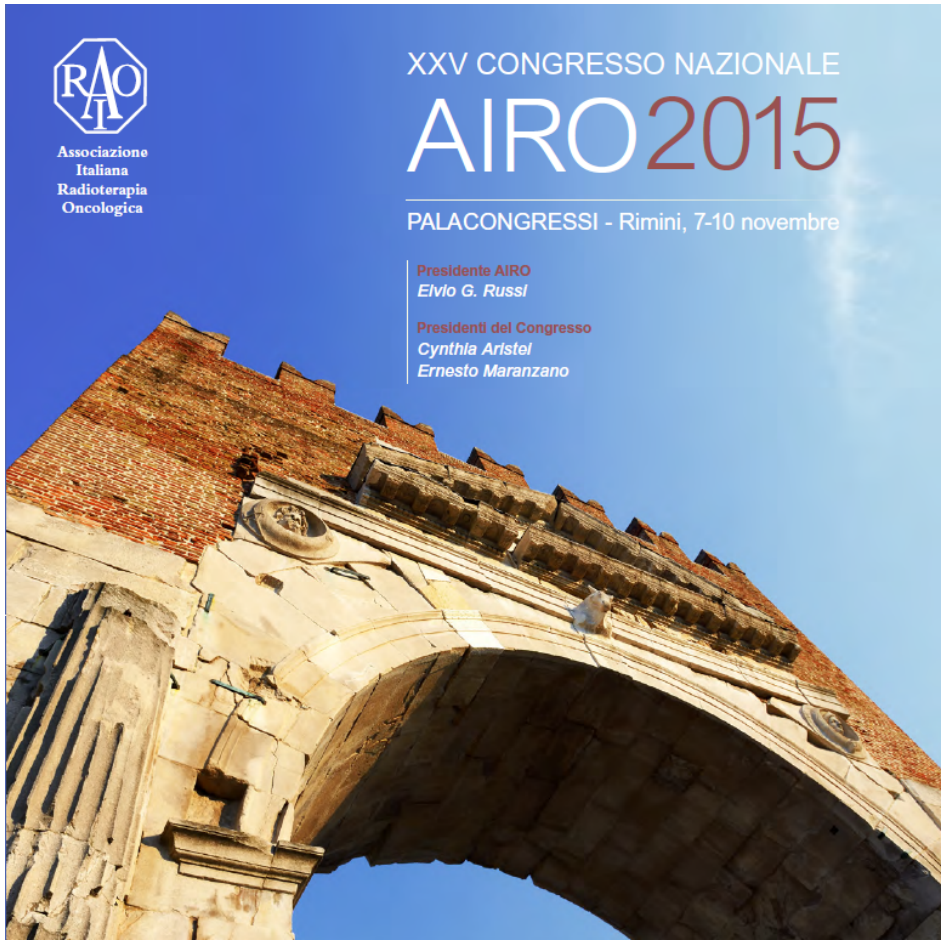

Evidenze e dubbi: quale approccio a quale paziente?

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DICHIARAZIONE

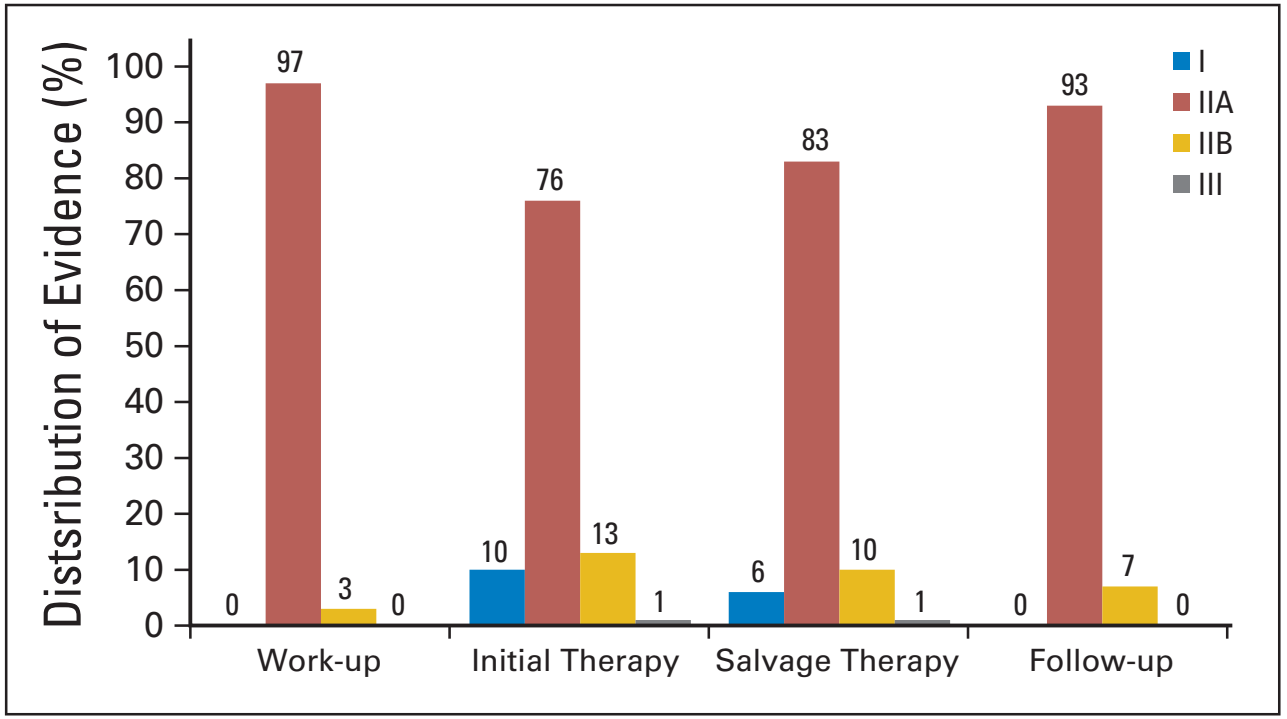
Relatore: Rolando M. D'Angelillo

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(Speaker Honoraria: Sanophi, Novartis)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(Astellas, Janseen)**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**

Terapie di salvataggio nella pratica clinica

Evidenze → poche e di bassa qualità



Poonacha TK, Go RS, J Clin Oncol 10;29:186-91, 2011

Terapie di salvataggio nella pratica clinica

Evidenze → poche e di bassa qualità

Dubbi → Tanti, perchè ogni paziente sembra un caso a sè

Navighiamo a vista?

Terapie di salvataggio nella pratica clinica

Recidive biochimiche → Storia naturale:

- Dopo Prostatectomia Radicale
- Dopo RT radicale
- Dopo PR + RTa
- Nella malattia metastatica
- Nella malattia resistente alla castrazione

Curiamo il PSA o il paziente?

Terapie di salvataggio nella pratica clinica

Recidive biochimiche → Storia naturale:

- Dopo Prostatectomia Radicale
- Dopo RT radicale
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- Nella malattia metastatica
- Nella malattia resistente alla castrazione

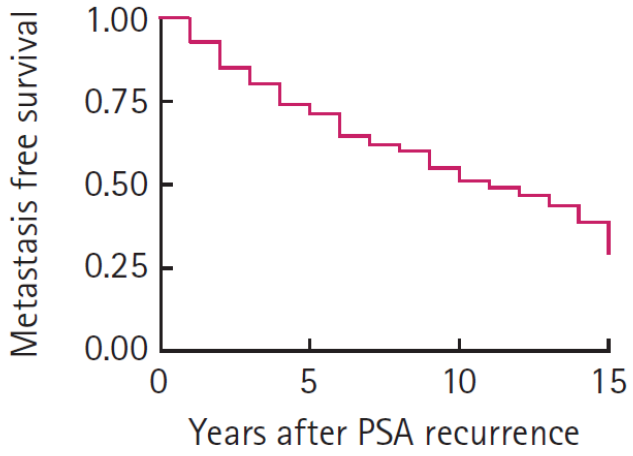
BJUI
BJU INTERNATIONAL

The natural history of metastatic progression in men with prostate-specific antigen recurrence after radical prostatectomy: long-term follow-up

Emmanuel S. Antonarakis, Zhaoyong Feng*, Bruce J. Trock*, Elizabeth B. Humphreys*, Michael A. Carducci, Alan W. Partin*, Patrick C. Walsh* and Mario A. Eisenberger

*Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, and *Brady Urological Institute, Johns Hopkins University, Baltimore, MD, USA*

FIG. 2. Kaplan–Meier estimate of overall MFS following PSA recurrence after radical prostatectomy, for the entire cohort of 450 men.



MFS mediana: ≈10 anni (8-14 aa)
@5aa: 67.3%
@10aa: 48.2%

Antanorakis ES et al, BJUI 109:32-39, 2011

Terapie di salvataggio dopo PR

Fattori prognostici

Studio	N° pz	Gleason	PSA DT	Tempo alla recidiva
Pound CR, 1999	1997	8-10	< 10 mesi	< 2 anni
Ward JF, 2003	3903	8-10	< 12 mesi	
Freedland SJ, 2005	379	8-10	< 9 mesi	≤ 3 anni
Choueiri TK, 2010	3071	8-10	< 6 mesi	
Teeter AE, 2011	345		< 9 mesi	
Boorjian SA, 2011	14632	8-10	< 6 mesi	
Antonarakis ES, 2012	450	8-10	< 3-9 mesi	
Buyyounouski MK, 2012	1722	8-10	< 3 mesi	<18 mesi

Fattore prognostico negativo | No fattore prognostico | Non riportato

Terapie di salvataggio dopo PR

PSA doubling time: come si misura ?

Natural log of 2 (0.693) divided by the slope of the relationship between the log of PSA and time of PSA measurement for each patient

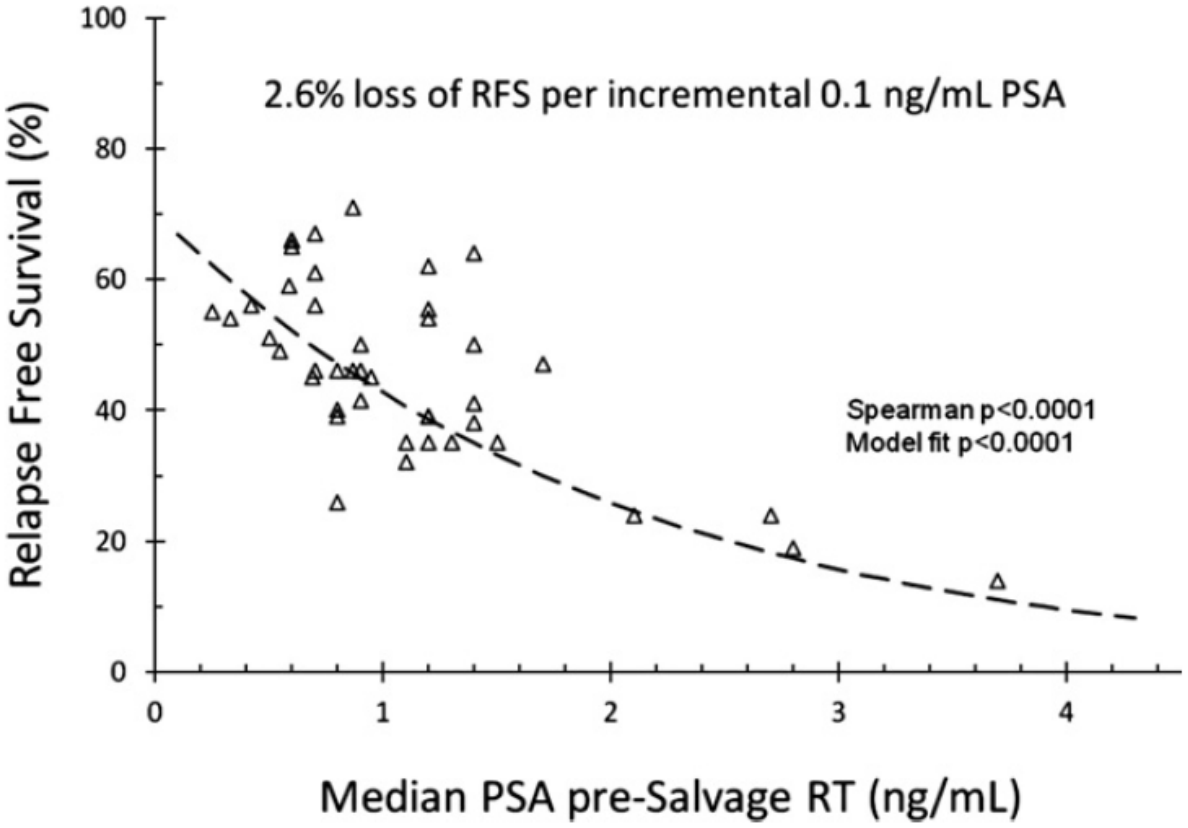
Pound CR et al, JAMA 281:1591-7, 1999

A minimum of two PSA levels collected ≥ 3 months apart are required

Antanorakis ES et al, BJUI 109:32-39, 2011

Terapie di salvataggio dopo PR

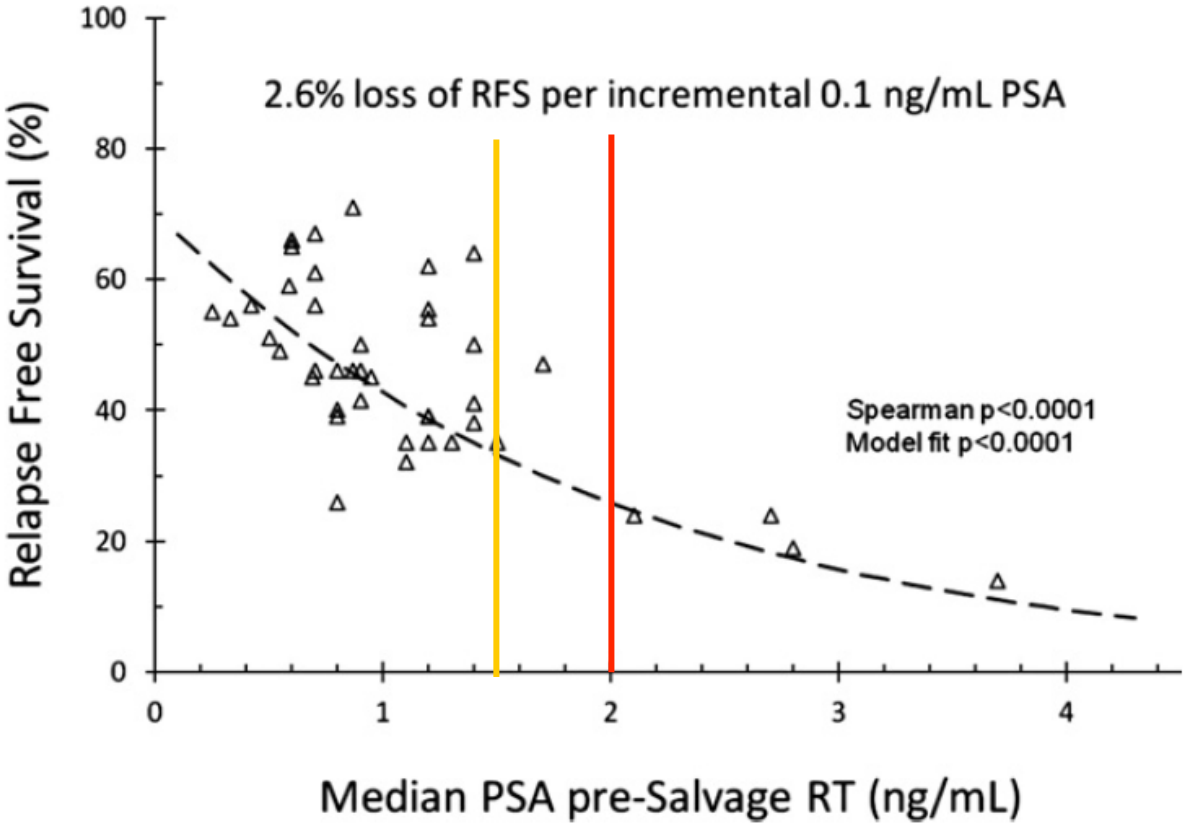
Effetto RT in base al PSA al momento della recidiva



King CR, Semin Radiat Oncol 23:215-221, 2013

Terapie di salvataggio dopo PR

Effetto RT in base al PSA al momento della recidiva



King CR, Semin Radiat Oncol 23:215-221, 2013

Terapie di salvataggio dopo PR

Effetto RT in base al PSA al momento della recidiva:

- impatto PSA al momento della RT di salvataggio è alto

- conviene trattare il paziente piuttosto che stabilire il PSADT

- 1,5-2 ng/ml potrebbe essere un valore soglia massimo accettabile

Terapie di salvataggio nella pratica clinica

Recidive biochimiche → Storia naturale:

- Dopo Prostatectomia Radicale
- Dopo RT radicale
- Dopo PR + RTa
- Nella malattia metastatica
- Nella malattia resistente alla castrazione

Terapie di salvataggio dopo RT radicale

Opzioni terapeutiche:

- Focali: Re-irradiazione, HIFU

- Prostatiche: Re-irradiazione, Chirurgia

- Sistemiche: terapia ormonale

Prostatectomia radicale dopo RT radicale

Studio	N° pz	Multifocale	VS+	Apice	Base
Huang WC, 2007	46	28%	28%	93%	50%
Leibovici D, 2011	50	34%	40%	72%	64%

Huang WC et al, J Urol 177:1324-1329, 2007
Leibovici D et al, J Urol 188, 98-102, 2012

Possiamo fidarci dei trattamenti focali ?
Oppure, meglio la BRT ?
Che impatto ha la RM multiparametrica?

Terapie di salvataggio nella pratica clinica

Recidive biochimiche → Storia naturale:

- Dopo Prostatectomia Radicale
- Dopo RT radicale
- Dopo PR + RTa
- Nella malattia metastatica
- Nella malattia resistente alla castrazione

Natural History of Biochemical Recurrence After Radical Prostatectomy with Adjuvant Radiation Therapy

Stephen A. Boorjian,* Matthew K. Tollefson, R. Houston Thompson, Laureano J. Rangel, Eric J. Bergstralh and R. Jeffrey Karnes

From the Departments of Urology (SAB, MKT, RHT, RJK) and Health Sciences Research (LJR, EJB), Mayo Clinic, Rochester, Minnesota

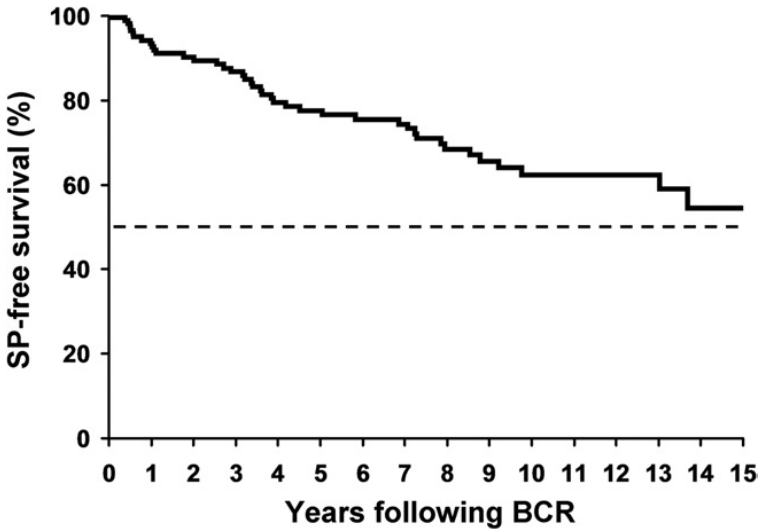


Figure 1. Kaplan-Meier estimated 15-year SP-free survival after BCR.

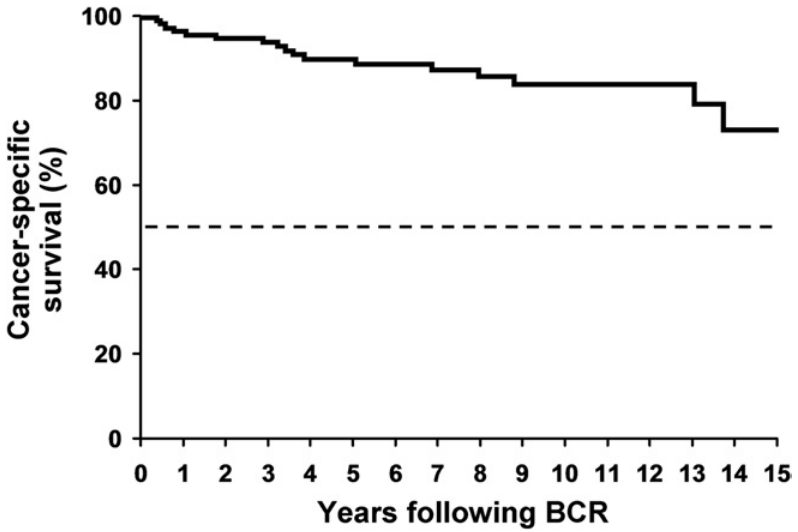


Figure 2. Kaplan-Meier curve estimated 15-year CSS after BCR

134 pz

Boorijan SA et al, J Urol 188, 98-102, 2012

Natural History of Biochemical Recurrence After Radical Prostatectomy with Adjuvant Radiation Therapy

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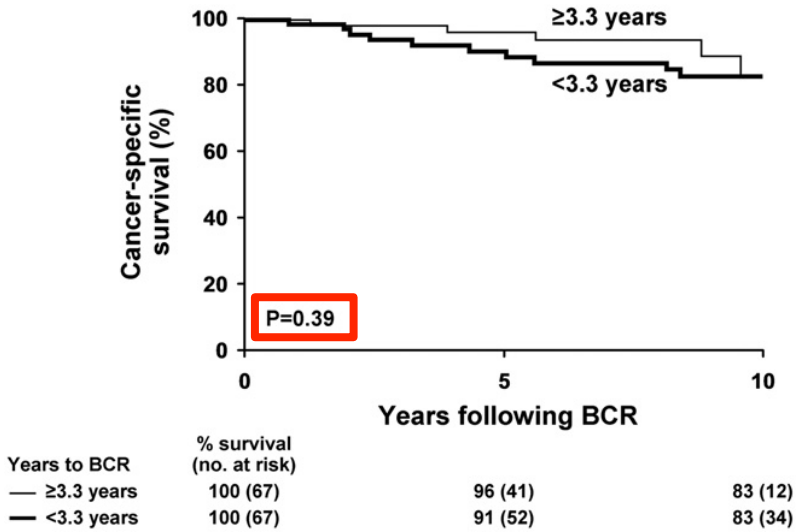


Figure 3. Kaplan-Meier estimated CSS after BCR, stratified by time from RP to BCR.

Table 3. *Multivariate analysis of factors associated with systemic progression following BCR after RP plus ART*

	HR (95% CI)	p Value
Pathological Gleason score	1.78 (1.11–2.87)	0.02
Pathological tumor stage	1.39 (0.98–1.97)	0.07
Pos surgical margin	1.34 (0.38–4.68)	0.65
PSA DT (referent 10 yrs or greater):		
Less than 6 mos	11.39 (3.92–33.1)	<0.0001
6 Mos or greater-less than 1 yr	6.82 (2.17–21.5)	0.001
1 Yr or greater-less than 10 yrs	3.84 (1.26–11.7)	0.02

Terapia ormonale immediata o differita ?

Boorijan SA et al, J Urol 188, 98-102, 2012

Immediate vs. deferred initiation of androgen deprivation therapy in prostate cancer patients with PSA-only relapse. An observational follow-up study

Presenting Author: **Xabier Garcia-Albeniz**[1]

Co-authors: **June M Chan**[3,4,5], **Alan Paciorek**[3,4], **Roger W Logan**[1], **Stacey A Kenfield**[5], **Matthew R Cooperberg**[3,4,5], **Peter R Carroll**[5], **Miguel A Hernán**[1,2].

Departments of [1]Epidemiology and [2]Biostatistics, Harvard School of Public Health. Boston, MA.
Departments of [3]Epidemiology, [4]Biostatistics and [5]Urology, University of California, San Francisco. San Francisco, CA.

ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Methods. Study population.

- **CaPSURE** (Cancer of the Prostate Strategic Urologic Research Endeavour). *University of California, San Francisco.*
  - Longitudinal observational study > 14,300 men with biopsy-proven prostate cancer.
  - Patients are treated and followed in usual practice setting.
  - Started in 1995, 43 study sites have enrolled patients nationwide.

- Baseline and sequential information on variables that determine treatment choices in routine practice.
  - **Baseline variables**: Gleason, % of positive biopsies, T-stage, type of primary treatment (radical prostatectomy vs. radiation), time from primary treatment to relapse, calendar year of relapse, age
  - **Time-varying variables**: PSA, Karnofsky performance status, bone pain, fatigue.

Methods. Study design.

Observational study

PSA-only relapse

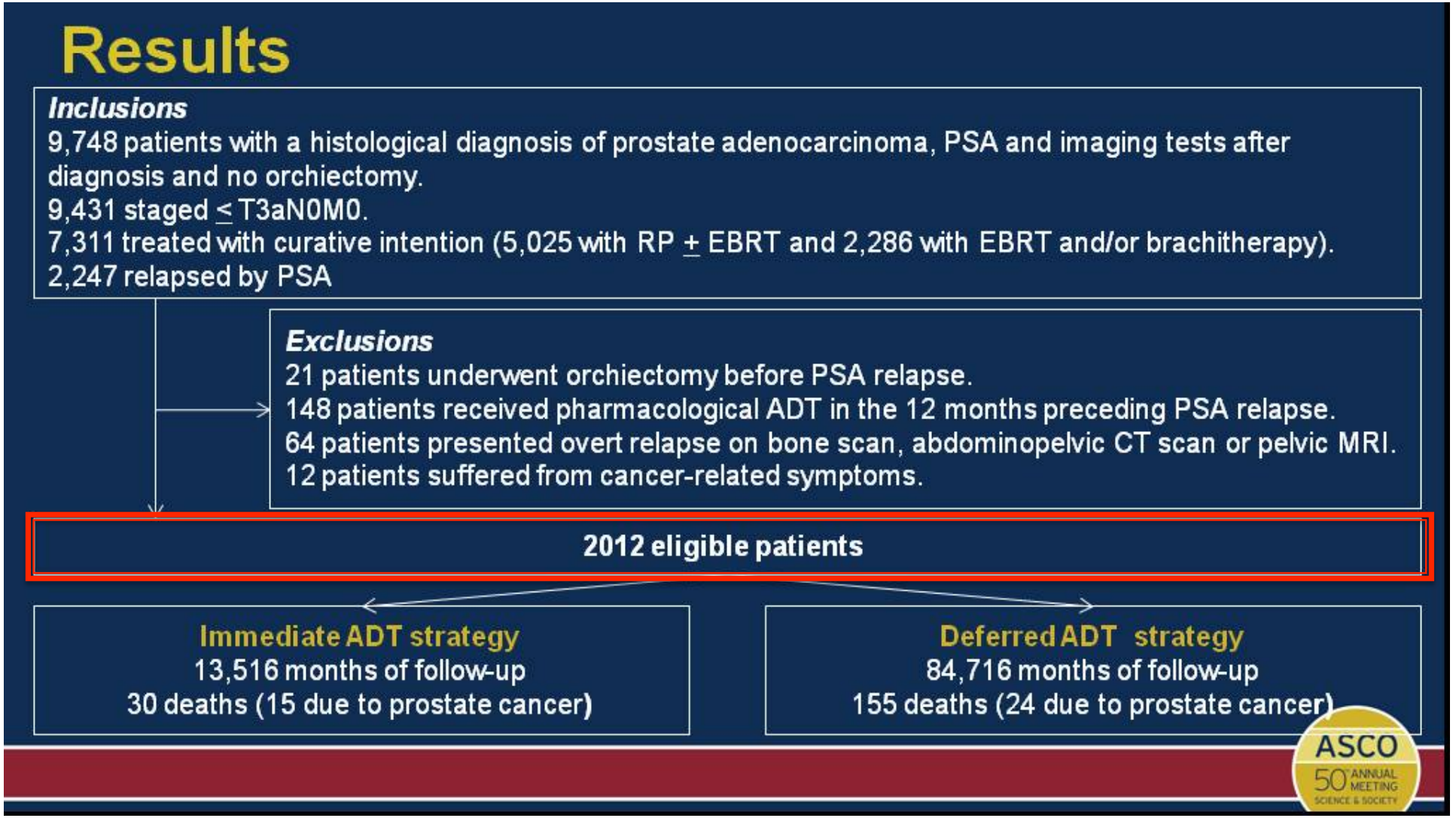
- **Immediate treatment**: ADT at study entry
- **Deferred treatment**: ADT at progression or ≥ 2 years after inclusion

Inclusion

- ≤ cT3a N0 M0 treated with radical intention either with prostatectomy or radiation (EBRT / brachy)
- PSA relapse
  - ≥ 0.2 ng/mL if primary treatment prostatectomy
  - three rising levels one month apart if primary treatment was radiation-based.

Exclusion

- Evidence of metastasis in CT scan, bone scan or pelvic MRI
- Symptoms: bone pain, weight loss, anorexia, abdominopelvic pain
- Orchiectomy
- ADT in the 12 months previous to relapse.


Results
Inclusions
9,748 patients with a histological diagnosis of prostate adenocarcinoma, PSA and imaging tests after diagnosis and no orchiectomy.
9,431 staged ≤ T3aN0M0.
7,311 treated with curative intention (5,025 with RP ± EBRT and 2,286 with EBRT and/or brachitherapy).
2,247 relapsed by PSA
Exclusions
21 patients underwent orchiectomy before PSA relapse.
148 patients received pharmacological ADT in the 12 months preceding PSA relapse.
64 patients presented overt relapse on bone scan, abdominopelvic CT scan or pelvic MRI.
12 patients suffered from cancer-related symptoms.
2012 eligible patients
Immediate ADT strategy
13,516 months of follow-up
30 deaths (15 due to prostate cancer)
Deferred ADT strategy
84,716 months of follow-up
155 deaths (24 due to prostate cancer)
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Results

Baseline characteristics

cT stage (%)	cT1	800 (40)
	cT2	1164 (58)
	cT3	48 (2)
Gleason	2-5	390 (19)
	6	808 (40)
	7-10	688 (34)
Primary treatment	RP +/- EBRT	1376 (68)
	EBRT / brachy	636 (32)
Median age at PSA relapse (IQR)		69 (63-75)
Median time since primary treatment, months (IQR)		27 (13-50)

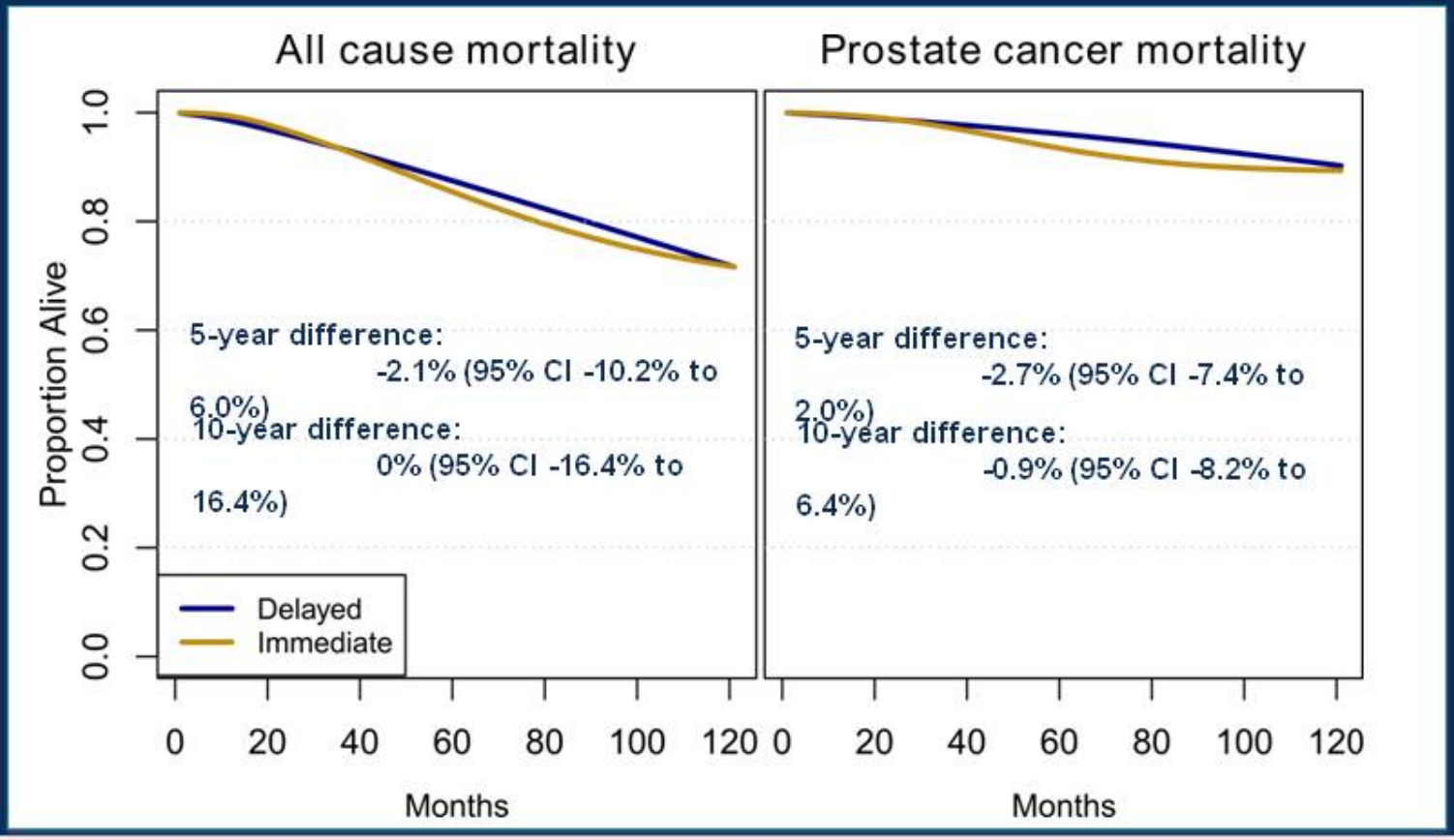
All cause mortality

	Immediate ADT	Deferred ADT
Hazard Ratio	**0.94 (0.51-1.73)**	Reference
5-year survival	85.1 (77.6-92.7)	87.2 (84.5-90.0)
10-year survival	71.6 (56.3-87.0)	71.6 (65.0-78.3)

Prostate cancer-specific mortality

	Immediate ADT	Deferred ADT
Hazard Ratio	**1.15 (0.33-3.97)**	Reference
5-year survival	93.3 (85.3-100)	96.0 (88.7-100)
10-year survival	89.4 (80.6-98.1)	90.2 (82.7-97.7)

Results


All cause mortality
Prostate cancer mortality
Proportion Alive
0.0
0.2
0.4
0.6
0.8
1.0
5-year difference:
-2.1% (95% CI -10.2% to 6.0%)
10-year difference:
0% (95% CI -16.4% to 16.4%)
5-year difference:
-2.7% (95% CI -7.4% to 2.0%)
10-year difference:
-0.9% (95% CI -8.2% to 6.4%)
Delayed
Immediate
0
20
40
60
80
100
120
Months
Months

Conclusions

- Our analysis suggests that patients undergoing immediate ADT initiation at PSA-only relapse had similar survival to those who deferred ADT initiation at progression or two or more years after PSA relapse in the absence of clinical progression
- Limitations: those of an observational study. Imprecise estimates.
- Preliminary answer: an ongoing phase III trial ("*A Collaborative Randomized Phase III Trial: the Timing of Intervention with Androgen Deprivation in Prostate Cancer Patients with Rising PSA*", clinicaltrials.gov ref: NCT00110162) will serve as gold standard.

XGA is a 2012-13 CaPSURE scholar and also a recipient of an "**ASISA Fellowship**" and a **SEOM (Sociedad Española de Oncología Médica)** grant. This work was partly funded by **NIH grant P01-CA134294**. **CaPSURE** is supported in part by an independent, educational grant from Abbott

Terapie di salvataggio nella pratica clinica

Recidive biochimiche → Storia naturale:

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Terapie di salvataggio nella pratica clinica

Recidive biochimiche → Storia naturale:

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- Dopo RT radicale
- Dopo PR + RTa
- Nella malattia metastatica → ADT
- Nella malattia resistente alla castrazione

Terapie di salvataggio nel CaP in progressione metastatica

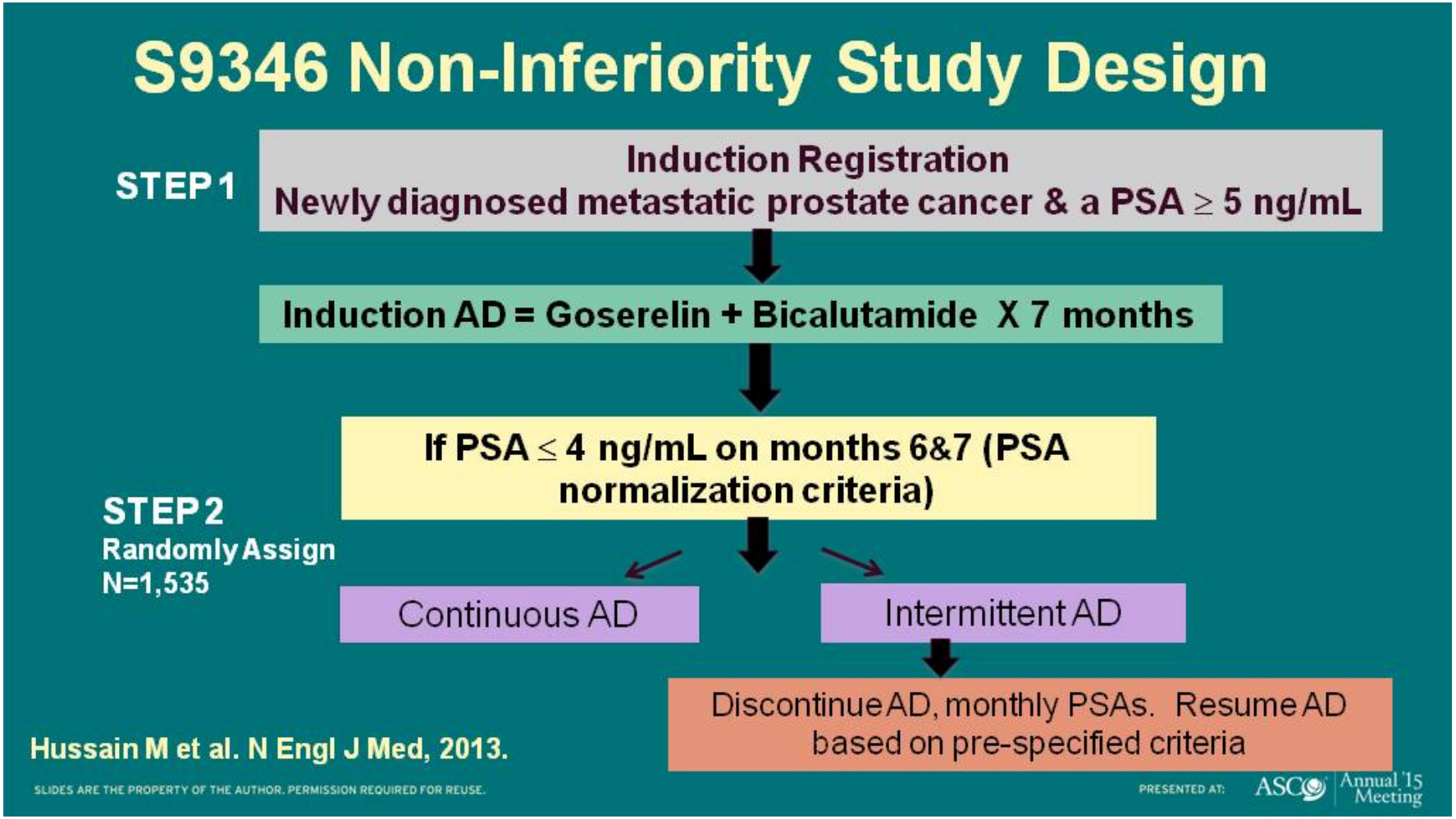
The NEW ENGLAND JOURNAL of MEDICINE

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.

SWOG 9346- INT0162, NEJM 368:1314-1325,2013



SWOG 9346- INT0162, NEJM 368:1314-1325,2013

Terapie di salvataggio nel CaP in progressione metastatica

Disegno dello studio

Sopravvivenza stimata con ADT continuativa: 35 mesi

Riduzione sopravvivenza accettata in intermittente:
7 mesi, HR=1.20

Miglioramento di ADT intermittente:
eventi cardiovascolari e QoL

SWOG 9346- INT0162, NEJM 368:1314-1325,2013

Terapie di salvataggio nel CaP in progressione metastatica

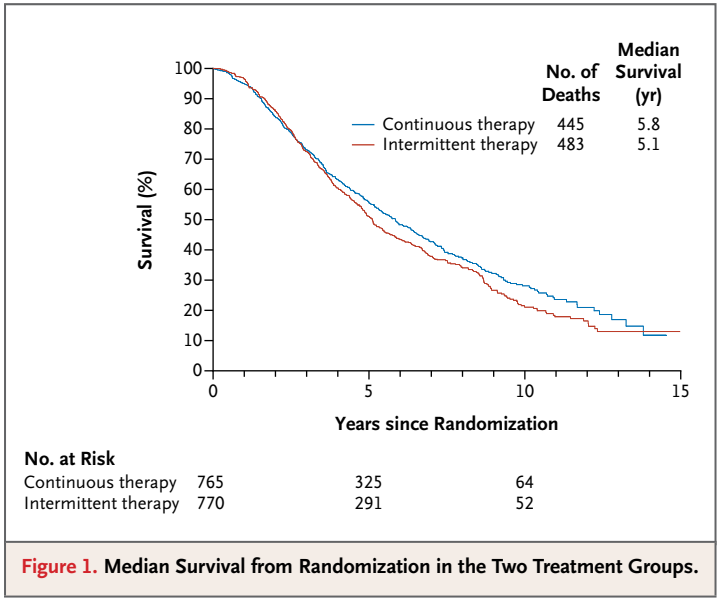
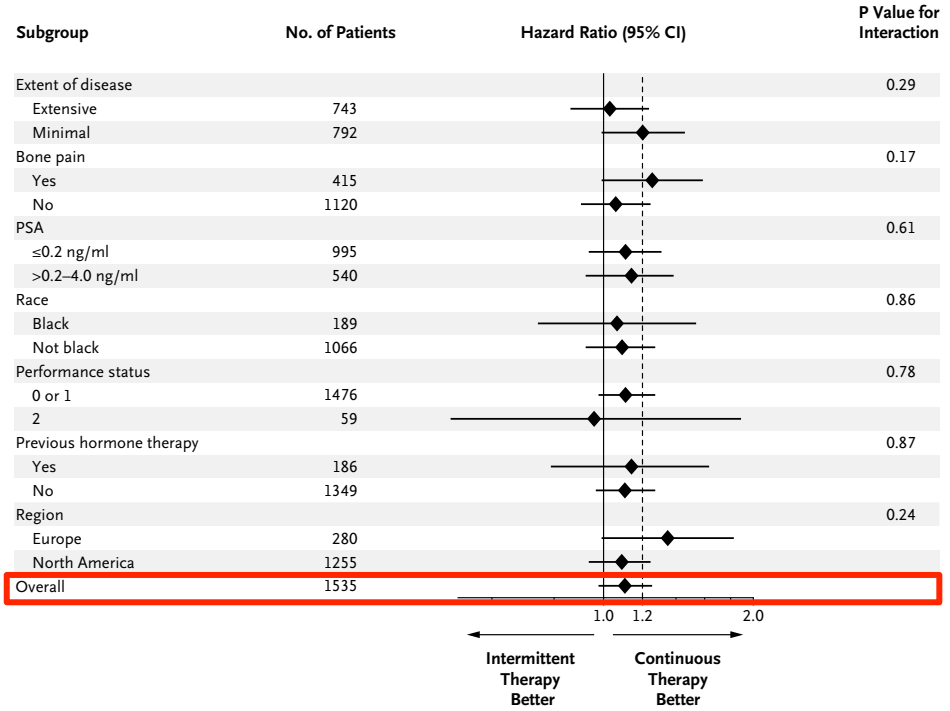


Figure 1. Median Survival from Randomization in the Two Treatment Groups.



SWOG 9346- INT0162, NEJM 368:1314-1325,2013

Terapie di salvataggio nel CaP in progressione metastatica

Table 2. Difference in the Mean Change from Randomization to Follow-up in Primary Quality-of-Life Outcomes, According to Treatment Group.

Outcome	Intermittent Therapy	Continuous Therapy	Difference, Intermittent–Continuous (95% CI)	P Value
Erectile dysfunction*				
Patients with erectile dysfunction at randomization (%)	82	85		
3-mo analysis				
No. of patients included	466	450		
Change from randomization	−7%	2%	−10 percentage points (−14 to −5)	<0.001
9-mo analysis				
No. of patients included	438	393		
Change from randomization	−8%	2%	−10 percentage points (−15 to −5)	<0.001
15-mo analysis				
No. of patients included	385	363		
Change from randomization	−3%	2%	−4 percentage points (−10 to 1)	0.12
High libido†				
Patients with high libido at randomization (%)	29	26		
3-mo analysis				
No. of patients included	68	45		
Change from randomization	16%	−2%	18 percentage points (1 to 36)	0.04
9-mo analysis				
No. of patients included	66	35		
Change from randomization	20%	−11%	31 percentage points (9 to 53)	0.01
15-mo analysis				
No. of patients included	46	31		
Change from randomization	13%	3%	10 percentage points (−16 to 36)	0.46
Vitality‡				
Score at randomization	59.7	59.8		
3-mo analysis				
No. of patients included	465	446		
Change from randomization	−0.11	−1.42	1.32 (−0.83 to 3.46)	0.23
9-mo analysis				
No. of patients included	439	392		
Change from randomization	−0.36	−3.07	2.71 (0.26 to 5.16)	0.03
15-mo analysis				
No. of patients included	386	372		
Change from randomization	−2.02	−3.02	1.00 (−1.59 to 3.59)	0.45

Table 2. (Continued.)

Outcome	Intermittent Therapy	Continuous Therapy	Difference, Intermittent–Continuous (95% CI)	P Value
Mental health‡				
Score at randomization	77.9	80.0		
3-mo analysis				
No. of patients included	479	471		
Change from randomization	1.92	−0.95	2.88 (1.00 to 4.76)	0.003
9-mo analysis				
No. of patients included	458	414		
Change from randomization	0.08	−1.94	2.01 (−0.17 to 4.19)	0.07
15-mo analysis				
No. of patients included	402	386		
Change from randomization	−0.64	−1.10	0.47 (−1.80 to 2.74)	0.69
Physical functioning‡				
Score at randomization	70.7	70.2		
3-mo analysis				
No. of patients included	475	469		
Change from randomization	0.09	−1.74	1.83 (−0.31 to 3.97)	0.09
9-mo analysis				
No. of patients included	456	415		
Change from randomization	−0.66	−3.67	3.01 (0.50 to 5.53)	0.02
15-mo analysis				
No. of patients included	397	385		
Change from randomization	−2.68	−5.72	3.04 (0.13 to 5.96)	0.04

SWOG 9346- INT0162, NEJM 368:1314-1325,2013

Long Term Consequences of Intermittent and Continuous Androgen Deprivation in Men with Metastatic Prostate Cancer on S9346

Dawn L. Hershman; Joseph M. Unger; Jason D. Wright, Scott Ramsey; Cathee Till; Catherine M. Tangen, William Barlow, Charles Blanke, Ian M Thompson, Maha Hussain

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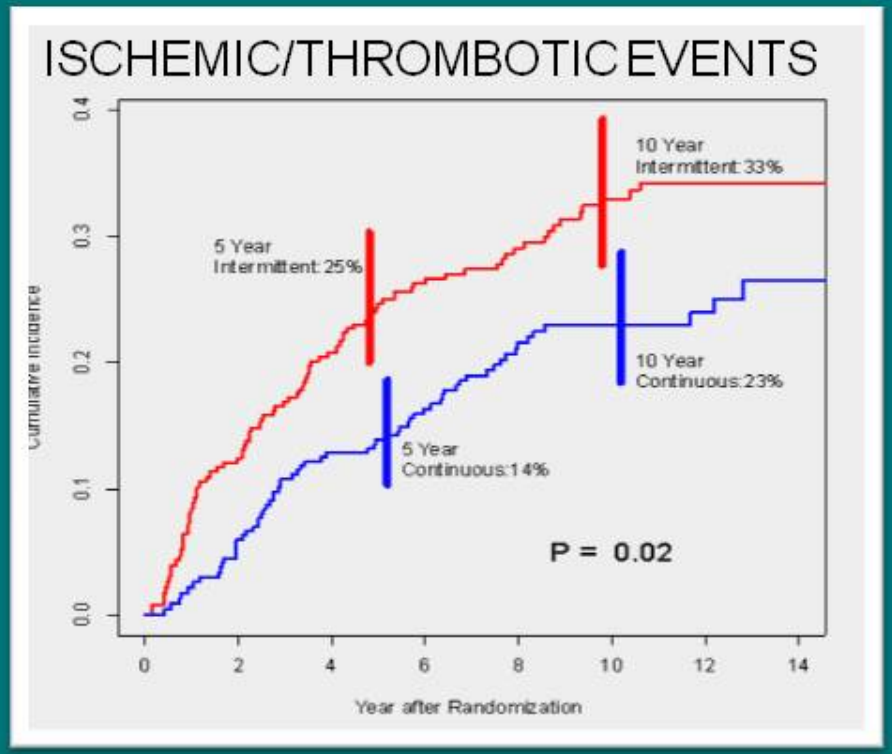
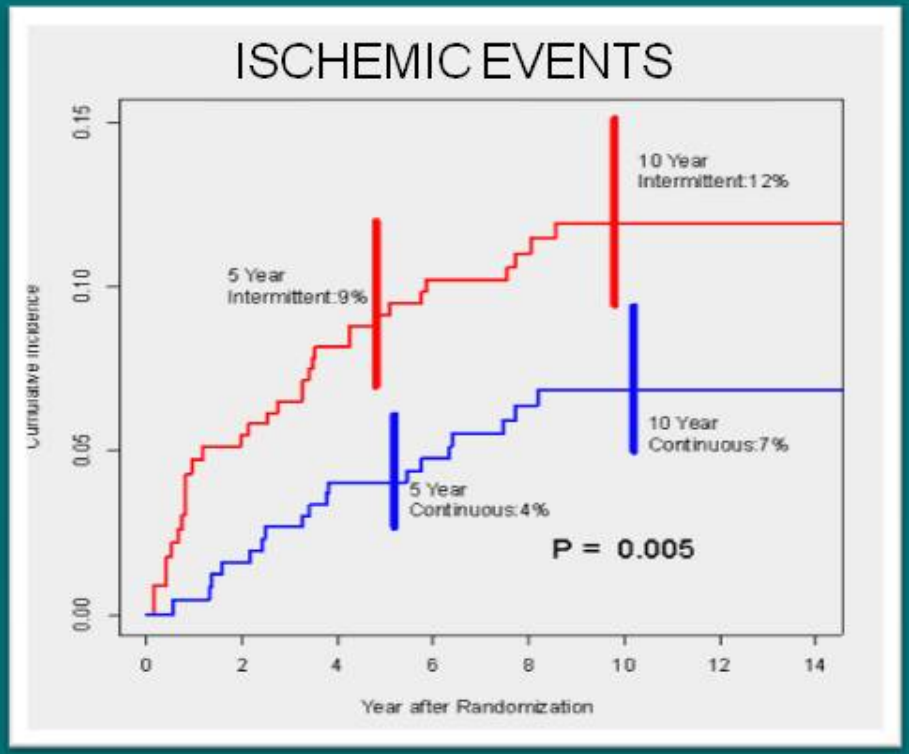
NCI R01CA134964

PRESENTED AT: ASCO Annual '15 Meeting

Presented By Dawn Hershman at 2015 ASCO Annual Meeting

Late Effects: Cumulative Incidence





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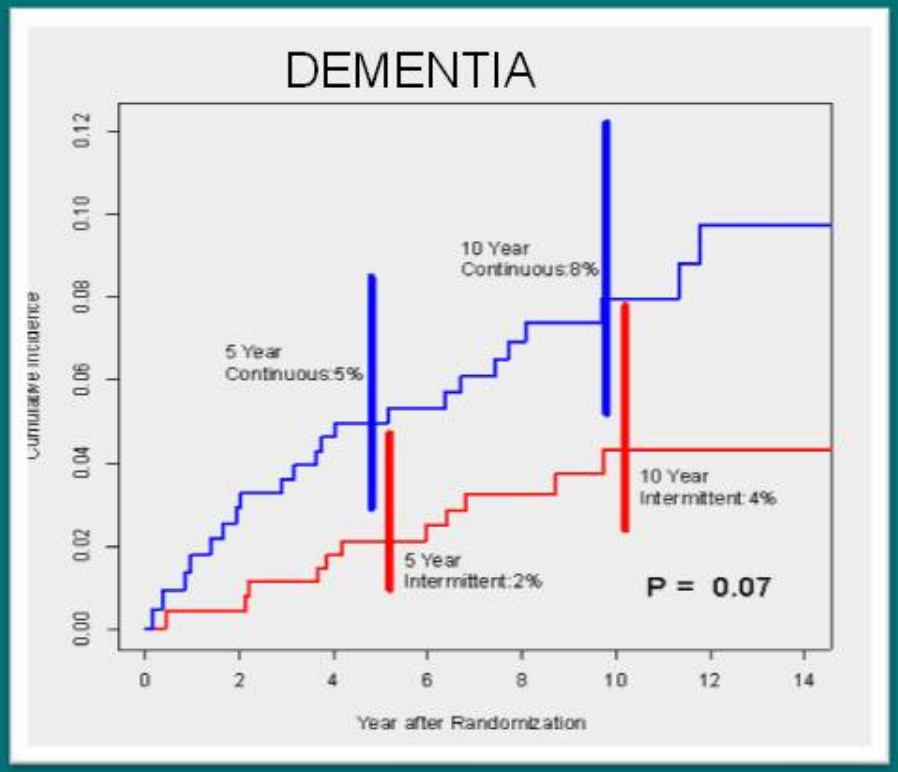
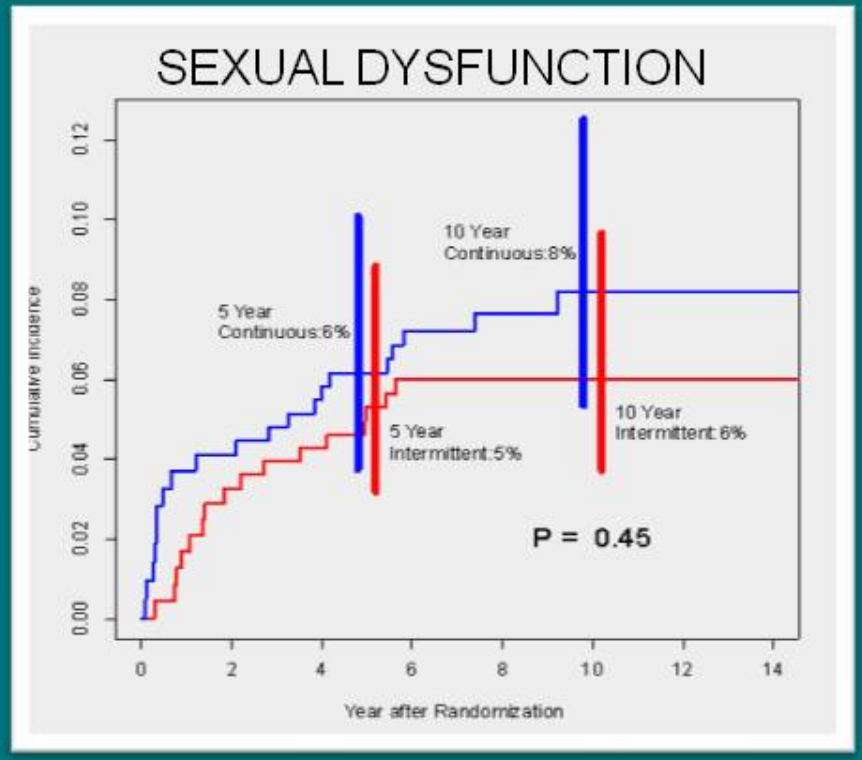
- Intermittent - Continuous

PRESENTED AT: ASCO Annual '15 Meeting

Presented By Dawn Hershman at 2015 ASCO Annual Meeting

Late Effects: Cumulative Incidence





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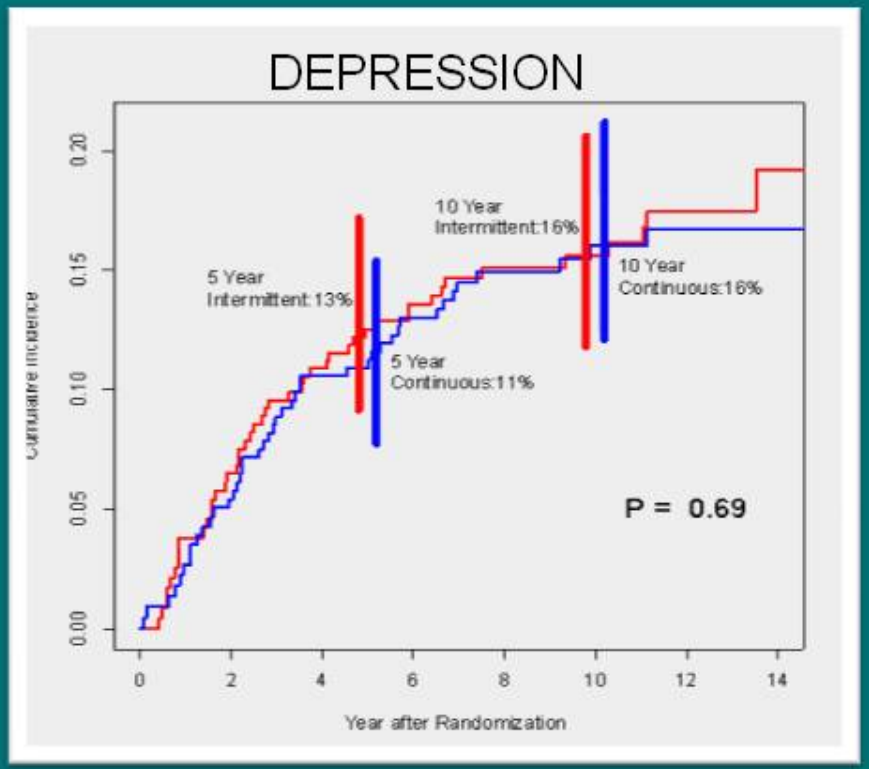
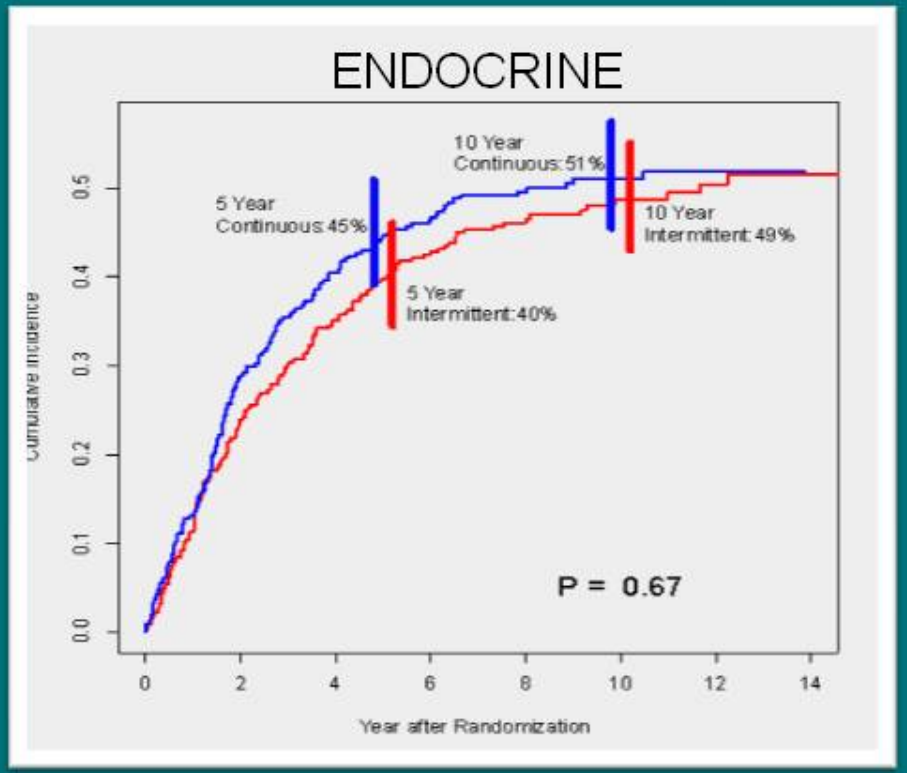
PRESENTED AT: ASCO Annual '15 Meeting

Late Effects: Cumulative Incidence





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- Intermittent - Continuous

PRESENTED AT: ASCO Annual '15 Meeting

Presented By Dawn Hershman at 2015 ASCO Annual Meeting

Terapie di salvataggio nella pratica clinica

Recidive biochimiche → dopo PR + RT:

- Possibile differire la terapia ormonale alla comparsa di lesioni secondarie

- Nel paziente M1, preferire la terapia continuativa a quella intermittente

Terapie di salvataggio nella pratica clinica

Recidive biochimiche → Storia naturale:

- Dopo Prostatectomia Radicale
- Dopo RT radicale
- Dopo PR + RTa
- Nella malattia metastatica
- Nella malattia resistente alla castrazione

Terapie di salvataggio nella pratica clinica

Recidive biochimiche → Storia naturale:

- Dopo Prostatectomia Radicale
- Dopo RT radicale
- Dopo PR + RTa
- Nella malattia metastatica
- Nella malattia resistente alla castrazione in assenza di Metastasi (M0)?

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Natural History of Rising Serum Prostate-Specific Antigen in Men With Castrate Nonmetastatic Prostate Cancer

Matthew R. Smith, Fairooz Kabbinavar, Fred Saad, Arif Hussain, Marc C. Gittelman, David L. Bilhartz, Chris Wynne, Robin Murray, Norman R. Zinner, Claude Schulman, Ronald Linnartz, Ming Zheng, Carsten Goessl, Yong-Jiang Hei, Eric J. Small, Richard Cook, and Celestia S. Higano

201 pazienti nel gruppo placebo di un trial di fase III interrotto per futilità

Acido zoledronico vs. Placebo

Smith MR, J Clin Oncol 23:2918-2925,2005

Storia naturale del CRPCa M0

Risultati

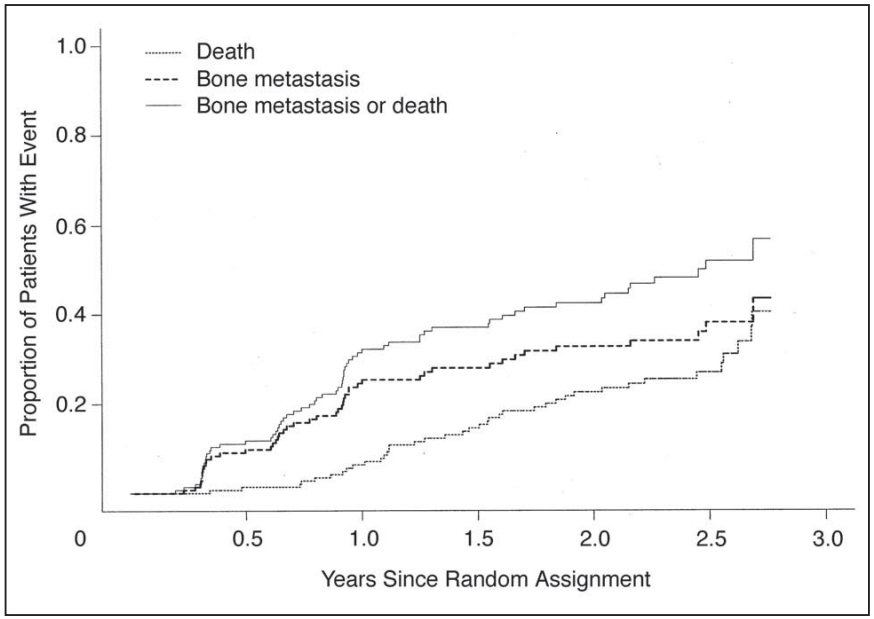

Fig 1. Kaplan-Meier time to first bone metastasis, death, and time to first bone metastasis or death.

Il 33% dei pazienti sviluppa una metastasi ossea a 2 anni

Smith MR, J Clin Oncol 23:2918-2925,2005

Storia naturale del CRPCa M0

Risultati

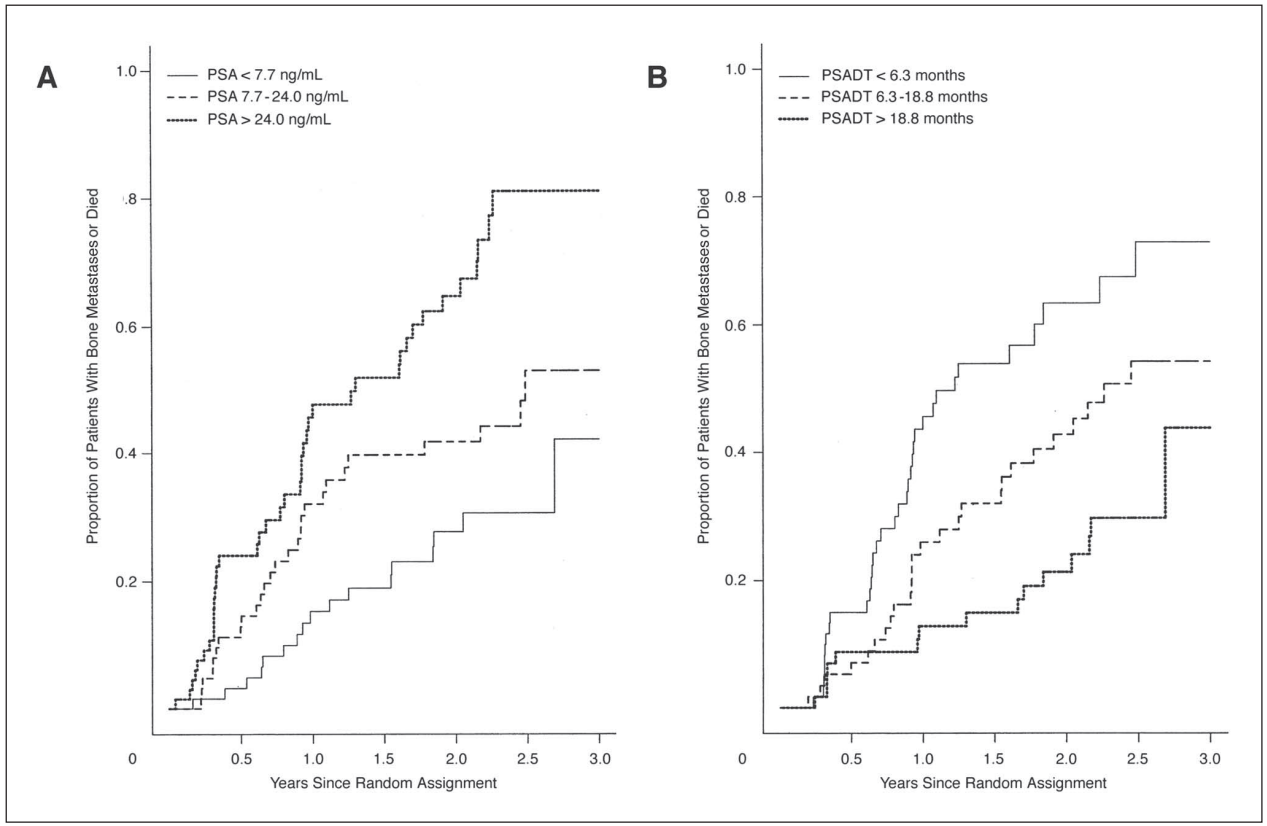

Fig 2. Kaplan-Meier time to bone metastasis or death according to tertiles of prostate-specific antigen (PSA) and PSA doubling time (PSADT).

Smith MR, J Clin Oncol 23:2918-2925,2005

Storia naturale del CRPCa M0

Quindi:

- Non tutti i pazienti con malattia resistente alla castrazione sviluppano in tempi brevi lesioni secondarie

- Monitorizzare in modo stretto i pazienti con PSADT <6 mesi con valori di PSA totale alti

Terapia del CRPCa metastatico

Nei pazienti metastatici:

- Se oligometastasi: che ruolo RT ?

- E nei pazienti con oligoprogressione ?

IN A POST HOC EXPLORATORY ANALYSIS OF STUDY COU-AA-301, we report on safety and tolerability of patients who had:

A. Localized clinical progression at a **SINGLE SITE** and
B. Received concomitant radiation

Percentage of patients receiving concomitant radiation was comparable

AA n = 791 n (%)	Placebo n = 394 n (%)	Total N = 1185 N (%)
88 (11.1)	48 (12.2)	136 (11.5)

Saad et al. AUA Conference 2012; Abstract 682 (Oral presentation)

COU-AA-301

Percentage of patients remaining on treatment post-SRE was not reduced with AA

Remaining on Treatment Post-SRE	AA n = 88 n (%)	Placebo n = 48 n (%)
≥ 30 days	64 (72.7)	32 (66.7)
≥ 12 weeks*	37 (42.1)	12 (25.0)

*range < 1 to 83 weeks, both groups

A higher percentage of patients was able to remain on treatment post-SRE with AA

Saad et al. AUA Conference 2012; Abstract 682 (Oral presentation)

Terapie di salvataggio nella pratica clinica

Dopo Prostatectomia Radicale

→ RT di salvataggio precoce

Dopo RT radicale

→ Valutare attentamente terapie focali

Dopo PR + RTa

→ Possibile differire ADT

Nella malattia metastatica

→ ADT continuativa

Nella malattia resistente alla castrazione

→ RT in caso di oligo-progressione

Navighiamo a vista?

Per fortuna abbiamo una bussola

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