



OLIGOMETASTASI ED OLIGOPROGRESSIONE: TRATTAMENTI ABLATIVI E NUOVI FARMACI NEL TRATTAMENTO DEL TUMORE PRIMITIVO E DELLA MALATTIA OLIGOMETASTATICA“



S. Arcangeli
S.Camillo-Forlanini
Dir. Prof. V. Donato





XXVI CONGRESSO NAZIONALE AIRO
XXX CONGRESSO NAZIONALE AIRB
IX CONGRESSO NAZIONALE AIRO GIOVANI



DICHIARAZIONE

Relatore: Stefano Arcangeli

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 **NIENTE DA DICHIARARE**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**
- Partecipazione ad Advisory Board **NIENTE DA DICHIARARE**
- Titolarità 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**

PERSPECTIVES

OPINION

Local treatment of metastatic cancer —killing the seed or disturbing the soil?

Scott C. Morgan and Chris C. Parker

Nat. Rev. Clin. Oncol. **8**, 504–506 (2011);

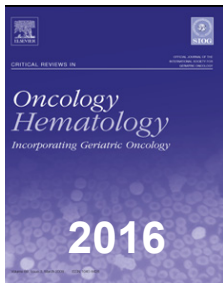


Società Italiana di Radioterapia
MATERIALE NON RIPRODUCIBILE



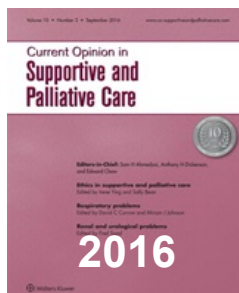
Treatment of the Primary Tumor in Metastatic Prostate Cancer: Current Concepts and Future Perspectives

Christopher E. Bayne^a, Stephen B. Williams^b, Matthew R. Cooperberg^c, Martin E. Gleave^d, Markus Graefen^e, Francesco Montorsi^f, Giacomo Novara^g, Marc C. Smaldone^h, Prasanna Sooriakumaran^{ij}, Peter N. Wiklundⁱ, Brian F. Chapin^{b,*}



“Hit the primary”: A paradigm shift in the treatment of metastatic prostate cancer?

Stefano Arcangeli^{a,*}, Thomas Zilli^b, Berardino De Bari^{c,1}, Filippo Alongi^{d,1}



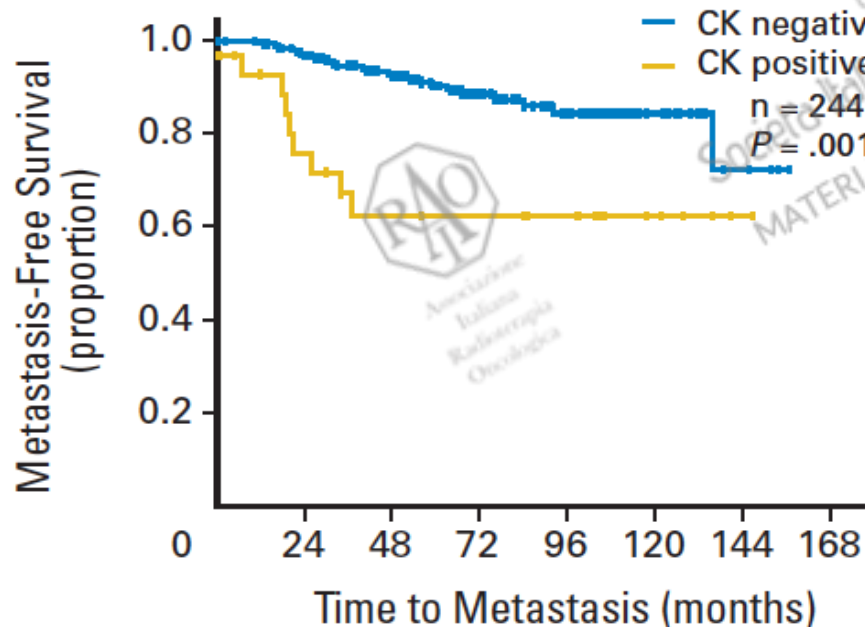
Rationale for local treatment in the management of metastatic prostate cancer

Giorgio Gandaglia^{a,b,c}, Nicola Fossati^{a,b,c}, Paolo Dell'Oglio^{a,b}, Marco Moschini^{a,b}, Vito Cucchiara^d, Nazareno Suardi^{a,b}, Alexandre Mottrie^c, Vincenzo Mirone^d, Francesco Montorsi^{a,b}, and Alberto Briganti^{a,b}

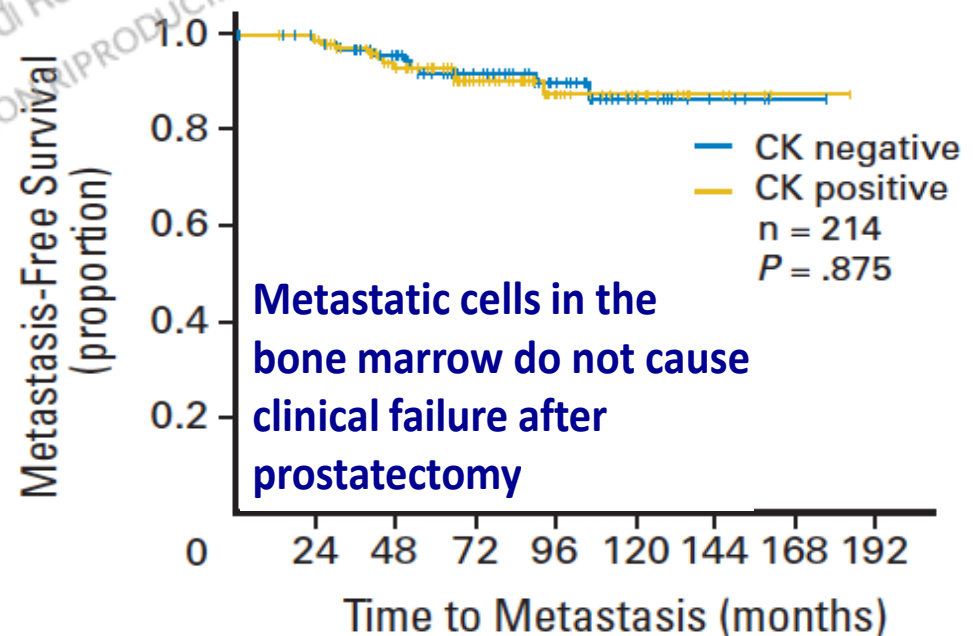
Perioperative activation of disseminated tumour cells in bone marrow of patients with prostate cancer

Dorothea Weckermann, Bernhard Polzer, Thomas Ragg, Andreas Blana, Günter Schlimok, Hans Arnholdt, Simone Bertz, Rolf Harzmann, Cristoph A. Klein

Pre-op bone marrow



Post-op bone marrow



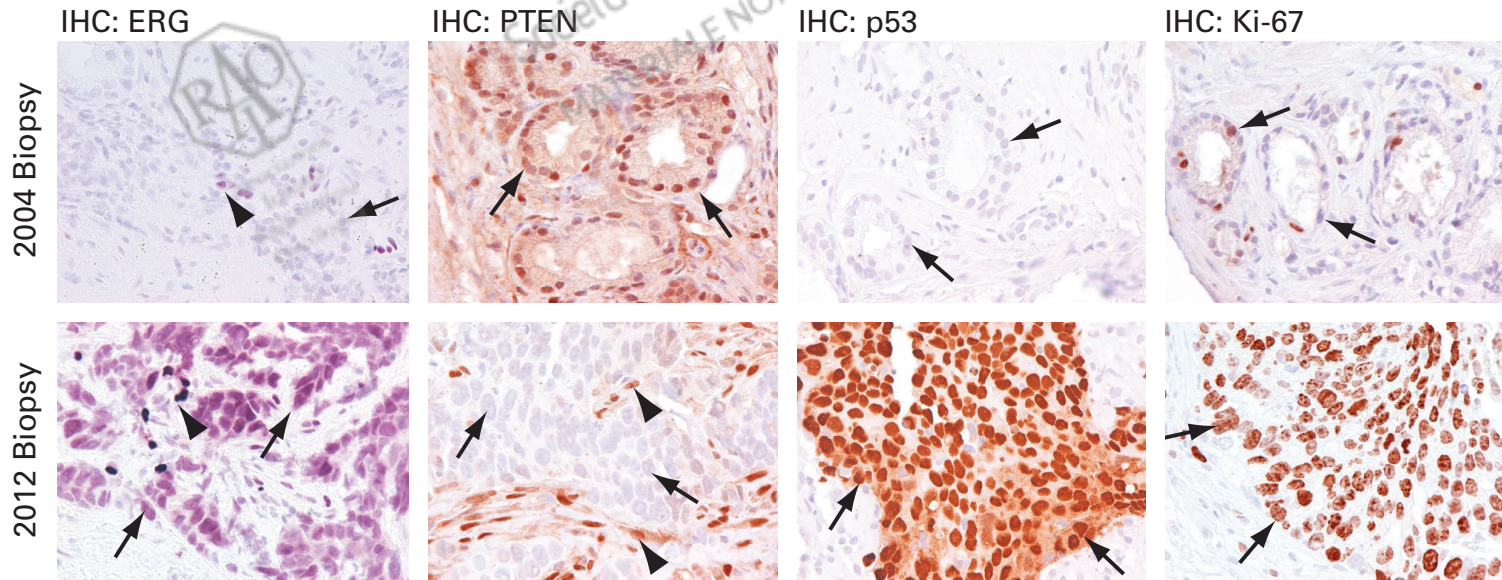
Diagnostic Challenges of Clonal Heterogeneity in Prostate Cancer

Haffner et al. JCO 2015

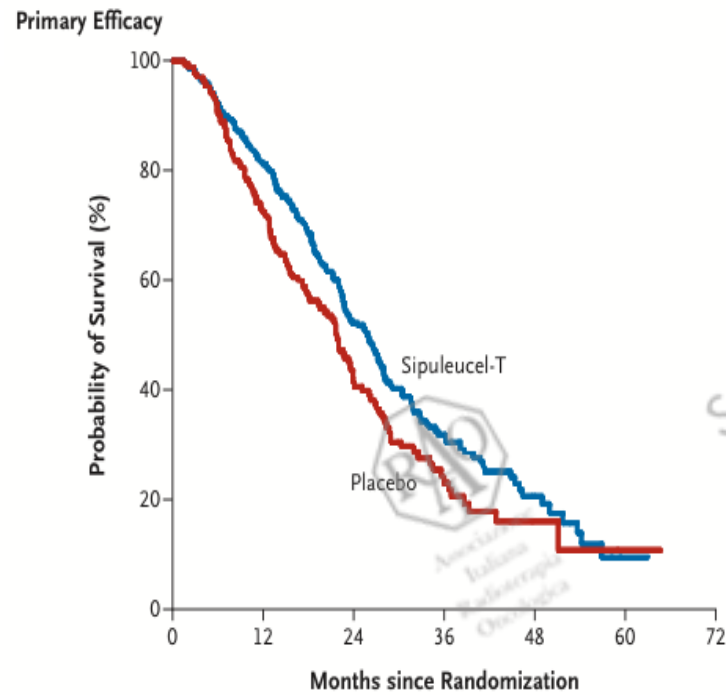
ADT selects castrate resistant clones in the primary tumour, which then drive disease

Biopsy	PTEN	ERG	p53	Ki-67
1997	Positive	Negative	Negative	< 10%
2003	Positive	Negative	Negative	< 10%
2004	Positive	Negative	Negative	< 10%
2006	Positive	Negative	Negative	< 10%
2007	Positive	Negative	Negative	< 10%
2012	Negative	Positive	Positive	> 75%

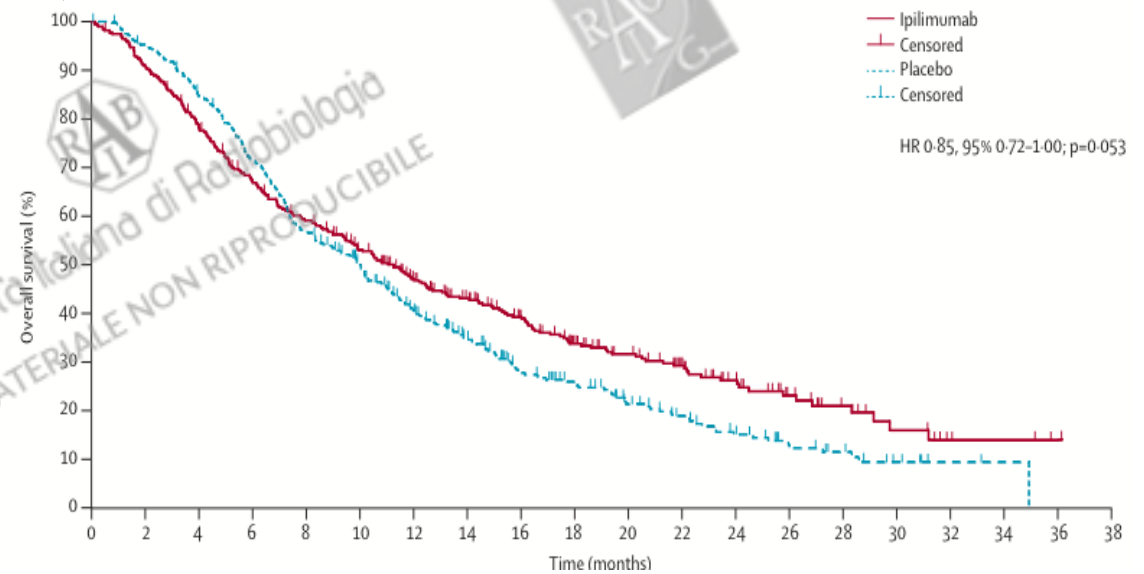
Positive
Negative



Primary tumour acts as immunological 'sink' – without primary tumour, immune system can more effectively destroy metastases

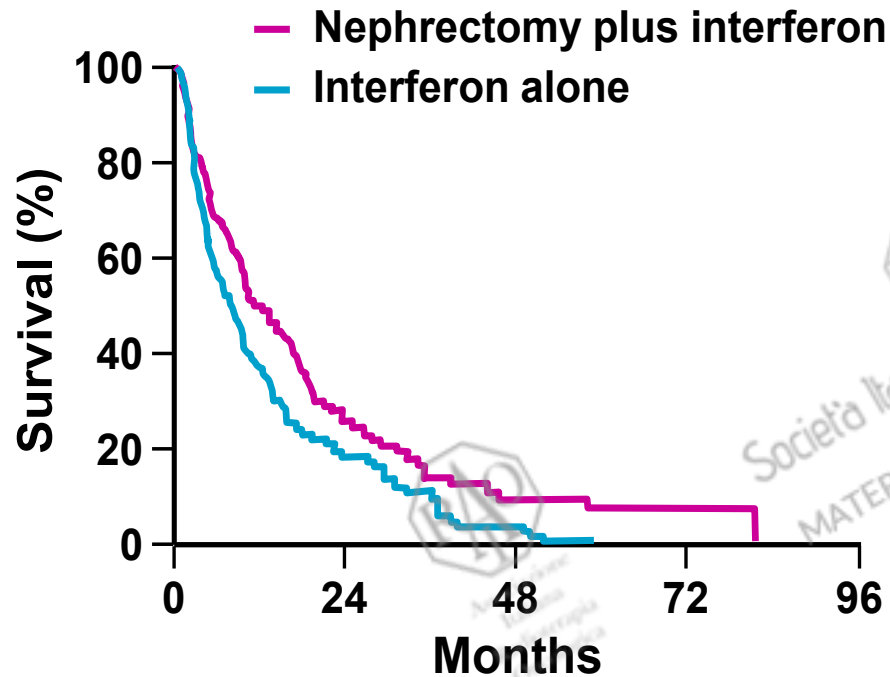


Kantoff PM *et al. NEJM* 2010;363:411

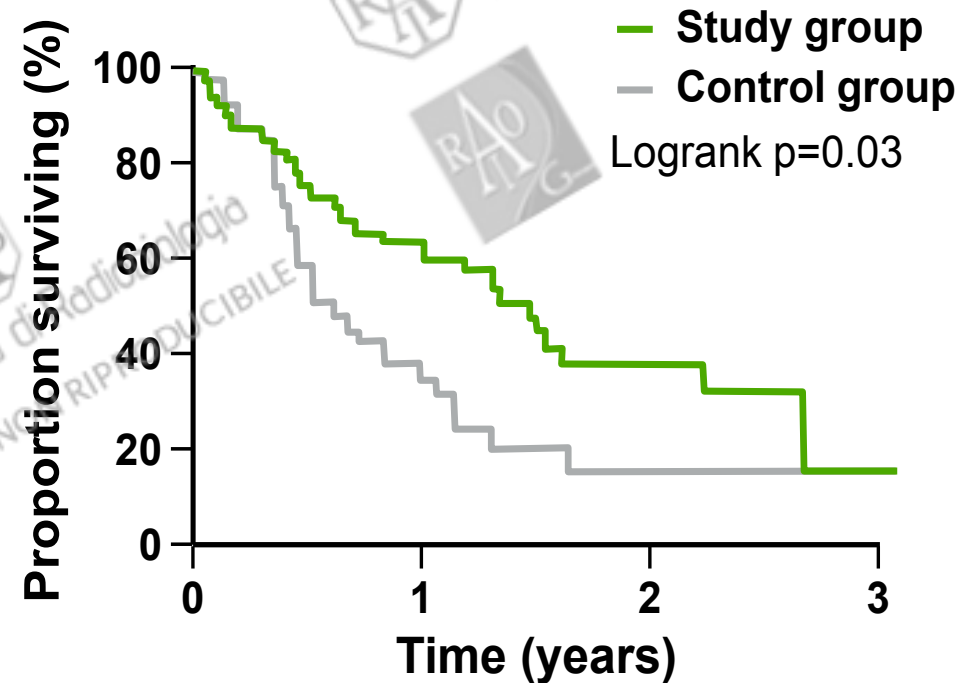


Kwon ED *et al. Lancet Oncol* 2014;15:700

Cytoreductive nephrectomy improves survival in metastatic renal cancer



SWOG 8949¹



EORTC 30947²

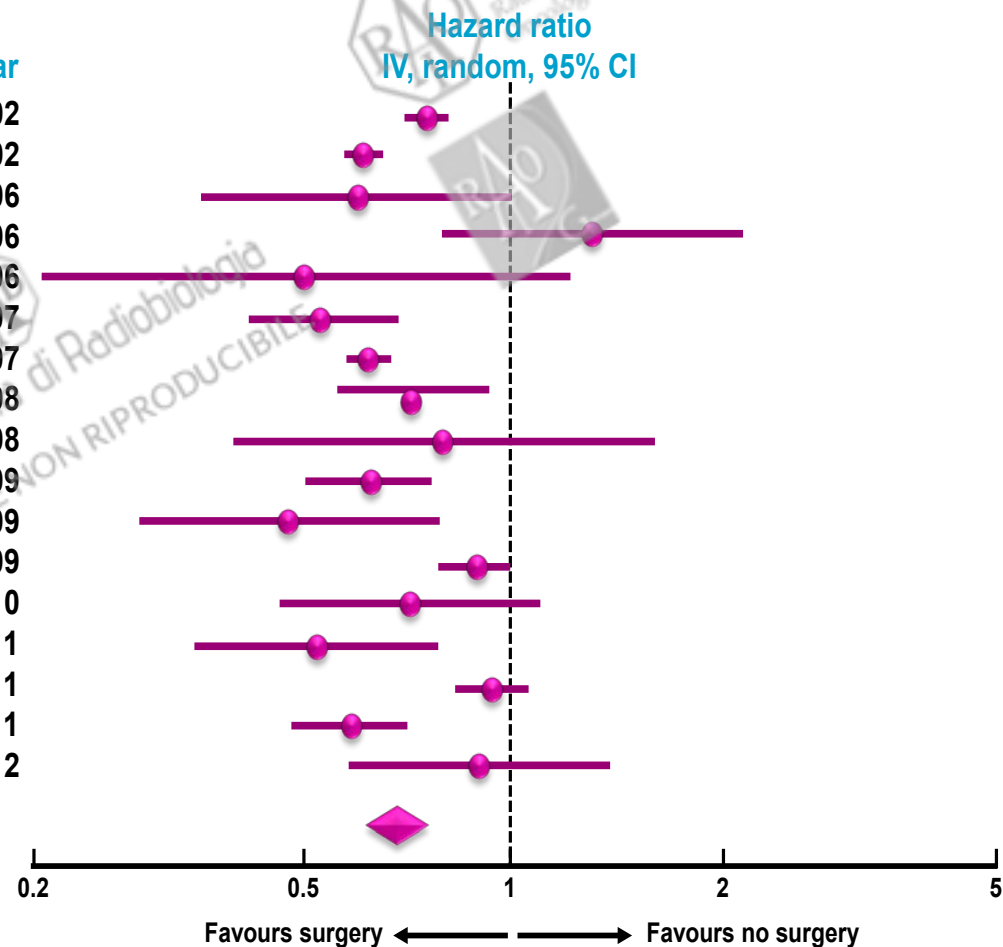
Adapted from: 1. Flanigan RC *et al. NEJM* 2001;345(23):1655-9.
2. Mickisch GH *et al. Lancet* 2001;358(9286):966-70.

Resection of the intact primary tumor in women with Stage IV breast cancer is associated with longer survival

Study or subgroup	Log (hazard ratio)	SE	Weight	Hazard ratio IV, random, 95% CI	Year
-Khan 2002 R1	-0.286	0.028	10.1%	0.75 [0.71, 0.79]	2002
Khan 2002 R0	-0.491	0.027	10.1%	0.61 [0.58, 0.65]	2002
Rapiti 2006 R0	-0.511	0.261	2.8%	0.60 [0.36, 1.00]	2006
Rapiti 2006 R1	0.262	0.246	3.1%	1.30 [0.80, 2.10]	2006
Babiera 2006	-0.693	0.443	1.2%	0.50 [0.21, 1.19]	2006
Fields 2007	-0.635	0.119	6.7%	0.53 [0.42, 0.67]	2007
Gnerlich 2007	-0.478	0.032	10.0%	0.62 [0.58, 0.66]	2007
Blanchard 2008	-0.342	0.125	6.4%	0.71 [0.56, 0.91]	2008
Hazard 2008	-0.226	0.354	1.8%	0.80 [0.40, 1.60]	2008
Ruiterkamp 2009	-0.478	0.102	7.4%	0.62 [0.51, 0.76]	2009
Bafford 2009	-0.75	0.25	3.0%	0.47 [0.29, 0.77]	2009
Shien 2009	-0.117	0.06	9.1%	0.89 [0.79, 1.00]	2009
Neuman 2010	-0.342	0.217	3.7%	0.71 [0.46, 1.09]	2010
Perez-Fidalgo 2011	0.654	0.202	4.0%	0.52 [0.35, 0.77]	2011
Dominici 2011	-0.062	0.057	9.2%	0.94 [0.84, 1.05]	2011
Booh Pathy 2011	-0.545	0.093	7.8%	0.58 [0.48, 0.70]	2011
Rashaan 2012	-0.105	0.216	3.7%	0.90 [0.59, 1.37]	2012
Total (95% CI)			100.0%	0.69 [0.63, 0.77]	

Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 110.08$, $df = 16$ ($P < 0.00001$); $I^2 = 85\%$
 Test for overall effect: $Z = 7.15$ ($P < 0.00001$)

Overall hazard ratio: 0.69 (95% CI 0.63, 0.77)



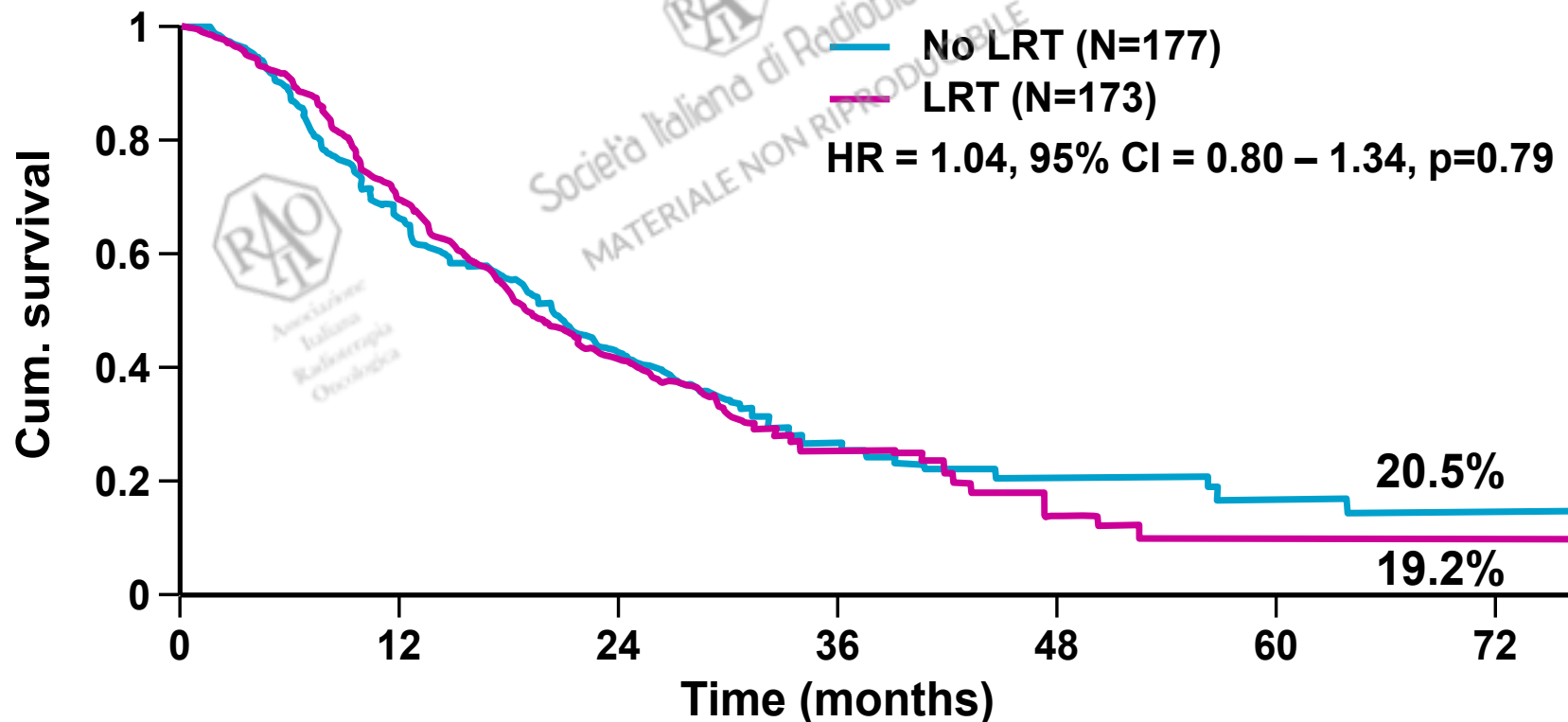
Adapted from: Petrelli F., & Barni S. *Medical Oncology* 2012, 29 (5):3282-90



Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial

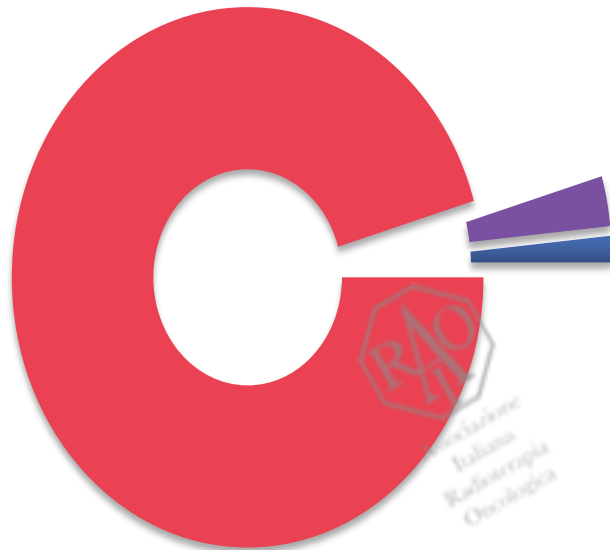
Rajendra Badwe, Rohini Hawaldar, Nita Nair, Rucho Kaushik, Vani Parmar, Shabina Siddique, Ashwini Budrukhar, Indraneel Mitra, Sudeep Gupta

Overall survival



Might men diagnosed with metastatic prostate cancer benefit from definitive treatment of the primary tumour? A SEER-based study

Stage IV CaP: SEER database (2004–2010)



- No surgery or radiotherapy - 7811 men
- Prostatectomy - 245 men
- Brachytherapy - 129 men

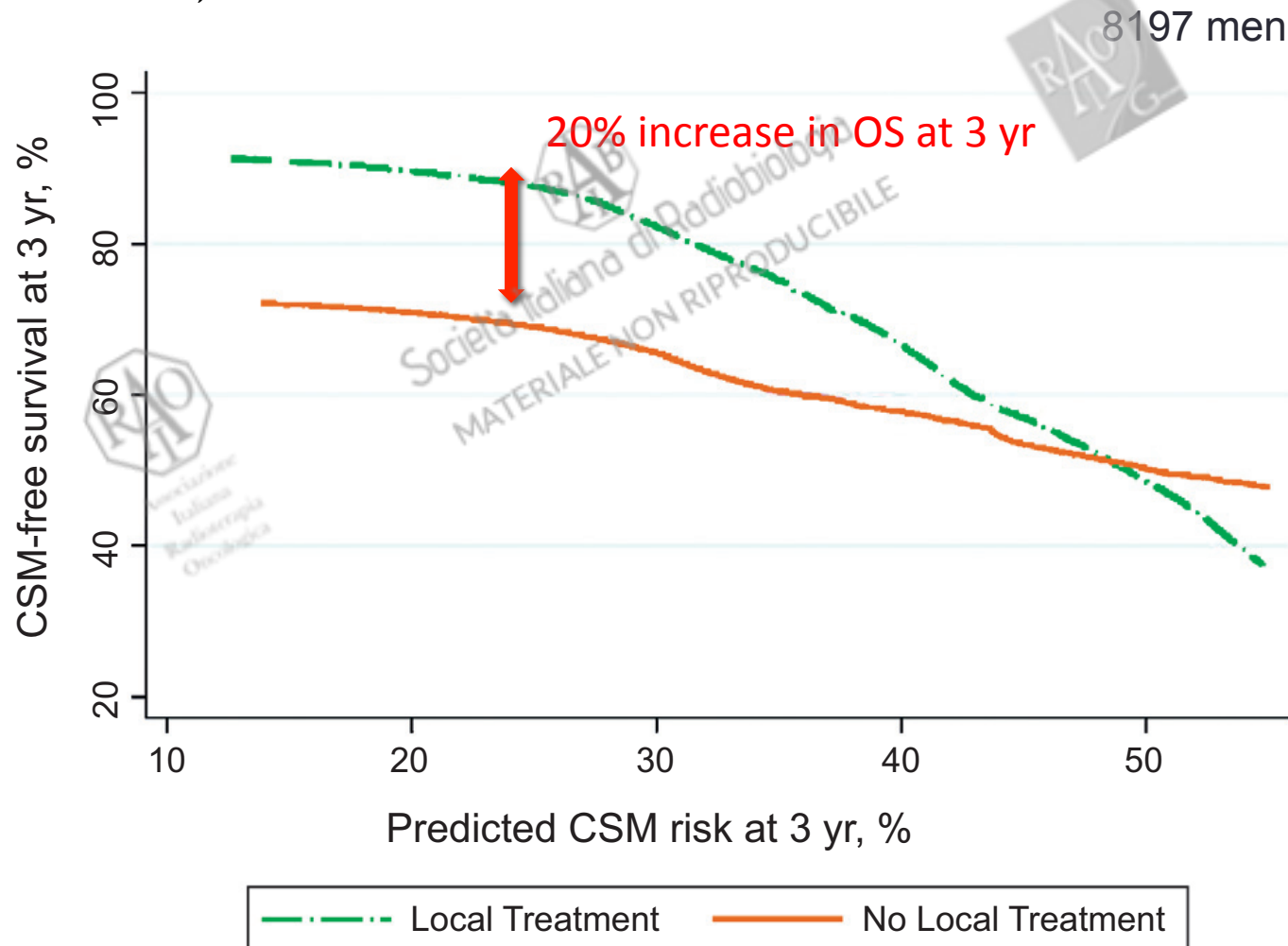
	5-year overall survival (%)	5-year disease-specific survival (%)
No surgery/ radiotherapy	22.5	48.7
Prostatectomy	67.4	75.8
Brachytherapy	52.6	61.3

No difference between groups in patients dying of non-CaP causes

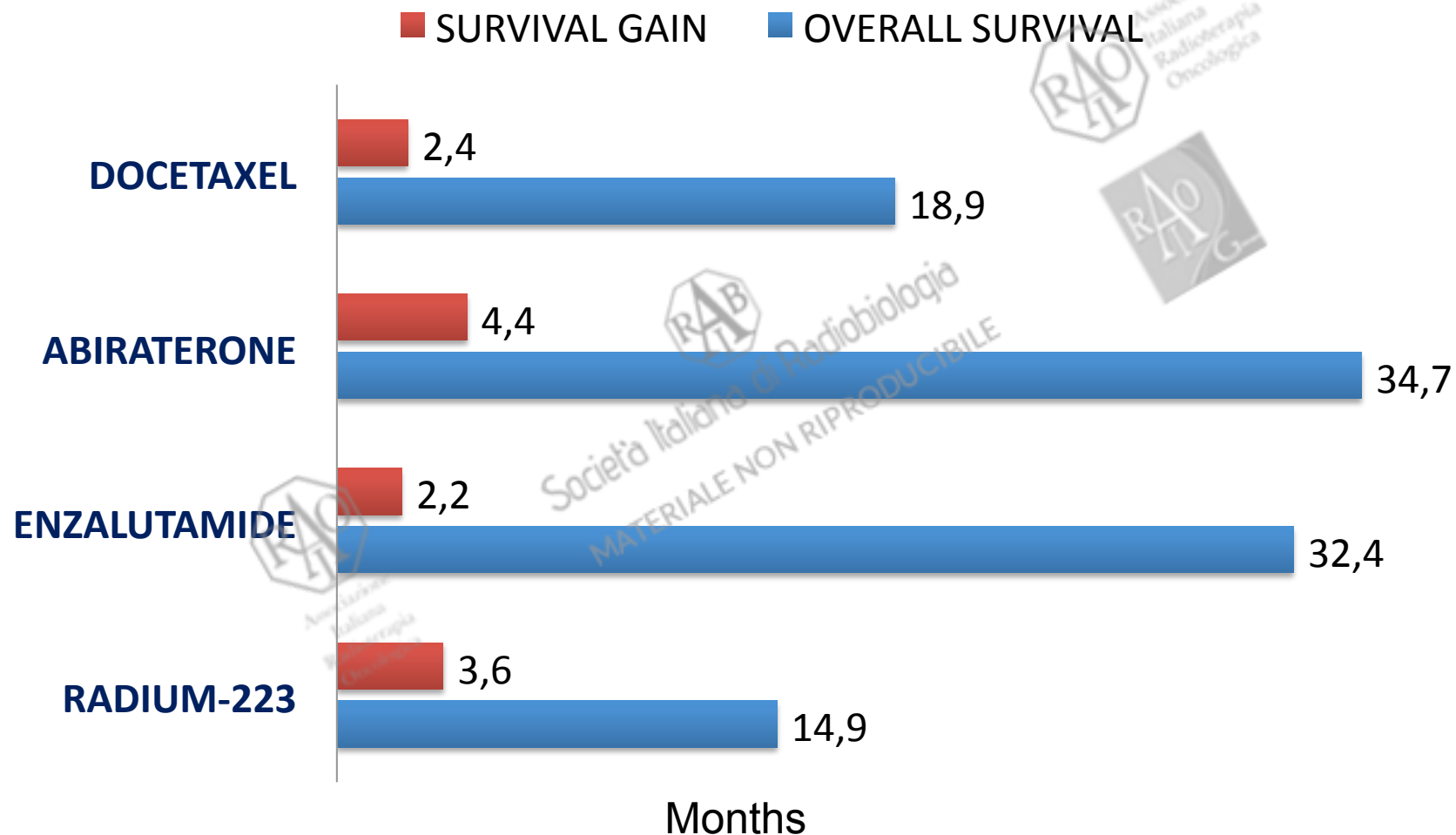


Identifying Optimal Candidates for Local Treatment of the Primary Tumor Among Patients Diagnosed with Metastatic Prostate Cancer: A SEER-based Study

Nicola Fossati^{a,b}, Quoc-Dien Trinh^c, Jesse Sammon^d, Akshay Sood^d, Alessandro Larcher^{b,e}, Maxine Sun^e, Pierre Karakiewicz^e, Giorgio Guazzoni^b, Francesco Montorsi^b, Alberto Briganti^b, Mani Menon^d, Firas Abdollah^{d,*}



Therapeutic Options that improve survival



¹Tannock et al. N Engl J Med. 2004

²Kantoff et al. N Engl J Med. 2010

³Ryan C et al. Lancet Oncology 2015

⁴Beer et al. N Engl J Med 2014

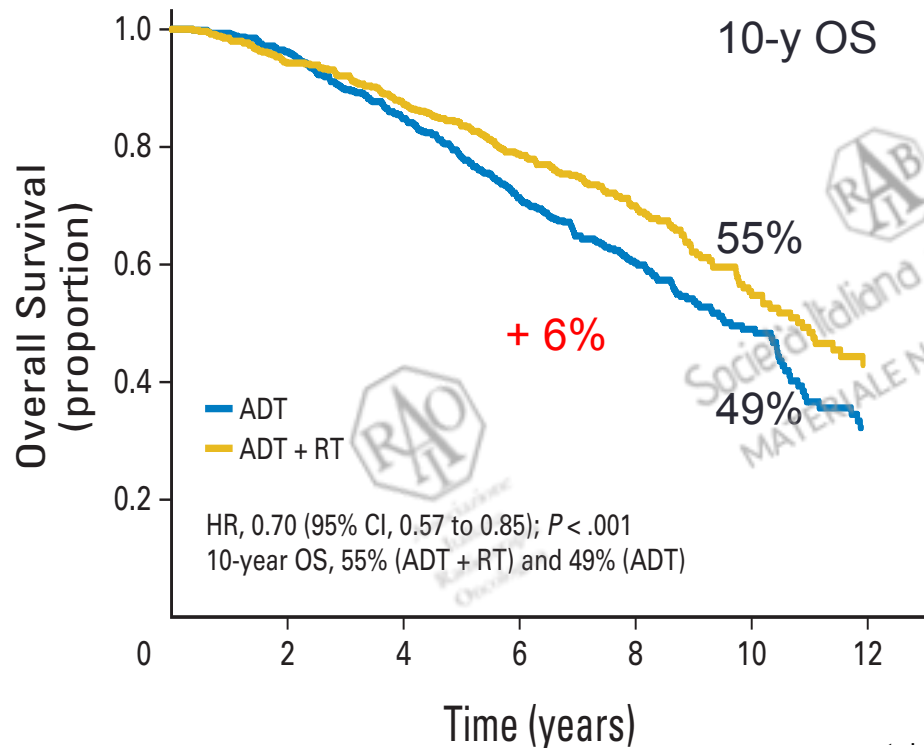
⁵Parker et al. N Engl J Med. 2013

Radiation therapy to the primary tumor in locally advanced prostate cancer is not “closing the barn door after the horse has bolted”

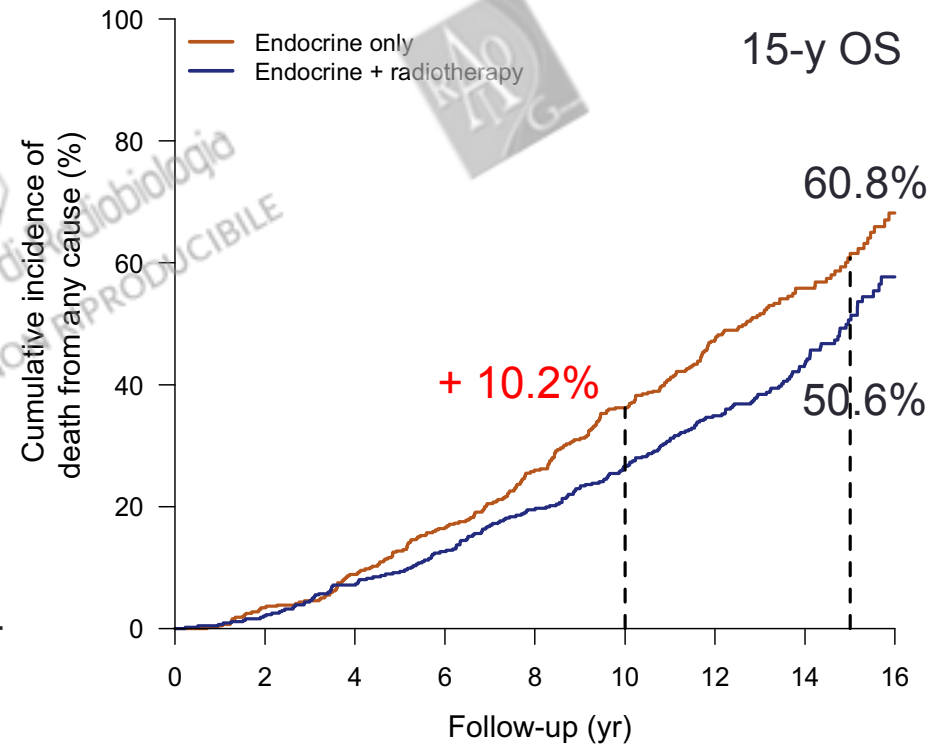
Nicholas G. Zaorsky¹, Mark A. Hallman¹, Marc C. Smaldone²



Prostate RT improves OS in locally advanced prostate cancer



NCI-MRC, JCO 2015

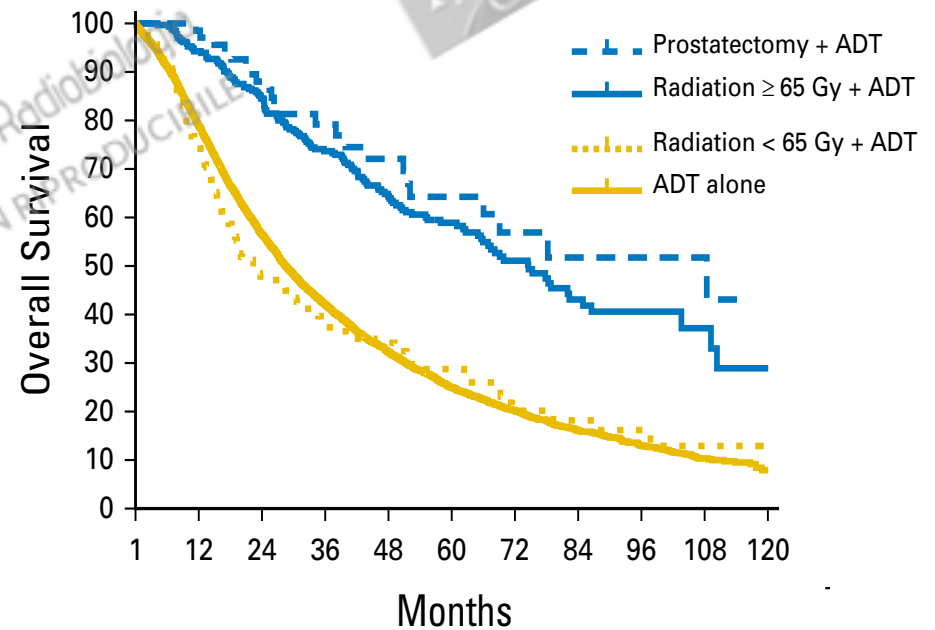
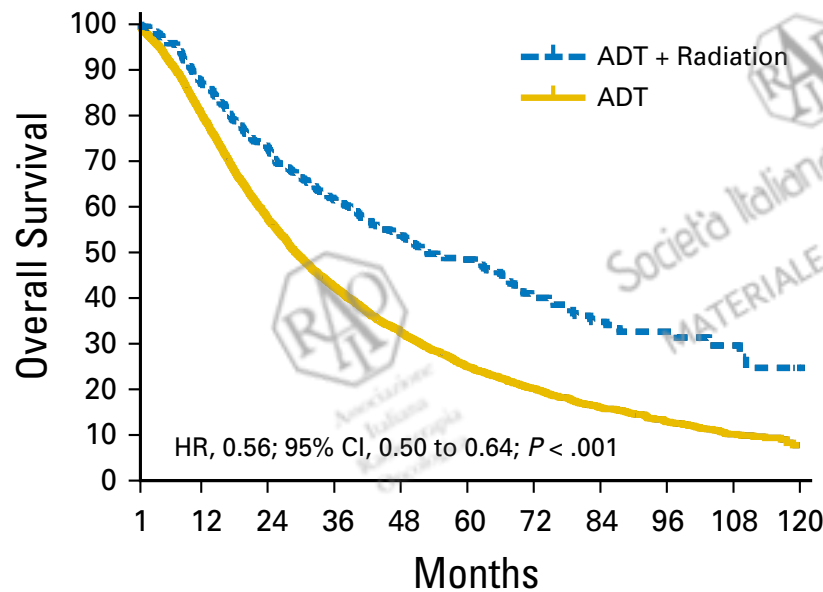


SPC-G7, Eur Urol 2016



Improved Survival With Prostate Radiation in Addition to Androgen Deprivation Therapy for Men With Newly Diagnosed Metastatic Prostate Cancer

Chad G. Rusthoven, Bernard L. Jones, Thomas W. Flaig, E. David Crawford, Matthew Koshy, David J. Sher, Usama Mahmood, Ronald C. Chen, Brian F. Chapin, Brian D. Kavanagh, and Thomas J. Pugh




ADT + Radiation	538	358	201	86	33	2
ADT	5,844	3,034	1,277	472	155	13
All Patients (N = 6,382)						

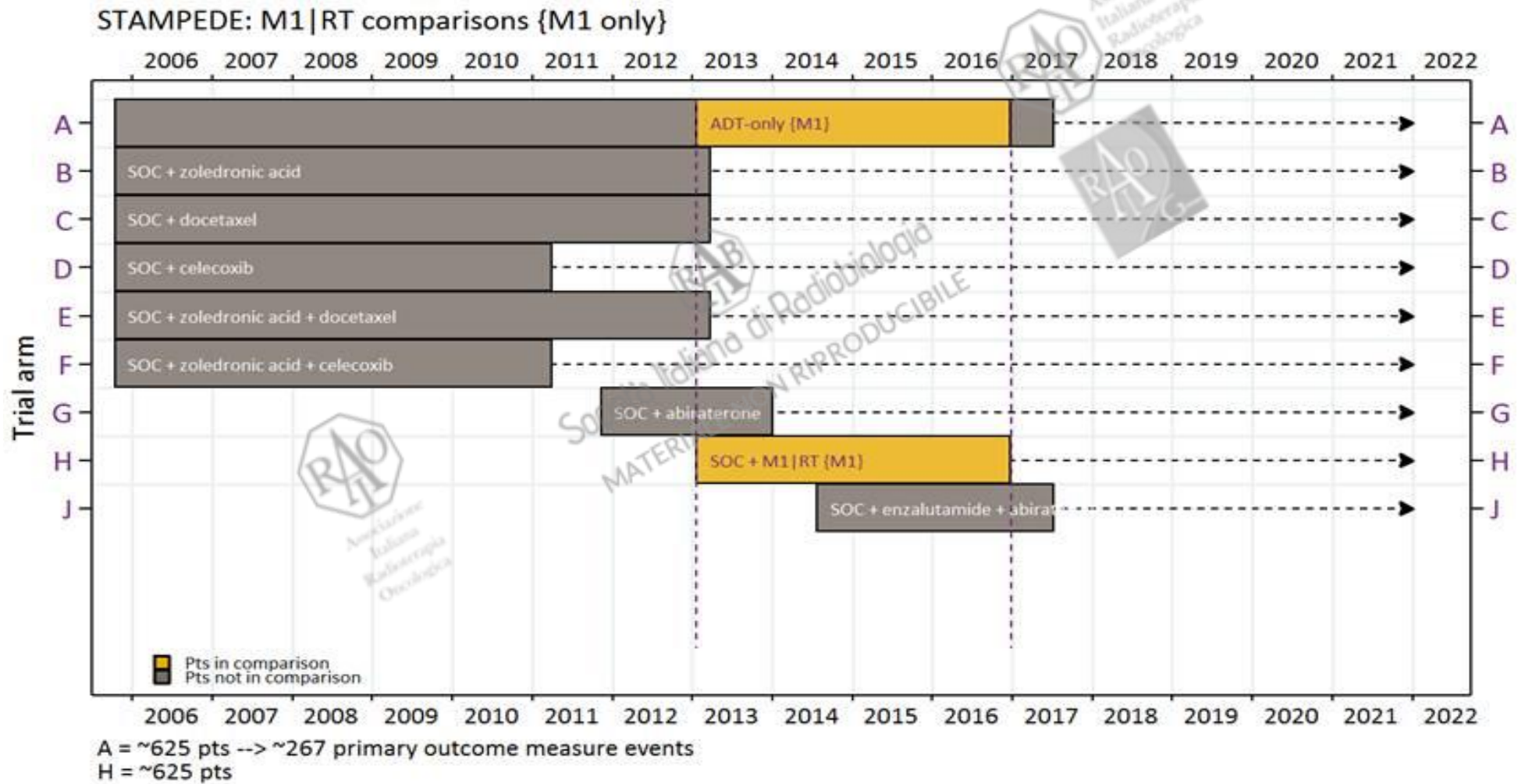


Improved Survival With Prostate Radiation in Addition to Androgen Deprivation Therapy for Men With Newly Diagnosed Metastatic Prostate Cancer

Chad G. Rusthoven, Bernard L. Jones, Thomas W. Flaig, E. David Crawford, Matthew Koshy, David J. Sher, Usama Mahmood, Ronald C. Chen, Brian F. Chapin, Brian D. Kavanagh, and Thomas J. Pugh

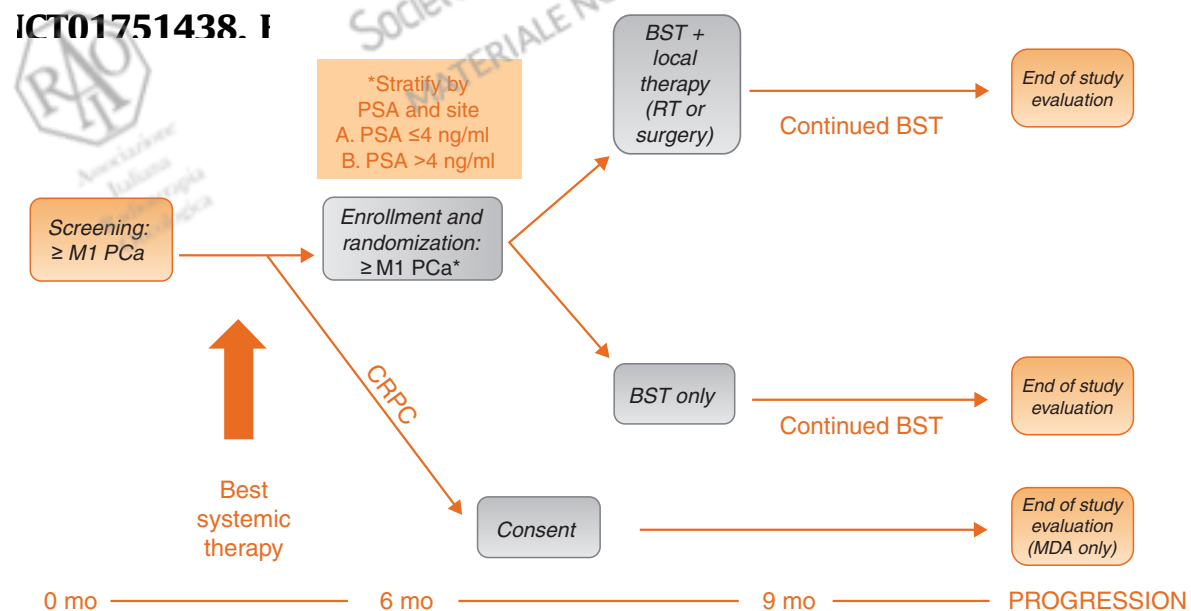
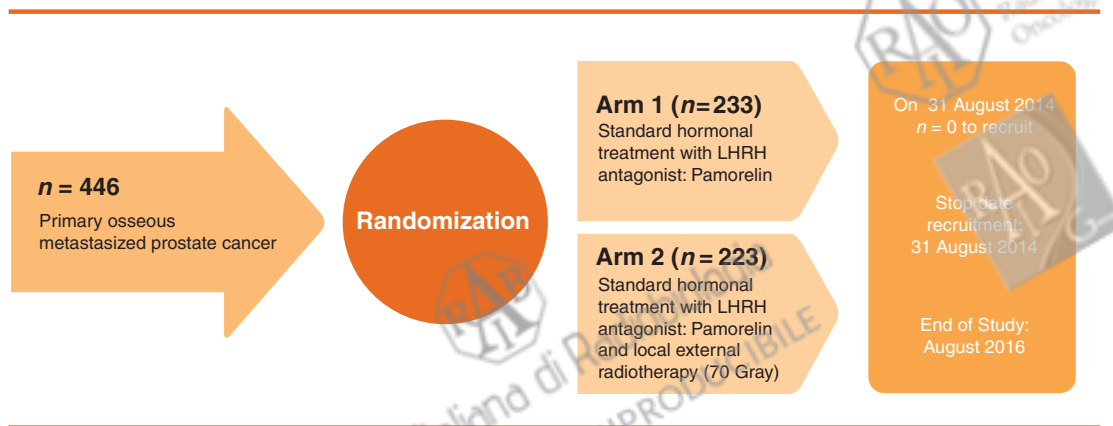
 <p>Prostate RT (added to ADT)</p>	18-month improvement in median OS
	16% improvement in 5-year OS
	33% reduction in the hazard of mortality (HR, 0.67)
<p>CHARTEED</p>	14-month median OS improvement
	20% 5-year OS improvement
	39% reduction in the hazard of mortality (HR, 0.61)
<p>STAMPEDE</p>	10-month median OS improvement
	8% 5-year OS improvement
	22% reduction in the hazard of mortality (HR, 0.78)

STAMPEDE trial design for M1 disease



RT to the prostate in the presence of oligometastatic disease: evidence in PCa

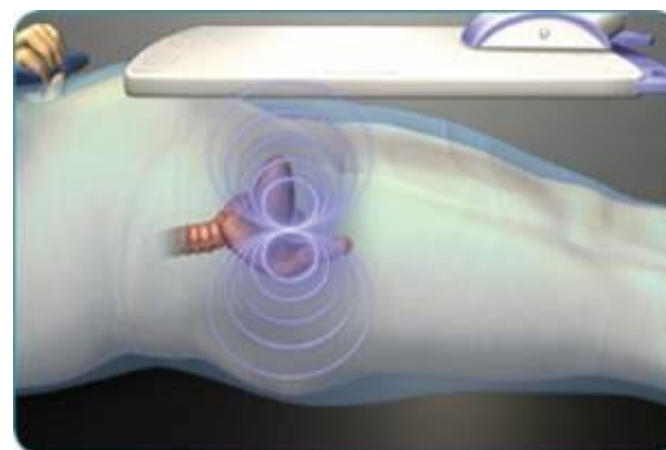
Clinical trials evaluating local therapy in distant mPCa



Oligometastases: SBRT



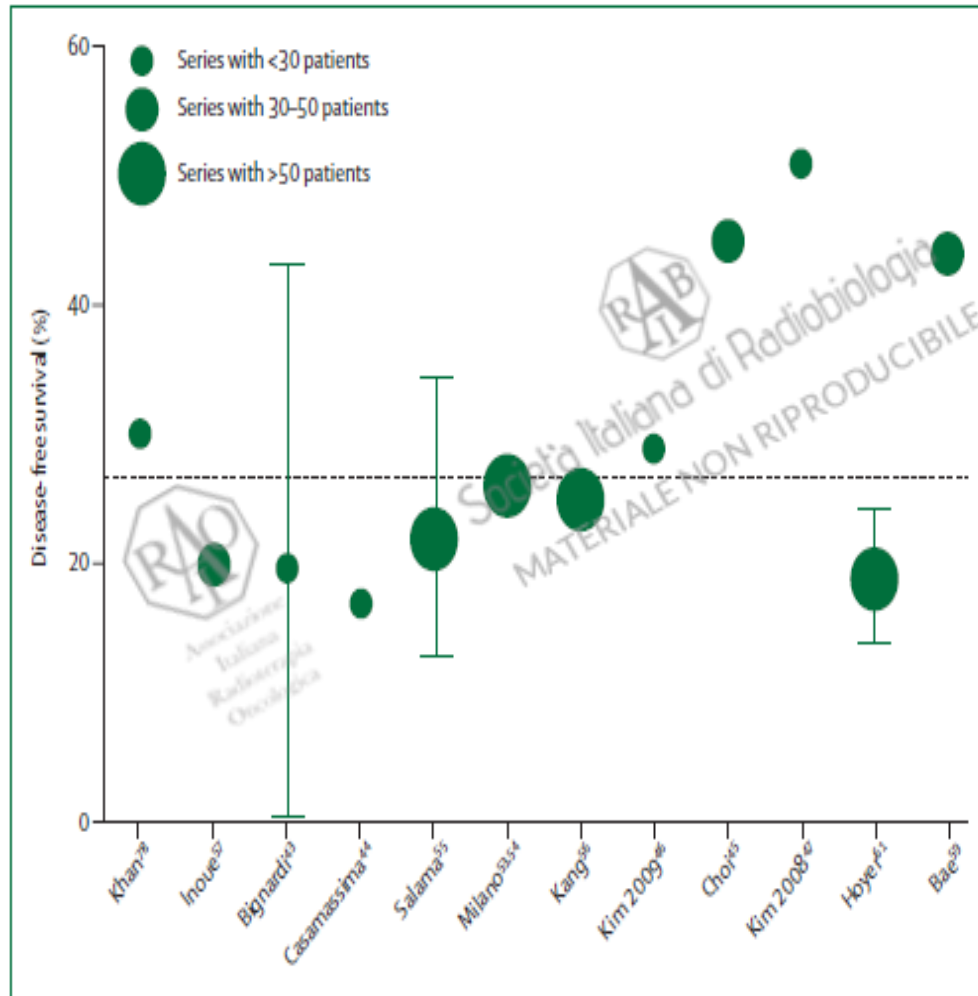
“We’ve found a mass. The good news is we have weapons of mass destruction.”



Società Italiana di Radiobiologia
MATERIALE NON RIPRODUCIBILE

Associazione
Italiana
Radioterapia
Oncologica

Oligometastases: SBRT evidence



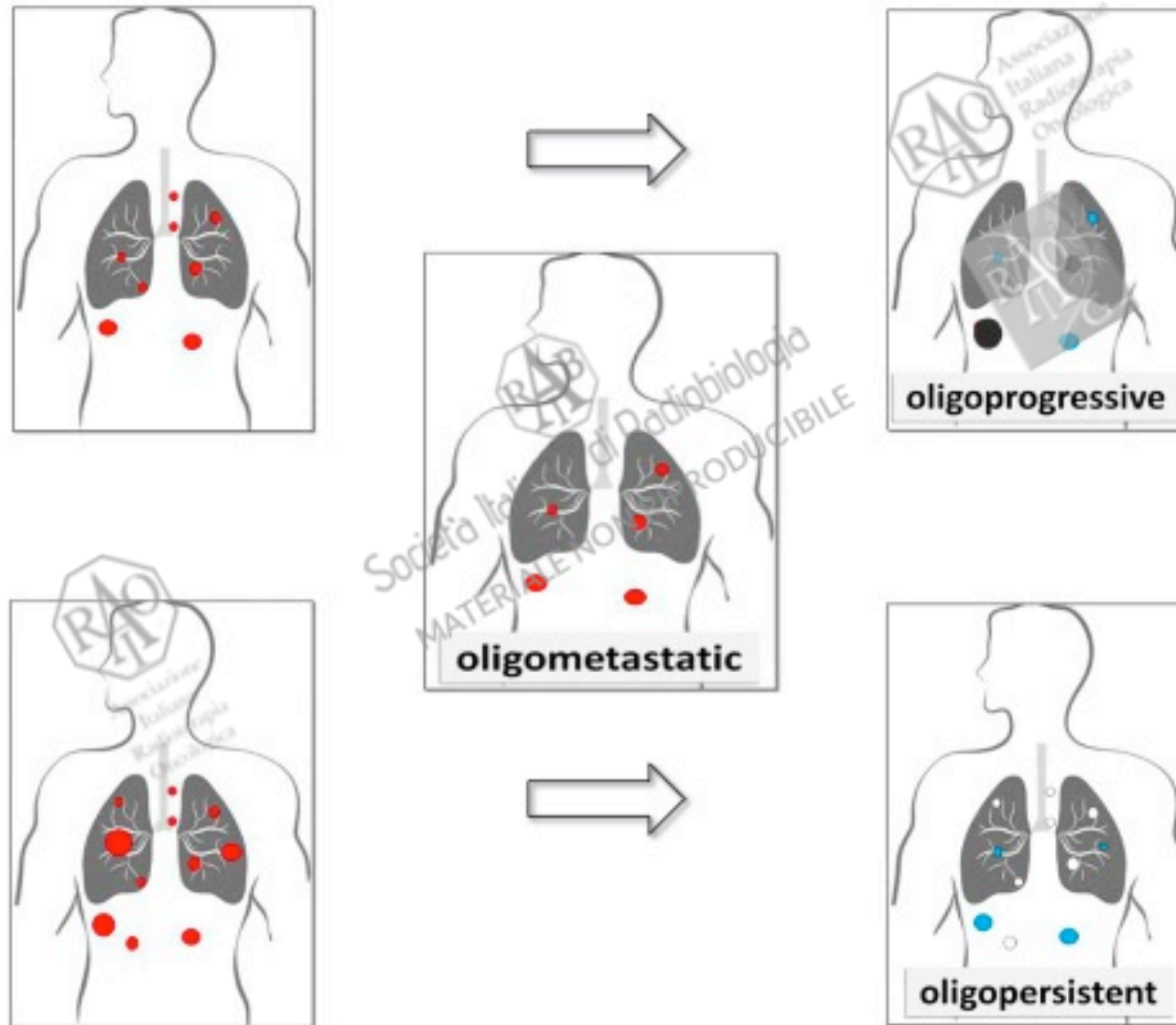
– Review of phase I/II studies and case series

– ~80% local control

– 25% progression - free survival at 2-3yrs

– Well tolerated

We've Got a Treatment, but What's the Disease?



no prospective trials on OS !

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

Karel Decaestecker¹, Gert De Meerleer², Filip Ameye³, Valerie Fonteyne², Bieke Lambert⁴, Steven Joniau⁵, Louke Delrue⁶, Ignace Billiet⁷, Wim Duthoy⁸, Sarah Junius⁹, Wouter Huyse⁶, Nicolaas Lumen¹ and Piet Ost^{2*}

Primary Outcome Measures: Androgen Deprivation Therapy Free Survival

patients with low volume metastases



Active clinical surveillance

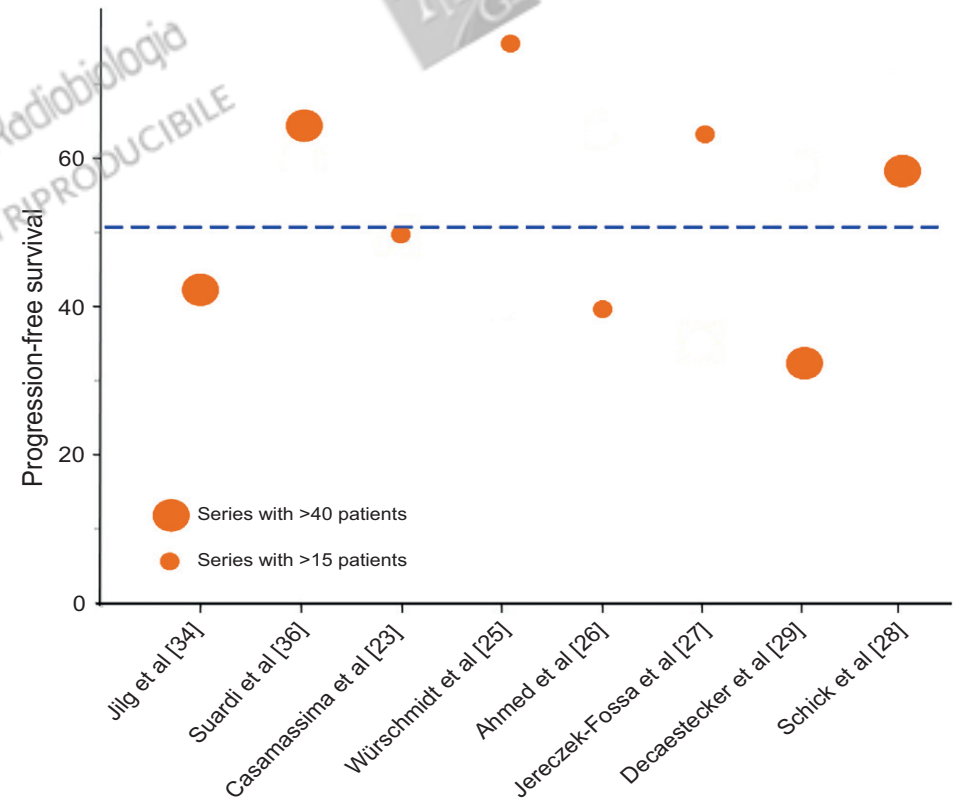
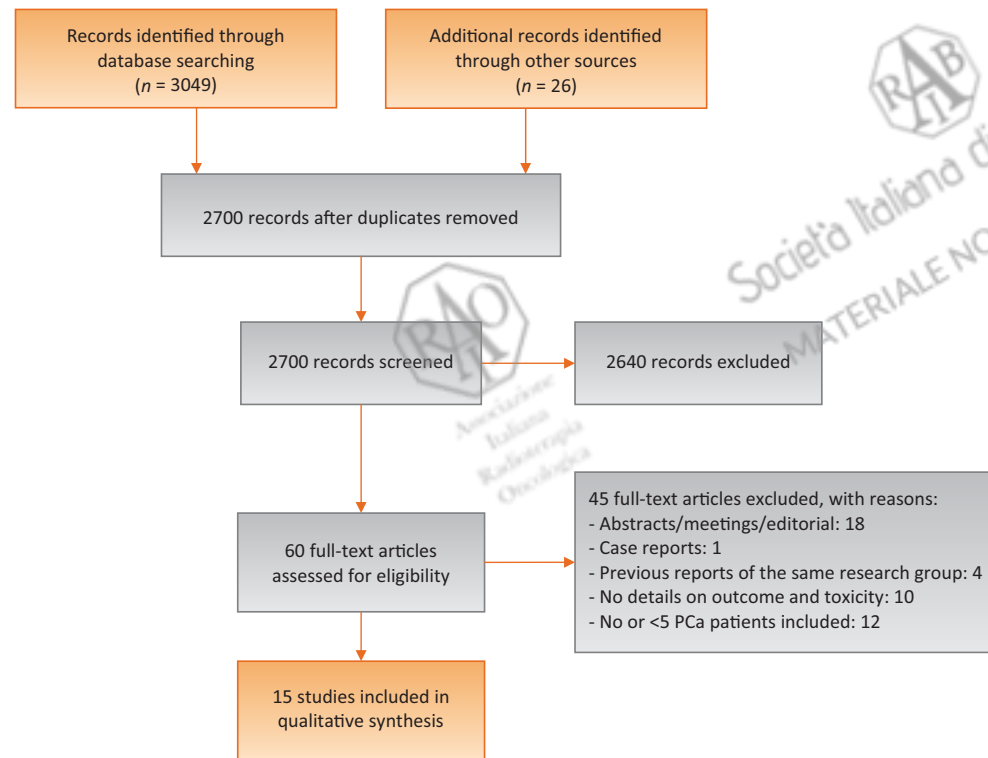


Surgery or SBRT



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

Piet Ost^{a,*}, Alberto Bossi^b, Karel Decaestecker^c, Gert De Meerleer^a, Gianluca Giannarini^d, R. Jeffrey Karnes^e, Mack Roach III^f, Alberto Briganti^g



**Management of patients with advanced prostate cancer:
Recommendations of the St.Gallen Advanced Prostate Cancer
Consensus Conference (APCCC) 2015**



most panel members did not identify indications for SBRT for either de novo oligometastatic, or oligorecurrent castration naïve prostate cancer

**NCCN Guidelines Version 3.2016
Prostate Cancer**

M1 →

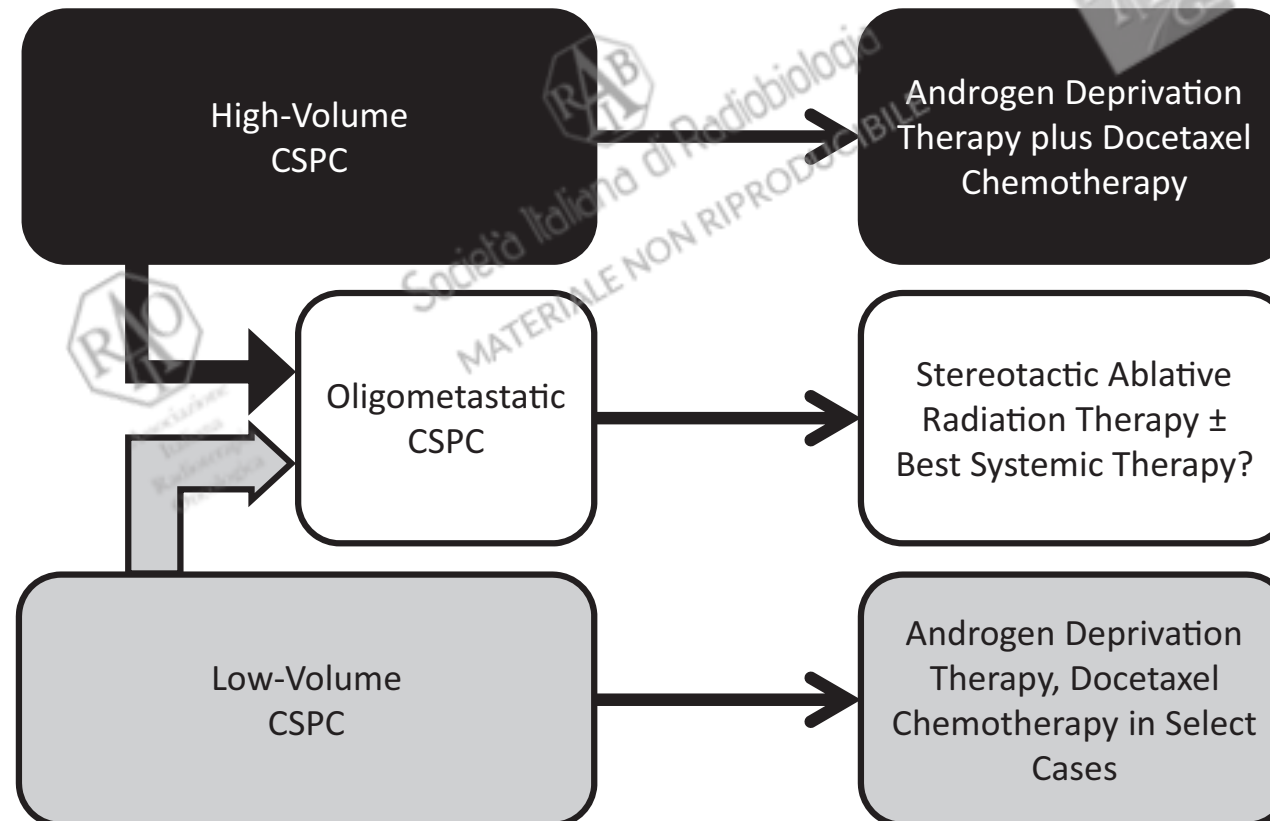
Orchiectomy
or
LHRH agonist ± antiandrogen^{I,v} ≥7 days to
prevent testosterone flare
or
LHRH agonist + antiandrogen^{I,v}
or
LHRH antagonist^{I,v}
or
Continuous ADT^{I,v} and docetaxel 75 mg/m²
with or without prednisone for 6 cycles^w

CRPC,
studies
positive
for
metastases

- Maintain castrate levels of serum testosterone (<50 ng/dL)
- Consider bone antiresorptive therapy with denosumab or zoledronic acid (both category 1) if bone metastases present
- Immunotherapy with sipuleucel-T if asymptomatic or minimally symptomatic, no liver metastases, life expectancy >6 mo, ECOG performance status 0–1 (category 1) ([See PROS-G](#))^{bb}
- Palliative RT for painful bony metastases
- Best supportive care

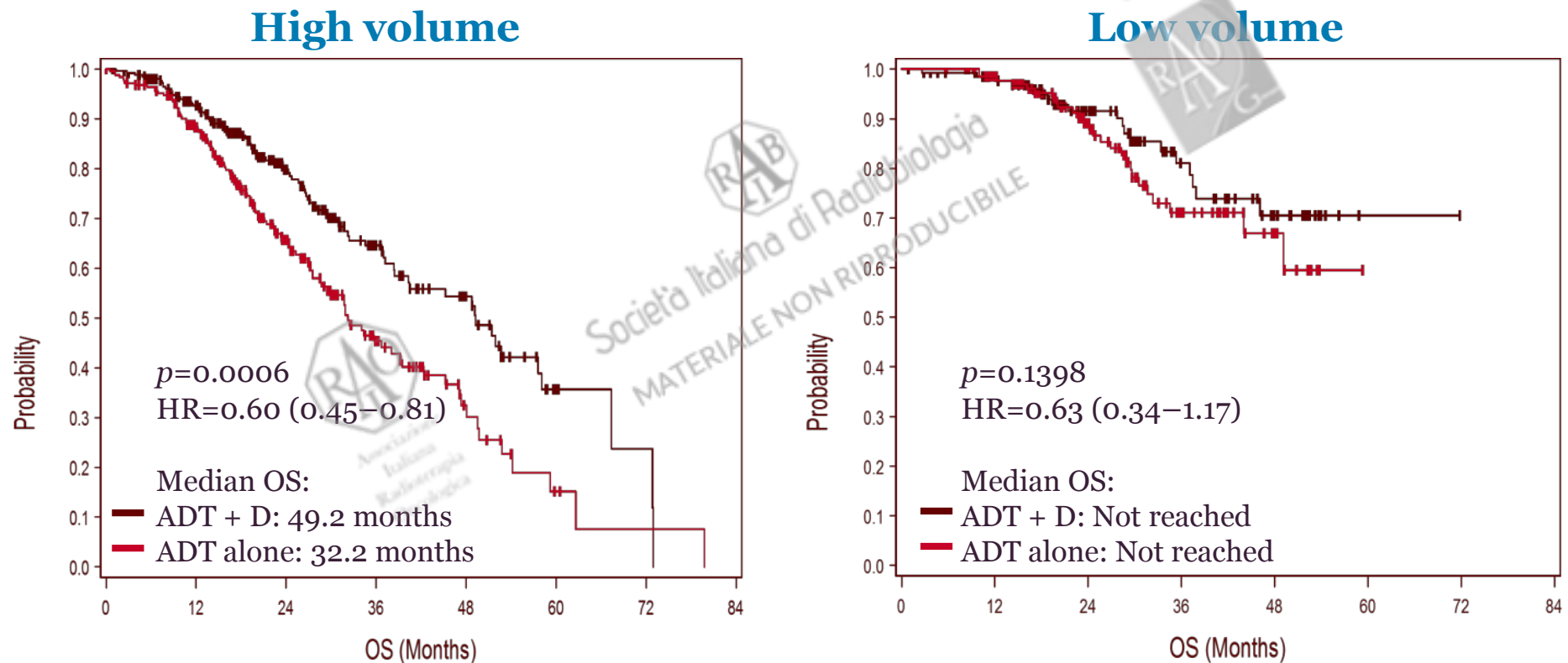
Disease volume and distribution as drivers of treatment decisions in metastatic prostate cancer: From chemohormonal therapy to stereotactic ablative radiotherapy of oligometastases

Ronak Saluja, B.Sc. Candidate^a, Patrick Cheung, M.D.^b, Katherine Zukotynski, M.D.^c,
Urban Emmenegger, M.D.^{a,d,e,*}

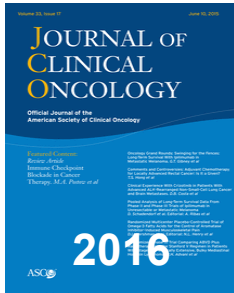


CHAARTED: Overall survival by extent of metastatic disease

Sweeney C *et al.* N ENGL J MED 373;8 AUGUST 20, 2015

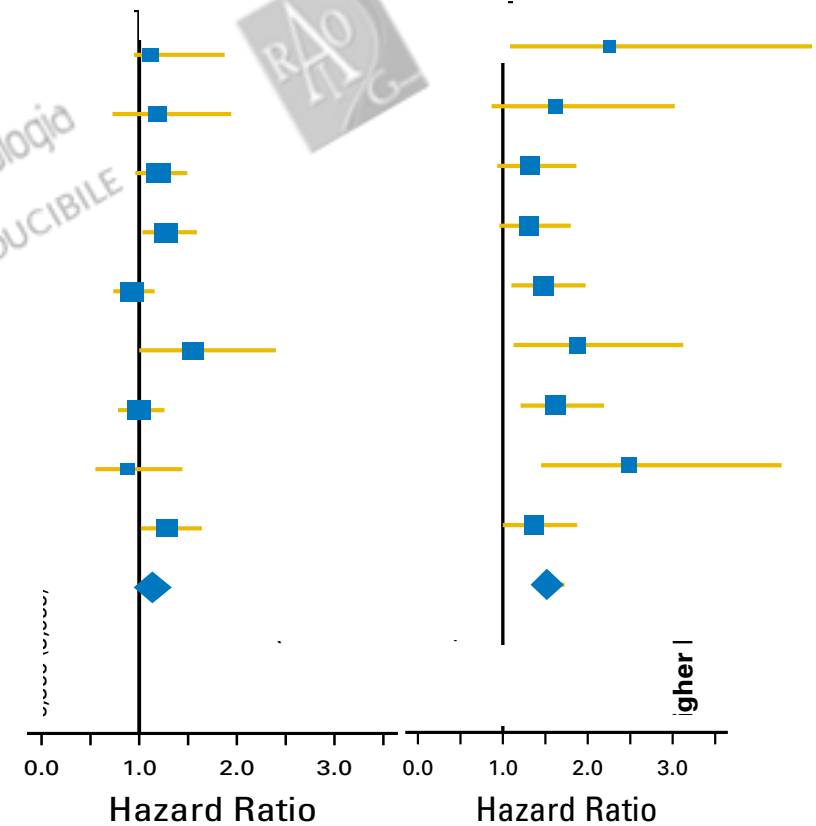
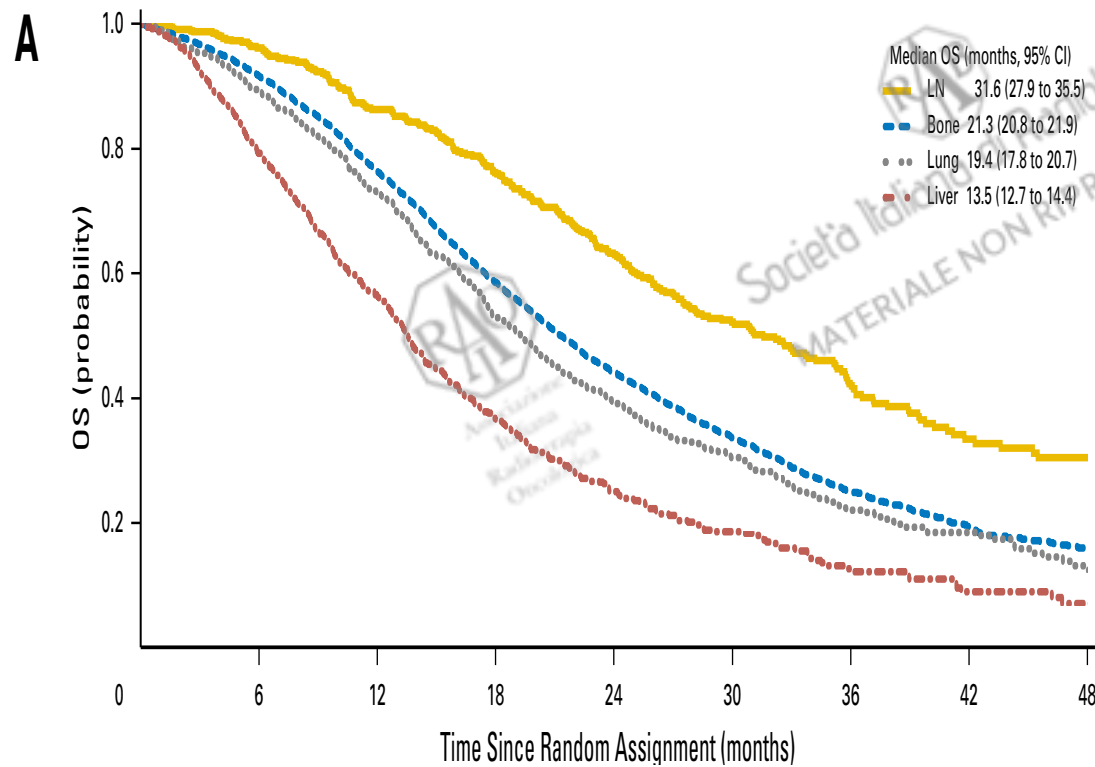


High volume: visceral metastases and/or 4 or more bone metastases with at least 1 beyond pelvis and vertebral column



Meta-Analysis Evaluating the Impact of Site of Metastasis on Overall Survival in Men With Castration-Resistant Prostate Cancer

Susan Halabi, William Kevin Kelly, Hua Ma, Haojin Zhou, Nicole C. Solomon, Karim Fizazi, Catherine M. Tangen, Mark Rosenthal, Daniel P. Petrylak, Maha Hussain, Nicholas J. Vogelzang, Ian M. Thompson, Kim N. Chi, Johann de Bono, Andrew J. Armstrong, Mario A. Eisenberger, Abderrahim Fandi, Shaoyi Li, John C. Araujo, Christopher J. Logothetis, David I. Quinn, Michael J. Morris, Celestia S. Higano, Ian F. Tannock, and Eric J. Small



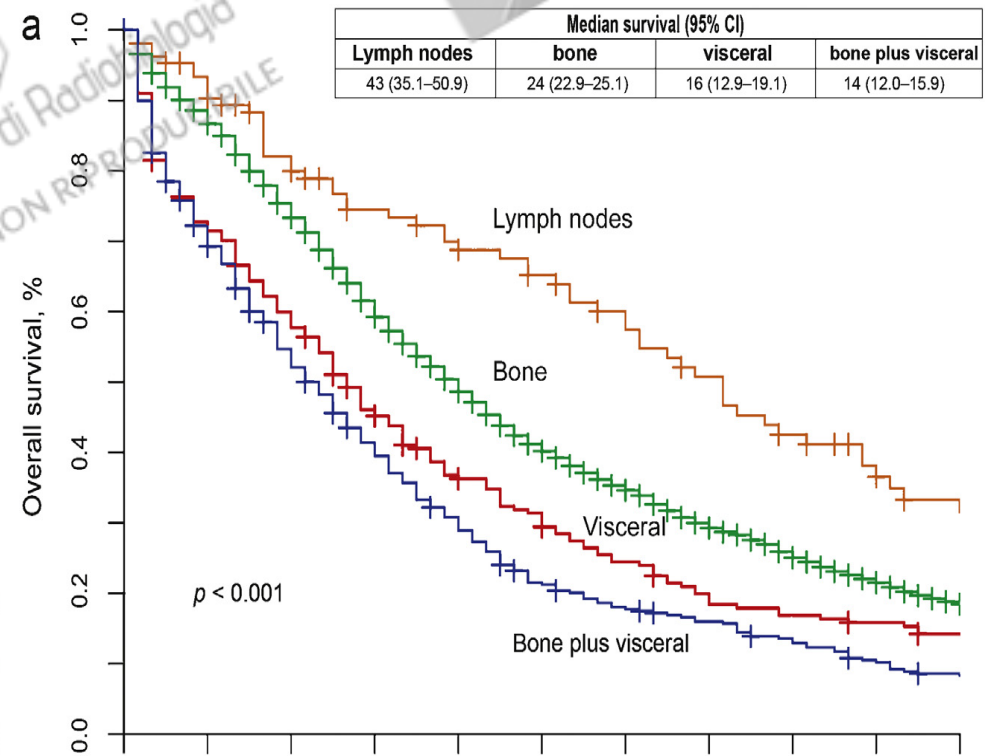
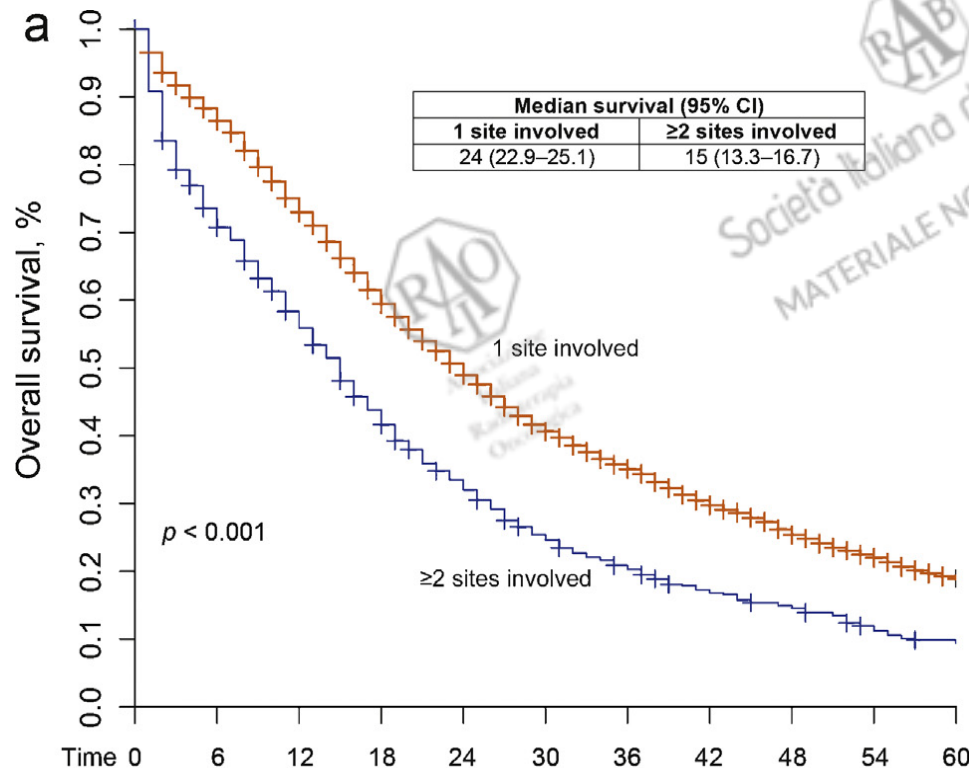
8,820 men with mCRPC who were treated with docetaxel



Impact of the Site of Metastases on Survival in Patients with Metastatic Prostate Cancer

Giorgio Gandaglia^{a,b,†,*}, Pierre I. Karakiewicz^{a,c,†}, Alberto Briganti^b, Nicolò Maria Passoni^b, Jonas Schiffmann^a, Vincent Trudeau^{a,c}, Markus Graefen^d, Francesco Montorsi^b, Maxine Sun^a

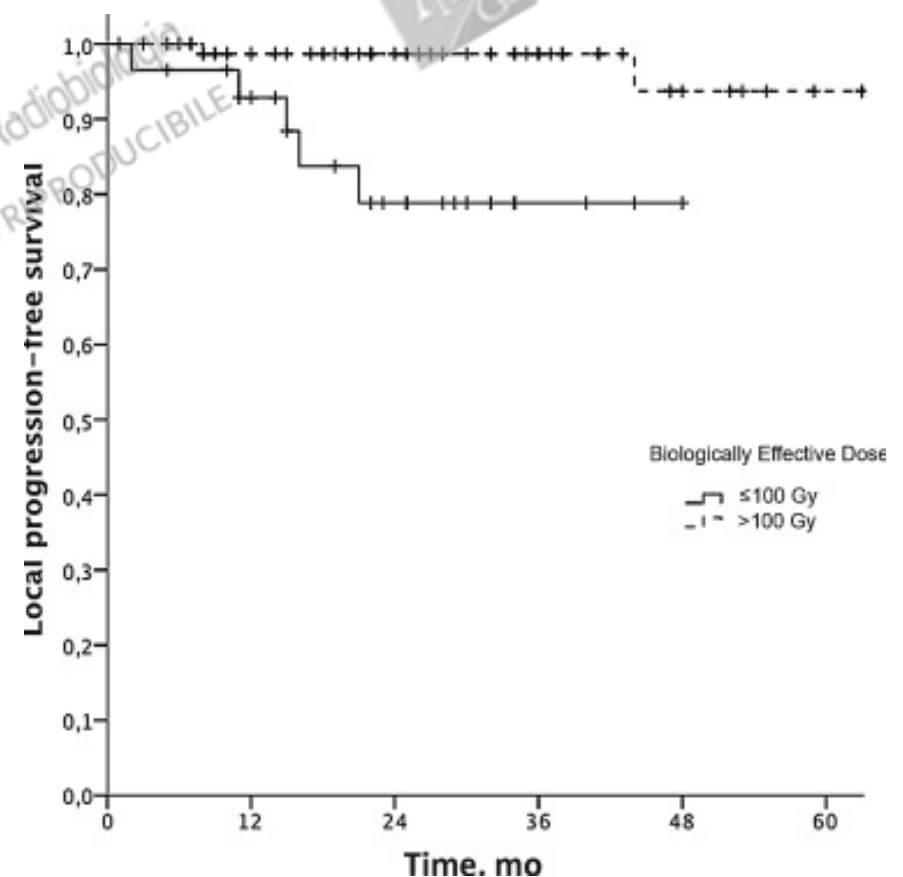
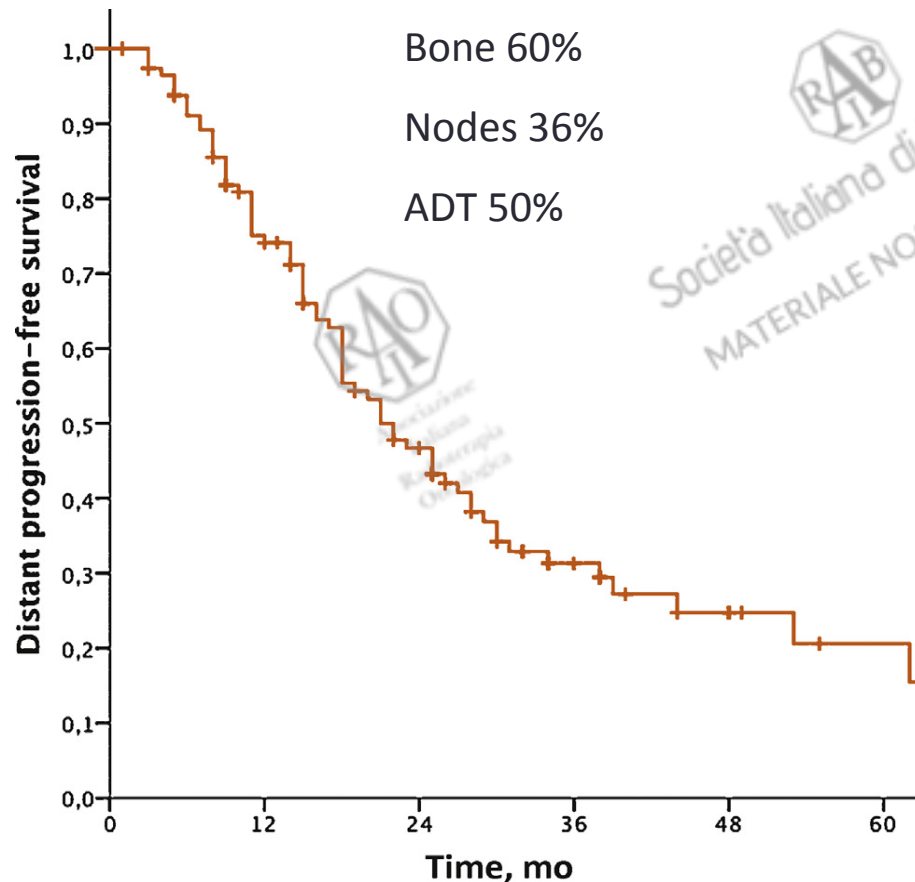
3857 patients with metastatic PCa





Progression-free Survival Following Stereotactic Body Radiotherapy for Oligometastatic Prostate Cancer Treatment-naïve Recurrence: A Multi-institutional Analysis

Piet Ost^{a,*}, Barbara Alicja Jereczek-Fossa^b, Nicholas Van As^c, Thomas Zilli^d,
Alexander Muacevic^e, Kenneth Olivier^f, Daniel Henderson^e, Franco Casamassima^g,
Roberto Orecchia^b, Alessia Surgo^b, Lindsay Brown^f, Alison Tree^c, Raymond Miralbell^d,
Gert De Meerleer^a



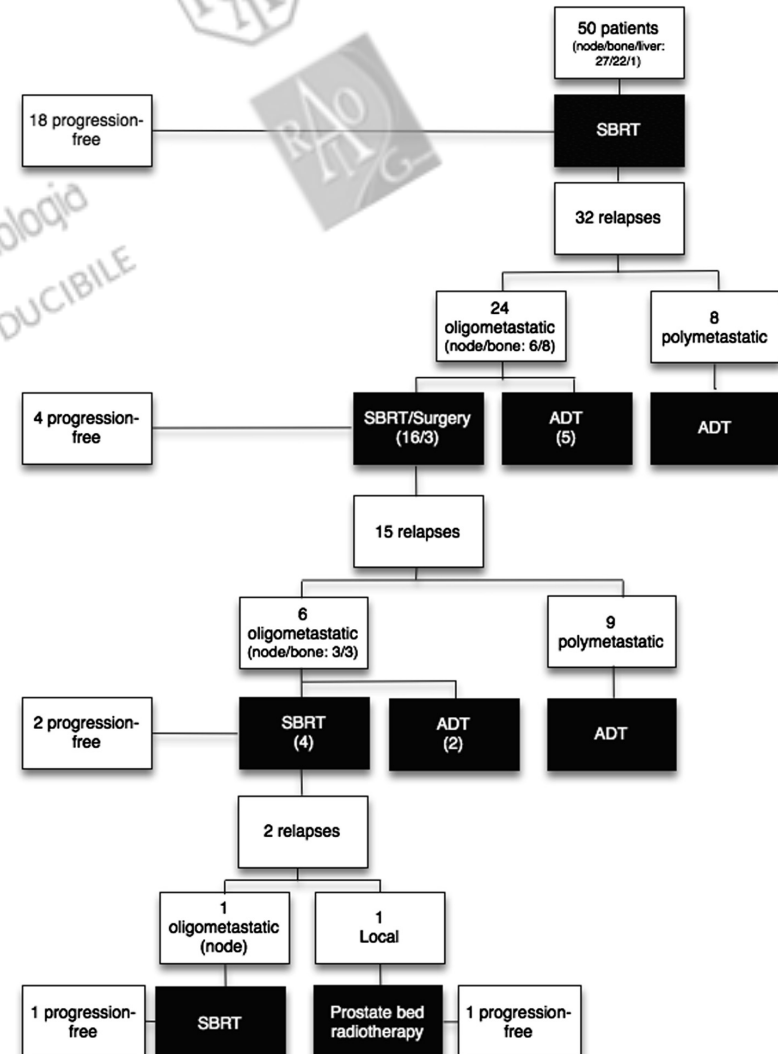
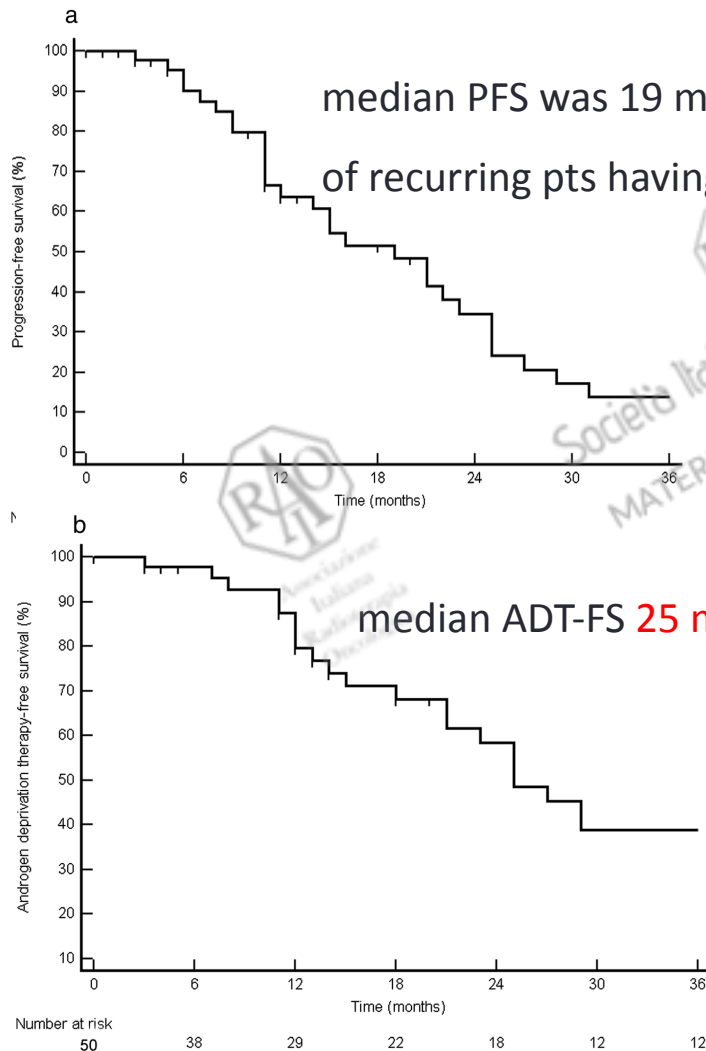


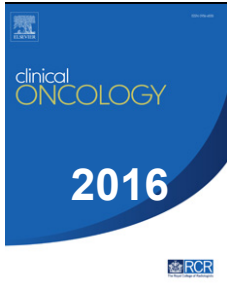
Repeated stereotactic body radiotherapy for oligometastatic prostate cancer recurrence

Karel Decaestecker¹, Gert De Meerleer², Bieke Lambert³, Louke Delrue⁴, Valérie Fonteyne², Tom Claeys¹, Filip De Vos⁵, Wouter Huysse⁴, Arne Hautekiet², Gaethan Maes² and Piet Ost^{2*}

2014

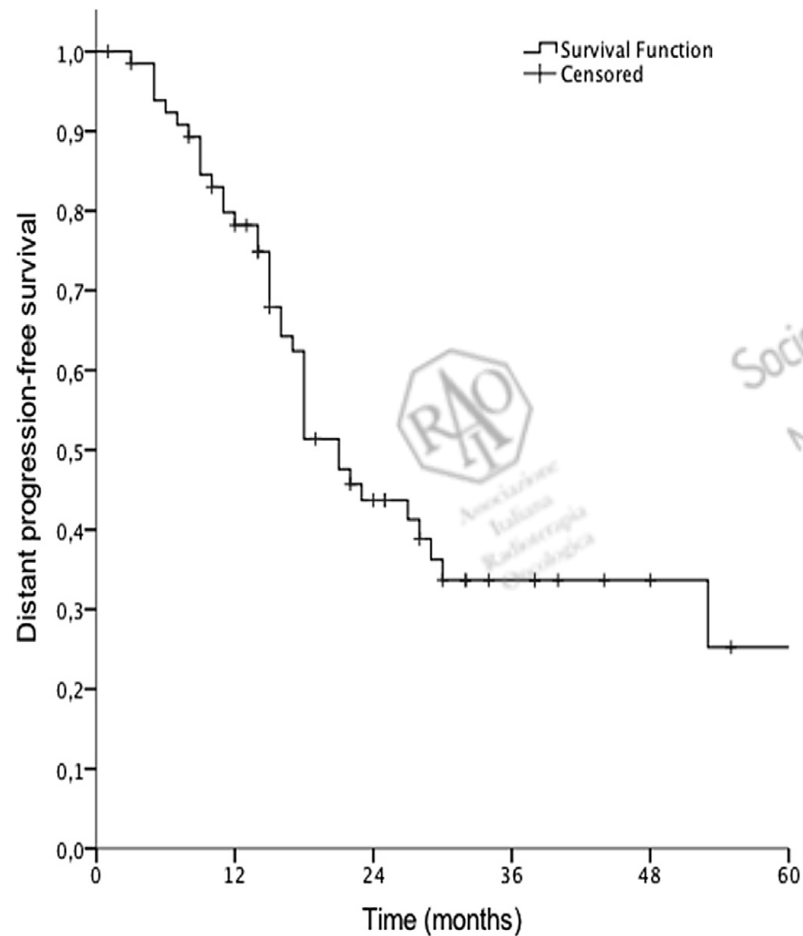
median follow-up of 2 years (8 – 52 mo)



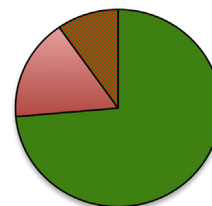
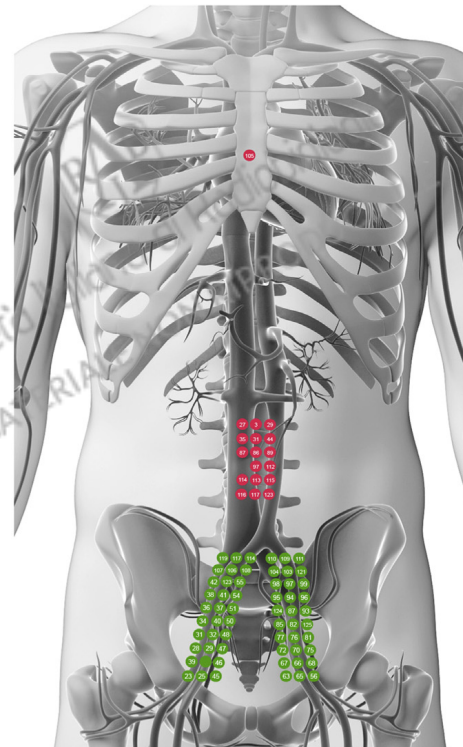


Pattern of Progression after Stereotactic Body Radiotherapy for Oligometastatic Prostate Cancer Nodal Recurrences

P. Ost^{*}, B.A. Jereczek-Fossa[†], N. Van As[‡], T. Zilli[§], A. Tree[‡], D. Henderson[‡], R. Orecchia[†], F. Casamassima[†], A. Surgo[†], R. Miralbell[§], G. De Meerleer^{*}

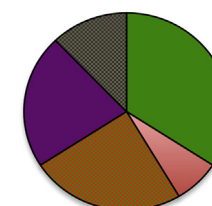
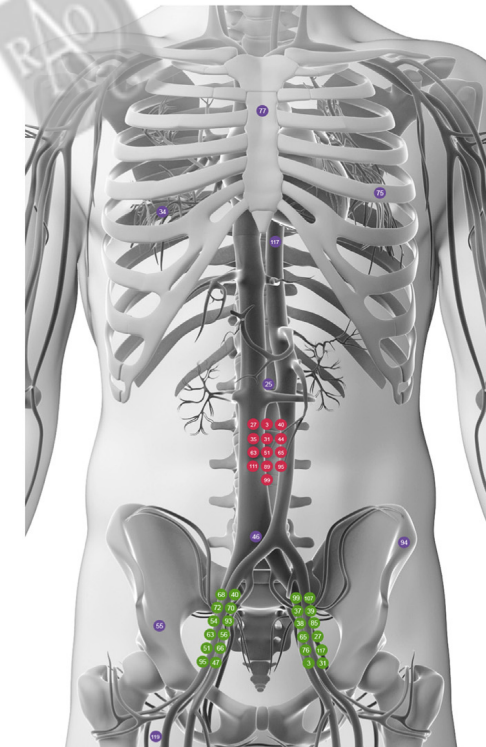


Distribution of lymph node metastases prior to SBRT (N = 72)



- N1 only
- M1a only
- N1 and M1a

Distribution of relapse pattern following SBRT (N= 41)



- N1 only
- M1a only
- N1 and M1a
- M1b or M1c only
- Combinations

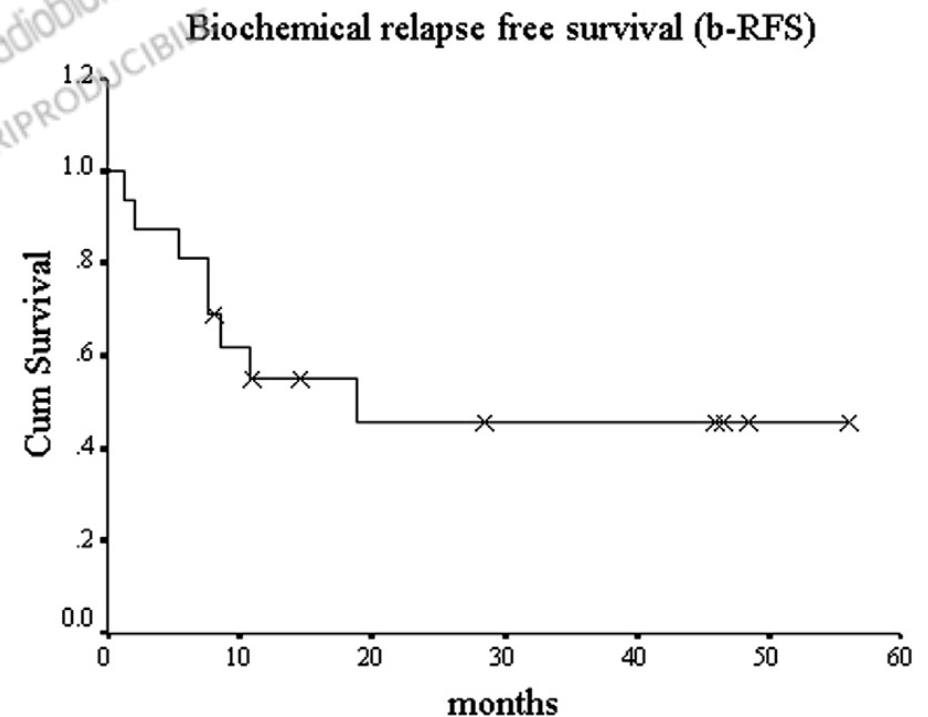
Original Study



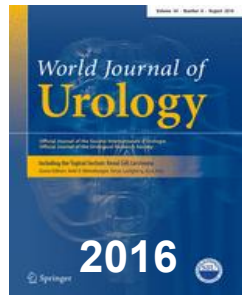
Salvage Stereotactic Body Radiotherapy for Patients With Prostate Cancer With Isolated Lymph Node Metastasis: A Single-Center Experience

Elisabetta Ponti, Gianluca Ingrosso, Alessandra Carosi, Luana Di Murro, Andrea Lancia, Franca Pietrasanta, Riccardo Santoni

	N	%
N° Fractions		
1	1	5.6
4	2	11.1
5	15	83.2
Total Dose (Gy)		
12 (1 × 12 Gy)	1	5.6
30 (4 × 7.5 Gy)	1	5.6
32 (4 × 8 Gy)	1	5.6
35 (5 × 7 Gy)	15	83.2
CVF (Dose Coverage Index)		
Mean	0.99	
Median	1.00	
CN (Dose Conformity Index)		
Mean	0.66	
Median	0.63	



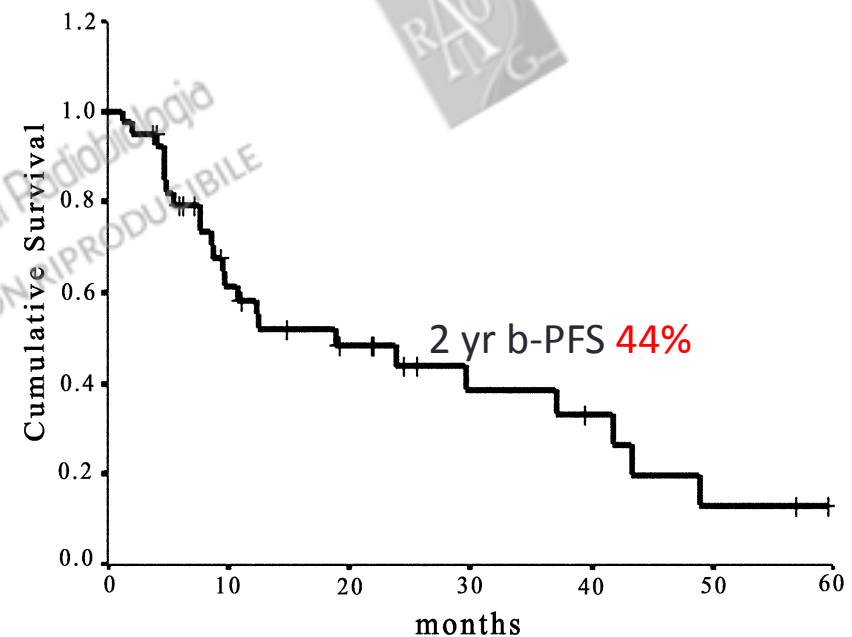
mean ADT deferment of **23.7** months (range, 2.5-51)



Stereotactic body radiotherapy in oligometastatic prostate cancer patients with isolated lymph nodes involvement: a two-institution experience

Gianluca Ingrosso¹ · Fabio Trippa² · Ernesto Maranzano² · Alessandra Carosi¹ · Elisabetta Ponti¹ · Fabio Arcidiacono² · Lorena Draghini² · Luana Di Murro¹ · Andrea Lancia¹ · Riccardo Santoni¹

	N	%
Total	47	100
<i>Site of lymph node metastasis</i>		
Supraclavicular	1	2.1
Lumbo-aortic	6	12.7
Common iliac	10	21.3
External iliac	15	31.9
Internal iliac	3	6.4
Obturator	7	15
Presacral	5	10.6
<i>Total dose (Gy)</i>		
12 (1 × 12 Gy)	1	2.1
25 (5 × 5 Gy)	1	2.1
30 (4 × 7.5 Gy)	1	2.1
30 (5 × 6 Gy)	6	12.7
32 (4 × 8 Gy)	1	2.1
35 (5 × 7 Gy)	23	48.9
40 (5 × 8 Gy)	13	27.7
50 (5 × 10 Gy)	1	2.1



LC 98%

G3 Tox 2.5%

mean ADT-FS 13.5 months (range, 2.06-37.13)

40% had one-node only PD outside the irradiated area



2016

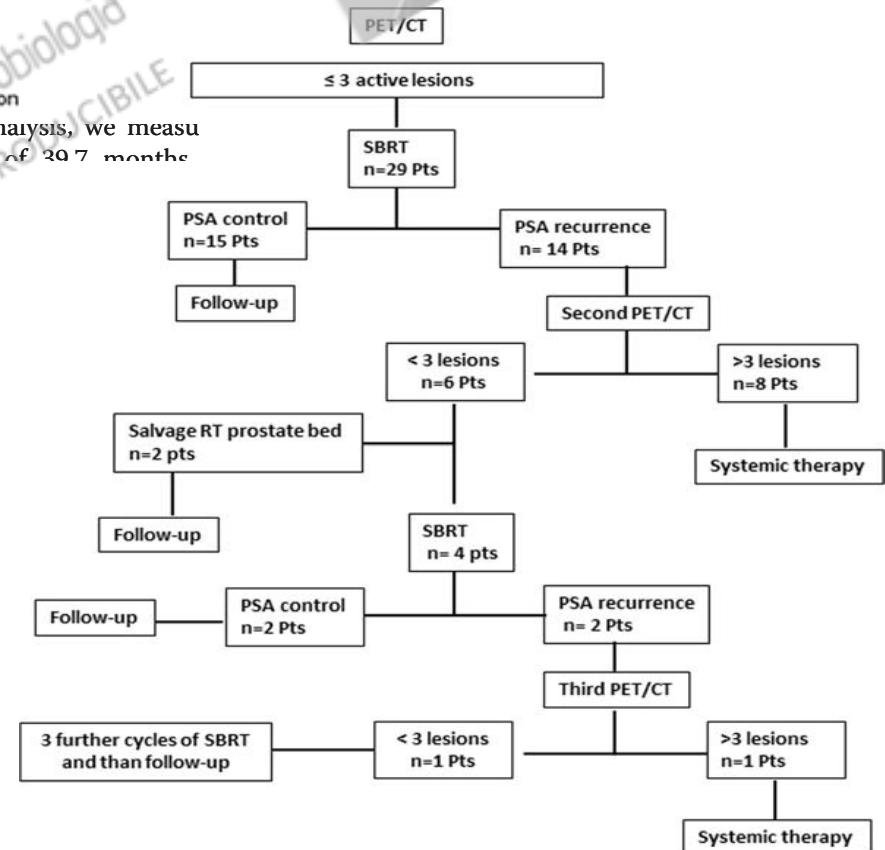
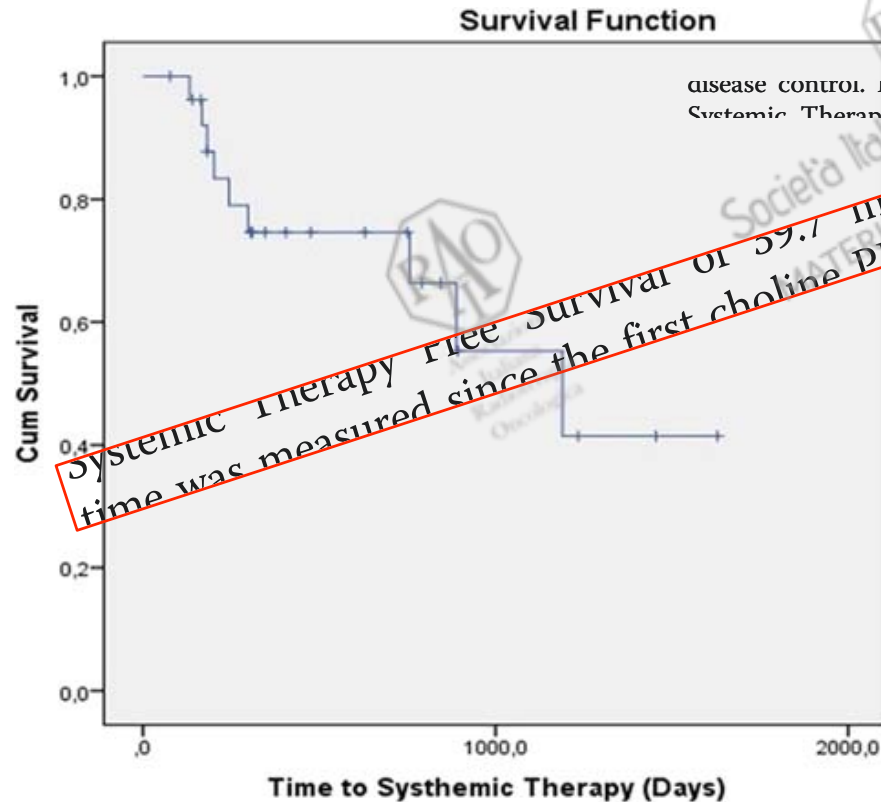
RESEARCH

Open Access



[¹⁸F]Choline PET/CT and stereotactic body radiotherapy on treatment decision making of oligometastatic prostate cancer patients: preliminary results

Francesco Pasqualetti^{1,9*}, Marco Panichi¹, Aldo Sainato¹, Fabrizio Matteucci¹, Luca Galli², Paola Cocuzza¹, Patrizia Ferrazza¹, Gabriele Coraggio¹, Giuseppe Pasqualetti³, Lisa Derosa², Martina Sollini³, Lorenzo Mannelli⁵, Simona Ortori⁶, Fabio Monzani⁴, Sergio Ricci², Carlo Greco⁷, Maria Grazia Fabrini¹ and Paola Anna Erba⁸



Linee guida Carcinoma della Prostata - AIRO 2016



Il concetto di “oligometastasi” indica uno stato int

Grado di raccomandazione SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
D	I pazienti oligometastatici o in oligoprogressione potrebbero essere trattati con trattamento radiante offrendo un eccellente controllo locale con un basso profilo di tossicità	Positiva debole



Seeing and Not Believing: Oligometastases and the Future of Metastatic Prostate Cancer

Eric A. Klein *

in the absence of an untreated control arm or alternative intervention as a comparator, it is only possible to judge the tolerability and toxicity of surgery or radiation in these patients, and not their therapeutic efficacy.

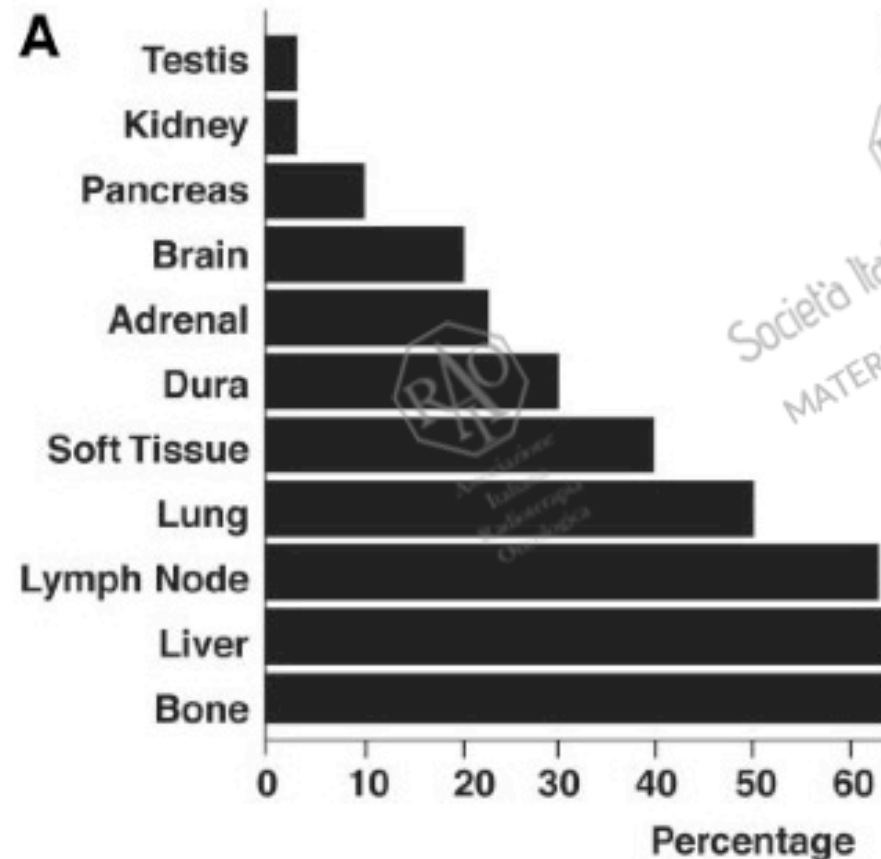
we must not confuse our *ability to treat* such disease safely with an *actual benefit* in doing so.

the paradigm of treating oligometastatic disease is limited by the inherent limitations of current imaging modalities.

Cancer
Research

Androgen-Independent Prostate Cancer Is a Heterogeneous Group of Diseases: Lessons from a Rapid Autopsy Program

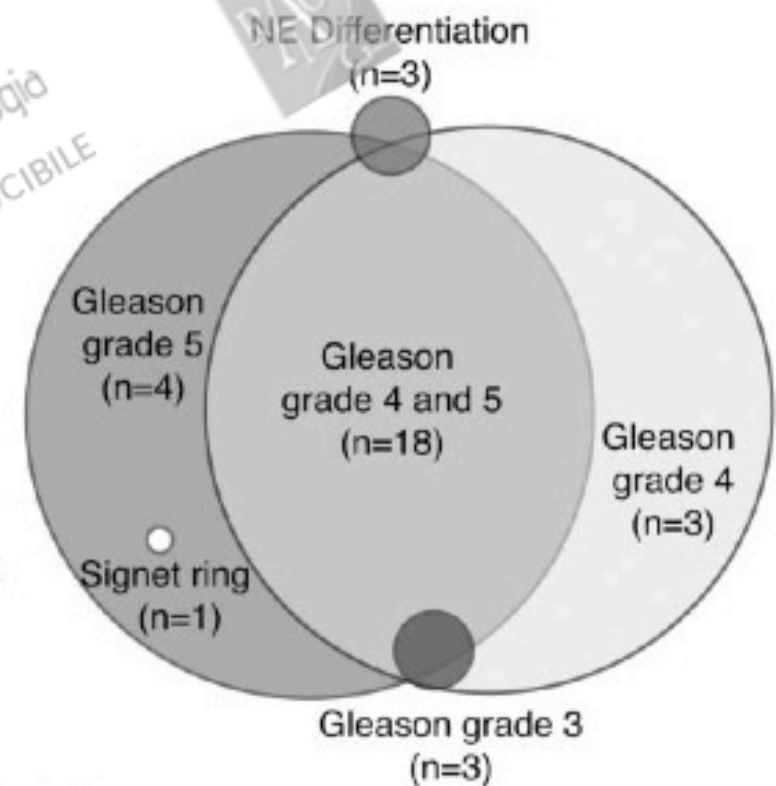
Rajal B. Shah,^{1,3} Rohit Mehra,¹ Arul M. Chinnaiyan,^{1,3} Ronglai Shen,⁴ Debashis Ghosh,⁴ Ming Zhou,¹ Gary R. MacVicar,² Soorynarayana Varambally,¹ Jason Harwood,¹ Tarek A. Bismar,⁵ Robert Kim,⁵ Mark A. Rubin,^{5,6,7} and Kenneth J. Pienta^{2,3}

**B**

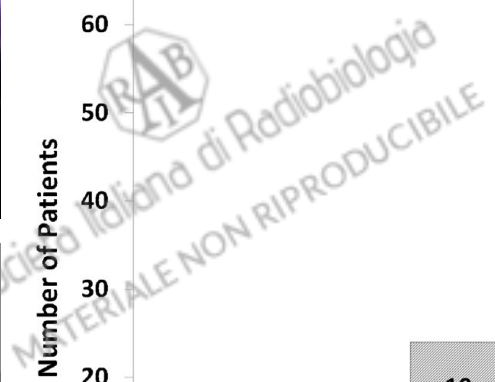
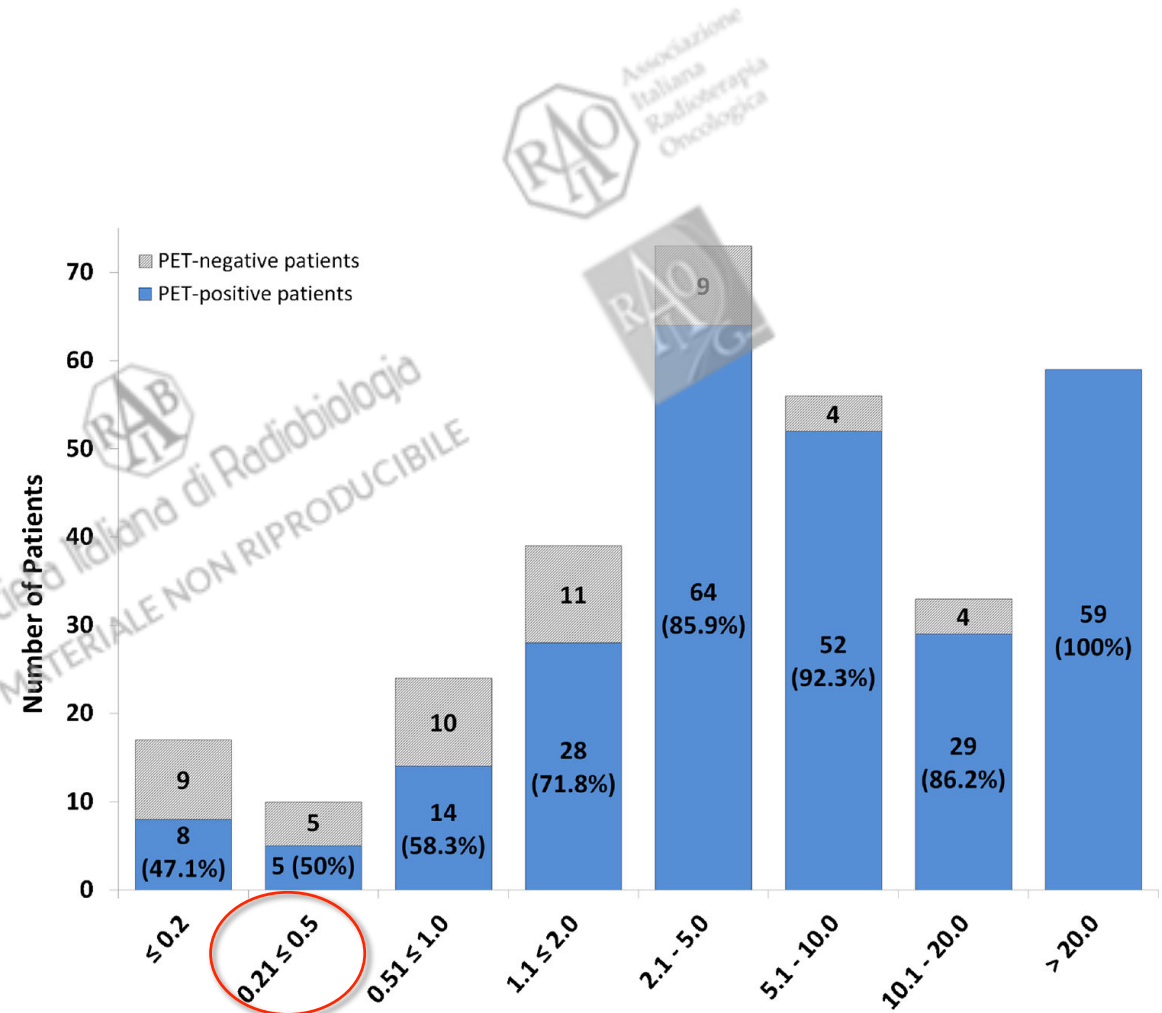
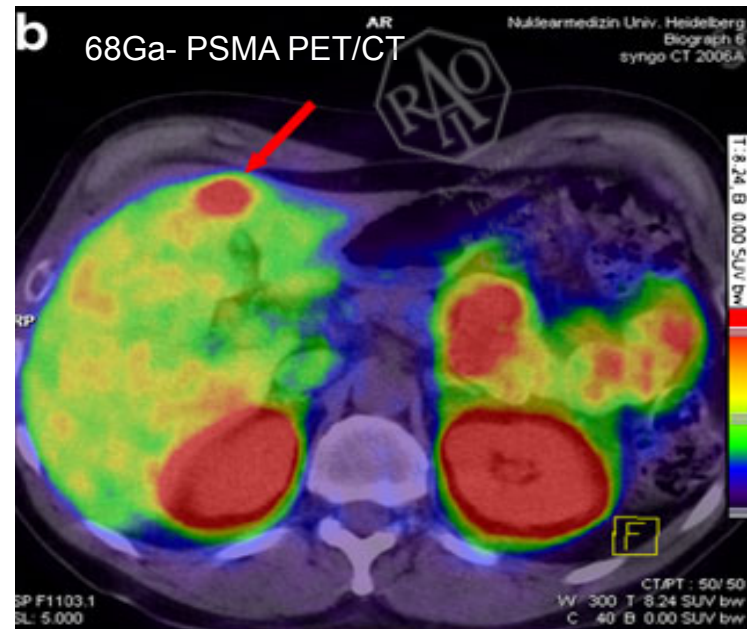
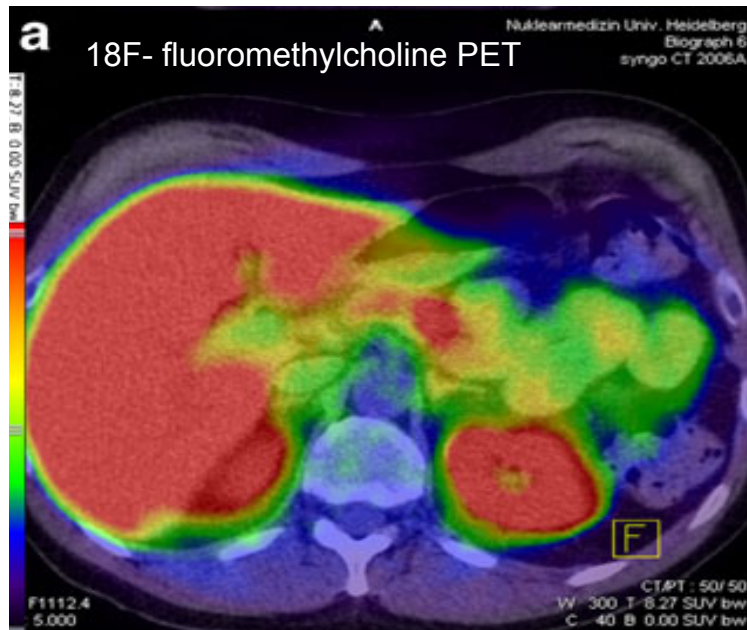
Società Italiana di Radiobiologia
MATERIALE NON RIPRODUCIBILE

Small Cell
(n=2)

Undifferentiated
(n=1)



⁶⁸Ga-labelled PSMA

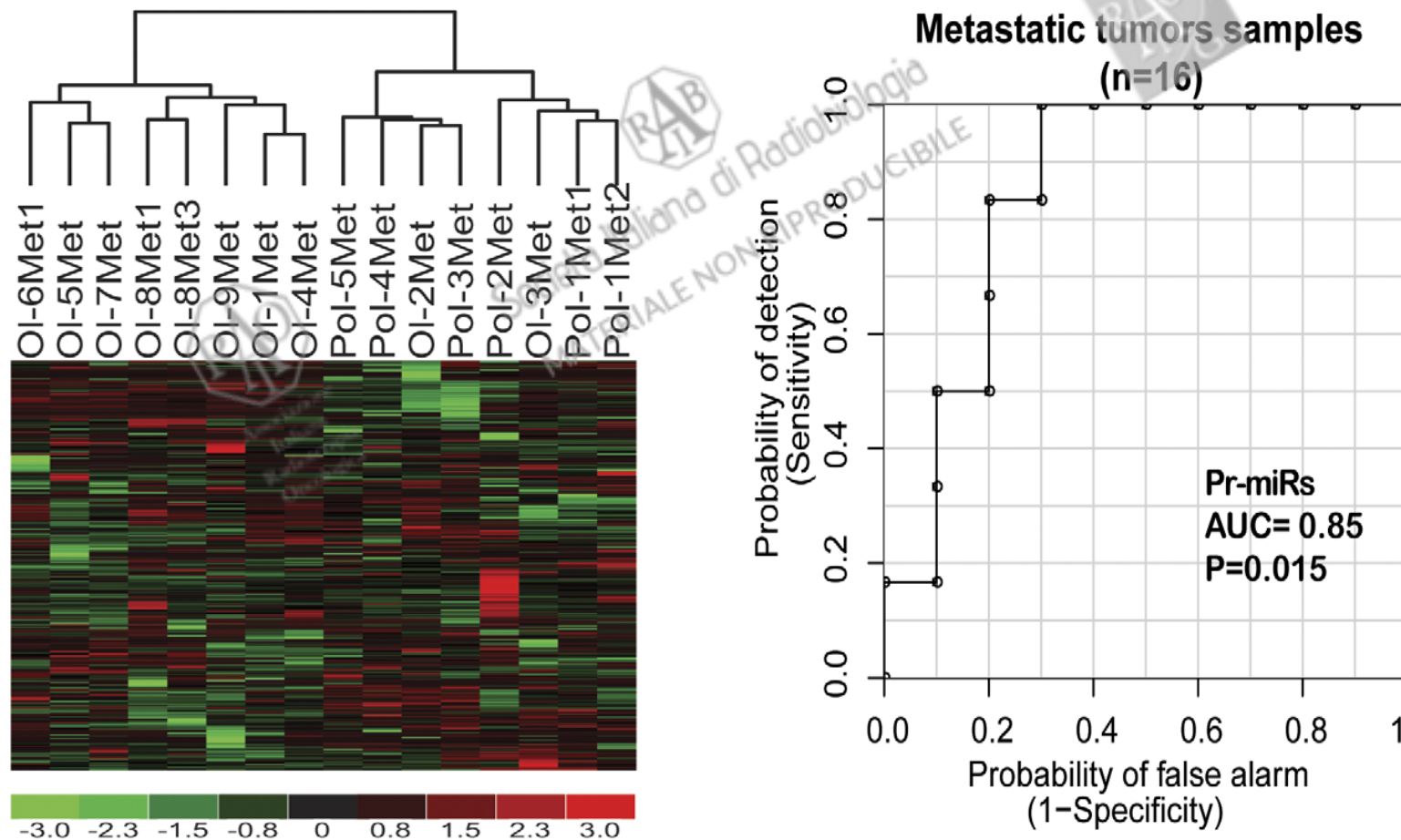


Oligometastases: the new paradigm and options for radiotherapy

- What is the difference in biologic behaviour between synchronous and metachronous lesions?
- How to use available imaging technologies for definition of the oligometastatic state?
- What would be the effective and safe combination with systemic therapeutics like biologicals or conventional chemotherapy?

MicroRNA Expression Characterizes Oligometastasis(es)

Yves A. Lussier^{1,2,3,4*}, H. Rosie Xing^{1,2,5,6}, Joseph K. Salama⁸, Nikolai N. Khodarev^{1,5}, Yong Huang^{1,3}, Qingbei Zhang^{3,6}, Sajid A. Khan⁷, Xinan Yang³, Michael D. Hasselle⁵, Thomas E. Darga⁵, Renuka Malik⁵, Hanli Fan⁶, Samantha Perakis⁵, Matthew Filippo⁵, Kimberly Corbin⁵, Younghee Lee³, Mitchell C. Posner⁷, Steven J. Chmura⁵, Samuel Hellman^{2,5}, Ralph R. Weichselbaum^{1,2,5*}





Message
d'amour des
dauphins

RAO
Società Italiana di Radiologia
ON RIPRODUCIBILE