Ruolo dell'ormonoterapia nei trattamenti radioterapici post-operatori

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A.O.U. San Luigi Gonzaga

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Evidence-based Series 3-17 Version 2.2010

Adjuvant Radiotherapy Following Radical Prostatectomy for Pathologic T3 or Margin-Positive Prostate Cancer

S.C. Morgan, C. Walker-Dilks, L.J. Eapen, E.W. Winquist, J.L. Chin, D.A. Loblaw and Members of the Genitourinary Cancer Disease Site Group

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

QUESTION

Does adjuvant radiotherapy (RT) following radical prostatectomy improve clinically important outcomes in patients with pathologic T3 or margin-positive prostate cancer compared with no adjuvant radiotherapy? The primary outcome of interest is overall survival (OS). Outcomes of secondary interest include prostate cancer-specific survival, metastasis-free survival, biochemical progression-free survival (bPFS), locoregional recurrence-free survival, time to initiation of androgen deprivation therapy (ADT), incidence of acute and late toxicity, and quality of life.

QUALIFYING STATEMENTS

The available data from randomized trials do not address:

- Whether salvage radiotherapy administered at the time of early biochemical failure confers outcomes equivalent to those of adjuvant radiotherapy.
- Whether androgen deprivation therapy given in conjunction with adjuvant radiotherapy improves outcomes over adjuvant radiotherapy alone.
- The optimal target volume, technique, or dose-fractionation schedule for adjuvant radiotherapy.
- The role for post-operative radiotherapy to involved or at-risk pelvic lymph nodes.

FUTURE RESEARCH

The enrolment of patients with R1, pT3a, or pT3b disease following prostatectomy in randomized trials comparing adjuvant radiotherapy with salvage radiotherapy instituted at early biochemical relapse is encouraged. Similarly, enrolment of these patients in trials comparing post-operative radiotherapy alone with post-operative radiotherapy in conjunction with androgen deprivation therapy is encouraged.

Original Article

Trends in the Use of Postprostatectomy Therapies for Patients With Prostate Cancer

A Surveillance, Epidemiology, and End Results Medicare Analysis

Nathan C. Sheets, MD[1]; Laura H. Hendrix, MS[1]; Ian M. Allen, MD[1,2]; and Ronald C. Chen, MD, MPH[1,3,4]

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For patients with prostate cancer not cured by prostatectomy alone, RT, either in the adjuvant or salvage setting, offers a potential for cure and is recommended by the National Comprehensive Cancer Network guidelines.[9] Conversely, the role of hormonal therapy either alone or in combination with RT in the postprostatectomy setting is currently unclear.[10]

Kumar S, Shelley M, Harrison C, Coles B, Wilt TJ, Mason MD. Neo-adjuvant and adjuvant hormone therapy for localised and locally advanced prostate cancer. *Cochrane Database Syst Rev.* 2006; (4):CD006019.

Comparison of biochemical relapse-free survival in the ART and observation arms as reported from the three randomized controlled trials.

	Follow-up	bRFS in ART arm	bRFS in observation arm	Hazard ratio	p-Value
EORTC 22911[18]	5 years	Overall: 74%	Overall: 52.6%	0.48	$p < 0.0001$
		Undetectable (≤0.2 ng/mL) PSA: 78.8%	Undetectable (≤0.2 ng/mL) PSA: 59.6%	0.50	$p < 0.0001$
		Detectable PSA: 62.6%	Detectable PSA: 37.6%	0.46	$p < 0.0001$
SWOG 8794[65]	10.6 years	Undetectable (≤0.4 ng/mL) PSA: 65.1%	Undetectable (≤0.4 ng/mL) PSA: 36%	0.43	p<.001
ARO96-02/AUO AP 09/95[20]	5 years	Undetectable (≤0.1 ng/mL) PSA: 72%	Undetectable (≤0.1 ng/mL) PSA: 54%	0.53	p = .0015

Cancer 2013;119:3295-301.

Radiation Therapy ± ADT following Radical Prostatectomy as:

- Adjuvant RT ± ADT – presence of adverse factors – undetectable PSA?
- Salvage RT ± ADT – rising PSA?
- Salvage RT ± ADT – clinically apparent recurrent tumor in the prostatic fossa?
- Adjuvant therapy – pN+ disease?

ADT alone RT ± ADT

Cancer Treatment Reviews 35 (2009) 540–546

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

ANTI-TUMOUR TREATMENT

Adjuvant hormone therapy for localised and locally advanced prostate carcinoma: A systematic review and meta-analysis of randomised trials

M.D. Shelley [a,*], S. Kumar [b,f], B. Coles [c,g], T. Wilt [d,h], J. Staffurth [e,i], M.D. Mason [e,j]

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[b] Department of Oncology, Velindre NHS Trust, Cardiff CF14 2TL, UK
[c] Cardiff Information Service, Cardiff University, Velindre NHS Trust, Cardiff CF14 2TL, UK
[d] Cochrane Prostate Diseases and Urologic Cancers Group, VA Centre for Chronic Disease Outcomes Research, Minneapolis, MN 55417, USA
[e] Cardiff University, School of Medicine, Research Department, Velindre NHS Trust, Cardiff CF14 2TL, UK

ADT only

The survival advantage for immediate (adjuvant) ADT after RP has only been proven in patients with positive-lymph-node PCa in a single randomised study (69,70). The updated results of this multicentre Eastern Cooperative Oncology Group study after a median follow-up of 11.9 years showed a significant improvement in overall survival, cancer-specific survival, and progression-free survival in lymph-node positive (N+) patients treated with immediate ADT (70).

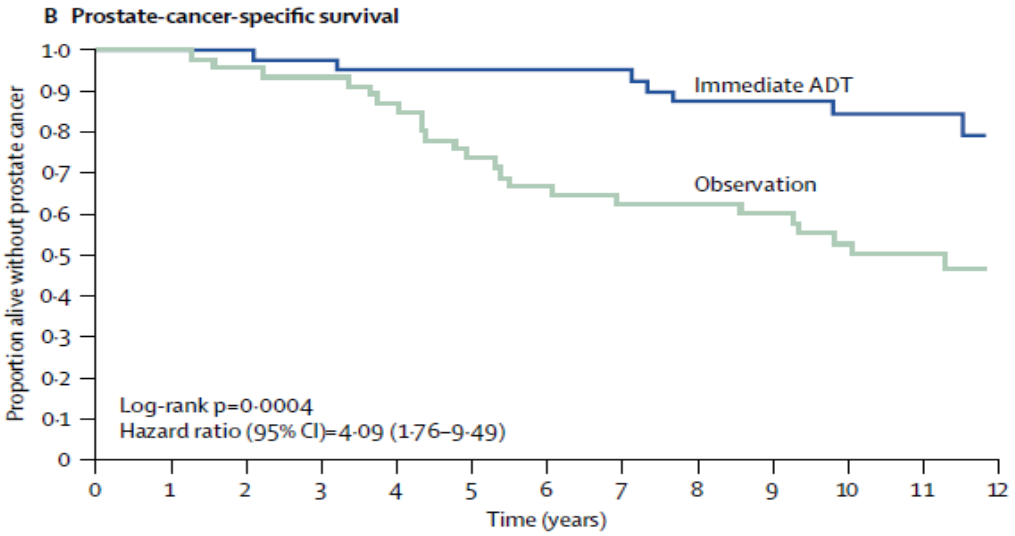
Characteristics of randomised studies of adjuvant treatment following radical prostatectomy (RP).

Trial	Country (recruitment dates)	Inclusion criteria and patient characteristics	Ineligibility criteria	Interventions (patients randomised)
Messing et al.[11]	Multi-centre USA (1988–1993)	Undergone radical prostatectomy and bilateral pelvic lymphadenectomy for clinically localised disease (no more than stage T2), but who were found on review of the histological studies to have nodal metastases. Median age 65.6 years (range: 45–78). Detectable PSA 20%, elevated acid phosphatase 12%. Gleason score <7 65%, ⩾7 35% (median 7). Informed consent	Metastases on radionuclide bone scans or chest X-ray films obtained before prostatectomy. Previous hormonal therapy	RP alone (n = 40) versus RP plus immediate hormone therapy (either goserelin 3.6 mg sc every 28 days until progression or bilateral orchidectomy, n = 38)
Wirth et al.[12]	Multi-centre Germany Austria (1989–1996)	Men with pT3-4pN0 prostate cancer of age <75 years (median 64, range 41–78). Tumour grades were G1 9%, G2 55%, G3 36%	Secondary primary cancer	RP alone (n = 157) versus RP plus adjuvant Flutamide 250 mg three time daily (total 750 mg a day) indefinitely
McLeod et al.[13]	Multi-national (not stated)	T1-4 MO any N prostate cancer clinically or pathologically confirmed. (mean age 67 years). Composite of 3 trials (trial 23, 24 and 25, powered for combined analysis), trial 23 only included patients who had undergone surgery or radiotherapy but trials 24 and 25 also included patients suitable for watchful waiting. Lymph node involvement was accepted in trial 23 but not in the other two	Distant metastasis on bone scan and lymph node involvement in trials 24 and 25	RP plus placebo versus RP Plus adjuvant bicalutamide (150 mg once daily). Numbers randomised unclear

pN+

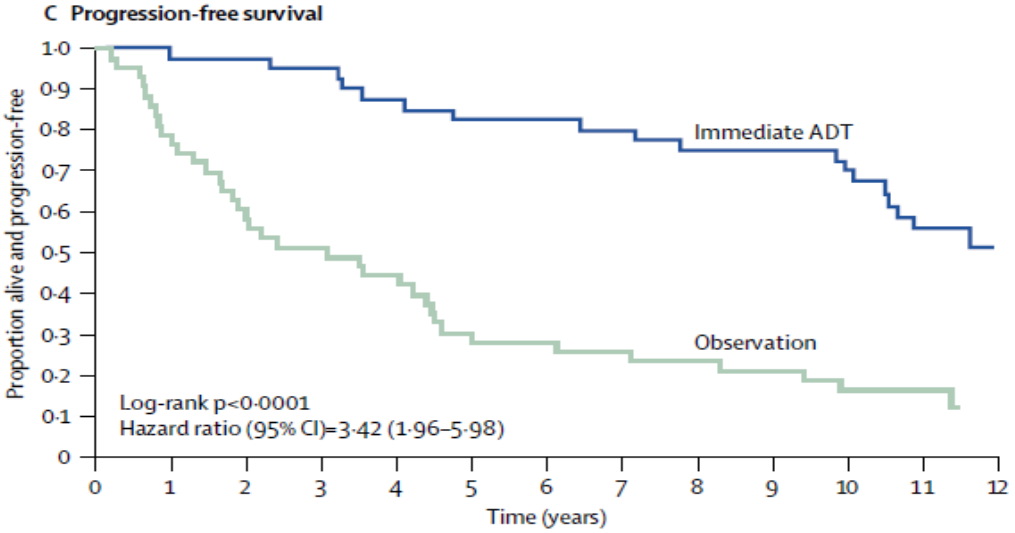
pN0

Any N



Number at risk

Immediate ADT	47	47	47	46	43	42	41	41	36	35	33	25	14
Observation	51	51	49	48	45	38	35	32	31	30	25	17	10



Lancet Oncol 2006; 7: 472–79

100 pts enrolled/98 eligible

11,9 years FU

Interpretation Early ADT benefits patients with nodal metastases who have undergone prostatectomy and lymphadenectomy, compared with those who receive deferred treatment. The beneficial effects of early ADT, rather than an imbalance in risk factors, are likely to explain the differences in outcomes between treatments.

Antiandrogen monotherapy in patients with localized or locally advanced prostate cancer: final results from the bicalutamide Early Prostate Cancer programme at a median follow-up of 9.7 years

BJUI
BJU INTERNATIONAL

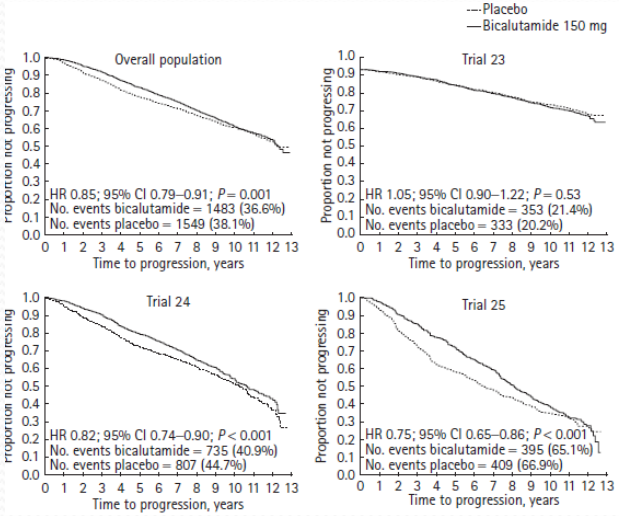
Peter Iversen, David G. McLeod*, William A. See†, Thomas Morris‡, Jon Armstrong‡ and Manfred P. Wirth§ on behalf of the Casodex Early Prostate Cancer Trialists' Group

*Department of Urology, Rigshospitalet, Copenhagen, Denmark, *Walter Reed Army Medical Center, Washington, DC, †Medical College of Wisconsin, Milwaukee, WI, USA, ‡AstraZeneca, Alderley Park, Macclesfield, UK, and §Technical University of Dresden, Dresden, Germany*

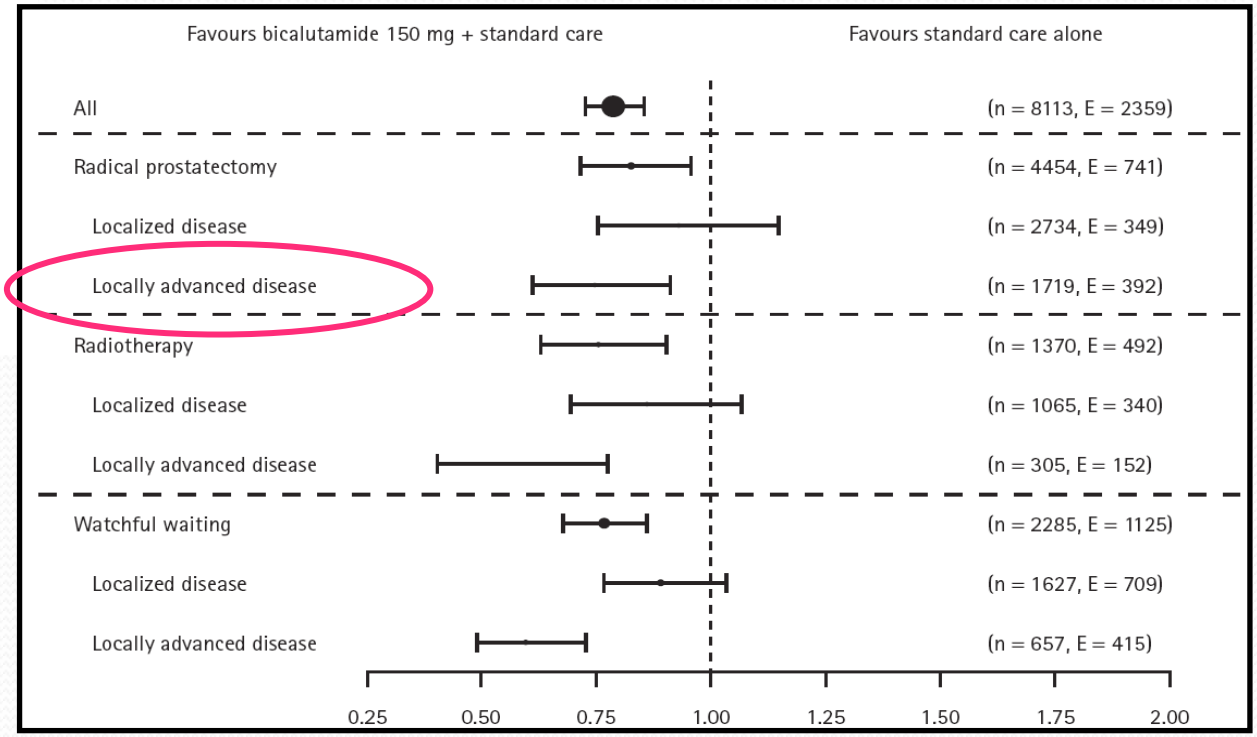
Accepted for publication 5 February 2010

OBJECTIVE

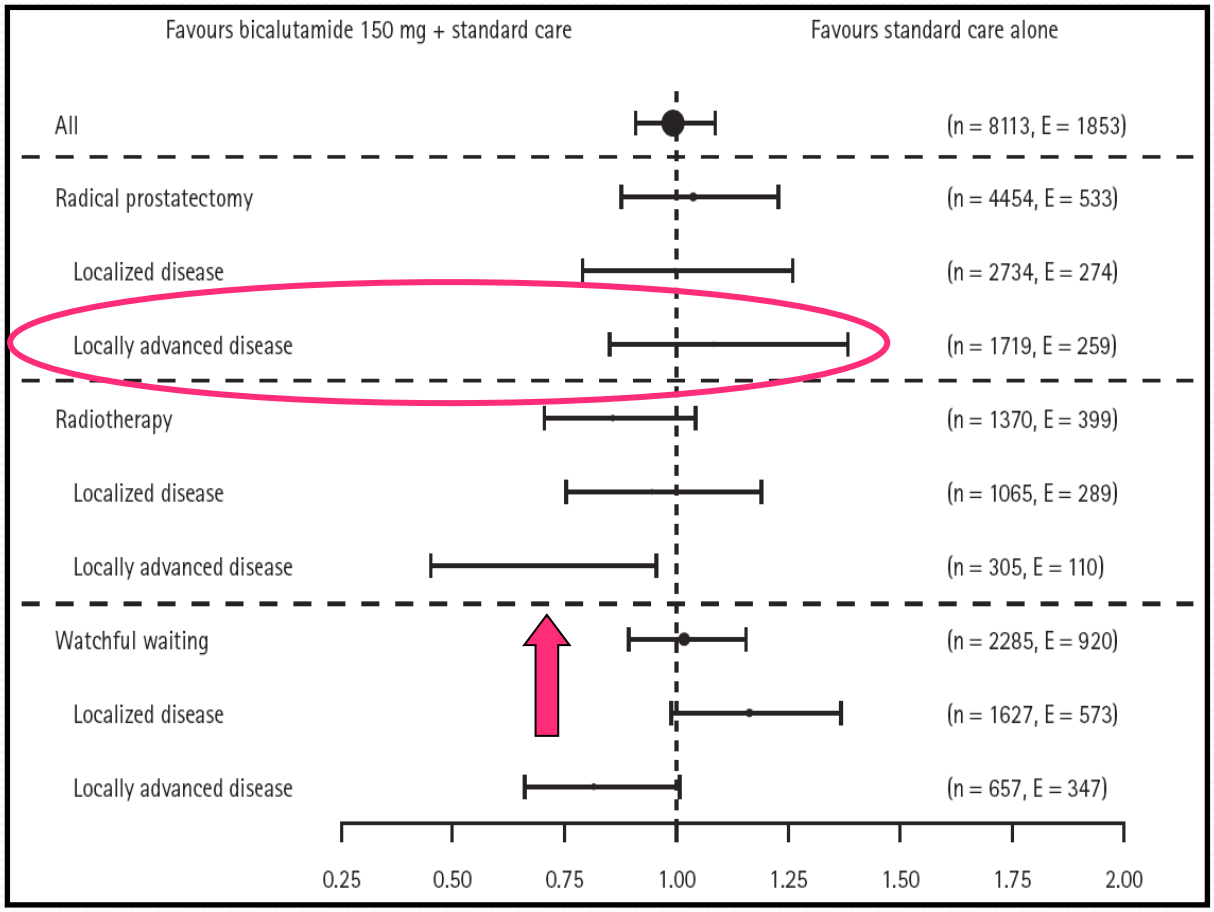
To evaluate the efficacy and tolerability of bicalutamide 150 mg once-daily as immediate hormonal therapy in patients with prostate cancer or as adjuvant to radical prostatectomy or radiotherapy.



EPC program: objective progression free-survival (prospective randomised trial, n=8116, FU 9,7 y)



EPC program: overall survival
(prospective randomised trial, n=8116, FU 9,7 y)



McLeod et al., BJU Int 2010

CONCLUSIONS

Bicalutamide 150 mg, either as monotherapy or adjuvant to standard care, improved PFS in patients with locally advanced prostate cancer, but not in patients with localized disease. A pre-planned subset analysis showed a benefit for OS in patients with locally advanced disease undergoing radiotherapy. Bicalutamide 150 mg might represent an alternative for patients with locally advanced prostate cancer considering androgen-deprivation therapy.

Prostate Cancer

Long-Term Follow-up of Patients with Prostate Cancer and Nodal Metastases Treated by Pelvic Lymphadenectomy and Radical Prostatectomy: The Positive Impact of Adjuvant Radiotherapy

Luigi F. Da Pozzo [a,*], Cesare Cozzarini [b], Alberto Briganti [a], Nazareno Suardi [a], Andrea Salonia [a], Roberto Bertini [a], Andrea Gallina [a], Marco Bianchi [a], Gemma V. Fantini [a], Angelo Bolognesi [b], Ferruccio Fazio [b], Francesco Montorsi [a], Patrizio Rigatti [a]

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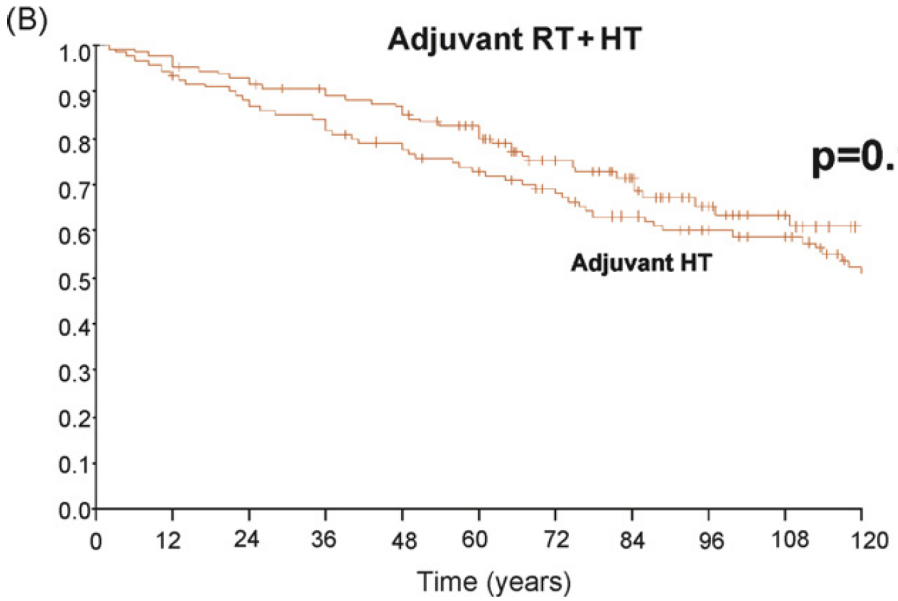
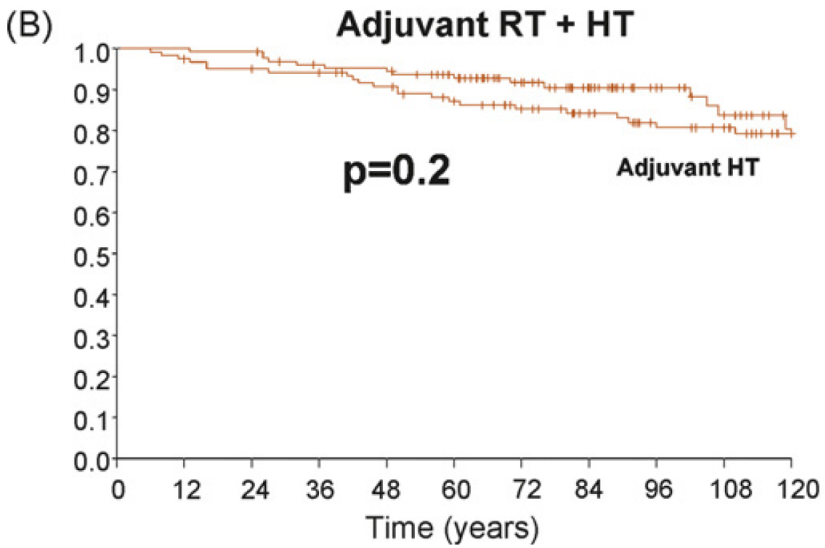
...and adjuvant RT±ADT in pN+ PCa?

250 pN+ pts

Biochemical failure



PCA-specific survival



Conclusions: This study is the first to report a significant protective role for adjuvant RT in BCR-free survival and CSS of node-positive patients.

EUROPEAN UROLOGY 55 (2009) 1003–1011

EUROPEAN UROLOGY 59 (2011) 832–840

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

European Association of Urology

Prostate Cancer

Combination of Adjuvant Hormonal and Radiation Therapy Significantly Prolongs Survival of Patients With pT2–4 pN+ Prostate Cancer: Results of a Matched Analysis

Alberto Briganti [a,], R. Jeffrey Karnes [b], Luigi Filippo Da Pozzo [c], Cesare Cozzarini [d], Umberto Capitanio [a], Andrea Gallina [a], Nazareno Suardi [a], Marco Bianchi [a], Manuela Tutolo [a], Andrea Salonia [a], Nadia Di Muzio [d], Patrizio Rigatti [a], Francesco Montorsi [a], Michael Blute [b]*

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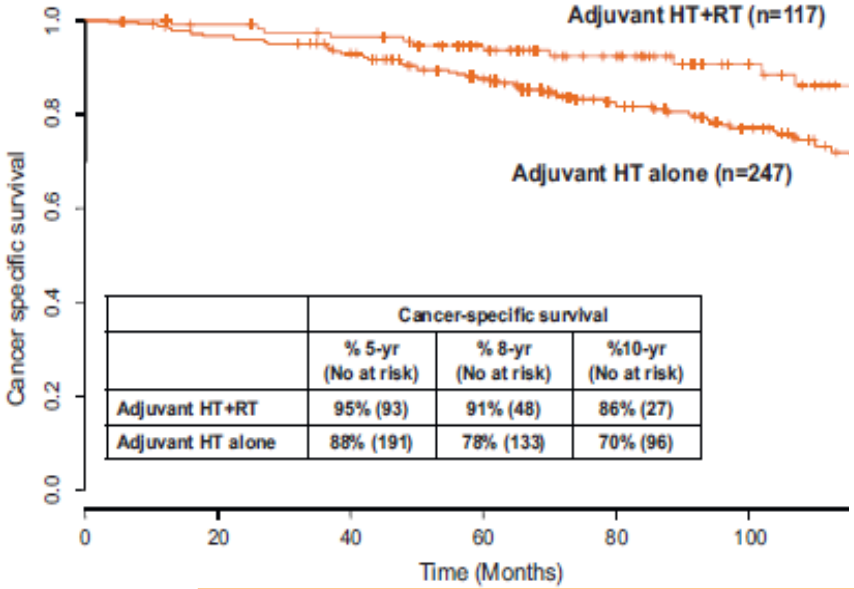
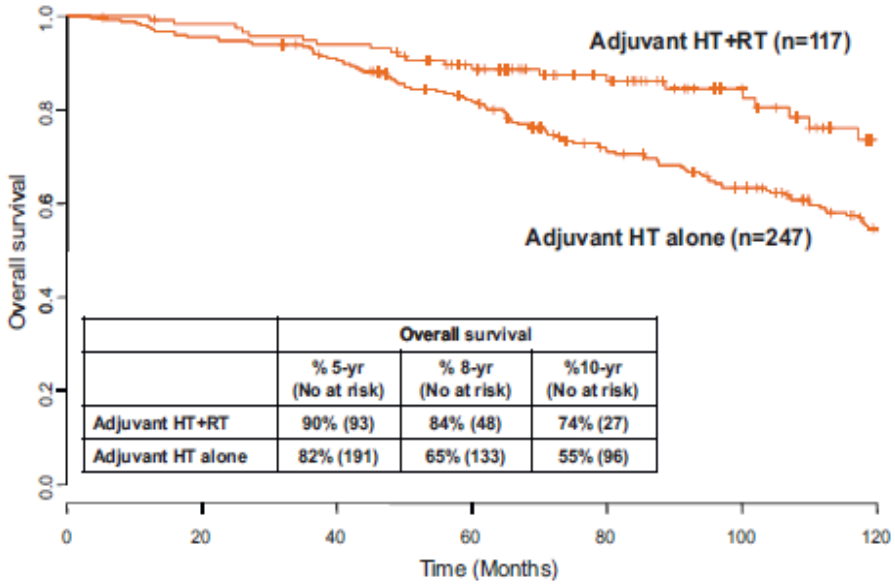
[d] Department of Radiotherapy, San Raffaele Scientific Institute, Milan, Italy

703 pN+ PCa pts

All population



	Cancer-specific survival		
	% 5-yr (No at risk)	% 8-yr (No at risk)	%10-yr (No at risk)
Adjuvant HT+RT	95% (93)	91% (48)	86% (27)
Adjuvant HT alone	88% (191)	78% (133)	70% (96)



	Overall survival		
	% 5-yr (No at risk)	% 8-yr (No at risk)	%10-yr (No at risk)
Adjuvant HT+RT	90% (93)	84% (48)	74% (27)
Adjuvant HT alone	82% (191)	65% (133)	55% (96)

Conclusions: Adjuvant RT plus HT significantly improved CSS and OS of pT2–4 pN1 patients, regardless of the extent of nodal invasion. These results reinforce the need for a multimodal approach in the treatment of node-positive prostate cancer.

Patterns of care and outcomes of radiotherapy for lymph node positivity after radical prostatectomy

Joshua R. Kaplan, Keith J. Kowalczyk*, Tudor Borza, Xiangmei Gu†, Stuart R. Lipsitz†, Paul L. Nguyen‡, David F. Friedlander§, Quoc-Dien Trinh¶ and Jim C. Hu††

*Division of Urologic Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, *Department of Urology, Georgetown University Hospital, Washington, DC, †Center for Surgery and Public Health, Brigham and Women's Hospital, Harvard Medical School, ‡Department of Radiation Oncology, Lank Center for Genitourinary Oncology, Dana Farber Cancer Institute, Boston, MA, §Vanderbilt University School of Medicine, Nashville, TN, ¶Vattikuti Urology Institute, Henry Ford Health System, Detroit, MI, and ††Department of Urology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA*

Objective

- To evaluate the use and outcomes of adjuvant radiation therapy (ART) for men with lymph node (LN)-positive disease after radical prostatectomy (RP) using a population-based approach.

Patients and Methods

- Surveillance, Epidemiology, and End Results (SEER)-Medicare linked data from 1995 to 2007 was used to identify 577 men with LN metastases discovered during RP and absence of distant metastases, of which 177 underwent ART ≤1 year of RP.
- Propensity score models were used to compare overall mortality and prostate cancer-specific mortality (PCSM) for men that did and those that did not receive ART.

Results

- Men in both groups received adjuvant androgen-deprivation therapy at similar rates after propensity weighting adjustments (33.6% vs 33.7%, P = 0.977).
- ART was not associated with differences in overall (5.09 vs 3.77 events per 100 person-years, P = 0.153) or PCSM (2.89 vs 1.31, P = 0.090) relative to men who did not receive ART.

Conclusions

- ART after RP in men with LN-positive prostate cancer was not associated with improved overall or disease-specific survival, in contrast to previous single-centre studies.
- Prospective randomised studies are needed to assess the effectiveness of ART in this patient population.

Keywords

prostate cancer, radical prostatectomy, radiation therapy, outcomes

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Protocol Info
Forms
Broadcasts
Contact Personnel

RTOG 8531 Protocol Information

Phase III Study of Zoladex Adjuvant to Radiotherapy in Unfavorable Prognosis Carcinoma of the Prostate

Protocol Documents

Protocol **Current Version Date:** 7/28/2005

Informed Consent

Summary of Changes

Principal Investigator: M.V. Pilepich, M.D.

Primary Objective:
Evaluation of the relative effectiveness of elective versus therapeutic Androgen deprivation with Zoladex on disease progression and survival, in a population of patients with carcinoma of the prostate who are at high risk of relapse and tumor related death.

Patient Population:
Patients with unfavorable prognosis adenocarcinoma of the prostate including those with clinical Stage A2, B with regional lymph node involvement (- D1), those with gross extension of the palpable primary tumor beyond the prostate (clinical stage C) with or without evidence of nodal involvement and those irradiated post-operatively (following radical prostatectomy) in whom there is pathologically documented penetration through the prostatic capsule in the margin of resection and/or seminal vesicle involvement.

Target Accrual: 931 **Current Accrual:** 977

Status: Closed to Accrual **Date:**

ADULT UROLOGY

ELSEVIER

DOES ANDROGEN SUPPRESSION ENHANCE THE EFFICACY OF POSTOPERATIVE IRRADIATION? A SECONDARY ANALYSIS OF RTOG 85-31

BENJAMIN W. CORN, KATHRYN WINTER, AND MILJENKO V. PILEPICH

139 pts

ABSTRACT

Objectives. To evaluate the effect of immediate androgen suppression in conjunction with standard external beam irradiation (RT) versus RT alone on a group of men after prostatectomy who had indications for adjuvant treatment.

Methods. A national prospective randomized trial (Radiation Therapy Oncology Group [RTOG] 85-31) comparing standard external beam RT plus immediate androgen suppression versus external beam RT alone with delayed hormonal treatment at relapse was initiated for patients with locally advanced adenocarcinoma of the prostate. One hundred thirty-nine of the patients in this trial had indications for adjuvant treatment after prostatectomy (eg, capsular penetration, seminal vesicle involvement). Seventy-one of the patients received RT with immediate androgen suppression (luteinizing hormone-releasing hormone [LHRH] agonist); 68 patients received RT alone with hormonal manipulation instituted only at the time of relapse.

71 RT +ADT

68 RT alone

Results. With a median follow-up of 5 years, the estimated progression-free survival rate (failure defined as prostate-specific antigen [PSA] greater than 0.5 ng/mL) was 65% for the men who received combination therapy and 42% for those treated by RT alone with hormones reserved for relapse ($P = 0.002$). Differences in the rates of freedom from biochemical relapse were observed when failure was defined as PSA of 1.0 to 3.9 ng/mL (71% versus 46%; $P = 0.008$) and PSA greater than 4.0 ng/mL (76% versus 55%; $P = 0.05$), respectively. No differences were observed between the groups with respect to the end points of local control, distant failure, and overall survival. The use of immediate androgen suppression (ie, LHRH agonists) and the absence of pathologic nodal involvement were independently associated with prolongation of freedom from biochemical relapse by multivariate analysis.

UROLOGY **54:** 495–502, 1999.

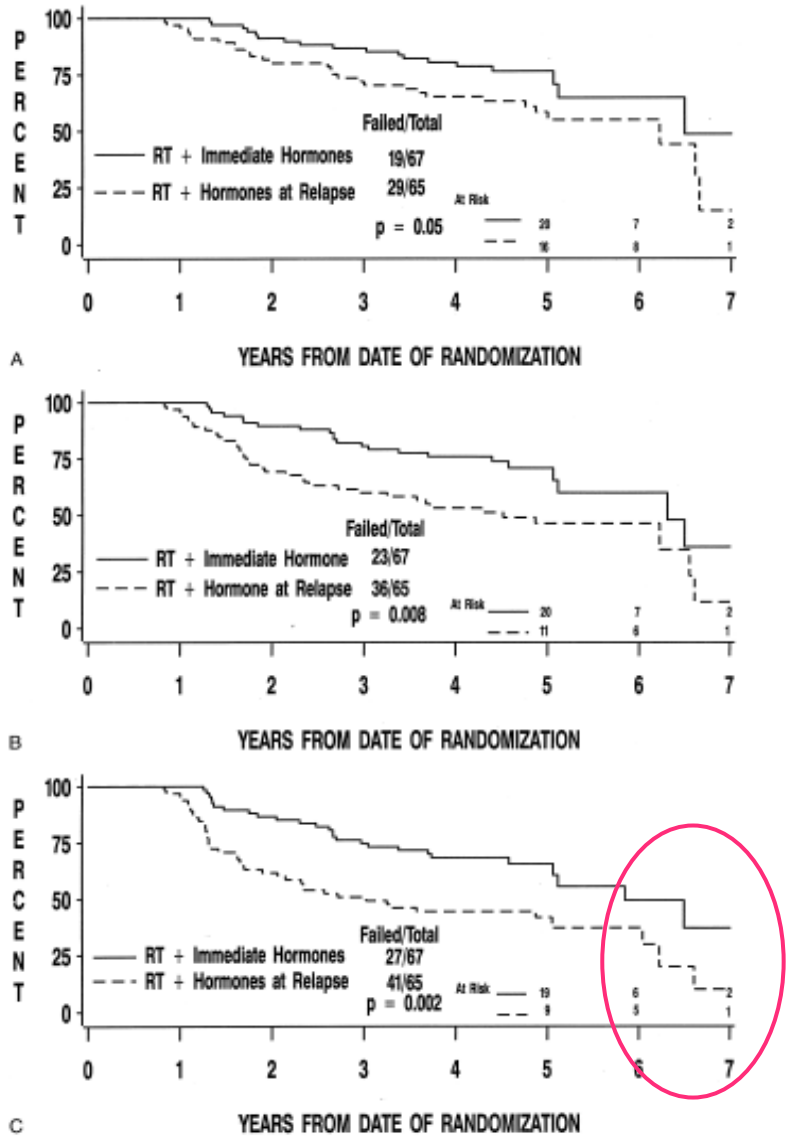


FIGURE 1. *FFBR as a function of treatment arm (RTOG 85-31). PSA normalization was defined as (A) less than 4.0 ng/mL, (B) less than 1.0 ng/mL, and (C) less than 0.5 ng/mL.*

Advantage only in FFBR, not in OS

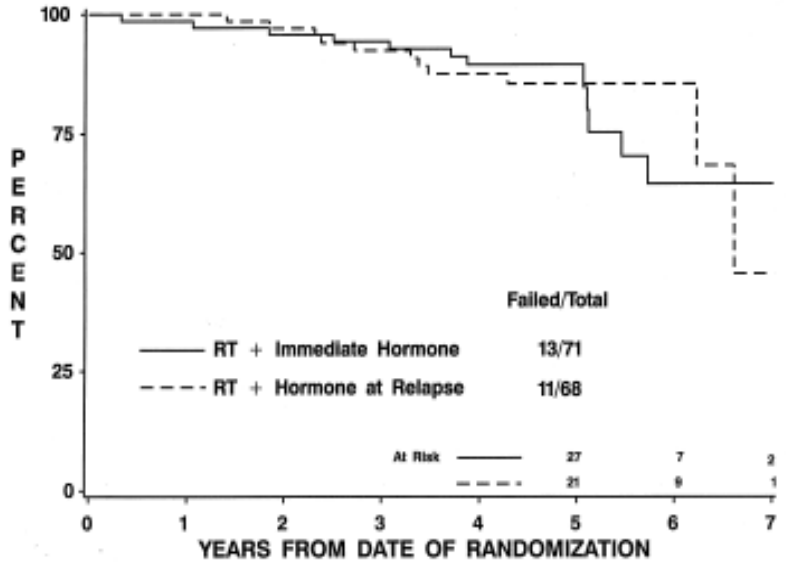


FIGURE 4. *Overall survival as a function of treatment arm (RTOG 85-31).*

Conclusions. Patients with prostate cancer and indications for postoperative RT should be considered for combined RT and hormonal manipulation. Because statistically significant advantages for this experimental approach could not be defined for all end points studied (in particular, overall survival), efforts should be made to enroll these patients in the recently activated RTOG trial (96-01) comparing RT plus placebo to the combination of RT plus Casodex in the postoperative setting. UROLOGY **54:** 495–502, 1999. © 1999,

Int. J. Radiation Oncology Biol. Phys., Vol. 61, No. 5, pp. 1285–1290, 2005

0360-3016/05/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2004.08.047

CLINICAL INVESTIGATION **Prostate**

ANDROGEN SUPPRESSION ADJUVANT TO DEFINITIVE RADIOTHERAPY IN PROSTATE CARCINOMA—LONG-TERM RESULTS OF PHASE III RTOG 85-31

Miljenko V. Pilepich, M.D.,* Kathryn Winter, M.S.,† Colleen A. Lawton, M.D.,‡ Robert E. Krisch, M.D.,§ Harvey B. Wolkov, M.D.,‖ Benjamin Movsas, M.D.,¶ Eugen B. Hug, M.D.,# Sucha O. Asbell, M.D.,** and David Grignon, M.D.††

*From University of California, Los Angeles, School of Medicine, Los Angeles, CA; †Radiation Therapy Oncology Group, Philadelphia, PA; ‡Medical College of Wisconsin, Milwaukee, WI; §University of Pennsylvania, Philadelphia, PA; ‖Radiology Associates of Sacramento, Sacramento, CA; ¶Fox Chase Cancer Center, Philadelphia, PA; #Dartmouth Hitchcock Medical Center, Lebanon, NH; **Albert Einstein Medical Center, Philadelphia, PA; ††Wayne State University, Detroit, MI

Table 3. Multivariate analysis results

	Absolute survival		Local failure		Distant failure		NED survival (PSA <1.5 ng/mL)		Disease-specific death	
Variable	HR	*p*	HR	*p*	HR	*p*	HR	*p*	HR	*p*
Treatment (Arm I vs. Arm II)	1.3	0.001	1.9	<0.0001	1.9	<0.0001	2.2	<0.0001	1.7	0.0003
Prostatectomy (yes vs. no)	1.8	0.0004	3.4	NS	2.2	<0.0001	2.1	<0.0001	2.3	0.0005
Nodal involvement (no vs. yes)	1.6	<0.0001	NS	<0.0001	1.8	<0.0001	1.7			
Central Gleason score (2–6 vs. 7–10)	1.7	<0.0001	1.5	0.0015	2.2	<0.0001	1.6			
Age (<70 vs. ≥70 y)	1.5	<0.0001	NS	NS	NS	NS	1.3			
Clinical stage (A-B vs. C)	1.4	0.027	NS	NS	NS	NS	1.3			

Abbreviations: HR = hazard ratio (data analyzed such that HR >1 indicated increased risk in endp
= not statistically signficant at 0.05 level.

Toxicity

CONCLUSION

The results of RTOG 85-31 substantiate a powerful beneficial effect of adjuvant androgen suppression. Although an improvement in all endpoints was substantiated for the entire study population, the adjuvant effect appeared preferentially in patients with a high Gleason score. This observation poses a significant practical question in the treatment of patients with a Gleason score of 2–6. Long-term adjuvant suppression with its cost and treatment-related morbidity (12–17) may not be justified in this population. However, patients with locally advanced (bulky) tumor with Gleason score 2–6 have been shown to benefit significantly from androgen suppression applied in a neoadjuvant format (as in RTOG 86-10). In patients with unfavorable prognosis carcinoma of the prostate (clinical Stage T3 or those with regional lymphatic involvement) who also have tumors with a high Gleason score, long-term application of androgen suppression could be adopted as a standard of care.

Original Article

Death From High-Risk Prostate Cancer Versus Cardiovascular Mortality With Hormonal Therapy

A Decision Analysis

Nataniel H. Lester-Coll, MD[1]; Samuel Z. Goldhaber, MD[2]; David J. Sher, MD, MPH[3]; and Anthony V. D'Amico, MD, PhD[4]

BACKGROUND: Randomized trials have demonstrated improved survival when hormonal therapy (HT) is added to radiation therapy (RT) for high-risk prostate cancer. However, it is still unknown whether men who have a history of myocardial infarction (MI) or MI risk factors achieve a superior outcome from HT. **METHODS:** A Markov decision analysis model was used to compare quality-adjusted life expectancy (QALE) in men aged 50, 60, and 70 years who received RT and no HT, 6 months of HT (short-term), or 3 years of HT (long-term) for high-risk prostate cancer stratified by cardiac risk group. **RESULTS:** In men with a history of MI, there was a decrease of 0.1 to 0.2 quality-adjusted life years and 0.5 to 0.6 quality-adjusted life years across all ages with short-term HT and long-term HT, respectively, compared with no HT. In men without MI, receipt of short-term or long-term HT was associated with a QALE benefit versus no HT in all cohorts. Among men without MI, the optimal duration of HT was a function of age and the number of MI risk factors. Long-term HT improved QALE (range, 1.4-5.4 years) for men aged 50 or 60 years except those with MI; whereas, for men aged 70 years with 4 cardiac risk factors, short-term and long-term HT yielded identical QALE. **CONCLUSIONS:** Men who received RT for high-risk prostate cancer and had a history of MI experienced net harm when they received HT. Men without MI gained a QALE benefit from HT, even if they had up to 4 cardiac risk factors. The optimal duration of HT is a function of patient age and the number of cardiac risk factors. ***Cancer*** **2013;119:1808–15.** *© 2013 American Cancer Society.*

In conclusion, most men with high-risk prostate cancer will benefit from long-term HT. However, compared with long-term HT, short-term HT maximizes QALE in a subset of men with MI risk factors. Given the potential interaction between HT and cardiovascular disease, it is important for the patient to recognize the importance of achieving optimal cardiovascular health.

We recommend pretherapy consultation with a cardiologist to quantify and, if possible, reverse MI risk factors.

Cancer May 15, 2013

JNCI JOURNAL OF THE NATIONAL CANCER INSTITUTE

Androgen Deprivation Therapy for Localized Prostate Cancer and the Risk of Cardiovascular Mortality

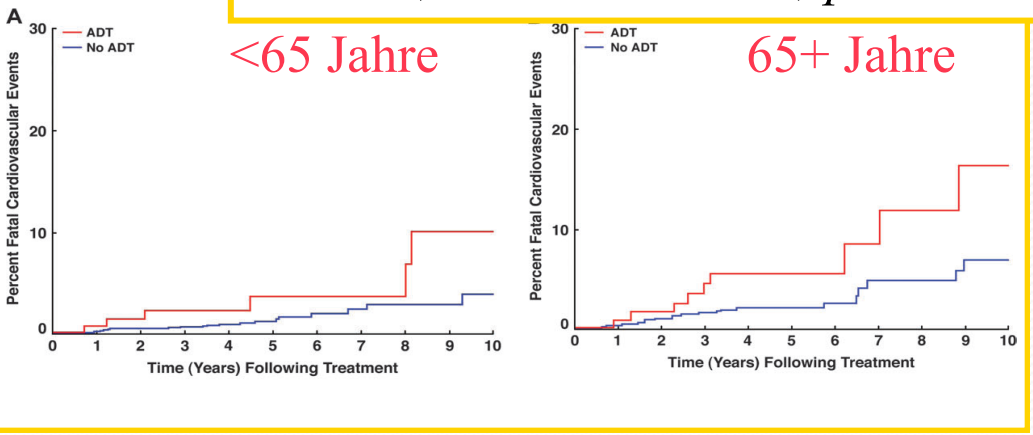
Henry K. Tsai, Anthony V. D'Amico, N

Methods From the Cancer of the Prostate Strategic Urologic Research Endeavor treated with radical prostatectomy and 1630 patients treated with externa therapy, or cryotherapy for localized prostate cancer were included in ...ng risks regression analyses were performed to assess whether use of ADT was as ... a shorter time to death from cardiovascular causes after controlling for age (as a continuous variable) and the presence of baseline cardiovascular disease risk factors. All tests for statistical significance were two-sided.

Results The median follow-up time was 3.8 years (range = 0.1–11.3 years). Among the 1015 patients who received ADT, the median duration of ADT use was 4.1 months (range = 1.0–32.9 months). In a competing risks regression analysis that controlled for age and risk factors for cardiovascular disease, both ADT use (adjusted hazard ratio [HR] = 2.6; 95% confidence interval [CI] = 1.4 to 4.7; P = .002) and age (adjusted HR = 1.07; 95% CI = 1.02 to 1.1; P = .003) were associated with statistically significantly increased risks of death from cardiovascular causes in patients treated with radical prostatectomy. Among patients 65 years or older treated with radical prostatectomy, the 5-year cumulative incidence of cardiovascular death was 5.5% (95% CI = 1.2% to 9.8%) in those who received ADT and 2.0% (95% CI = 1.1% to 3.0%) in those who did not. Among patients 65 years or older treated with external beam radiation therapy, brachytherapy, or cryotherapy, ADT use was associated with a higher cumulative incidence of death from cardiovascular causes, but the difference did not reach statistical significance.

Conclusions The use of ADT appears to be associated with an increased risk of death from cardiovascular causes in patients undergoing radical prostatectomy for localized prostate cancer.

HR: 2.6; 95% CI: 1.4-4.7; p =0.002



J Natl Cancer Inst 2007;99:1516–24

Obesity and Mortality in Men With Locally Advanced Prostate Cancer

Analysis of RTOG 85-31

RESULTS. The 5-year PCSM rate for men with BMI <25 kg/m^2 was 6.5%, compared with 13.1% and 12.2% in men with BMI ≥25 to <30 and BMI ≥30, respectively (Gray's $P = .005$). In multivariate analyses, greater BMI was significantly associated with higher PCSM (for BMI ≥25 to <30, hazard ratio [HR] 1.52, 95% confidence interval [CI], 1.02–2.27, $P = .04$; for BMI ≥30, HR 1.64, 95% CI, 1.01–2.66, $P = .04$). BMI was not associated with nonprostate cancer or all-cause mortality.

CONCLUSIONS. Greater baseline BMI is independently associated with higher PCSM in men with locally advanced prostate cancer. Further studies are warranted to evaluate the mechanism(s) for increased cancer-specific mortality and to assess whether weight loss after prostate cancer diagnosis alters disease course. ***Cancer*** **2007;110:2691–99.**

Data available for 788 pts

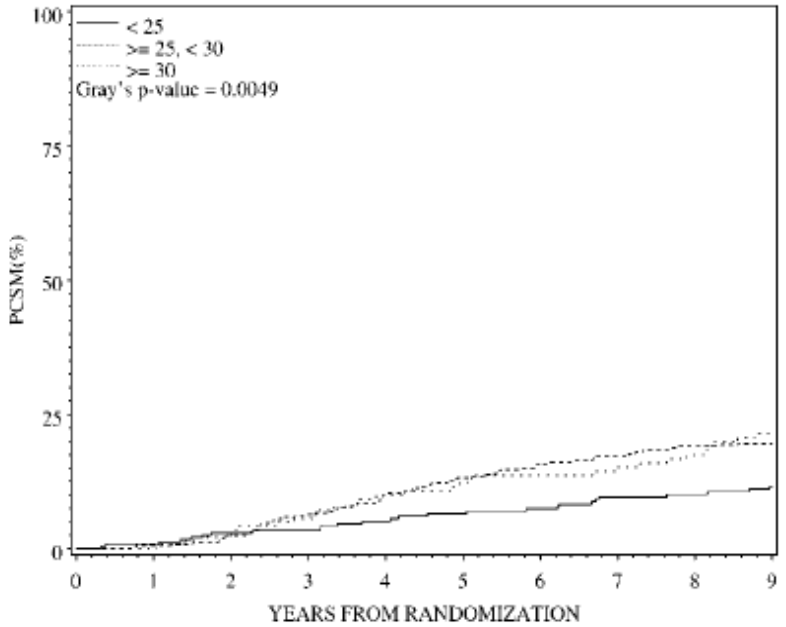


FIGURE 2. Time to prostate cancer-specific mortality (PCSM) by body mass index (BMI) category.

Guidelines

Adjuvant and Salvage Radiation Therapy After Prostatectomy: American Society for Radiation Oncology/American Urological Association Guidelines

Richard K. Valicenti, MD, MBA,* Ian Thompson Jr., MD,† Peter Albertsen, MD, MS,‡ Brian J. Davis, MD, PhD,§ S. Larry Goldenberg, MD,‖ J. Stuart Wolf, MD,¶ Oliver Sartor, MD,# Eric Klein, MD,** Carol Hahn, MD,†† Jeff Michalski, MD, MBA,‡‡ Mack Roach III, MD,§§ and Martha M. Faraday, PhD‖‖

CME ASTRO

International Journal of Radiation Oncology biology • physics

Volume 86 • Number 5 • 2013

Use of androgen deprivation therapies

Key questions are whether, when, for how long, and in what form androgen deprivation therapy (ADT) should be administered. The literature review attempted to address these questions by examining studies that focused on the use of ADT in patients who underwent prostatectomy and then ART or SRT. The Panel's conclusion was that, given the methodological weaknesses of this literature, it is not possible to provide guidance regarding the use of ADT in conjunction with RT. These weaknesses include nonrandomized study designs; small sample sizes and lack of statistical power; lack of group equivalence on pathological risk factors; large differences in ADT protocols, including when it was administered and for how long; primary focus on biochemical recurrence; and other differences relevant to efficacy such as differences in RT techniques, targets, and total Gy administered. Randomized controlled trials are needed to provide definitive evidence.

Guideline statement

NONE!!!

Adjuvant and Salvage Radiotherapy After Prostatectomy: AUA/ASTRO Guideline

Ian M. Thompson,* Richard K. Valicenti,* Peter Albertsen, Brian J. Davis, S. Larry Goldenberg, Carol Hahn, Eric Klein, Jeff Michalski, Mack Roach, Oliver Sartor, J. Stuart Wolf, Jr. and Martha M. Faraday

From the American Urological Association Education and Research, Inc., Linthicum, Maryland, and the American Society for Radiation Oncology, Fairfax, Virginia

0022-5347/13/1902-0441/0
THE JOURNAL OF UROLOGY®

Research Needs and Future Directions

Ongoing clinical trials

Ongoing clinical trials (eg, RTOG 0534, RTOG 9601, RADICALS, RAVES) will help to clarify the role of ART or SRT, the value of combining RT with other therapies, and potentially make clear which patients are more likely to benefit from specific therapeutic approaches.

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RTOG 9601 Protocol Information

A Phase III Trial of Radiation Therapy with or without Casodex in Patients with PSA Elevation Following Radical Prostatectomy for pT3N0 Carcinoma of the Prostate

Protocol Documents

Protocol **Current Version Date:** 12/31/2008

Informed Consent

Summary of Changes

Principal Investigator: William U. Shipley, M.D.

Primary Objective:
To compare overall survival outcome of radiation therapy plus Casodex to radiation therapy plus placebo by a randomized trial for patients who, following radical prostatectomy demonstrating pathologic T3 disease and pathologic N0 disease status, have an elevated PSA (either as persistence or as a relapse) and have no evidence of metastatic disease

Patient Population:
Pathologic stage T3 N0 with radical prostatectomy, or pT2 pN0 with a positive inked resection margin or positive prostate fossa/anastamosis biopsy

Target Accrual: 810 **Current Accrual:** 840

Status: Closed to Accrual **Date:**

International Journal of Radiation Oncology biology • physics
Official Journal of the American Society for Radiation Oncology ASTRO

58 **Initial Report of RTOG 9601: A Phase III Trial in Prostate Cancer: Anti-androgen Therapy (AAT) with Bicalutamide during and after Radiation Therapy (RT) Improves Freedom from Progression and Reduces the Incidence of Metastatic Disease in Patients following Radical Prostatectomy (RP) with pT2-3, N0 Disease, and Elevated PSA Levels**

W. U. Shipley[1], D. Hunt[2], H. Lukka[3], P. Major[3], N. M. Heney[1], D. Grignon[4], M. Patel[3], J. Bahary[5], C. Lawton[6], H. Sandler[7]

[1]Massachusetts General Hospital, Boston, MA, [2]RTOG Statistical Center, Philadelphia, PA, [3]McMaster University Juravinski Cancer Center, Hamilton,, ON, Canada, [4]Indiana University, Indianapolis, IN, [5]University of Montreal (CHUM), Montreal, QC, Canada, [6]Medical College of Wisconsin, Milwaukee, WI, [7]Cedars-Sinai Cancer Center, Los Angeles, CA

Purpose/Objective(s): To test if long term AAT when combined with RT in these patients with prostate cancer (PC) will improve cancer control outcomes as well as overall survival.

Materials/Methods: Post-RP patients with pT3,N0 or with pT2,N0 (and also positive margins) who have an elevated PSA were entered on a Phase III, double-blinded, placebo-controlled trial of RT alone (64.8 Gy in 36 fractions of 1.8 Gy) Vs RT plus AAT (24 months of bicalutamide, 150mg QD) during and after RT. The primary end-point is overall survival.

Results: From 3/98 to 3/03, 771 eligible patients (median age 65) were randomized to RT plus AAT (387) or RT alone (383). Pretreatment characteristics were balanced. 252 patients (33%) were pT2,N0 and 518 patients (67%) were pT3,N0. 672 patients (87%) had a PSA nadir after RP of < 0.5 ng/mL. 655 patients (85%) had an entry PSA value of <1.6, 115 patients (15%) had an entry PSA of 1.6-3.9. Median follow-up in surviving patients was 7.1 years. The actuarial overall survival at 7 years was 91% for RT plus AAT and 86% for RT alone. Too few "primary end-point events" have occurred as yet to allow a statistical comparison between these groups. PSA progression was defined as a PSA > 0.4 ng/mL in patients whose protocol treatment resulted in an undetectable PSA or, if not, when the PSA rose 0.3 ng/mL above the entry PSA. Freedom From PSA Progression (FFP) estimated at 7 years was 57% for RT plus AAT and 40% for RT alone ($p < 0.0001$); for 226 patients with GS < 7 were 63% and 50% ($p < 0.02$): for 411 GS 7 these were 55% and 39% ($p < 0.0006$), and for 134 GS 8-10 were 56% and 26% ($p < 0.0008$). The cumulative incidence of metastatic PC at 7 years was less in the RT and AAT arm, 7.4% (25 patients),Vs 12.6% (46 patients) in the RT and placebo arm ($p < 0.04$). Late Grade III and Grade IV toxicity were similar in the bicalutamide and placebo arms. By category the combined Grade III plus Grade IV toxicities for RT and AAT and RT alone were: for bladder 5.9% Vs 5.0%, bowel 2.3% Vs 1.4%, cardiac 2.8% Vs 1.8%. Gynecomastia (mostly all Grades I and II) differed significantly, 89% and 15%. In the RT plus AAT arm Grade III was the highest liver toxicity observed which occurred in 3 of 387 patients.

Conclusions: The addition of 24 months of peripheral androgen blockade (AAT) during and after RT significantly improved FFP and reduced the incidence of metastatic PC without adding significantly to radiation toxicity. The significance of benefit in overall survival, as well analysis of risk-stratified subsets, must await longer follow-up.

771 eligible pts

FFP

57% vs 40%
p<0,001

Inc. Met PCa

7,4% vs 12,6%
p<0,04

Shipley WU et al.,Int J Radiat Oncol Biol Phys. 2010;78:S27

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Clinical Trials

EORTC protocol 22043 - 30041

Immediate or early salvage post-operative external radiotherapy combined with concomitant and adjuvant hormonal treatment versus immediate or early salvage post-operative external radiotherapy alone in pT3a-b R0-1 cN0M0/pT2R1 cN0M0, Gleason score 5-10 prostatic carcinoma. A phase III study.

Trial Status	Closed for recruitment
Dates	Date of activation: 18-May-09
Data management at EORTC	Full
Phase	3
Randomized trial	Yes
Type	Adjuvant
Targeted Sample size	EORTC Groups: 600 - All Groups: 600
Number of steps	1
Drug	Leuprorelin
Study Staff	**Michel Bolla** (Study Coordinator) - CHU de Grenoble **Steven Joniau** (Study Coordinator) - U.Z. Leuven - Ca **Laurence Collette** (Statistician) - EORTC Headquarte **Isabelle Meulders** (Data Manager) - EORTC Headqua

Radiotherapy and Oncology 107 (2013) 346–351

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Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Quality assurance in prostate RT

Quality assurance of the EORTC 22043-30041 trial in post-operative radiotherapy in prostate cancer: Results of the Dummy Run procedure

Paul A. Fenton [a,b,*], Coen Hurkmans [c], Akos Gulyban [a], Jorien van der Leer [c], Oscar Matzinger [a,d], Philip Poortmans [e], Laurence Collette [a], Michel Bolla [f]

[a] EORTC Headquarters, Brussels, Belgium; [b] Department of Radiotherapy, University Hospital Southampton, UK; [c] Department of Radiation Oncology, Catharina Hospital, Eindhoven, The Netherlands; [d] Department of Radiation Oncology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; [e] Department of Radiation Oncology, Institute Verbeeten, Tilburg, The Netherlands; [f] Centre Hospitalier Régional Universitaire de Grenoble, Grenoble, France

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RTOG 0534 Protocol Information

A Phase III Trial of Short Term Androgen Deprivation With Pelvic Lymph Node or Prostate Bed Only Radiotherapy (SPPORT) in Prostate Cancer Patients With a Rising PSA After Radical Prostatectomy

Protocol Documents

Protocol

Current Version Date: 11/23/2011

Informed Consent

Summary of Changes

Track Amendments/ Update

Case Credits/Reimbursement Info

Prostate bed RT
Prostate bed RT with ADT
Prostate bed + Node RT with ADT

Principal Investigator: Alan Pollack, MD, PhD

Primary Objective:
To determine whether the addition of NC-STAD to PBRT improves freedom from progression (FFP) [maintenance of a PSA less than the nadir+2 ng/mL, absence of clinical failure and absence of death from any cause] for 5 years, over that of PBRT alone in men treated with salvage RT after radical prostatectomy;
To determine whether NC-STAD+PLNRT+PBRT improves FFP over that of NC-STAD+PBRT and PBRT alone in men treated with salvage RT after radical prostatectomy.

Patient Population:
Lymph node negative adenocarcinoma of the prostate treated with radical prostatectomy. Post-radical prostatectomy PSA of > = 0.1 - < 2.0 ng/mL; pathologic T3N0/Nx disease or pathologic T2N0/Nx disease, with or without a positive prostatectomy surgical margin; Gleason < = 9

Target Accrual: 1764

Current Accrual: 1468

Status: Open to Accrual

Date:

2007 BJU INTERNATIONAL | 99, 1376–1379

Radiotherapy and androgen deprivation in combination after local surgery (RADICALS): A new Medical Research Council/National Cancer Institute of Canada phase III trial of adjuvant treatment after radical prostatectomy

Chris Parker, Matthew R. Sydes[1], Charles Catton[2], Howard Kynaston[3], John Logue[4], Claire Murphy[1], Rachel C. Morgan[1], Kilian Mellon[5], Chris Morash[6], Wendy Parulekar[7], Mahesh K.B. Parmar[1], Heather Payne[8], Colleen Savage[7], Jim Stansfeld[9] and Noel W. Clarke[10] (The RADICALS Trial Management Group)

Clinical Oncology (2007) **19**: 167–171
doi:10.1016/j.clon.2007.01.001

Editorial

RADICALS (Radiotherapy and Androgen Deprivation in Combination after Local Surgery)

C. Parker*, N. Clarke†, J. Logue‡, H. Payne§, C. Catton‖, H. Kynaston¶, C. Murphy**, R. Morgan**, C. Morash††, W. Parulekar‡‡, M. Parmar**, C. Savage‡‡, J. Stansfeld§§, M. Sydes**
(The RADICALS Trial Management Group)

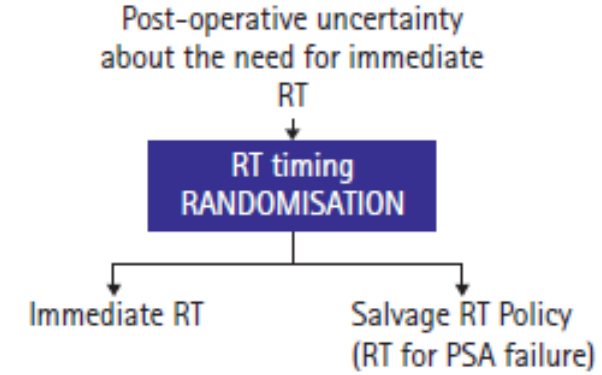
**Academic Unit of Radiotherapy and Oncology, Institute of Cancer Research and the Royal Marsden NHS Foundation Trust, Downs Road, Sutton, Surrey SM2 5PT, UK; †Salford Royal Hospitals NHS Trust, Salford M6 8HD, UK; ‡Christie Hospital NHS Trust, Manchester M20 4BX, UK; §Department of Oncology, UCH, 250 Euston Road, London NW1 2PQ, UK; ‖Princess Margaret Hospital, 610 University Avenue, Toronto, ON, Canada M5G 2M9; ¶Department of Urology, University Hospital of Wales, Heath Park, Cardiff CF14 4XW, UK; **MRC Clinical Trials Unit, 222 Euston Road, London NW1 2DA, UK; ††University of Ottawa, The Ottawa Hospital General Campus, 501 Smyth Road, Ottawa, ON, Canada K1H 8L6; ‡‡National Cancer Institute of Canada (NCIC) Clinical Trials Group, 10 Stuart Street, Kingston, Ontario, Canada K7L 3N6; §§PCaSO Prostate Cancer Network, PO Box 66, Emsworth, Hampshire PO10 7ZP, UK*

RADICAL PROSTATECTOMY

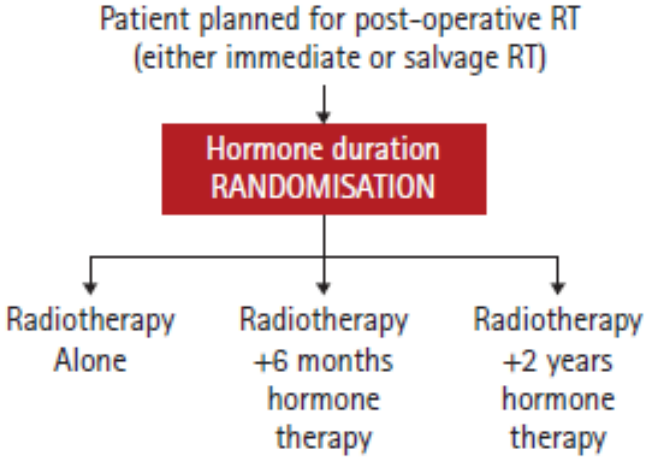
Two randomisation

- Timing of postoperative RT
- Duration of hormone therapy

RADICALS – RT timing randomisation:
Immediate RT vs salvage RT post-operatively



RADICALS – hormone duration randomisation:
Use of hormones with post-operative RT



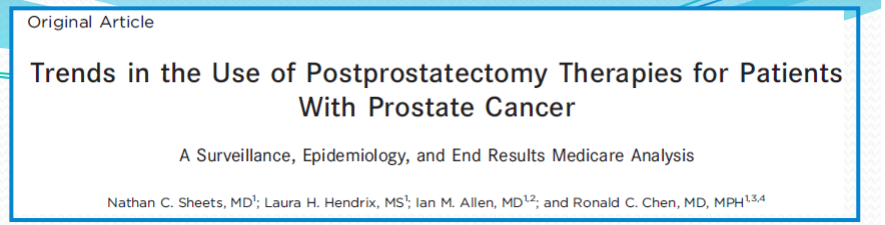
Guidelines

Radiotherapy and Oncology 88 (2008) 10–19
www.thegreenjournal.com

Post-prostatectomy radiation therapy: Consensus guidelines of the Australian and New Zealand Radiation Oncology Genito-Urinary Group

Mark A. Sidhom[a,*], Andrew B. Kneebone[a], Margot Lehman[b], Kirsty L. Wiltshire[c], Jeremy L. Millar[d], Rahul K. Mukherjee[e], Thomas P. Shakespeare[f], Keen-Hun Tai[g]

[a]Cancer Therapy Centre, Liverpool Hospital, NSW, Australia, [b]Southern Zone Radiation Oncology, Princess Alexandra Hospital, Qld, Australia, [c]Northern Sydney Cancer Centre, Royal North Shore Hospital, NSW, Australia, [d]William Buckland Radiotherapy Centre, The Alfred Hospital, Vic., Australia, [e]Department of Radiation Oncology, The Cancer Institute, National University, Singapore, [f]North Coast Cancer Institute, Coffs Harbour, NSW, Australia, [g]Peter MacCallum Cancer Centre and Department of Pathology, University of Melbourne, Vic., Australia



Original Article

Trends in the Use of Postprostatectomy Therapies for Patients With Prostate Cancer

A Surveillance, Epidemiology, and End Results Medicare Analysis

Nathan C. Sheets, MD[1]; Laura H. Hendrix, MS[1]; Ian M. Allen, MD[1,2]; and Ronald C. Chen, MD, MPH[1,3,4]

Summary

- The role of ADT in conjunction with post-prostatectomy RT is yet to be defined (data only from retrospective non randomized clinical trials).
- Some retrospective studies report an improvement in bPFS, but not in OS, with the addition of hormones to RT in the adjuvant [Corn, RTOG 8531; King, IJROBP 2004] and salvage [Eulau, IJROBP 1998; Cheung, IJROBP 2005] settings,
- Until randomised evidence is available, the addition of ADT to post-prostatectomy RT may be considered for patients with high risk features that have poor outcomes with RT alone - high pre-salvage PSA (>1 ng/ml), high GS and macroscopic local recurrence [Hayes, JCO 2005].
- The RTOG 96-01 has completed accrual and we are waiting for long—term FU.

Table 4
Guideline 4: what is the role of adjuvant hormonal therapy?

	Level of evidence	Reference
4.1. The role of hormonal therapy in conjunction with radiotherapy following a radical prostatectomy is yet to be defined	IV	Consensus
4.2. Androgen suppression may be beneficial in men at high risk of local or distant failure with radiotherapy alone	III	[43–46]
4.3. Hormonal therapy as a primary salvage modality does not offer the potential for cure	IV	Consensus

The Washington Post

NELSON MANDELA 1918-2013

A nation's healer is dead

Grazie dell'attenzione

Original Article

Trends in the Use of Postprostatectomy Therapies for Patients With Prostate Cancer

A Surveillance, Epidemiology, and End Results Medicare Analysis

Nathan C. Sheets, MD[1]; Laura H. Hendrix, MS[1]; Ian M. Allen, MD[1,2]; and Ronald C. Chen, MD, MPH[1,3,4]

[1]Department of Radiation Oncology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; [2]School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; [3]Cecil G. Sheps Center for Health Services Research, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; [4]Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

- **SEER database**
- **3460 RP from 2000 to 2006**
- **Within 3 ys after RP, 1076 pts (31%) received further therapies →RT 850 (25%) and**
- **adjuvant RT (within 6 mo after RP): 43%**

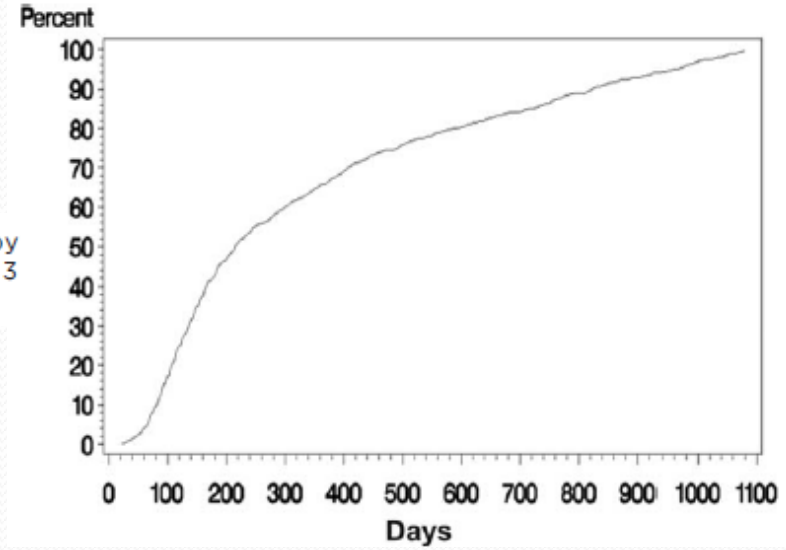


Figure 1. The cumulative incidence of receipt of radiotherapy is shown for all patients treated with radiotherapy within 3 years of undergoing surgery (N = 850).

CONCLUSIONS: Rates of postprostatectomy RT remain low and the timing of RT has not appreciably changed since the publication of the randomized trials supporting the use of adjuvant RT. The use of hormone therapy is almost as common as RT, despite a relative lack of evidence supporting its use in this setting. ***Cancer*** **2013;119:3295-301**. © *2013 American Cancer Society.*

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journal homepage: www.thegreenjournal.com

Prostate cancer radiotherapy

Evaluating the utility of a patient decision aid for potential participants of a prostate cancer trial (RAVES-TROG 08.03)

Puma Sundaresan [a,*], Sandra Turner [b], Andrew Kneebone [c], Maria Pearse [d], Phyllis Butow [e]

[a] Department of Radiation Oncology, Royal Prince Alfred Hospital, Camperdown, Australia; [b] Westmead Cancer Care Centre, Westmead Hospital, Australia; [c] Northern Sydney Cancer Centre, St. Leonards, Australia; [d] Department of Radiation Oncology, Auckland City Hospital, New Zealand; [e] Centre for Medical Psychology and Evidence Based Decision-Making, University of Sydney, Australia

- **RAVES (Radiotherapy-Adjuvant vs Early Salvage Clinical Trial)**
- **Trans Tasman Radiation Oncology Group (TROG), Urological Society and Urogenital and Prostate Cancer Trial Group**
- **Hypothesis that close monitoring with early salvage RT in the event of a PSA rise, is as effective as immediate adjuvant RT in high-risk patients after RP**

Radiotherapy and Oncology 101 (2011) 521–524