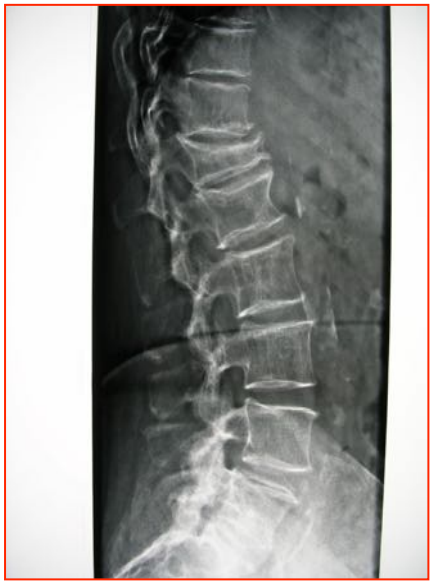
Radioterapia e ormoni

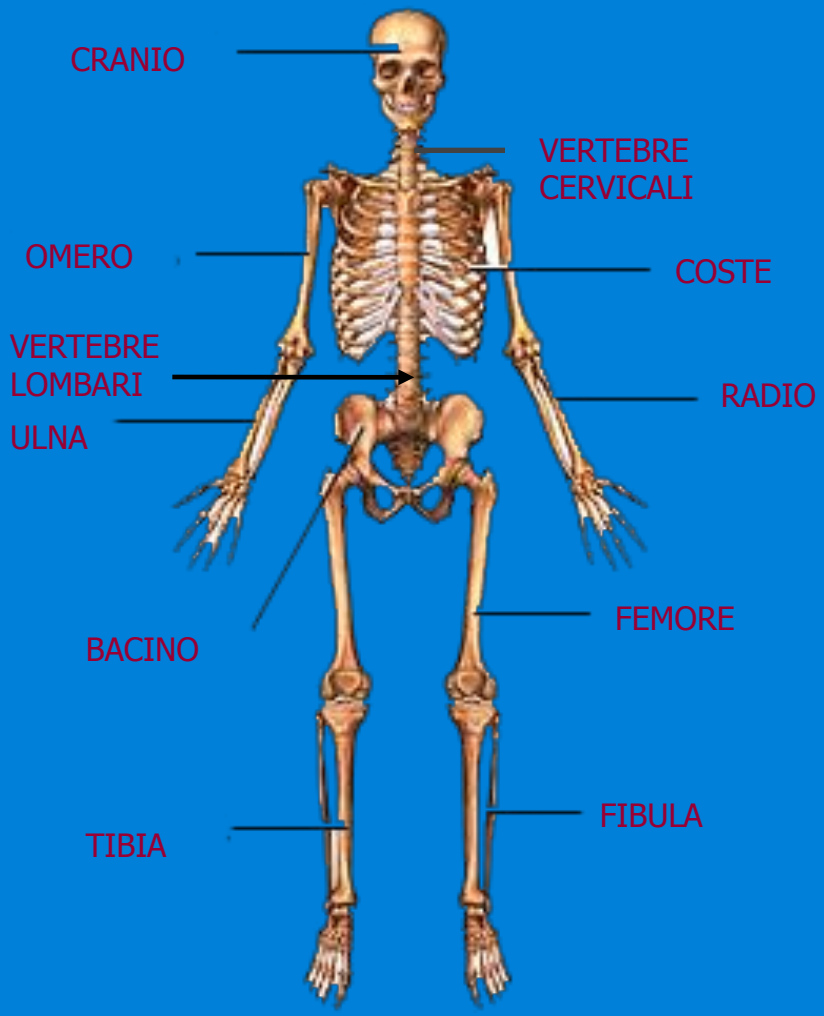


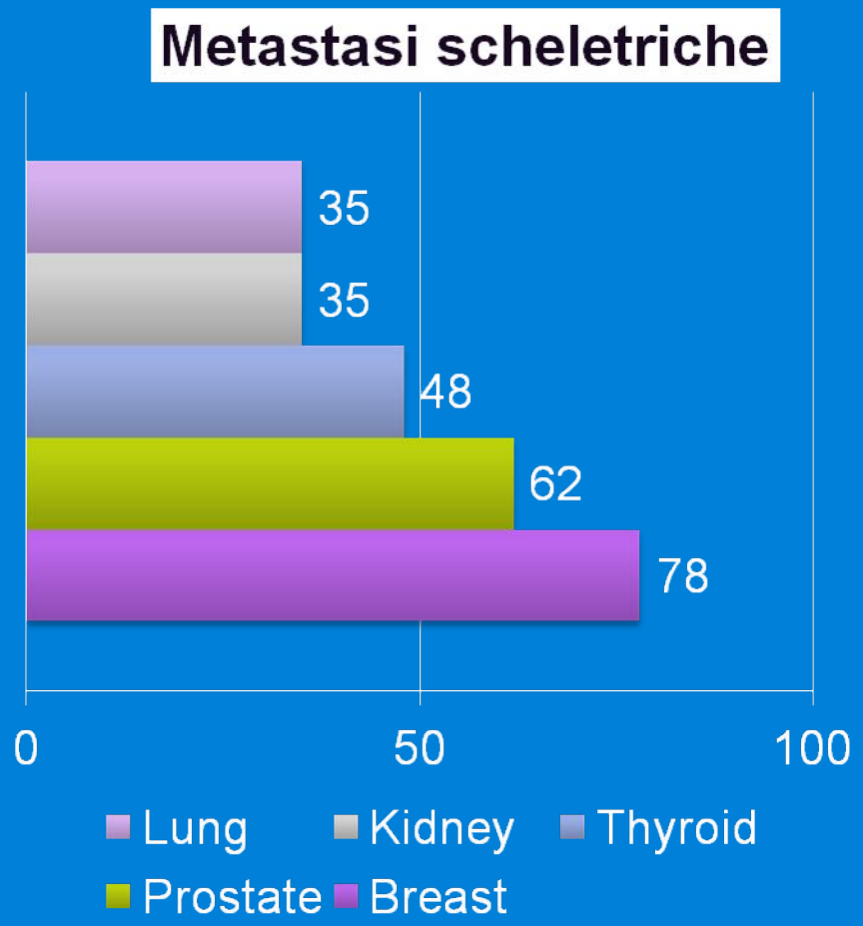
Giovanni Rosti

Direttore Oncologia 3viso

Associazione Italiana Radioterapia Oncologica

Dimensioni del problema

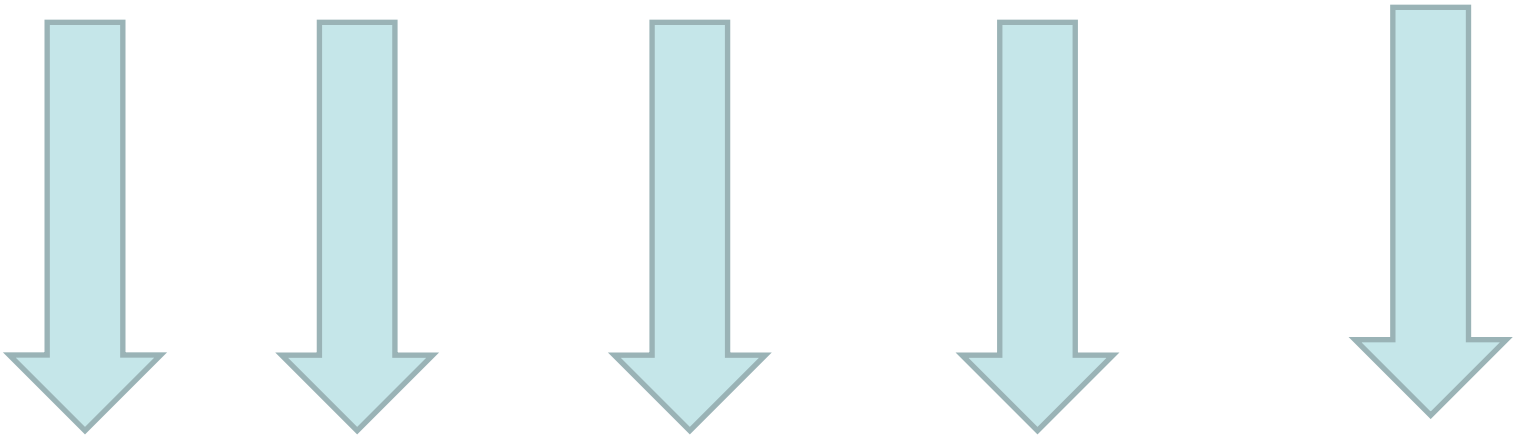




Coleman RE. ClinCancerRes

	Mammella	Polmone	Prostata
Teca	28%	16%	14%
Coste	59%	65%	50%
Rachide	60%	65%	60%
Lunghe	32%	27%	38%
Pelvi	38%	25%	57%

La frattura patologica ha conseguenze enormi



Cliniche Sociali Economiche Qualità di Vita **Prognostiche**

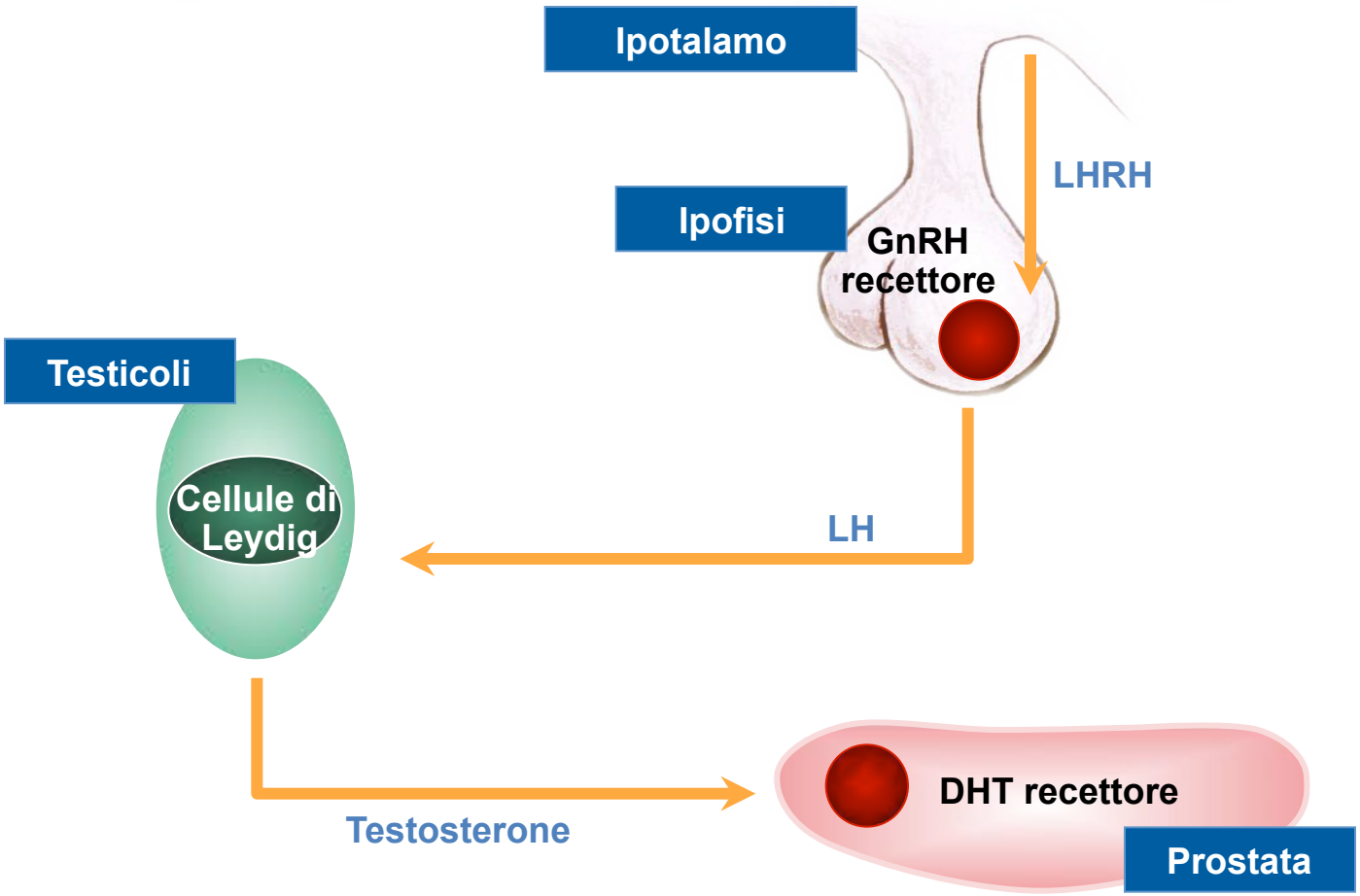
Impact on Survival: Fractures Negatively Affect Survival

- Pathologic fractures correlate with a significantly increased relative risk of death[1,2]

– Breast cancer	1.52 (1.28, 1.81)	*P* < .0001
– Multiple myeloma	1.44 (1.06, 1.95)	*P* = .02
– Prostate cancer	1.29 (1.01, 1.65)	*P* = .04
– Lung cancer / Other	1.08 (0.87, 1.34)	*P* = .49

1. Hei Y-J, et al. Presented at: 28th Annual SABCS, 2005, Abstract 6036.
2. Saad F, et al. Presented at: ECCO 2005. Abstract 1265.

Asse Ipotalamo-Ipofisi-Gonadi



Che fare di fronte alle mets scheletriche?

1)Trattamento sistemico

Trattamenti target verso il tumore

- **manipolazioni endocrine**
- **chemioterapia**
- **farmaci a bersaglio molecolare**

Trattamenti target sull'osso

- **inibizione ostoclasti (BFs, denosumab)**

2) Cure locali

Chirurgia, radioterapia esterna..

3) Terapia di supporto e del dolore

SIMULTANEOUS CARE

Screening

Elaborazione lutto

TERAPIE ANTITUMORALI

R I A B I L I T A Z I O N E

Il modello giusto !

Cure di supporto - Cure palliative

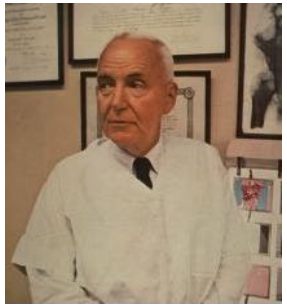
(Fatigue, dolore, supp.sociale, nutrizionale, psicologico, spirituale)

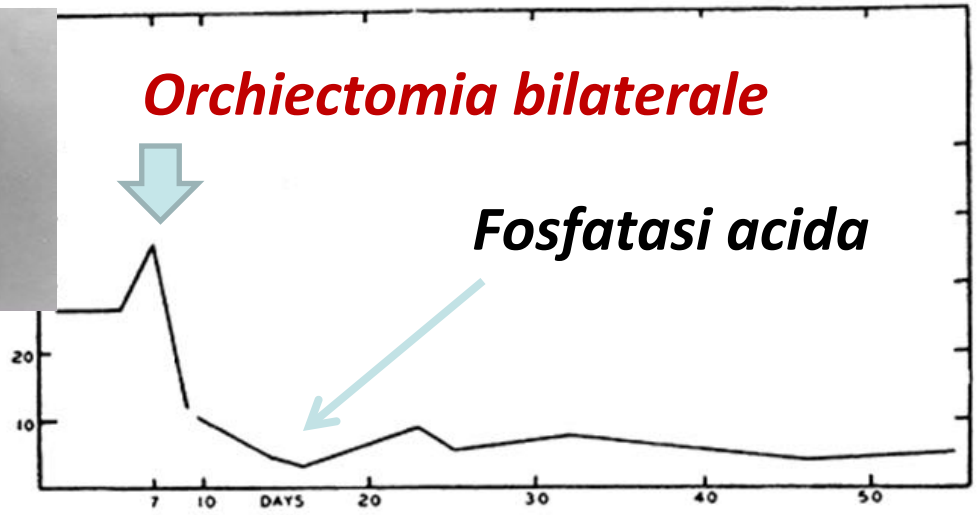
1941

I. The Effect of Castration, of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate*

Charles Huggins, M.D., and Clarence V. Hodges, M.D.

(From the Department of Surgery, the University of Chicago, Chicago, Illinois)

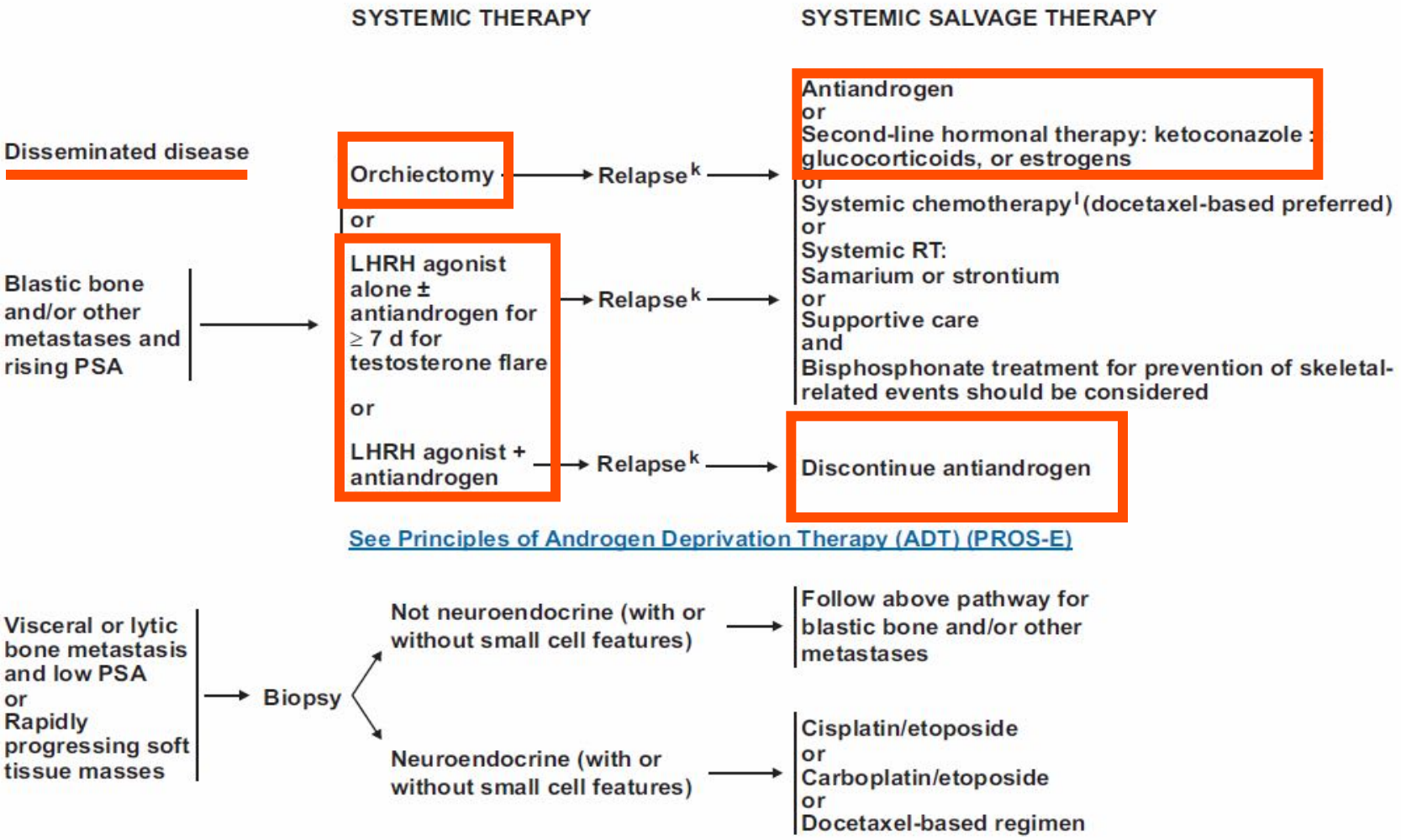




Nel 1941, Huggins e Hodges dimostrano per la prima volta la responsività del carcinoma prostatico metastatico alla deprivazione androgenica (castrazione chirurgica)

Huggins C., Hodges C. Cancer Res, 1941

Prostate Cancer

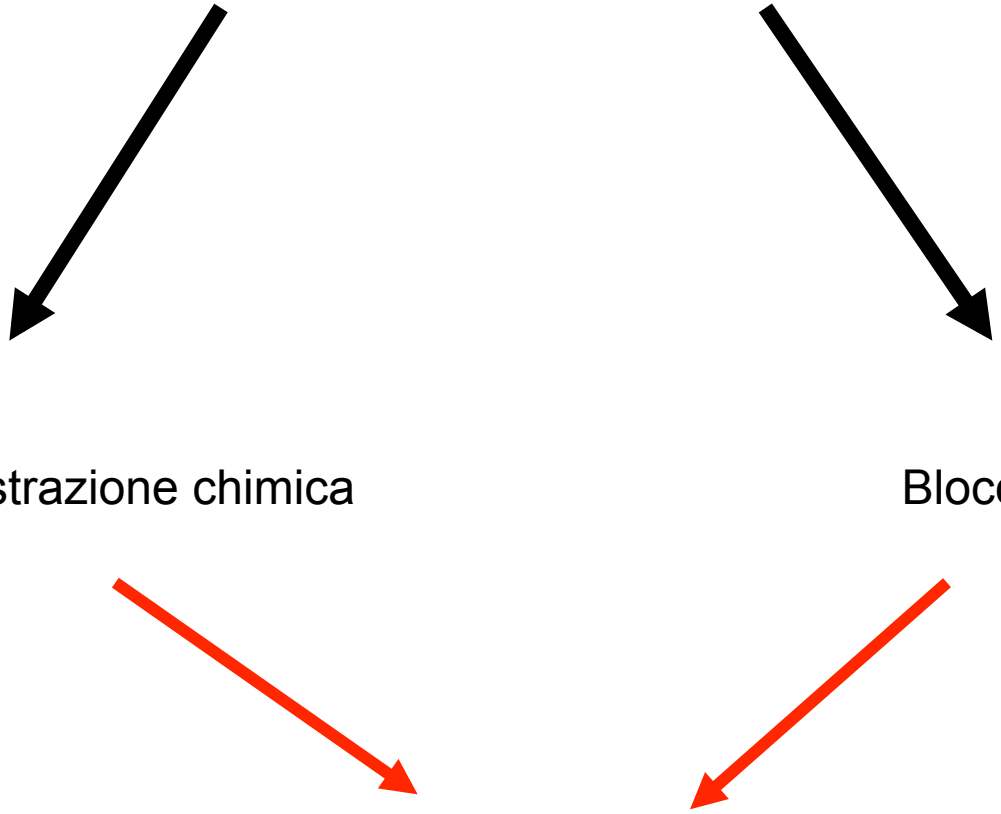


[k] Assure castrate level of testosterone.

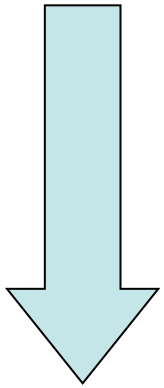
[l] See Principles of Chemotherapy (PROS-F).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Ormonoterapia nel carcinoma della prostata avanzato



Livello di testosterone dopo castrazione nel 2013



< 20 ng/dL (0,7 nmol/L) **

** secondo alcuni Autori il livello è < 50 ng/dl (1,7 nmol/L)

Sono tutti uguali i LH-RH agonisti ?

Pari efficacia

Diversa efficienza

Attenzione al flare phenomenon, da non confondere con progressione

o inefficacia della terapia radiante

Grandi volumi, sintomi, malattia ossea

Flare-up

Aumento transitorio di testosteronemia con conseguente stimolazione della crescita tumorale

Precipitazione di compressione midollare

Ostruzione vie urinarie

Aumento del dolore

Esistono anche LH-RH antagonisti

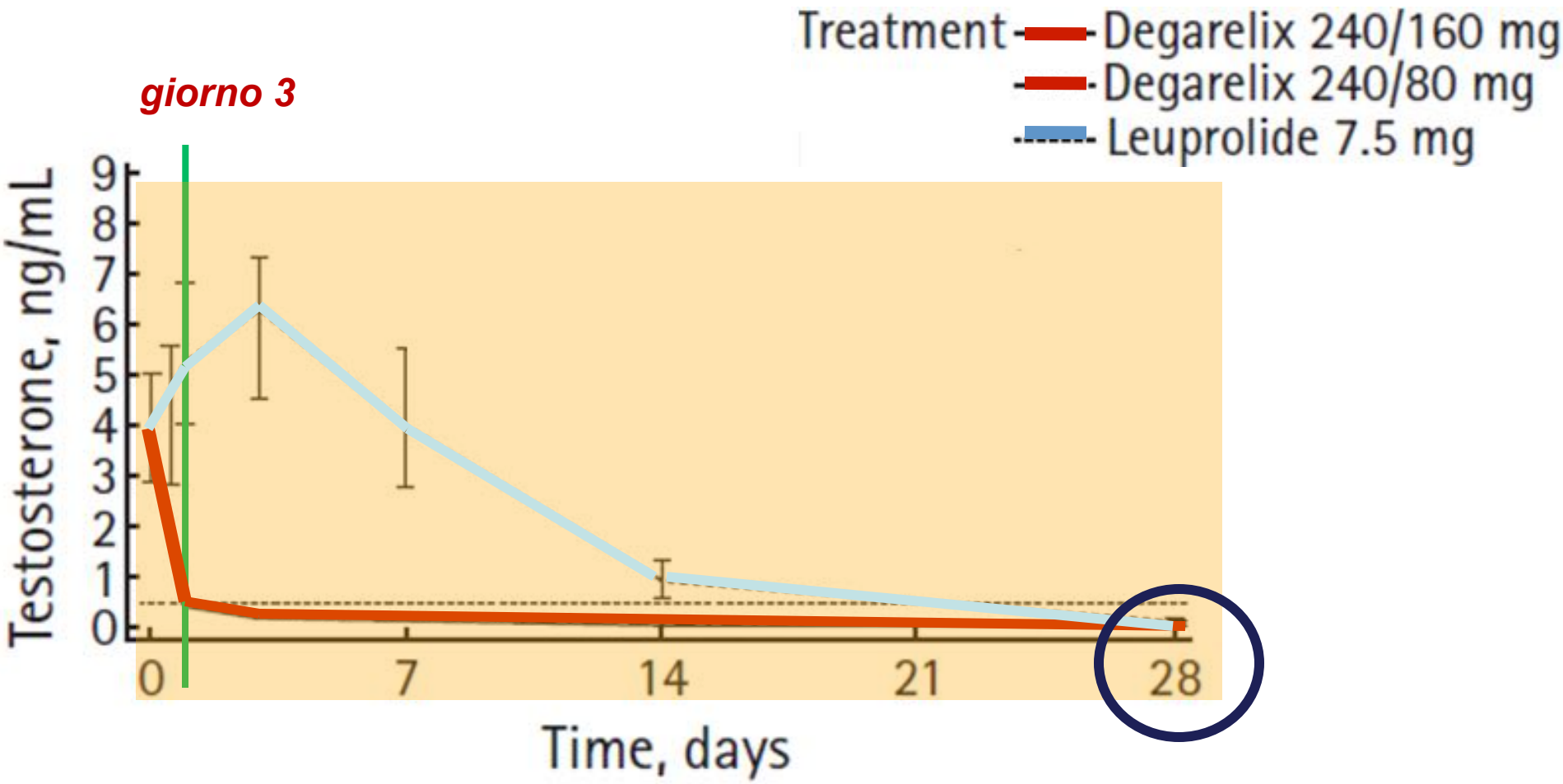
abarelix (una meteora)

degarelix

Secondo EAU : forse degarelix meglio in pazienti con grosso volume alla colonna

Estrogeni : espulsi dal trattamento , tentano di rientare.
Efficacia pari a LH-RH ago, ma tossicità cardiovascolare.

Cinetica delle testosteronemia in corso di terapia con degarelix



Klotz L. ET AL., BJU Int 2008

Terapia con antiandrgeni

Non steroidei (nilutamide, flutamide, bicalutamide)

Steroidei : ciproterone acetato

Progestinici : (MAP, megestrolo acetato).

Effetti collaterali: ginecomastia, mastalgia,
Però preservano libido e densità ossea

Bicalutamide potrebbe essere sostituta per chi non può fare

LH-RH agonisti.

LH RH agonisti : non a costo zero

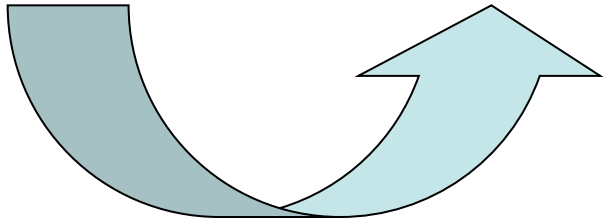
Flare-up

Riduzione massa muscolare

Osteoporosi

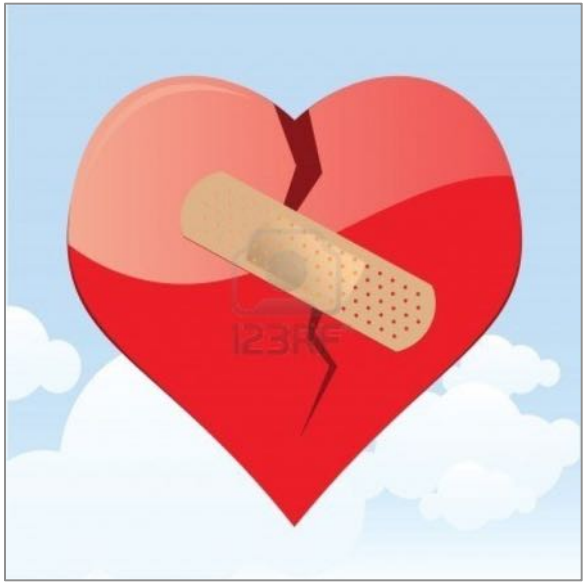
Anemizzazione

Deterioramento Qualità di Vita



Alzi la mano chi fa fare i questionari di Qualità di Vita

Sindrome metabolica



Aumento LDL

Aumento trigliceridi

Riduzione HDL

Ipertensione arteriosa

Ridotta tolleranza glucidica

Aumento del rischio cardiovascolare

"‥ It is plausible that ADT could increase cardiovascular risk…."

ASTRO
TARGETING CANCER CARE

American Heart Association
Learn and Live

American Cancer Society

American Urological Association, Inc.

Ma una metanalisi su oltre 4000 pazienti con malattia non metastatica ha mostrato che il rischio cardiovascolare della deprivazione androgenica non è superiore ai controlli. Ciò non è influenzato dalla durata della ADT.

Nguyen PL, JAMA,2011

Ma in chi ha avuto cardiopatia pregressa,

la ADT aggiunta alla RT peggiora il rischio

cardiovascolare .

News dall'ASCO 2013

Dagarelix sembra in grado di ridurre il rischio di eventi cardiaci

e la morte del 50% in cardiopatici!

Albertsen P., ASCO 2013 (abstr.42)

Sindrome metabolica associata a ipogonadismo

Criteri per la diagnosi (almeno 3)

Aumento glicemia> 120 mg/dl

Aumento trigliceridi > 150 mg/dl

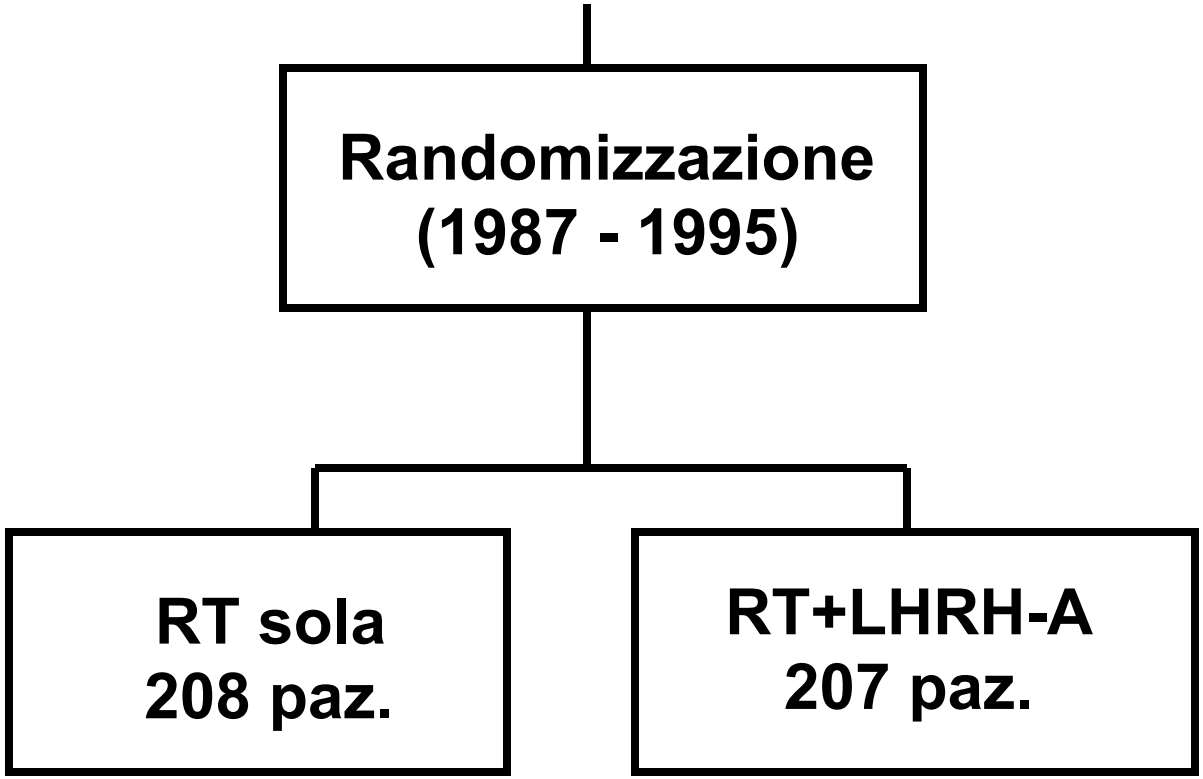
LDL < 40 mg/dl

Aumento circonf. vita 102 cm

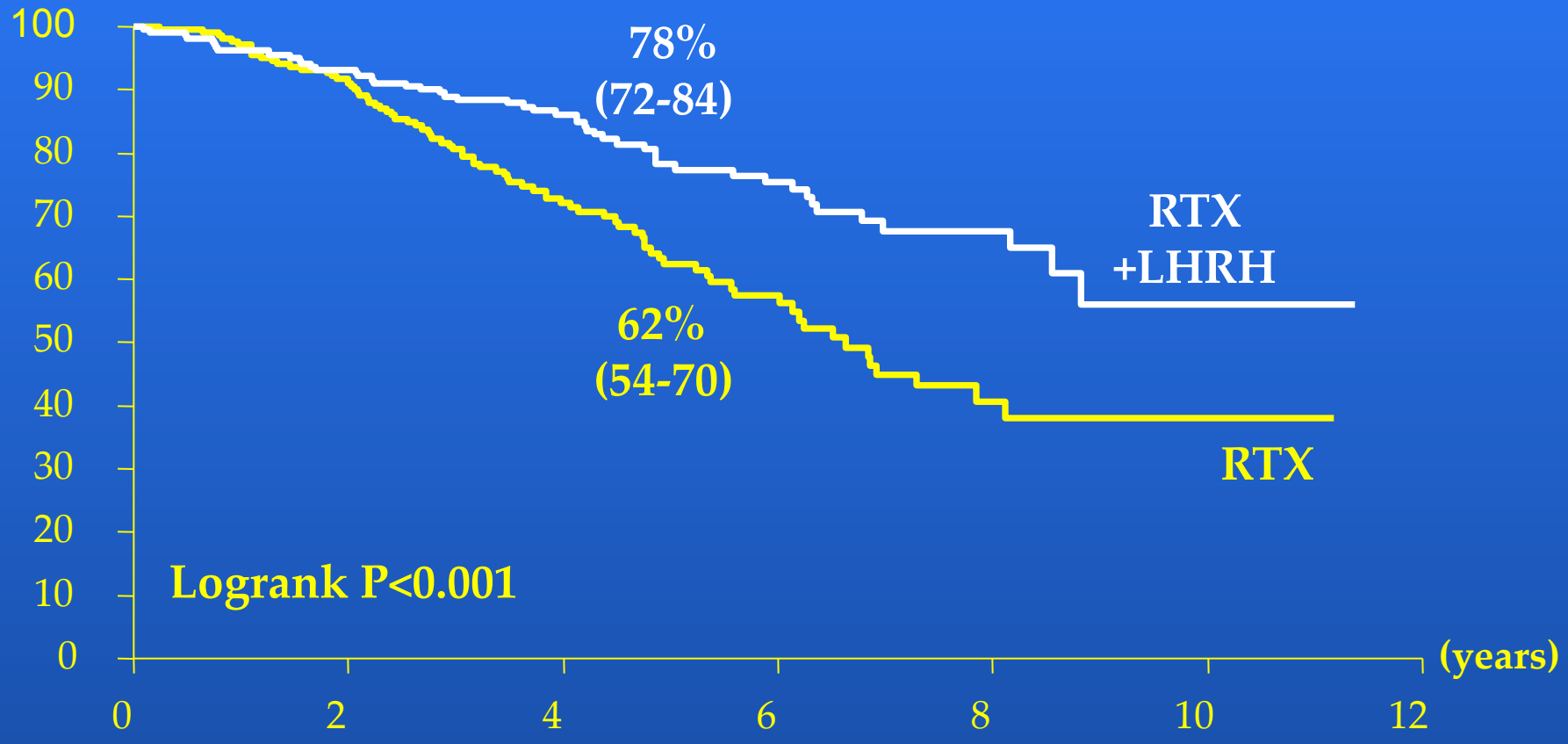
Aumento PA

EORTC 22863

Adenocarcinoma prostatico
T1-T2 G3, T3-T4 ogni G



Sopravvivenza globale

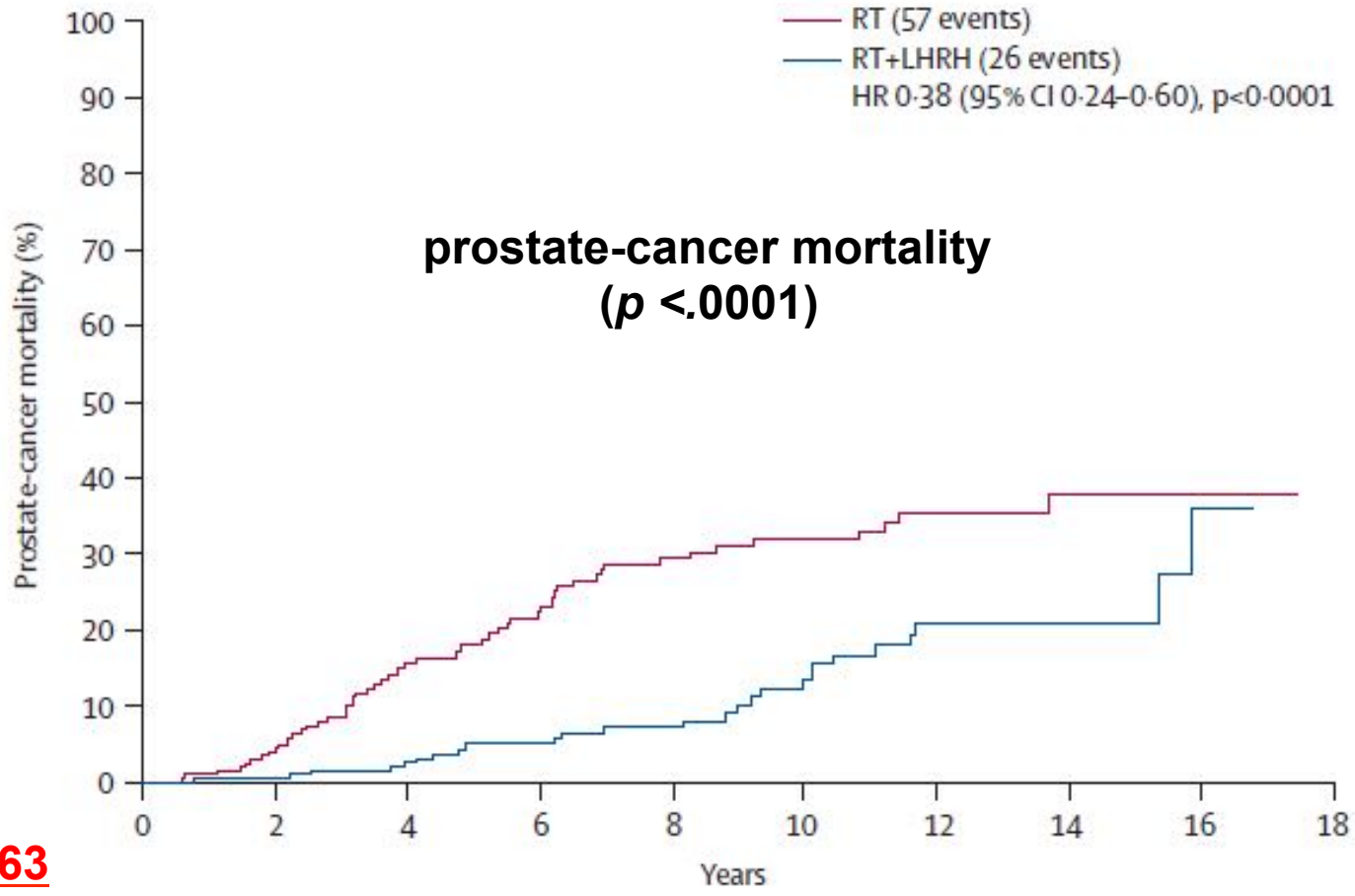


O	N	Number of patients at risk :					
81	208	177	106	46	16	3	RTX
50	207	183	142	71	24	5	RTX+LHRH

Bolla M et al. Lancet 2002 ; 360:103-108

Lancet Oncol 2010; 11: 1066–73

External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study



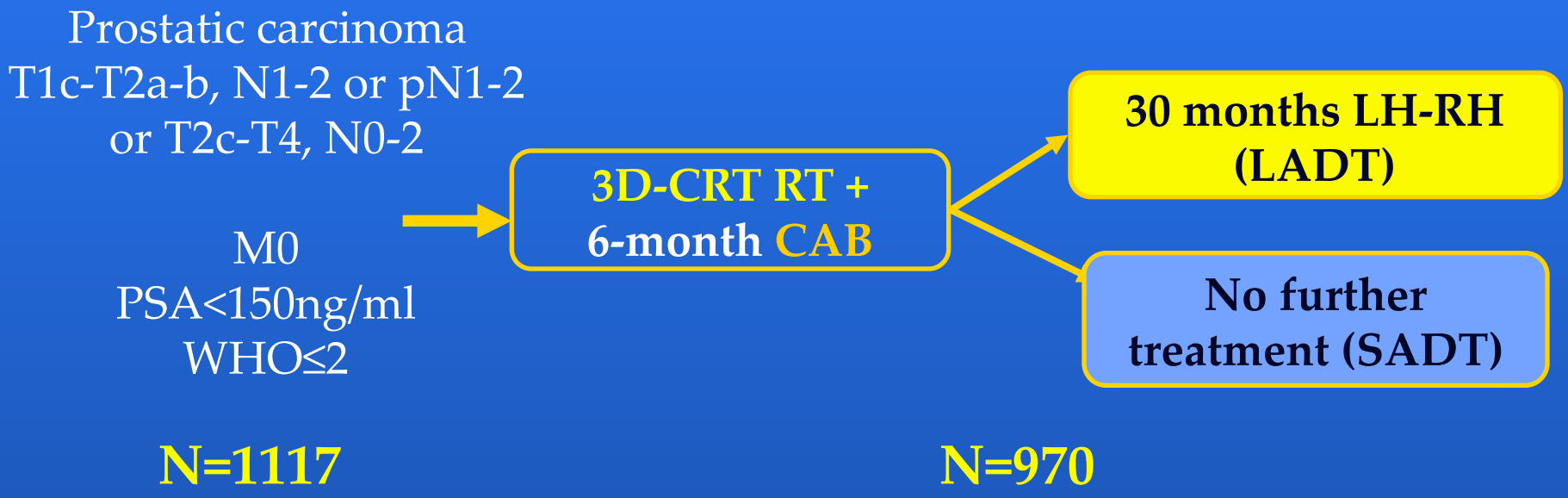
EORTC 22863

Duration of Androgen Suppression in the Treatment of Prostate Cancer

Michel Bolla, M.D., Theodorus M. de Reijke, M.D., Ph.D.,
Geertjan Van Tienhoven, M.D., Ph.D.,
Alphonsus C.M. Van den Bergh, M.D., Ph.D., Jorg Oddens, M.D.,
Philip M.P. Poortmans, M.D., Ph.D., Eliahu Gez, M.D., Paul Kil, M.D., Ph.D.,
Atif Akdas, M.D., Guy Soete, M.D., Oleg Kariakine, M.D.,
Elsbietha M. van der Steen-Banasik, M.D., Elena Musat, M.D.,
Marianne Piérart, M.S., Murielle E. Mauer, Ph.D., and Laurence Collette, Ph.D.,
for the EORTC Radiation Oncology Group and Genito-Urinary Tract Cancer Group*

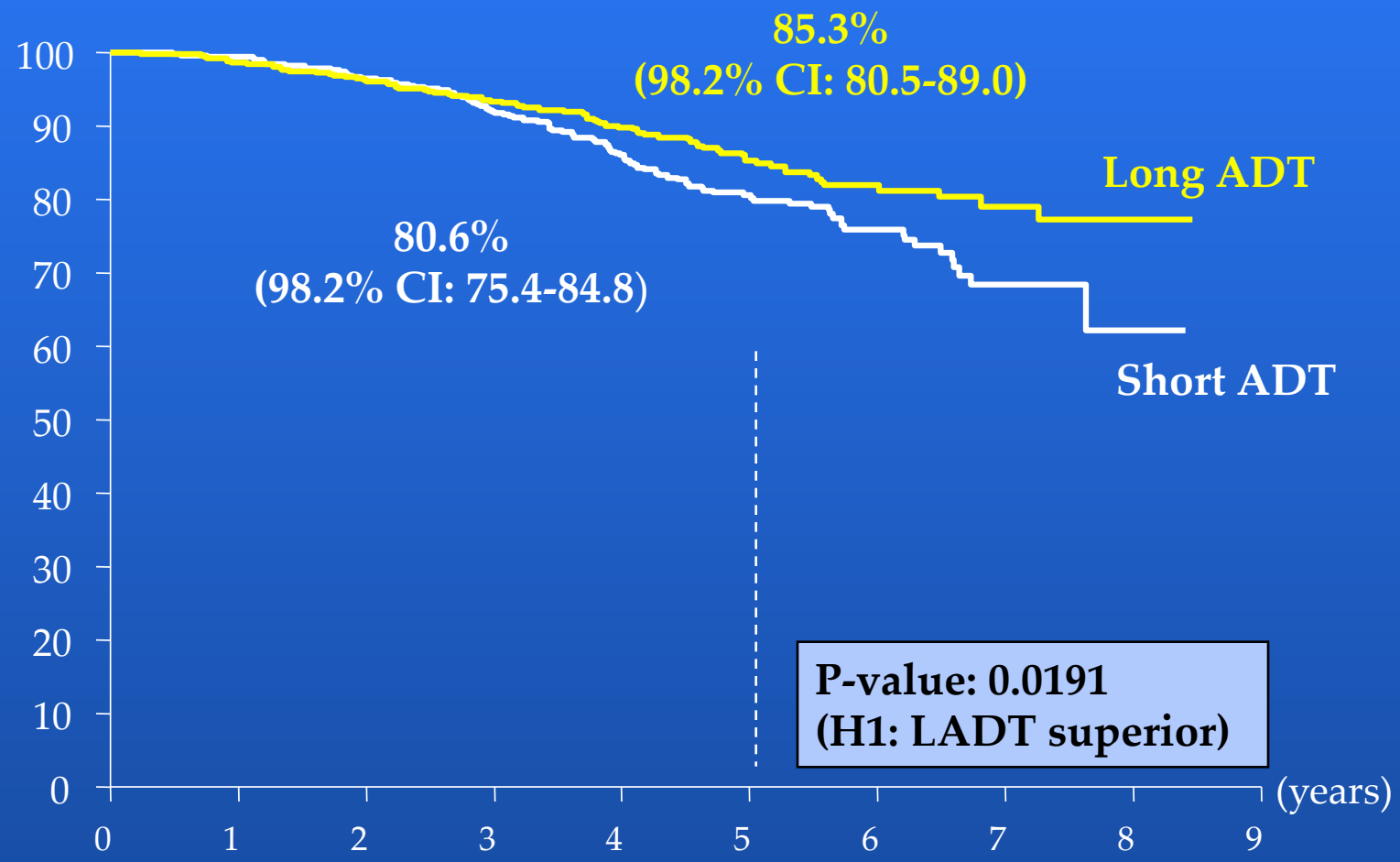
N Engl J Med 2009;360:2516-27.

EORTC 22961: Schema dello studio



Primary objective: To demonstrate non inferior overall survival with 6-months adjuvant hormonal treatment compared to 3-years adjuvant ADT treatment

Overall survival



O	N	Number of patients at risk :								
100	483	470	452	409	332	235	122	37	4	Short ADT
73	487	476	450	414	354	239	130	52	17	Long ADT

Bolla M et al. J Clin Oncol 2007 ; 25 : 238 s (suppl; abstr 5014)

Epidural compression of the cauda equina caused by vertebral osteoblastic metastasis of prostatic carcinoma: resolution by hormonal therapy

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email KSusuki@aol.com
Received 26 April 1999 and in revised form 16 August 1999 Accepted 25 August 1999

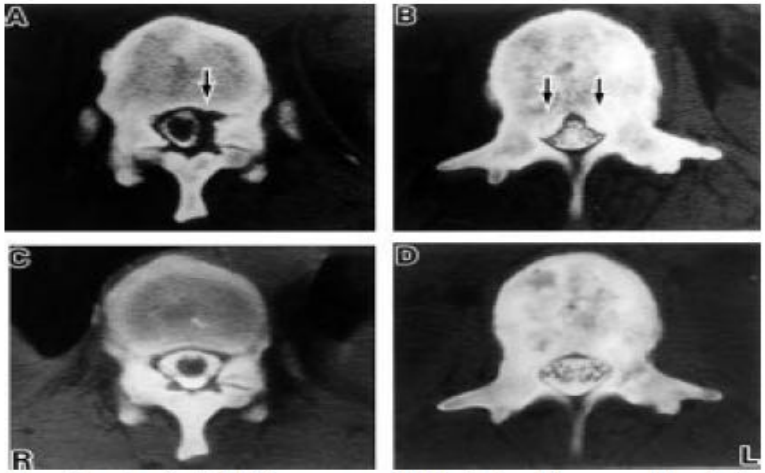
Abstract

A 59 year old man with prostatic carcinoma developed epidural compression of the cauda equina caused by bony expansion from a vertebral osteoblastic metastasis. For medical reasons he could not undergo radiation or surgery. Hormonal therapy alone relieved his low back pain and restored ambulation and urinary function. Postmyelography CT showed that the bony expansion from the vertebra had completely disappeared after treatment. This is the first report of remarkable improvement due to hormonal therapy alone.

(*J Neurol Neurosurg Psychiatry* 2000;**68**:514–515)

Keywords: prostatic carcinoma; osteoblastic metastasis; epidural compression; hormonal therapy

Compression of the spinal cord and cauda equina is an important neurological complication of prostatic carcinoma.[1] Direct tumour extension from a vertebral metastasis is the most common mechanism. Epidural compression caused by bony expansion from a vertebral osteoblastic metastasis, a rare occurrence,[2–5] is thought to be an absolute indication for surgical decompression.[2] We describe a case of epidural compression of the cauda equina due to such an uncommon condition, which was treated successfully with hormonal therapy alone.



Postmyelography spinal CT. Before treatment: (A) the spinal cord is compressed laterally by the epidural mass (arrow) on the left side of the body of Th11; (B) the vertebral canal is narrowed by bony expansion (arrows) from both sides of the body at L2. After treatment: (C) the epidural mass in the body of Th11 has disappeared; (D) bony expansion from the body of L2 has also disappeared.

Case report

A previously healthy 59 year old man developed low back pain in September 1997, and the pain gradually worsened. He began to notice paraesthesia in both legs in February 1998. One month later, he developed weakness and severe paraesthesia in both legs and could not walk.

In August 1998, he was admitted to our hospital, at which time anaemia was apparent. There was no neurological abnormality in the cranial nerves or upper limbs. Atrophy of the right lower limb was apparent. Muscle tone was decreased to grade 3–4 (Medical Research Council) power in the right lower limb and grade 4–5 in the left. Deep tendon reflexes were pathologically depressed in both lower limbs, and the Lasègue sign was positive on both sides. Hypaesthesia was present below L1 area on his right side and the S1 area on the left side, but the saddle area was normal. Although bowel dysfunction was not apparent, he developed urinary retention several days after admission.

Haematological investigations disclosed anaemia (Hb 7.3 g/dl) and thrombocytopenia (84 000/μl). Serological investigations showed an increased alkaline phosphatase of 5301 U/l, and lactic dehydrogenase of 751 U/l. Cerebrospinal fluid had increased protein, 63 mg/dl, but normal cellularity. Plain radiography showed multiple osteoblastic lesions involving the thoracic and lumbar vertebral bodies, and pelvis. A nuclear bone scan showed multiple hot spots in the skull, vertebrae, ribs, humeri, and femora, consistent with multiple bone metastases. Myelography showed narrowing of the vertebral canal in the body of Th11, L2. Postmyelography spinal CT showed an epidural mass in the body of Th11 and bony expansion from the body of L2 into the vertebral canal (figure).

To BAT or not to BAT ? **

** Molto, ma molto adattato da Sir William Shakespeare, The Hamlet,1518

BAT ha lieve beneficio rispetto a LH-RH da solo

circa < 5% che compare dopo i 5 anni.

Studi metodologicamente non perfetti.

Apprezzabile solo con non-steroidei

Enorme aumento del costo della terapia.

To IADor not to IAD ? **

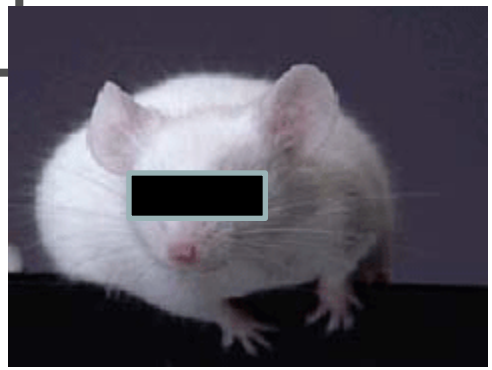
** Molto, ma molto adattato da Sir William Shakespeare, The Hamlet,1518

Perché mai dovremmo fare una terapia intermittente ?

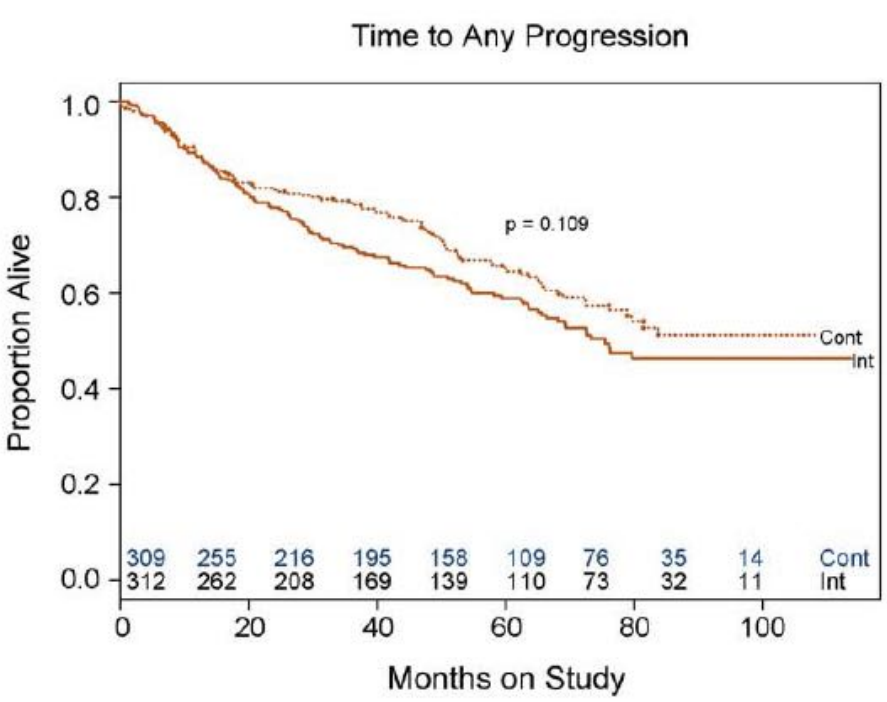
Nel tumore prostatico ipotesi di Bruchovsky

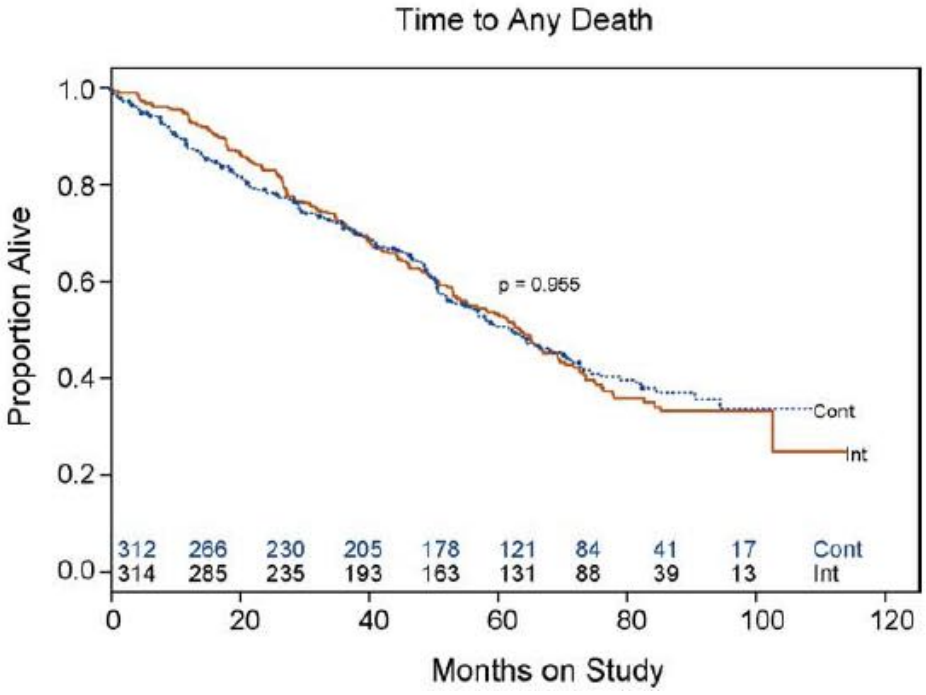
“ritardo nello sviluppo di androgeno-indipendenza

se i tumori venivano riesposti ad androgeni”



Intermittente o no?





Calais Da Silva F., et al., Eur Urol., 2009

Studio Canadese NCIC CTG PR7

Rialzo del PSA dopo radioterapia o chirurgia no mets

Sopravvivenza globale identica .

Qualità di vita migliore per intermittente

Southwest Oncology Group
A National Clinical Research Group

Studio SWOG 9346

Pazienti metastatici che avevano riduzione di PSA $\leq$ 4

Studio inconclusivo per non inferiorità

La terapia intermittente (IAD) non è inferiore alla continua, ma il profilo di tollerabilità e la QoL per i pazienti è migliore soprattutto per la sessualità.

A questo proposito : la sessualità del paziente oncologico,

e’ ancora un unmet need!!!

Alzi la mano chi regolarmente segue le problematiche sessuali

Benefici della deprivazione androgenica nel paziente metastatico

Paziente asintomatico

La deprivazione androgenica immediata è in grado di ritardare la progressione verso la malattia sintomatica e di ridurre il rischio di complicanze legate alla progressione

Paziente sintomatico

Palliazione dei sintomi

Riduzione del rischio di

- ✓ **Compressione spinale**
- ✓ **Ostruzione ureterale**
- ✓ **Fratture patologiche**
- ✓ **Extrabone mets**

EAU Guidelines, 2012

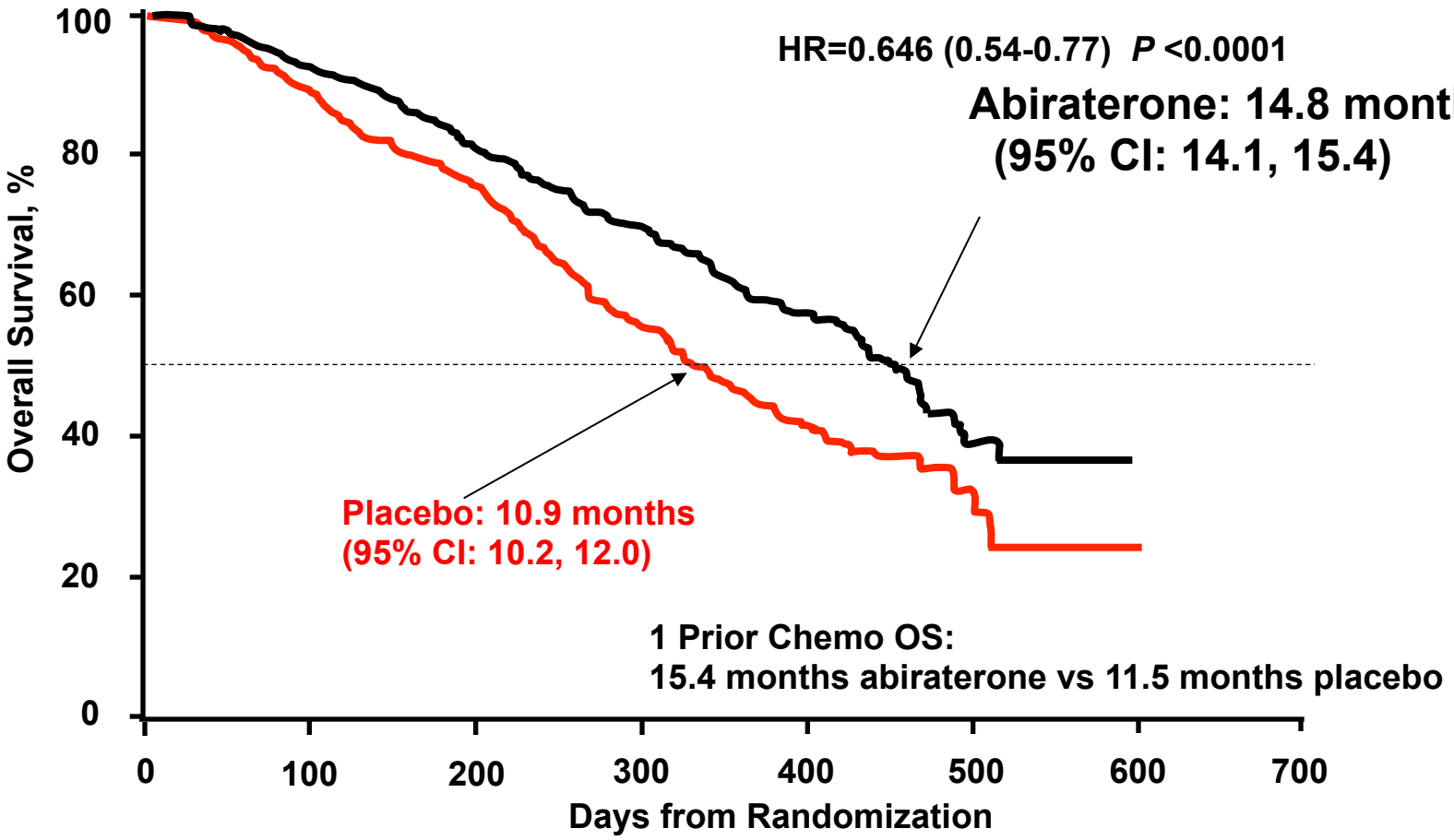
La terapia attuale del carcinoma prostatico metastatico

M+	Watchful waiting	No standard option. May have worse survival/more complications than with immediate hormonal therapy. Requires very close follow-up	B
	Radical prostatectomy	Not an option	C
	Radiotherapy	Not an option for curative intent; therapeutic option in combination with androgen deprivation for treatment of local cancer-derived symptoms	C
	Hormonal	Standard therapy. Mandatory in symptomatic patients	A

L'ormonoterapia rappresenta lo standard terapeutico per i pazienti affetti da carcinoma prostatico metastatico (Grado di Raccomandazione:A)

EAU Guidelines, 2012

Arriva abiraterone .



Abiraterone	797	728	631	475	204	25	0
Placebo	398	352	296	180	69	8	1

Situazione nel 2010

Situazione domattina

— Amici, mi accorgo ora che il tempo concessomi sta per finire...