Intermittent Hormone Blockage Beyond Evidence and Recommendations

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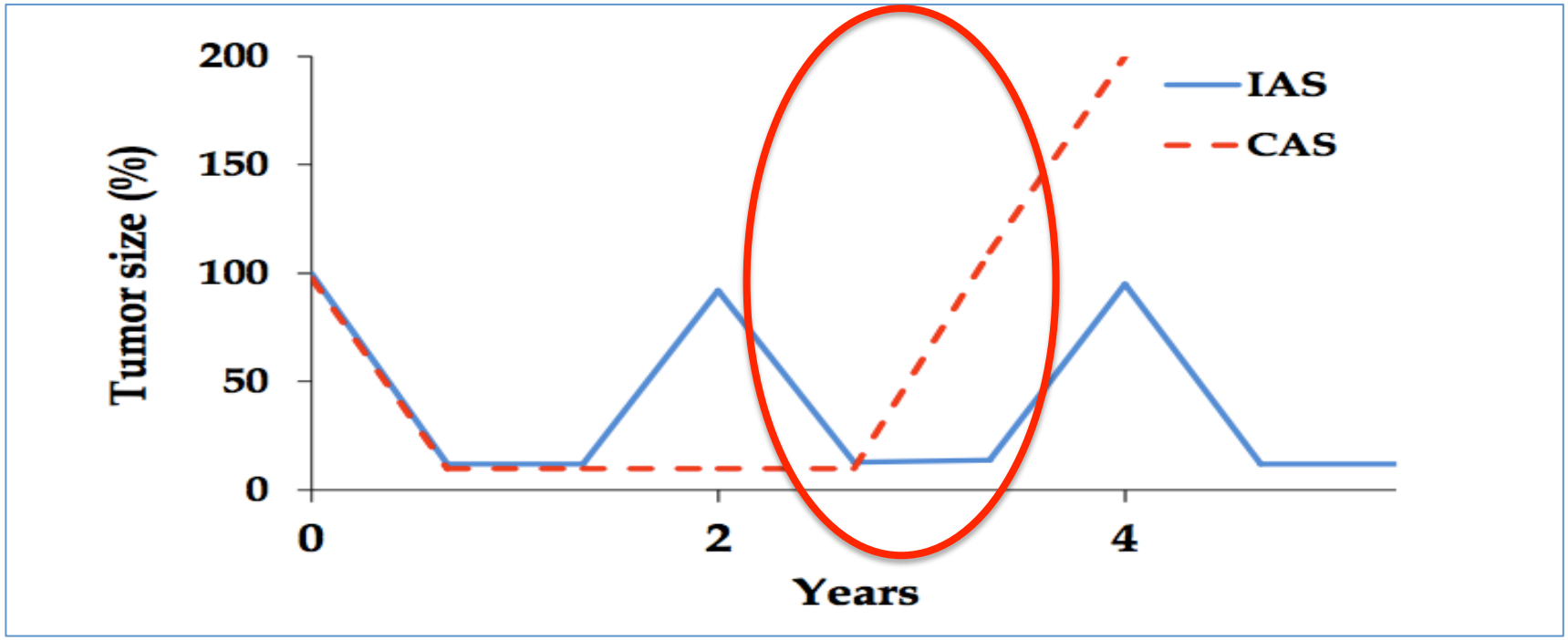
Intermittent Androgen Deprivation Therapy (IAD) Definition

Alternating periods of treatment with "intervals off treatment" to allow hormone recovery between cycles

- **Aims of IADT**
  - To delay development of castration resistance
  - To reduce the side effects and costs of androgen deprivation therapy

Rationale for IAD

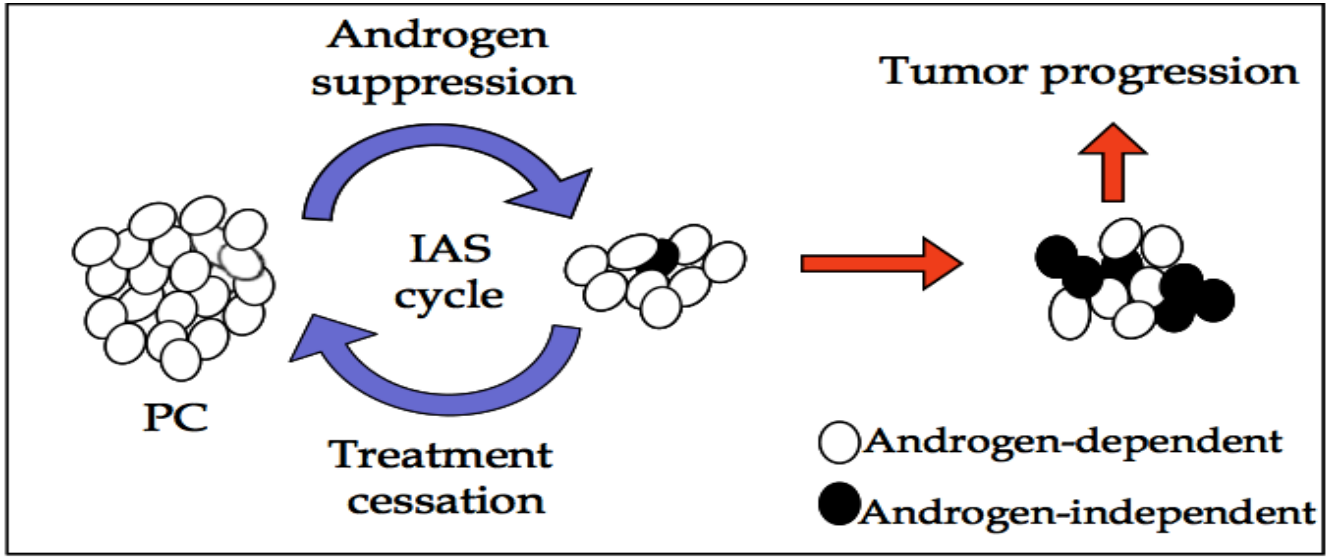
- **Experimental data indicate that castrate-independent progression may <u>begin early after castration</u> (coinciding with the cessation of androgen-induced differentiation of stem cells)**



Bruchovsky et al 1990

Rationale for IAD

Preclinical data support the hypothesis that re-exposure of prostate cancer stem cells to androgens, could reestablish the apoptotic potential of androgen dependent cells (prolonging the time to development of androgen independence)



Bruchovsky et al 1990

Current Evidence on IADT

- IADT is not inferior to continuous ADT
- Insufficient data to determine whether IADT is able to prevent the long-term complications of ADT

19 Prospective Phase II studies **8 Randomized Phase III studies**

Abrahamsson, 2010

Intermittent Androgen Deprivation Therapy (IAD

Prospective Phase II studies

Phase II Clinical Trials

Phase II trials on intermittent androgen suppression vs. continuous androgen deprivation therapy in prostate cancer

Study	Sample size (*N*)	Follow-up (months)	Patient population	PSA nadir (ng/ml)	PSA trigger (ng/ml)
Klotz [2] (1986)	20	36	D2	Pre-PSA era	Pre-PSA era
Higano [5] (1996)	22	26	PSA failure+D2	<0.1	>10
Grossfeld [6] (1998)	47	24	T1c–T4	0.1 - 4	>10
Goldenberg [7] (1999)	87	65	A2–D2	4	10–20
Prapotnich [8] (1999)	566	81	Advanced	<4	>10
Bouchot [9] (2000)	44	44	D2	<4	>20
Strum [10] (2000)	52	66	T1c–D2	0	>5
Sciarra [11] (2000)	51	48	T2–T3 (rising PSA)	<4	
Pether [12] (2003)	102	50	A2–D2	<4	10–20
De La taille [13] (2003)	146	46	T1–T4, M1	<4	>10
Lane [14] (2004)	75	134	All	<4	>20
Malone [15] (2005)	95	69	All	<4	>10
Cury [16] (2006)	39	56	T1 - 3	<4	>10
Bruchovsky [17] (2006)	103	50	T1b–T3 (rising PSA)	<4	>10
Spry [18] (2006)	250	30	All	<4	>20

Modest sample size

Heterogeneous Population

Abrahamsson, 2010

Phase 2 studies
Results

The end points of most phase 2 studies were safety and feasibility of IADT

- IADT was well tolerated
- Potential benefit of IAD in various group of patients
- Patient QoL generally improved during off treatment periods

But

- No data on percentage of responders
- No data on survival
- No data on which patients are most likely to benefit from IADT

Phase 2 studies: Results

- **The majority of studies emphasized the need to monitor <u>testosterone levels</u> of pts using IAD**

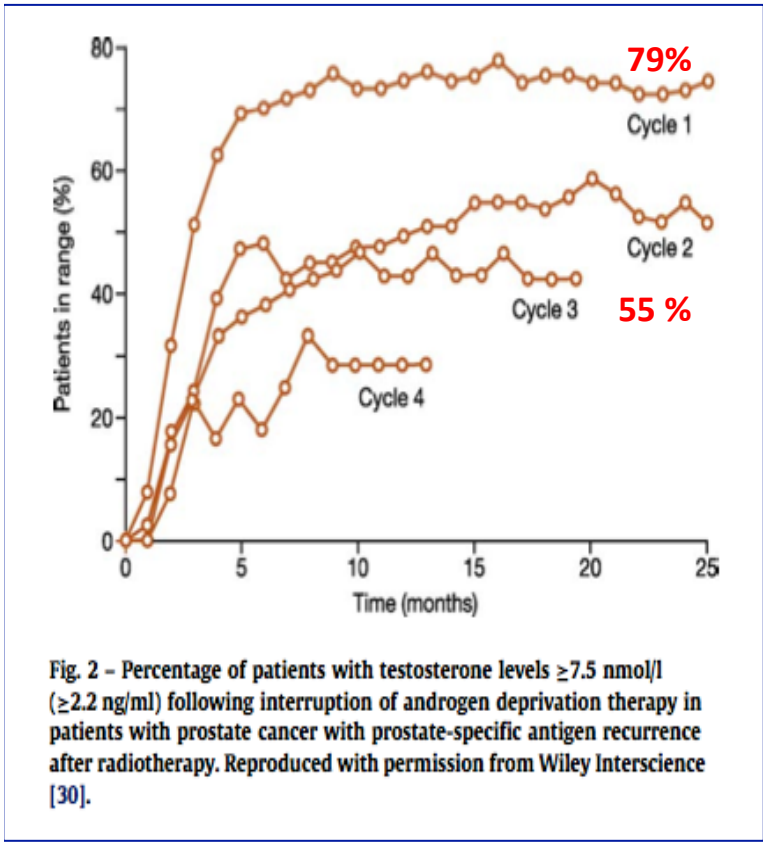


Fig. 2 – Percentage of patients with testosterone levels ≥7.5 nmol/l (≥2.2 ng/ml) following interruption of androgen deprivation therapy in patients with prostate cancer with prostate-specific antigen recurrence after radiotherapy. Reproduced with permission from Wiley Interscience [30].

Tunn et al. 2012

- Higher proportion of patients with serum testosterone normalised following the first cycle compared with subsequent cycles

- **Factors influencing time to delay in testosterone normalisation include:**
  - advanced age
  - low baseline testosterone levels
  - duration of ADT

- **A close relationship between the recoveries of serum testosterone and PSA:**
  - Patients who quickly recovered serum testosterone had more rapid rise in serum PSA levels and a shorter time off therapy

Meta- Analysis by Shaw et al.

TABLE 1 The contributing studies and IHT protocols

Ref	Origin	N	Stage of disease	Type of treatment	PSA nadir, ng/mL for adequate response	Restart PSA, ng/mL	% off at 2 years
[18]	CA, USA	53	L & A	MAB	<0.05	>5	13
[19]	MI, USA	104	L, R & A	MAB/mono	<4	>10	39
[11]	Ottawa	86	L, R & A	MAB/mono	<4	>10	20
[14]	CA, USA	53	L & R	MAB/mono	<4, NPT <0.1 after RxT/RP	>10 or >50% baseline	36
[12]	Paris, France	160	L, R & A	MAB/mono	<1 NPT <0.05 after RP <4 after RxT	>10 >4 after RP	11
[13]	Vancouver	101	L, R & A	MAB/mono	<2	>10 >4 after RP	17
[17]	Perth, Australia	239	L, R & A	MAB	Variable – all 9 months treatment	>20	31
[15]	London, UK	125	L, R & A	MAB/mono	<4	>20	30
[16]	Paris, France	411	L, R & A	MAB	<4	>20	40
[10]	Europe	114	A	MAB	<20 or <20% initial	>20 or >1.5 × nadir	6 (at 1 year)

L, localized disease treated primarily with IHT; R, recurrent disease with no evidence of metastasis; A, advanced disease N+/M+ mono, monotherapy with LHRH/antiandrogen. RxT, radiotherapy.

Shaw et al 2007

Meta- Analysis by Shaw et al.

- 1446 patients
- 10 phase II trials

- The 5-year overall survival was estimated to be
  - 90 % in patients with localized disease
  - 86 % in patients with biochemical recurrence
  - 68 % in metastatic disease

Shaw et al 2007

Meta- Analysis by Shaw et al.

- The analysis identified as important predictors of outcome:
  - **PSA at initiation of IADT**
  - **Nadir PSA after the first treatment period**
  - **Duration of the first off-treatment period**

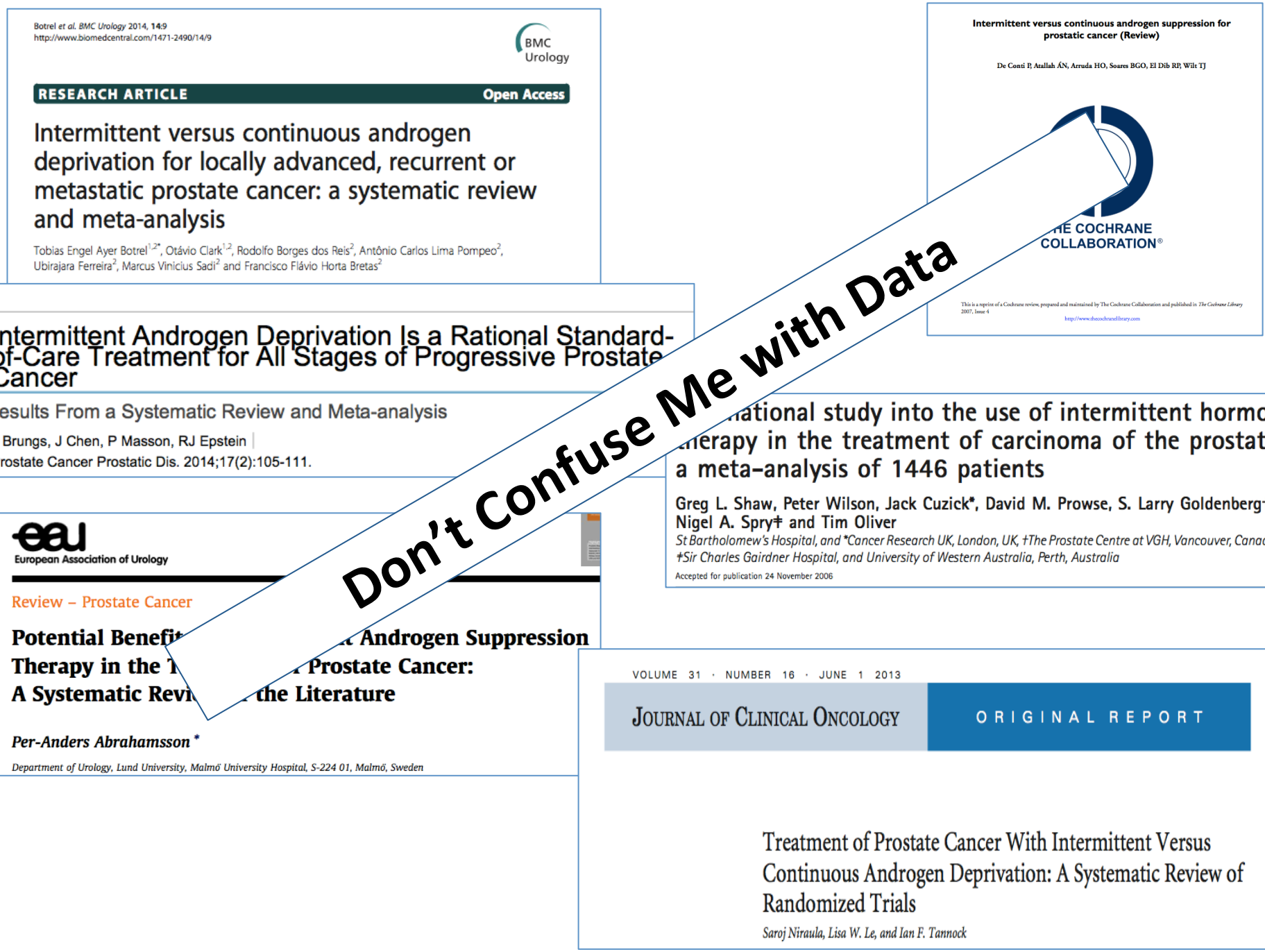
- Patients treated with IADT spent a mean of 39 % of time off treatment

Shaw et al 2007

Open Questions from the Phase II Studies

- **Phase 3 trials aimed to answer questions about**:
  - Survival
  - Percentage of responders
  - Which patients are most likely to benefit from IADT

8 Randomized Phase III studies


Botrel et al. BMC Urology 2014, 14:9
http://www.biomedcentral.com/1471-2490/14/9
BMC Urology
RESEARCH ARTICLE
Open Access
Intermittent versus continuous androgen deprivation for locally advanced, recurrent or metastatic prostate cancer: a systematic review and meta-analysis
Tobias Engel Ayer Botrel[1,2*], Otávio Clark[1,2], Rodolfo Borges dos Reis[2], Antônio Carlos Lima Pompeo[2], Ubirajara Ferreira[2], Marcus Vinicius Sadi[2] and Francisco Flávio Horta Bretas[2]
Intermittent versus continuous androgen suppression for prostatic cancer (Review)
De Conti P, Atallah ÁN, Arruda HO, Soares BGO, El Dib RP, Wilt TJ
THE COCHRANE COLLABORATION®
This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in The Cochrane Library 2007, Issue 4
http://www.thecochranelibrary.com
Intermittent Androgen Deprivation Is a Rational Standard-of-Care Treatment for All Stages of Progressive Prostate Cancer
Results From a Systematic Review and Meta-analysis
D Brungs, J Chen, P Masson, RJ Epstein
Prostate Cancer Prostatic Dis. 2014;17(2):105-111.
national study into the use of intermittent hormone therapy in the treatment of carcinoma of the prostate: a meta-analysis of 1446 patients
Greg L. Shaw, Peter Wilson, Jack Cuzick*, David M. Prowse, S. Larry Goldenberg†, Nigel A. Spry‡ and Tim Oliver
St Bartholomew's Hospital, and *Cancer Research UK, London, UK, †The Prostate Centre at VGH, Vancouver, Canada, and ‡Sir Charles Gairdner Hospital, and University of Western Australia, Perth, Australia
Accepted for publication 24 November 2006
Don't Confuse Me with Data
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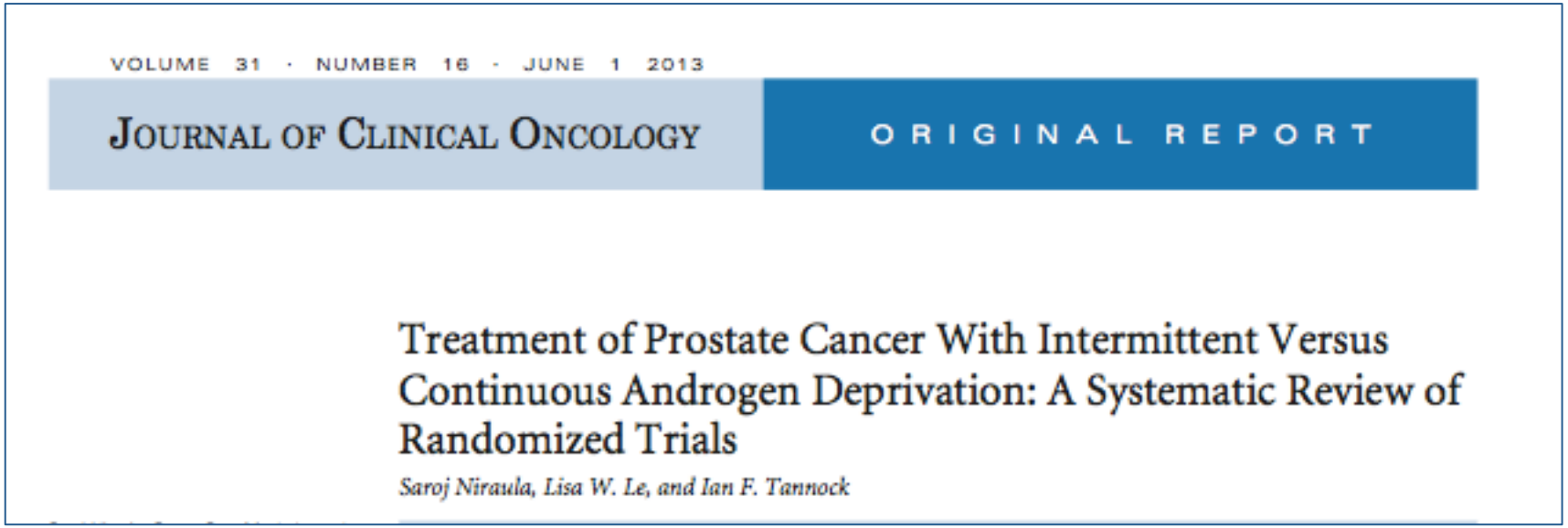
European Association of Urology
Review – Prostate Cancer
Potential Benefit Androgen Suppression Therapy in the T Prostate Cancer: A Systematic Revi the Literature
Per-Anders Abrahamsson *
Department of Urology, Lund University, Malmö University Hospital, S-224 01, Malmö, Sweden
VOLUME 31 · NUMBER 16 · JUNE 1 2013
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT
Treatment of Prostate Cancer With Intermittent Versus Continuous Androgen Deprivation: A Systematic Review of Randomized Trials
Saroj Niraula, Lisa W. Le, and Ian F. Tannock

Systematic Review of Randomized Trials



VOLUME 31 · NUMBER 16 · JUNE 1 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Treatment of Prostate Cancer With Intermittent Versus Continuous Androgen Deprivation: A Systematic Review of Randomized Trials

Saroj Niraula, Lisa W. Le, and Ian F. Tannock

Intermittent vs. continuous ADT in PC
Systematic Review of Randomised Trials

- **Nine studies with 5,508 patients, published 2002 – 2012**
- **Eligibility for randomisation to CAD vs. IAD required postinduction PSA ≤4 ng/ml (in 7 out of 9 of the included studies)**
  - No information about patients who were registered but did not achieve sufficient reduction in PSA for random assignment
- **Primary endpoint**
  - OS in 3 studies
  - TTP (biochemical/radiologic) in 6 studies
- **Secondary endpoint**
  - OS in 4 studies
  - TTP in 3 studies
- **Other secondary endpoints**
  - QoL parameters in 7 out of 9 studies
- The systematic review estimated costs of treatment

Niraula S *et al.* J Clin Oncol 2013;31(16):2029-2036

The studies included patients wih different stages of disese

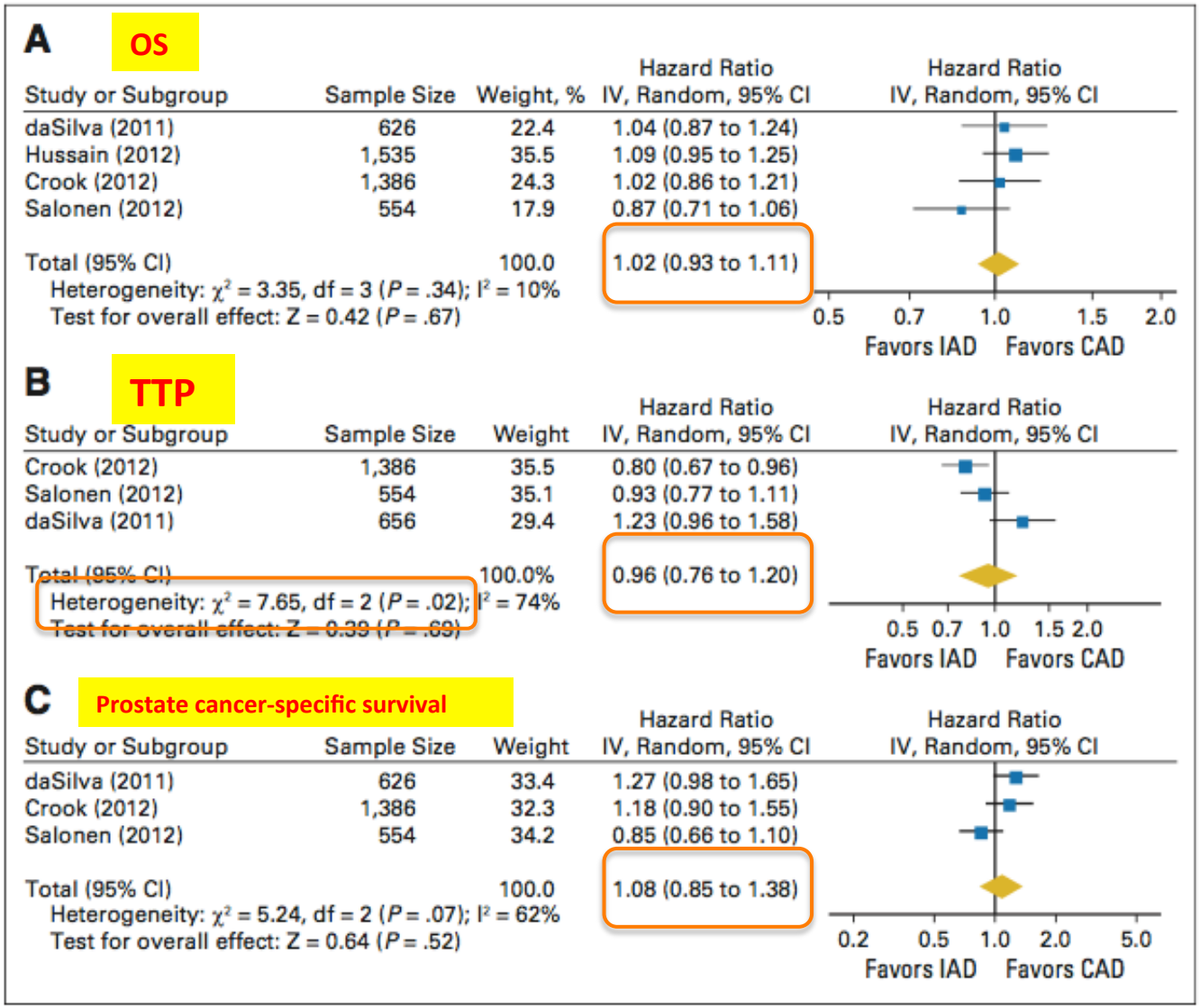
Table 1. Important Features of Included Studies

Study	Sample Size (No.)	End Points	Median Follow-Up (months)	Study Population	Drugs Used for ADT	Strategy to Stop ADT	Strategy to Start ADT	Predefined QoL Measures
de Leval et al[28] (2002)	68	Primary: TTP	31 (mean)	Locally advanced, metastatic, or relapsing PSA after radical prostatectomy for localized CaP	Goserelin + flutamide	PSA ≤ 4 ng/mL on 2 successive measurements 2-3 months apart	PSA ≥ 10 ng/mL	Not mentioned
Schasfoort et al[25] (2003)	193	Primary: TTP; secondary: OS, QoL	25	Locally advanced or metastatic CaP	Buserelin + nilutamide	PSA < 4 ng/mL	PSA ≥ 20 ng/mL (for metastatic); PSA ≥ 10 ng/mL (for locally advanced)	Not mentioned
Miller et al[26] (2007)	335	Primary: TTP; secondary: OS, QoL, tolerability	51	Locally advanced or metastatic CaP	Goserelin + bicalutamide	PSA < 4 ng/mL or < 90% of baseline	PSA ≥ 10 ng/mL	EORTC/AUO questionnaire
Calais da Silva et al[24,30] (2011)	626	Primary: TTP; secondary: OS, QoL	57	Locally advanced or metastatic CaP	GnRH agonist (not named) + cyproterone	PSA < 4 ng/mL or < 80% of baseline after 3 months of ADT	PSA ≥ 10 ng/mL or ≥ 20% above nadir	EORTC QLQ-C30 QoL questionnaire and the EORTC Prostate Cancer Module
[illegible]	[illegible]	[illegible]	[illegible]	Localized CaP with relapsing PSA after radical prostatectomy	Leuprolide + cyproterone	PSA < 0.5 ng/mL	PSA ≥ 3 ng/mL	Not mentioned
Crook et al[21] (2012)*	1,386	Primary: OS; secondary: TTP, QoL	83	Localized RT-treated CaP with relapsing PSA	Multiple combinations	PSA < 4 ng/mL and no clinical progression	PSA ≥ 10 ng/mL	EORTC QLQ-C30 QoL questionnaire and trial-specific questionnaires
Mottet et al[22] (2012)	173	Primary: OS; secondary: TTP, QoL	47	Metastatic CaP	Leuprolide + flutamide	PSA < 4 ng/mL	PSA > 10 ng/mL or symptomatic progression	EORTC QLQ-C30 QoL
Salonen et al[27,31] (2012, 2013)	554	Primary: TTP; secondary: OS, treatment failure	65	Locally advanced or metastatic CaP	Goserelin + cyproterone (first 12 days)	PSA < 10.0 ng/mL or decreased at least by 50% (baseline PSA < 20.0 ng/mL)	PSA > 20 ng/mL or > baseline	Validated 30-item questionnaire
Hussain et al[23] (2012)*	1,535	Primary: OS, QoL; secondary: TTP	100	Metastatic hormone-sensitive CaP	Goserelin + bicalutamide	PSA ≤ 4 ng/mL	PSA ≥ 20 ng/mL or > baseline if baseline PSA < 20 ng/mL	SWOG QOL questionnaire: impotence, libido, energy, physical and emotional function

NOTE. TTP and progression-free survival have been used interchangeably.
Abbreviations: ADT, androgen-deprivation therapy; AUO, Association of Urologic Oncology; CaP, prostate cancer; EORTC, European Organisation for Research and Treatment of Cancer; GnRH, gonadotropin-releasing hormone; OS, overall survival; PSA, prostate-specific antigen; QLQ-C30, Quality of Life Questionnaire C30; QoL, quality of life; RT, radiotherapy; SWOG, Southwest Oncology Group; TTP, time to progression.
*Designed to test noninferiority of intermittent androgen deprivation compared with continuous androgen deprivation.

Niraula S *et al.* J Clin Oncol 2013;31(16):2029-2036

Pooled estimate of hazard ratios for (A) overall survival, (B) time to progression, and (C) prostate cancer–specific survival of intermittent androgen deprivation (IAD) compared with continuous androgen deprivation (CAD) in men with prostate cancer



Niraula S *et al.* J Clin Oncol 2013;31(16):2029-2036

Quality of Life
Intermittent vs. continuous ADT in PC
Systematic Review of Randomised Trials

- **Six of the nine studies reported QoL results with validated questionnaires**
- Patients on **IAD** had better scores for
  - **sexual dysfunction**
  - **hot flashes**
  - **impaired physical function**
- Significant superiority of overall QoL for men receiving IAD in only one study
- **Estimated cost of treatment**
  - Substantial cost saving with the use of IAD (half-the-price of CAD)

Niraula S *et al.* J Clin Oncol 2013;31(16):2029-2036

Systematic Review of Randomized Trials
Conclusions

- **The results do not support the preclinical data, suggesting that IAD is superior in delaying progression to hormonal resistance**
- **Support IAD because of similar survival using less therapy resulting in less cost, inconvenience, and potential toxicity**
- **Treatment with IAD requires initial reduction of PSA to a low level**
- **There was minimal representation in studies of patients with severe symptoms or visceral disease**
  - **Premature to recommend IAD for these population**

There is fair evidence to recommend use of IAD instead of CAD for the treatment of **men with relapsing, locally advanced, or metastatic prostate cancer who achieve a good initial response to androgen deprivation (Grade B recommendation)**

Critical analysis

- **Many patients in the trials received ADT for unproven indications (T3-4 N0 with PSA relapse after RT)**
- **Heterogeneous patient populations**
- **Modest Cohort sizes in 3 studies**
  - Underpowered statistics
- **Apparent consensus in most trials on the PSA level designated for ADT discontinuation (<4 ng/ml), less uniform criteria for resuming treatment (>10 ng/ml or >20 ng/ml, depending on the stage and the presence of symptoms)**
- **Different treatment regimens**
- **Inconsistent End Points**
- **Few data on long term side effects**
- **Limited stratification of the results for parameters such as Gleason score, disease extension**

Phase III Studies designed to determine whether IAD could be shown to be noninferior to CAD

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 6, 2012 VOL. 367 NO. 10

Intermittent Androgen Suppression for Rising PSA Level after Radiotherapy

Juanita M. Crook, M.D., Christopher J. O'Callaghan, D.V.M., Ph.D., Graeme Duncan, M.D., David P. Dearnaley, M.D., Celestia S. Higano, M.D., Eric M. Horwitz, M.D., Eliot Frymire, M.A., Shawn Malone, M.D., Joseph Chin, M.D., Abdenour Nabid, M.D., Padraig Warde, M.B., Thomas Corbett, M.D., Steve Angyalfi, M.D., S. Larry Goldenberg, M.D., Mary K. Gospodarowicz, M.D., Fred Saad, M.D., John P. Logue, M.R.C.P., Emma Hall, Ph.D., Paul F. Schellhammer, M.D., Keyue Ding, Ph.D., and Laurence Klotz, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intermittent versus Continuous Androgen Deprivation in Prostate Cancer

Maha Hussain, M.D., Catherine M. Tangen, Dr.P.H., Donna L. Berry, Ph.D., R.N., Celestia S. Higano, M.D., E. David Crawford, M.D., Glenn Liu, M.D., George Wilding, M.D., Stephen Prescott, M.D., Subramanian Kanaga Sundaram, M.D., Eric Jay Small, M.D., Nancy Ann Dawson, M.D., Bryan J. Donnelly, M.D., Peter M. Venner, M.D., Ulka N. Vaishampayan, M.D., Paul F. Schellhammer, M.D., David I. Quinn, M.D., Ph.D., Derek Raghavan, M.D., Ph.D., Benjamin Ely, M.S., Carol M. Moinpour, Ph.D., Nicholas J. Vogelzang, M.D., and Ian M. Thompson, Jr., M.D.

N ENGL J MED 368;14 NEJM.ORG APRIL 4, 2013

IAD vs CAD for PSA Only Relapses: The NCIC Trial

- 1386 patients with biochemical recurrence after previous external beam radiotherapy (EBRT), either de novo (89 %) or following prior radical prostatectomy (11 %)
- Patients with a PSA >3 ng/ml, at least 1 year after completion of EBRT

8 months ADT

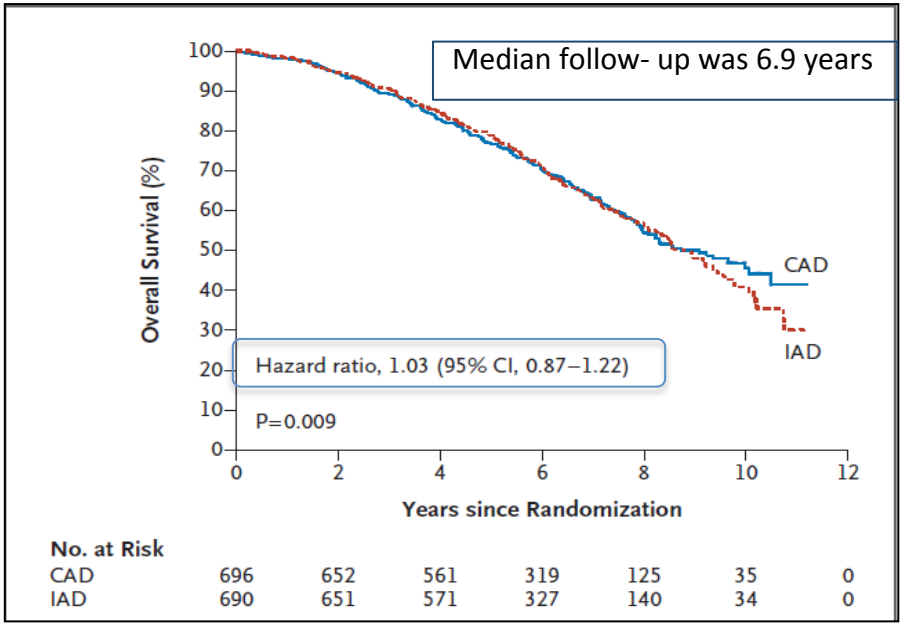
if PSA <4

R

Continuous ADT

Intermittent ADT

Recycled when PSA > 10



- **Primary end point**: Overall Survival
- **Secondary end points:** Quality of Life, Time to Castration-Resistant Disease, and Duration of Nontreatment Intervals

QoL: IAD better for: physical function, fatigue, hot flashes, libido, urinary symptoms

J.M. Crook et al, 2012

Population

- Patients with a PSA >3 ng/ml, in the absence of distant metastases and at least 1 year after completion of EBRT
- Patients in the intermittent arm were eligible for interruption of treatment after 8 months, if the PSA was < 4 ng/ml and in decreasing
- The trigger to reinitiate therapy was a PSA >10 ng/ml or evidence of clinical progression
- If the off-treatment period was ≤ 2 months, ADT was resumed in continuous fashion

- **The primary end point**: Overall Survival
- **Secondary end points:** Quality of Life, Time to Castration-Resistant Disease, and Duration of Nontreatment Intervals

K.M. Crook et al 2012

Table 1. **Baseline Characteristics of the Patients.***

Characteristic	Intermittent Therapy (N=690)	Continuous Therapy (N=696)	Total (N=1386)
Prior radical prostatectomy — no. (%)			
Yes	79 (11.4)	79 (11.4)	158 (11.4)
No	611 (88.6)	616 (88.5)	1227 (88.5)
Missing data	0	1 (0.1)	1 (0.1)
Time since radiotherapy — no. (%)			
1 to 3 yr	146 (21.2)	150 (21.6)	296 (21.4)
>3 yr	542 (78.6)	543 (78.0)	1085 (78.3)
Missing data	2 (0.3)	3 (0.4)	5 (0.4)
Baseline PSA level — no. (%)			
3–15 ng/ml	531 (77.0)	535 (76.9)	1066 (76.9)
>15 ng/ml	159 (23.0)	160 (23.0)	319 (23.0)
Missing data	0	1 (0.1)	1 (0.1)
Prior hormone therapy — no. (%)			
No	419 (60.7)	424 (60.9)	843 (60.8)
Yes	271 (39.3)	271 (38.9)	542 (39.1)
Missing data	0	1 (0.1)	1 (0.1)
Age — yr			
Median	74.2	74.4	74.2
Range	29.4–89.7	45.3–88.9	29.4–89.7
ECOG performance status — no. (%)†			
0	548 (79.4)	568 (81.6)	1116 (80.5)
1	142 (20.6)	127 (18.2)	269 (19.4)
Missing data	0	1 (0.1)	1 (0.1)
Malignant prostate — no. (%)‡			
No	517 (74.9)	503 (72.3)	1020 (73.6)
Yes	135 (19.6)	150 (21.6)	285 (20.6)
Missing data or unknown	38 (5.5)	43 (6.2)	81 (5.8)

K.M. Crook et al 2012

Overall Survival in the Intention-to-Treat Population

A difference in survival of less than 8 % at 7 years, was determined to be the limit for non-inferiority or an upper bound of the confidence interval of the hazard ratio of 1.25

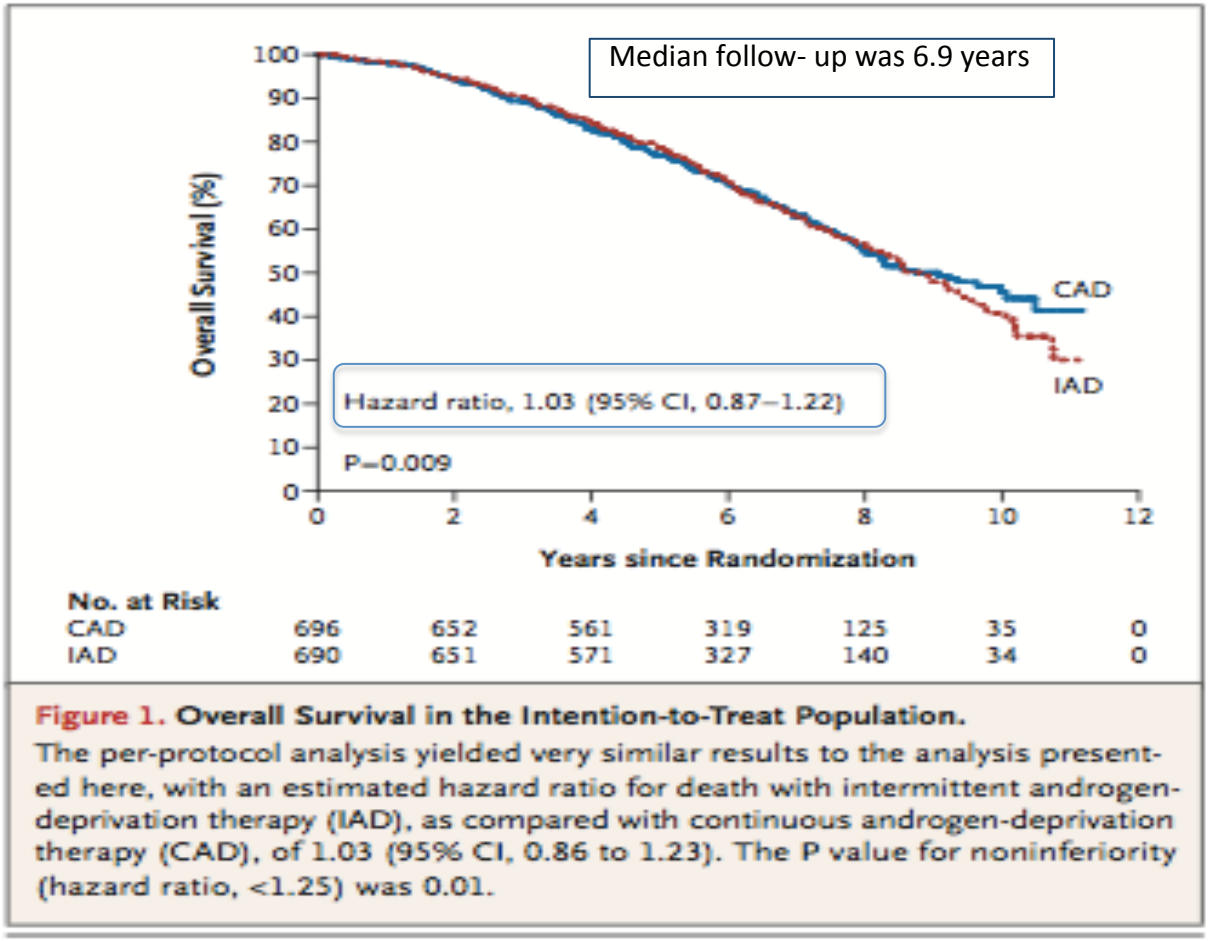
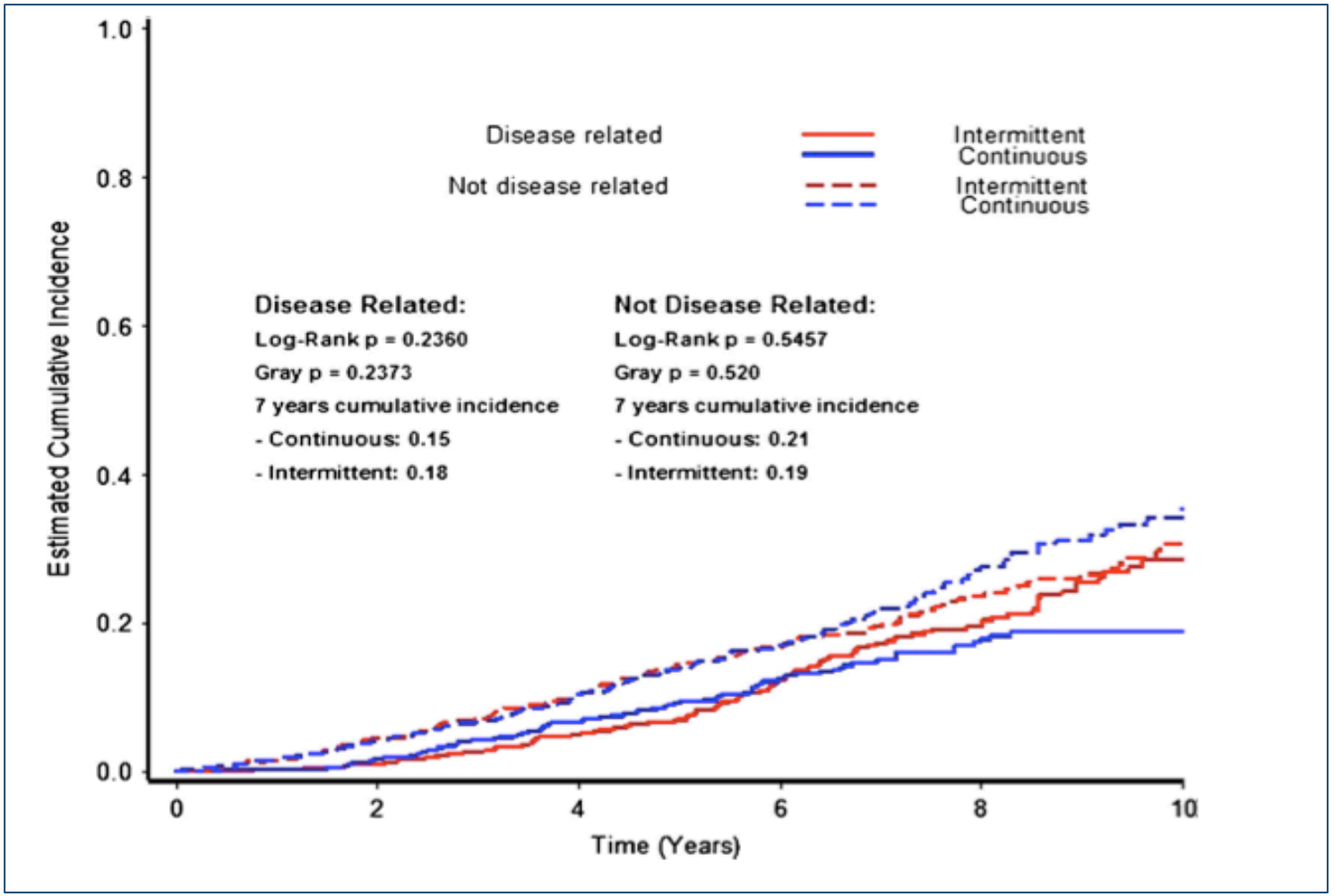


Figure 1. Overall Survival in the Intention-to-Treat Population.
The per-protocol analysis yielded very similar results to the analysis presented here, with an estimated hazard ratio for death with intermittent androgen-deprivation therapy (IAD), as compared with continuous androgen-deprivation therapy (CAD), of 1.03 (95% CI, 0.86 to 1.23). The P value for noninferiority (hazard ratio, <1.25) was 0.01.

Disease Specific Survival

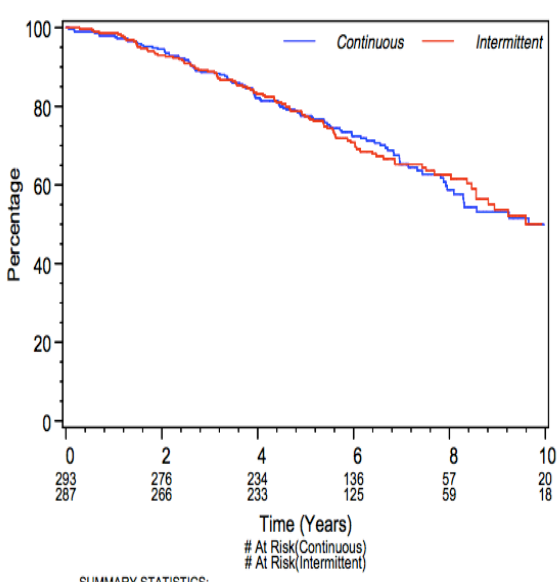


- **More deaths from prostate cancer occurred in the IAD arm compared to CAD (41 and 34 % respectively)**
- **Increase in non-prostate cancer-related deaths in the CAD arm, resulting in similar overall survival**

Overall survival by treatment arm for 3 Gleason score Groups

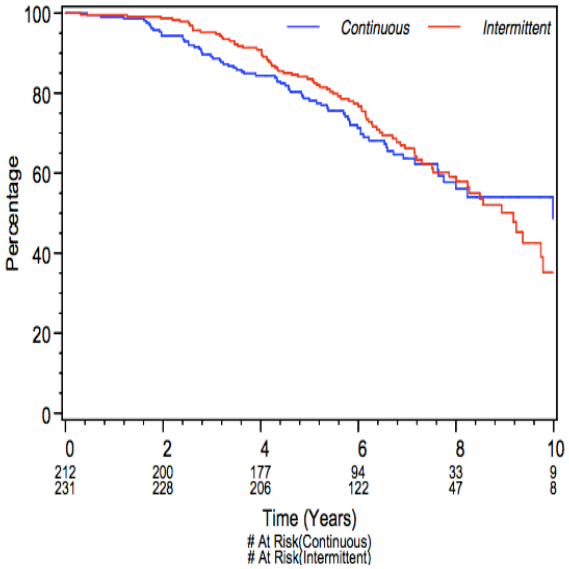
Unplanned Subgroup analysis

Gs 2-6 = 42.6%,



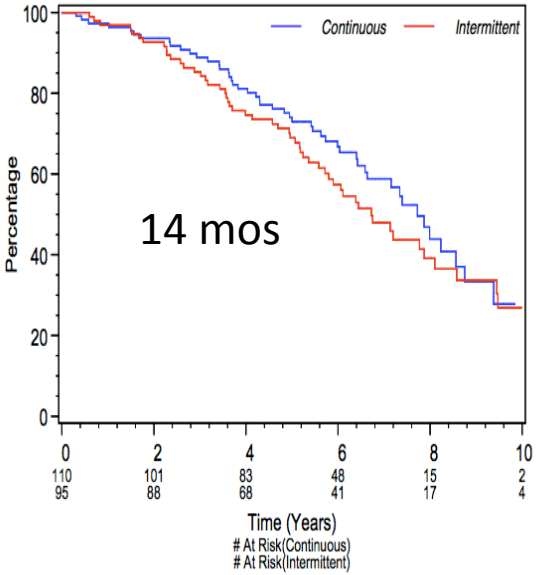
Hazard Ratio of Intermittent/ Continuous: 1.001
95 % C.I. 0.758, 1.321)

Gs 7 = 33.0%



Hazard Ratio of Intermittent/ Continuous: 0.977
95 % C.I. (0.713, 1.339)

Gs 8-10 = 15.2%



Hazard Ratio of Intermittent/ Continuous: 1.2
95 % C.I. (0.827, 1.814)

Quality of life

- QoL was determined at fixed time points using the EORTC quality of life instrument (QLQ-C30)
- **Intermittent therapy was associated with**
  - improved scores for hot flashes
  - desire for sexual activity
  - urinary symptoms
  - trend toward improvement in fatigue

NCIC Clinical Trials Group PR7
Conclusions

This trial is the first to provide level 1 evidence that IAD is not inferior to CAD in terms of overall survival in men with biochemical recurrence after definitive radiation therapy in the absence of metastatic disease

The sample size of the study does not have the power to detect a small or moderate difference, but the approximately 14 month greater median survival for Gleason 8-10 receiving CAD, suggests caution in this group

Intermittent vs. continuous ADT in PC

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ORIGINAL ARTICLE

Intermittent versus Continuous Androgen Deprivation in Prostate Cancer

Maha Hussain, M.D., Catherine M. Tangen, Dr.P.H., Donna L. Berry, Ph.D., R.N., Celestia S. Higano, M.D., E. David Crawford, M.D., Glenn Liu, M.D., George Wilding, M.D., Stephen Prescott, M.D., Subramanian Kanaga Sundaram, M.D., Eric Jay Small, M.D., Nancy Ann Dawson, M.D., Bryan J. Donnelly, M.D., Peter M. Venner, M.D., Ulka N. Vaishampayan, M.D., Paul F. Schellhammer, M.D., David I. Quinn, M.D., Ph.D., Derek Raghavan, M.D., Ph.D., Benjamin Ely, M.S., Carol M. Moinpour, Ph.D., Nicholas J. Vogelzang, M.D., and Ian M. Thompson, Jr., M.D.

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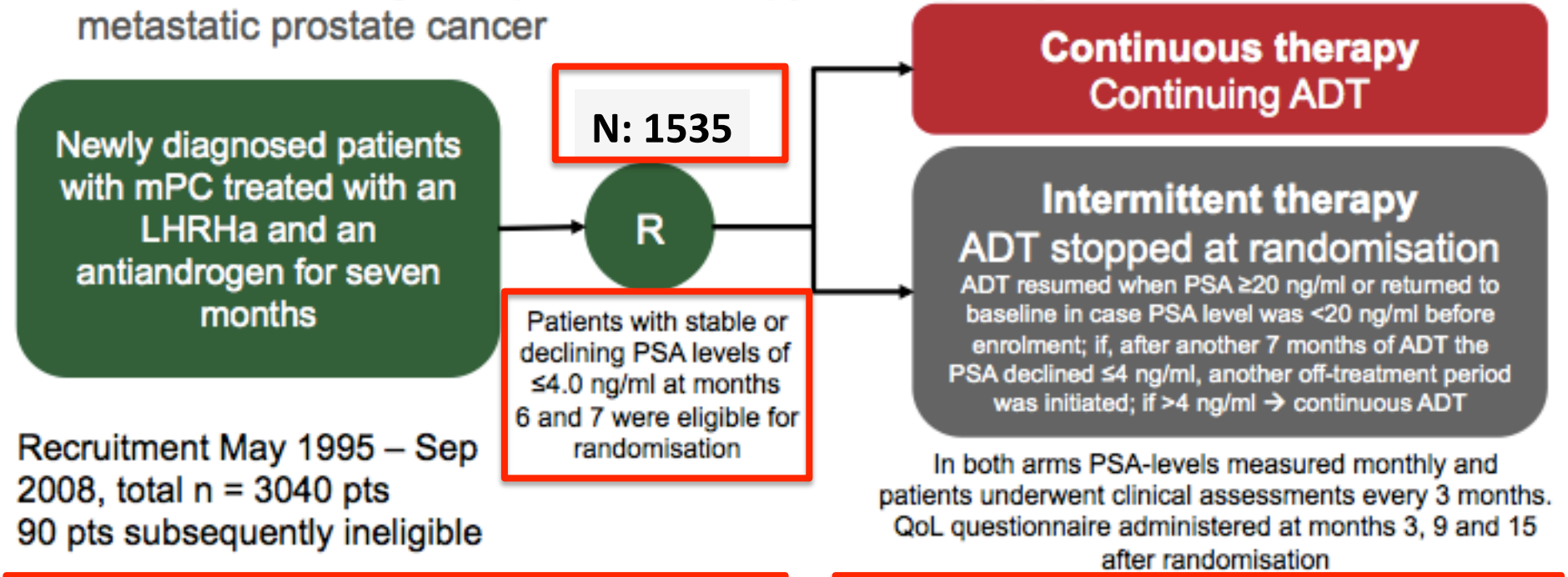
Intermittent vs. continuous ADT in mPC - Study design

- A randomised, prospective, Phase III non-inferiority study of continuous vs. intermittent androgen-deprivation therapy in newly diagnosed, hormone-sensitive metastatic prostate cancer



Recruitment May 1995 – Sep 2008, total n = 3040 pts
90 pts subsequently ineligible

In both arms PSA-levels measured monthly and patients underwent clinical assessments every 3 months. QoL questionnaire administered at months 3, 9 and 15 after randomisation

Stratification before randomisation:
- PS (0 – 1 vs 2)
- Prior hormone therapy (any vs none)
- Extent of the disease (minimal vs extensive

Co-Primary objectives:
- Non-inferiority of intermittent ADT to continuous ADT with respect to survival (one-sided test with HR upper boundary of 1.20
- QoL at 3 months after randomisation

ADT, androgen deprivation therapy; mPC, metastatic prostate cancer; LHRHa, luteinizing hormone-releasing hormone agonist; PS, performance status; PSA, prostate-specific antigen; HR, hazard ratio; QoL, quality of life

Hussain M *et al.* N Engl J Med 2013;368(14):1314-1325

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Intermittent versus Continuous Androgen Deprivation in Prostate Cancer

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Intermittent vs. continuous ADT in mPC - Study design

- **1505** (of 3040 registered to the trial) **developed castration resistance in the first 7 months and were not eligible for randomization**

- Disease extent was categorized as per the accepted SWOG definition:
  - ***extensive*** if present in ribs, long bones, or visceral organs
  - ***limited disease*** for any extent of involvement in the axial skeleton

Intermittent therapy

ADT stopped at randomisation

ADT resumed when PSA ≥20 ng/ml or returned to baseline in case PSA level was <20 ng/ml before enrolment; if, after another 7 months of ADT the PSA declined ≤4 ng/ml, another off-treatment period was initiated; if >4 ng/ml → continuous ADT

In both arms PSA-levels measured monthly and patients underwent clinical assessments every 3 months. QoL questionnaire administered at months 3, 9 and 15 after randomisation

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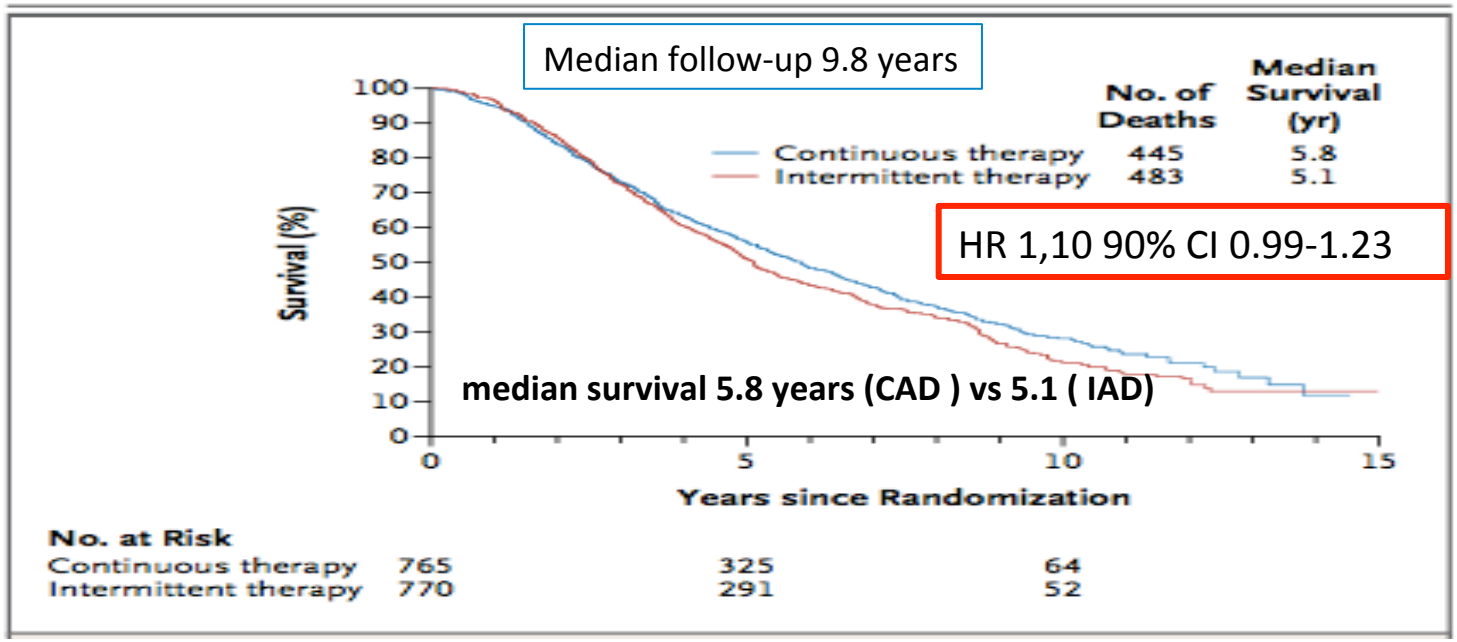
Median Survival from Randomization in the Two Treatment Groups



- **A 10 % relative increase in the risk of death in the IAD arm** (HR, adjusted for stratification factors was 1.10; 90 % CI, 0.99 to 1.23)
- **A 20 % increased risk of death in the intermittent arm could not be ruled out since the upper limit of 90% CI = 1.23**

- **Not possible to conclude that intermittent ADT noninferior to continuous ADT with respect to survival**
- **Not possible to conclude that intermittent ADT significantly inferior to continuous ADT either (the lower limit of 90% CI is below 1.00)**
- **Findings statistically inconclusive**

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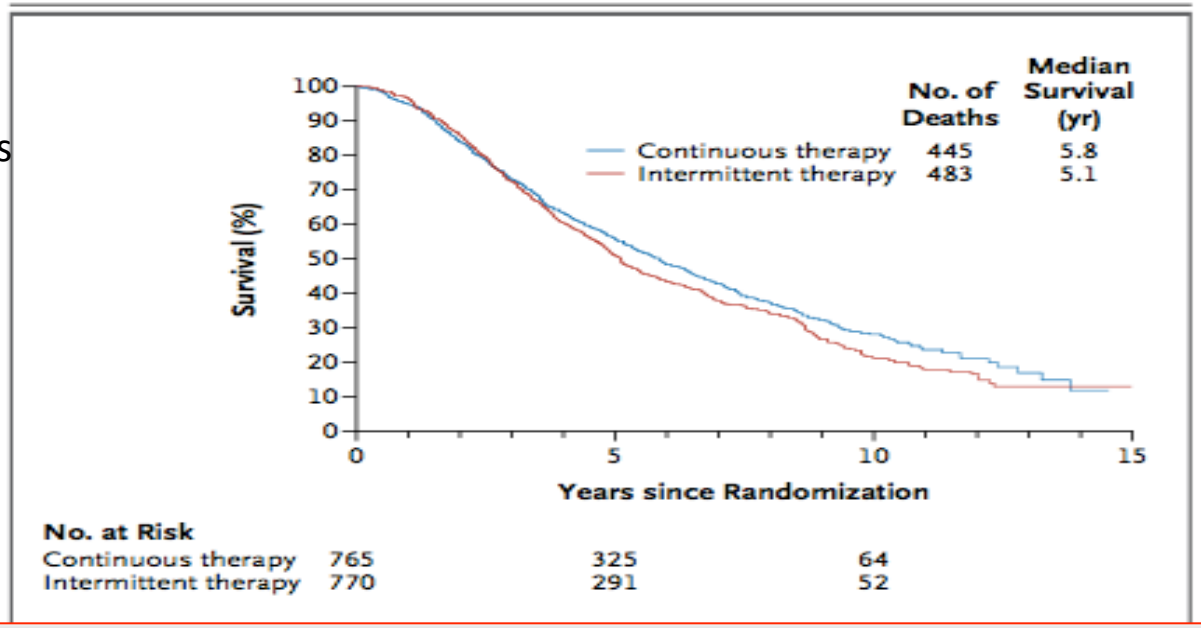
Median Survival from Randomization in the Two Treatment Groups

Median follow-up 9.8 years

Expected Median Survival 35 mos

Median survival **5.8 years (CAD)** vs **5.1 years (IAD)**

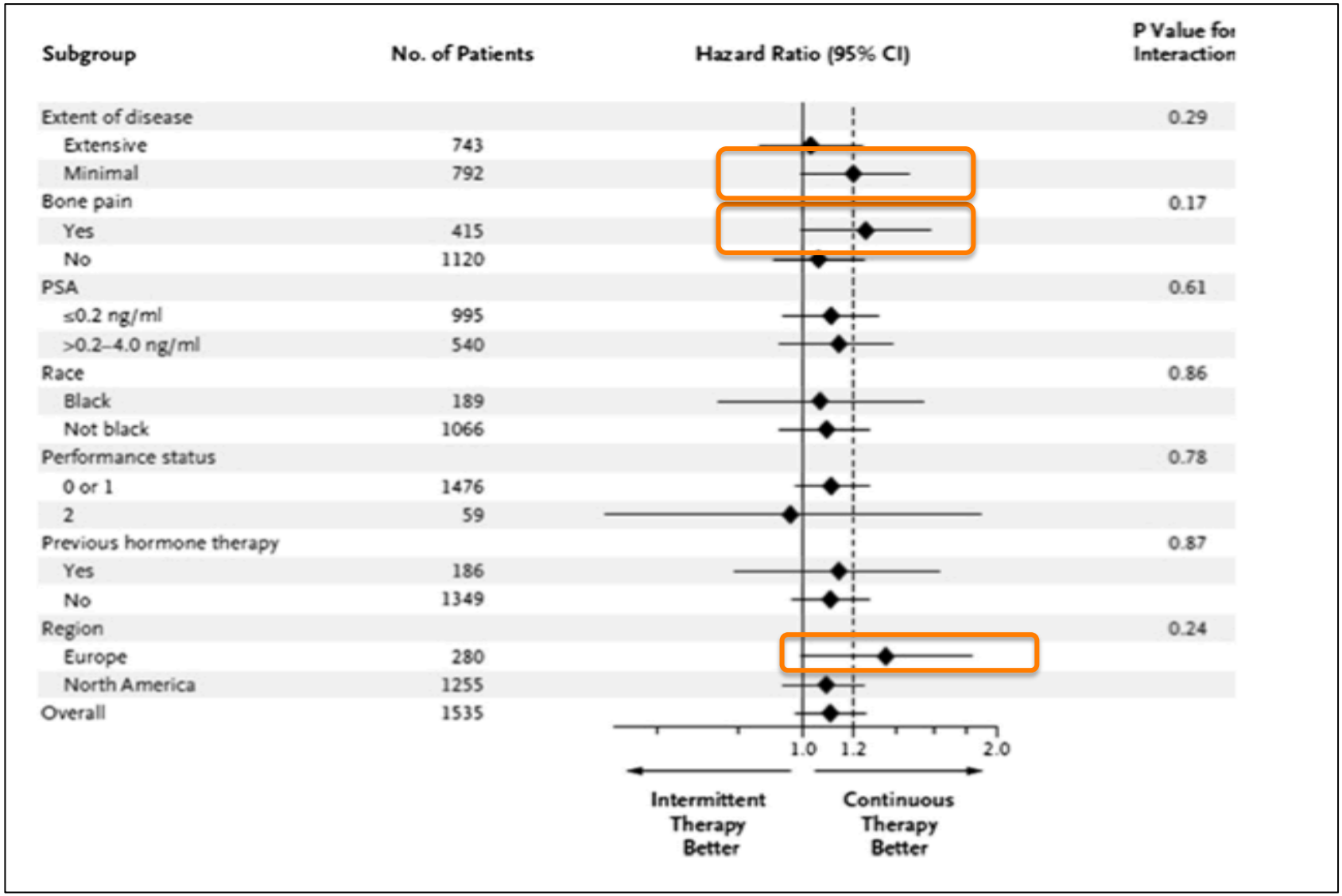
HR 1.10; 90% CI 0.99-1.23



Predetermined acceptable decrease in overall survival for non-inferiority = 20 % (7 mos) with an upper limit of the hazard ratio of 1.2

- **A 20 % increased risk of death in the intermittent arm could not be ruled out since the upper limit of 90% CI = 1.23**
- **Not possible to conclude that IADT is noninferior to CADT with respect to survival**
- **Not possible to conclude that IADT is significantly inferior to CADT (the lower limit of 90% CI is below 1.00)**
- **Findings statistically inconclusive**

IAD vs CAD in mPCa



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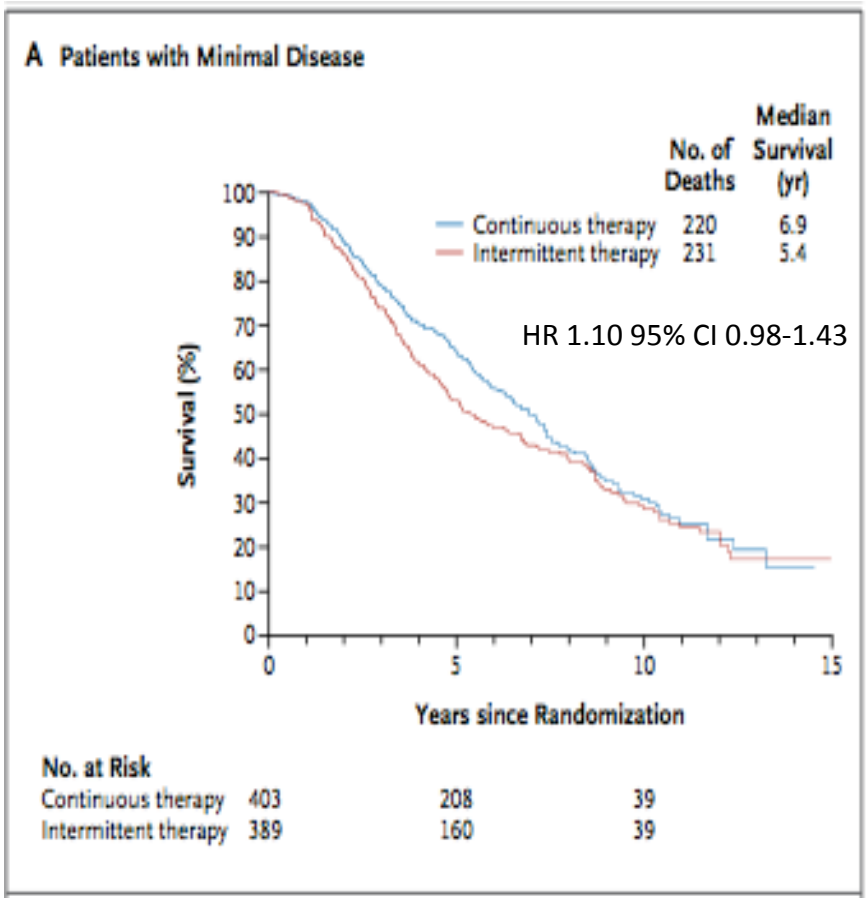
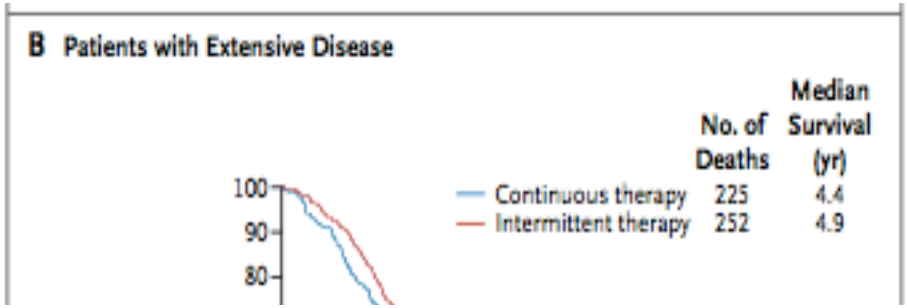
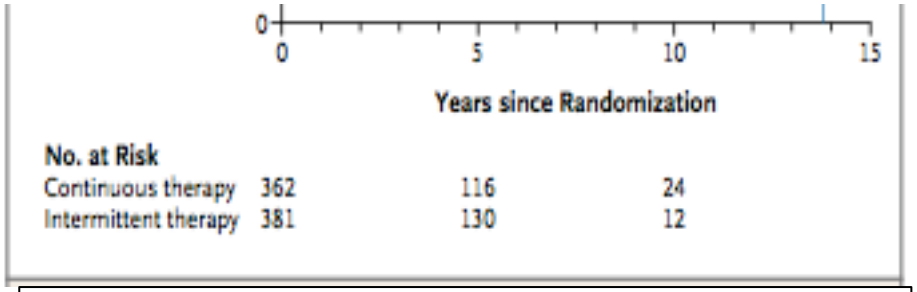
Median Survival from Randomization in the Two Study Groups, according to the *Extend of Disease*





This subgroup analysis should be interpreted with caution because the definition of "extensive disease" was nonstandard and included presence of nonaxial skeletal metastasis



Patients with minimal disease:
Median OS 6.9 years (CADT) vs 5.4 yrs (IADT),
HR 1.19, 95% CI 0.98-1.43

Patients with extensive disease:
Median OS 4.4 yrs (CADT) vs 4.9 yrs (IADT)
HR 1.02, 95% CI 0.85-1.22

IAD vs CAD in mPCa
Conclusions

- **The results concerning non-inferiority of IADT vs CADT with respect to survival among patients with hormone sensitive mPCa were <u>statistically inconclusive</u>**
  - However, nearly the entire confidence interval favours continuous ADT
  - Intermittent ADT may compromise survival

IAD vs CAD
Quality of Life Results

- **Available from 1162 patients**: 568 in the CAD group and 594 in the IAD group
- No testosterone data was collected
  - **At 3 months:** Intermittent therapy was associated with **better erectile function** ($p<0.001$) and **mental health** ($p=0.003$) well before testosterone recovery is expected
  - Scores for **libido** also favoured intermittent therapy ($p=0.04$) (at non-significant level)
  - **At 9 months: 4 out of 5 QoL scores** still favoured intermittent therapy (at non-significant level)
  - **At 15 months** only **physical functioning** scored higher in the intermittent arm (at non-significant level)
    - **At 15 months,** 78% of the men in the intermittent group had resumed hormone therapy

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Comments on PR7 and SWOG Studies

- PR7 study and SWOG 9346 were both noninferiority trials, and the delta for inferiority was established prior to accrual
- Both trials show a 7 % increase in deaths from prostate cancer in the intermittent arms
- Both trials under estimated the median survival for their study populations, 7 years in PR7 (actual >9 years) and 35 months for SWOG 9346 (actual >5 years)
- Subset analysis in both trials helps to elucidate survival differences
  - The prognostic value of the Gleason Score and its importance in choosing between IADT or CADT has been suggested by an unplanned subgroup analysis of PR7
  - In the metastatic setting, an intermittent approach may be reasonable to offer men with asymptomatic metastatic disease with Gleason score 7 or less

Conclusion

- Data from studies suggest that IADT can produce oncologic results similar to those of CADT :
  - **In patients with biochemical recurrence** (after definitive external beam RT, either de novo or following RP)
  - **In men with asymptomatic metastatic disease**

- The best population for IAD has still to be fully characterized

- Advantages include improved QoL and significant cost savings
  - Data are still insufficient to determine whether IAD is able to prevent long-term complications related to ADT

- **A high Gleason score (>7)** may be associated with a decrease in overall survival with IAD, which must be discussed as a potential trade off for improved quality of life

… In Clinical Practice

- Induction course of treatment for 6-9 mo
  - *This induction period is empiric*
- Pts who achieve a > 95% PSA response by may discontinue therapy
- The ADT can be stopped only:
  - If patient is well-informed and compliant;
  - Without clinical progression;
  - In presence or clear PSA response
- Pts who fail to reduce PSA to <0.2–0.4 ng/ml should be maintained on treatment
- Pts who have a short off-treatment interval (<6 mo before rise in PSA to >5 ng/ml) should return to continuous therapy

… In Clinical Practice

- Selected high-risk pts with excellent PSA response may be considered for IADT
- Pts should have PSA and testosterone assayed every 3 mo during the off-treatment interval
- Treatment should be resumed when PSA reaches 10–20 ng/ml
- Pts with bulky tumors, a massive burden of nodal and bone metastases, hepatic metastases, PSA >100 ng/ml, rapidly rising PSA (>5 ng/ml per month), or persistent pain from bone metastases are not good candidates for IAD