Oligometastatic (PCa) State: hype, hope and holes in knowledge

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Radiation Oncology
UNIVERSITY OF TORONTO

UHN Princess Margaret Cancer Centre

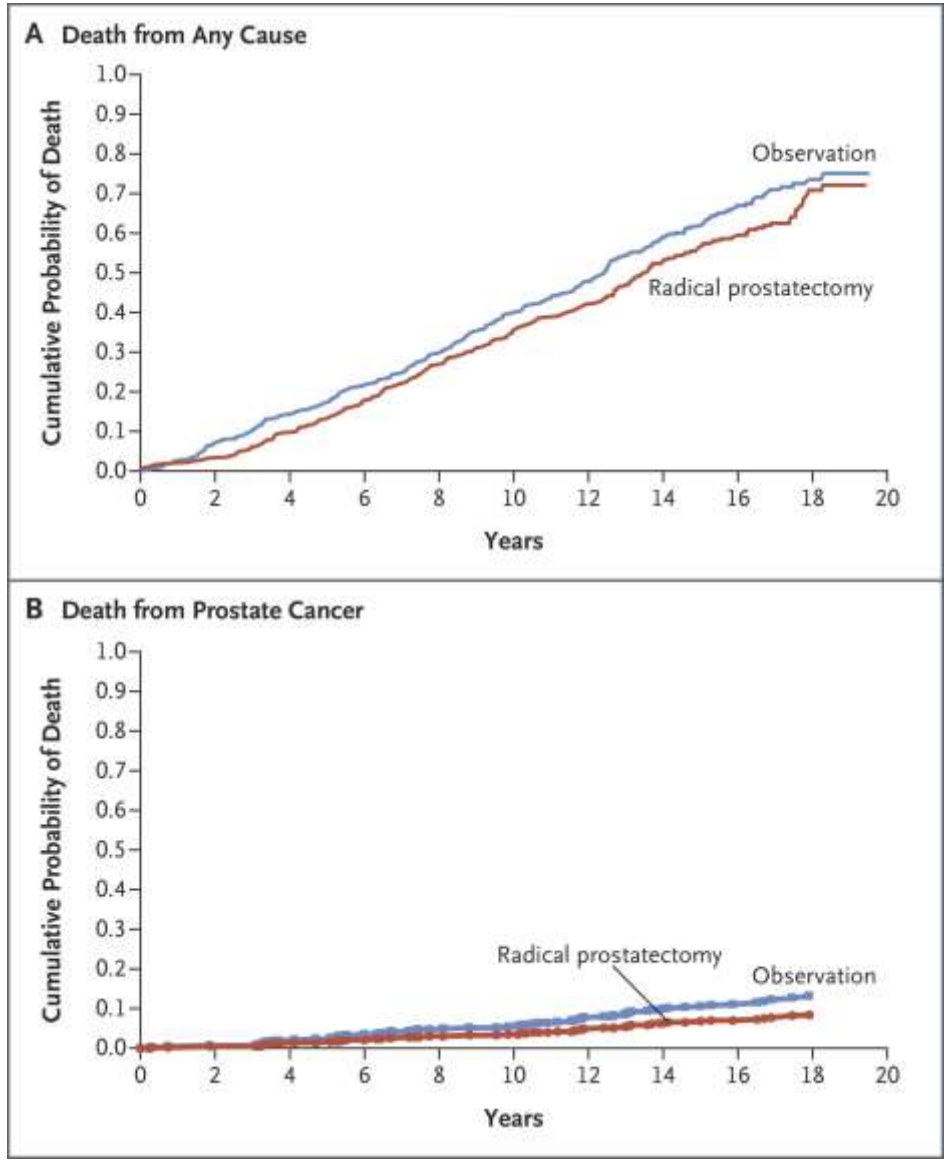
Disclosures

No relevant for this talk

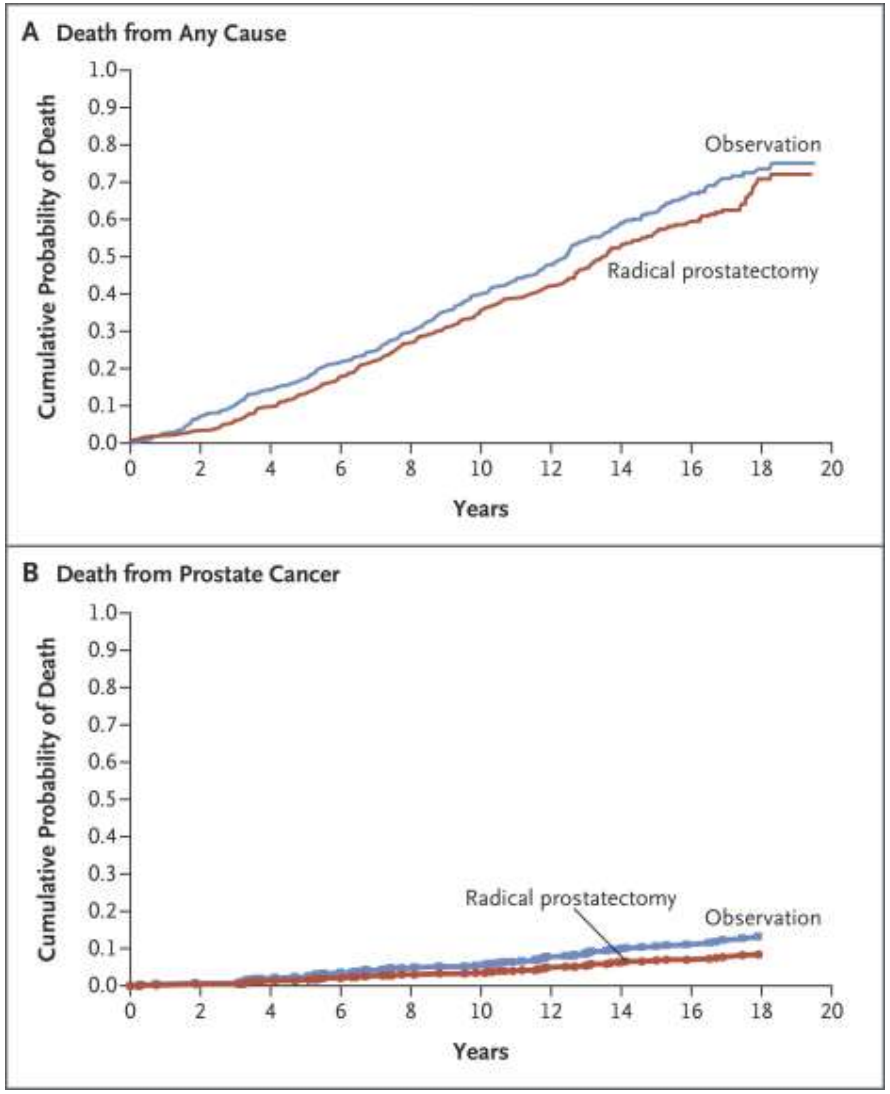
	Company/ Organization	Details
I am a member of an **Advisory Board or equivalent** with a commercial or non-commercial organization	Vaccinex Inc (VCNX, Nasdaq)	
I have **received a grant(s**) or an honorarium from a commercial or non-commercial organization.	Abbvie, Astellas, Sanofi, GenomeDX.	Grants
I **hold investments** in a pharmaceutical organization, medical devices company or communications firm.	Vaccinex Inc (VCNX, Nasdaq) Avicanna Inc	Stock Options
I am currently participating in or have participated in a **clinical trial** within the past two years.	NRG-GU006 (local PI) FPX-01-01 (RLT anti IGF-1R)	Janssen and GenomeDX Fusion Pharmaceuticals Inc

Disclosures

First lets contextualize the non-‘extreme’



Oh boy….


A Death from Any Cause
Cumulative Probability of Death
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Observation
Radical prostatectomy
0 2 4 6 8 10 12 14 16 18 20
Years
B Death from Prostate Cancer
Cumulative Probability of Death
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Radical prostatectomy
Observation
0 2 4 6 8 10 12 14 16 18 20
Years


Drink
this much
every
day!
A FULL
BIG
GLASS

Presentation Schema

- Oligometastatic (OM) State in Oncology
  - Overarching hypothesis
  - Evidence of existence and treatment benefit
  - Some definitions
- OM/OR State in PCa
  - Evidence supporting existence
  - Treatment results
- Final thoughts

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Oligometastatic State

- M1 = incurable…. but….
  - “Cancer comprises a biological spectrum, extending from when a disease is localized to one that is systemic when first detectable but **with many intermediate states**.”
  - “An attractive consequence [of the] oligometastatic state is that some patients should be **amenable to a curative therapeutic strategy**”
- Hot topic

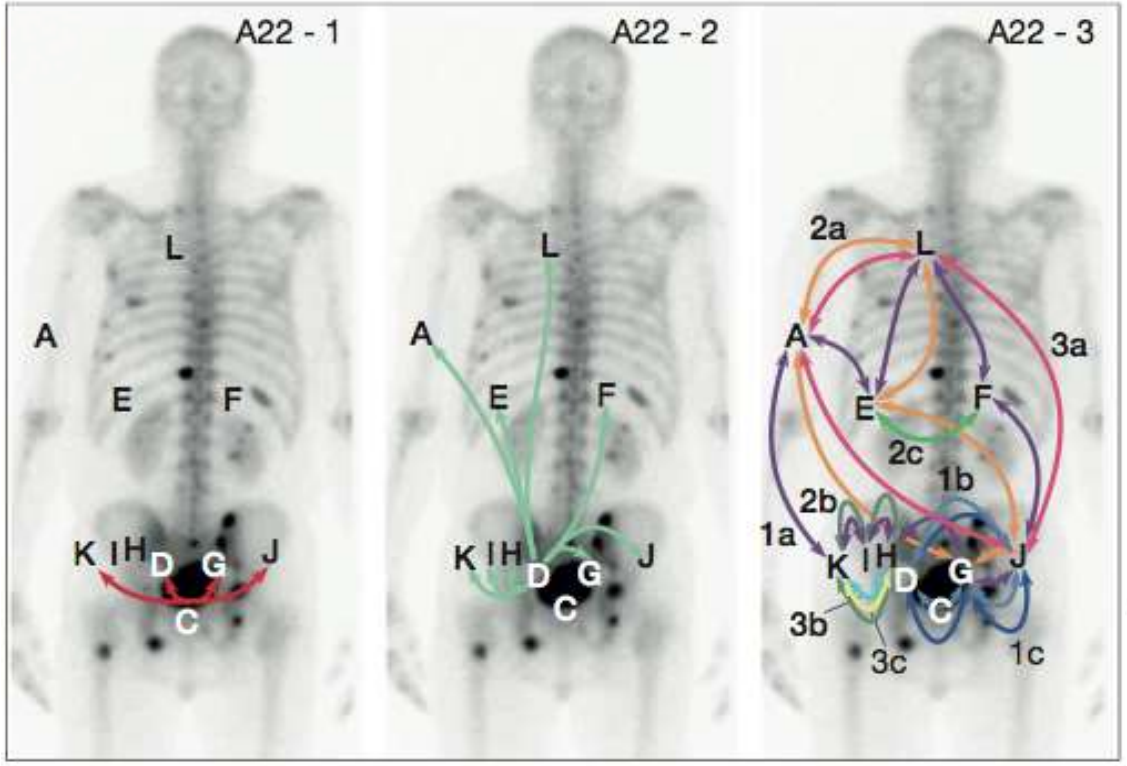
Hellman & Weichselbaum. JCO 1995

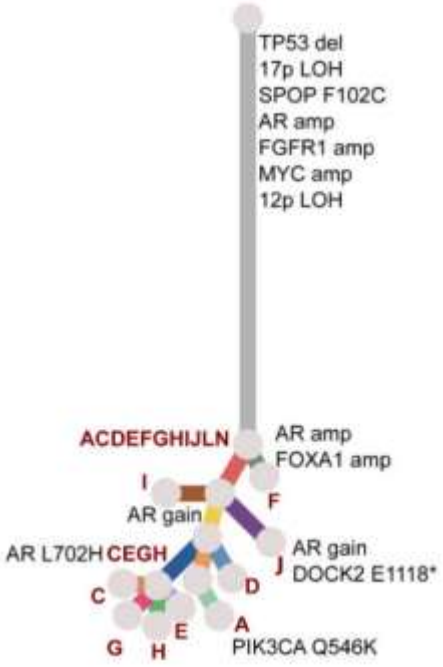
Substantiation of the Paradigm

- Translational research
- Improved imaging methods
- Improved systemic therapies to treat additional microscopic sites (contradictory?)
- Advancements in surgery (e.g. laparoscopic, robotic)
- Advancements in radiotherapy (e.g. SBRT)

But question remains: Fact or Fantasy?

Example in PCa: Biologic Correlate





- Complex (and various) seeding patterns

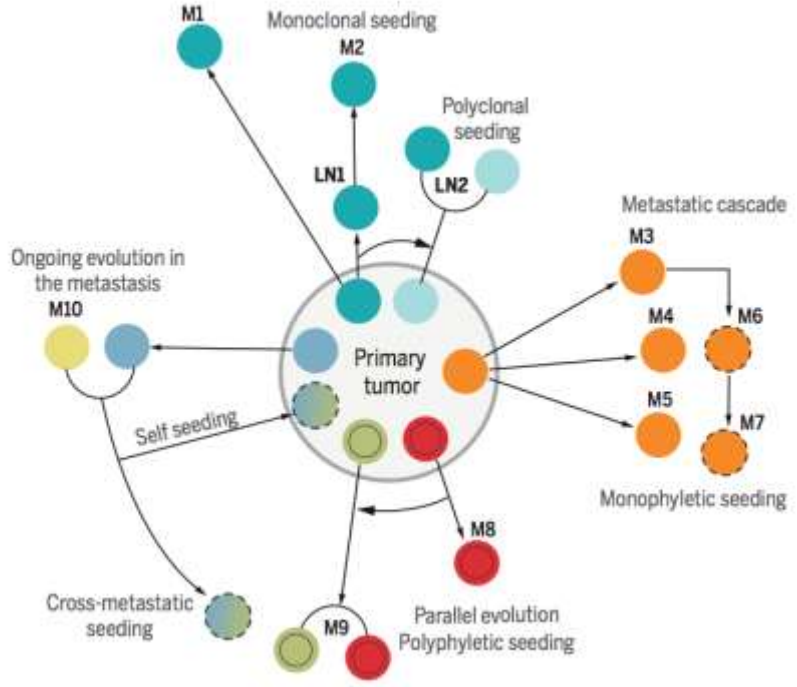
- Mets can evolve capacity to seed subsequent Mets: rapid succession, little intervening evolution

Potential(s): Prevent/Delay CRPC emergence? Cure?

Gundem et al. Nature 2015 ; Shen. Nature 2015

OM State: Clinical arguments (aka evidence)

- Subset of patients with M1 disease do well
- Non-randomized experience(s)
- Randomized evidence
- Refining definitions:
  - synchronous vs metachronous
  - de novo vs OM recurrence vs OM progression
- Recent trials



Models simpler that reality: Complexity imported into the clinics

Turajlic and Swanton. Science 2016

Observational & Obstinate-ional Evidence

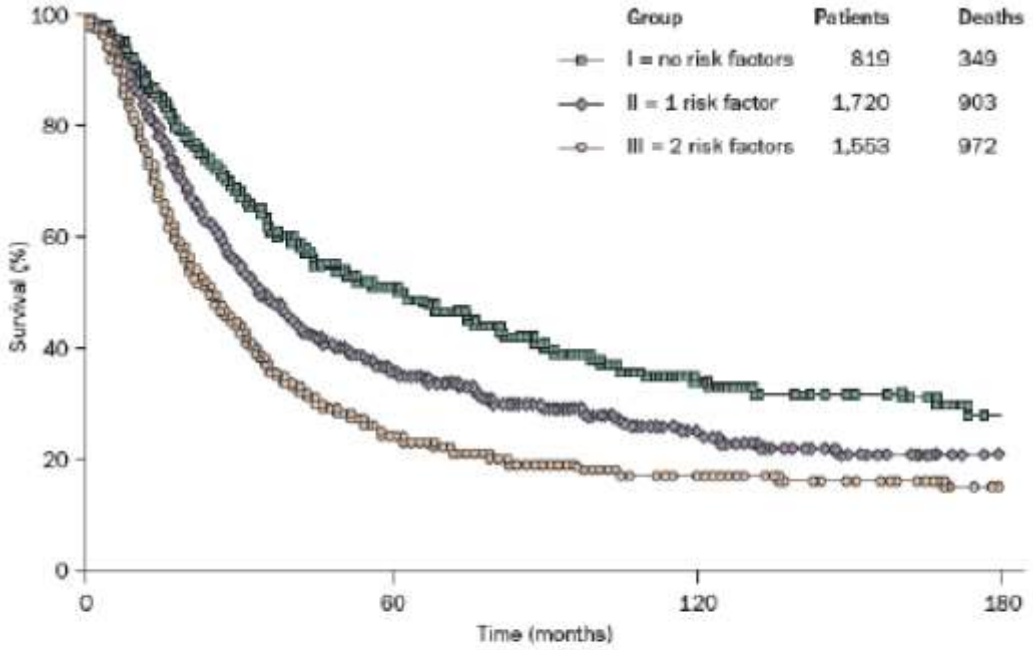


Figure 1 | Survival of patients undergoing pulmonary resection of metastatic tumors. Each curve represents the survival of patients with an increasing number of risk factors for recurrence as determined by a retrospective review of the data.[7] These categories are: group I, a single resectable metastasis with a disease-free interval from primary tumor to metastasis of ≥36 months; group II, multiple metastases or a disease-free interval <36 months; group III, multiple metastases and a disease-free interval <36 months. The size, number and tumor type are risk factors for recurrence. Permission obtained from Elsevier © Pastorino, U. *et al. J. Thorac. Cardiovasc. Surg.* **113**, 37–49 (1997).

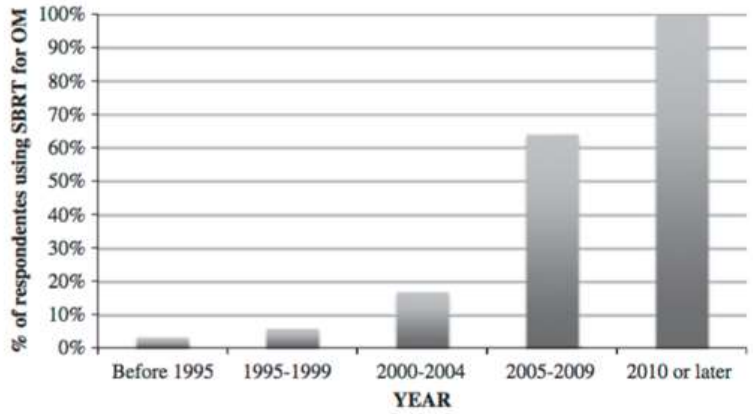


FIGURE 1. Cumulative percentage of respondents using stereotactic body radiotherapy (SBRT) for oligometastases during the defined time intervals.

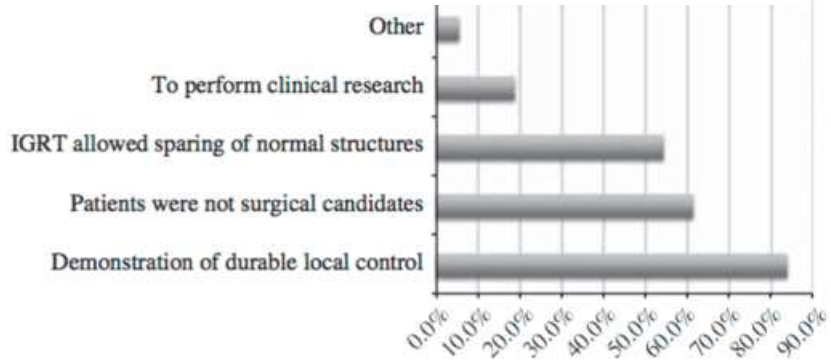
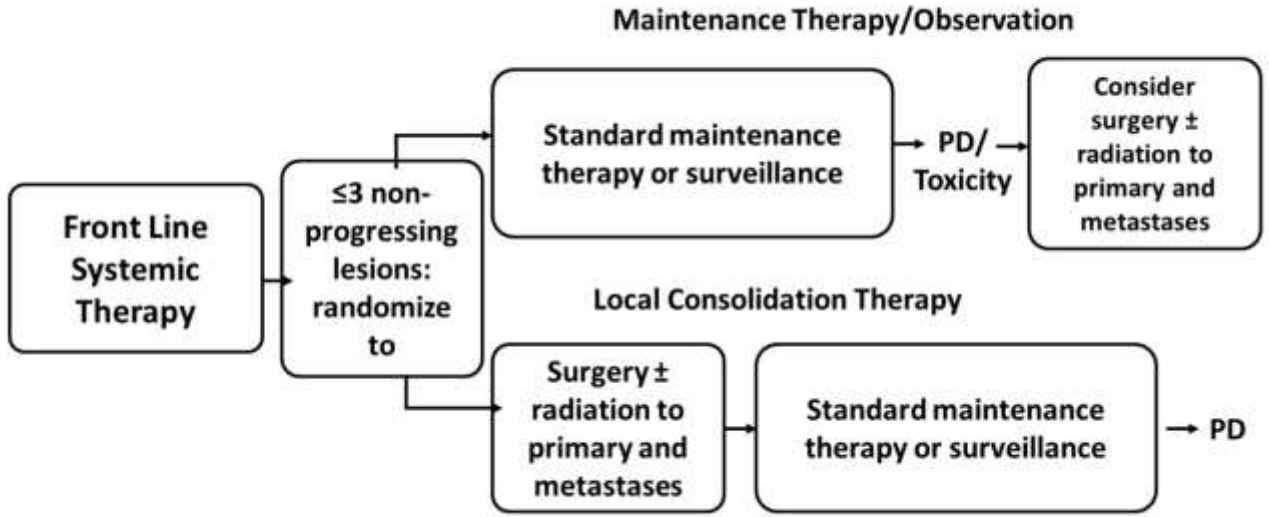
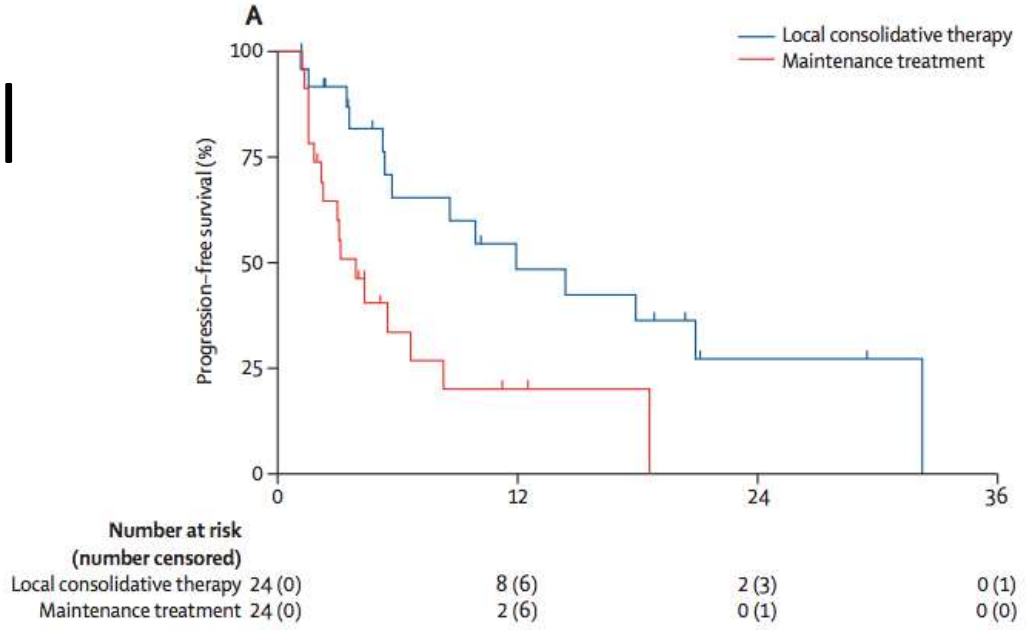


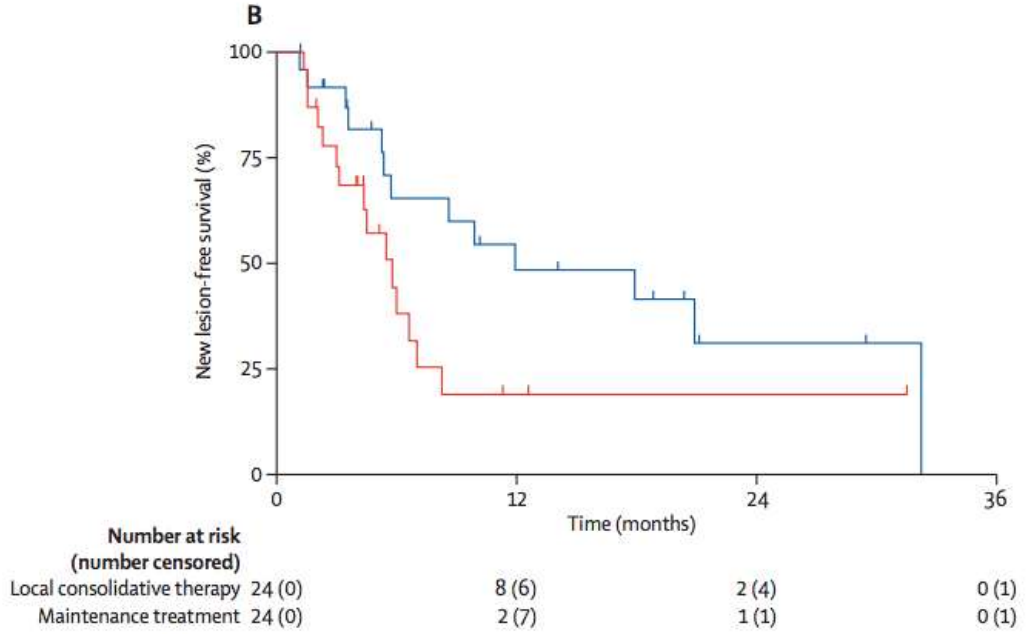
FIGURE 2. Reasons for adopting stereotactic body radiotherapy (SBRT) to treat oligometastases. IGRT indicates image-guided radiation therapy.

Weichselbaum and Hellman, Nat Rev Clin Onc 2011;
Lewis et al. Am J Clin Oncol 2016

Gomez's (MDACC) Trial







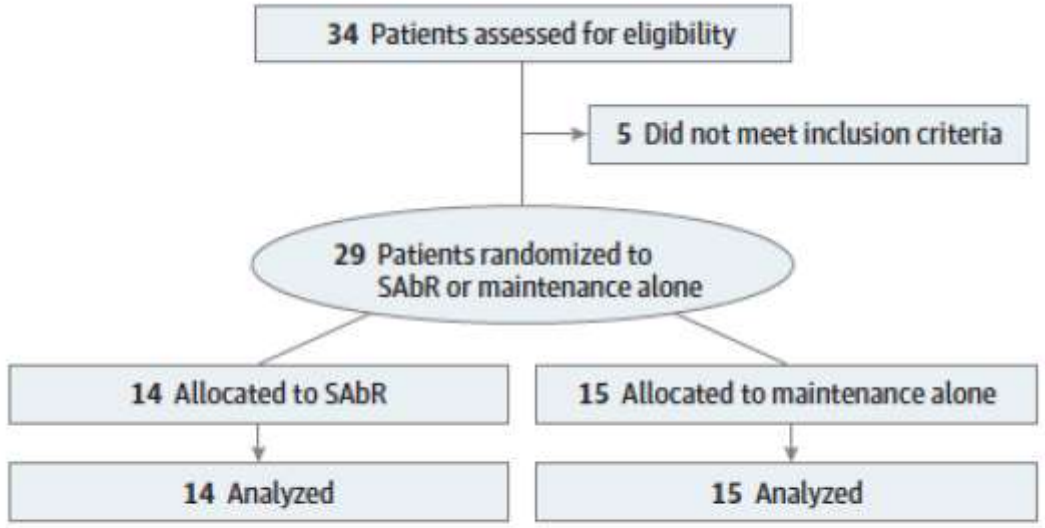
Gomez et al. Lancet Oncol 2016

Ph 2 RCT: UT Southwestern

JAMA Oncology | Original Investigation

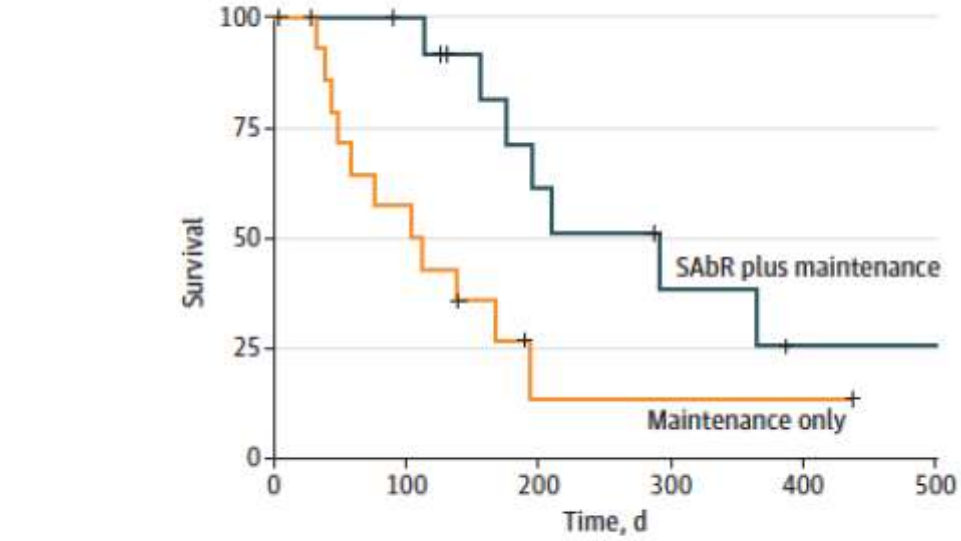
Consolidative Radiotherapy for Limited Metastatic Non-Small-Cell Lung Cancer
A Phase 2 Randomized Clinical Trial

Puneeth Iyengar, MD, PhD; Zabi Wardak, MD; David E. Gerber, MD; Vasu Tumati, MD; Chul Ahn, PhD; Randall S. Hughes, MD; Jonathan E. Dowell, MD; Naga Cheedella, MD; Lucien Nedzi, MD; Kenneth D. Westover, MD, PhD; Suprabha Pulipparacharuvil, PhD; Hak Choy, MD; Robert D. Timmerman, MD



SAbR indicates stereotactic ablative radiotherapy.

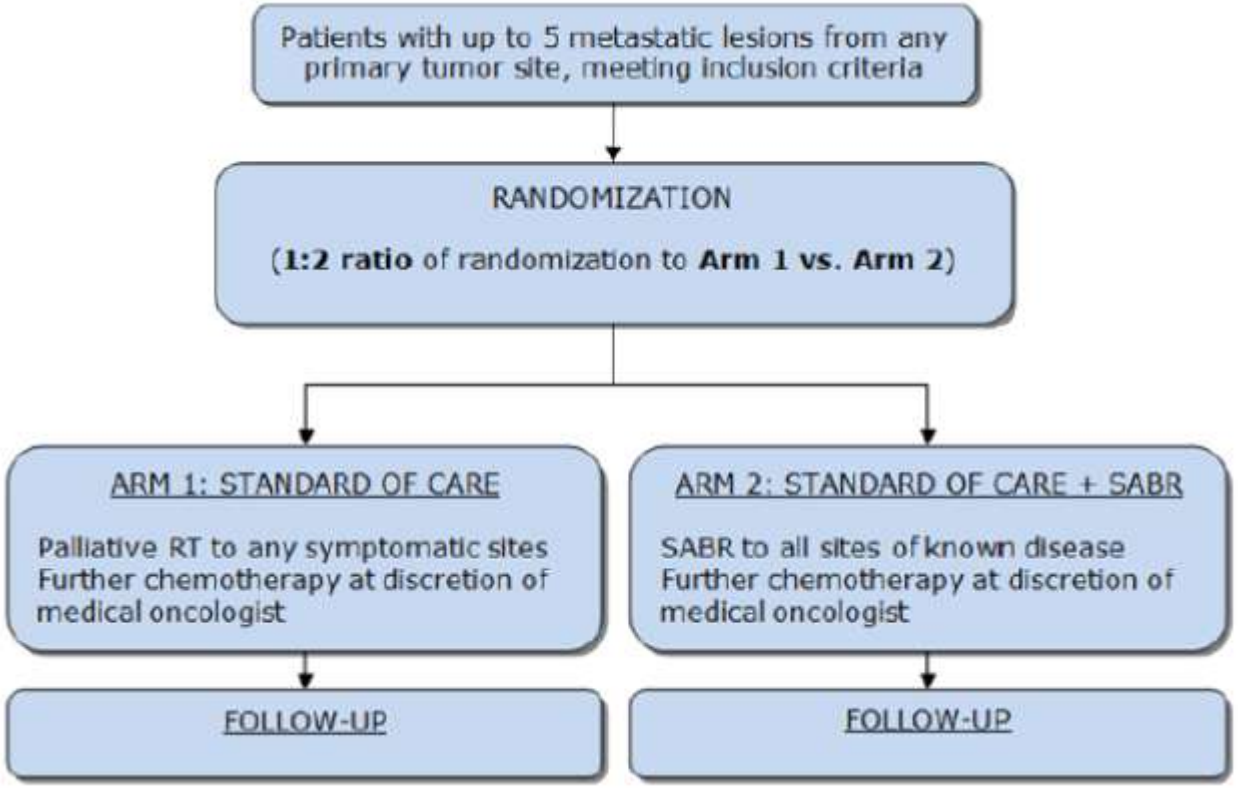
Figure 2. Analysis of Progression-Free Survival

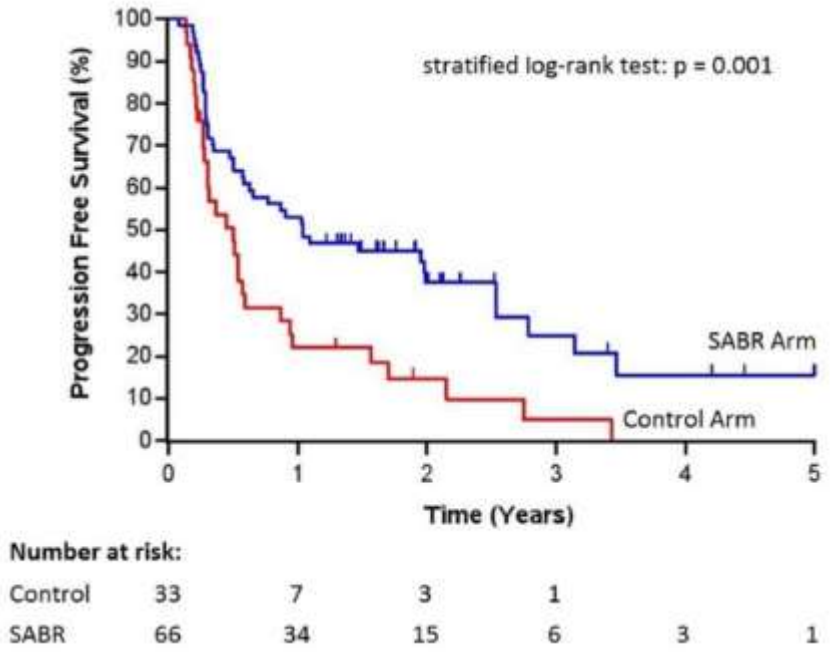


No. at risk					
SAbR plus maintenance	14	12	6	3	1
Maintenance only	15	8	1	1	1

Iyengar et al. JAMA Oncol 2018

Phase 2 RCT: SABR-COMET

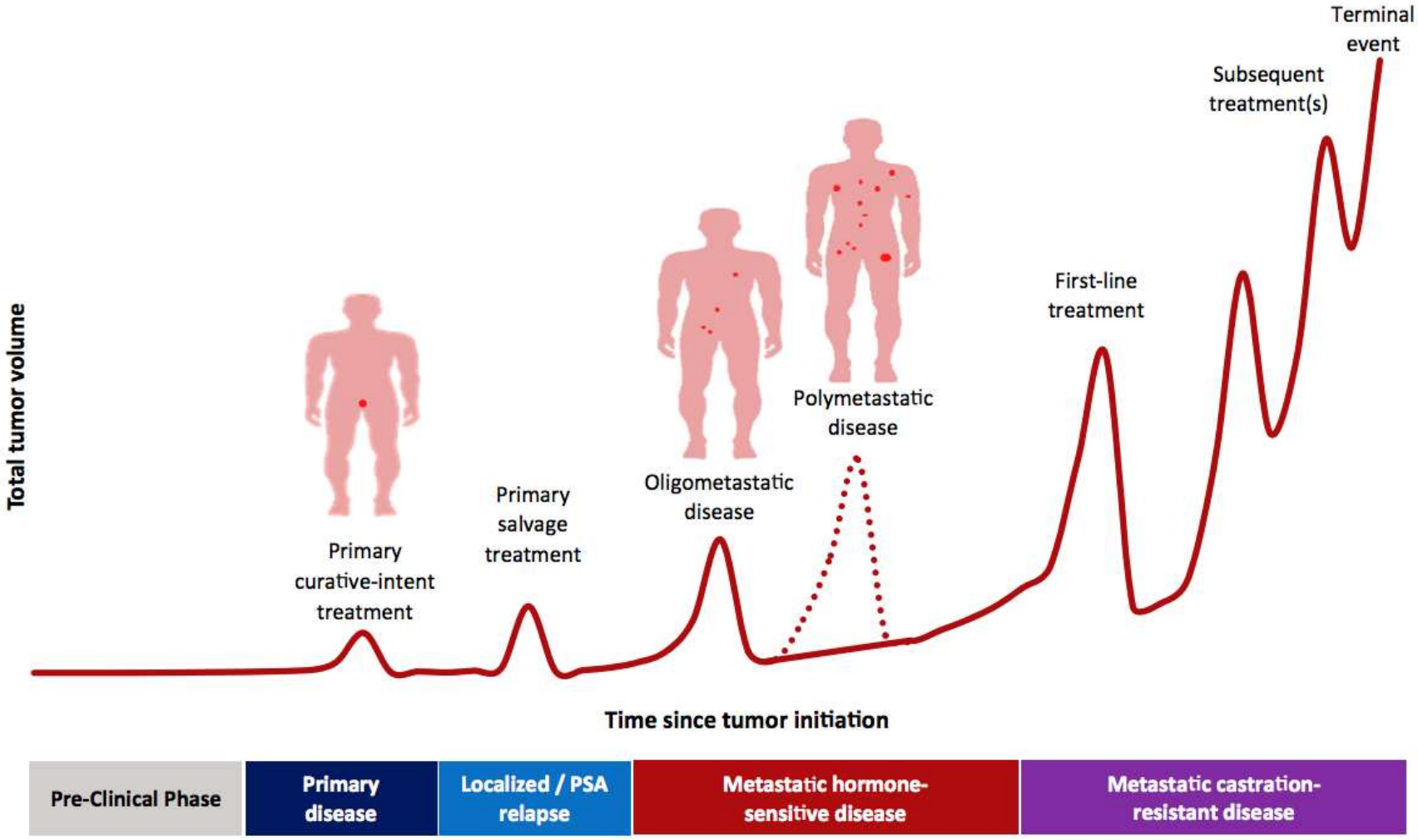




Increased AEs G2-5; No differences in OS, QoL or use of systemic agents

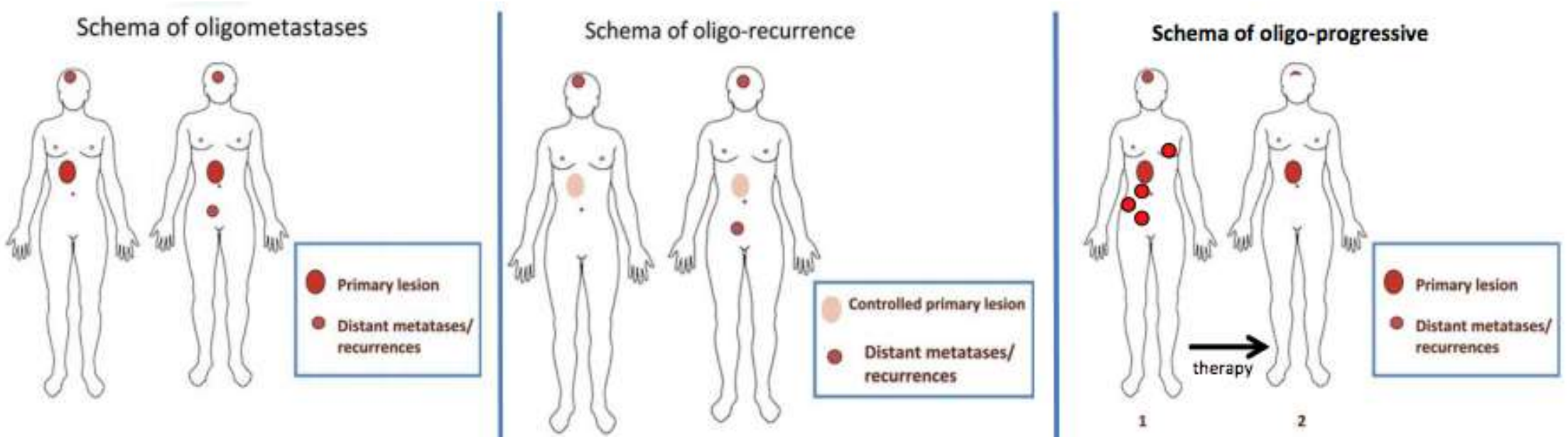
Courtesy of D Palma - ASTRO 2018

Context: Natural History of PCa



Rao et al. – ASCO Book 2019

Definitions



Others:

- Oligo-recurrence: systemic, regional
- Oligo-metastasis: synchronous, metachronous

Different disease states with distinct biology/prognosis

Presentation Schema

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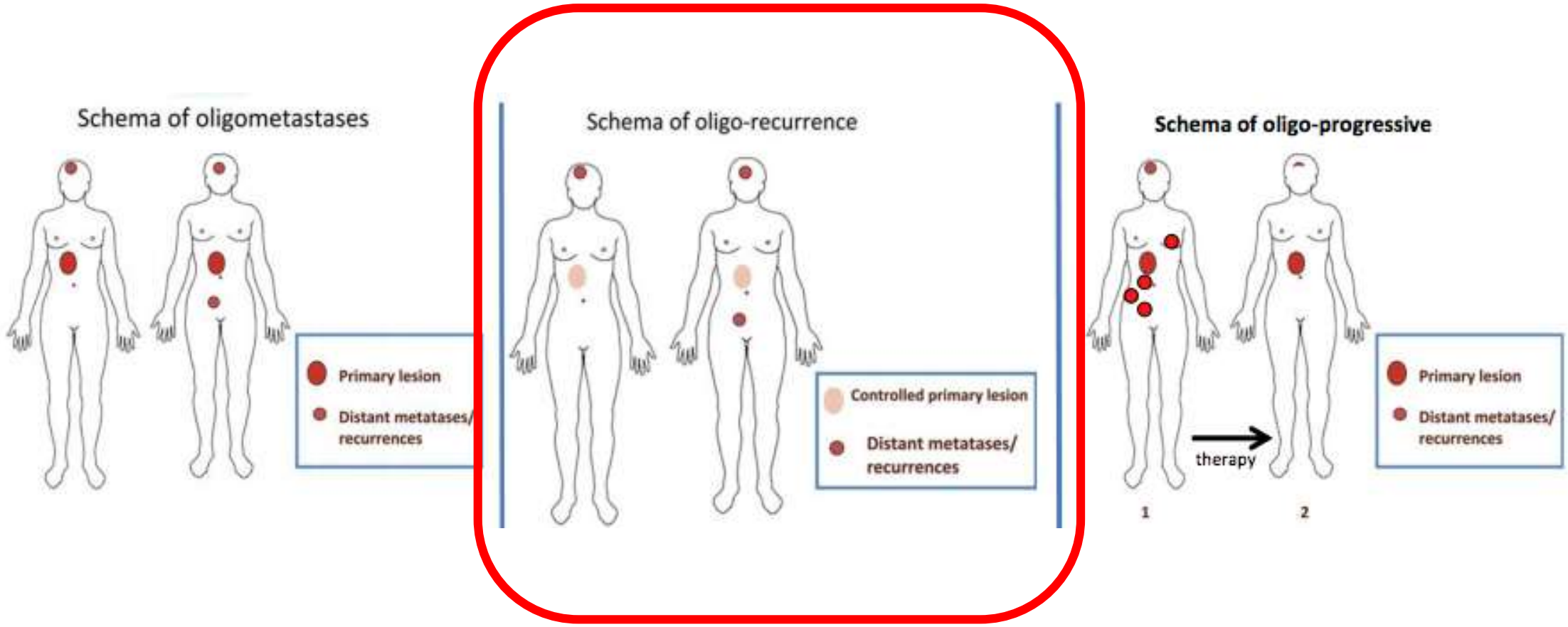
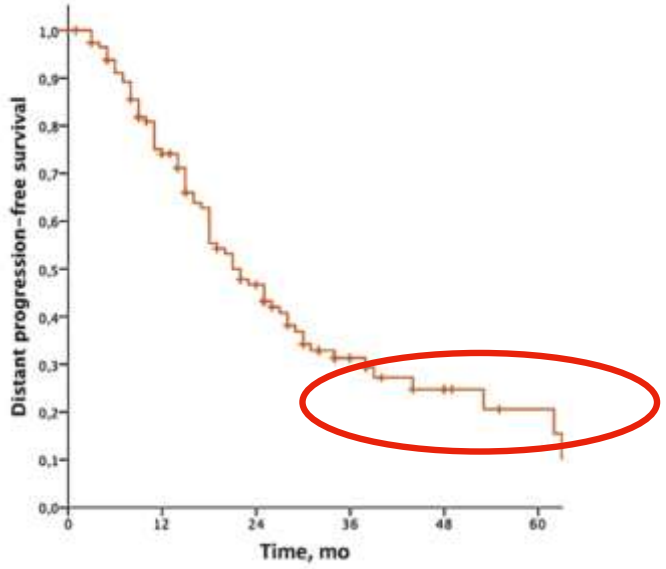
2 (less uncommon) scenarios



OM in PCa: Does exist?

Table 1 – Patient characteristics

Characteristics	All patients (*n* = 119)
Age at PCa diagnosis, yr	
Median (IQR)	61 (56–65)
Follow-up from PCa diagnosis, yr	
Median (IQR)	7.2 (5.0–9.3)
Primary therapy, *n* (%)	
Radical prostatectomy alone	21 (17.6)
Radical prostatectomy with postoperative RT	37 (31.1)
Radical prostatectomy with postoperative RT and ADT	31 (26.1)
Radiotherapy and ADT	22 (18.5)
Radiotherapy alone	8 (6.7)
PSA at initial diagnosis, ng/ml	
Mean (range)	18.1 (1.3–180)
Median (IQR)	10.7 (6.8–19)
Unknown	9
EAU prognostic grouping at initial diagnosis, *n* (%)	
Low	5 (4.2)
Intermediate	30 (25.2)
High	51 (42.9)
Very high	30 (25.2)
Unknown	3 (2.5)
Interval from diagnosis to metastases, yr	
Mean (range)	5.0 (0.2–16.8)
Median (IQR)	4.7 (2.7–6.6)
PSA level at first documented metastases, ng/ml	
Mean (range)	9.6 (0.1–116.7)
Median (IQR)	4.0 (1.6–8.8)
Unknown	1
PSA DT at first documented metastases, mo	
Mean (range)	5.6 (1.0–30.0)
Median (IQR)	3.9 (2.9–6.9)
Unknown	36
No. of lesions at diagnosis of metastases, *n* (%)	
One metastasis	86 (72.3)
Two metastases	22 (18.5)
Three metastases	11 (9.2)
Primary site of metastases, *n* (%)	
Lymph nodes	72 (60)
Pelvic	53 (45)
Obturator	12 (10)
Internal iliac	9 (8)
External iliac	17 (14)
Presacral	2 (2)
Common iliac	6 (5)
Combination of nodal sites	7 (6)
Extrapelvic	12 (10)
Both	7 (6)
Bones, *n* (%)	43 (36)
Axial	22 (18)
Appendicular	17 (14)
Both	4 (3)
Viscera, *n* (%)	
Liver	1 (1)
Lung	1 (1)
Node and/or bone and/or viscera, *n* (%)	2 (2)
Imaging modality at recurrence, *n* (%)	
Choline PET-CT	92 (77)
FDG PET-CT	24 (20)
MRI	3 (3)
Adjuvant ADT, *n* (%)	
No	59 (50)
Yes	60 (50)
Duration of ADT, mo, median (range)	2 mo (1–8 mo)

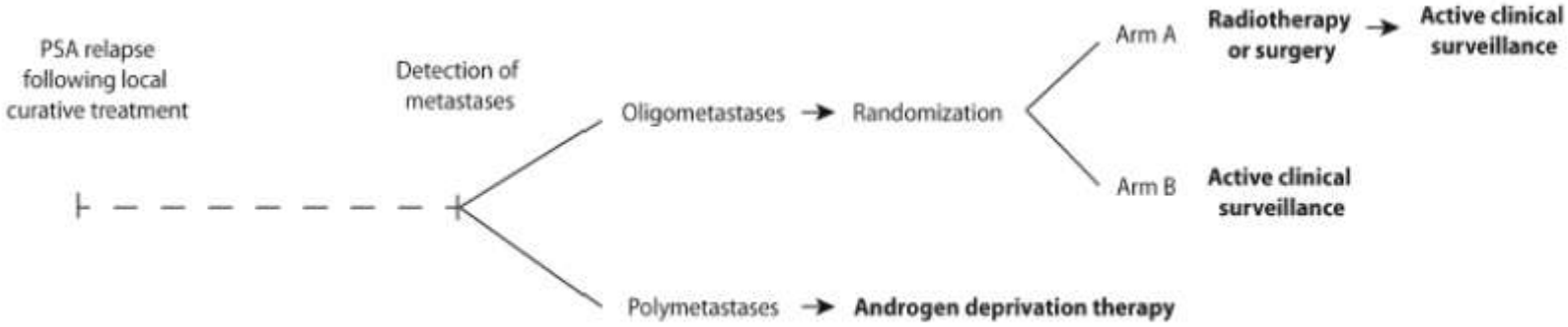


Ost et al. Eur Urol 2018

First study in PCa: STOMP Trial

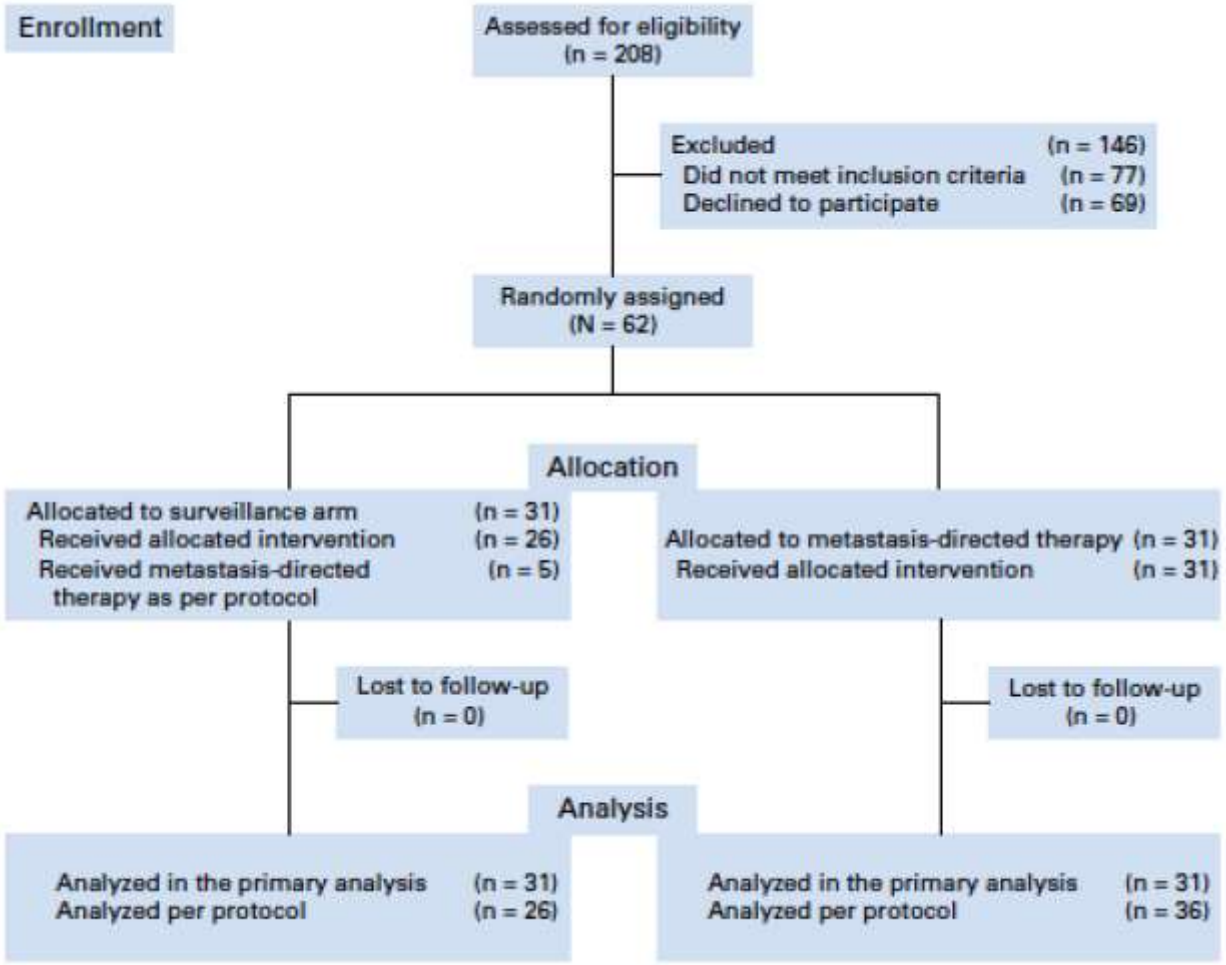
Surveillance or metastasis-directed Therapy for OligoMetastatic Prostate cancer recurrence (STOMP): study protocol for a randomized phase II trial

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

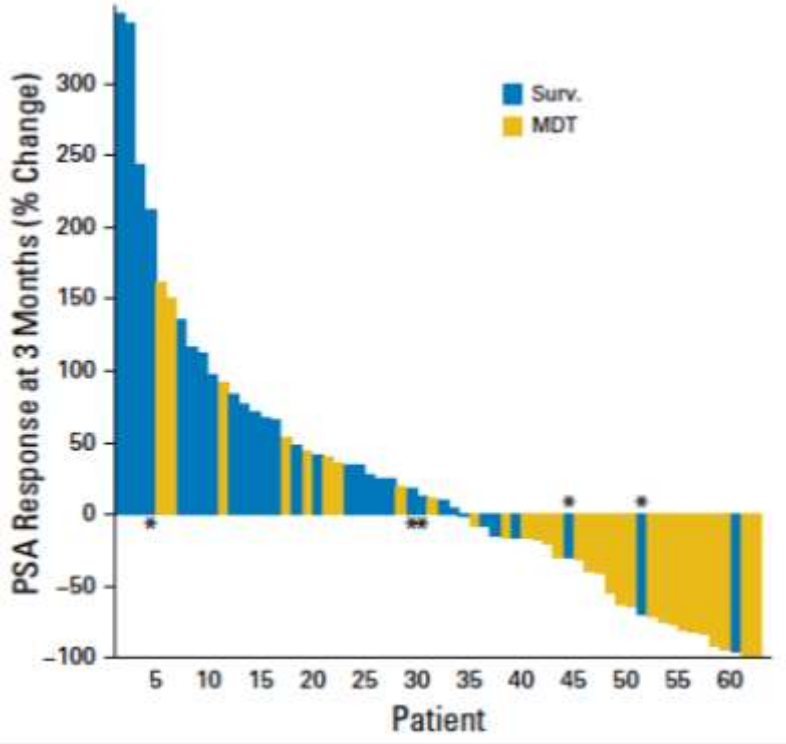
STOMP Trial

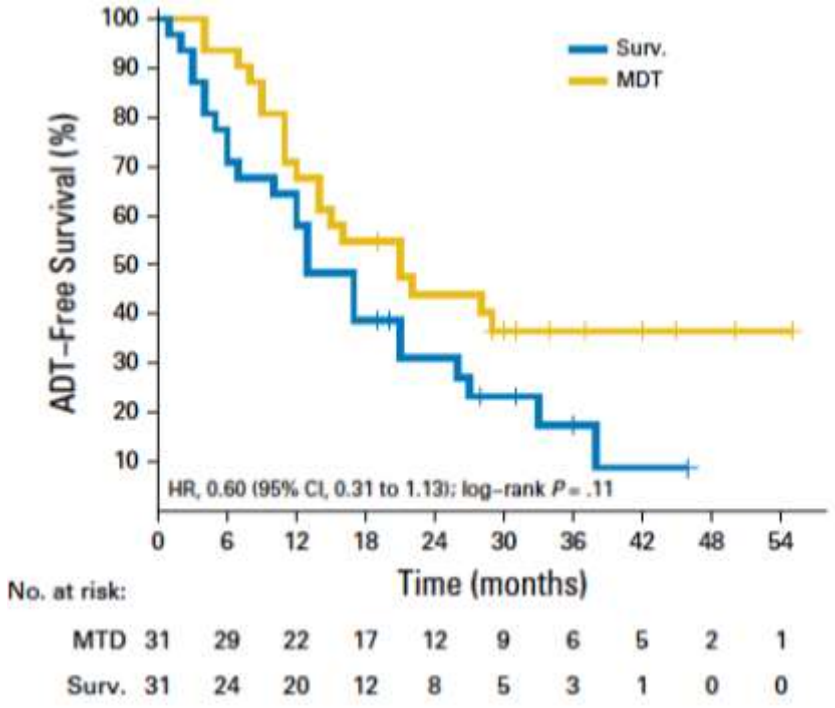


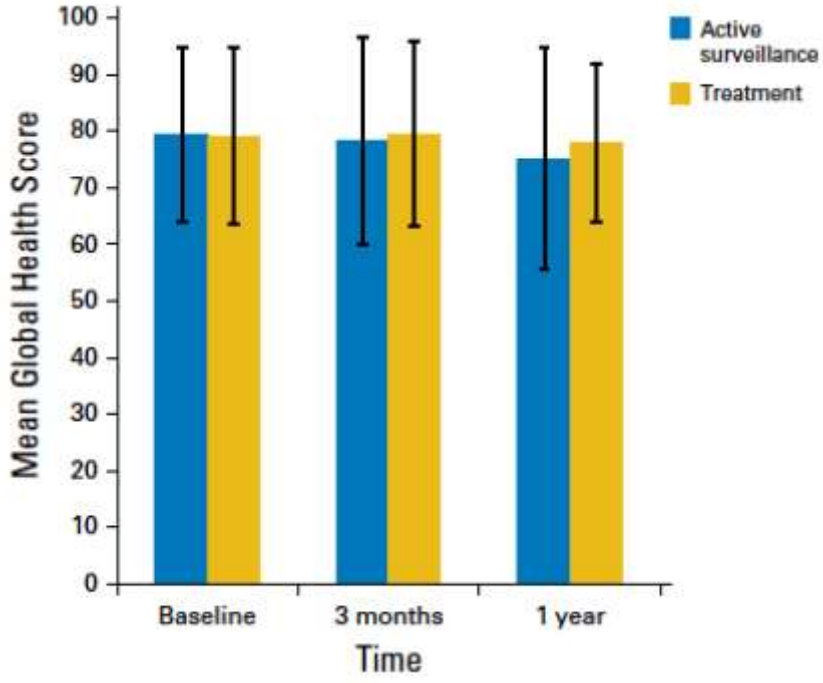
Characteristic	Surveillance (n = 31)	Metastasis-Directed Therapy (n = 31)
Age at PCa diagnosis, years		
Mean (range)	63.3 (47-79)	60.8 (43-75)
Median (IQR)	64.0 (58-69)	62 (57-66)
PSA at PCa diagnosis, ng/mL		
Mean (range)	12.1 (2.5-36.2)	22.0 (3.5-114.0)
Median (IQR)	10.5 (7.3-15.3)	14.4 (8.6-27.3)
Gleason score		
≤ 6	10 (32.3)	4 (12.9)
7	11 (32.3)	17 (54.8)
≥ 8	10 (32.3)	10 (32.3)
Primary tumor classification		
p/c T1	4 (12.9)	2 (6.5)
p/c T2	13 (41.9)	9 (29.0)
p/c T3 or T4	14 (45.2)	20 (64.5)
Nodal status at PCa diagnosis		
pNx/cN0	5 (16.1)	2 (6.5)
pN0	24 (77.4)	25 (80.6)
pN1	2 (6.5)	4 (12.9)
Type of treatment at PCa diagnosis		
RP	5 (16.1)	2 (6.5)
RT	8 (25.8)	7 (22.6)
RP and RT	18 (58.1)	22 (70.9)
ADT at PCa diagnosis		
No	16 (51.6)	19 (61.3)
Yes	15 (48.4)	12 (38.7)
Time between PCa diagnosis and inclusion, years		
Mean (range)	6.3 (0.5-22.9)	5.9 (0.6-14.2)
Median (IQR)	4.9 (3.3-8.0)	5.3 (3.5-8.3)
PSA at inclusion, ng/mL		
Mean (range)	6.9 (0.3-31.0)	9 (0.7-44.5)
Median (IQR)	3.8 (0.8-9.6)	5.3 (2.8-12)
PSA-DT at inclusion		
≤ 3 months	10 (32.3)	10 (32.3)
> 3 months	21 (67.7)	21 (67.7)
No. of metastases		
1	9 (29.0)	18 (58.1)
2	10 (32.3)	6 (19.3)
3	12 (38.7)	7 (22.6)
Location of metastases		
Nodal	17 (54.8)	17 (54.8)
N1	8 (25.8)	13 (41.9)
M1a	5 (16.2)	4 (12.9)
Combination of N1 and M1a	4 (12.9)	0 (0.0)
Non-nodal	14 (45.2)	14 (45.2)
M1b	11 (35.5)	13 (41.9)
Combination of N1/M1a and M1b	3 (9.7)	0 (0.0)
M1c	0 (0.0)	1 (3.3)

Ost et al. JCO 2018

Randomized Phase 2: SBRT vs Observation

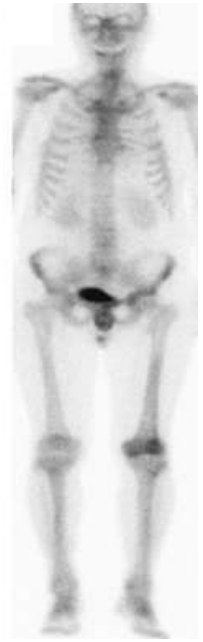


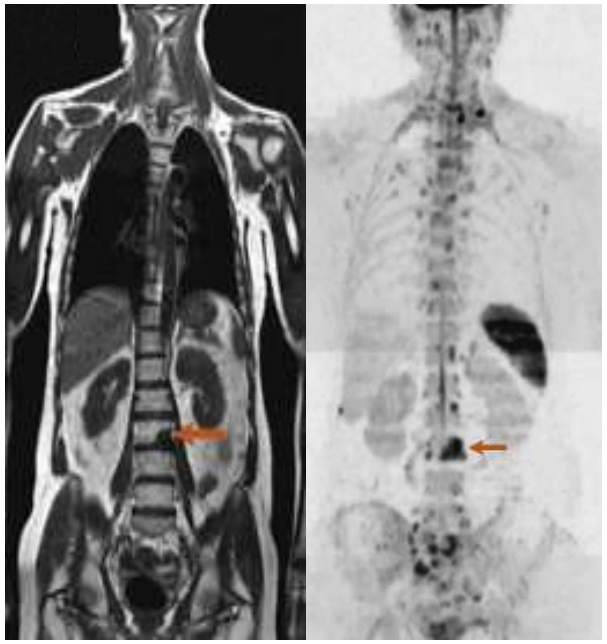




Ost et al. JCO 2018

PSMA MRgRT: Schema





Work Package 2: Therapeutics

MRgRT SABR

Discover *new curative-intent treatment*
Unprecedented precision and accuracy

Clinical Problem

Recurrent PCa post Surgery ± Radiotherapy

No evidence of disease In conventional studies (BS and CT)

Work Package 1: Diagnostics

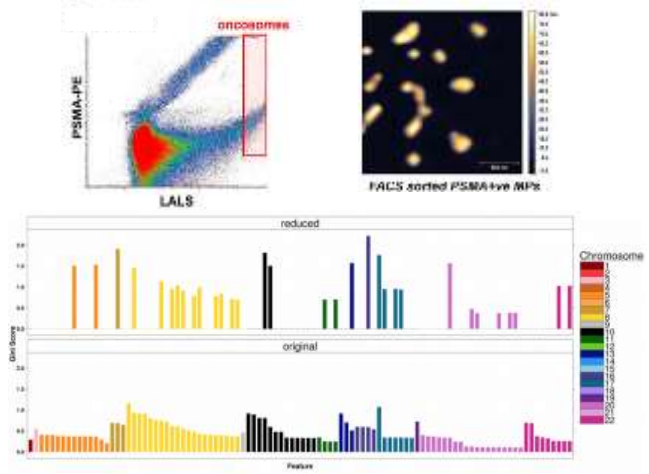
[^{18}F]DCFPyL PET/MRI

Unveil *and characterize new early molecularly-defined oligometastatic state*

Work Package 3: Translational

PSA^{2} liquid biopsy
Tissue/Fluids samples

Response monitoring and outcome prediction.
Seed *translational studies.*



PSMA MRgRT: Design

Primary endpoint:

NED (biochemical CR [PSA <0.05])

H0: RR<5%

Ha: RR>20%

*2-stage design, **n=37***

Secondary endpoints:

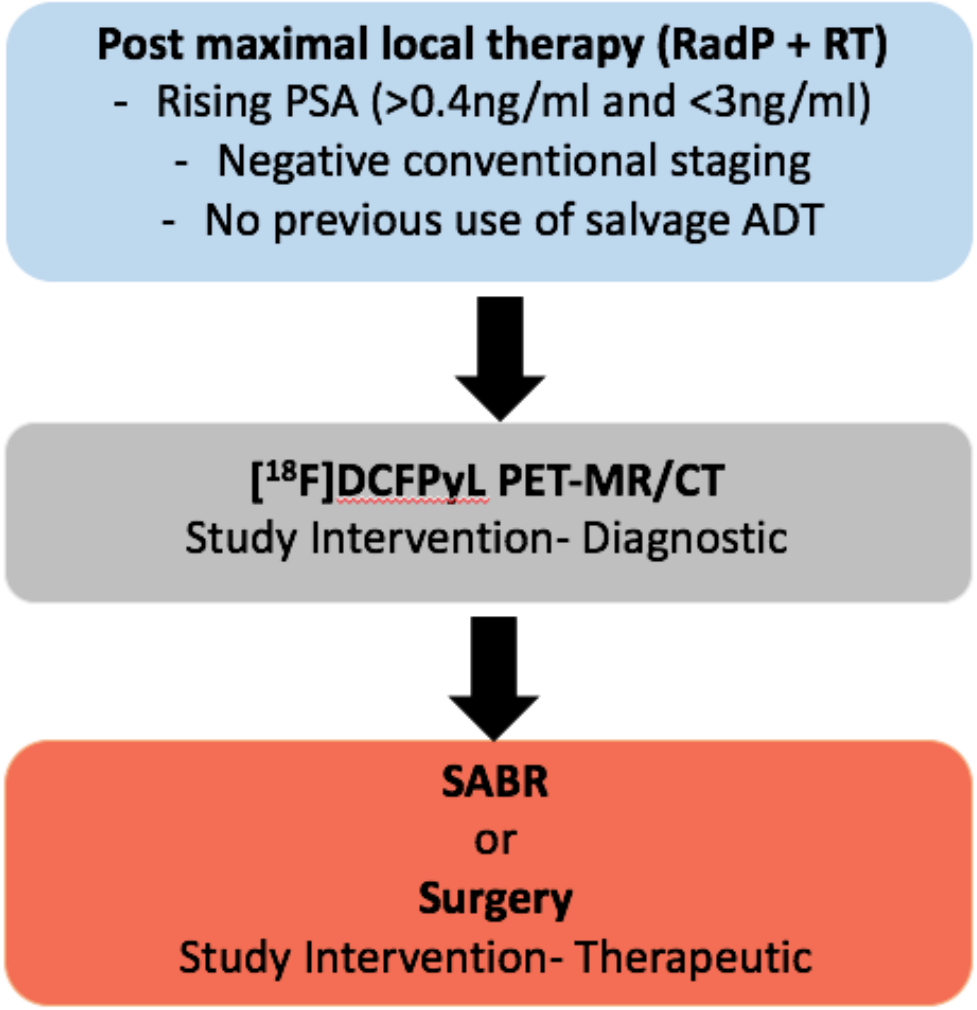
SABR toxicities

Qualitative and quantitative imaging metrics of PET/MR

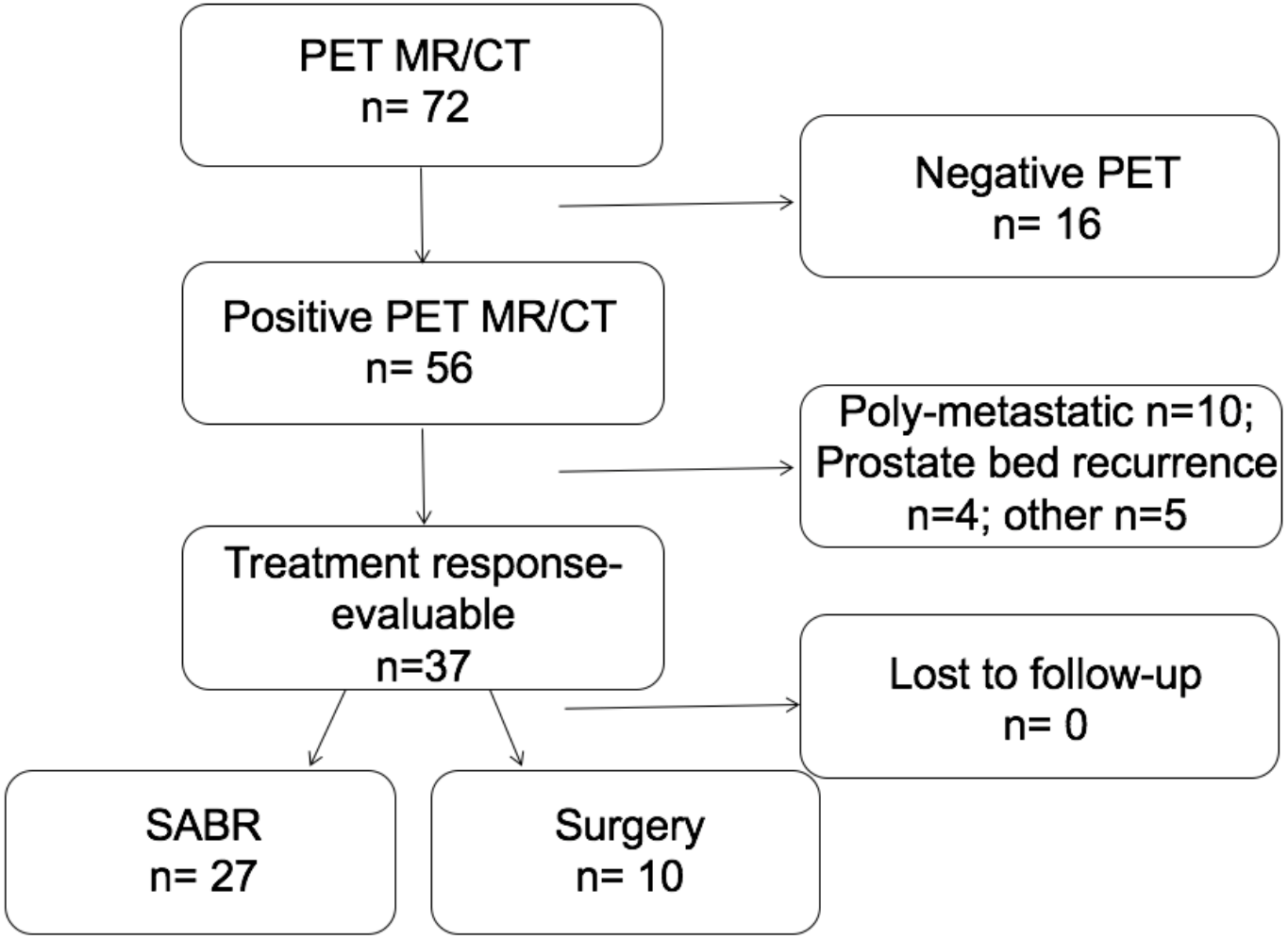
Correlates of SABR treatment outcomes and PSA2 kinetics.

^{18}F-DCFPyL PET/MRI molecular response post SABR

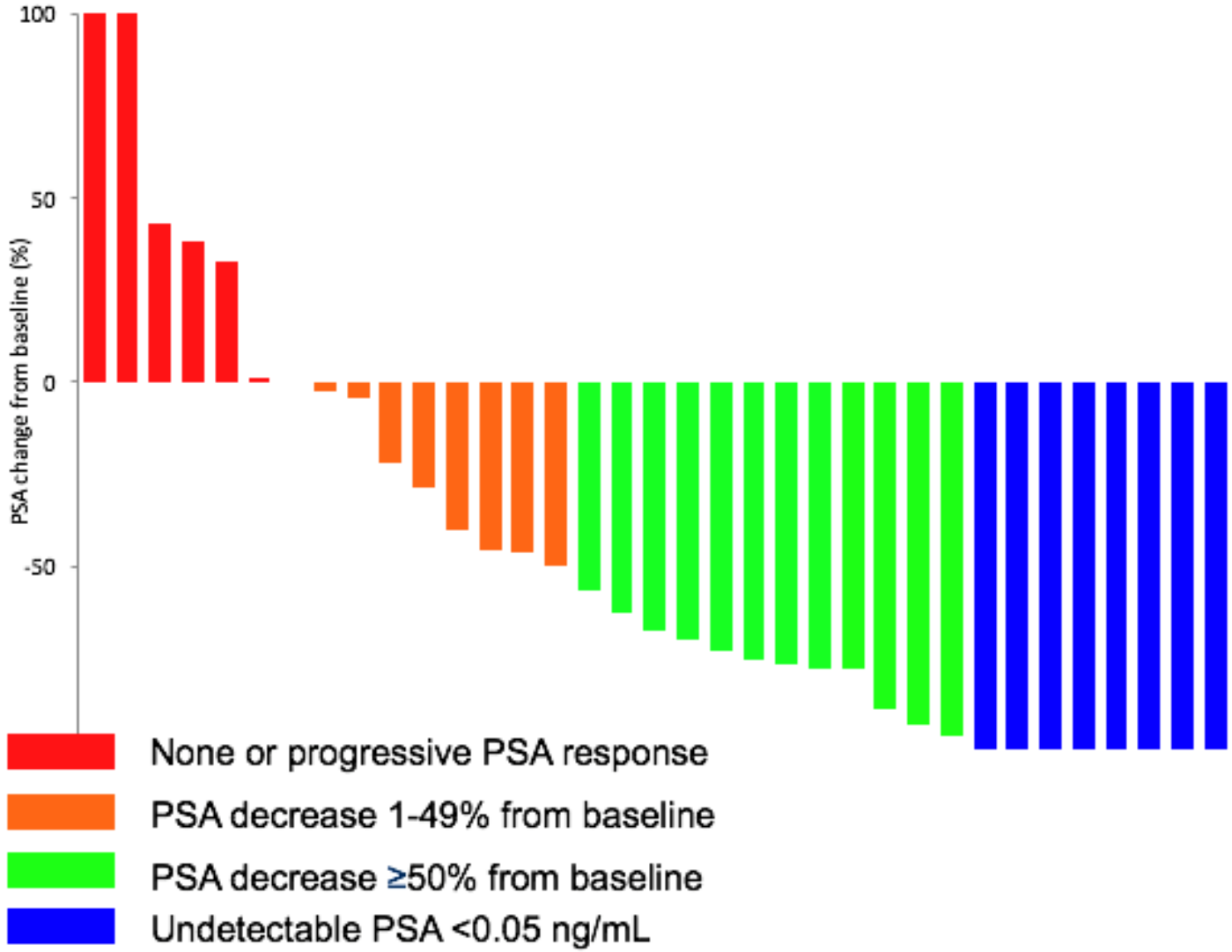
Comparative performance between ^{18}F-DCFPyL PET/MR and PET/CT



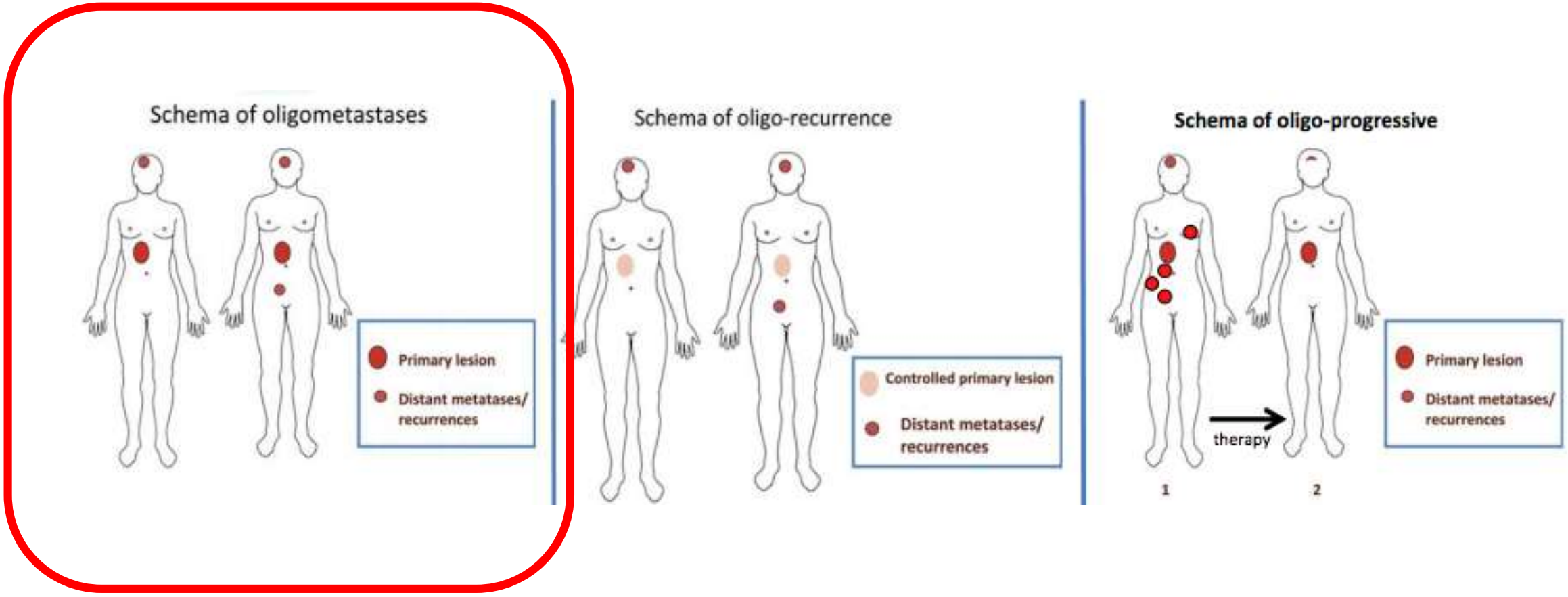
PSMA MRgRT: Consort



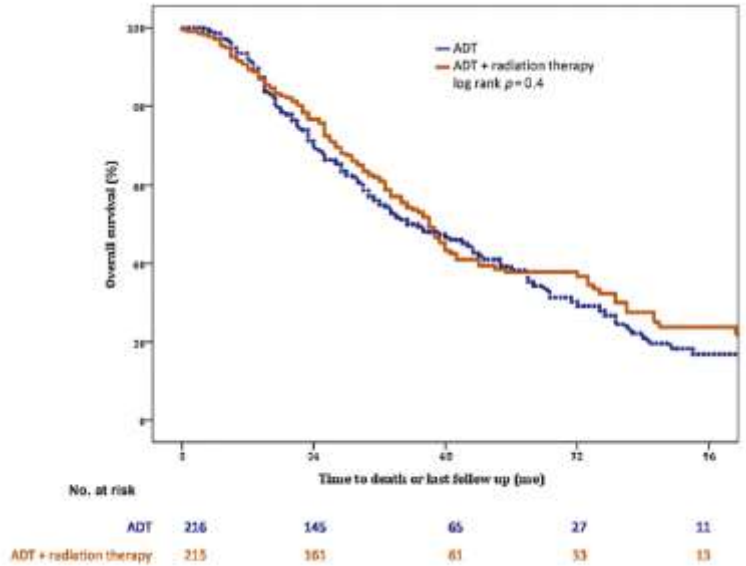
PSMA MRgRT: Response @ 3 (n=6) or 6mo (n=29)

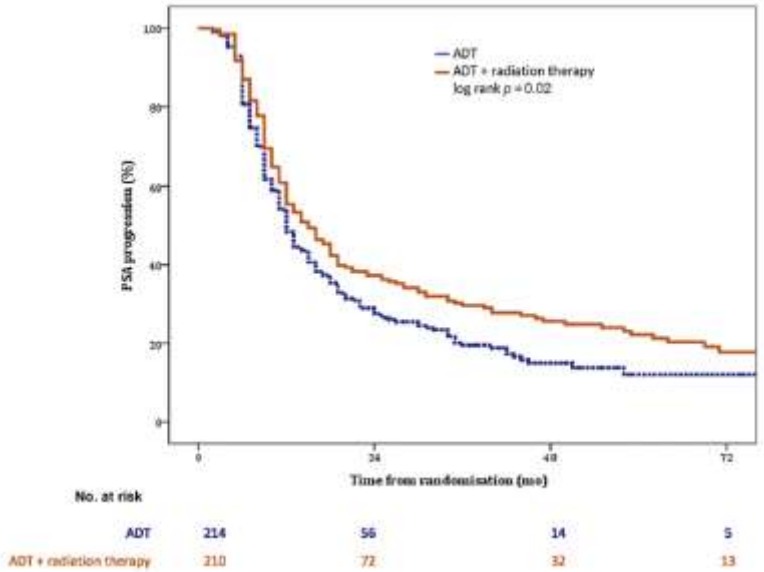


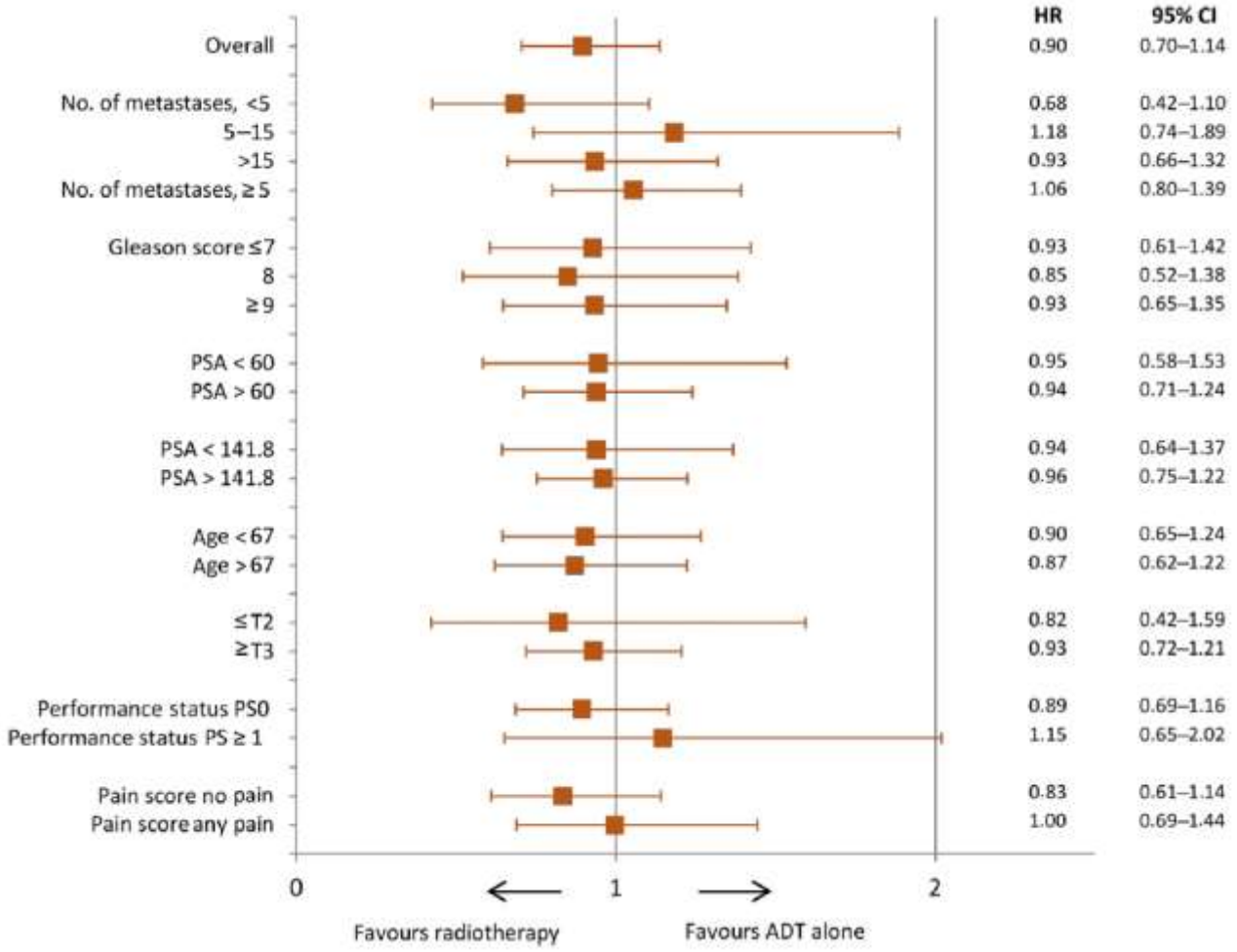
2 (less uncommon) scenarios



HORRAD

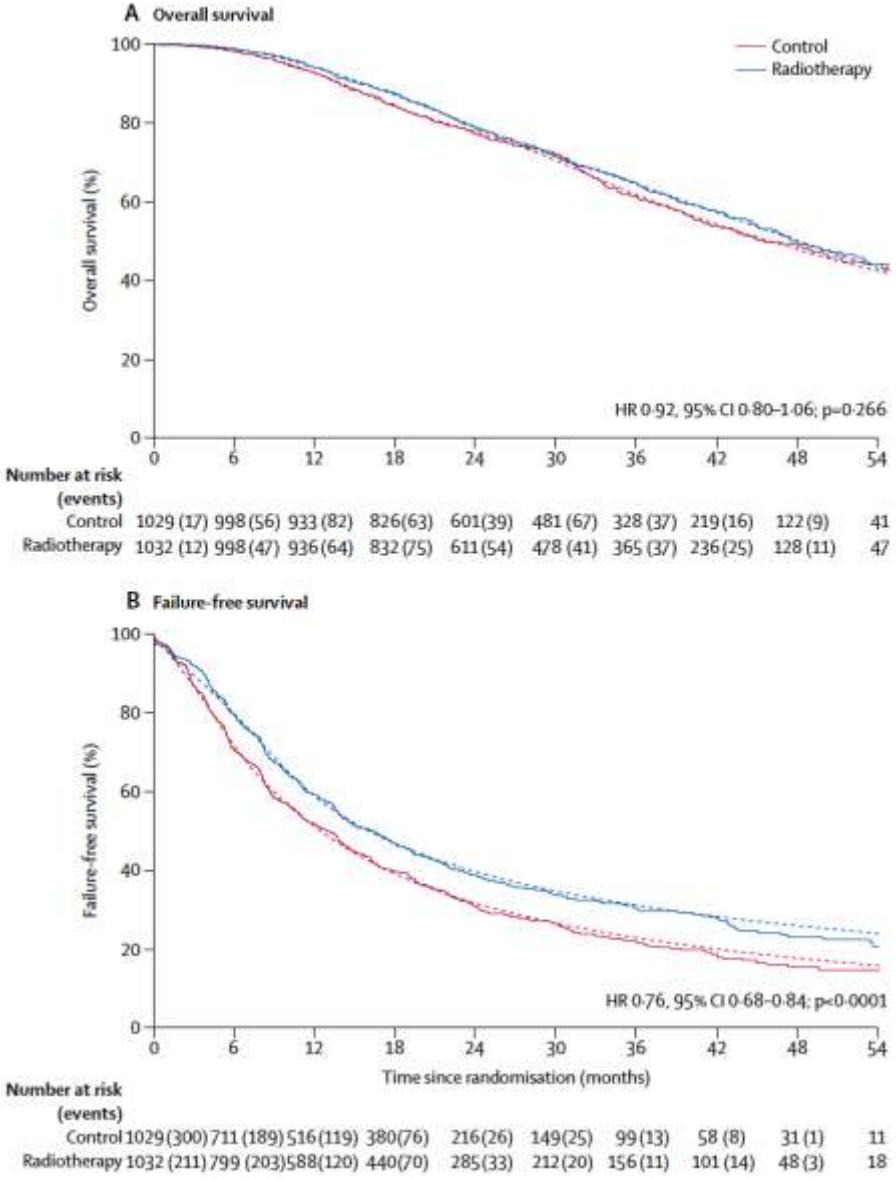


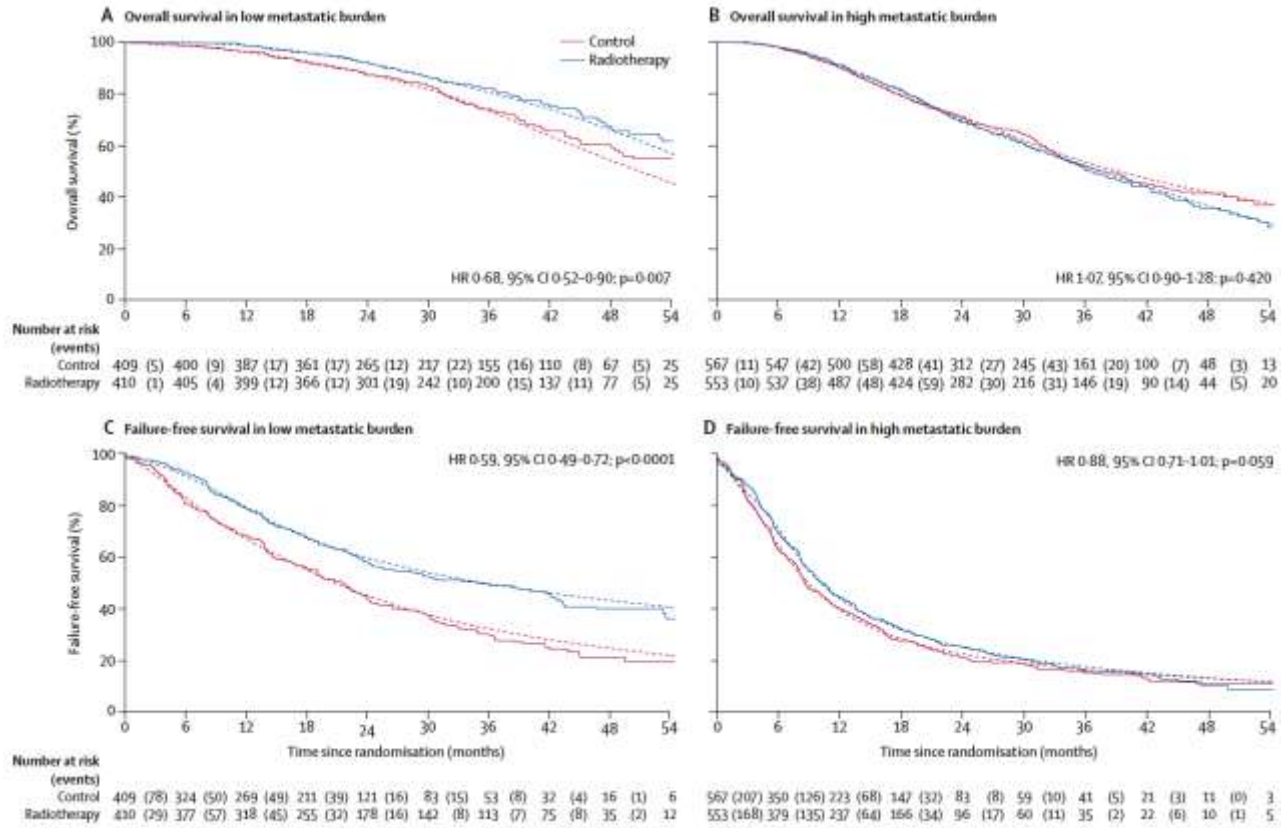




Boevé et al. Eur Urol 2019

STAMPEDE (H)

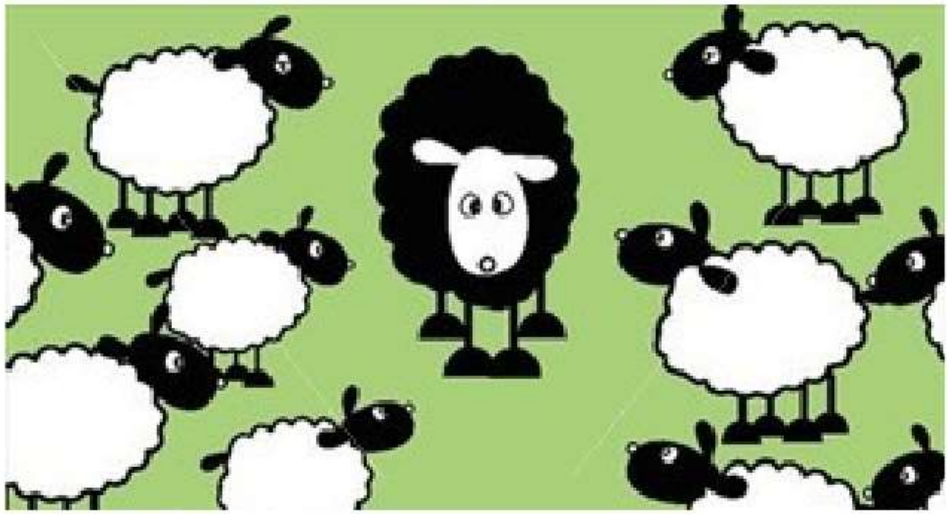




Let's see STAMPEDE M…

Parker et al. NEJM 2018

Something going wrong…



Fundamental elements of a crime

- Action or omission
- Defined by the law (“criminality”)
- Unlawful
- *Dolus* (intent or overt negligence)
- Culpability

Something going wrong…

Discussion

This randomised comparison of more than 2000 patients with metastatic prostate cancer showed that local radiotherapy to the prostate did not improve overall survival for unselected patients. However, a prespecified analysis showed that prostate radiotherapy did improve overall survival (from 73% to 81% at 3 years) in those with a low metastatic burden, which represented 40% of the comparison population.

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Only in **very few** instances can we be confident that subgroup analyses provide a better estimate of effect than the overall results of trials

#staysafe #stayconsistent

Fundam

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- Defi
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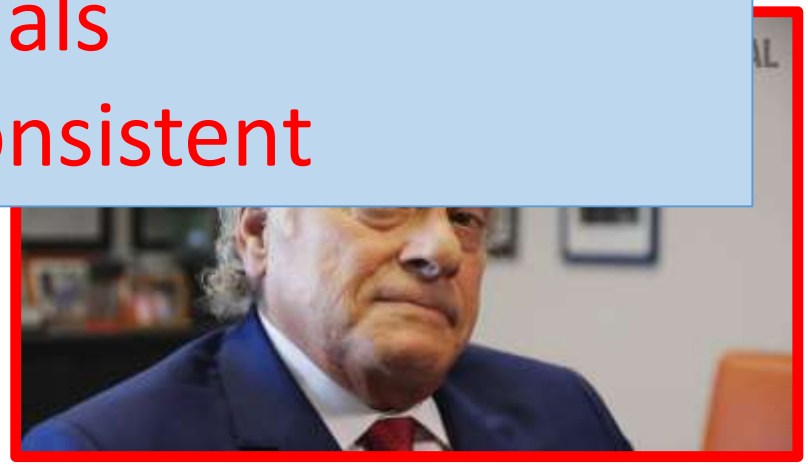
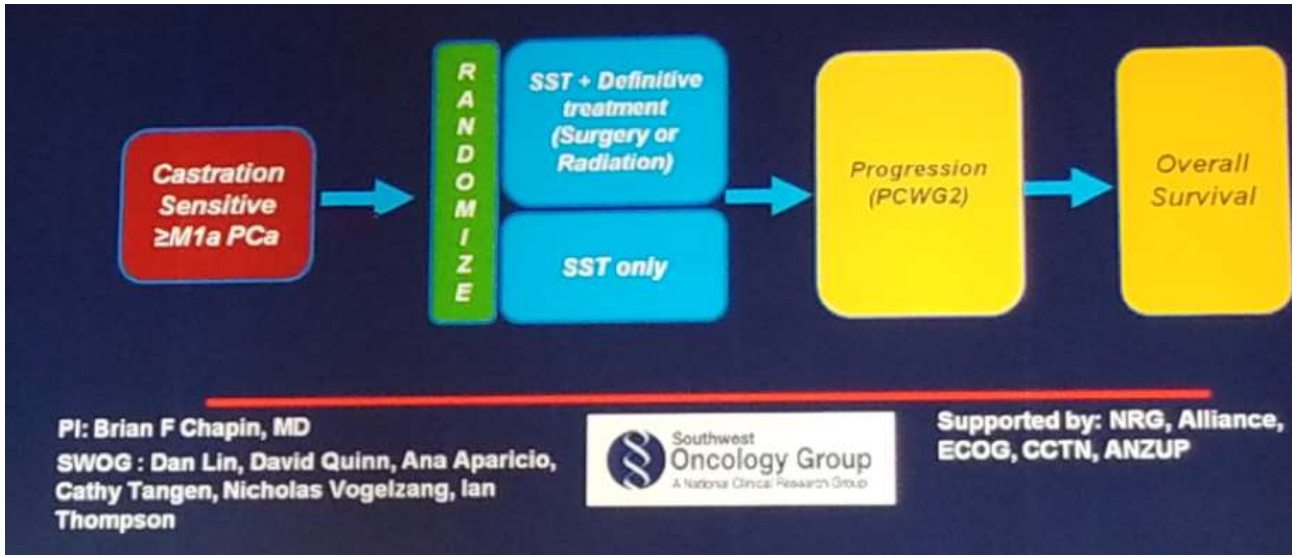
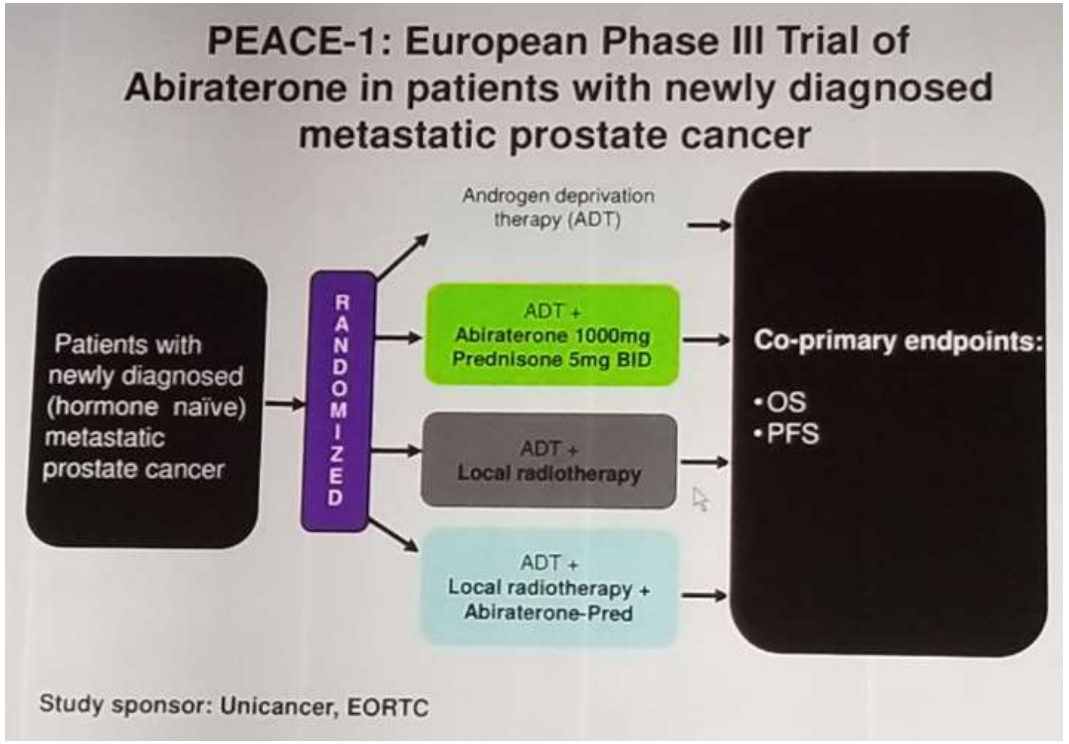


Evidence to treat? to cut?

SWOG S1802 (n=1273)



PEACE-1 (n=1168)



OS yet to come…

Presentation Schema

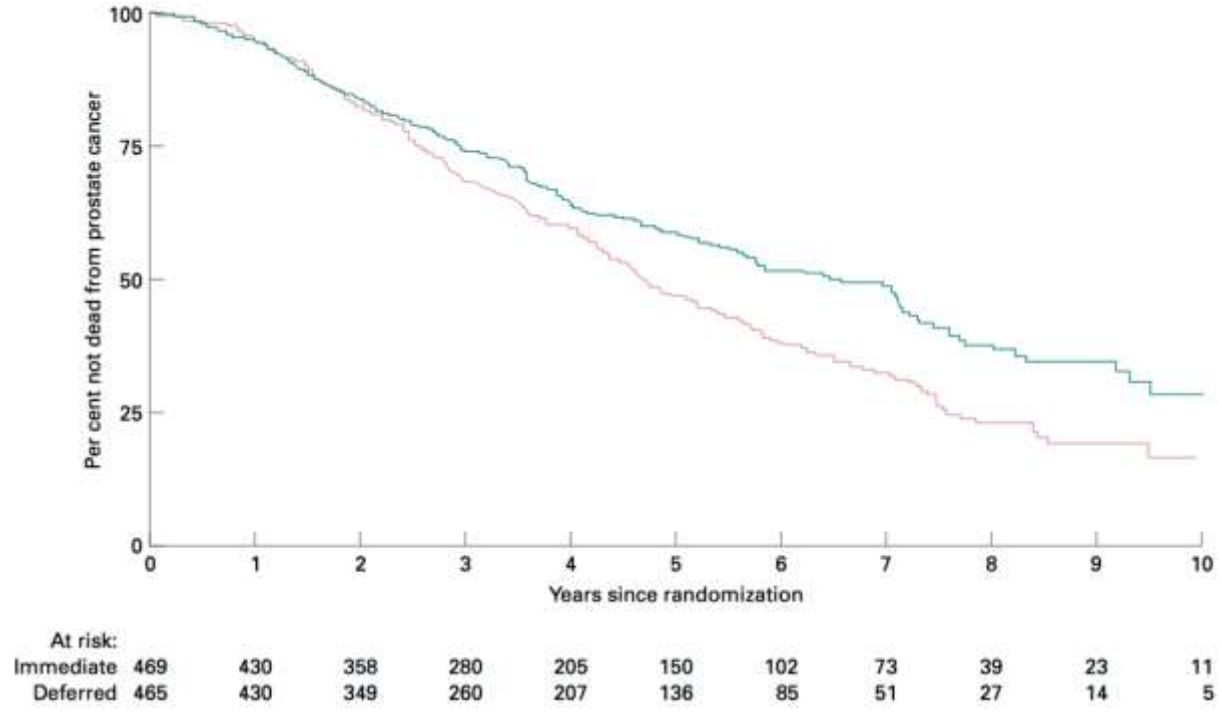
- Oligometastatic (OM) State in Oncology
  - Overarching hypothesis
  - Definitions
  - Evidence of existence and treatment benefit
- OM State in PCa
  - Evidence supporting existence
  - Treatment results
- Personal opinion(s)

Questions remain: Why MDT in PCa?

- Cure (?): alone?, combined with systemic therapy?
- Delay ADT and other systemic agents
- Improve local control (symptomatic progression)
- Decrease metastases seeding sources (PFS?)
- Improved response to AR-targeting agents (?)
- Delay emergence of mCRPC (?)
- Improve OS?

IMO: Oligorecurrent > Oligometastatic

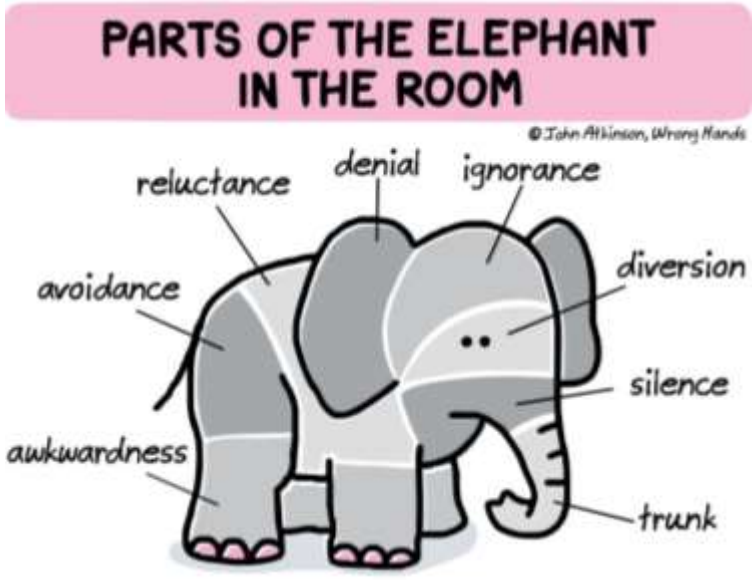
What's Old Is New Again



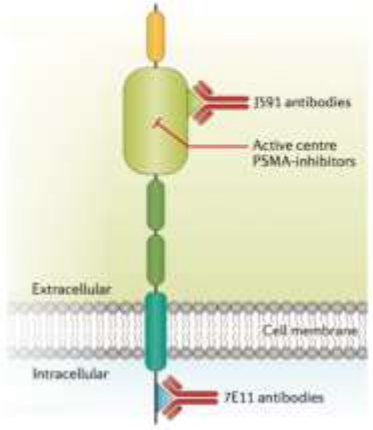
Earlier treatment (when lower disease burden) = Higher response to ADT and PCSS/OS

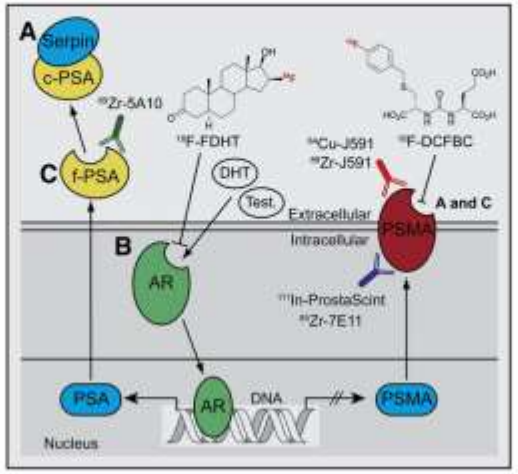
MRC Trial. BJU 1997

Will Rogers: here we go again! #weloveyou



New kid in block: PSMA (Prostate-Specific Membrane Antigen)





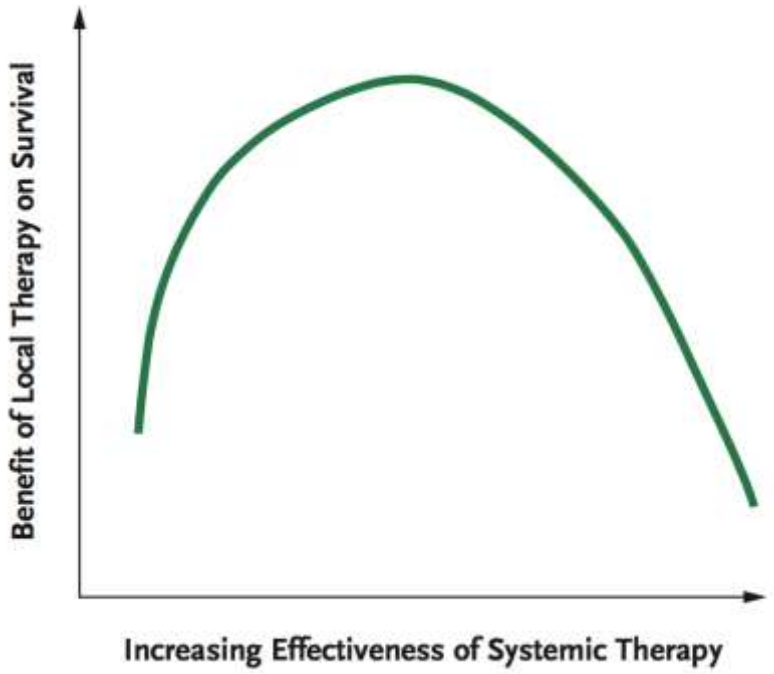
- High ratio (1:100-1000) tumour to non-target expression
- 11p (commonly intact in PCa)
- Internalization upon binding (improved imaging and therapeutic efficacy)

All what we've discussed pertains to the pre-PSMA era

So Far…

- The lower the burden of (*untreated*) disease, the better the response to systemic Tx.

- But:
  - Cure has not been shown
  - OM state remains a **working hypothesis**



Further modulated (at least) by:

- *Burden of disease*
- *Biology*

Punglia et al. NEJM 2007

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