Associazione Italiana Radioterapia Oncologica

Programmi terapeutici per la neoplasia prostatica: EBM e appropriatezza

Standard clinici della malattia in progressione

Stefano Pergolizzi

Padova, 8-11 Novembre 2014

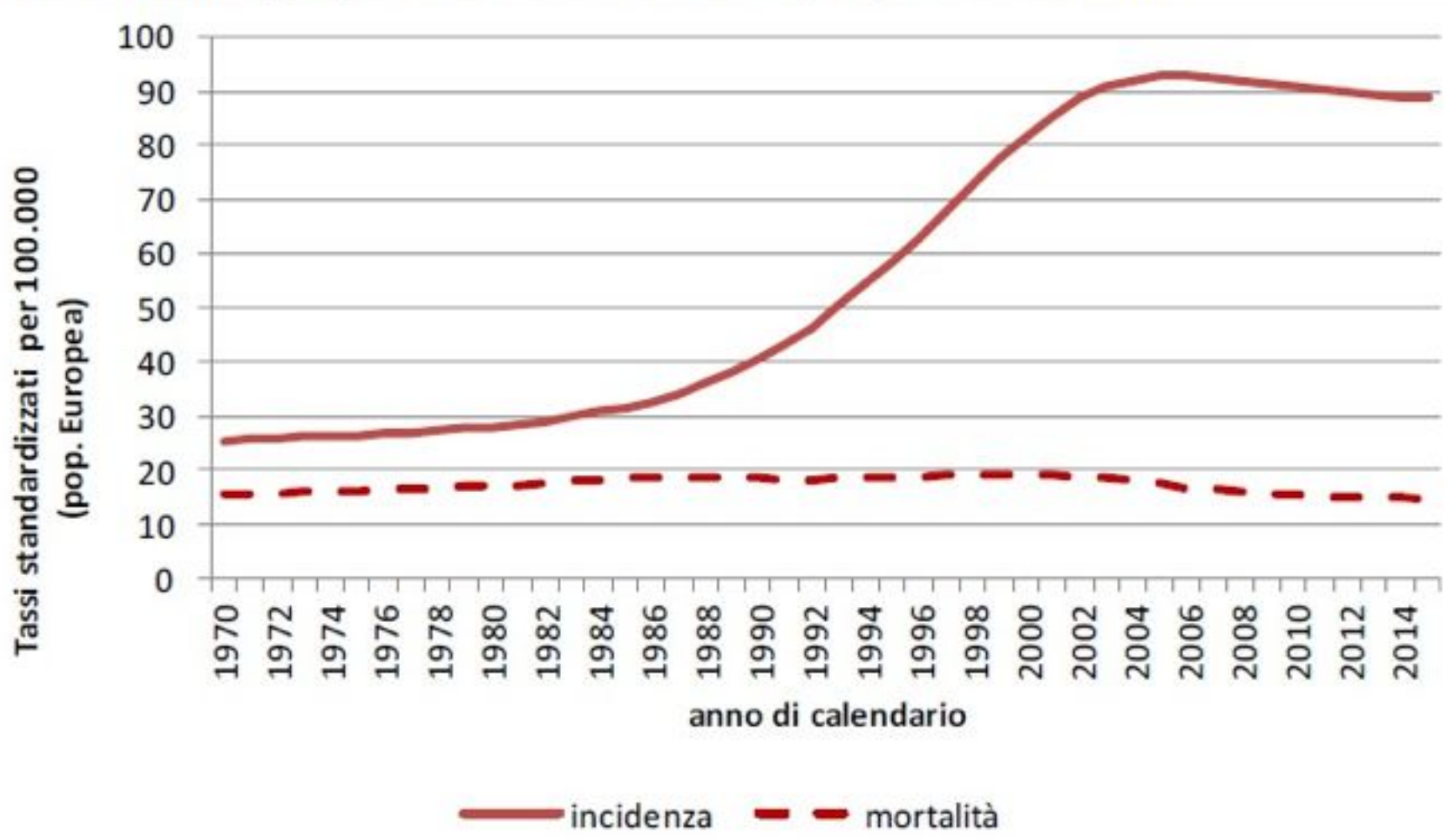
Progressione del carcinoma prostatico

Malattia localizzata

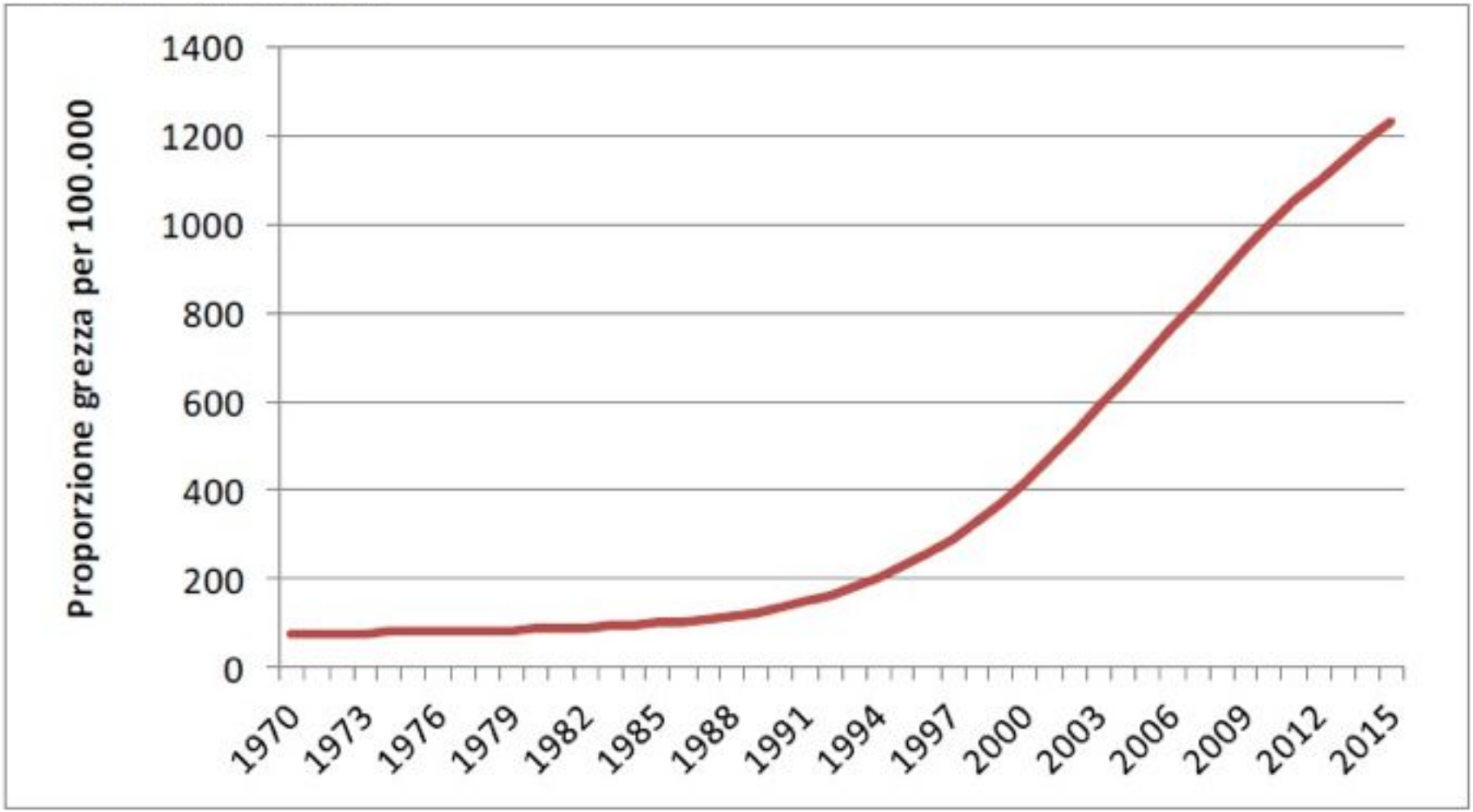
Solo incremento del PSA

Malattia metastatica

Morte


Tassi standardizzati per 100.000 (pop. Europea)
100
90
80
70
60
50
40
30
20
10
0
1970
1972
1974
1976
1978
1980
1982
1984
1986
1988
1990
1992
1994
1996
1998
2000
2002
2004
2006
2008
2010
2012
2014
anno di calendario
incidenza
mortalità


AIRO 2014



Prevalenza in Italia

Quadri clinici

A — Recidiva biochimica dopo chirurgia
Recidiva Locale dopo RT

B
- Recidiva Regionale
- Progressione “oligometastatica”

C — Progressione con metastasi plurime

D
- Progressione durante ADT
- Malattia resistente alla castrazione

Quadri clinici

Recidiva biochimica dopo chirurgia

Recidiva Locale dopo RT

rTX rN0 rM0

Definizione

Recidiva biochimica dopo chirurgia

PSA >0.2ng/ml (due incrementi consecutivi)

Stephenson AJ
JCO 2006

Recidiva locale dopo radioterapia

PSA 2ng/ml al di sopra del nadir postRT

Roach III M
IJROBP 2006

Recidiva biochimica dopo chirurgia

Terapia

PSA <0.5	Radioterapia sola DT 64-66Gy
PSA >0.5 PSA DT <12 mesi GS >8 pT3b	Radioterapia DT 64-66Gy + **ADT**

Heidenreich A Eur Urol 2014

Recidiva biochimica dopo chirurgia
Risultati a 6aa (BiR-FS)

PSA Val.	%
<0.5	48
>0.51 <1	40
>1.01 <1.5	28
>1.5	18

Stephenson A JCO 2007
Swanson GP SWOG 8794 JCO 2007

Recidiva locale dopo radioterapia

Terapia

Prostatectomia radicale

No comorbidità **Aspett.vita >10aa**

rT1-2 **GS ≤7** **PSA <10**

Criochirurgia **Se chirurgia non indicata**

HIFU **No standard**

RT Retreatment (EBRT-BrachiRT) **Standard ??**

ADT **nel 93% dei casi**

Recidiva locale dopo radioterapia
Risultati

Prostatectomia radicale

	5aa (%)	10aa (%)
BiR-FS	47-82	28-53
OS	70-83	54-89

Chade Eur Urol 2012

Criochirurgia

	5aa (%)
BiR-FS	21-50
OS	85

Eisenberg Urology 2008
Pisters J Urol 2008
Chade Eur Urol 2012

Quadri clinici

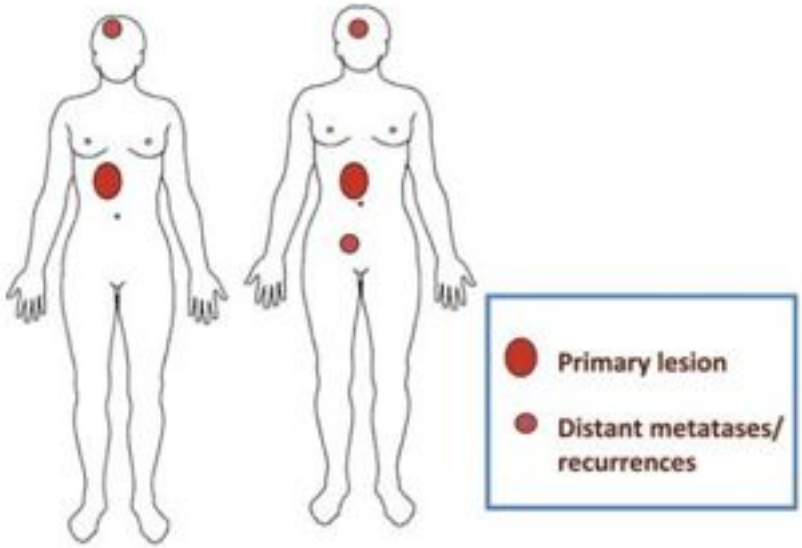
Recidiva Regionale

Oligorecidiva

Progressione “oligometastatica”

rT0 rN0-1 rM0-1a-b

Schema of oligometastases



Schema of oligo-recurrence

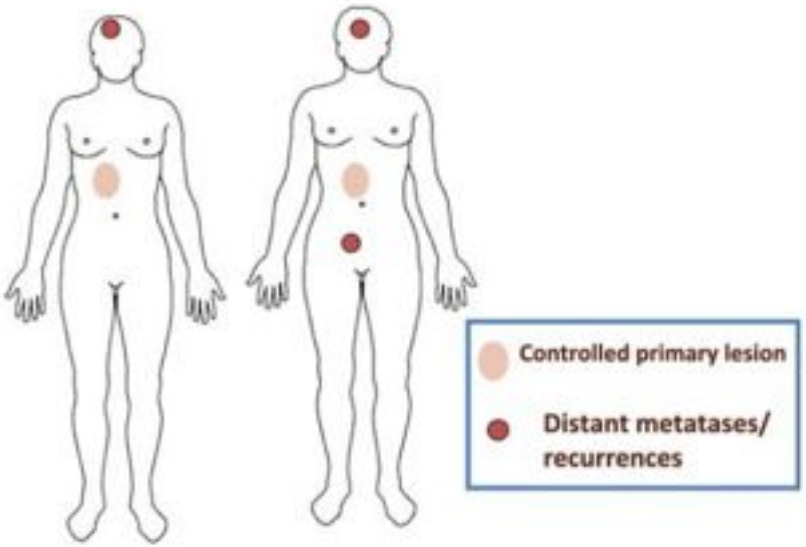


Table 1. Oligometastases and oligo-recurrence

	Oligometastases	Oligo-recurrence
Reference	Hellman and Weichselbaum (1)	Niibe et al. (2,3,4)
Primary lesion	Uncontrolled/controlled	Controlled
No. of distant/metastases/ recurrences	One to several	One to several (one is better)

Yuzuru Niibe* and Kazushige Hayakawa
Jpn J Clin Oncol 2010;40:107– 1110

Padova, 8-11 Novembre 2014

Malattia in stadio rIV ormono-sensibile

Deprivazione androgenica

↓

Analogo LH-RH +/- antiandrogeno non steroideo

standard attuale

American Society of Clinical Oncology practice guideline.
J Clin Oncol 25:1596-1605, 2007

Although no randomised trials are available comparing MDT with no treatment or other therapeutic options, these treatment options are routinely offered to patients based on the promising data of large registries and case series……

Treasure T, Milosevic M, Fiorentino F, Macbeth F. Pulmonary metastasectomy: what is the practice and where is the evidence for effectiveness? Thorax 2014;69:946–9.

Garden OJ, Rees M, Poston GJ, et al. Guidelines for resection of colorectal cancer liver metastases. Gut 2006;55(Suppl 3):iii1–8.

Recidiva Regionale

Oligorecidiva

Progressione “oligometastatica”

Terapia “diretta alle metastasi”

Chirurgia (rN1)

Radioterapia (rN1, rM1a-b)


ARTICLE IN PRESS

EUROPEAN UROLOGY XXX (2014) XXX–XXX

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

European Association of Urology

Platinum Priority – Review – Prostate Cancer

Metastasis-directed Therapy of Regional and Distant Recurrences After Curative Treatment of Prostate Cancer: A Systematic Review of the Literature

Piet Ost, Alberto Bossi, Karel Decaestecker, Gert De Meerleer, Gianluca Giannarini, R. Jeffrey Karnes, Mack Roach III, Alberto Briganti

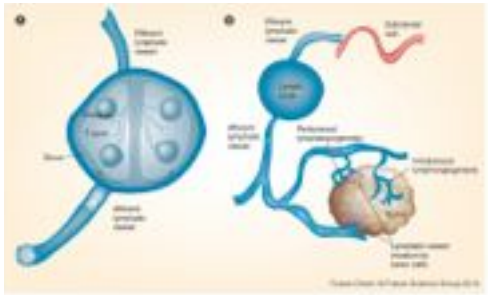
Recidiva Regionale
Chirurgia (rN1)

Fattori prognostici

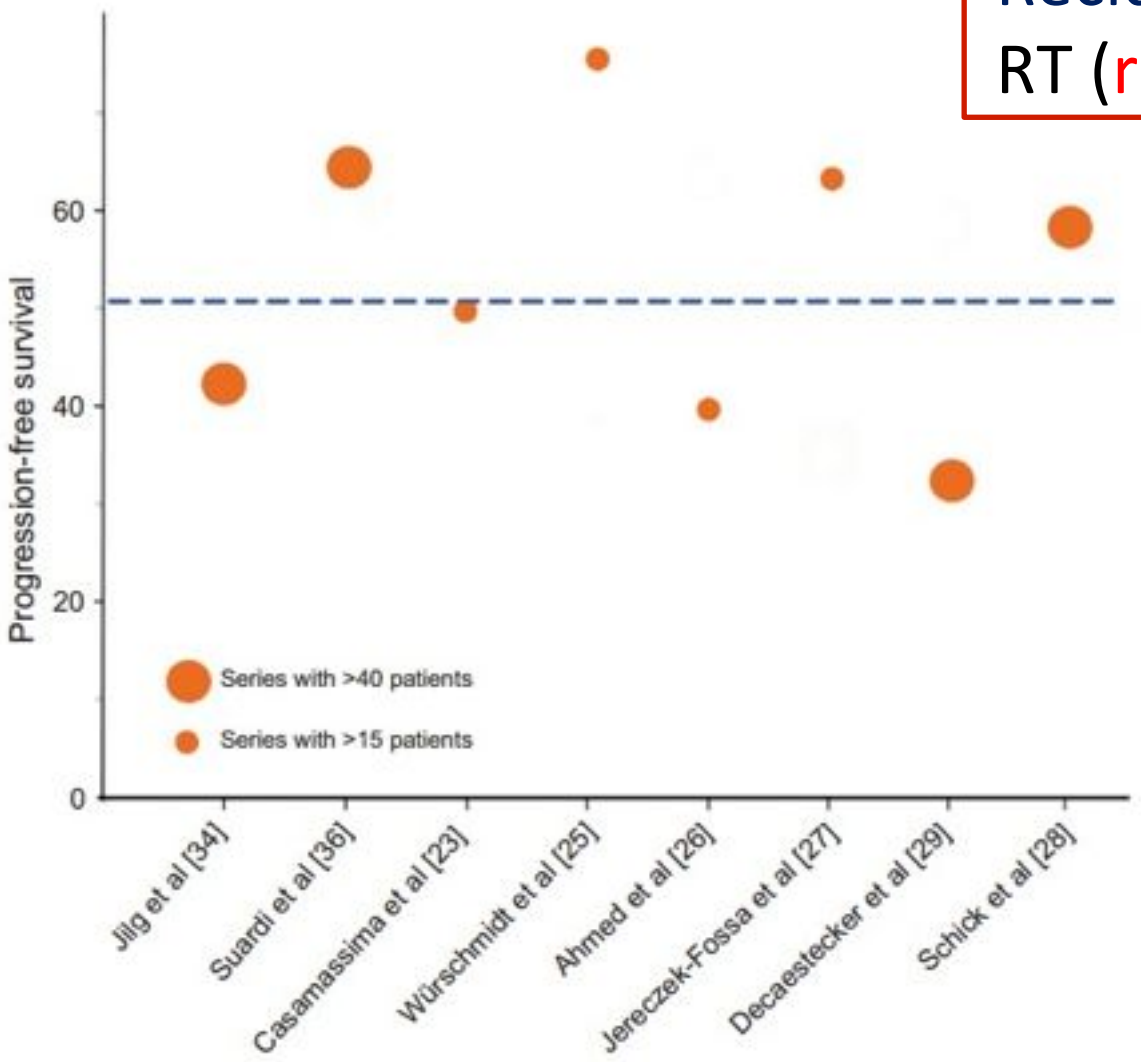
		PSA <2.1	GS <8
PFS	3aa	5aa	8aa
	43-64	52	38

Suardi N — Eur Urol. In press.
Jilg CA — J Urol 2012

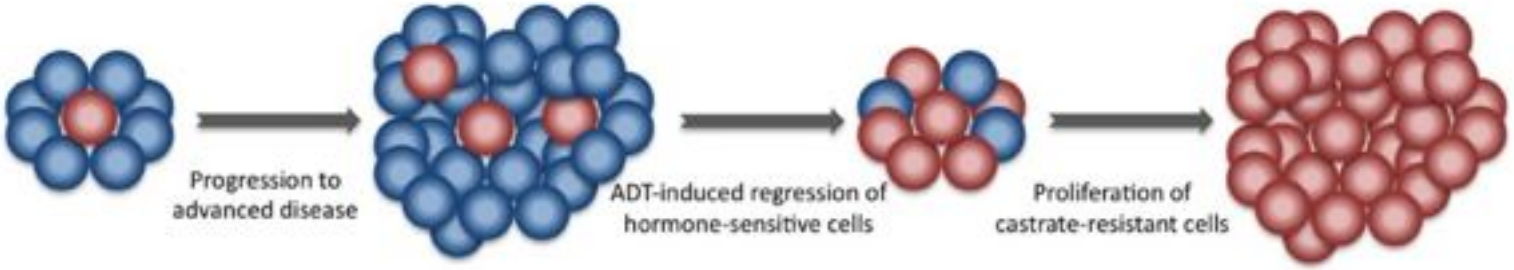
LND rPD alone in 47-59%

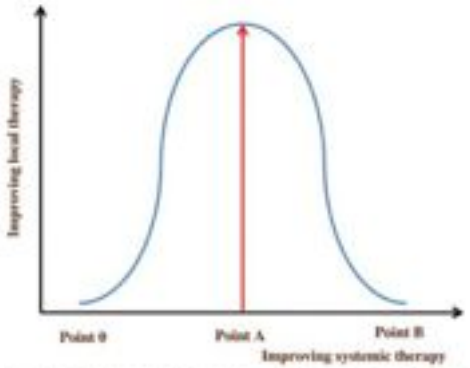


Recidiva IV stadio
RT (rN1-rM1a-b)



PFS at 1–3 yr of follow-up for studies with >15 pts.





frontiers in
ONCOLOGY

REVIEW ARTICLE

Rationale for stereotactic body radiation therapy in treating patients with oligometastatic hormone-naïve prostate cancer

*Onita Bhattasali[1], Leonard N. Chen[1], Michael Tong[1], Siyuan Lei[1], Brian T. Collins[1], Pranay Krishnan[2], Christopher Kalhorn[3], John H. Lynch[4], Simeng Suy[1], Anatoly Dritschilo[1], Nancy A. Dawson[5] and Sean P. Collins[1]**

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[4] Department of Urology, Georgetown University Hospital, Washington, DC, USA
[5] Department of Oncology, Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC, USA

Decaestecker et al. BMC Cancer 2014, 14:671
http://www.biomedcentral.com/1471-2407/14/671

BMC Cancer

STUDY PROTOCOL Open Access

Surveillance or metastasis-directed Therapy for OligoMetastatic Prostate cancer recurrence (STOMP): study protocol for a randomized phase II trial

Karel Decaestecker[1], Gert De Meerleer[2], Filip Ameye[3], Valerie Fonteyne[2], Bieke Lambert[4], Steven Joniau[5], Louke Delrue[6], Ignace Billiet[7], Wim Duthoy[8], Sarah Junius[9], Wouter Huysse[6], Nicolaas Lumen[1] and Piet Ost[2*]

Padova, 8-11 Novembre 2014

Quadri clinici

Progressione con metastasi plurime

Sintomatico

Asintomatico

rTX rNX rM1c

VOLUME 23 · NUMBER 13 · MAY 1 2005

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

Men with prostate cancer, no bone metastases, and rising PSA despite androgen deprivation therapy have a relatively indolent natural history

Only one third of men developed bone metastases at 2 years, and the median metastasis-free survival was approximately 30 months.

Baseline PSA and PSA velocity independently predicted time to first bone metastasis, overall survival, and bone metastasis–free survival.

Malattia resistente alla castrazione

Definizione

-Testosteronemia < 50ng/ml o < 1.7 nmol/l

-3 incrementi consecutivi PSA (a distanza 1 settimana)
2 incrementi del 50% oltre nadir con PSA >2

-Terapia androgeno-deprivativa è stata convertita in BAT;

-La monoterapia con antiandrogeno puro è stata convertita in BAT;

-BAT già convertito con stop antiandrogeno

- Ulteriore PD OSS o LYM o OTH

TABLE 1. Timeline of Drug Approvals in Prostate Cancer

Agent	Indication for New Agent	FDA Approval
Leuprolide acetate	Palliative treatment of advanced prostate cancer	4/9/1985*
Strontium-89	Painful skeletal metastases	6/18/1993
Samarium-153	Relief of pain in patients with confirmed osteoblastic metastatic bone lesions	3/28/1997
Zoledronic acid	Treatment of osteolytic, osteoblastic, and mixed bone metastases of solid tumors in conjunction with standard antineoplastic therapy	2/25/2002
Docetaxel[46]	mCRPC	5/19/2004
Degarelix	Advanced prostate cancer	12/24/2008
Sipuleucel-T[5]	Asymptomatic or minimally symptomatic mCRPC	4/29/2010
Cabazitaxel[3]	mCRPC post-docetaxel	6/17/2010
Denosumab[4]	Prevention of SREs in patients with bone metastases	11/18/2010
	Patients at high risk of fracture from receiving ADT for non-metastatic prostate cancer	9/19/2011
Abiraterone acetate[2,7]	mCRPC post-docetaxel	4/28/2011
	Therapy-naive CRPC	12/10/2012
Enzalutamide[8]	mCRPC post-docetaxel	8/31/2012
Radium-223 Dichloride[6]	CRPC with symptomatic bone metastases and no known visceral metastatic disease	5/15/2013

Table 1 | Prostate-specific antigen response rate of new chemotherapeutic agents for metastatic CRPC.

Trial	Treatment group	Drug class	Mechanism of action	Control group	Treatment group response rate (%)	Control group response rate (%)	*P*-value
TAX 327	Docetaxel + prednisone	Taxoid	Microtubule disassembly inhibitor	Mitoxantrone + prednisone	45	32	<0.001
TROPIC	Cabazitaxel + prednisone	Taxoid	Microtubule disassembly inhibitor	Mitoxantrone + prednisone	39.2	17.8	=0.0002
COU-AA301	Abiraterone + prednisone	Hormonal agent	Cytochrome P4S0 17A1 inhibitor	Placebo + prednisone	29	6	<0.001
AFFIRM	En2alutamide	Hormonal agent	Androgen receptor antagonist	Placebo	54	2	<0.001
IMPACT	Sipuleucel-T	Cancer vaccine	PA2024 activated peripheral-blood mononuclear cells	Placebo	2.6	1.3	Not significant
ALSYMPCA	Radium-223	Radio pharmaceutical	Bone-targeted alpha radiation	Placebo	16	6	<0.001

Phase III COU-AA-301 Study
1195 pts

- mCRPC
- PD dopo docetaxel
- PSA progression

R

Abiraterone + Prednisone

(n = 797)

Placebo + Prednisone

(n = 398)0

OS Mediana: 15.8 vs 11.2 months

Fizazi K et al. *Lancet Oncol* 2012;13(10):

Phase III TAX-327 Study of Docetaxel
1006 pts

- **Pazienti con mCRPC**
- **PSA in aumento**

R

Docetaxel ogni 3 wk
+ Prednisone

Docetaxel settimanale
+ Prednisone

Mitoxantrone
+ Prednisone

OS Mediana: 19.2 vs 17.8 vs 16.3 mesi

50% decremento PSA: 45% vs 48% vs 32%

Riduzione dolore: 35% vs 31% vs 22%

Miglioramento QoL: 22% vs 23% vs 13%

Berthold DR et al. *J Clin Oncol* 2008
Tannock IF et al. *N Eng J Med*

Phase III TROPIC Study of Cabazitaxel
755 pts

Pazienti in PD durante o dopo terapia con docetaxel

R

Cabazitaxel + Prednisone (n = 378)

Mitoxantrone + Prednisone (n = 377)

OS Mediana: 15.1 vs 12.7 mesi

PFS mediana: 2.8 vs 1.4 mesi

Tossicità Grado 3 aumentata con cabazitaxel: neutropenia, diarrea

www.clinicaltrials.gov; April 2013 (NCT00417079)
De Bono JS et al. *Lancet* 2010;376(9747):1147-1154.

EUROPEAN UROLOGY 65 (2014) 467–479

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

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European Association of Urology

Guidelines

EAU Guidelines on Prostate Cancer. Part II: Treatment of Advanced, Relapsing, and Castration-Resistant Prostate Cancer

Axel Heidenreich[a,], Patrick J. Bastian[b], Joaquim Bellmunt[c], Michel Bolla[d], Steven Joniau[e], Theodor van der Kwast[f], Malcolm Mason[g], Vsevolod Matveev[h], Thomas Wiegel[i], Filiberto Zattoni[j], Nicolas Mottet[k,l]*

Currently, **there is lack of evidence on a specific sequence of therapy**.

…..physicians should adhere to the inclusion criteria of the various clinical trials when treating **real-world patients** with CRPC.

Furthermore, the EAU guideline panel on PCa believes that **any patient with Pca and especially CRPC is on a clinical trial**

Table 5 – Recommendations for medical therapy in castration-resistant prostate cancer

Recommendations	GR
• Ideally, patients with CRPC should be counselled, managed, and treated in a multidisciplinary team.	B
• In nonmetastatic CRPC, cytotoxic therapy should only be considered in clinical trials.	B
• In patients with a rise in PSA only, two consecutive increases of PSA serum levels above a previous reference level should be documented.	B
• Prior to treatment, PSA serum levels should be >2 ng/ml to assure correct interpretation of therapeutic efficacy.	B
• Abiraterone/prednisone should be considered in CRPC patients with asymptomatic or mildly symptomatic metastases and a low metastatic burden due to its survival benefit.	A
• In patients with metastatic CRPC and who are candidates for cytotoxic therapy, docetaxel 75 mg/m^2 every 3 wk has shown a significant survival benefit.	A
• Abiraterone/prednisone should be considered in CRPC patients who received prior docetaxel treatment as an effective second-line treatment option due to its benefit in overall survival and radiographic progression-free survival and QoL.	A
• Enzalutamide should be considered in CRPC patients as an effective second-line treatment due to its benefit in overall survival and radiographic progression-free survival and QoL.	B
• Cabazitaxel should be considered as effective second-line treatment following docetaxel.	A
• Second-line docetaxel may be considered in previously responding patients to docetaxel. Otherwise, treatment is tailored to the individual patient.	C
• Radium-223 should be considered in CRPC patients with osseous metastases due to its benefit in overall survival, QoL, and pain.	A

CRPC = castration-resistant prostate cancer; GR = grade of recommendation; PSA = prostate-specific antigen; QoL = quality of life.

Guidelines

EAU Guidelines on Prostate Cancer. Part II: Treatment of Advanced, Relapsing, and Castration-Resistant Prostate Cancer

Axel Heidenreich[a,], Patrick J. Bastian[b], Joaquim Bellmunt[c], Michel Bolla[d], Steven Joniau[e], Theodor van der Kwast[f], Malcolm Mason[g], Vsevolod Matveev[h], Thomas Wiegel[i], Filiberto Zattoni[j], Nicolas Mottet[k,*]*

Padova, 8-11 Novembre 2014

Nella malattia prostatica in progressione la radioterapia

ha ruolo in **TUTTI** i quadri clinici

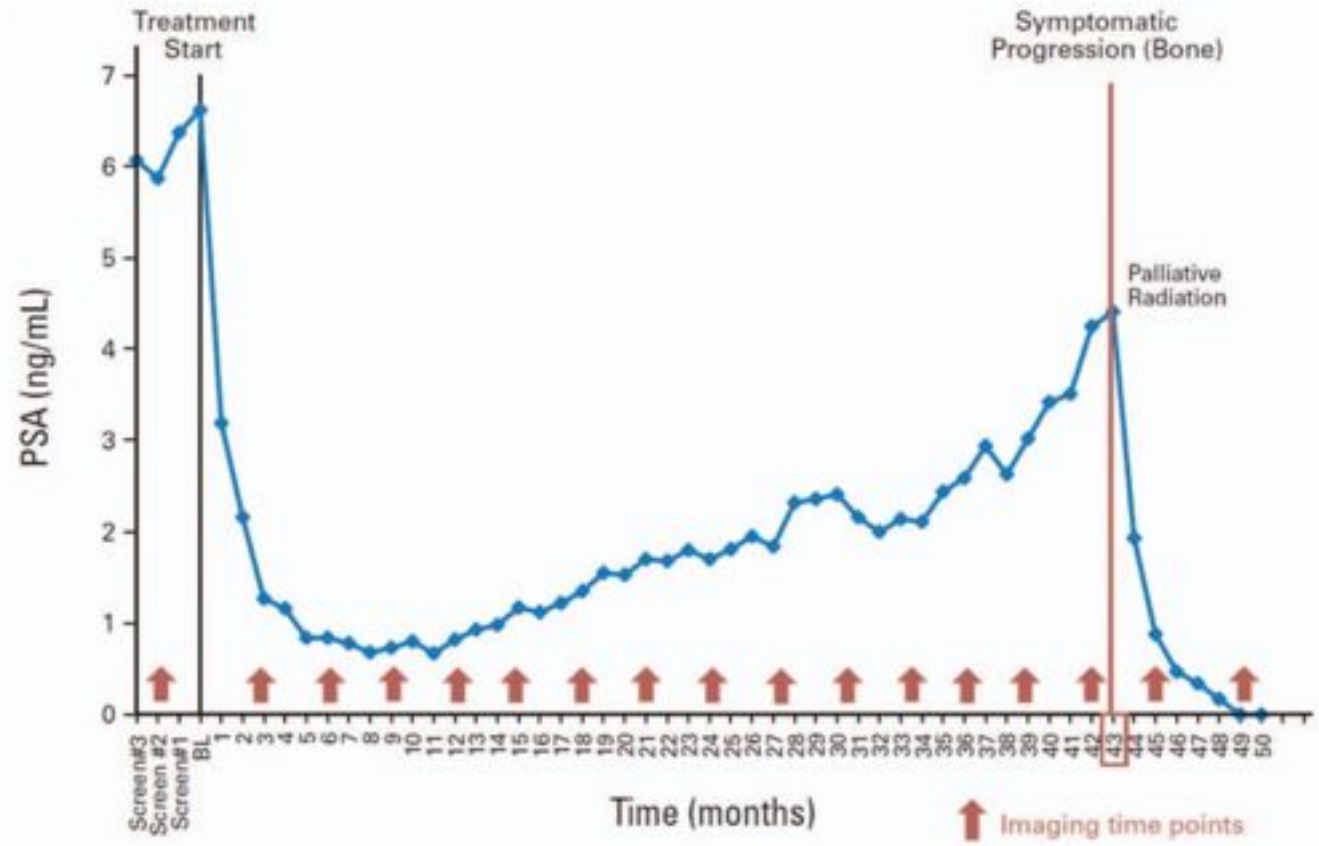

FIG 4. PSA drift: A slow rise in PSA after an initial rapid decline with no evidence of radiographic or clinical progression for 28 months while receiving abiraterone acetate plus prednisone. From Scher HI, et al. *J Clin Oncol.* 2011;29:3695-3704.