Localized Carcinoma of Prostate : Landmark Trials

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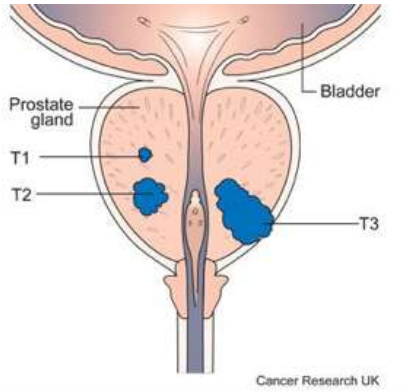
Localized Ca Prostate: T1 – T3a No

Tumor	
T0	No evidence primary tumor
T1	Not detectable on DRE/imaging
T1 a/b	Incidental finding in specimen resected for another reason
T1c	Detected on biopsy for raised PSA
T2	Detectable on DRE/imaging, confined to prostate
T2a	In < one half of one lobe of prostate
T2b	In > one half of one lobe of prostate
T2c	In both lobes of prostate
T3	Spread outside prostate
T3a	Spread to prostate capsule
T3b	Spread to seminal vesicles
T4	Spread to local structures
Nodes	
N0	No spread to nodes
N1	Spread to pelvic nodes
Metastases	
M0	No evidence of spread outside the pelvis
M1a	Spread to distant lymph nodes e.g. para-aortic
M1b	Spread to bone
M1c	Visceral spread +/- bone e.g. liver, lungs

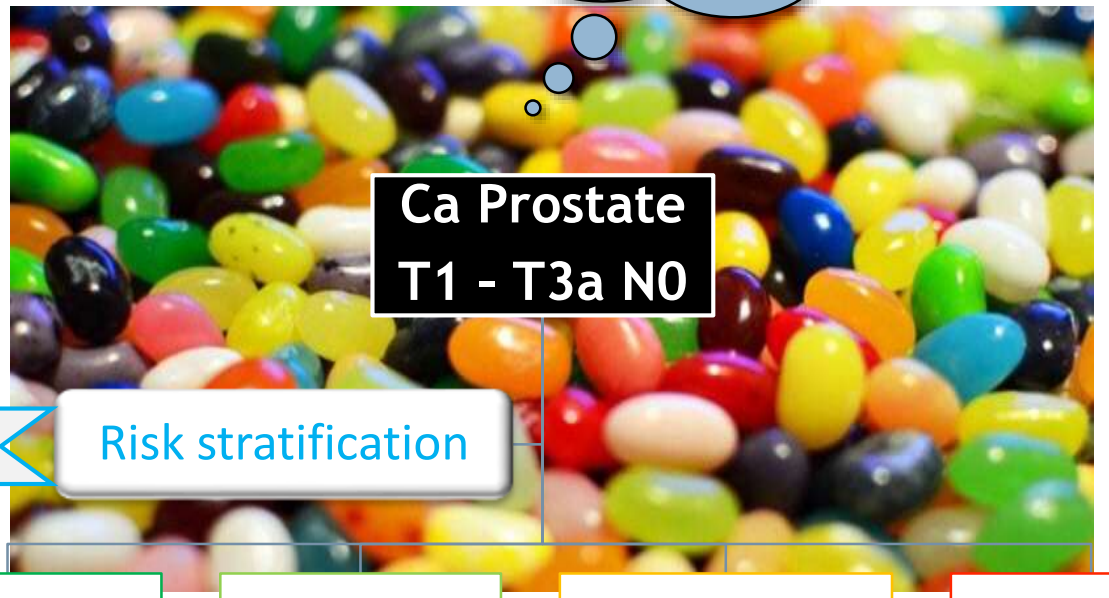


- **Serum PSA**
- **DRE**
- **TRUS / MRI Pelvis**
- **TRUS guided Biopsy – 10 – 12 core**
- **Gleason score**
- **CECT Abdomen (L.N involvement)**
- **Bone scan – if PSA > 20**
- **PSMA PET CT scan (Optional)**

Management:

Risk Group	Clinical/Pathologic Features See Staging (ST-1)		
Very low[f]	Has all of the following: • cT1c • Grade Group 1 • PSA <10 ng/mL • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core[g] • PSA density <0.15 ng/mL/g		
Low[f]	Has all of the following but does not qualify for very low risk: • cT1–cT2a • Grade Group 1 • PSA <10 ng/mL		
Intermediate[f]	Has all of the following: • No high-risk group features • No very-high-risk group features • Has one or more intermediate risk factors (IRFs): ▸ cT2b–cT2c ▸ Grade Group 2 or 3 ▸ PSA 10–20 ng/mL	Favorable intermediate	Has all of the following: • 1 IRF • Grade Group 1 or 2 • <50% biopsy cores positive (eg, <6 of 12 cores)[g]
		Unfavorable intermediate	Has one or more of the following: • 2 or 3 IRFs • Grade Group 3 • ≥ 50% biopsy cores positive (eg, ≥ 6 of 12 cores)[g]
High	Has no very-high-risk features and has exactly one high-risk feature: • cT3a OR • Grade Group 4 or Grade Group 5 OR • PSA >20 ng/mL		
Very high	Has at least one of the following: • cT3b–cT4 • Primary Gleason pattern 5 • 2 or 3 high-risk features • >4 cores with Grade Group 4 or 5		

Life expectancy



Risk stratification

- Very low risk
- Low risk
- Intermediate
  - Favourable
  - Unfavourable
- High risk

Watchful Waiting

Very low risk
Low risk

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Radical Prostatectomy versus Watchful Waiting in Early Prostate Cancer

Anna Bill-Axelson, M.D., Lars Holmberg, M.D., Ph.D., Mirja Ruutu, M.D., Ph.D., Michael Häggman, M.D., Ph.D., Swen-Olof Andersson, M.D., Ph.D., Stefan Bratell, M.D., Ph.D., Anders Spångberg, M.D., Ph.D., Christer Busch, M.D., Ph.D., Stig Nordling, M.D., Ph.D., Hans Garmo, Ph.D., Juni Palmgren, Ph.D., Hans-Olov Adami, M.D., Ph.D., Bo Johan Norlén, M.D., Ph.D., and Jan-Erik Johansson, M.D., Ph.D., for the Scandinavian Prostate Cancer Group Study No. 4*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 19, 2012 VOL. 367 NO. 3

Radical Prostatectomy versus Observation for Localized Prostate Cancer

Timothy J. Wilt, M.D., M.P.H., Michael K. Brawer, M.D., Karen M. Jones, M.S., Michael J. Barry, M.D., William J. Aronson, M.D., Steven Fox, M.D., M.P.H., Jeffrey R. Gingrich, M.D., John T. Wei, M.D., Patricia Gilhooly, M.D., B. Mayer Grob, M.D., Imad Nsouli, M.D., Padmini Iyer, M.D., Ruben Cartagena, M.D., Glenn Snider, M.D., Claus Roehrborn, M.D., Ph.D., Roohollah Sharifi, M.D., William Blank, M.D., Parikshit Pandya, M.D., Gerald L. Andriole, M.D., Daniel Culkin, M.D., and Thomas Wheeler, M.D., for the Prostate Cancer Intervention versus Observation Trial (PIVOT) Study Group

SPCG - 4

Radical Prostatectomy vs Watchful Waiting In Early Prostate Cancer

NEJM, 2002, 2008, 2015, 2020

Purpose: survival benefit of Radical prostatectomy in early prostate cancer

Methods

Oct, 1989 – Feb, 1999
Clinical stage: T1b, T1c,T2
N - 695 (< 75 yrs)

R

- Surgery
- WW

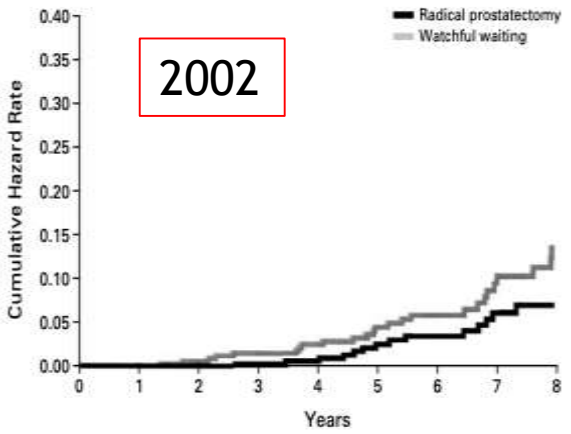
Follow up: 6 monthly for 2 years then annually
Clinical exam,
Hb, Cr, PSA, Alk P
Blinded evaluation of cause of death

Primary end point:
- Death due to prostate cancer

Secondary end points:
- Overall mortality,
- metastasis-free survival
- local progression

Results

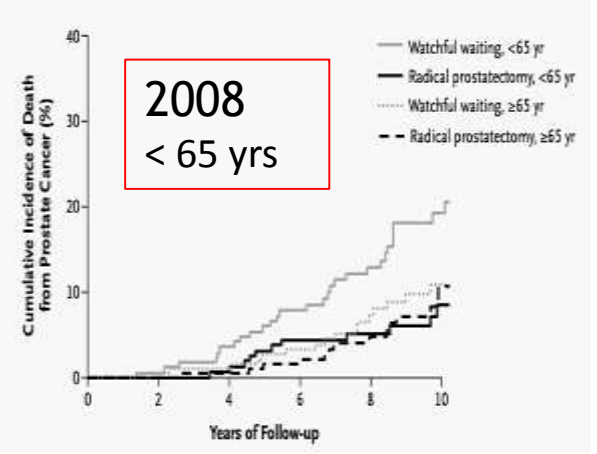
2002



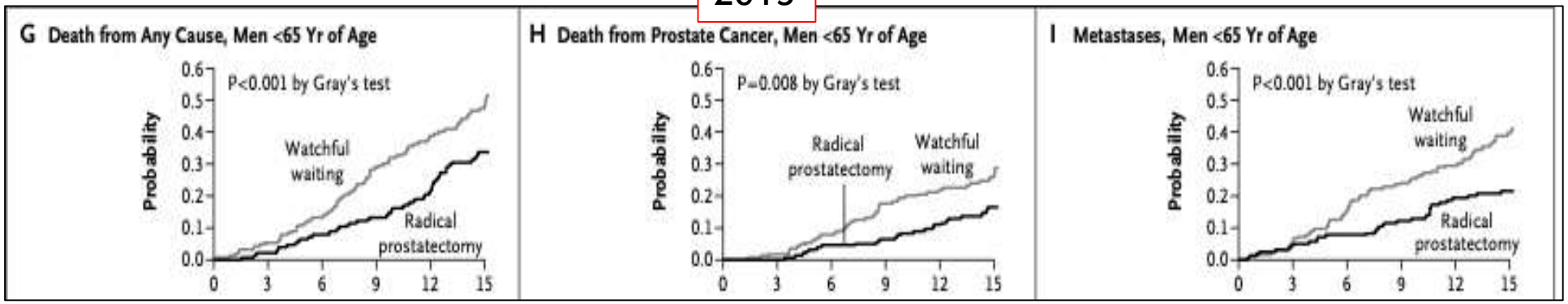
Radical prostatectomy:
↓ death from prostate cancer

Benefit is more in pt < 65 yrs
In surgery group: extra-prostatic extension / margin +ve poor prognostic factors – need adjuvant T/t

2008
< 65 yrs



2015



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Results

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Radical Prostatectomy or Watchful Waiting in Prostate Cancer — 29-Year Follow-up

Clinically detected + Localized prostate cancer + Long life expectancy
=> benefited from Radical prostatectomy (i.e mean of 2.9 yrs of life gained)

Risk of Death from prostate cancer:
- High Gleason score (> 7)
- Extracapsular extension +ve in the radical prostatectomy specimens

PIVOT

Radical Prostatectomy vs Observation for Localized Prostate Cancer

Timothy et al
NEJM, 2012

Purpose: Effectiveness of Surgery vs Observation in localized Ca Prostate, detected by PSA testing

Methods

Nov 1994 - Jan 2002
Localized Ca Prostate
N - 731

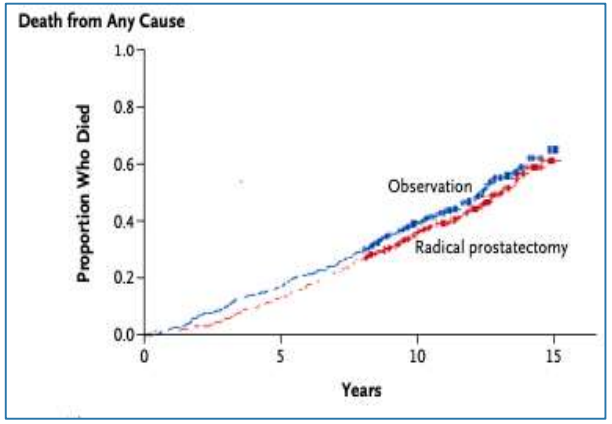
R

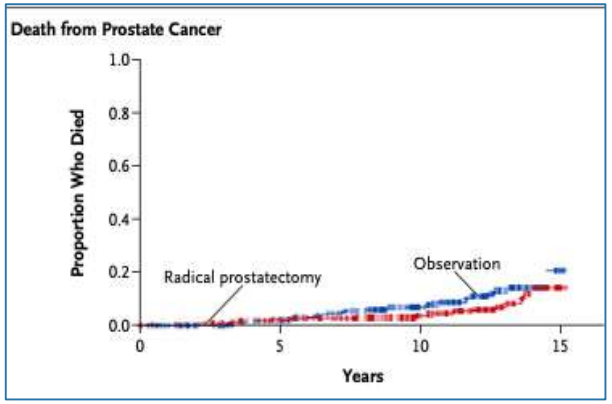
- Surgery
- Observation

F.U. till Jan, 2010
Every 6 months

Primary outcome:
- **All-cause mortality**

Secondary outcome
- **Prostate-cancer mortality**





Results

NO sig. diff. b/w groups

- All-cause mortality: according to age, Gleason score (<7 vs. ≥7), self-reported race, self-reported performance status, score on the Charlson comorbidity index
- Prostate-cancer mortality: according to age, race, score on the Charlson comorbidity index, or self-reported performance status

Subgroup analyses

Surgery might reduce mortality among men with *higher PSA values* and possibly among men with *higher-risk tumors*,

But not among men with PSA levels < / = 10 ng/ml or less or among men with low-risk tumors.

C O N C L U S I O N

Radical prostatectomy did not significantly reduce all-cause or prostate-cancer mortality, as compared with observation

PIVOT

Radical Prostatectomy vs Observation for Localized Prostate Cancer

Timothy et al
NEJM, 2017
EU 2020

Purpose: Effectiveness of Surgery vs Observation in localized Ca Prostate, detected by PSA testing

Methods

Nov 1994 - Jan 2002
Localized Ca Prostate
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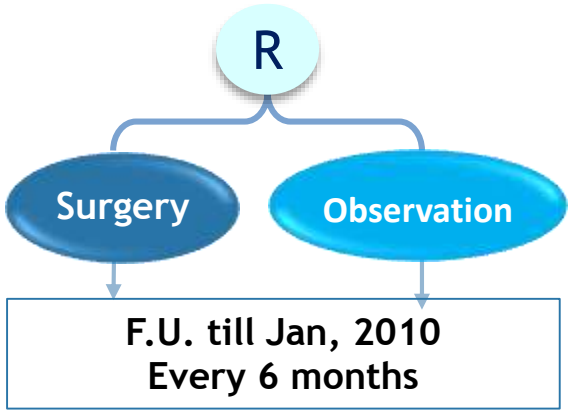
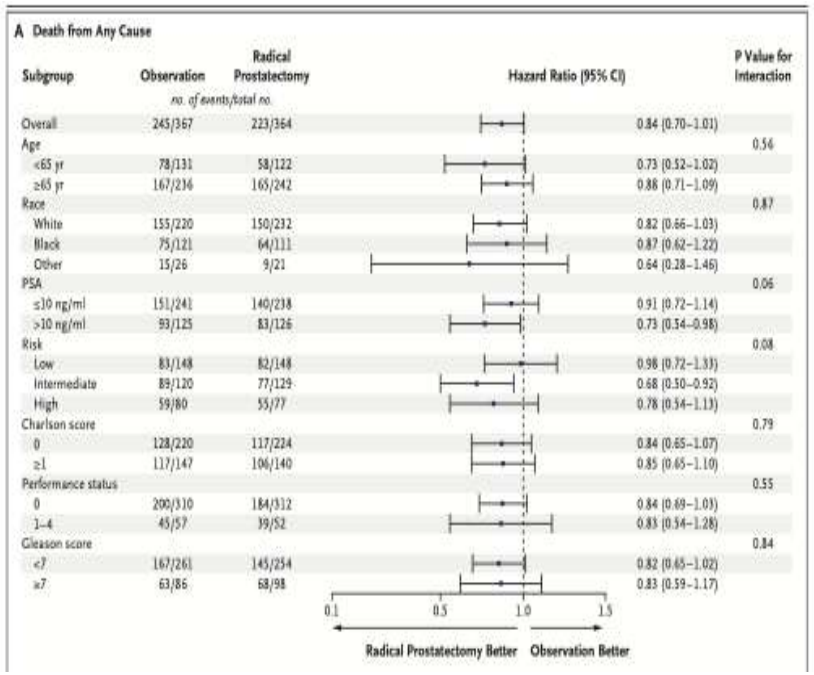


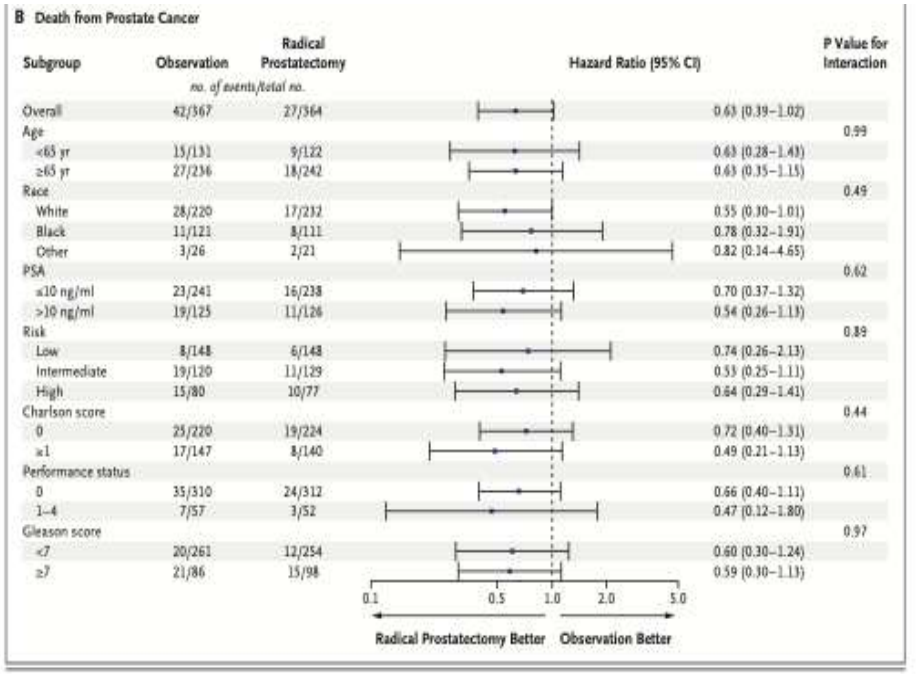
F.U. till Jan, 2010
Every 6 months

Primary outcome:
- **All-cause mortality**

Secondary outcome
- **Prostate-cancer mortality**



R E S U L T S



C O N C L U S I O N

- **Surgery was *not associated* with significantly lower all-cause or prostate-cancer mortality than observation.**
- Surgery arm (in comp. with Observation arm)
  - More adverse events
  - Lower frequency of T/t for ds progression (*asymptomatic/ local/ bioch. Progression)*

PIVOT

Radical Prostatectomy vs Observation for Localized Prostate Cancer

Timothy et al
NEJM, 2017
EU 2020

Purpose: Effectiveness of Surgery vs Observation in localized Ca Prostate, detected by PSA testing

Methods

Nov 1994 - Jan 2002
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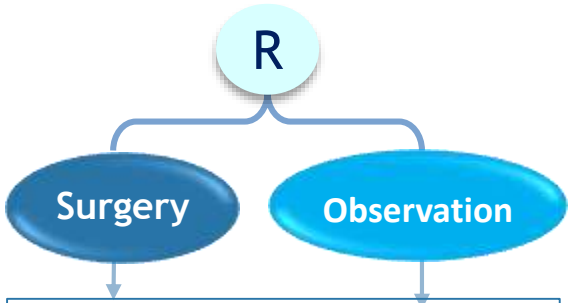
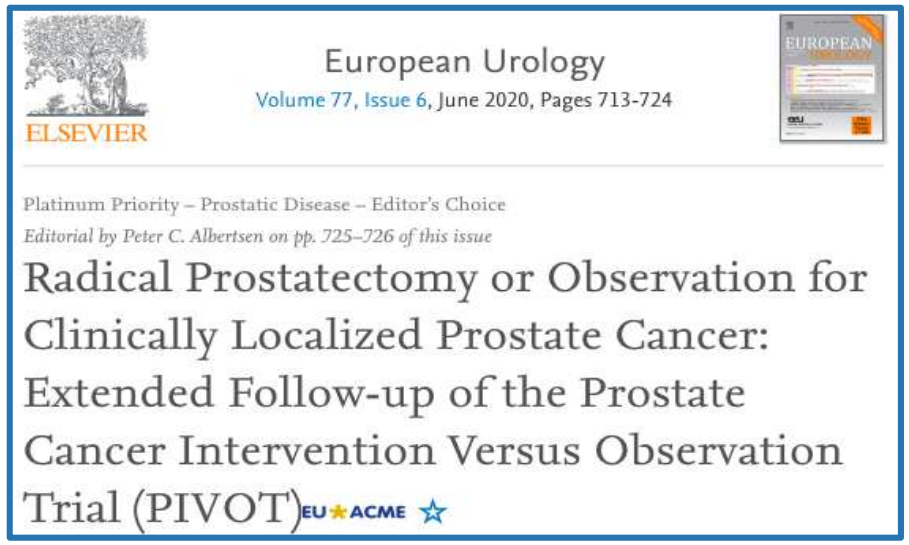


F.U. till Jan, 2010
Every 6 months

Primary outcome:
- **All-cause mortality**

Secondary outcome
- **Prostate-cancer mortality**


ELSEVIER
European Urology
Volume 77, Issue 6, June 2020, Pages 713-724

Platinum Priority – Prostatic Disease – Editor's Choice

Editorial by Peter C. Albertsen on pp. 725–726 of this issue

Radical Prostatectomy or Observation for Clinically Localized Prostate Cancer: Extended Follow-up of the Prostate Cancer Intervention Versus Observation Trial (PIVOT) EU ★ ACME ☆

Surgery was a/w small but very long term all-cause mortality
- Relative reduction was 8%,
- Absolute reduction of 5.7 %
- Mean survival increase of 1 yr.

Absolute effects did not vary markedly by patient characteristics.

- Differences were larger *favoring surgery* among men
  - aged < 65 yrs,
  - white race,
  - better health status,
  - fewer comorbidities,
  - >34% +ve biopsy cores,
  - intermediate risk disease

*** *Results were not adjusted for multiple comparisons, & could not assess outcomes other than all-cause mortality.*

Active Surveillance

Low risk
Intermediate risk

VOLUME 28 · NUMBER 1 · JANUARY 1 2010
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

VOLUME 33 · NUMBER 3 · JANUARY 20 2015
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Clinical Results of Long-Term Follow-Up of a Large, Active Surveillance Cohort With Localized Prostate Cancer

Laurence Klotz, Liying Zhang, Adam Lam, Robert Nam, Alexandre Mamedov, and Andrew Loblaw

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 OCTOBER 13, 2016 VOL. 375 NO. 15

10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer

F.C. Hamdy, J.L. Donovan, J.A. Lane, M. Mason, C. Metcalfe, P. Holding, M. Davis, T.J. Peters, E.L. Turner, R.M. Martin, J. Oxley, M. Robinson, J. Staffurth, E. Walsh, P. Bollina, J. Catto, A. Doble, A. Doherty, D. Gillatt, R. Kockelbergh, H. Kynaston, A. Paul, P. Powell, S. Prescott, D.J. Rosario, E. Rowe, and D.E. Neal, for the ProtecT Study Group*

Single arm Cohort

Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer

Klotz et al JCO, 2010 & 2015

Purpose: to assess the feasibility of an observation protocol with selective, delayed intervention by using PSA kinetics and/or histologic progression as triggers for intervention.

Methods

Favourable risk Ca Prostate

Surveillance

PSA: @ 3 m for 2 yrs => @ 6 m in stable pts.
Confirmatory biopsy:
6 - 12 months after the initial biopsy -> then every 3 - 4 years until pt 80 yrs old.

Definitive intervention

- PSA DT < 3 yrs,
- GS progression (4+3 or greater)
- unequivocal clinical progression.

Outcome measures:

- Overall survival
- Disease- sp survival,
- Rate of treatment,
- PSA failure rate in the treated patients.

- At 5, 10, 15 yrs, 75.7%, 63.5%, and 55.0% of patients remained untreated and on surveillance.
- Cumulative hazard ratio for nonprostate-to-prostate cancer mortality was 9.2:1.
- 2.8% of patients have developed metastatic disease,
- 1.5% have died of prostate cancer.

  This mortality rate is consistent with expected mortality in favorable-risk patients managed with initial definitive intervention.

C O N C L U S I O N

Active surveillance for favorable-risk prostate cancer and intermediate-risk disease in men older than 70 years is feasible and appears safe in the 10- to 15-year time frame. **2010**

Active surveillance for favorable-risk prostate cancer is feasible and seems safe in the 15-year time frame. 2015

ProtecT study

10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer

Hamdy et al NEJM, 2016

Purpose: Comparative effectiveness of T/t for Ca Prostate, detected by PSA testing

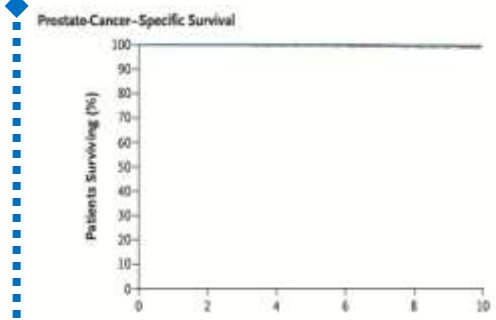
Methods

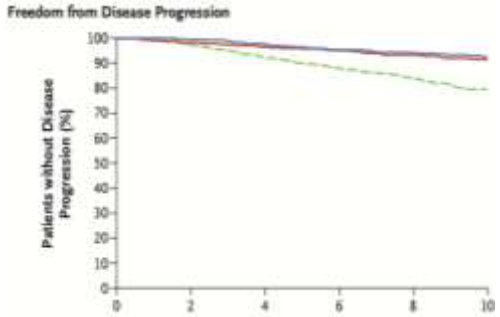
1999 - 2009
Localized Ca Prostate
N - 1643

R

- **Ac.Monit** — If PSA ↑ by 50% in 12 m -> T/t
- **Sx** → Adj / salvage RT if ECS +ve, Margin +ve, PSA >0.2
- **RT** (74 Gy)+ HT(NA & Conc)

- **Primary outcome:** Prostate-cancer mortality
- **Secondary outcomes:** Disease progression, Metastases, All-cause deaths.





Results

Med. F.U. 10 yr	Active Monit (95% CI)	Surgery (95% CI)	RT (95% CI)	Overall	P value
Prostate sp Death	8	5	4	17	P = 0.48
Overall Death				169	P = 0.87
Mets	33 (4.5 to 8.8)	13 (1.4 – 4.2)	16 (1.9 – 4.9)	62	P=0.004
Ds prog.	112 (19.0 – 27.5	46 (6.7 – 11.9)	46 (6.7 – 12)	204	P <0.001

CONCLUSION

Prostate-cancer–sp mortality:
- Low irrespective of the T/t
- No sig. diff among T/t.

Surgery & RT: ↓ incidences
- Disease progression
- Metastases

Surgery vs Radiotherapy

No Level 1 evidence comparing the efficacy of radical prostatectomy and radiotherapy for patients with **clinically-localized prostate cancer**.

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

2016

European Association of Urology

Platinum Priority – Review – Prostate Cancer
Editorial by Martin Spahn, Alan Dal Pra, Daniel Aebersold and Bertrand Tombal on pp. 31–32 of this issue

Surgery Versus Radiotherapy for Clinically-localized Prostate Cancer: A Systematic Review and Meta-analysis

Christopher J.D. Wallis [a,b,c], Refik Saskin [c,d], Richard Choo [e], Sender Herschorn [a,b], Ronald T. Kodama [a,b], Raj Satkunasivam [a,b], Prakesh S. Shah [c,f,g], Cyril Danjoux [h], Robert K. Nam [a,b,c,]*

Conclusions:

- **RT is a/w an increased risk of overall and prostate cancer-specific mortality *compared with surgery***
- ***based on observational data with low to moderate risk of bias*.**

19 studies - low to moderate risk of bias
118830 patients were pooled.

Risk of overall & prostate cancer-specific mortality higher for pts treated with RT compared with surgery.

Subgroup analyses by

- risk group,
- radiation regimen,
- time period,
- follow-up length

did not alter the direction of results.

These data, <u>combined with the forthcoming randomized data</u>, may aid clinical decision making.

Post prostatectomy Radiotherapy

Early Salvage

Adjuvant

Adjuvant Radiotherapy for Pathologically Advanced Prostate Cancer
A Randomized Clinical Trial

JAMA, 2006

Timing of radiotherapy after radical prostatectomy (RADICALS-RT): a randomised, controlled phase 3 trial

2020

Christopher C Parker, Noel W Clarke, Adrian D Cook, Howard G Kynaston, Peter Meidahl Petersen, Charles Catton, William Cross, John Logue, Wendy Parulekar, Heather Payne, Rajendra Persad, Holly Pickering, Fred Saad, Juliette Anderson, Amit Bahl, David Bottomley, Klaus Brasso, Rohit Chahal, Peter W Cooke, Ben Eddy, Stephanie Gibbs, Chee Goh, Sandeep Gujral, Catherine Heath, Alastair Henderson, Ramasamy Jaganathan, Henrik Jakobsen, Nicholas D James, Subramanian Kanaga Sundaram, Kathryn Lees, Jason Lester, Henriette Lindberg, Julian Money-Kyrle, Stephen Morris, Joe O'Sullivan, Peter Ostler, Lisa Owen, Prashant Patel, Alvan Pope, Richard Popert, Rakesh Raman, Martin Andreas Røder, Ian Sayers, Matthew Simms, Jim Wilson, Anjali Zarkar, Mahesh K B Parmar, Matthew R Sydes

Adjuvant Radiotherapy for Pathologically Advanced Prostate Cancer – A Randomized clinical Trial

JAMA, 2006
Ian M Thompson jr et al
RCT

Comparison of outcomes of Adjuvant Radiotherapy Vs Observation for patients with Extraprostatic Disease

16 weeks

Radical Prostatectomy+ PLND
- pT3
- EPE /Margin +ve/ SVI
- Negative Bone Scan

Excluded Node Positive

R

Observation
n=211

RT -> 60-64Gy/ 30-32Fr
n=214

FU

End Points (ITT)

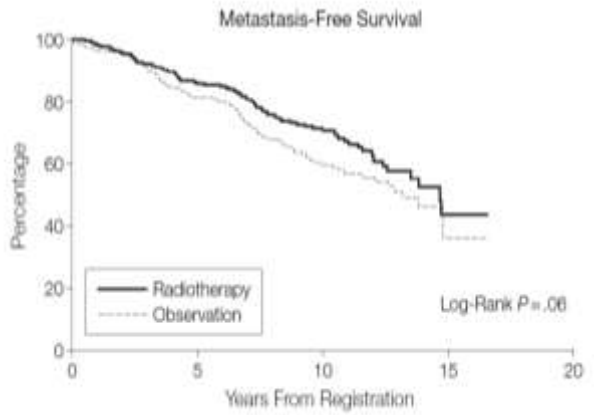
Primary End Point
Mets Free Survival

Secondary End Point
PSA relapse free interval
Recurrence free survival & OS
Time to start ADT

R E S U L T (Median FU 10.6yrs)

	Obs	RT	HR	sig
Mets-Free Survival (Median)	13.2yrs	14.7yrs	0.75	0.06
PSA- RFS (Median)	3.1yrs	10.3yrs	0.43	<0.001
RFS (Median)	9.9yrs	13.8yrs	0.62	0.001
OS (Median)	13.8yrs	14.7yrs	0.80	0.16
Time to ADT (5yrs)	21%	10%	0.45	<0.001

70 patients in Observation arm received RT after PSA relapse



The extent of disease at randomization was related to risk of both PSA relapse and Objective Recurrence

Radiotherapy was associated with significantly high complication rates (Urinary and Rectal)

As one third of observational arm received radiotherapy after PSA relapse, late radiotherapy could be a reasonable alternative approach

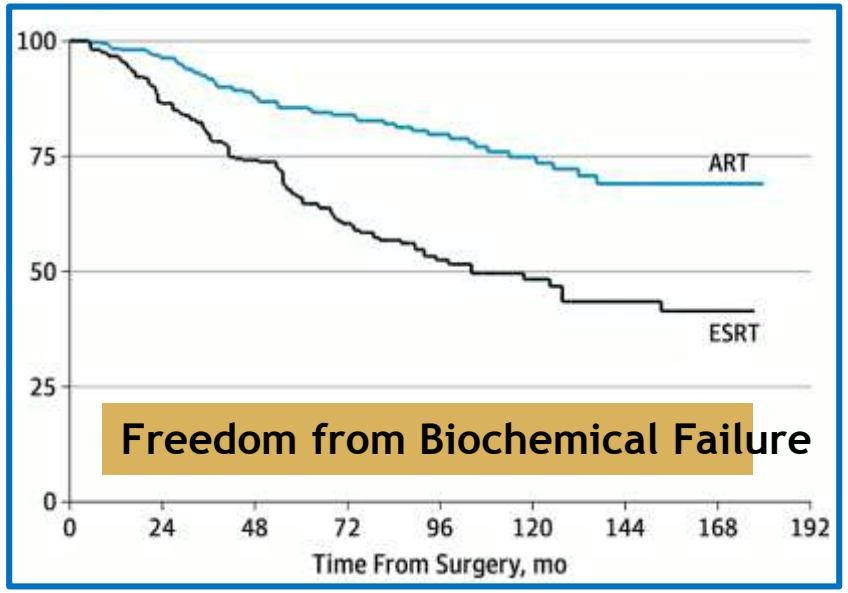
CONCLUSION : Adjuvant Radiotherapy significantly reduces risk of PSA-Relapse & Disease recurrence

Comparison Between Adjuvant and Early-Salvage Postprostatectomy Radiotherapy for Prostate Cancer With Adverse Pathological Features

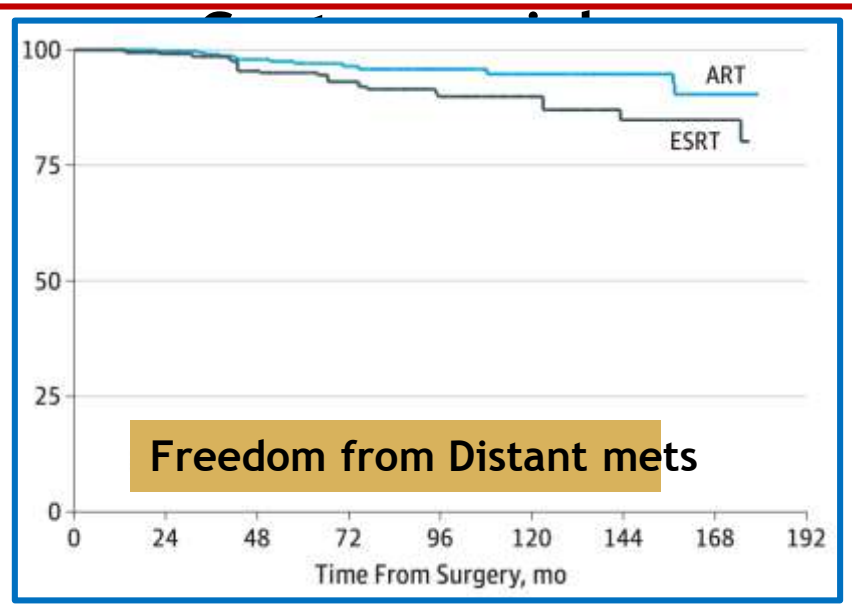
Hawang et al
JAMA, 2018
Retrospective

To compare the clinical outcomes of postoperative Adjuvant RT (ART) and Early Salvage RT (ESRT) administered to patients with adverse pathological features.

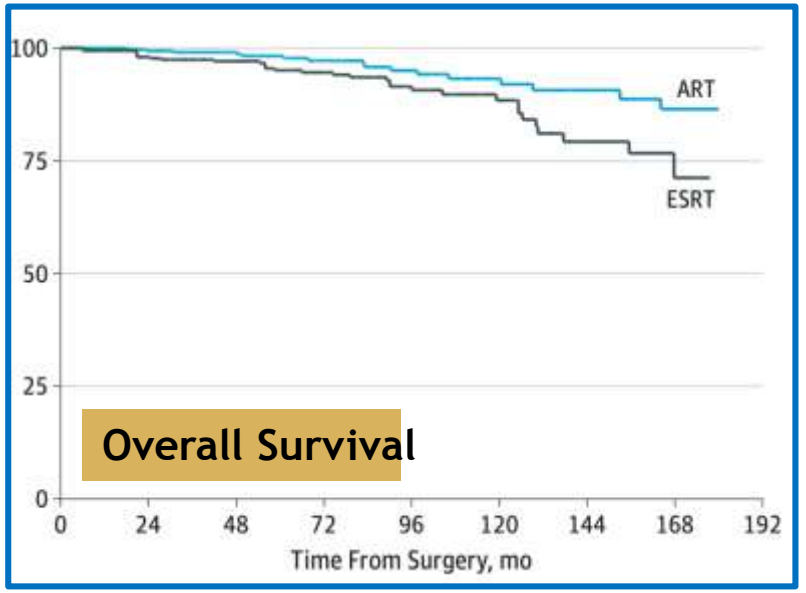
Optimal timing of Postop. RT for Prostate Ca with adverse pathological feature:



Freedom from Biochemical Failure



Freedom from Distant mets



Overall Survival

Ca - Prostate with adverse pathological features may benefit from postprostatectomy ART rather than surveillance followed by Early Salvage RT (ESRT).

Timing of radiotherapy after radical prostatectomy (RADICALS-RT): a randomised, controlled phase 3 trial

Parker et al
Lancet, 2020
RCT Phase III

Positive Margins or

pT4, Gleason 7-10, preop PSA

66Gy/33Fr

52.2Gy/20

ART ≤ 6 months

Trigger: PSA > 0.1 ng/ml and rising or 3 consecutive rises

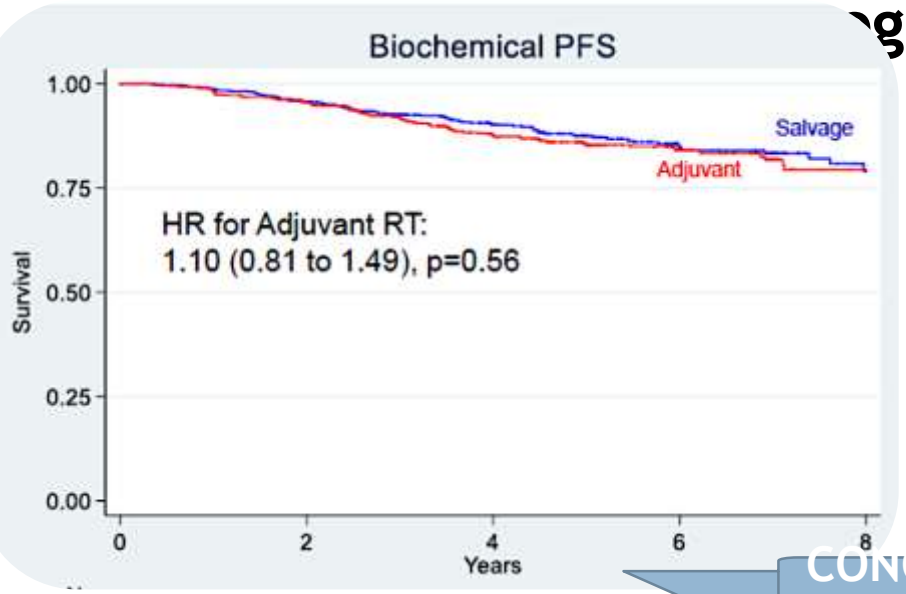
eSRT ≤ 2 months of trigger

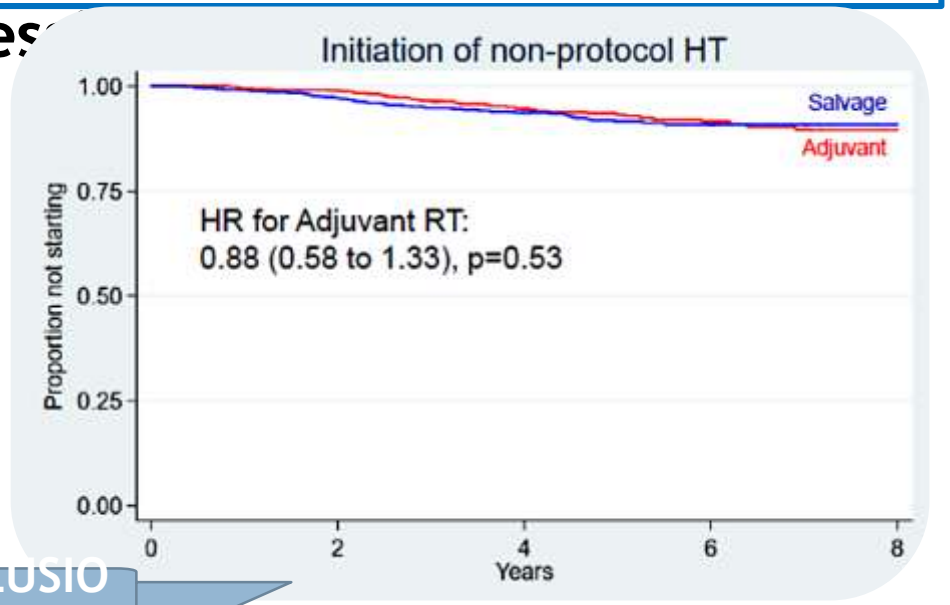
Distant Mets Free Survival

Superioriyty Trial

1396 patients
Median FU: 5 years

RADICALS-RT compared adjuvant RT against a policy of early salvage radiotherapy (eSRT) in the event of PSA biochemical progres





CONCLUSION

- RADICALS-RT trial did not show any benefit for adjuvant RT in comparison to salvage RT for PSA biochemical progression.
- Adjuvant RT increases the risk of urinary and bowel morbidity.
- Observation with salvage t/t for PSA biochemical progression should be the current standard of care after radical prostatectomy.

Radical RT

Dose

Fractionation

- Dose escalation
- Hypofractionation

Dose-Response in Radiotherapy for Localized Prostate Cancer: Results of the Dutch Multicenter Randomized Phase III Trial Comparing 68 Gy of Radiotherapy With 78 Gy

Peeters et al
JCO, 2006

PRIMARY END POINT :
- Freedom from failure (FFF).

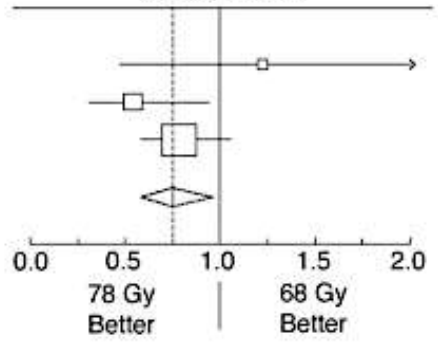
OTHER END POINTS :
- Freedom From Clinical Failure (FFCF)
- Overall Survival (OS)
- Toxicity.

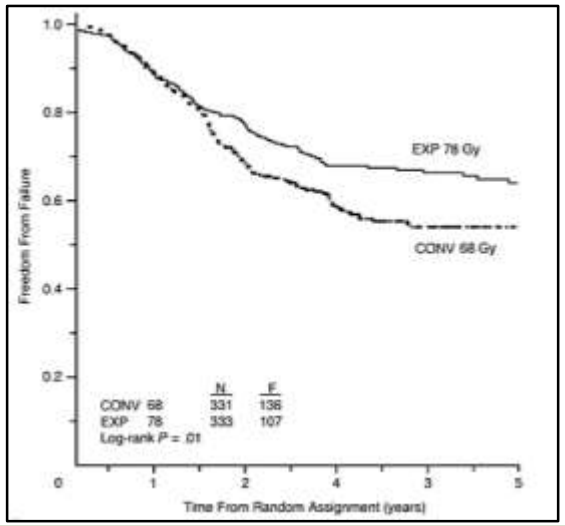
1997 - 2003 **R** → RT (68 Gy) / RT (78 Gy)

- Ph I PTV (68 Gy) = (Prostate with or without SV + 10 mm; 0mm towards rectum) 68 Gy
- Ph II PTV (78Gy) = Margin 5 mm

RESULTS : Median F.U 51 months

Risk	Faliure/Patients 78 Gy	68 Gy
Low	10/64	7/56
Intermediate	19/92	32/90
High	78/177	97/185
Total	107/333 (32%)	136/331 (41%)





5-year FFF rate, 64% v 54%, P = .02

INCLUSION CRITERIA:
- Adenoca Prostate
- All T stages
- iPSA < 60 mcg/L (Except T1a and well-differentiated (or GS 5) T1b-c tumors with iPSA 4 mcg/L).
- KPS 80.

Table 1. Treatment Groups (I, II, III, and IV)

		Treatment Group					
		T1b, T1c, T2a*				T2b,* T3a	T3b, T4
Gleason Score	Differentiation	iPSA 0-4 µg/L	iPSA 4-10 µg/L	iPSA 10-20 µg/L	iPSA 20-60 µg/L	iPSA 0-60 µg/L	iPSA 0-60 µg/L
2-4	Good	I	I	I	II	III	IV
5-7	Moderate	I	II	II	III	III	IV
8-10	Poor	II	III	III	III	III	IV

CONCLUSION:

Increasing RT dose from 68Gy to 78Gy is beneficial for Prostate ca in terms of FFF at the cost of slightly higher, but acceptable, late Rectal bleeding and Rectal incontinence.

LONG-TERM FAILURE PATTERNS AND SURVIVAL IN A RANDOMIZED DOSE-ESCALATION TRIAL FOR PROSTATE CANCER. WHO DIES OF DISEASE?

Kuban et al IJROBP, 2011

PURPOSE:

To report long-term failure patterns and survival with dose escalation for Prostate ca.

PRIMARY END POINT :

Freedom from clinical or biochemical failure

1993-1998 **R**

- Arm A (N=150) RT (70 Gy/35#)
- Arm B (N=151) RT (78 Gy /39#)

INCLUSION CRITERIA:

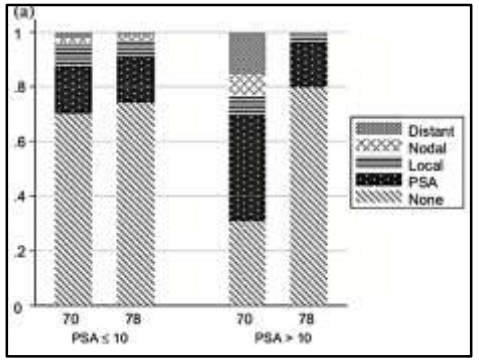
- stage T1-T3 N0M0 (1992 AJCC staging system)
- Pre t/t serum PSA PSA =10 ng/mL or >10 ng/mL.
- No previous pelvic RT/Radical prostatectomy/Androgen ablation.

RESULTS : Median F.U 9 years

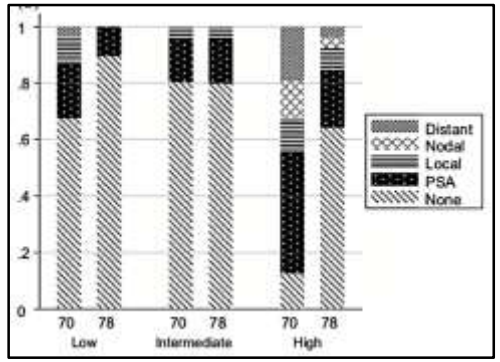
- At 10 years after t/t, 16% of high-risk patients treated with 70 Gy died of disease as compared to 4% of patients treated with 78 Gy (p = 0.05).
- Patients with pre t/t PSA>10 ng/mL has higher biochemical and clinical failures rates when treated to 70 Gy (14% vs. 2% ; p = 0.03).
- Patients <70 years old at t/t died of Prostate ca 3 times more frequently than of other causes when received 70 Gy, whereas those treated to 78 Gy died of other causes more frequently.

FACTORS PREDICTING FOR DEATH FROM PROSTATE CA:

- Pre t/t PSA >10.5 ng/mL
- Gleason score 9 and 10
- Recurrence within 2.6 years of RT
- Doubling time of <3.6 months at time of recurrence.



Comparison of failure patterns by dose, within PSA stratification groups



Comparison of failure patterns by dose within risk groups

CONCLUSION:

Moderate dose escalation (78 Gy) decreases biochemical and clinical failure as well as prostate cancer death in High risk Prostate ca with pre treatment PSA >10 ng/mL.

Conventional Vs Hypofractionated high-dose IMRT for prostate cancer: 5yr outcomes of the randomized, non-inferioirity, phase 3 CHHiP trial

Lancet, 2016
D Dearnaley et al
Ph 3 RCT

To compare the efficacy and toxicity of hypofractionated schedules to conventional fractionation

cT1b-T3aN0M0
PSA<30ng/ml
Risk of LNI, SVI <30%
WHO PS 0-1

3-6mo ADT (Except Low-Risk)

R

- 74Gy/ 37Fr/ 7.4 weeks — n=1065
- 60Gy/ 20Fr/ 4 weeks — n=1074
- 57Gy/ 19Fr/ 3.8 weeks — n=1077

Preliminary Analysis of Safety of Hypofractionation was published in Lancet 2012 — n=457

Excluded
Gleason Score ≥ 8
Life Expectance < 10yrs
h/o Pelvic RT & ADT

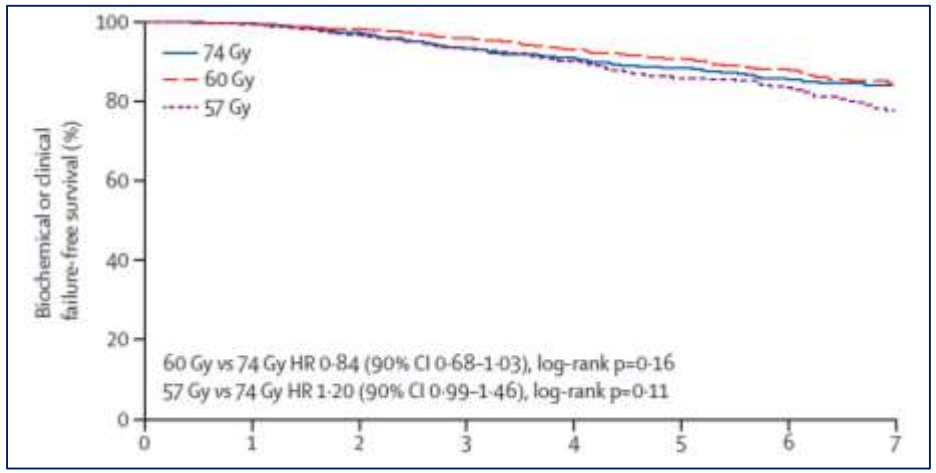
End Points (ITT) - Non-Inferiority Design

Biochemical/ Clinical Failure Free Rate

Secondary End Point
DFS & OS
Acute & Late Toxicity
Metastasis & Recommencement of ADT

R E S U L T S (Median FU 62mo)

5Yrs	74Gy	60Gy	57Gy
Bio/Clinical Failure Free Rate	88.3%	90.6% HR 0.84	85.9% HR 1.20
RTOG Acute Gr≥2 Bowel (at Peak)	25%	38%	38%
RTOG Acute Gr≥2 Bladder (at Peak)	46%	49%	46%
Bowel (Late)	13.7%	11.9%	11.3%
Bladder (Late)	9.1%	11.7%	6.6%



Adjusted HRs (Age, Risk group, GS, PSA, ADT) was similar to primary findings. Subgroup analysis did not show any significant difference except for age (>69yrs) was associated with reduced failure rate for 60Gy

No Significant difference was observed for OS

Patient Reported outcomes were similar for late toxicities (Bladder/ Bowel/ Sexual Function)

tionated RT 60 Gy /20 Fr is non-inferior to conventional RT 74 Gy/37 Fr

ES-v1-GU004

Hypofractionated vs conventionally fractionated RT for patients with localised prostate ca (HYPRO): final

Lancet, 2016, Incrocci et al, Multicentre, open-label, Ph III

Aim: To show superiority of hypofractionation compared with conventional fractionation in terms of RFS in Ca

- Intermediate to high-risk localised Ca Prostate
- T1b-T4/NX-N0/MX-M0 cases; Initial PSA ≤ 60 mcg/L
- WHO PS=0-2
- Low-risk disease (T1b-T2a, GS ≤6, or PSA <10 µg/L) excluded
- 7 Dutch centres; 2007-2010

R

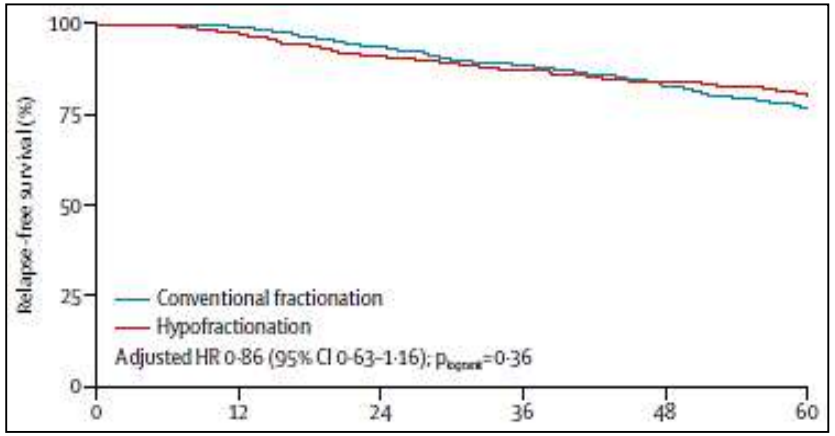
Hypofractionated RT
(n=407)
64·6 Gy/19 # [@ 3·4 Gy/#, 3 fr/week]

Conventionally fractionated RT
(n=397)
78 Gy/39 # [@ 2 Gy/#, 5 fr/week]

67% patients received conc. ADT for median 32 months, as per institutional protocol.

Results (Median FU= 60 months)

- 5-yr RFS→ 80.5% in hypofractionation arm vs 77·1% in conventional fractionation (adjusted HR-0·86, 95% CI-0·63-1·16; p=0·36).
- ≥Gr 2 acute GI & ≥Gr 3 late GU toxicities significantly higher with Hypofractionated RT.



Conclusion

- Hypofractionated RT not superior to conventional RT with respect to 5-yr RFS.
- This hypofractionated RT regimen cannot be regarded as standard of care for intermediate / high-risk Ca prostate.

Randomized Trial of a Hypofractionated Radiation Regimen for the Treatment of Localized Prostate Cancer (PROFIT Trial)

Catton et al JCO, 2017 RCT

Prostate cancer exhibits a a/b-value, So RT of fewer and larger fractions would increase therapeutic efficacy.

INCLUSION CRITERIA:

Intermediate-risk prostate cancer

T1 to 2a, Gleason score <= 6, and PSA <=10.1-20 ng/mL;

T2b to 2c, Gleason <=6, and PSA <= 20 ng/mL;

T1 to 2, Gleason = 7, and PS

May, 2006-November, 2011 → R

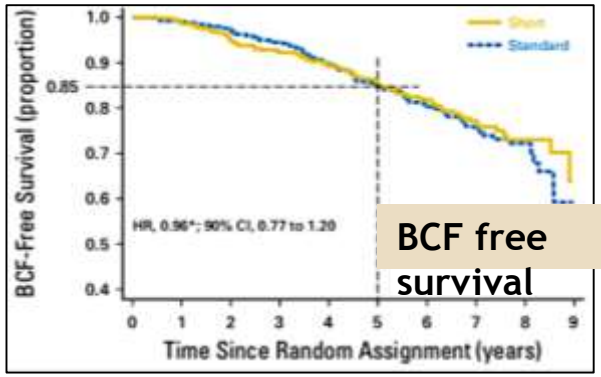
- Arm A (N=598). conventional RT (78 Gy/39#/8 weeks)
- Arm B (N=608) Hypofractionated RT (60 Gy /20#/4 weeks)

*ADT not permitted with t/t.

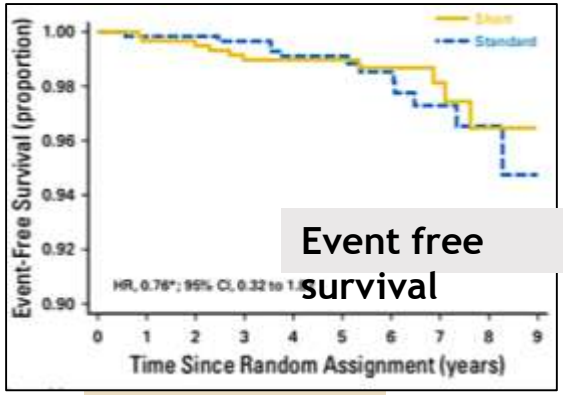
EXCLUSION CRITERIA

- Ca Prostate diagnosed 6 months before study entry,
- Previous t/t for prostate ca or prior Pelvic RT.
- Any malignancy diagnosed within 5 years of entry except for nonmelanoma skin cancer,
- RT t/t plan doesn't meet dose constraints for hypo# arm.

RESULTS : Median F.U 6 years



BCF free survival



Event free survival

Outcome (as first event)	Treatment Arm (No.) Short (n = 608)	Standard (n = 598)
Biochemical-clinical failure	109	117
PSA failure (Phoenix definition)	97	100
Death as a result of prostate cancer	4	4
Local recurrence	2	2
Distant recurrence	3	5
Started hormonal therapy	3	6

BCF Component Outcomes by t/t Arm

Similar

Grade	Acute		Late	
	Hypo#	Conv. #	Hypo#	Conv. #
GI Toxicity				
2	16	10	7.4	11
3	0.7	0.	1.5	2.7
GU Toxicity				
2	27	27	20	19
3	3.9	4	2	2.8

CONCLUSION:

- Hypofractionated RT regimen is not inferior to conventional RT and is not associated with increased late toxicity.
- It is more convenient for patients and should be considered for intermediate-risk prostate cancer.

HYPO-RT-PC

Ultra-hypo# vs conv# RT for Prostate cancer: 5-year outcomes

Widmark et al Lancet, 2019

To assess non-inferiority of ultra-hypofractionation compared with conventional fractionation.

Methods

Intermediate & High risk
N - 1180

R

- **Ultra hypo#** — 42.7 Gy in 7 fr, 2.5 wks
- **Conv #** — 78 Gy in 39 fr, 8 wks

No ADT was allowed

Primary end point:
- Time to biochemical or clinical failure

Non-inferiority margin: 4% at 5 yrs, critical HR limit of 1·338.

Primary end point

FFS at 5 years - 84% (95% CI 80–87) in both T/t group; adjusted HR of 1·002 (95% CI 0·758–1·325; log-rank p=0·99).

Results

Physician-reported outcomes

>/= Gr 2	Ultra hypo#	Conv #	P value
Ac urinary	28 %	23 %	0.057
@ 1 yr	6 %	2 %	0.0037
@ 5 yr	5%	5%	1.00

Patient-reported outcomes

- Significantly more acute urinary and bowel symptoms in the ultra-hypo# group
- No significant increases in late symptoms, except for increased urinary symptoms at 1-yr FU

C O N C L U S I O N

Ultra-hypo# RT:
- Non-inferior for intermediate-to-high risk Ca Prostate regarding FFS.
- Early side-effects are more pronounced

BUT late toxicity is similar in both T/t groups.

POP – RT
Clinical outcome

WPRT vs PoRT in High Risk CA Prostate, cN0
(risk of L.N +ve >20%)

JCO, 2021
V. Murthy et al
Ph III RCT
TMH Mumbai

Purpose: To assess efficacy of WPRT (prophylactic) vs PoRT

Methods

High risk Ca Prostate, cN0
Risk of L.N inv >20%

R

ADT >/= 24 m

WPRT | PoRT

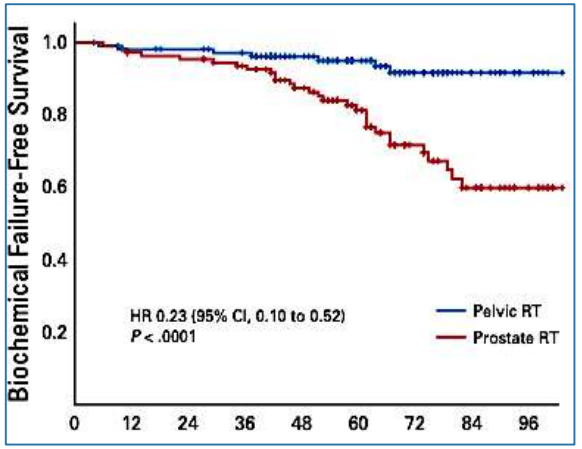
Prostate: 68 Gy / 25 fr / 5 wks
Pelvic L. N: 50 Gy / 25 fr/ 5 wks

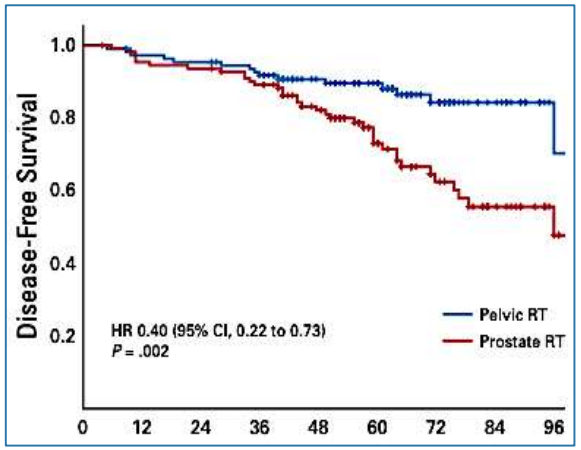
Primary end points:
- BFFS (5 yrs)

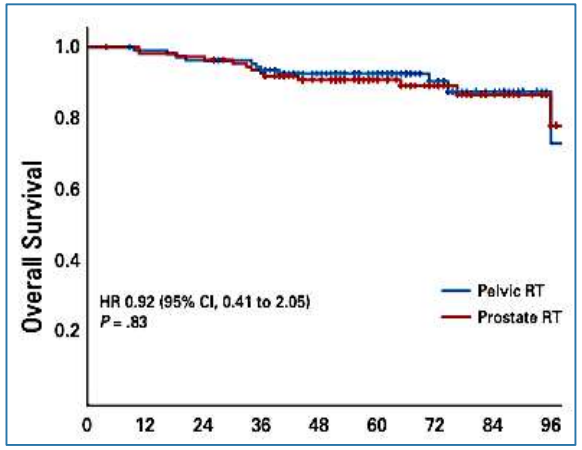
Secondary end Points:
- DFS
- OS
- (DMFS)

Results

WPRT is significantly better than PoRT in terms of BFFS & DFS, across prognostic subgroups, *but not for OS*.







C O N C L U S I O N

Prophylactic WPRT (using contemporary dose and technique of RT) along with long-term ADT for high-risk & very high-risk prostate cancer should be routinely considered as standard.

POP – RT QOL outcome

Late toxicity and quality of life with prostate only or whole pelvic radiation therapy in high risk prostate cancer (POP-RT): A randomised trial

Green Journal, 2020
V. Murthy et al
Ph III RCT

Aim: To report toxicity and quality of life (QOL) outcomes from a randomised trial of prostate only Versus whole pelvic radiotherapy in high risk, node negative prostate cancer.

Methods

High risk Ca Prostate, cN0
Risk of L.N inv >20%

R

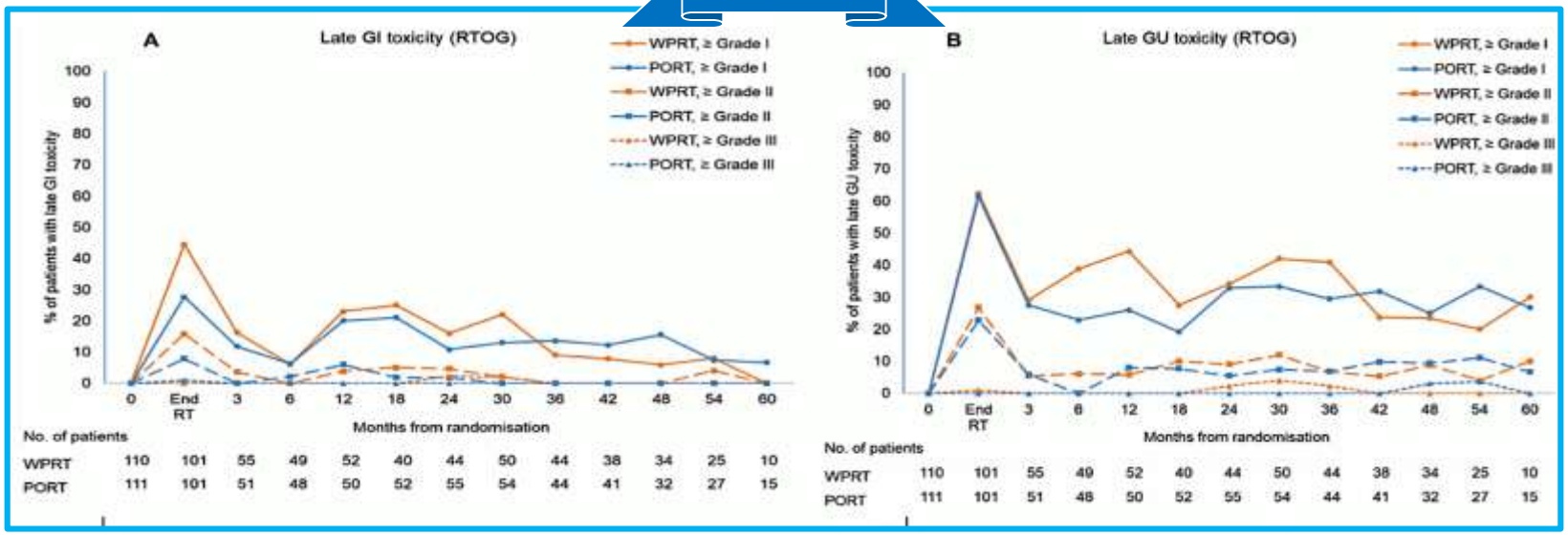
ADT >/= 24 m

- WPRT N=110
- PoRT N=114

Prostate: 68 Gy / 25 fr / 5 wks
Pelvic L.N: 50 Gy / 25 fr/ 5 wks

- GU & GI toxicities by RTOG.
- QOL assessed by EORTC QLQ-C30 and PR-25 questionnaire pre-t/t & every 3–6 months post RT

Results



CONCLUSION

- WPRT with hypofractionated IG-IMRT resulted in increased Grade II or higher late GU toxicity as compared to prostate only RT.
- This was not reflected in the patient reported QOL.

ASCENDE - RT

Analysis of T/t related morbidity for RCT comparing LDR vs Dose-Escalated Ext Beam Boost for High- & Int-med risk Prostate

Sree Rodda IJROBP, 2017

Purpose: To report the genitourinary (GU) and gastrointestinal (GI) morbidity and erectile dysfunction

Methods

High- & Int-med risk Ca Prostate (N-398)

R

After 8 months of ADT

- DE-EBRT
- LDR-PB

Prostate + SV + L.N : 46 Gy / 23 fr

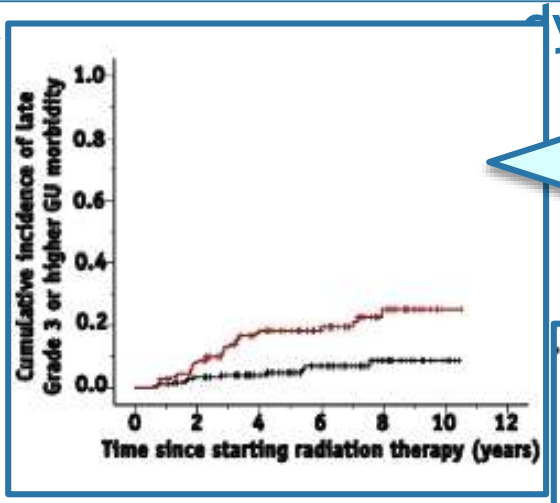
Prostate: 32 Gy 16 fr

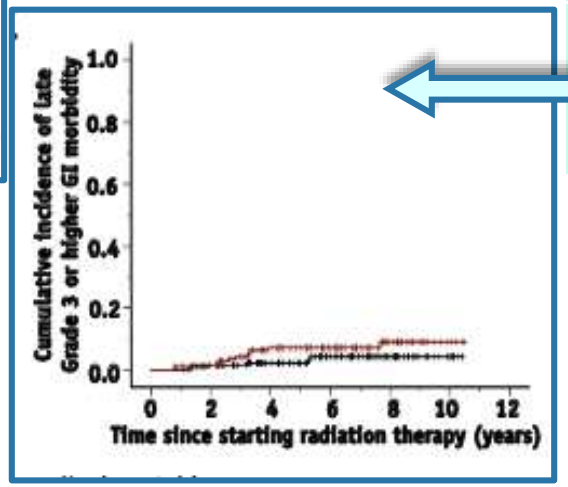
After 2 - 3 wks

I^{125}

Analysis of
- Acute GU & GI morbidity
- Late GU & GI morbidity
- Erectile function

Results





Among pt with adequate baseline erectile fn:
=> Similar fn at 5 years
- 45% of LDR-PB
- 37% of DE-EBRT

(P = 0.30)

@ 5 yrs	LDR-PB	DE-EBRT	P value
Gr 3 GU (incidence)	18.4 %	5.2 %	<0.001
Gr 3 GI (incidence)	8.1 %	3.2 %	0.124

LIMITATIONS

- Centralized real-time review of RT not included in the protocol.
- Optimal duration of ADT and role of Elective Nodal RT - not clearly defined.
- Older EBRT techniques (early 2000)
- ~~Specific DVH criteria not specified~~

C O N C L U S I O N

- Incidence of acute and late GU morbidity was higher after LDR-PB boost.
- > 80% of LDR-PB minimal / no GU side effects at 5 years follow-up.
- DE-EBRT arm twice likely to experience biochemical recurrence

Hormone therapy

Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma—Long-term results of phase III RTOG 85-31

IJROBP, 2005
Pilepich M et al
RCT

Effectiveness of adjuvant Androgen Suppression on disease progression and survival in High Risk Prostate Ca

Adenocarcinoma
cT3 or Node Positive
Post op - Margin +ve/ SVI
KPS >60%

Excluded
Palpable Tumor Dimension ≥25cm

* PSA determination was not widely available

n=477

R

RT + Goserelin

- Goserelin started on last week of RT
- Continued till progression
- 65-70 Gy, 1.8-2Gy/Fr
- 60-65Gy, 1.8-2Gy/Fr (Post Op)

RT alone

- Goserelin at Relapse

n=468

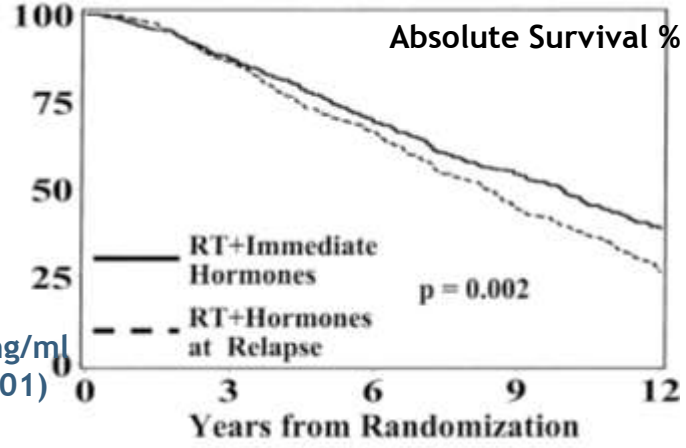
End Points (ITT)

OS
Local Control
DFS

R E S U L T (Median FU 7.6Yrs)

10yrs	RT	RT+ADT	sig
OS	39%	49%	0.002
Disease Sp. Mortality	22%	16%	0.005
Local Failure	38%	23%	<0.0001
Distant Mets	39%	24%	<0.0001

Time to Disease (DFS) Survival with PSA<1.5ng/ml
31% in Adj Arm Vs 9% in RT alone Arm at 10yrs (p<0.0001)



Factors influencing better Outcome (Multivariate Analysis)

Androgen Suppression
Prostatectomy
Node Negative status
Low Gleason Score (2-6)*

*Centrally reviewed

CONCLUSION : Patients with unfavorable prognosis (cT3/N+ve) and High GS do better with long term ADT

Androgen Suppression and Radiation (AST + RT) vs Radiation (RT) Alone for Prostate Cancer

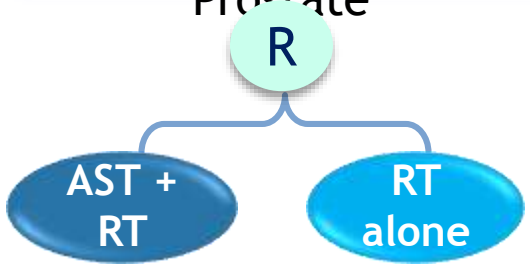
JAMA
RCT, 2008
D'AMICO

Aim

- To compare 6 months of AST and radiation therapy (RT) to RT alone
- To assess the interaction between level of comorbidity and all-cause mortality.

Methods

Dec, 1995 - Apr, 2001
Localized *but* unfavorable risk Ca Prostate

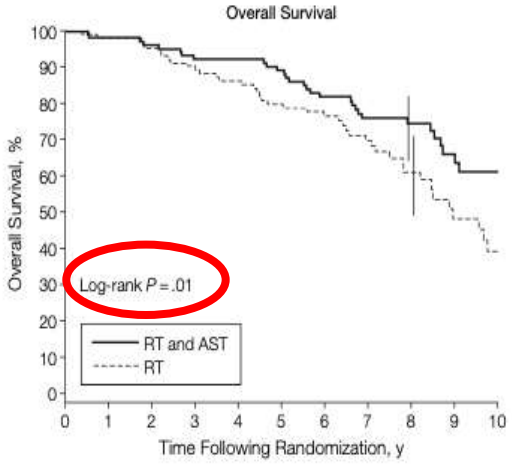


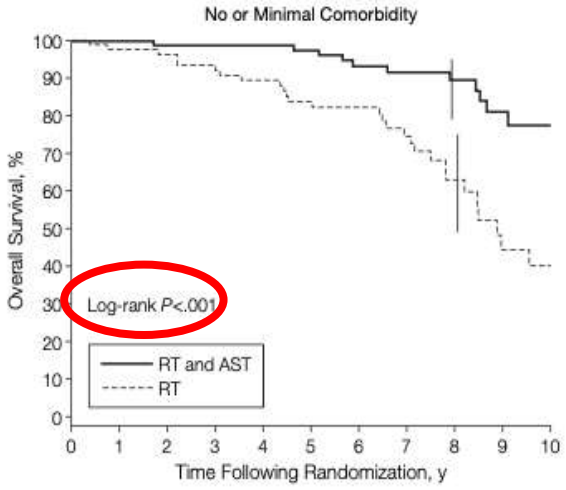
Time to all-cause Mortality

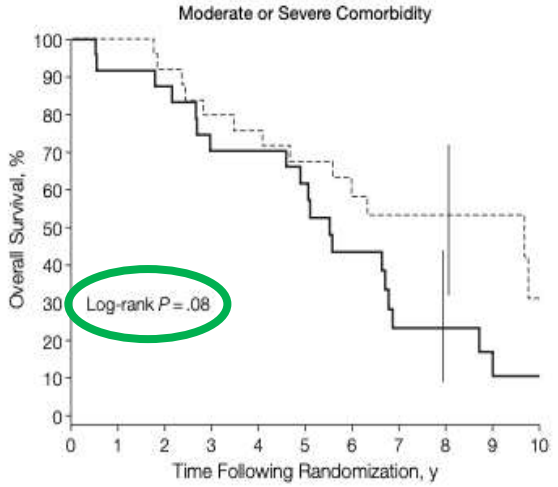
All cause mortality estimates stratified by randomized treatment group and further stratified in a post-randomization analysis by the Adult Comorbidity Evaluation 27 comorbidity score

Results

Median follow-up of 7.6 years







CONCLUSION

- 6 months of Androgen Suppression Therapy to RT resulted in increased OS
- This result may pertain only to men without moderate or severe comorbidity.

But this requires further assessment in a clinical trial specifically designed to assess this interaction.

Something different for someone

ADT plus Docetaxel and Estramustine Vs ADT alone for patients of High Risk localised Prostate Cancer (GETUG 12): Phase 3 RCT

Lancet, 2015
Fizazi K et al
Ph 3 RCT

To assess whether Docetaxel and Estramustine could improve outcome in high risk localized prostate cancer

Adenocarcinoma
T3/T4, pN+, M0
PSA ≥ 20ng/ml GS ≥ 8
Age<80yrs, ECOG ≤2
Life Expectancy >10yrs

Excluded

Active infection, h/o - thromboembolic events, uncontrolled cardiac co-morbidities, contraindication to Aspirin

Stratification

R

n=207

ADT + Doce + Estramustine

- 3 monthly Goserelin x 3yrs
- Doce on D2, 70mg/m2 - 3 wkly x 4 cycles
- Estramustine for 5 days - 3 wkly x 4 cycles

n=206

ADT alone

- 3 monthly Goserelin x 3yrs

- RP/ Local RT
- After 3 months of starting

Local Therapy

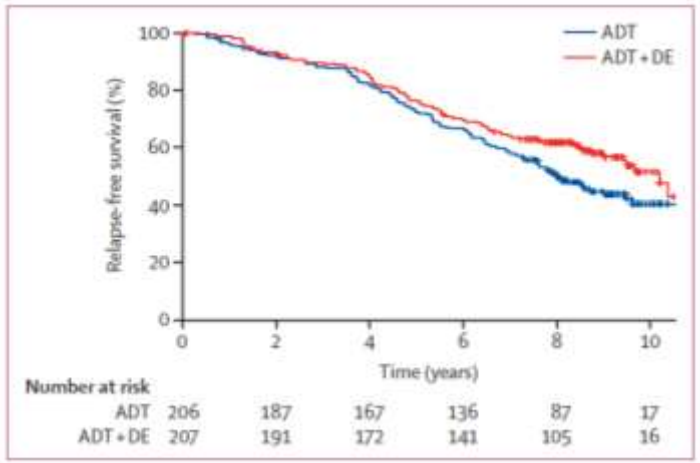
End Points (ITT)

Relapse Free Survival (RFS)

R E S U L T (Median FU 8.8 Yrs)

8 yrs	ADT	ADT+DE	sig
RFS	50%	62%	0.017
Metastasis	20%	15%	-
≥ Gr2 Toxicity	18%	21%	0.61
2nd Cancer	11%	13%	0.57

8yr OS - 83% (All Patients)
>90% received planned Doce + Estramustine
87% received Local RT
6% underwent Prostatectomy



1st study to test Docetaxel in localized high risk Prostate Ca

Significantly improved RFS
Biochemical Failure was the most common Relapse event

Patients with GS <8 derived greater benefit from Chemo

DE was well tolerated with no treatment related death and low Thromboembolic event (2%)

CONCLUSION : Adding Doce + Estramustine to ADT improved RFS without significant increase in toxicity

EORTC 30891

Using PSA to guide Timing of Androgen Deprivation in pt with T0–4 N0–2 M0 Prostate Cancer not Suitable for Local Curative T/t

Studer et al
European Urology 2014

Purpose: To compare Immediate versus Deferred androgen-deprivation therapy (ADT) in T0-4,N0-2,M0 Ca Prostate

Methods

Recently diag. as **non-mets Ca Prostate**

- Age: ≤ 80yrs,
- no prior local / systemic T/t
- either refused or unsuitable for local curative T/t

Feb, 1990 - Jan, 1999

N - 939

R

- Immediate ADT
- Delayed ADT

Primary endpoint : (in Present Inv)

Prostate Cancer-specific Survival

Initial trial : (2006, JCO): OS

- ✓ *sig. ↑ (modest) in OS in Imm ADT*

But NO significant diff. in

- *CaP Sp. mortality*
- *Symptom-free survival.*

Analyzed for –

- PSA data at baseline
- PSA doubling time (PSADT)

*in patients receiving **no ADT***

- Time to PSA relapse (>2 ng/ml) *in patients whose PSA declined to <2 ng/ml within first year after **immediate ADT***

Results

In both arms

Median F.U. 7.8 yrs

- Baseline PSA >50ng/ml:
  > 3.5-fold higher risk of PCa Death *comp. to pts with baseline PSA <8 ng/ml.*
- Baseline PSA b/w 8 - 50 ng/ml:
  ~ 7.5-fold higher risk of PCa Death in pts with PSADT < 12 month *comp to pts with PSADT > 12 month*

C O N C L U S I O N

Baseline PSA > 50 ng/ml and/or a PSA Doubling Time < 12 mo

increased risk to die from PCa and *might have benefited from immediate ADT**

* *evaluation of this topic was not part of the original protocol, require validation by independent data.*

Points to be remembered

- Life expectancy is crucial in decision making of treatment protocol in Localized Carcinoma Prostate
- Localized Ca Prostate is heterogeneous group – including all risk group except Very High Risk group
- Surgery vs RT remains controversial.
- Management should be individualized.
- Long term follow up is very important but data / techniques become out-dated.

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