - Margin +ve
 - SV +ve
 - Capsule penetration - Focal or established
- ◆ Post-op PSA kinetics

Adjuvant RT for Prostate Cancer

Postoperative irradiation of the prostatic bed for node negative patients with undetectable PSA following radical prostatectomy

Adjuvant RT for Prostate Cancer

Postoperative irradiation of the prostatic bed for **node negative** patients with undetectable PSA following radical prostatectomy

Adjuvant RT for Prostate Cancer

Postoperative irradiation of the prostatic bed for **node negative** patients with **undetectable PSA** following radical prostatectomy

Adjuvant RT Case Series

<u>Author</u>	<u>n</u>	<u>bNED</u>
Morris, 1997	40	88%
Valicenti, 1999	52	88%
Catton, 2001	51	81%
Choo, 2002	73	88%
Do, 2002	42	88%
Kalapurakal, 2002	35	86%
Mayer, 2002	29	85%
Taylor, 2003	75	88%
Tsien, 2003	38	53%
Kamat, 2003	62	90%

Numerous
small, generally
unhelpful
studies

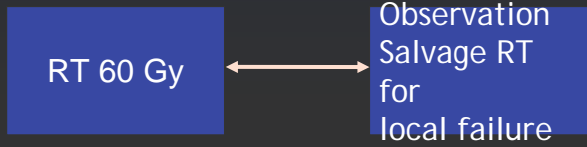
Randomized studies -adjuvant

EORTC 22911 –pT3



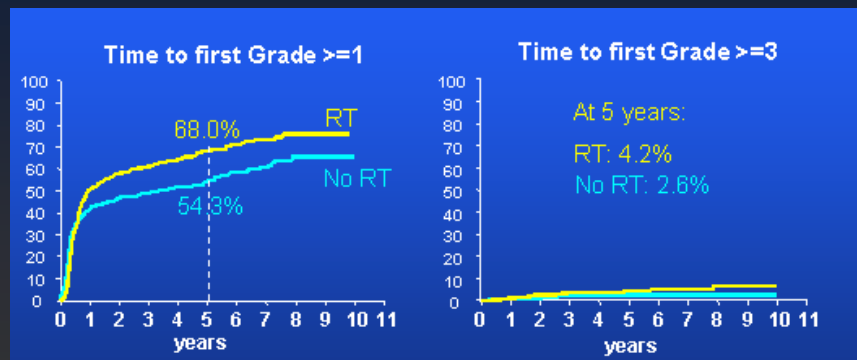
Randomised trial of post-op RT (60Gy)

- capsule invasion (64%), positive margins (50%), seminal vesicle (13%) invasion
- G1 13%, G2 63%, G3 24%
- 1005 patients accrued, patients well balanced
- Median follow-up 5 years



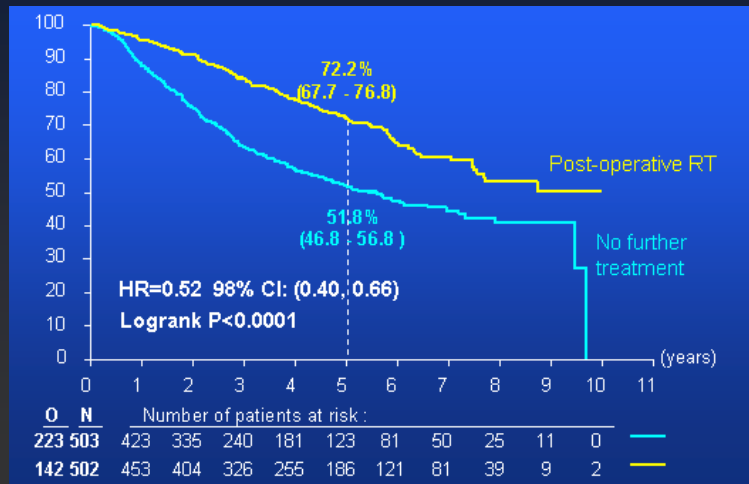
Bolla, ASCO & ASTRO 2004

EORTC 22911 – late toxicity

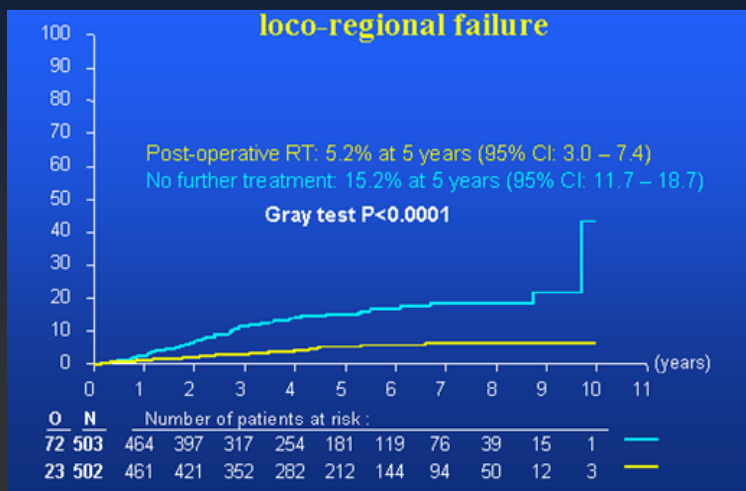


Bolla, ASCO 2004

EORTC 22911 – relapse rate



EORTC 22911 – Loco-regional failure



EORTC 22911



	<u>RRP alone</u>	<u>RRP/EBRT</u>	<u>HR</u>
bNED	52%	72%	0.52
Clinical PFS	75%	83%	
Grade 1-2 tox	54%	68%	
Grade 3 tox	2.6%	4.2%	

No survival data yet (only 89 deaths)



Bolla, ASCO 2004

NCIC PR-2 / SWOG 8794



Prostatectomy

Extra-capsular
+ve margins
+ve SV's

RT 60-64 Gy

Observation

No stratification by Pre-RT PSA



Thompson, AUA May 2005

NCIC PR-2



1^o endpoint - metastasis free survival

- ◆ 1988-1995
 - 473 pts with reviewed pT3 cancer
 - Followed until death
 - Median follow-up 9.7 years



Thompson, AUA May 2005

NCIC PR-2



	<u>Adjuvant RT</u>	<u>Obs</u>	<u>HR</u>	<u>p</u>
PSA relapse (<0.4ng/ml)	53%	77%	0.51	<0.001
PFS	67%	48%	0.59	0.001
Mets -free	71%	61%	0.8	0.17
O/S	74%	63%	0.76	0.11



Thompson, AUA May 2005

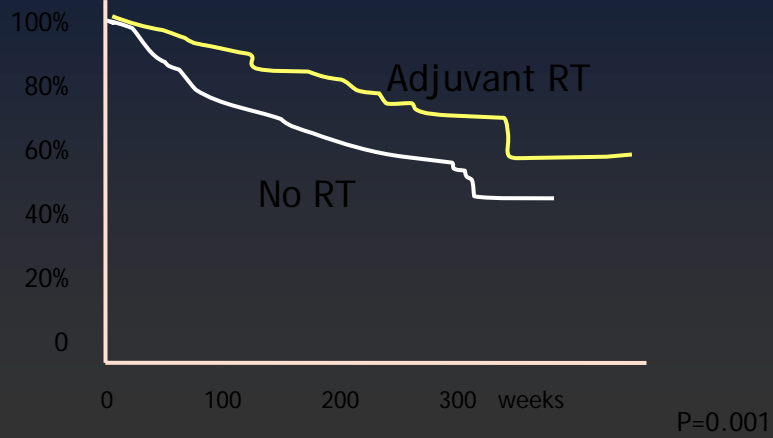
German phase 3 trial

- ◆ pT3 cancer
 - Undetectable post-op PSA
- ◆ Randomized to adjuvant RT or not
 - 60Gy, 3-d conformal RT
 - 2-3 months post-op
- ◆ Median follow-up 3 years
- ◆ Stratified for
 - Gleason, N-ADT use,
 - Margin status, pT3a v. pT3b v. pT3c

German phase 3 trial

- ◆ 140 randomized to adjuvant RT
 - 32 told by Urologist not to have the RT!
 - 108 followed protocol treatment
- ◆ 153 randomized to no therapy
 - 6 had RT

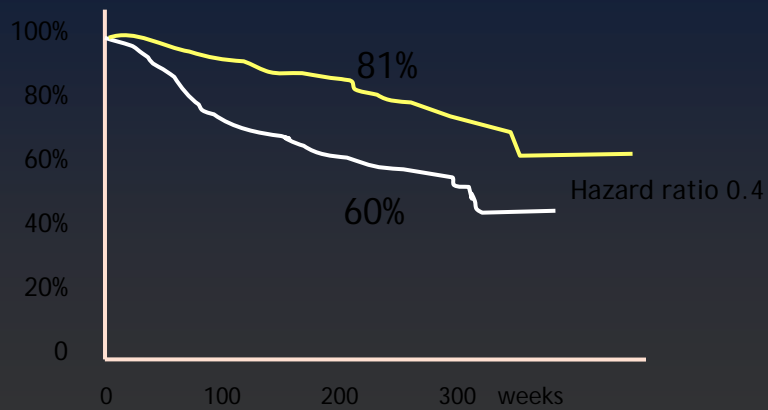
Progression free survival Intention to treat analysis



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T. Wiegel et al., ASCO 2005

Progression free survival protocol - delivered analysis



BC Cancer Agency
CARE & RESEARCH

T. Wiegel et al., ASCO 2005

Toxicity

◆ Acute

- Grade 2 12%
- Grade 3 3%

◆ Late

- Grade 2 6%
- Grade 3 2%

PFS: Predictive factors of benefit

Significant factors

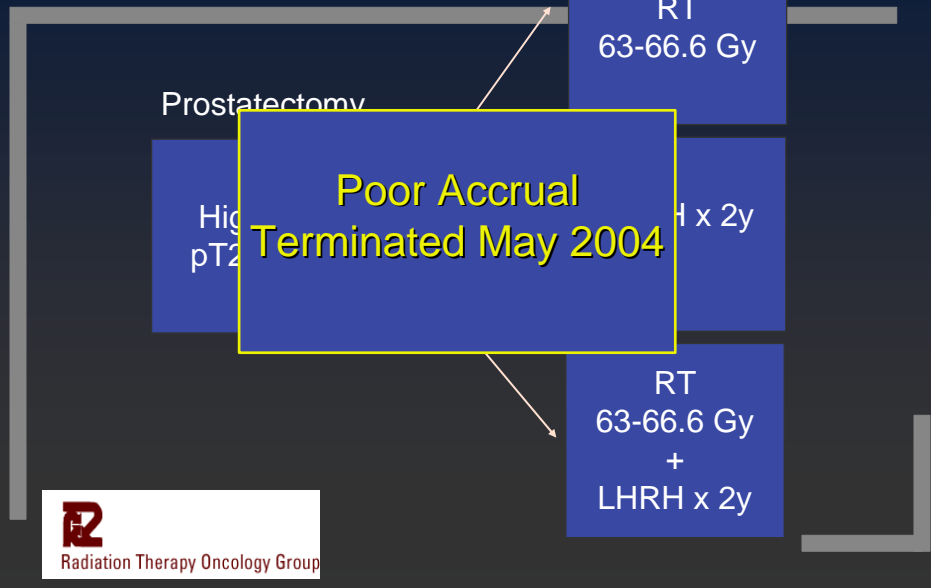
iPSA > 10

Gleason 2-6

SV -ve

Margin +ve

RTOG P-0011



Summary randomized trials

All 3 concordant for

- ◆ ~50% decrease PSA failure rate
- ◆ ~40% decrease clinical relapse rate

Most mature trial

- ◆ 10% absolute improvement M+ and death rates

But what about waiting for
the PSA to rise?

- SALVAGE RADIATION?

Salvage RT

- ◆ *Early:*
 - *When the PSA starts to rise*
- ◆ *Late (?too late)*
 - *For PSA's >2*
 - *For local relapse*

Pollack Multi-institution analysis

- ◆ 1168 men
 - minimum of 12 mo follow-up post-RT
 - 68% salvage RT
 - ◆ Persistent PSA group
 - ◆ Delayed rise group
 - 16% adjuvant RT (RT within a year, PSA<0.2)
 - Median follow-up 6 years

Recursive partitioning

	<u>Factors</u>	<u>bNED</u>
Group 1	PSA<0.2, no SVI	84%
Group 2	PSA<0.2, & SVI <i>or</i> PSA 0.2-1, No SVI, GS2-7	56%
Group 3	PSA 0.2-1, SVI, GS2-7	33%
Group 4	PSA>1, GS 2-7	26%
Group 5	GS 8-10, PSA<0.2	14%

MVA – adverse features

- ◆ **Metastasis**
 - SV+ve, margin -ve, Gleason 8-10
- ◆ **Overall survival**
 - SV+ve, margin -ve
- ◆ Patients who received **salvage RT** as opposed to adjuvant

Benefit of adjuvant v salvage

	<u>Adjuvant</u>	<u>Salvage</u>
bNED	72%	35%
Mets	1%	10%
Death	4%	7%

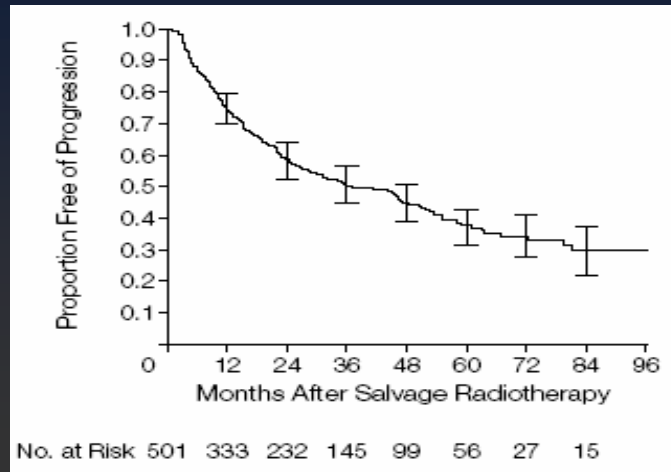
MVA – Salvage RT

	<u>p value</u>
SV +ve	p=0.00
Higher pre-RT PSA	p<0.001
Gleason 8-10	p=0.0006
-ve margins	ns
Higher RT dose	ns
ADT	ns

Salvage Radiotherapy for Recurrence

- ◆ 5 tertiary centres combined data
- ◆ 1987-2002
- ◆ 501 Patients - all received RT
 - Mean age 62
 - 96% PSA \geq 0.2
 - 21% Biopsy +
 - 32% Persistent PSA Post prostatectomy
 - 17% Neoadjuvant hormones - median 3 months
 - RT dose median 6480
 - Median FU 45 Months

They did not do well



MVA – predictors of progression

<u>Factor</u>	<u>p</u>	<u>HR</u>
Gleason 7 (v 4-6)	0.06	1.5
Gleason 8 (v 4-6)	0.001	2.6
Post-op PSA >2 (v <1)	0.001	2.3
-ve margin	0.001	1.9
PSAdt <10months	0.001	1.7
SV +ve	0.02	1.4

MVA – predictors of progression

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Gleason 7 (v 4-6)	0.06	1.5
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Post-op PSA >2 (v <1)	0.001	2.3
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What about using hormones as well or instead?

With salvage RT - Only phase 2 data

Study	Follow-up (yr)	Arm	HT Duration (mo)	n
Wiegel <i>et al.</i> ²⁰	10	RT + AA	Orchiectomy	27
		RT		29
Taylor <i>et al.</i> ²¹	5	RT + AA	24	35
		RT		36
de la Taille <i>et al.</i> ²²	3	RT + AA	4-6	34
		RT		18
Katz <i>et al.</i> ²³	4	RT + AA	3	45
		RT		70
Eulau <i>et al.</i> ²⁴	5	RT + AA	6	29
		RT		74
King <i>et al.</i> ²⁵	5	RT + AA	4	50
		RT		79
Song <i>et al.</i> ²⁶	4	RT + AA	4	30
		RT		31
Corn <i>et al.</i> ²⁷	5	RT + AA	Indefinite	71
		RT		68

Stephenson MVA – non significant factors

Factor

iPSA > 10

Extra-capsular extension

Time to relapse < 12 mo

Neoadjuvant -ADT

Lower RT dose

Stephenson MVA – non significant factors

Factor

iPSA>10

Extra-capsular extension

Time to relapse <12 mo

Neoadjuvant -ADT

Lower RT dose



Stephenson JAMA, March 17, 2004—Vol 291, No. 11

RTOG 96-01

◆ pT3 cancer

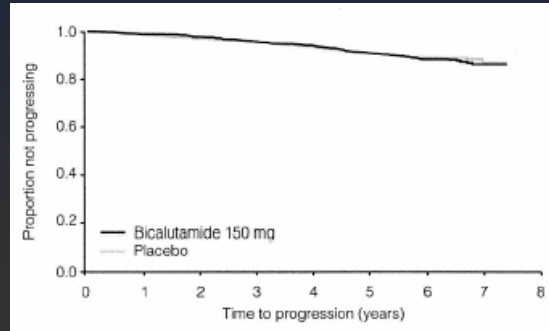
- Randomized to RT +/- bicalutamide 150
- Stratified by
 - ◆ NA-ADT,
 - ◆ Margin +ve,
 - ◆ PSA nadir<0.5,
 - ◆ PSA entry <.1.5
- 840 randomized
- Closed 3/2003 - results pending



EPC data at 5.4 yrs median f/up

N American trial (23)

- ◆ Increased deaths in bicalutamide group (8.8 v 8.1%)
- ◆ Significantly so in w/waiting trial (EU) (25 v 20%)



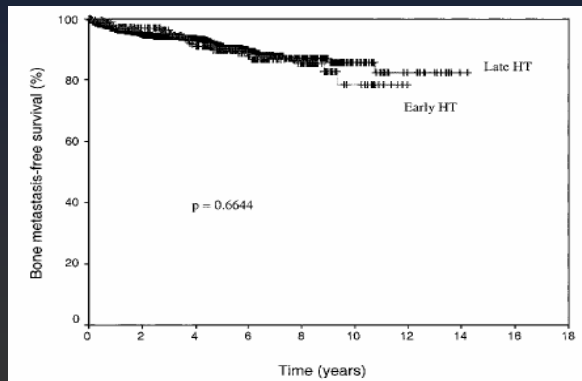
DoD Prostate Registry

1352 Pts

- ◆ PSA failure (>0.2)
- ◆ Median age 64
- ◆ Median f/up 5 years
- ◆ 3 groups
 - No ADT 58%
 - Early ADT 21%
 - Late ADT 21%

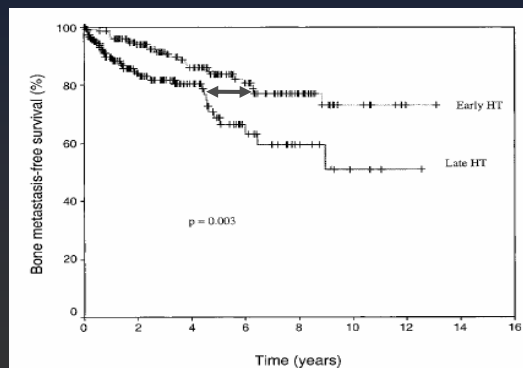
Timing of ADT - overall

- ◆ No impact on development of mets



Timing of ADT - subgroups

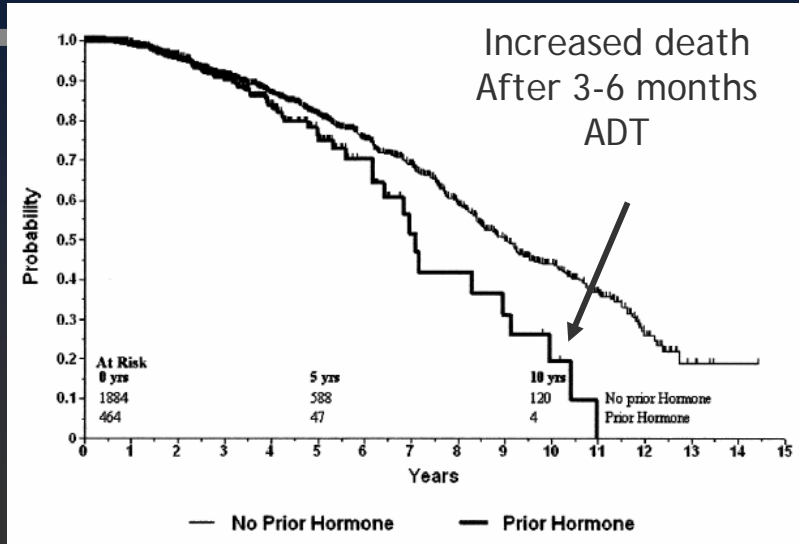
- ◆ PSA <10 at institution of ADT



Delayed fatal effects of ADT?

Impact of 3-6 months ADT on overall survival in men with low-intermediate Ca prostate

DAVID C. BEYER
Int. J. Radiation Oncology Biol. Phys.,
Vol. 61, No. 5, pp. 1299-1305, 2005



DAVID C. BEYER
Int. J. Radiation Oncology Biol. Phys., Vol. 61, No. 5, pp. 1299-1305, 2005

The patient's perspective

Patients must be consulted

- ◆ Men who underwent RRP
 - Are generally 'young'
 - Fit
 - Chose a curative approach
- Adjuvant or (early) salvage therapy should be discussed with them
 - As many will likely want to pursue it

Conclusions

1. Adjuvant RT is an acceptable approach in pT3 patients who prefer immediate treatment. (*Level 1 evidence*)
2. No definite recommendation can be made about the relative therapeutic benefit of immediate adjuvant RT vs. 'early delayed' salvage RT at the time of PSA failure. Patients should be informed about the advantages and disadvantages of both approaches to assist them in decision making.

Conclusions

1. Patients who choose not to have RT should be followed closely, and considered for salvage RT at the first indication of PSA elevation. (*Level 4 evidence*)
1. The value of androgen suppression in combination with radiotherapy is unknown.
1. Adjuvant bicalutamide is of no value (*Level 1 evidence*)

BC management guidelines

For discussion

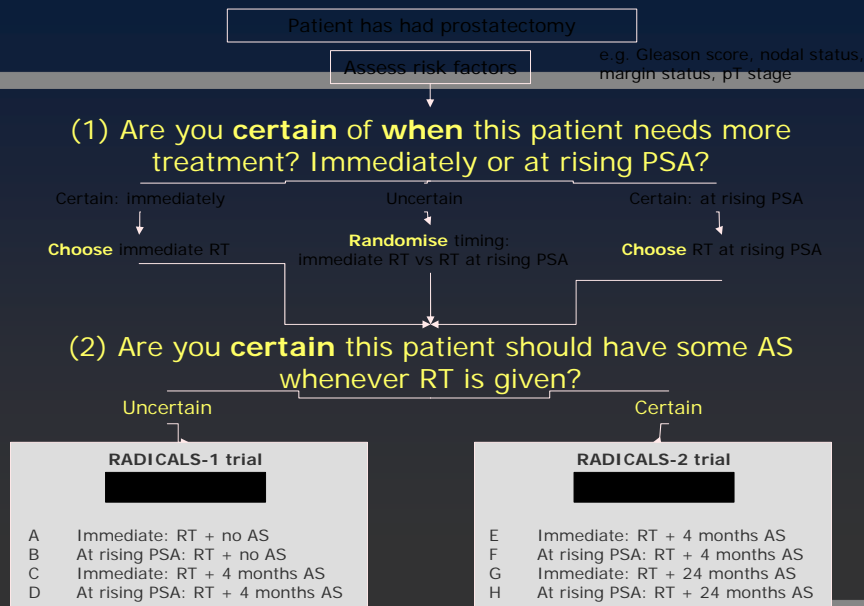
Patients should be referred for

- ◆ Adjuvant radiation therapy
 - if pT3, or margin +ve (except focal)
- ◆ Salvage radiation
 - when PSA relapse has occurred (>0.2)
 - ◆ treatment is more effective earlier rather than later

Trial proposals



RADICALS trials - design chart UK-MRC



¹ Can choose or randomise timing of RT: immediately or at rising PSA

A Phase 3 Trial Of RT With Or Without Short Term Androgen Deprivation For Patients With A Rising PSA After Radical Prostatectomy - Pollack

S	<u>SV Involvement</u>	R	Arm 1: PBO RT
T	1. No 2. Yes	N	
R	<u>Prostatectomy Gleason score</u>	D	vs Arm II: WP RT
A		1. Gleason ≤7 2. Gleason 8-10	O
T	<u>Pre-Radiotherapy PSA Level</u>	M	vs Arm III: PBO RT +STAD
I		1. PSA ≤1 ng/ml 2. PSA >1 ng/ml	I
F	Margin status? Undissected nodes?	Z	vs Arm IV: WP RT + STAD
Y		E	

SV = seminal vesicle; PBO =prostate bed only; WP =whole pelvis; RT =radiotherapy; STAD =short term androgen deprivation

Pollack trial proposal

- ◆ To determine
 - whether WP is better than PBO and
 - STAD+RT is better than RT alone
- ◆ PSA relapse primary endpoint
 - (freedom from a PSA >0.4 ng/ml and rising at >12 mo after RT)
- ◆ Freedom from distant metastasis, cause specific survival and overall survival rates secondary endpoints.
- ◆ Acute and late morbidity.
- ◆ Quality of life.

+ translational components

- ◆ molecular markers from archival prostatectomy specimens, such as
 - Cox-2, p53, Ki-67, DNA-ploidy, bcl-2, bax, MDM2 and p16
- ◆ To collect pretreatment serum for future proteomics studies.