Il ruolo della Radioterapia nel trattamento del carcinoma prostatico mHSPC

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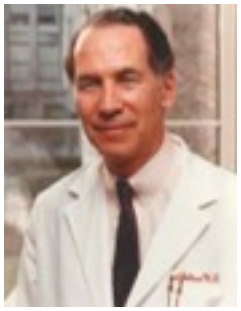
Oligometastatic concept



Greek root *"oligo"* meaning few

- ✓ First proposed by S. Hellmann and R. Weichselbaum in 1995
- ✓ Clinical condition of metastasis where tumors have restricted metastatic capacity
- ✓ Implications: local treatment of metastatic lesion is curative

Oligometastatic prostate cancer (OmPCa)

No Consensus Definition

Most ongoing studies define OmPCa as limited # of metastatic sites

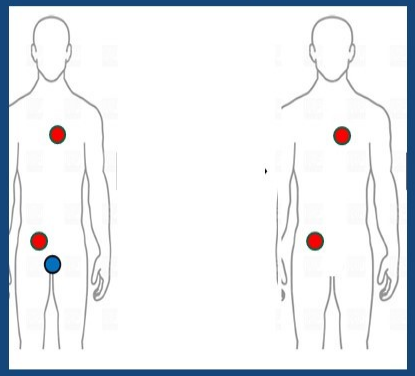
- Typically less than 5
- Typically excluding Liver/Lung/Brain Lesions
- Typically Axial (vs Appendicular) Skeleton

- Imaging: CONVENTIONAL
- Timing: Synchronous/Metachronous

Soloway Cancer 1988; Sweeney NEJM 2015; Hussain NEJM 2013; Eisenberg NEJM 1998; Crawford NEJM 1989

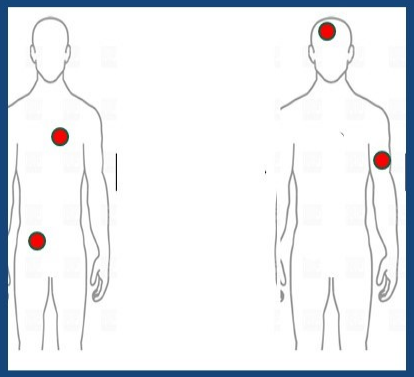
Considerations for consensus definition

Timing



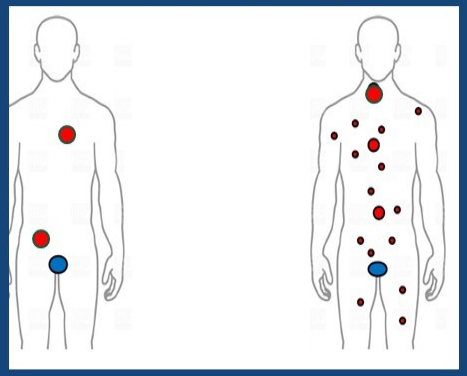
Synchronous vs Metachronous

Location



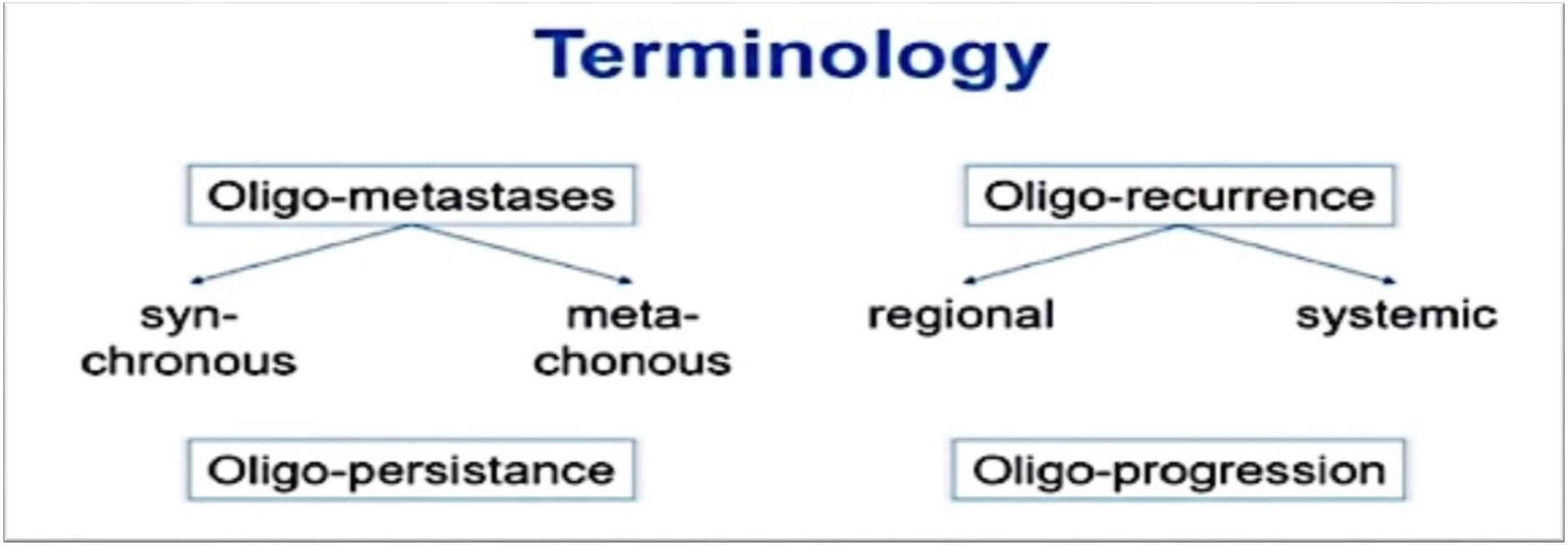
Axial vs Appendicular
Bony vs Visceral

Imaging



Conventional vs Advanced

...oligomeanings



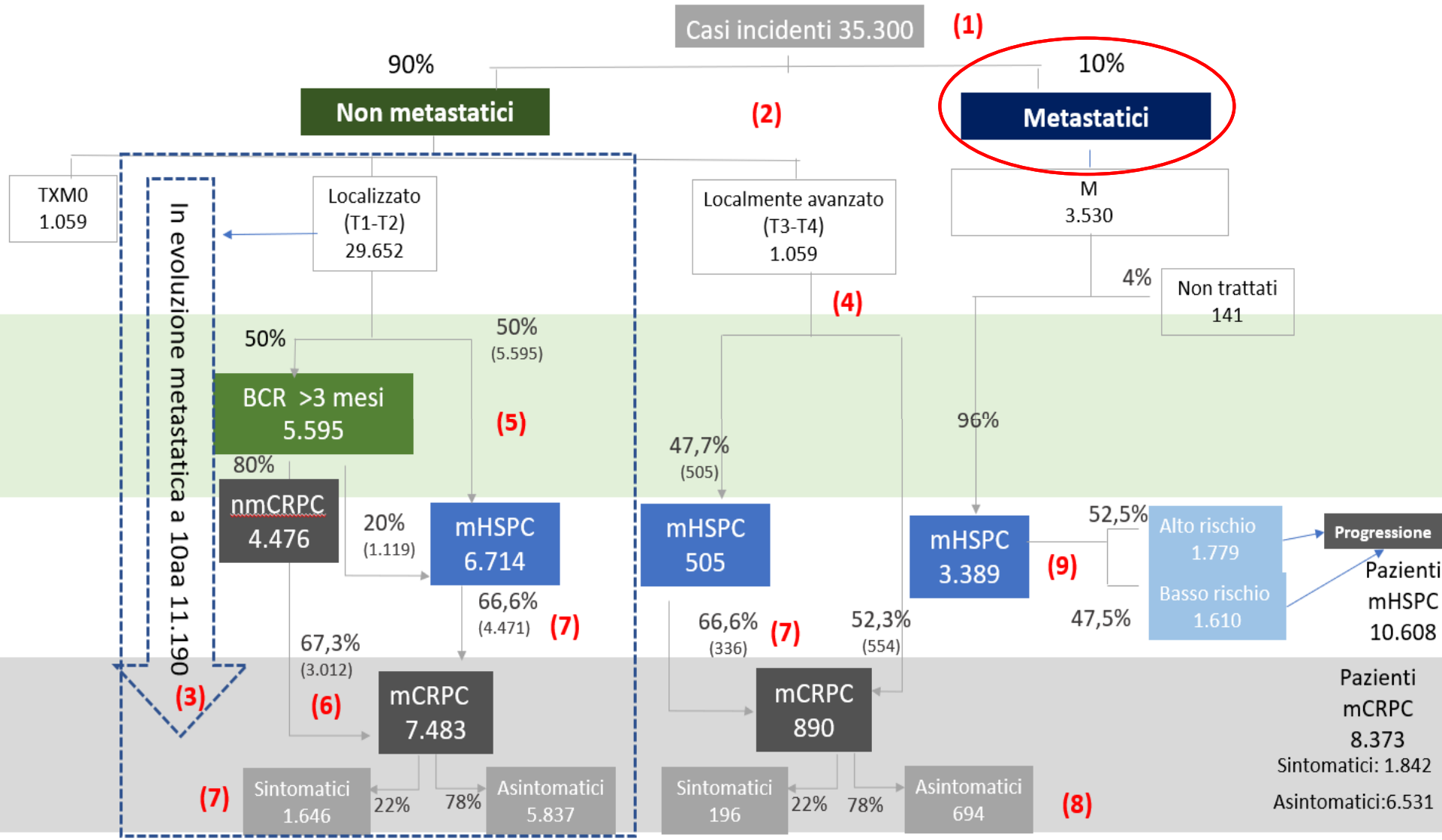
(Oligo) Metastatic Prostate Cancer

- ✓ *De novo* metastatic castration sensiti disease at diagnosis with untreated primary
- ✓ Metachronous cas sensitive disease (primary controlled)

Evidence from RCT

(Oligo) Metastatic Prostate Cancer

- ✓ *De novo* metastatic castration sensitive disease at diagnosis with untreated primary
- ✓ Metachronous castration sensitive disease (primary controlled)


Casi incidenti 35.300
(1)
90%
Non metastatici
(2)
10%
Metastatici
TXM0
1.059
In evoluzione metastatica a 10aa 11.190
(3)
Localizzato
(T1-T2)
29.652
Localmente avanzato
(T3-T4)
1.059
M
3.530
4%
Non trattati
141
(4)
50%
50%
(5.595)
BCR >3 mesi
5.595
(5)
96%
47,7%
(505)
80%
nmCRPC
4.476
20%
(1.119)
mHSPC
6.714
mHSPC
505
mHSPC
3.389
(9)
52,5%
Alto rischio
1.779
Basso rischio
1.610
47,5%
Progressione
Pazienti
mHSPC
10.608
66,6%
(4.471)
(7)
66,6%
(336)
(7)
52,3%
(554)
67,3%
(3.012)
(6)
mCRPC
7.483
mCRPC
890
Pazienti
mCRPC
8.373
Sintomatici: 1.842
Asintomatici:6.531
(7)
Sintomatici
1.646
22%
78%
Asintomatici
5.837
Sintomatici
196
22%
78%
Asintomatici
694
(8)

mHSPC with OS as Primary Endpoint

Study; Total No. (enrollment period)	Experimental Treatment Arm	
GETUG-AFU15[1]; 385 (Oct 2004 to Dec 2008)	Docetaxel	
CHAARTED[3];790 (July 2006 to July 2012)	Docetaxel	0.72 (0.59-0.89); *P* = .001
STAMPEDE-C[3]; 1,817 (Oct 2005 to Mar 2013)	Docetaxel	0.76 (0.[illegible] .005
STAMPEDE-A[4]; 1,002 (Nov 2011 to Jan 2014)	Abiraterone	.001
LATITUDE[5]; 1,199 (Feb 2013 t[illegible]		0.66 (0.56-.78); *P* < .0001
ENZAM[illegible] (Mar 2[illegible]	Enzalutamide	0.67 (0.52-0.86); *P* = .002
TITAN[7]; 1[illegible] 2015 to July 20[illegible]	Apalutamide	0.67 (0.51-0.89); *P* = .005

Practice-changing trials

…but

The benefit of the combination of DOC or ARTA is uncertain

- **in patients with low volume disease* (GETUG-AFU15 and CHAARTED trials)**
- **in older patients* (≥ 70-75 yrs): in the STAMPEDE, ENZAMET, LATITUDE, and TITAN trials**

*the 95% CI for the OS HRs crossed 1

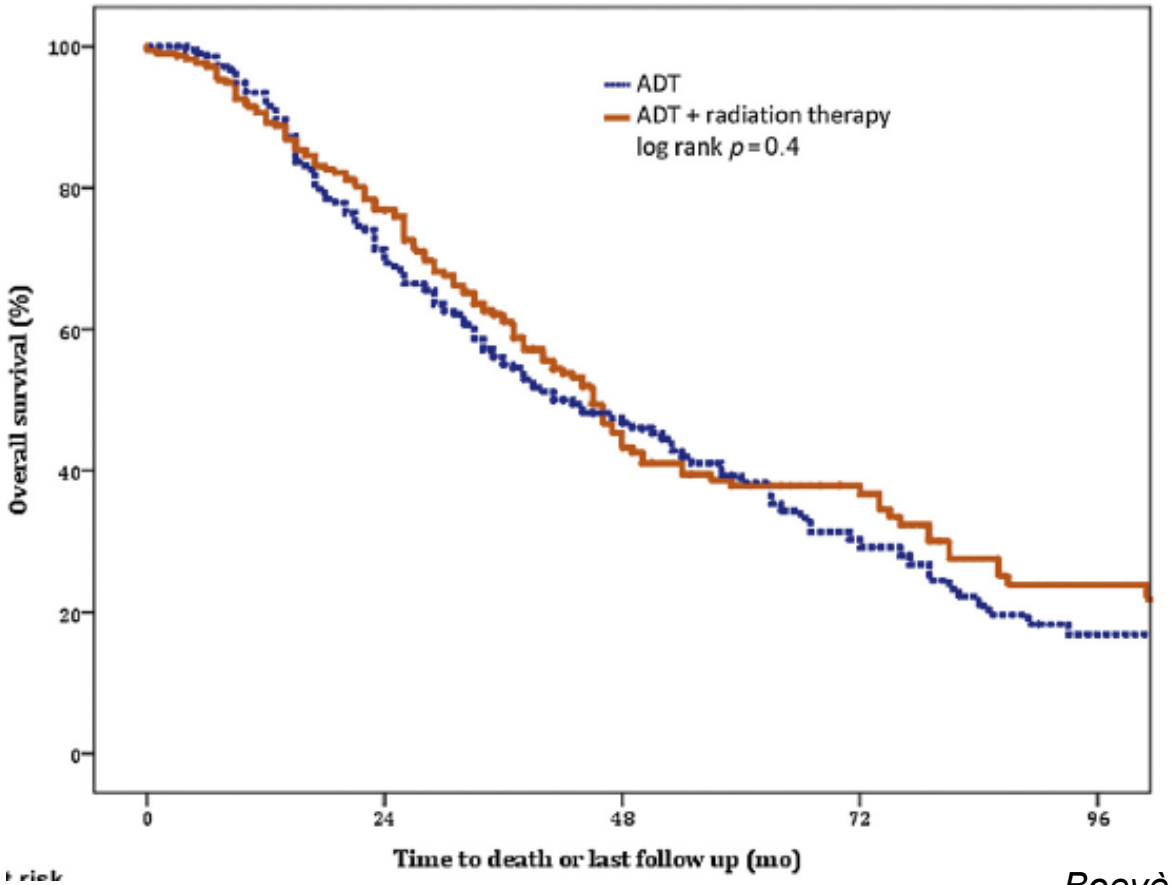
Evidences supporting the role of local treatment in mHSPC

RCT assessing local treatment in mHSPC

Study	Study arms	Patient population	Radiotherapy dose (Gy)/no. of daily fractions	Stratification factors	Primary endpoint	Sample size
HORRAD [1]	ADT vs ADT + EBRT	≥M1a disease (any volume) on standard imaging	70/35 or 57.76/19	No stratification	OS	425
STAMPEDE arm H [2]	ADT vs ADT + EBRT	≥M1a disease (any volume) on standard imaging	55/20 or 36/6 (weekly)	• Center • Age (<70 vs ≥70 yr) • Nodal involvement (negative vs indeterminate vs positive) • WHO PS • Type of ADT • Use of aspirin or NSAID • Use of docetaxel[a]	OS	2061
PEACE-1 (NCT01957436)	ADT (SOC) vs ADT + abiraterone + prednisone vs ADT + EBRT vs ADT + abiraterone + prednisone + EBRT	≥M1a disease (any volume) on standard imaging	74/37	• Center • PS (0 vs 1–2) • Disease extent: LN only vs bone (± LNs) vs presence of visceral metastases • LHRH agonist vs LHRH antagonist vs bilateral orchiectomy	OS and PFS (CRPC PFS)	916
SWOG 1802 (NCT03678025)	SOC vs SOC + local treatment (RP or EBRT)	≥M1a disease (any volume) on standard imaging	79.2–80/44–10 or 60/20 or 36.25/5	• Time between initiation of systemic therapy and step 1 registration • RP vs EBRT • PSA level at randomization (≤4 vs >4 ng/ml) • Disease volume by standard imaging: polymetastatic (>4 sites) vs oligometastatic and no prior treatment vs oligometastatic and prior treatment	OS	1200
TRoMbone (ISRCTN15704862)	SOC vs SOC + RP	Oligometastasis (1–3 osseous lesions on standard imaging), no visceral metastases	NA	Center	Feasibility + expansion cohort (OS)	50
g-RAMPP (NCT02454543)	SOC vs SOC + RP	Oligometastasis (1–5 osseous lesions on standard imaging or PET), no visceral metastases, N1 allowed	NA	NA	PCSS	452

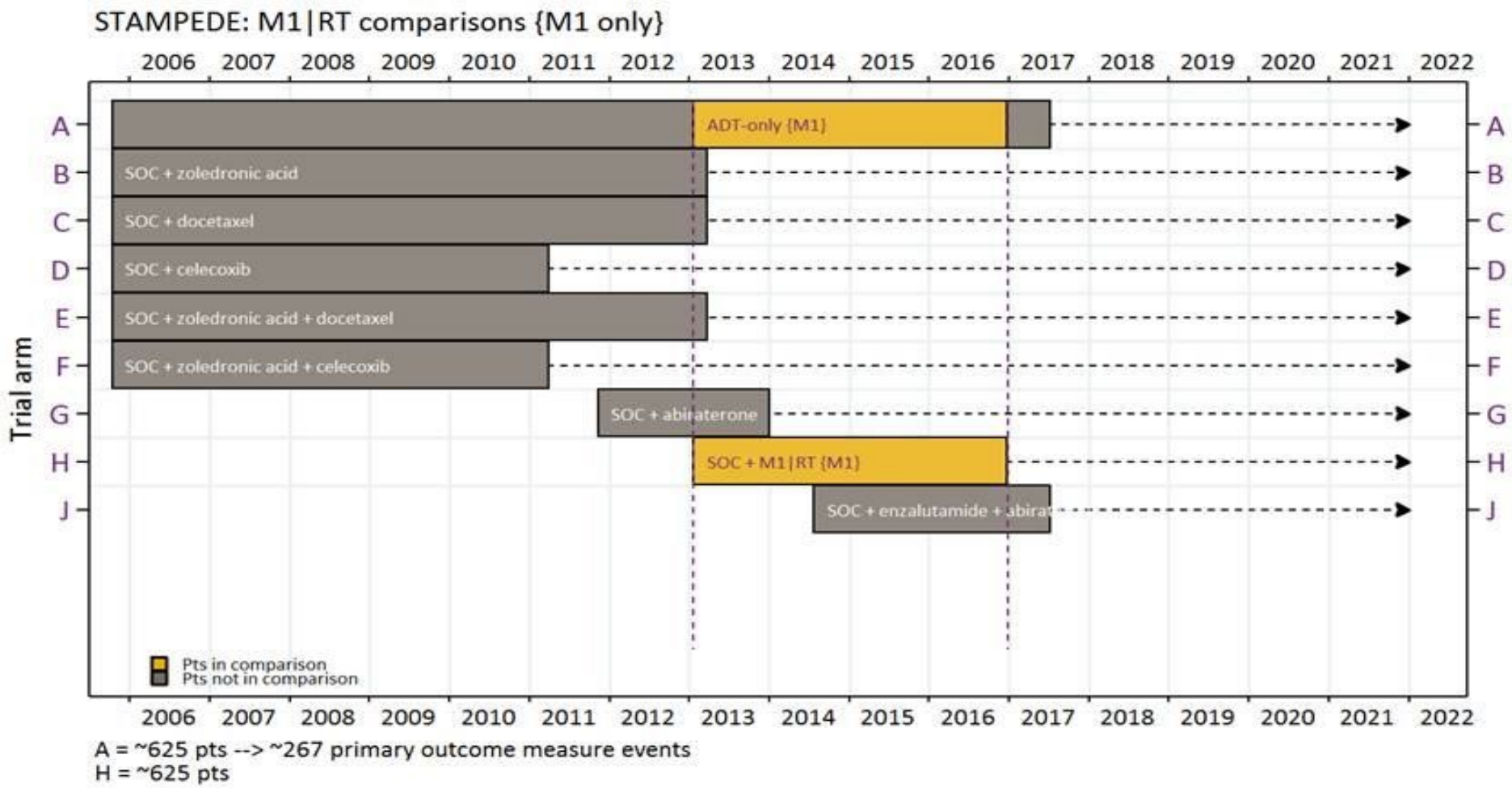
Effect on Survival of Androgen Deprivation Therapy Alone Compared to Androgen Deprivation Therapy Combined with Concurrent Radiation Therapy to the Prostate in Patients with Primary Bone Metastatic Prostate Cancer in a Prospective Randomised Clinical Trial: Data from the HORRAD Trial

Median PSA was 142 ng/ml and 67% of patients had > 5 bone metastases



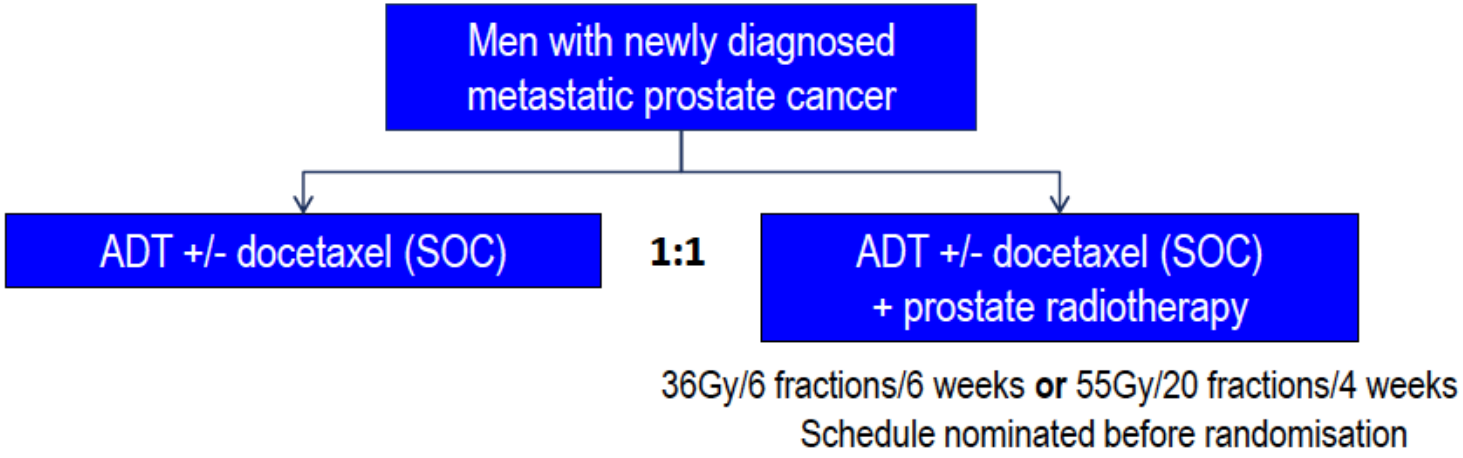
Boevè et al. Eur Urol. 2018

STAMPEDE trial design for M1 disease



Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial

Study design



Stratification variables

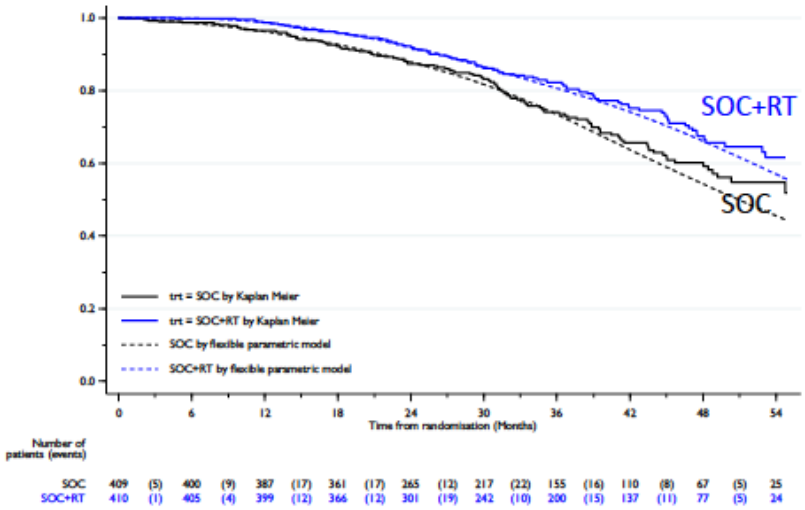
Age (<70 vs ≥70 years), nodal involvement (N0 vs N1 vs Nx), randomising site, WHO performance status (0 vs 1 or 2), type of ADT, aspirin or NSAID use, docetaxel use

Parker et al. Lancet Oncol 2018

Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial

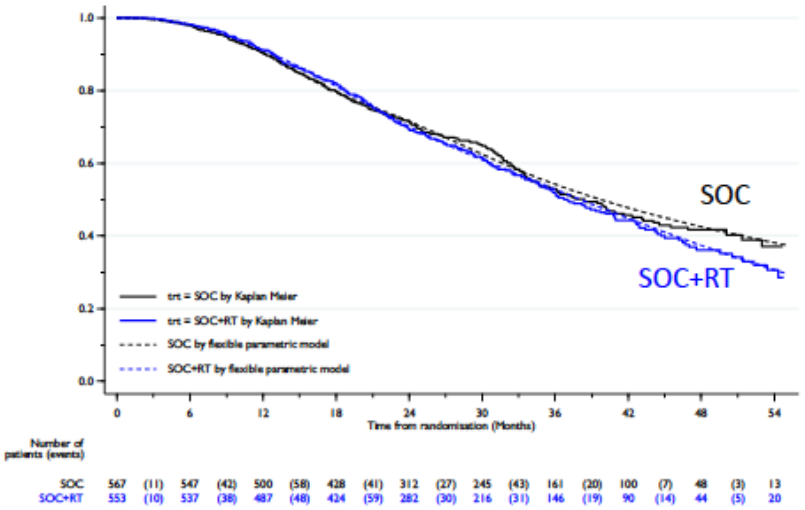
Overall survival: metastatic burden subgroup analysis

Low burden



HR: 0.68 (95% CI 0.52-0.90); p=0.007
3 year OS (%): SOC = 73%
SOC+RT = 81%

High burden



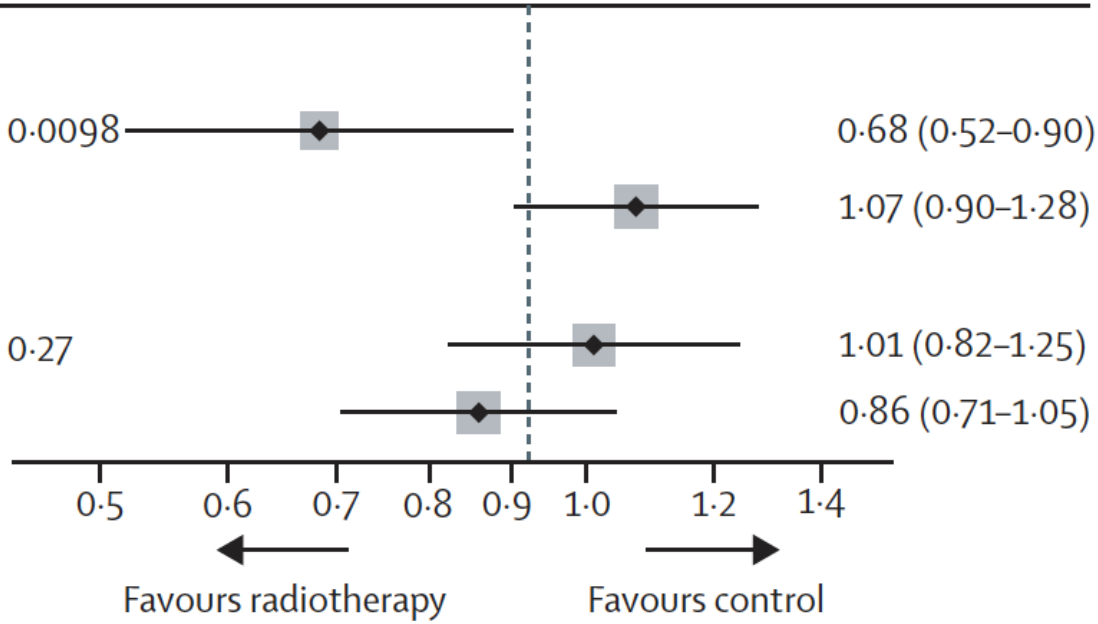
HR: 1.07 (95% CI 0.90-1.28); p=0.420
3 year OS (%): SOC = 54%
SOC+RT = 53%

Parker et al. Lancet Oncol 2018

Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial

A

	Control	Radiotherapy	Interaction p value	HR (95% CI)
	Deaths/N	Deaths/N		
Metastatic burden				
Low burden	116/409	90/410	0·0098	0·68 (0·52–0·90)
High burden	252/567	257/553		1·07 (0·90–1·28)
Radiotherapy schedule				
Weekly	179/482	182/497	0·27	1·01 (0·82–1·25)
Daily	212/547	188/535		0·86 (0·71–1·05)



Parker et al. Lancet Oncol 2018

Low metastatic burden disease is sometimes known as oligometastatic. Although this term is widely used, it is imprecise and potentially misleading because it implies only a small number of metastases. Patients with low metastatic burden disease, according to the CHAARTED definition, may have an unlimited number of metastases provided they are confined to lymph nodes and the axial skeleton.

Parker et al. Lancet Oncol 2018

European Association of Urology

ESTRO European Society for RADIOTHERAPY & ONCOLOGY

European Society of Urogenital Radiology

SIOG INTERNATIONAL SOCIETY OF GERIATRIC ONCOLOGY

Offer castration combined with prostate radiotherapy to patients whose first presentation is M1 disease and who have low volume of disease by CHAARTED criteria.	Weak

Comparison with other recently approved options for low-risk M1 patients

Endpoint	Abiraterone[1,2]	RT to the primary[3]
Absolute 3-yr OS benefit	4%	8%
Grade ≥3 Toxicity	14%	1%
Treatment duration	Often for years (until progression)	As few as 6 treatments
Estimated costs (US)	>$300,000	<$20,000

[1]*Fizazi K et al. NEJM 2017*

[2]*James N et al. NEJM 2017*

[3]*Parker K et al. Lancet Oncol 2018*

Open Issues

- **RT and abiraterone together ?**

  No concerning safety interaction from the STAMPEDE

- **Any benefit in treating metastatic sites ?**

  The next arm of STAMPEDE (arm M) randomizes patients to systemic therapy and RT to the primary ± metastasis-directed therapy

(Oligo) Metastatic Prostate Cancer

- ✓ *De novo* metastatic castration sensitive disease at diagnosis with untreated primary
- ✓ Metachronous castration sensitive disease (primary controlled)

- **75% of patients with recurrence after primary therapy have ≤3 involved sites***

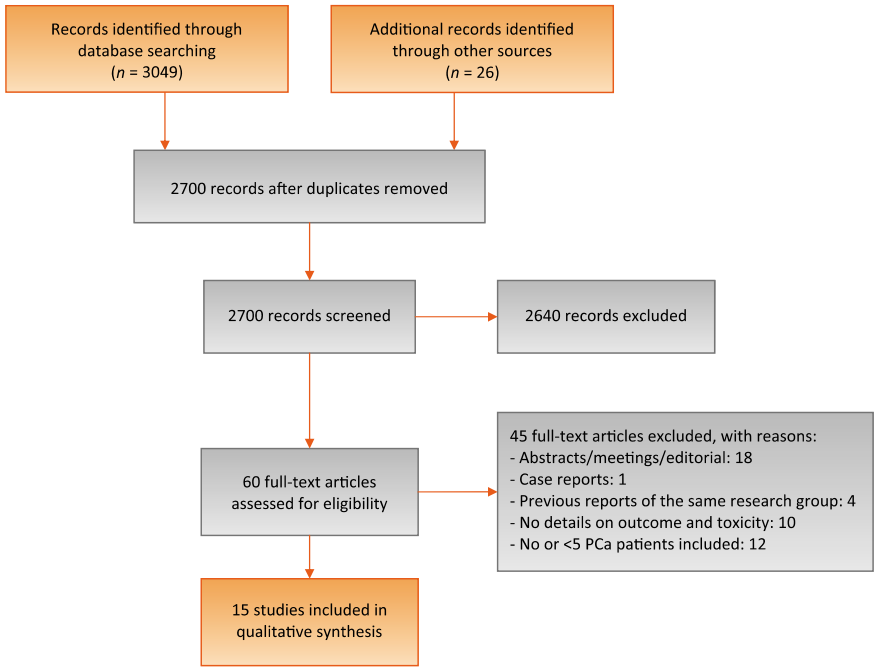
*Singh D, et al. Int J Radiat Oncol Biol Phys. 2004;58:3-10.
Schweizer MT,et al. Ann Oncol. 2013;24:2881-2886.
Sridharan S, et al. Radiother Oncol. 2016;121:98-102.
De Bruycker A, et al. BJU Int. 2017;120:815-821.

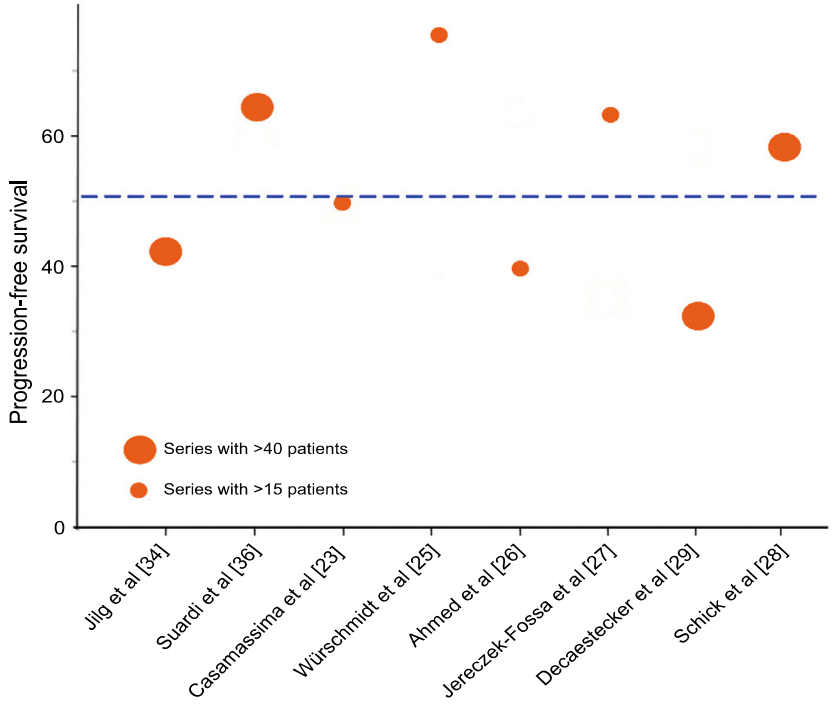
- **The benefit of the combination of DOC or ARTA is uncertain in the subset of men developing metastatic disease after initial local treatment***

*the 95% CI for the OS HRs crossed 1(GETUG-AFU15, CHAARTED and ENZAMET)

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]





Ost et al. Eur Urol 2015

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]

Complication type	Muacevic et al. [24] (*n* = 40), no. (%)	Würschmidt et al.* [25] (*n* = 15), no. (%)	Ahmed et al. [26] (*n* = 17), no. (%)	Jereczek-Fossa et al. [27] (*n* = 19), no. (%)	Decaestecker et al. [29] (*n* = 50), no. (%)	Total (*n* = 141), no. (%)
Grade 1						
Bone pain	0 (0)	0 (0)	0 (0)	0 (0)	3 (6)	3 (2)
Asymptomatic fracture	1 (2.5)	0 (0)	0 (0)	0 (0)	1 (2)	2 (1.4)
Fatigue	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	1 (0.7)
Rectal toxicity	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	2 (1.4)
Urinary toxicity	0 (0)	0 (0)	0 (0)	2 (11)	0 (0)	2 (1.4)
Grade 2						
Nausea requiring antiemetics	5 (12.5)	0 (0)	0 (0)	0 (0)	0 (0)	5 (3.5)
Rectal toxicity	0 (0)	2 (13.3)	0 (0)	1 (5)	2 (4)	5 (3.5)
Urinary toxicity	0 (0)	0 (0)	0 (0)	1 (5)	1 (2)	2 (1.4)
Grade 3						
Urinary toxicity	0 (0)	0 (0)	0 (0)	1 (5)	0 (0)	1 (0.7)

Ost et al, Eur Urol 2015

Long-term Outcomes of Salvage Lymph Node Dissection for Clinically Recurrent Prostate Cancer: Results of a Single-institution Series with a Minimum Follow-up of 5 Years

Nazareno Suardi [a,†], Giorgio Gandaglia [a,†], Andrea Gallina [a], Ettore Di Trapani [a], Vincenzo Scattoni [a], Damiano Vizziello [a], Vito Cucchiara [a], Roberto Bertini [a], Renzo Colombo [a], Maria Picchio [b], Giampiero Giovacchini [b], Francesco Montorsi [a], Alberto Briganti [a,]*

Complication type	Clavien grade	Overall, *n* (%)
Fever	1	18 (30.5)
Lymphorrhea	1	12 (20.3)
Deep venous thrombosis	2	1 (1.7)
Ileus	2	12 (20.3)
Lymphocele requiring drainage	3a	7 (11.2)
Wound infection	3a	3 (5.1)
Surgical reintervention	3b	1 (1.7)

Suardi et al, Eur Urol 2015

What are the data supporting ablative therapy in mHSPC?

Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial

20% from prostate cancer

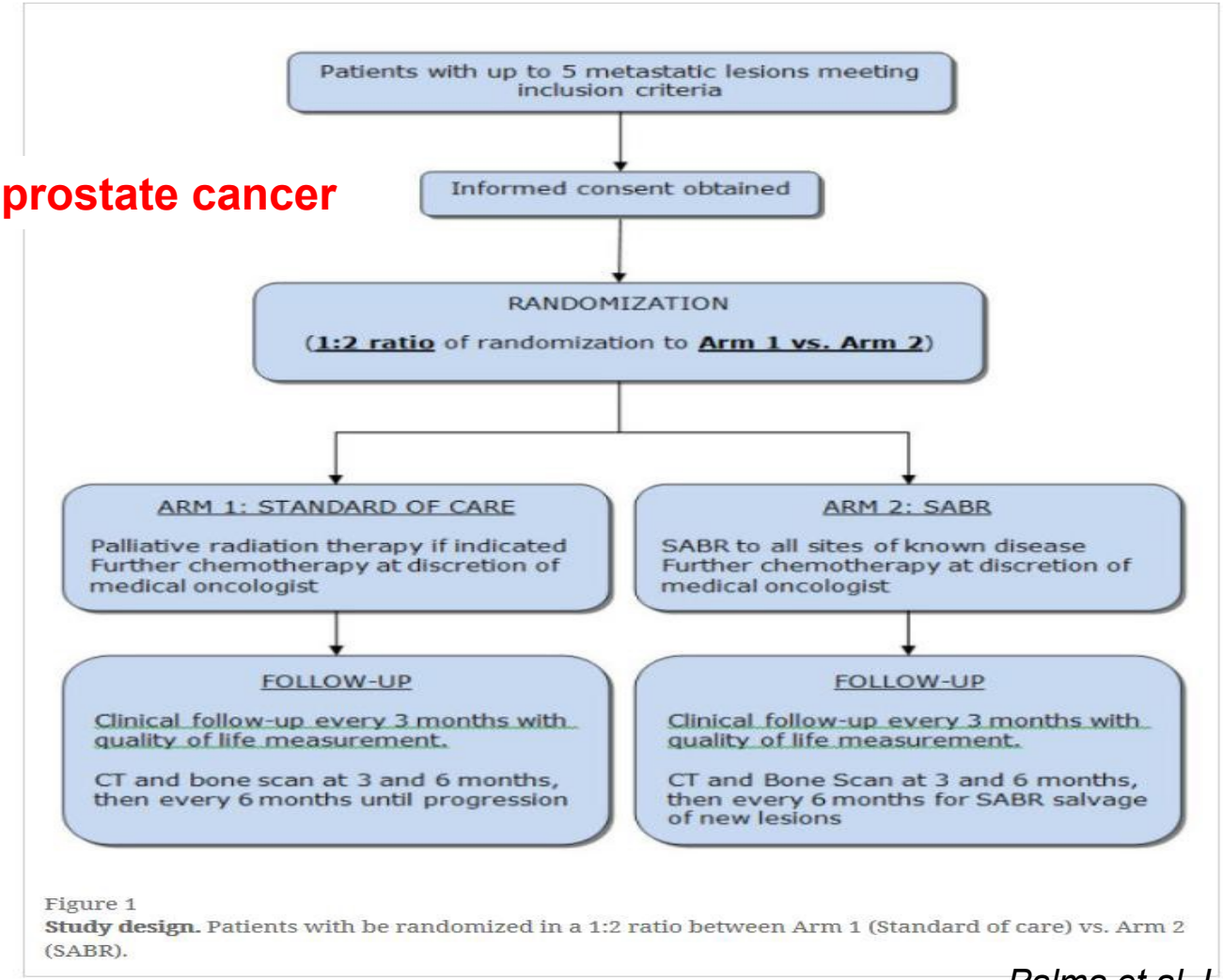
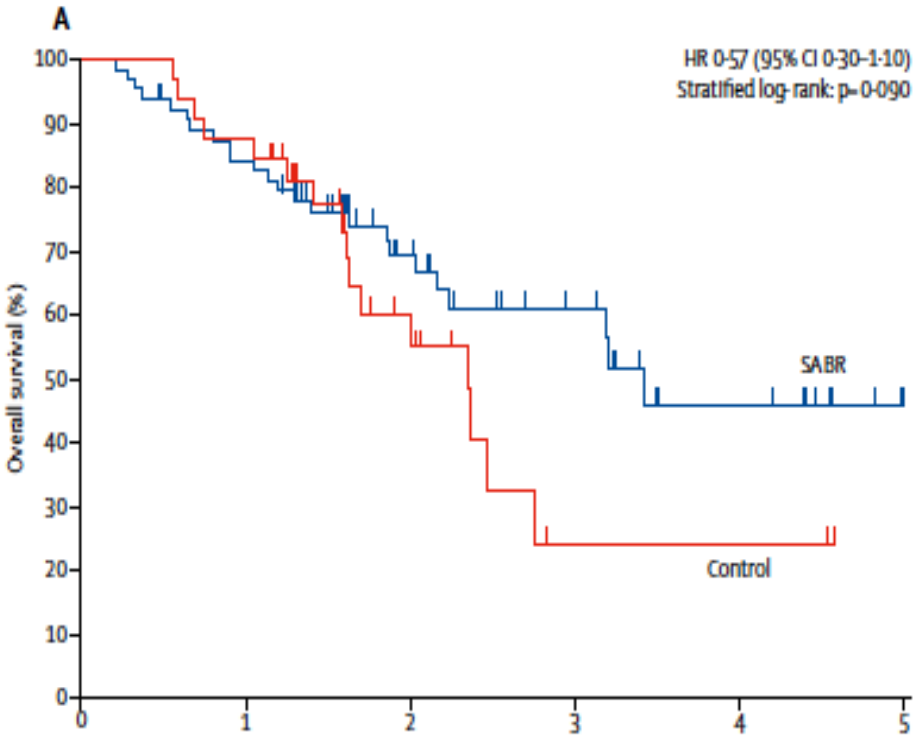


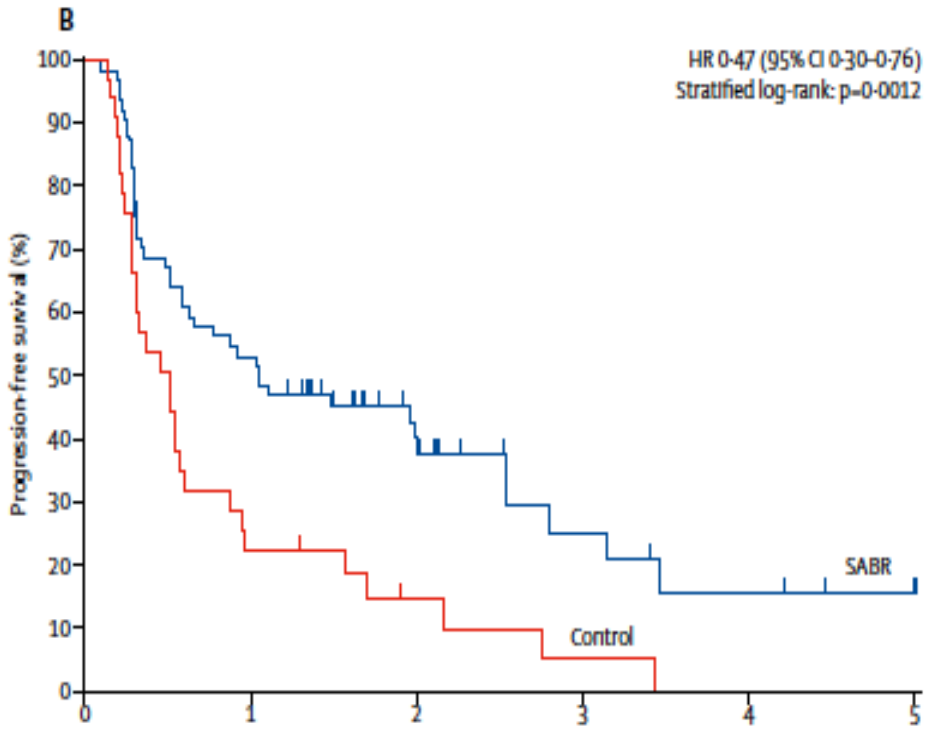
Figure 1
Study design. Patients with be randomized in a 1:2 ratio between Arm 1 (Standard of care) vs. Arm 2 (SABR).

Palma et al, Lancet Oncol 2019

Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial

Median follow up: 26 months



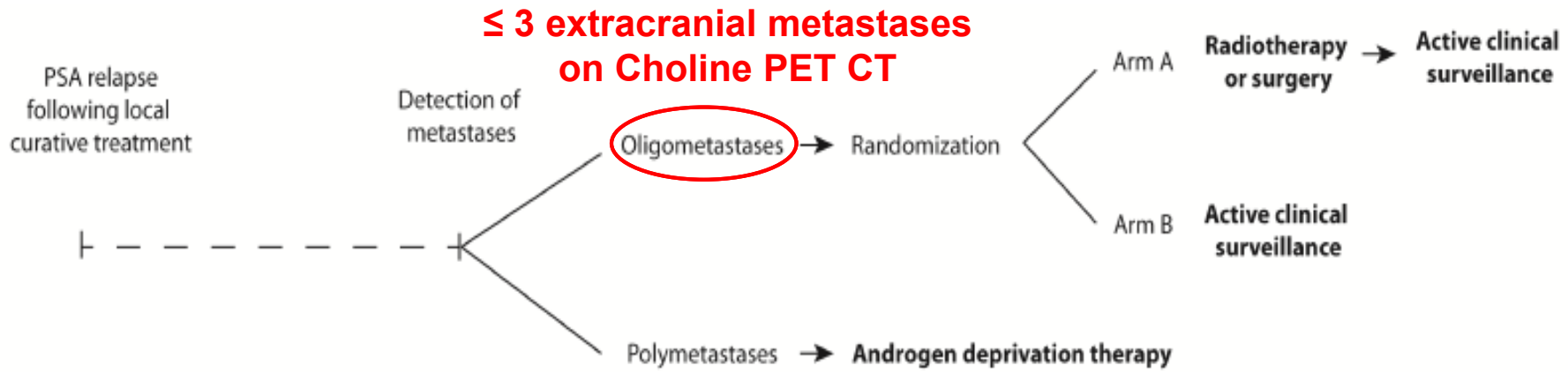


Palma et al, Lancet Oncol 2019

STUDY PROTOCOL Open Access

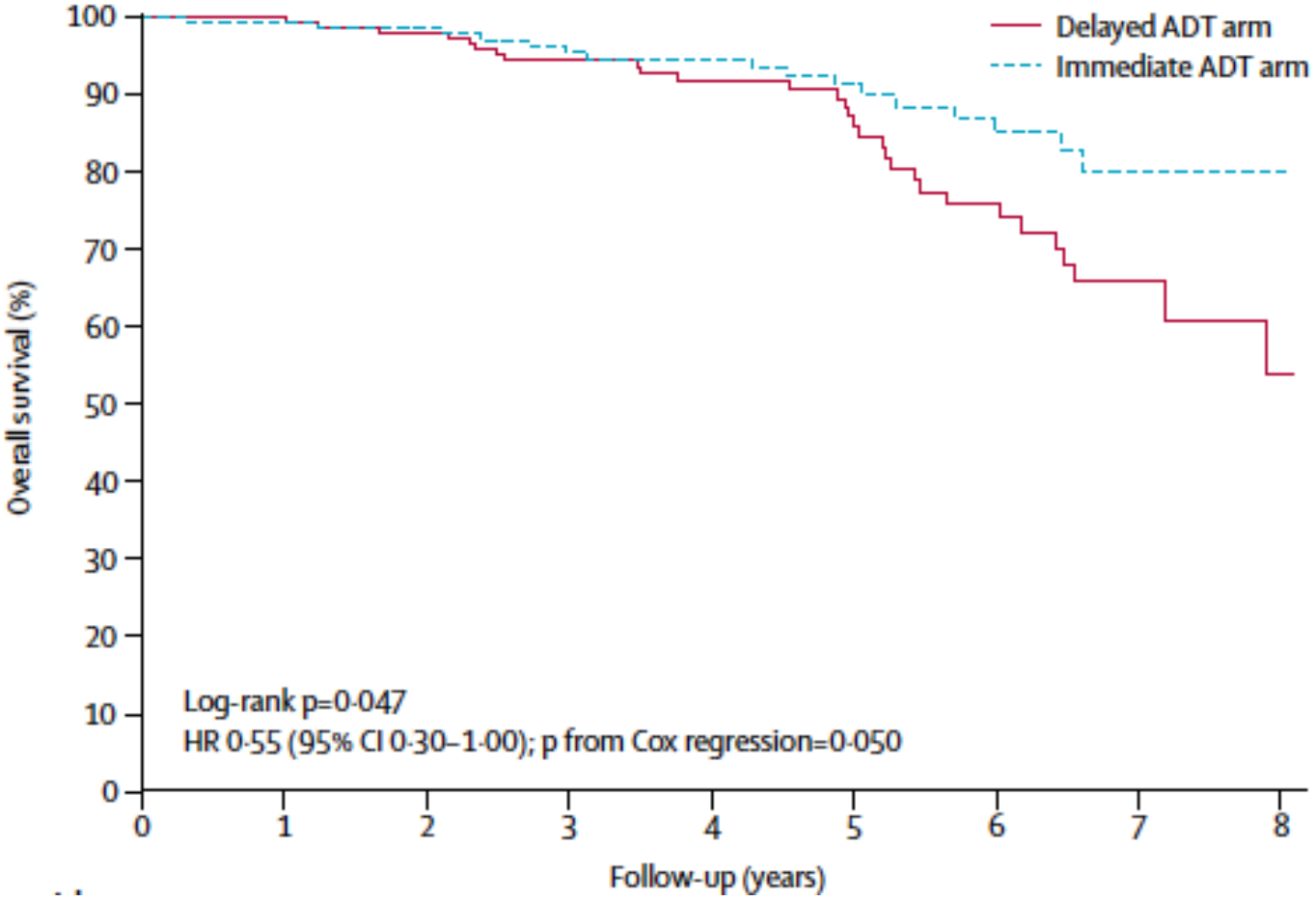
Surveillance or metastasis-directed Therapy for OligoMetastatic Prostate cancer recurrence (STOMP): study protocol for a randomized phase II trial

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*]



Reasons to start ADT: local progression, symptomatic progression or polymetastatic progression

Timing of androgen-deprivation therapy in patients with prostate cancer with a rising PSA (TROG 03.06 and VCOG PR 01-03 [TOAD]): a randomised, multicentre, non-blinded, phase 3 trial



Duchesne et al. Lancet Oncol 2016

Statistical Analysis

This study used a randomized phase II design to determine which arm was justified to be tested in a subsequent phase III trial, with an α and β of 0.20,[18,19] to detect an improvement in ADT-free survival from 12 months in the surveillance group to 24 months in the MDT group. The effect size was based on retrospective studies in the same type of patients.[9,20,21] This corresponds to a hazard ratio (HR) of 0.50. In view of these assumptions, the trial required 62 patients randomly assigned over 36 months, with an additional follow-up of 12 months (assuming a 5% dropout rate).

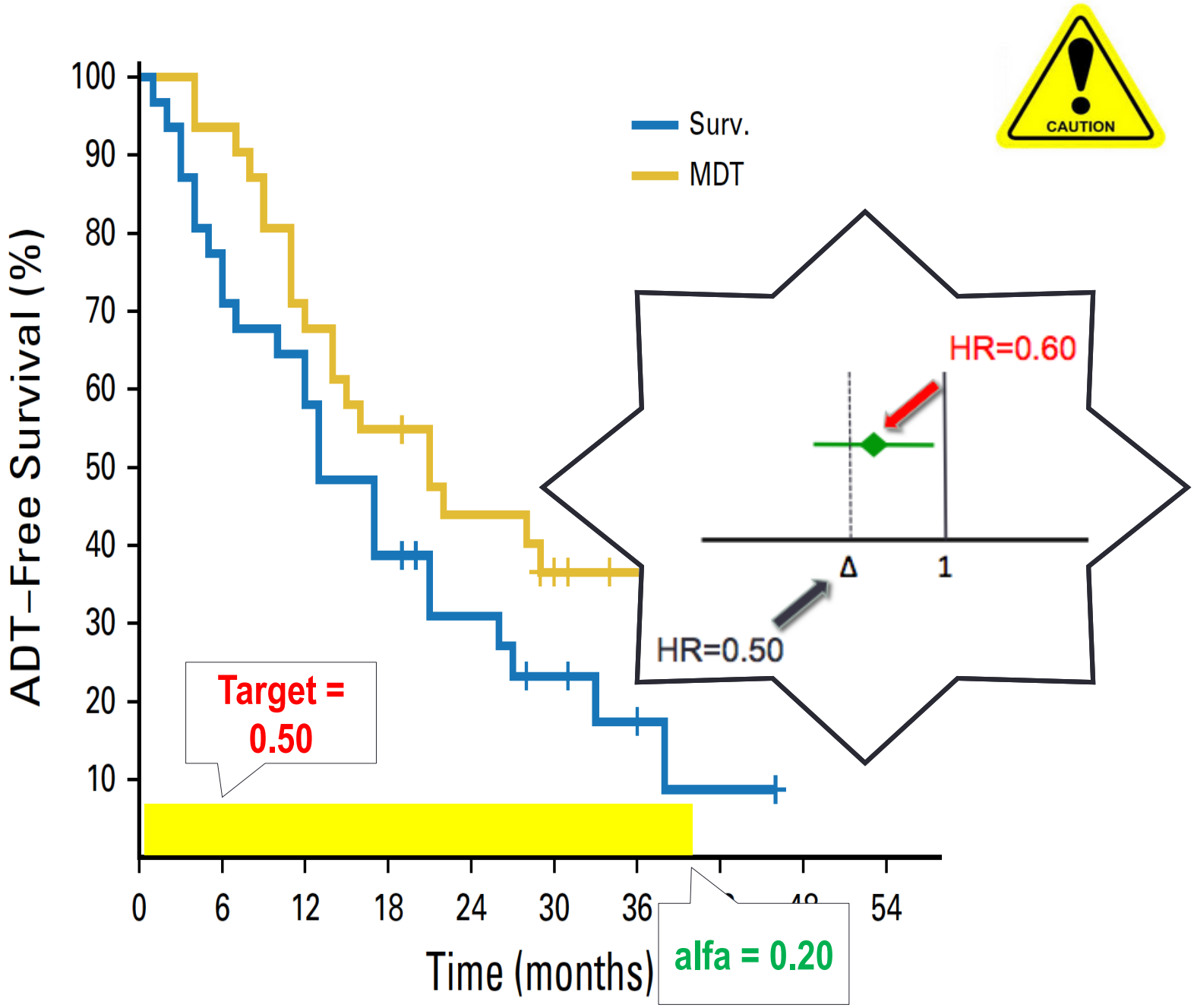

CAUTION
Surv.
MDT
ADT–Free Survival (%)
100
90
80
70
60
50
40
30
20
10
0
6
12
18
24
30
36
54
Time (months)
HR=0.60
Δ
1
HR=0.50
Target = 0.50
alfa = 0.20

Table 2. Indications for Starting Androgen Deprivation Therapy

Indication	Surveillance (n = 31)	Metastasis-Directed Therapy (n = 31)
Not started yet	6 (19)	12 (39)
Polymetastatic progression	16 (55)	19 (61)
Local progression	6 (23)	0 (0)
Symptomatic progression	3 (10)*	0 (0)

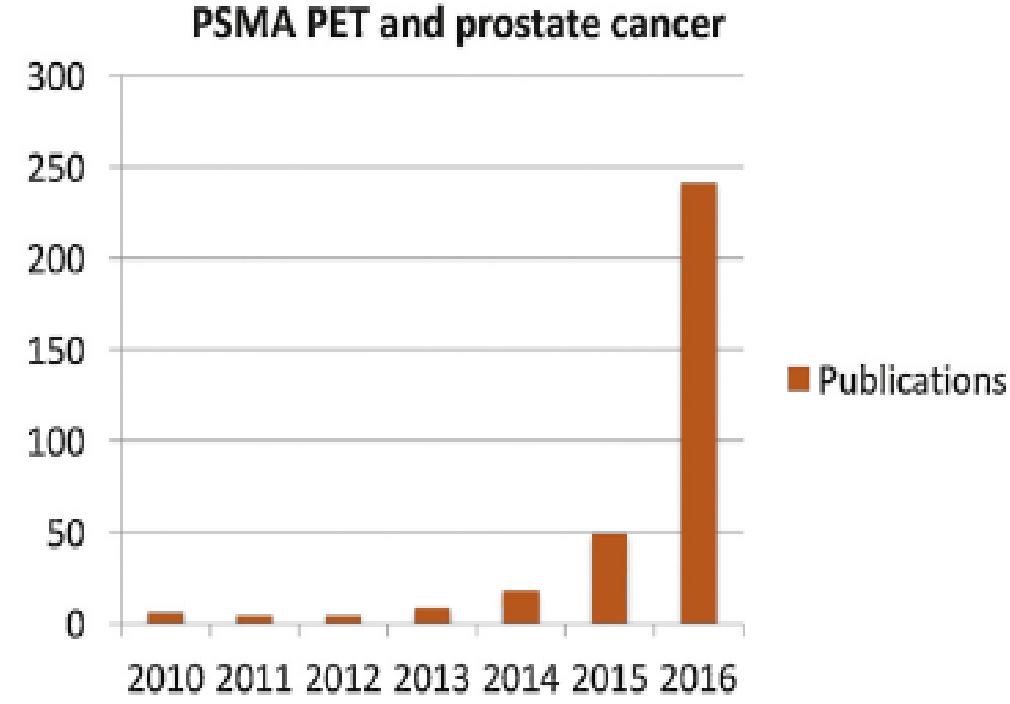
NOTE. Data are presented as No. (%).
*Two patients with symptomatic progression also showed local and polymetastatic progression.

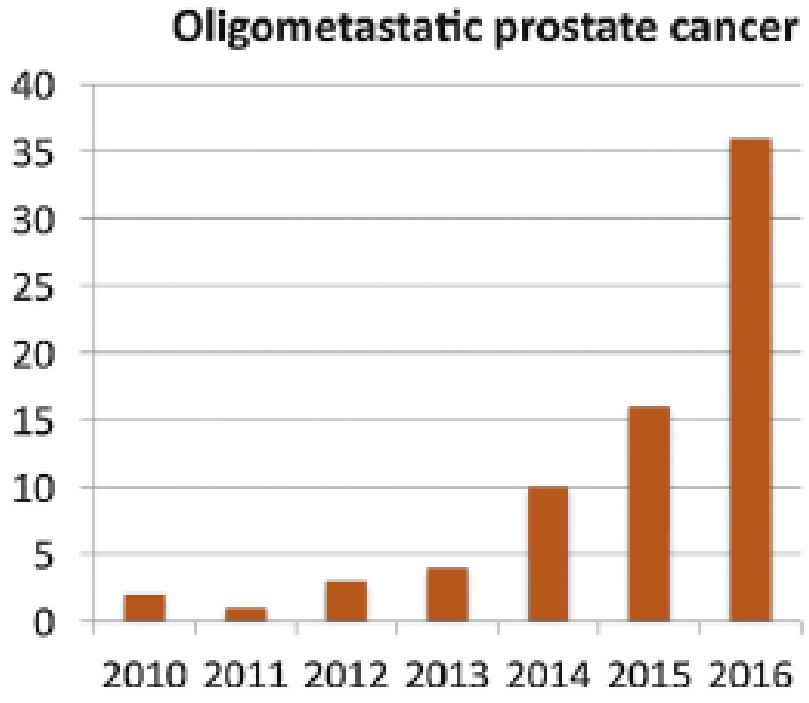
Ost et al. JCO 2018

"Gotta Catch 'em All", or Do We? *Pokemet* Approach to Metastatic Prostate Cancer

Declan G. Murphy [a,b,c,*], *Christopher J. Sweeney* [d], *Bertrand Tombal* [e]

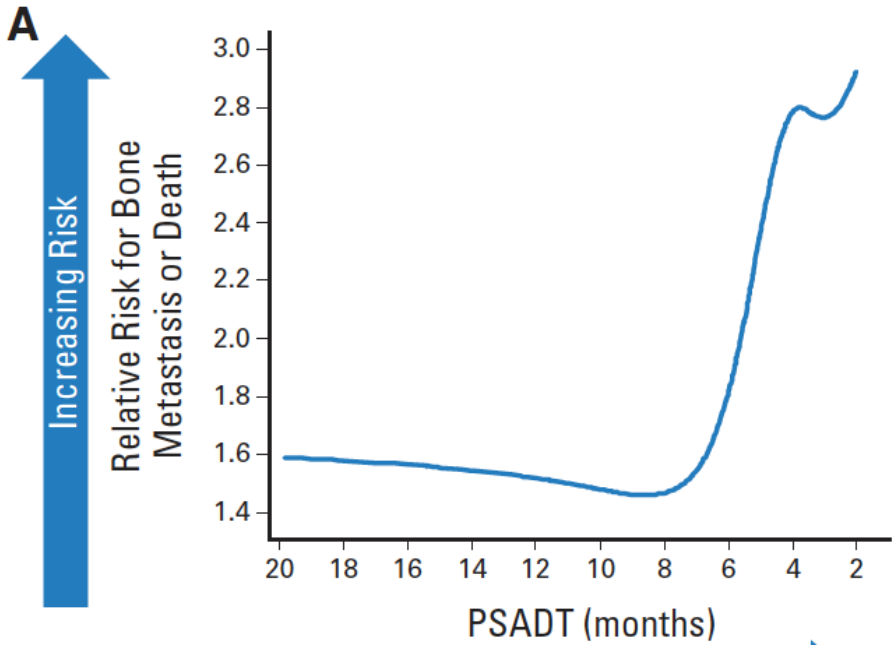
PoKéMeT
Gotta catch 'em all!

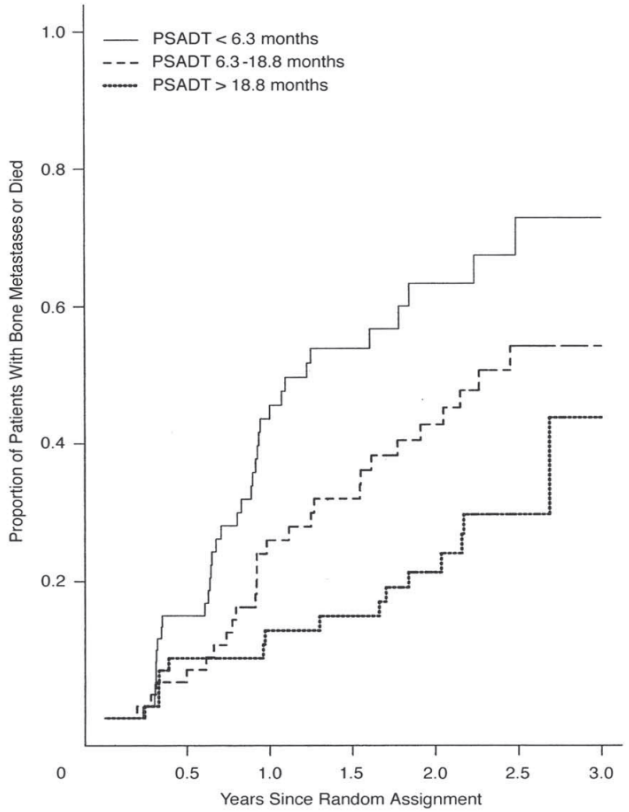




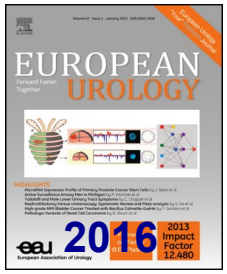
Murphy et al. Eur Urol 2017

PSA-DT <6 mos & new bone mets



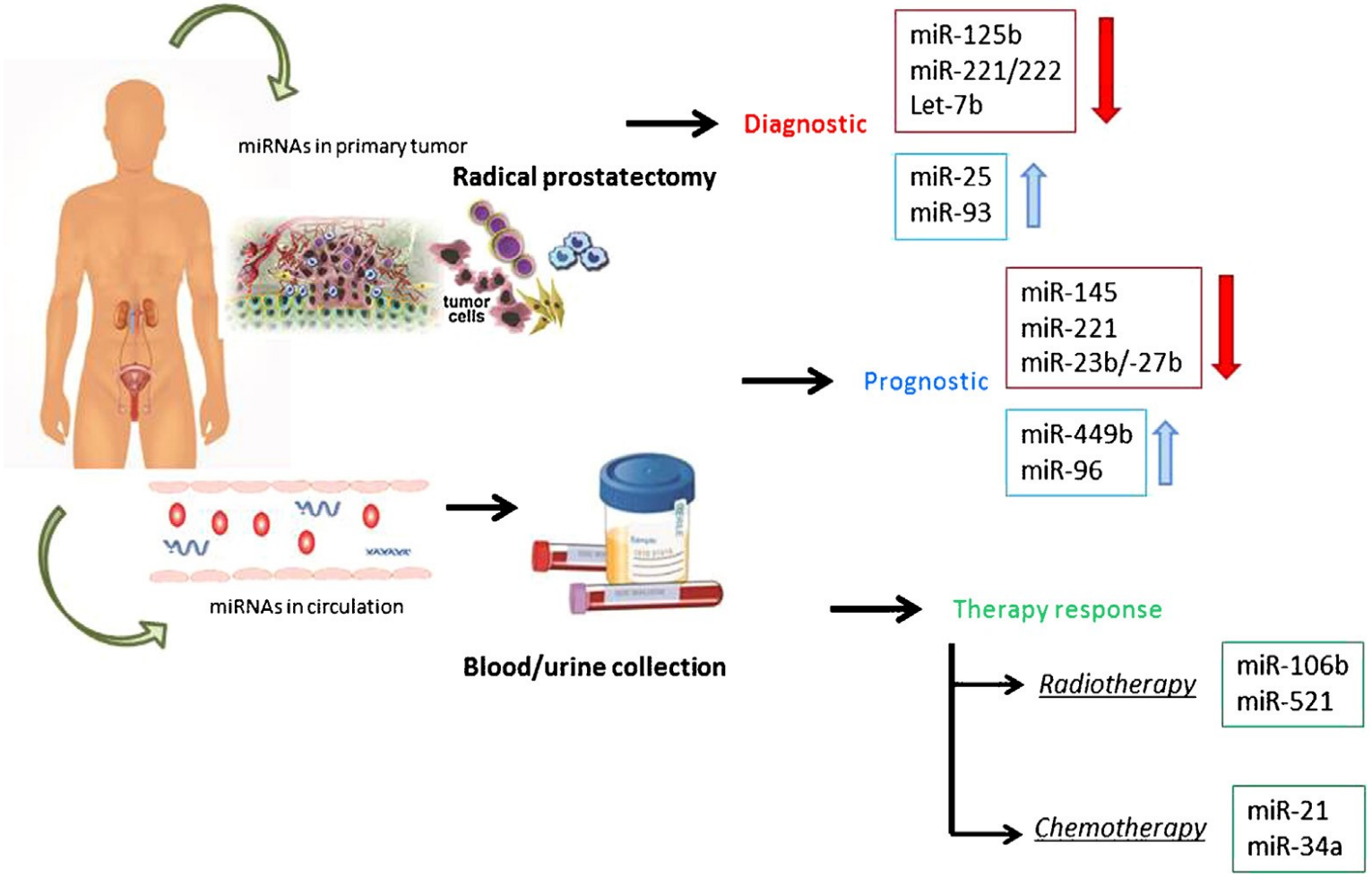


Smith MR et al. J Clin Oncol 2013;31:3800-06.
Smith MR et al. J Clin Oncol 2005;23:2918-25.



The Potential of MicroRNAs as Prostate Cancer Biomarkers

Linda Fabris[a], Yvonne Ceder[b], Arul M. Chinnaiyan[c], Guido W. Jenster[d], Karina D. Sorensen[e], Scott Tomlins[c], Tapio Visakorpi[f], George A. Calin[a,g,*]



Staging the Metastatic Spectrum Through Integration of Clinical and Molecular Features

Corey C. Foster, MD[1]; Sean P. Pitroda, MD[1]; and Ralph R. Weichselbaum, MD[1]

Although a genomic categorization of oligometastatic disease is starting to identify subsets with highly favorable prognoses, using molecular biomarkers to stage a broader spectrum of metastatic patients should be attempted, because even individuals with more than five metastases can have favorable outcomes.

Understand the biology of patient's disease, not just his clinical course!

Foster et al. JCO 2019

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

or

A Brief History of Hypofractionation and its Relationship to Stereotactic Radiosurgery

DAVID I. ROSENTHAL, ELI GLATSTEIN

The Oncologist 1996;1:1-7


Thank you