FACULTY OF MEDICINE
AND HEALTH SCIENCES

DEPARTMENT OF RADIATION ONCOLOGY AND EXPERIMENTAL CANCER RESEARCH

OLIGOMETASTATIC PROSTATE CANCER

PICKING THE FINEST CHERRIES!

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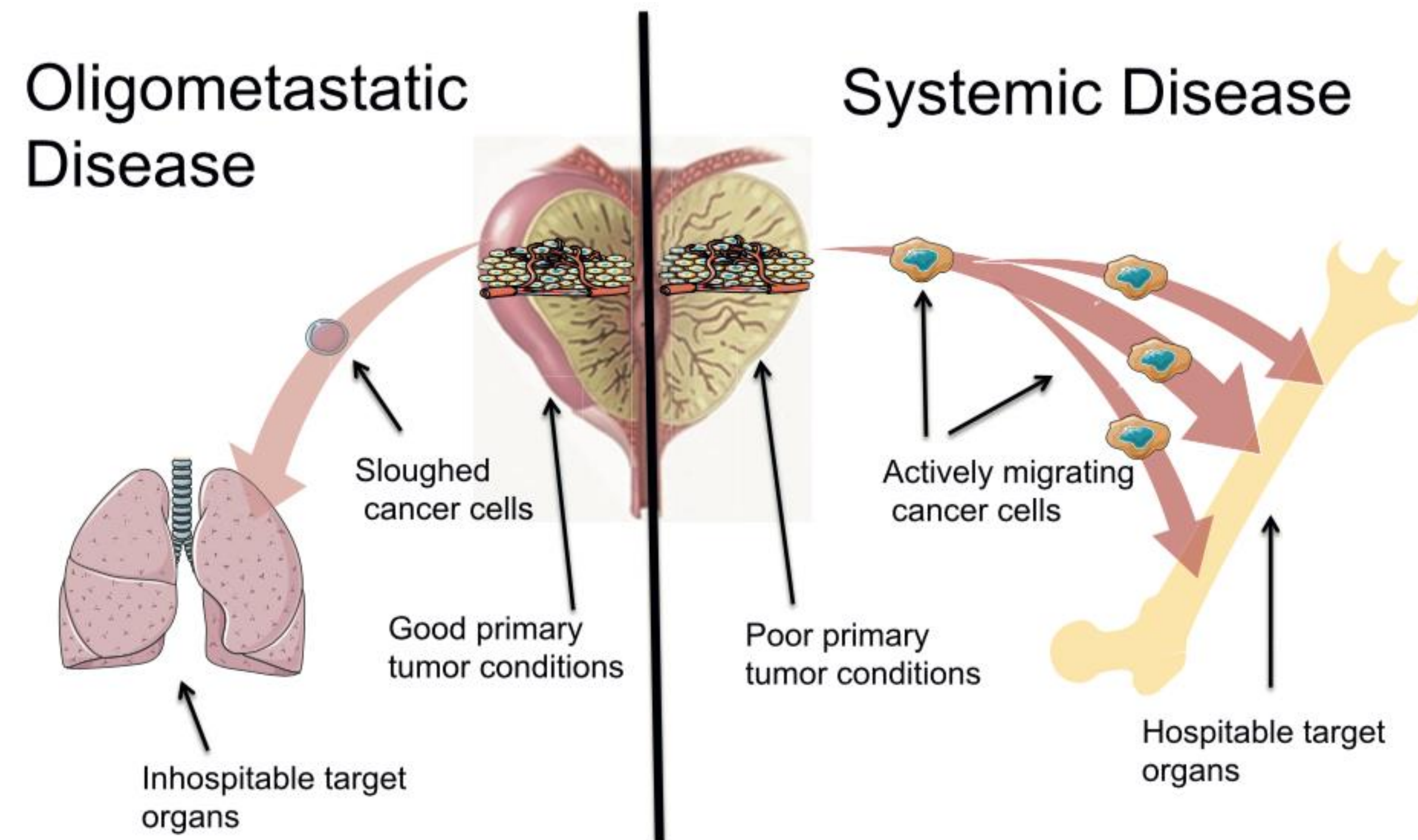
BIOLOGICAL RATIONALE

If metastases are able to metastasize and systemic therapy induces more resistant and lethal clones, the addition of local therapy directed at primary tumor/metastases might delay lethal disease progression…



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DE NOVO (OLIGO)METASTASES

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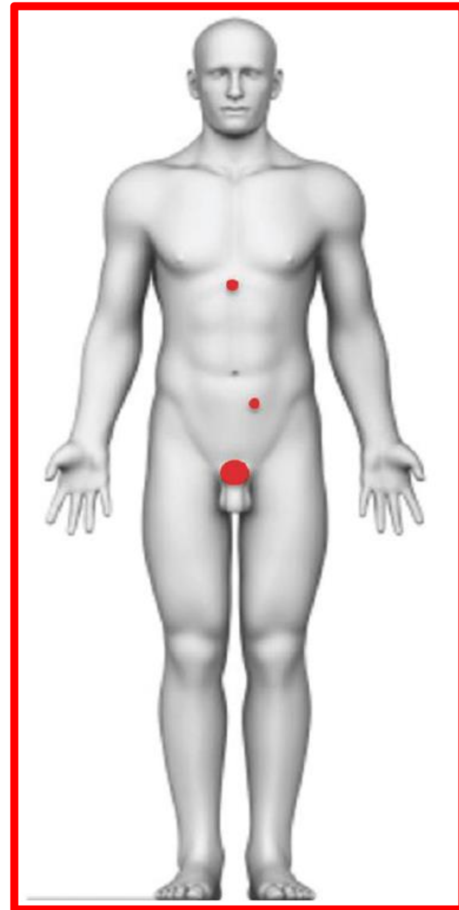
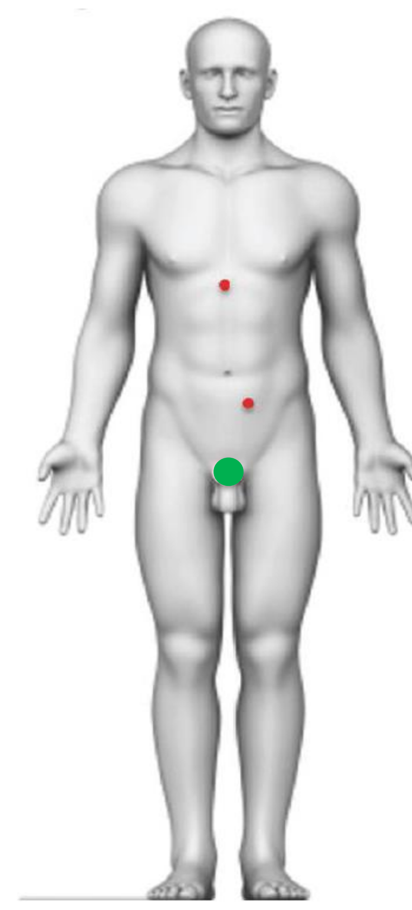
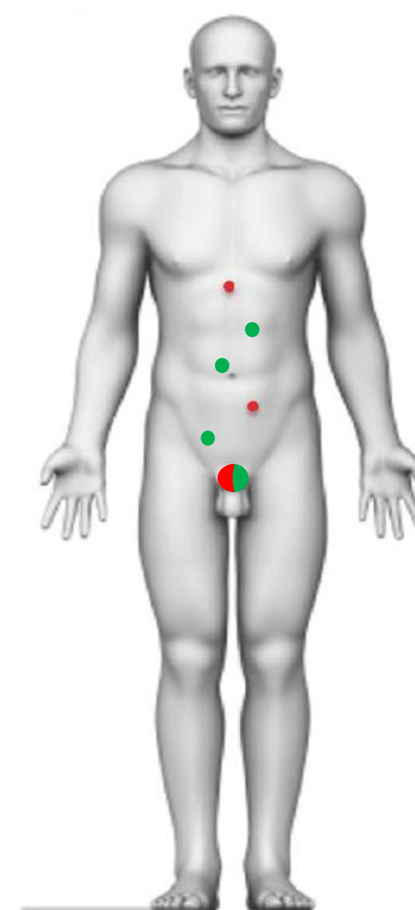
DE NOVO OLIGOMETASTATIC DISEASE

- Uncontrolled lesion
- Controlled lesion







Category name	De novo oligometastases (synchronous oligometastases)	Oligometastatic recurrence (metachronous oligometastases)	Oligometastatic progression (induced oligometastases)
Primary tumor status	Not controlled	Controlled	Controlled/ucontrolled
Systemic treatment	Naive	Naive	Resistant
Location of metastases	N1 or M1	N1 or M1	N1 or M1

RATIONALE PRO

Improved local control

- Early androgen deprivation therapy (ADT) does not delay the receipt of subsequent palliative therapies

- **Removal of a persistent source of future metastases**

- **Improved response to systemic treatments**
  - Treatment of the primary tumour improves the efficacy of ADT in locally advanced and/or node+ disease

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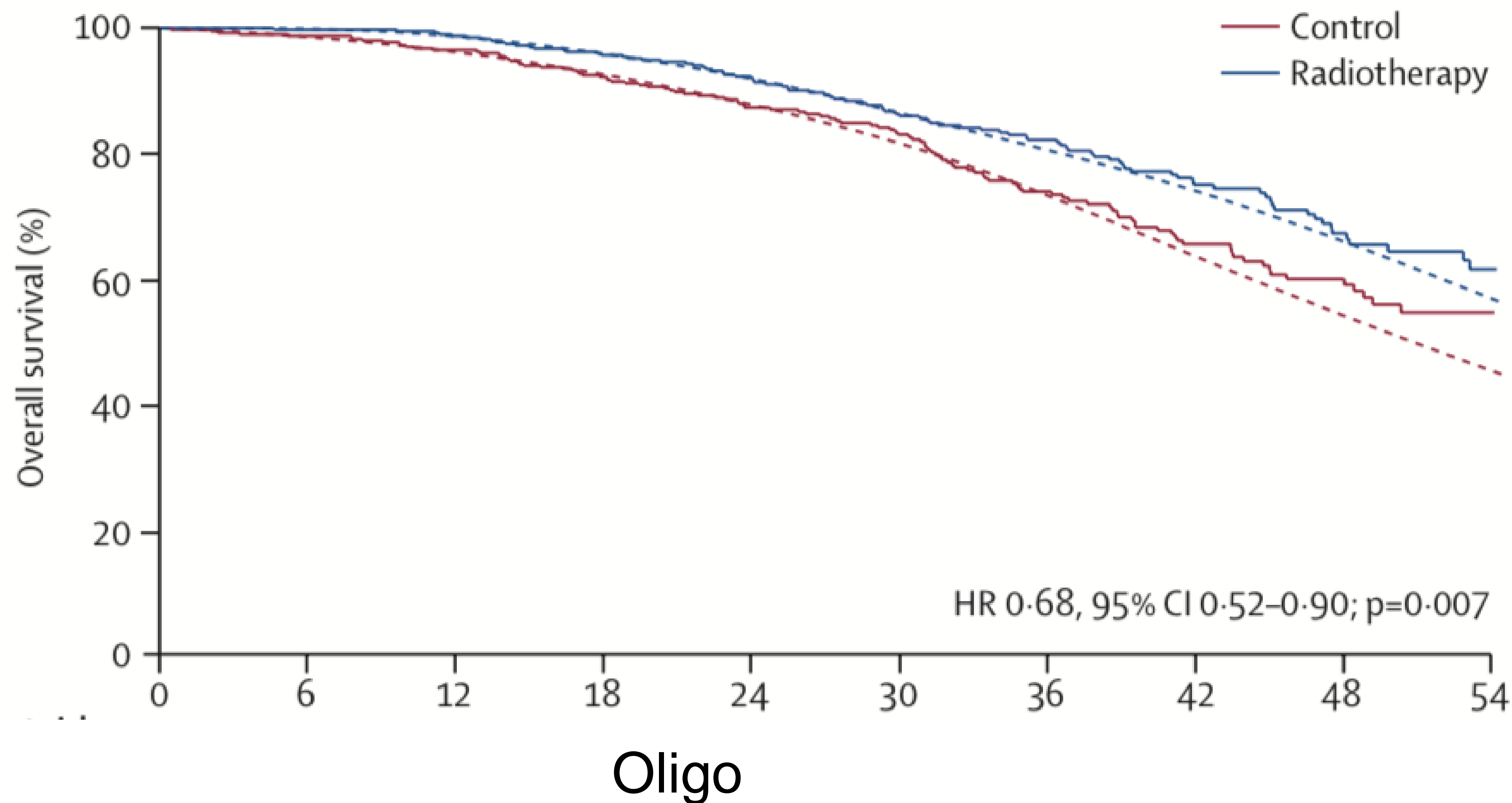
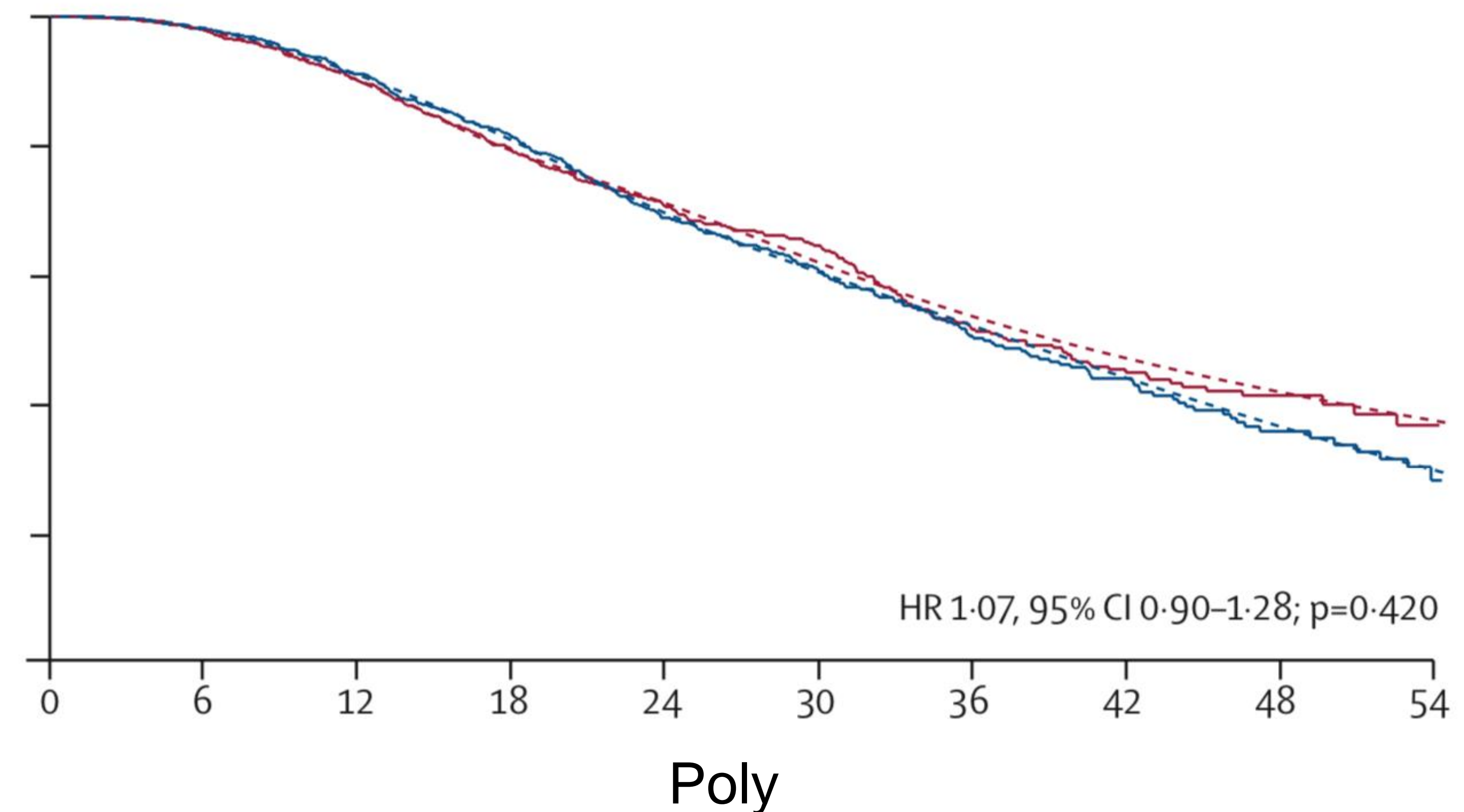
STANDARD OF CARE VS SOC+RADIOTHERAPY

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



Oligo



Poly

Prostate radiotherapy should be a standard treatment option for men with a low metastatic burden

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C. Parker et al. Lancet 2018

ADT VS ADT+RT

	Weekly schedule (n=437)	Daily schedule (n=483)	Total (n=920)
Bladder			
Grade 0	152 (35%)	142 (29%)	294 (32%)
Grade 1 or 2	262 (60%)	318 (66%)	580 (63%)
Grade 3 or 4	20 (5%)	23 (5%)	43 (5%)
Missing	3	0	3
Bowel			
Grade 0	231 (53%)	185 (38%)	416 (45%)
Grade 1 or 2	205 (47%)	290 (60%)	495 (54%)
Grade 3 or 4	1 (<1%)	7 (1%)	8 (1%)
Missing	0	1	1

RTOG=Radiation Therapy Oncology Group.

***Table 4:* Worst reported acute radiotherapy bladder and bowel toxic effect (RTOG scale) in patients allocated radiotherapy**

	Control (n=187)*	Radiotherapy (n=988)
Diarrhoea	1 (1%)	12 (1%)
Proctitis	0 (0%)	11 (1%)
Cystitis	0 (0%)	7 (1%)
Haematuria	0 (0%)	6 (1%)
Rectal–anal stricture	0 (0%)	0 (0%)
Urethral stricture	0 (0%)	4 (<1%)
Rectal ulcer	0 (0%)	0 (0%)
Bowel obstruction	0 (0%)	1 (<1%)

Treatment groups correspond to the safety population. There were no reported grade 5 late radiotherapy toxic events. RTOG=Radiation Therapy Oncology Group. *Relates to patients assigned control who had some radiotherapy at some point.

***Table 5:* Grade 3 or 4 worst late radiotherapy toxicity score (RTOG scale) in patients who received radiotherapy (for research or progression)**

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C. Parker et al. Lancet 2018

OLIGORECURRENCE

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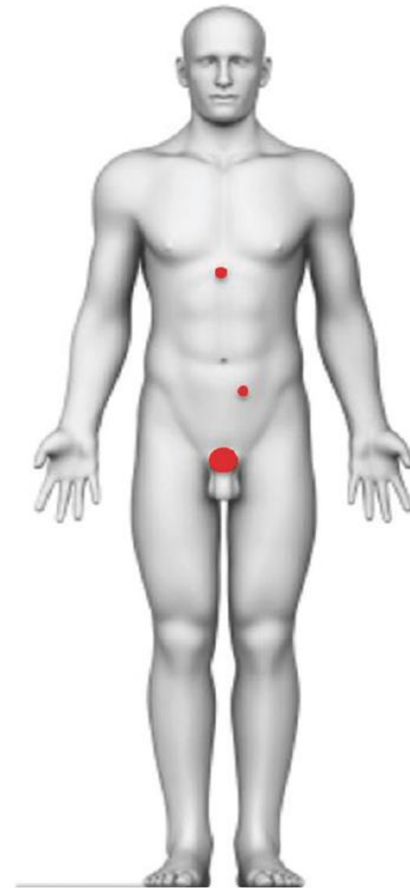
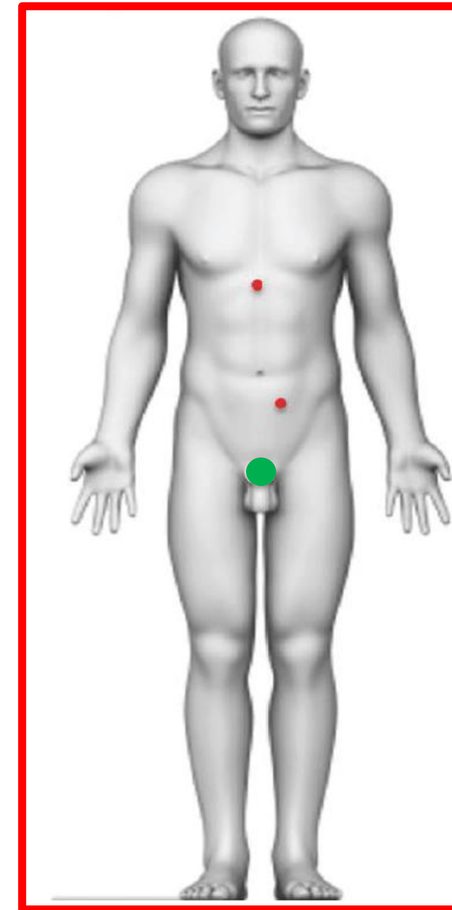
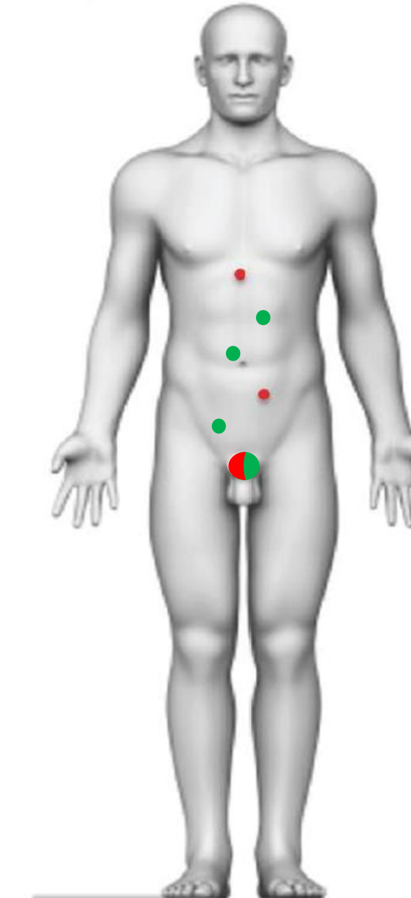
OLIGOMETASTATIC RECURRENCE

- Uncontrolled lesion
- Controlled lesion







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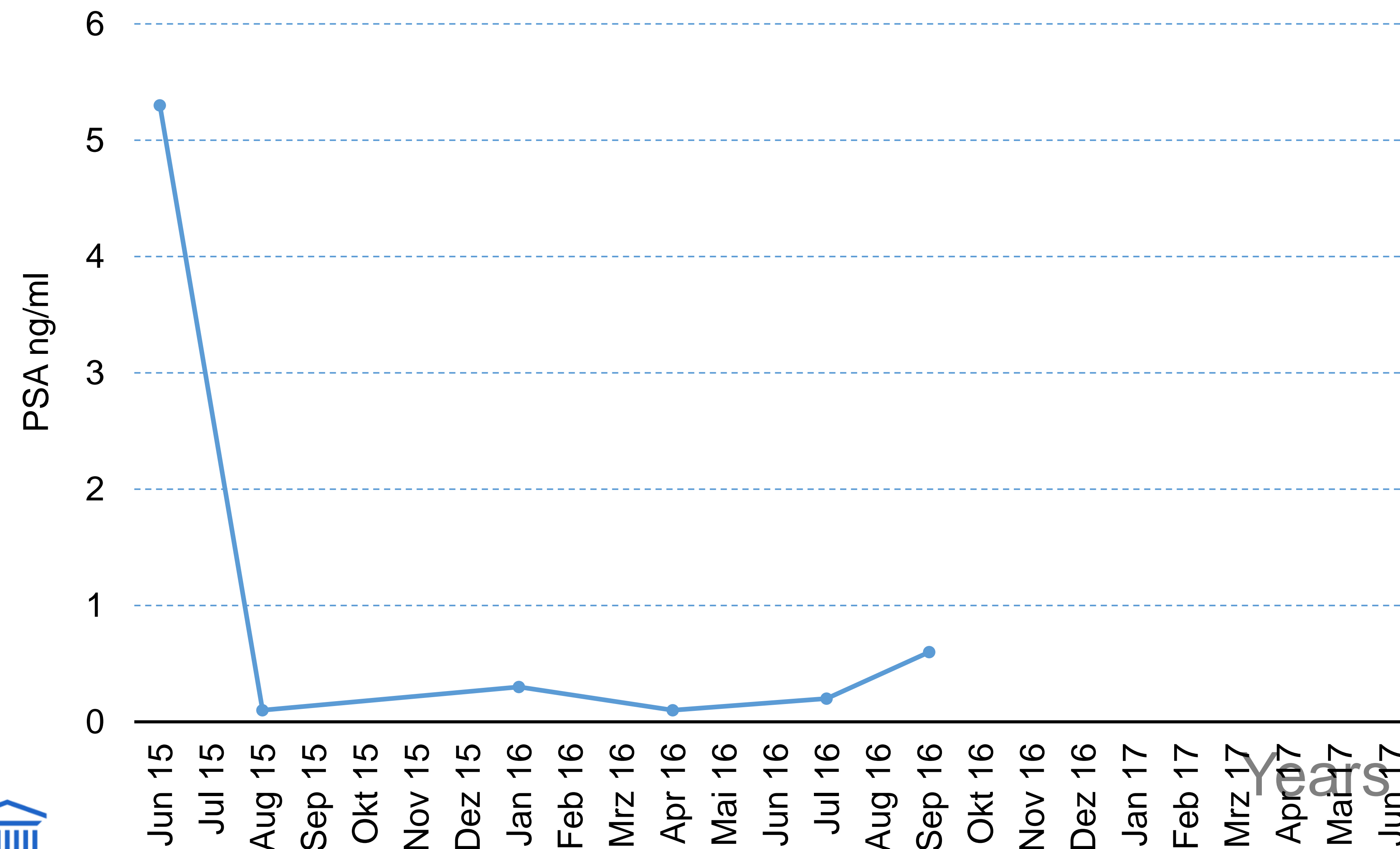
A FAMILIAR TALE

- 61 year old male; PSA 5.3ng/ml
- MRI and biopsy: Gleason 3+4=7 in 6/21 cores
- RARP: pT3a 4+3=7; N0; neg margin
- Salvage radiotherapy



Up to 30% of localized prostate cancer patients

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WHAT DO THE GUIDELINES SAY ON RE-STAGING?

Prostate-specific antigen (PSA) recurrence after radical prostatectomy	LE	Strength rating
Perform imaging only if the outcome will influence subsequent treatment decisions.		Strong
If the PSA level is ≥ 1 ng/mL, perform a prostate-specific membrane antigen positron emission tomography computed tomography (PSMA PET/CT), if available, or a choline PET/CT imaging otherwise.	2b	Weak
PSA recurrence after radiotherapy		
Perform prostate multiparametric magnetic resonance imaging to localise abnormal areas and guide biopsies in patients who are considered candidates for local salvage therapy.	3	Strong
Perform PSMA PET/CT (if available) or choline PET/CT imaging to rule out positive lymph nodes or distant metastases in patients fit for curative salvage treatment.	2b	Strong

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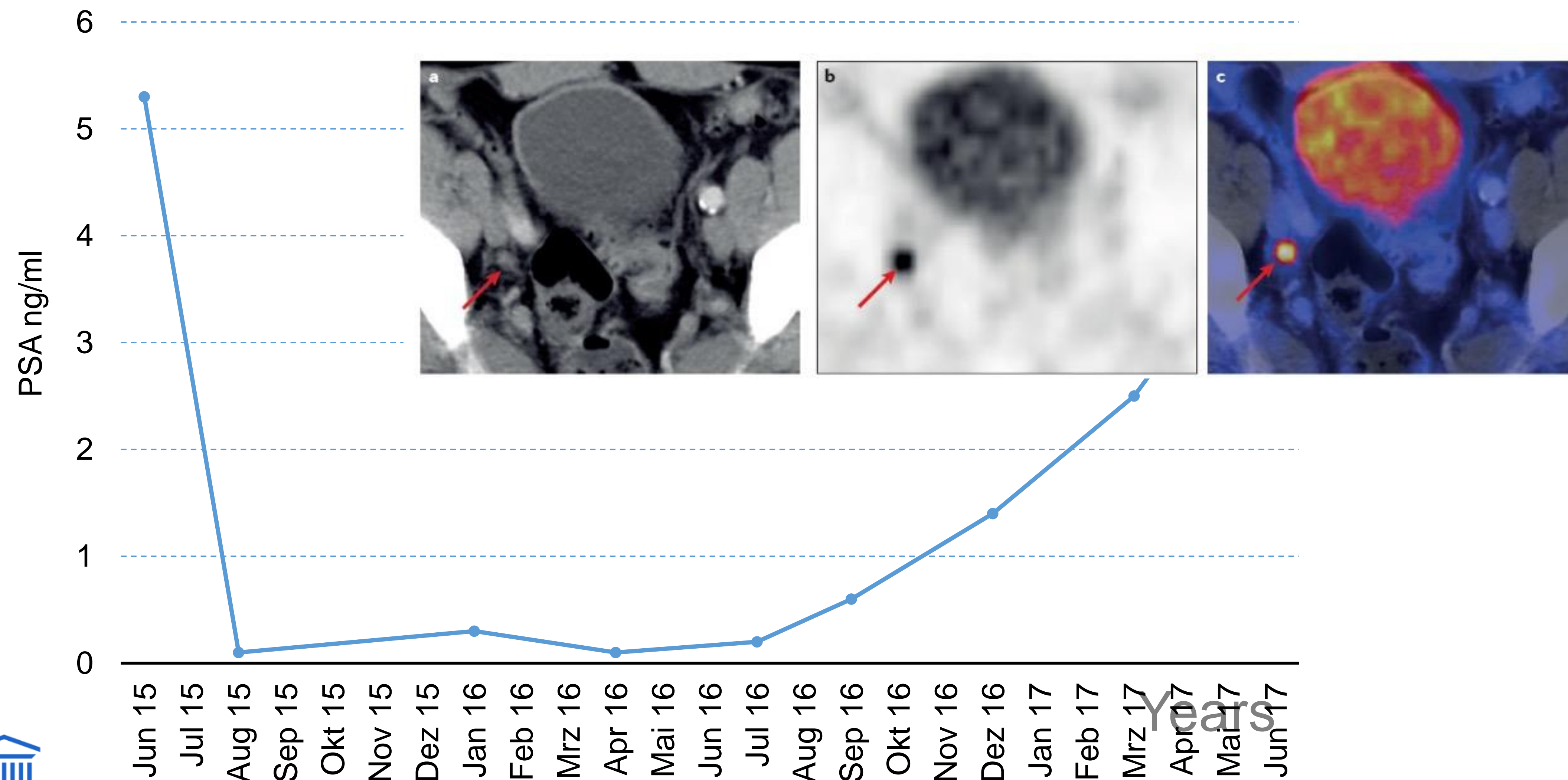
A FAMILIAR TALE

- 61 year old male; PSA 5.3ng/ml
- RARP: pT3a, pN0 (0/18), ISUP 3, neg margin
- Salvage radiotherapy for rising PSA



Proposed treatment ?

A. Observation with ADT at time of progression
B. Immediate ADT
C. ADT + Docetaxel
D. MDT (any surgical or RT option)
E. MDT + systemic therapy of choice

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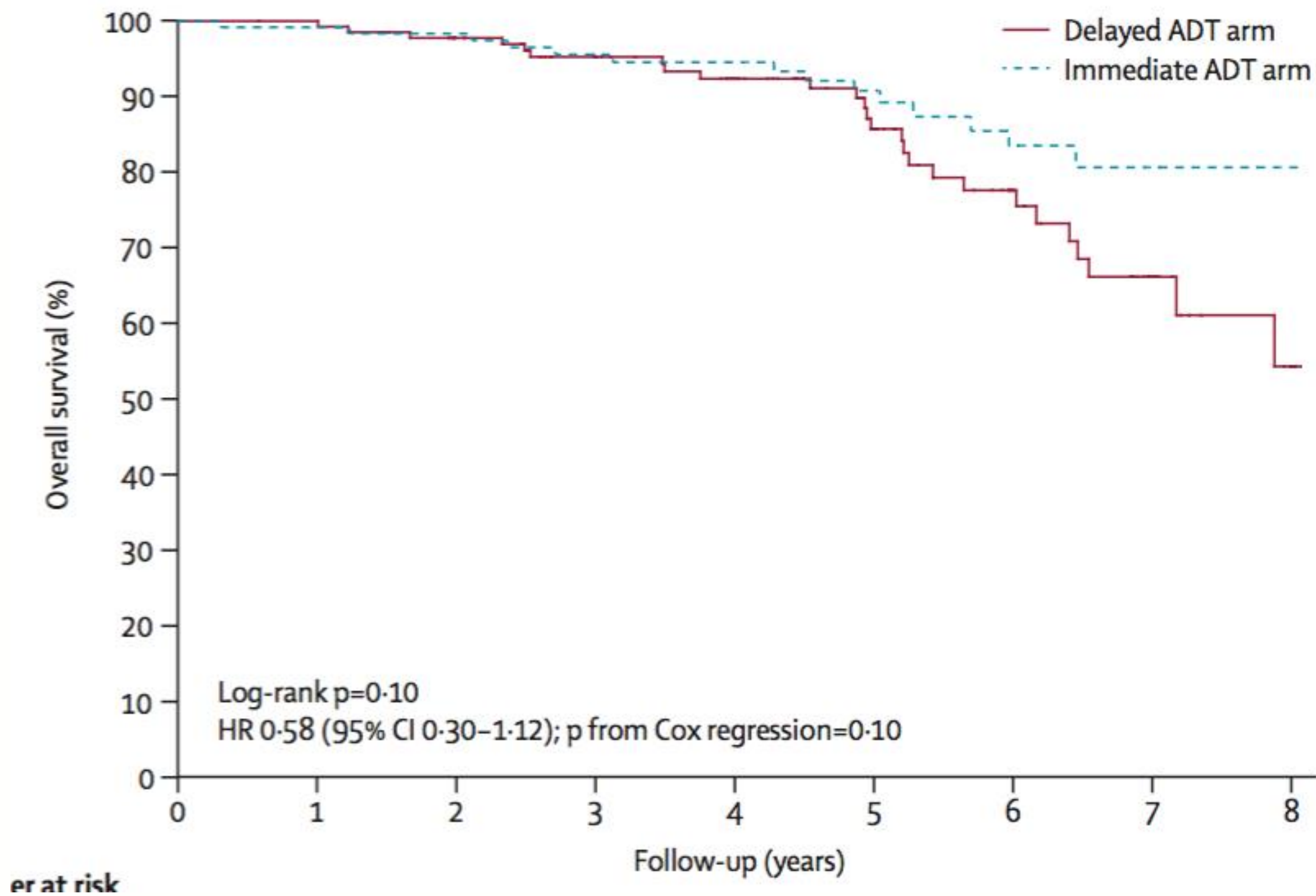
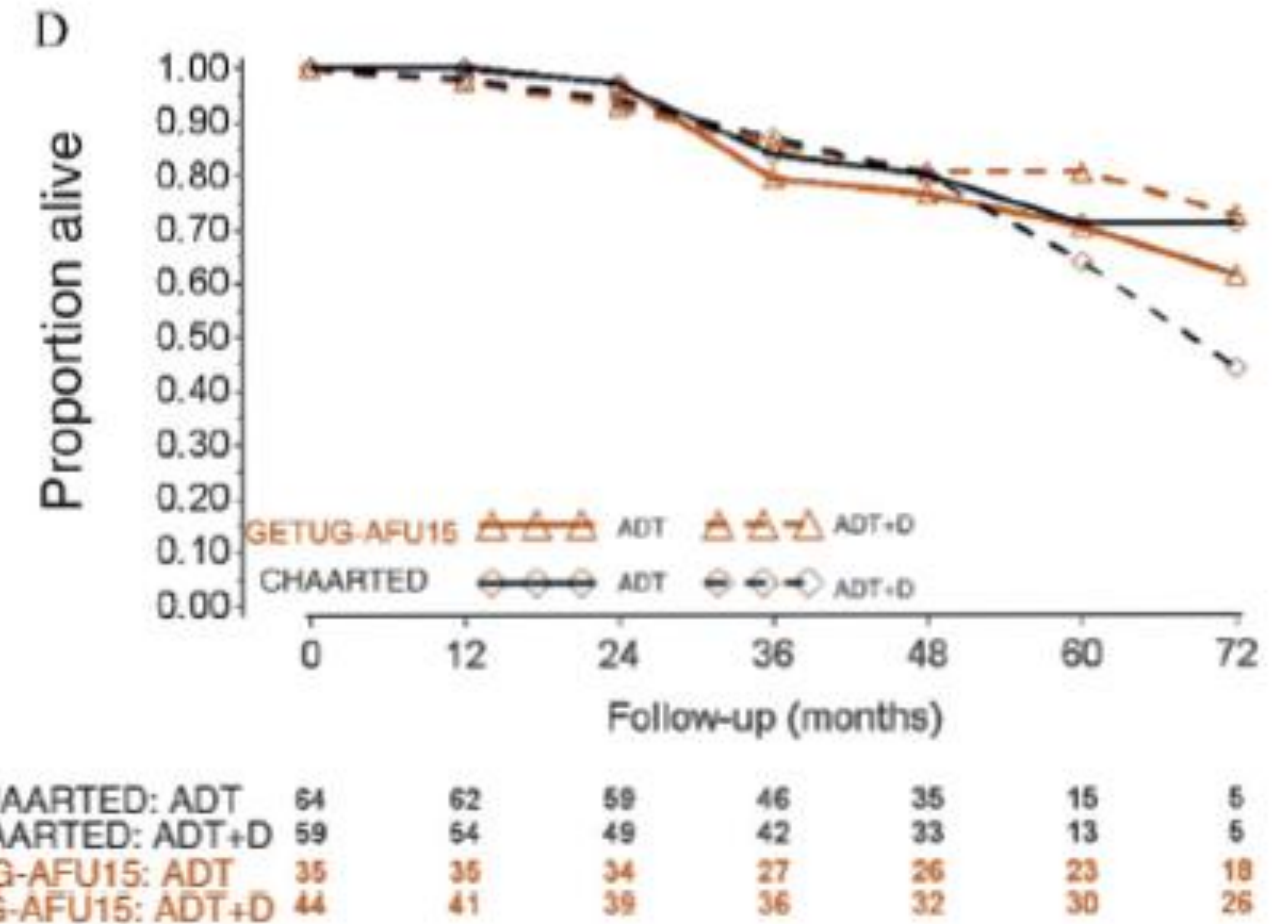
PSA DT calculated on https://www.mskcc.org/nomograms/prostate/psa_doubling_time

WHAT DO THE GUIDELINES SAY ON SYSTEMIC THERAPY?

Recommendations for systemic salvage treatment	
Do not offer androgen deprivation therapy to M0 patients with a PSA-DT > twelve months.	Strong





TOAD-trial: No survival benefit of immediate ADT

CHAARTED + GETUG15: No survival benefit of immediate ADT + Docetaxel

METASTASIS-DIRECTED THERAPY FOR OLIGOMETASTASES

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LOW LEVEL OF EVIDENCE

Platinum Priority – Review – Prostate Cancer

Editorial by XXX on pp. x–y of this issue

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]*

Conclusions: MDT is a promising approach for oligometastatic PCa recurrence, but the low level of evidence generated by small case series does not allow extrapolation to a standard of care.

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OLIGOMETASTASES: A HYPE?

Roderick v/d Bergh
@roodvdb

Als antwoord op @EUplatinum en @declangmurphy

@EUplatinum @declangmurphy @LoebStacy Treating oligometastatic disease, #pokemet or #whack-a-mole ?!

Platinum Opinion

"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]*

Platinum Priority – Editorial and Reply from Authors

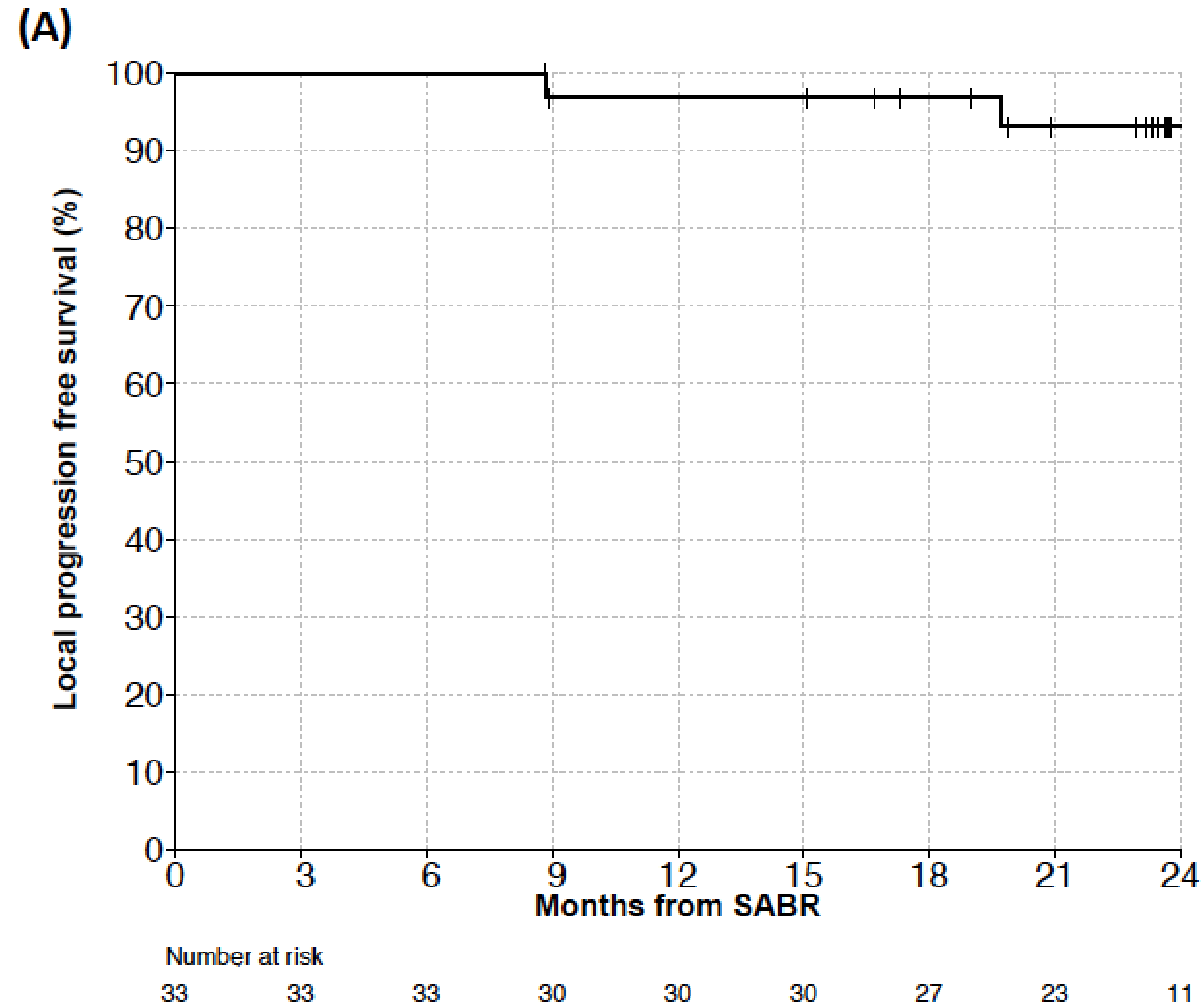
Referring to the article published on pp. 9–12 of this issue

Is There Another Bite of the Cherry? The Case for Radical Local Therapy for Oligometastatic Disease in Prostate Cancer

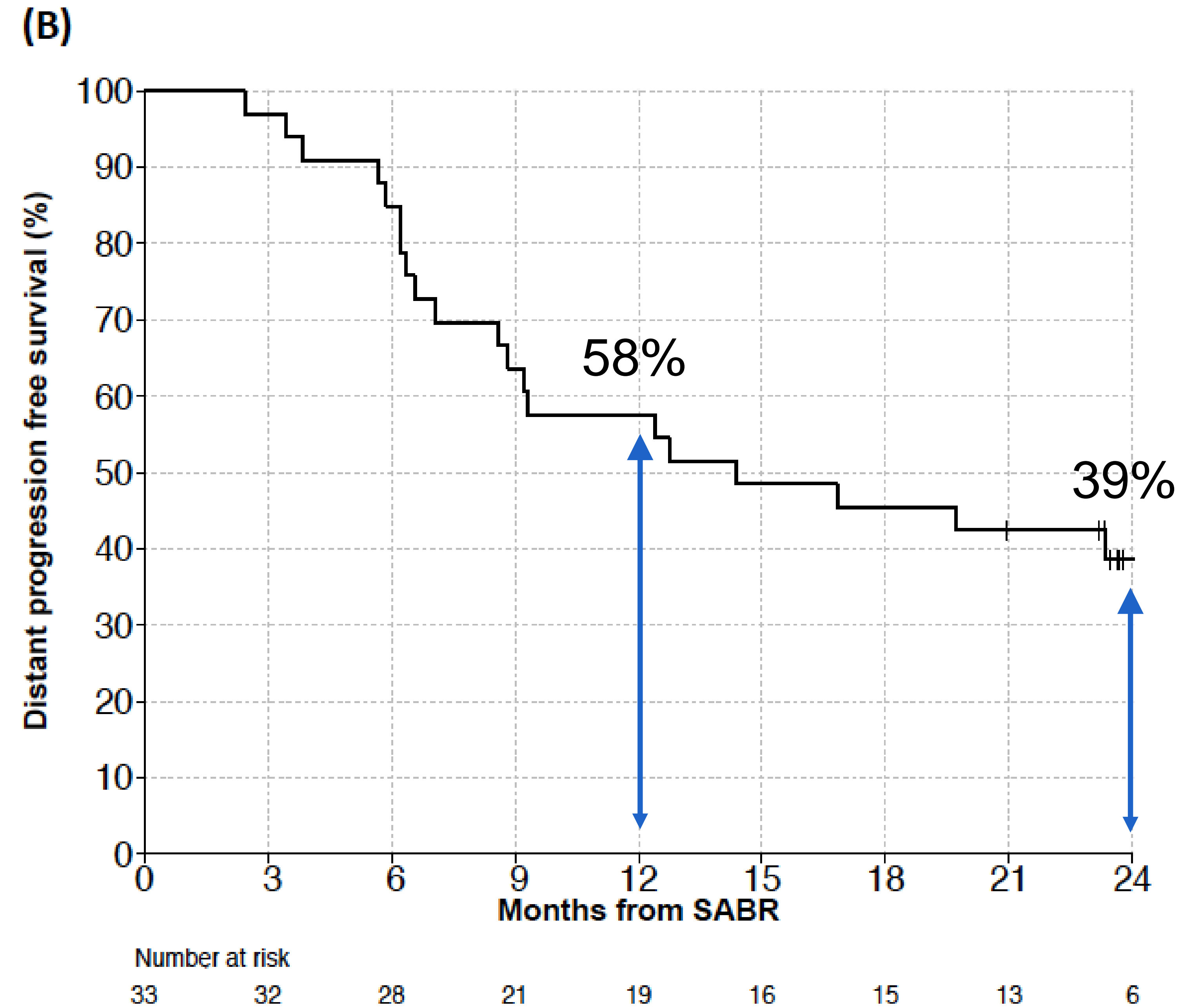
Vincent Khoo [a,b,c,]*

POPSTAR-TRIAL

POPSTAR-TRIAL: SINGLE FRACTION STEREOTACTIC BODY RADIOTHERAPY FOR OLIGOMETASTATIC PROSTATECANCER: A PROSPECTIVE CLINICAL TRIAL



Local control



Distant progression

Siva et al. Eur Urol 2018 (in press)

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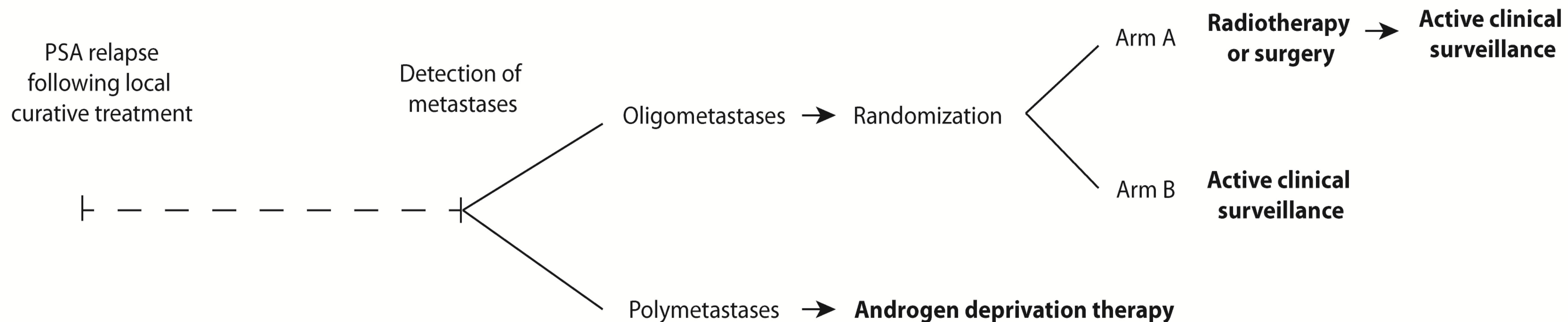
STOMP-TRIAL: PROOF OF CONCEPT

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

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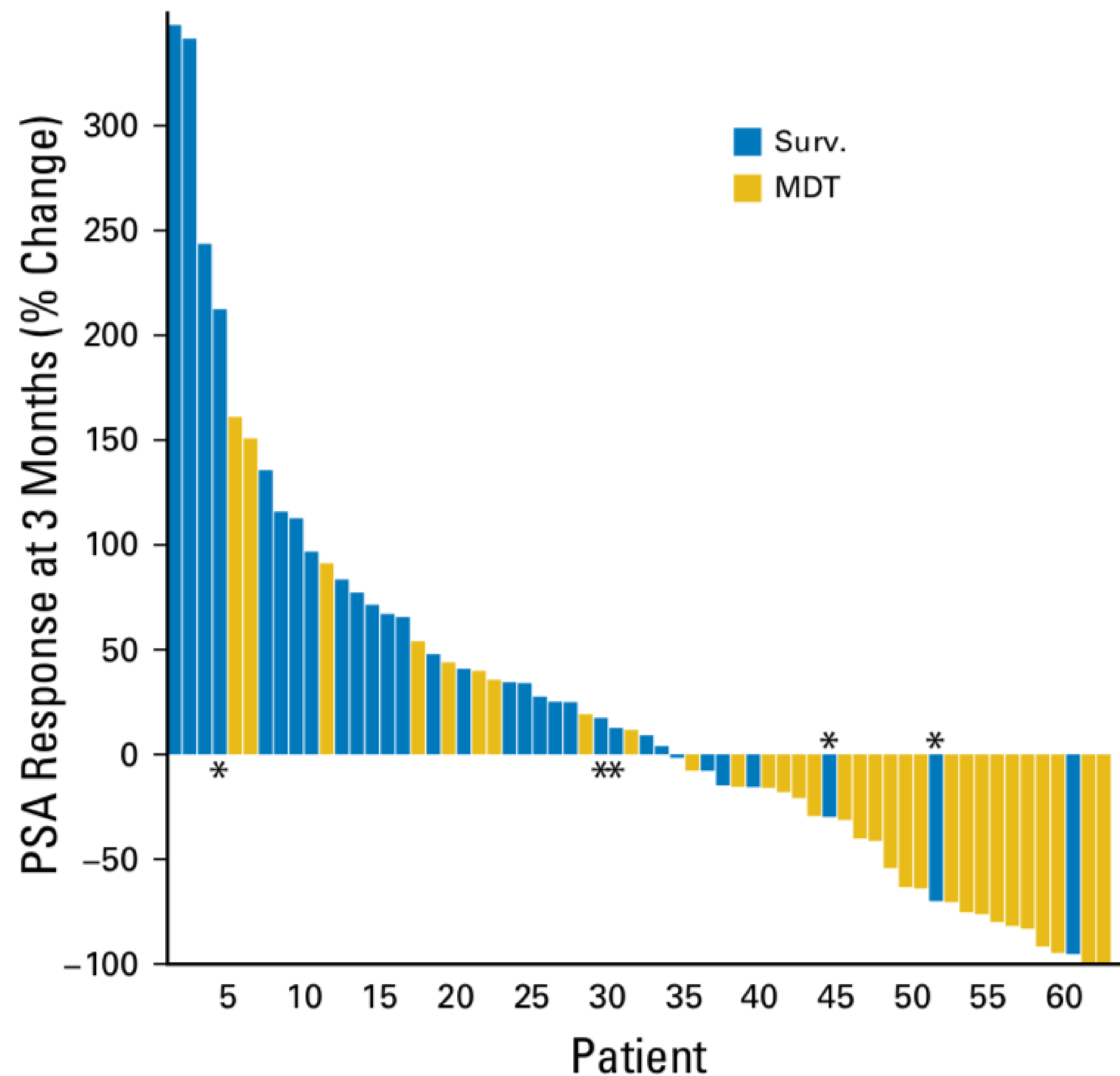
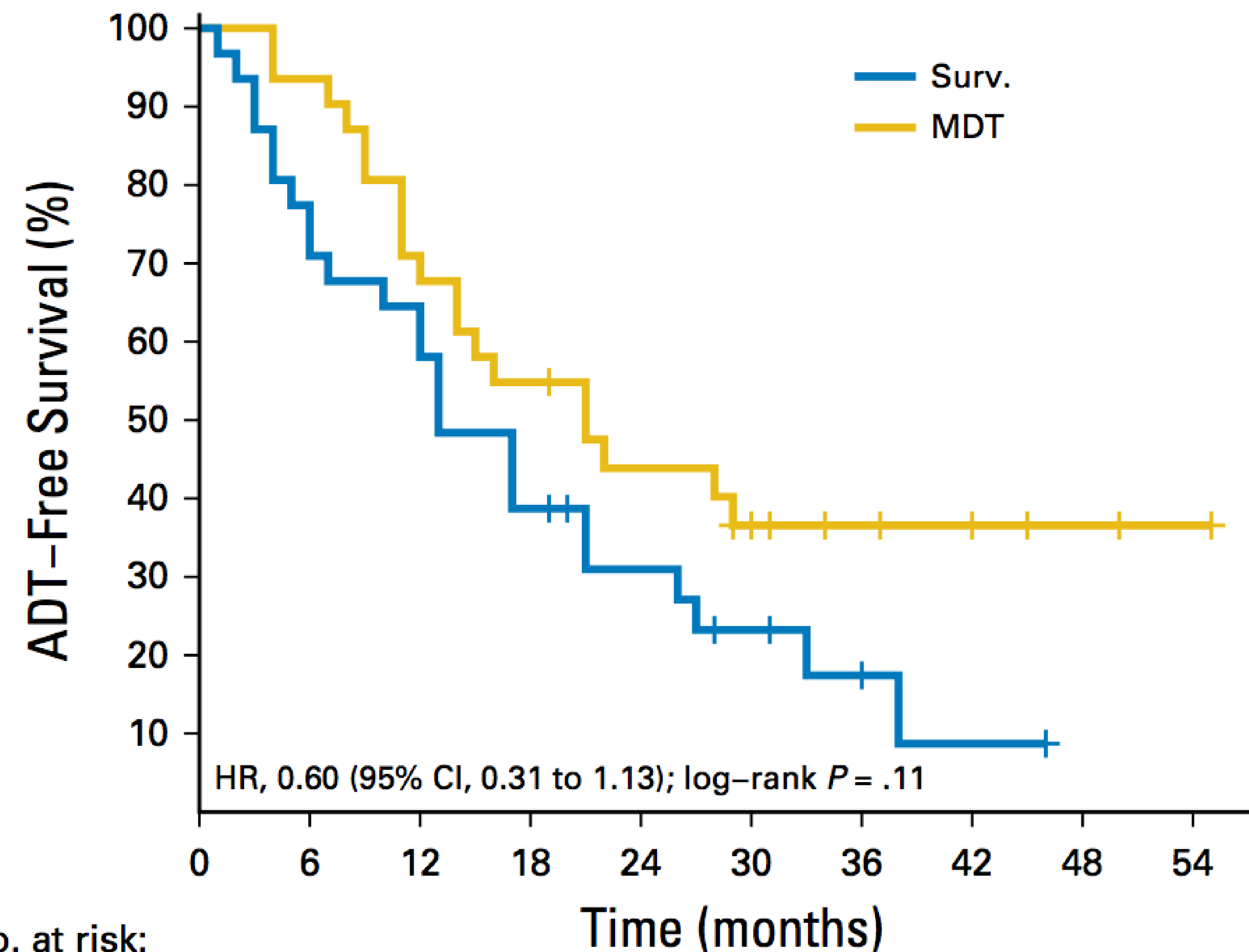
Decaestecker et al. 2014 BMC Cancer

RESULTS





Surveillance: 35% of pts have a PSA decline

MDT: 75% of pts have a PSA decline

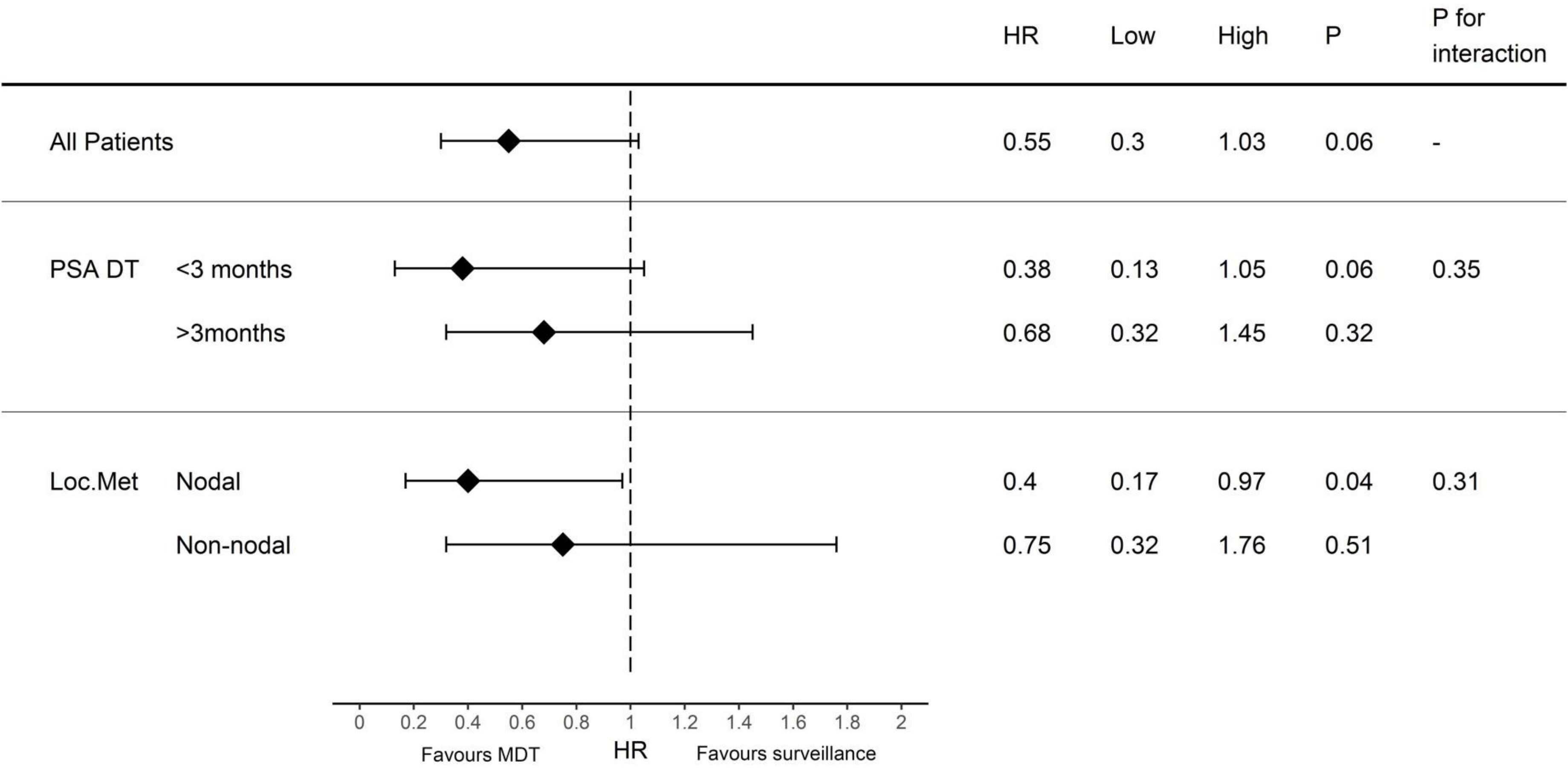
ITT: median ADT-free survival 13 months vs 21 months

HR: 0.60 [95% CI: 0.31 – 1.13], log-rank p=0.11

Ost et al. JCO 2018

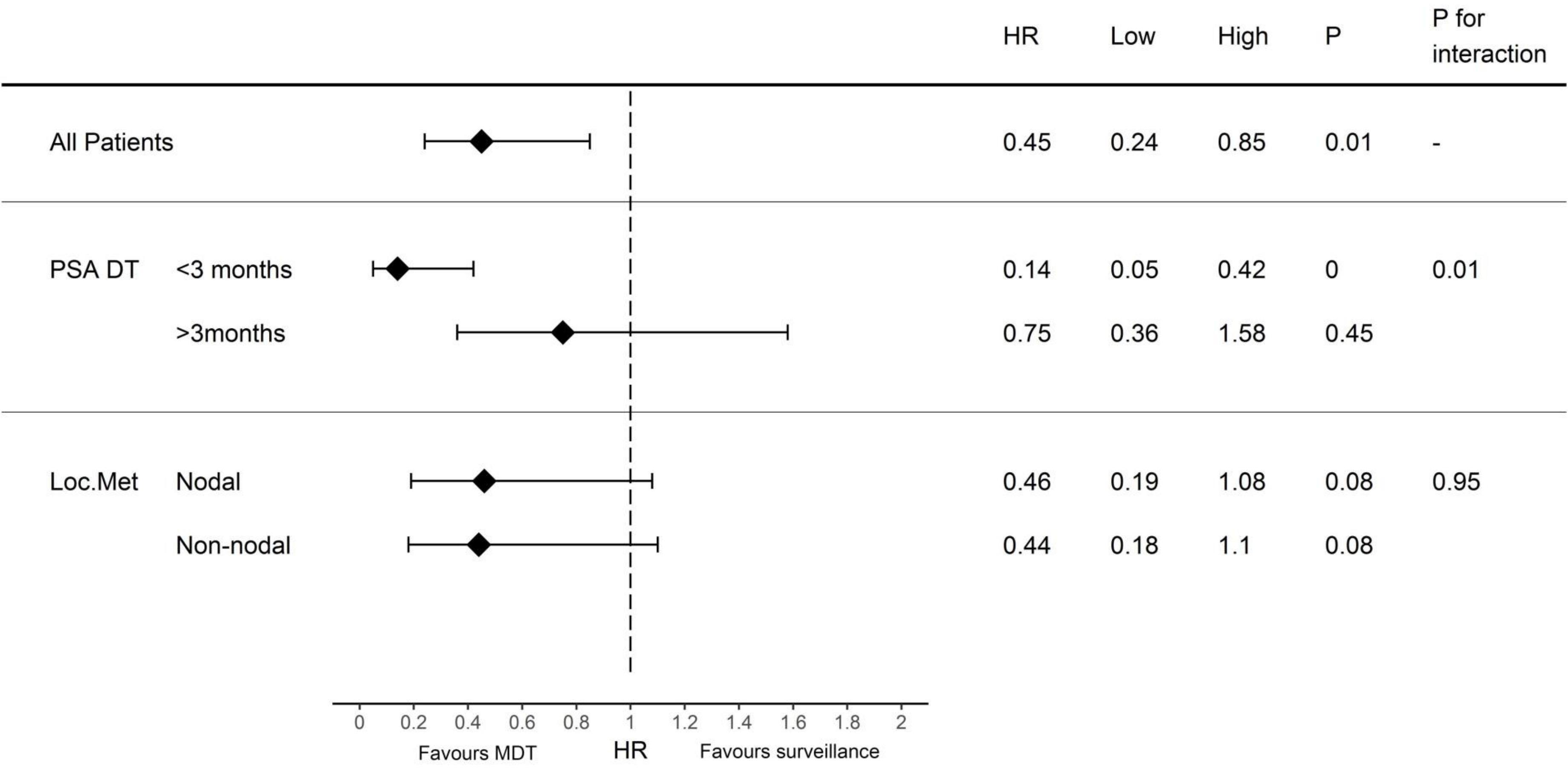
SUBGROUP ANALYSIS ON STRATIFICATION FACTORS

ITT



		HR	Low	High	P	P for interaction
All Patients		0.55	0.3	1.03	0.06	-
PSA DT	<3 months	0.38	0.13	1.05	0.06	0.35
	>3months	0.68	0.32	1.45	0.32	
Loc.Met	Nodal	0.4	0.17	0.97	0.04	0.31
	Non-nodal	0.75	0.32	1.76	0.51	

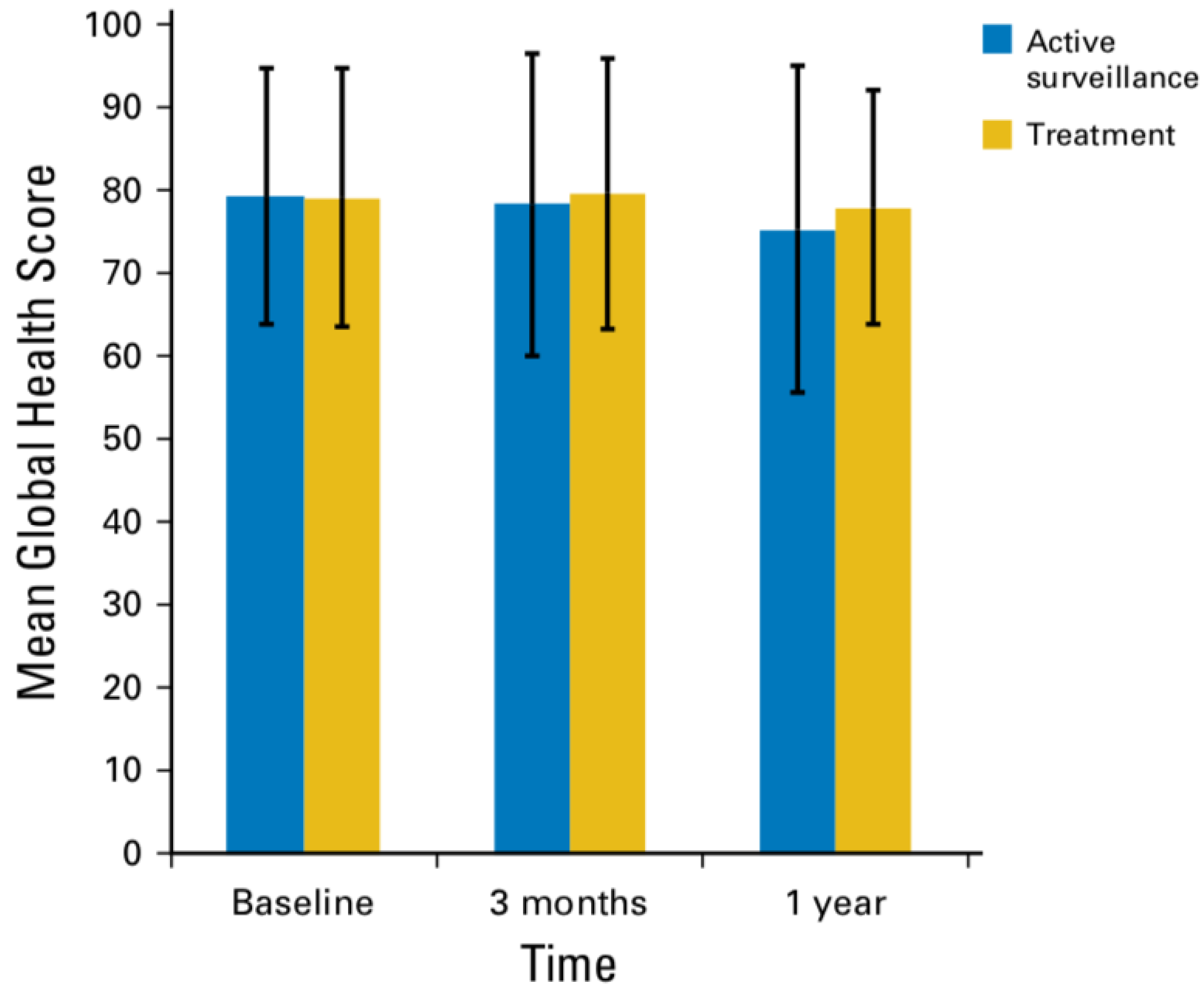
PP



		HR	Low	High	P	P for interaction
All Patients		0.45	0.24	0.85	0.01	-
PSA DT	<3 months	0.14	0.05	0.42	0	0.01
	>3months	0.75	0.36	1.58	0.45	
Loc.Met	Nodal	0.46	0.19	1.08	0.08	0.95
	Non-nodal	0.44	0.18	1.1	0.08	

The effect of MDT might be larger for pts with a PSA DT <3 months

TOXICITY AND QOL



No grade 2 or higher toxicity

No QOL difference between arms

Ost et al. JCO 2018

TAKE HOME MESSAGE

The first evidence of local therapy for "Oligometastases" is positive!

MDT POTENTIAL IMPACT ON SURVIVAL?

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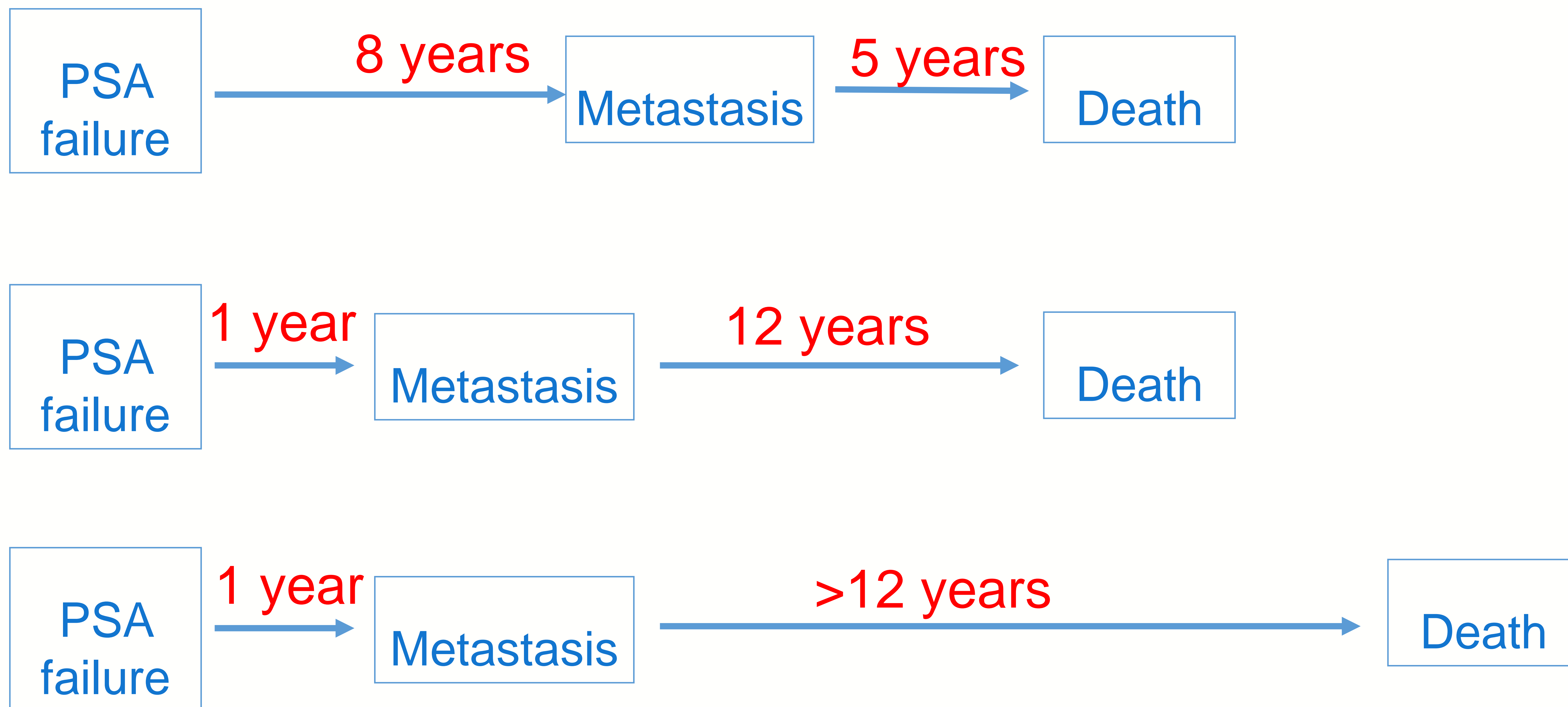
DOES EARLIER DETECTION AND TREATMENT OF METASTASES CHANGE DISEASE COURSE?



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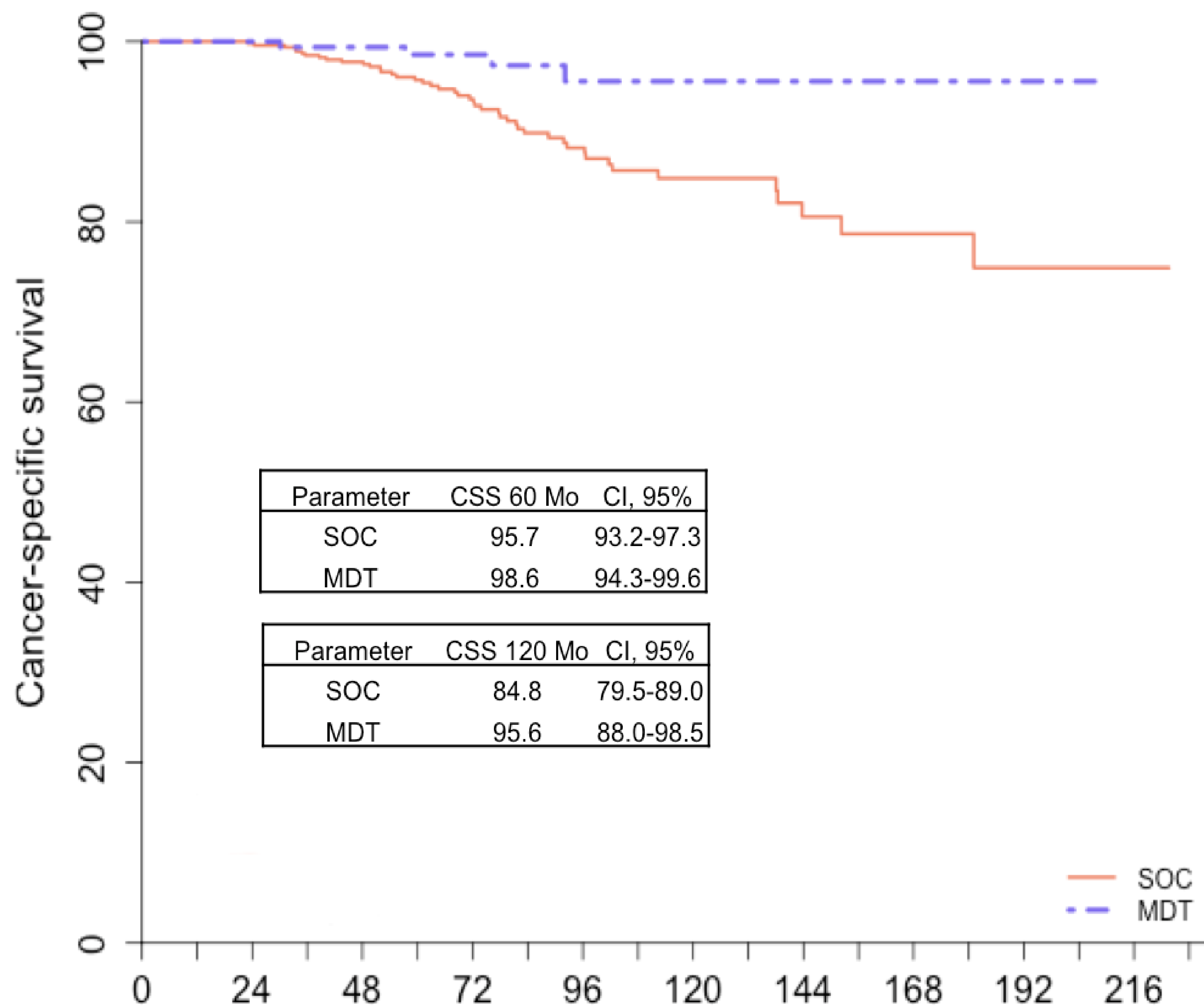
STANDARD OF CARE VS MDT: MATCHED CASE



- Patients with a PSA relapse following RP + postop RT

- SOC = delayed or immediate ADT
- MDT = sLND or SBRT for N1/M1a

- 3% CSS gain @ 5yr
- 10% CSS gain @ 10 yr

Steuber et al. Eur Urol Focus 2018

CONCLUSIONS

CONCLUSION

- The oligometastatic state exists in prostate cancer.
- Radiotherapy for newly diagnosed low volume metastatic Pca is standard of care
- Metastasis-directed therapy for recurrences is promising?
- Trials are coming:
  - SABR-COMET-3, ORIOLE, CORE NCT02759783 and STORM,…

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