Local treatments in the management of metastatic disease

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Local treatment to the primary tumor (Rt or Surg)

Rationale

Evidences

- **Radiotherapy**
- **Surgery**

Metastasis-directed therapy in oligometastatic disease

Definition of the *'oligo-state'*

Evidences

- **Castration naive**
- **Castration resistant**
  - ✓**Oligoprogression on ADT**
  - ✓**Oligoprogression on ARTA**

Modulo dichiarazione conflitto di interessi

Tutti i rapporti finanziari intercorsi negli ultimi due anni devono essere dichiarati.

☐ Non ho rapporti (finanziari o di altro tipo) con le Aziende del farmaco

X Ho / ho avuto rapporti (finanziari o di altro tipo) con le Aziende del farmaco

Relationship	**Company/Organization**
Consulting	Sanofi
Congress Honoraria	Sanofi, Amgen, Novartis, AstraZeneca
Congress Support and Sponsoring	Astellas, Janssen, Sanofi, Novartis, AstraZeneca, Eli Lilly, Roche, Amgen, Merk, BMS, Pfizer, Servier

70 years old

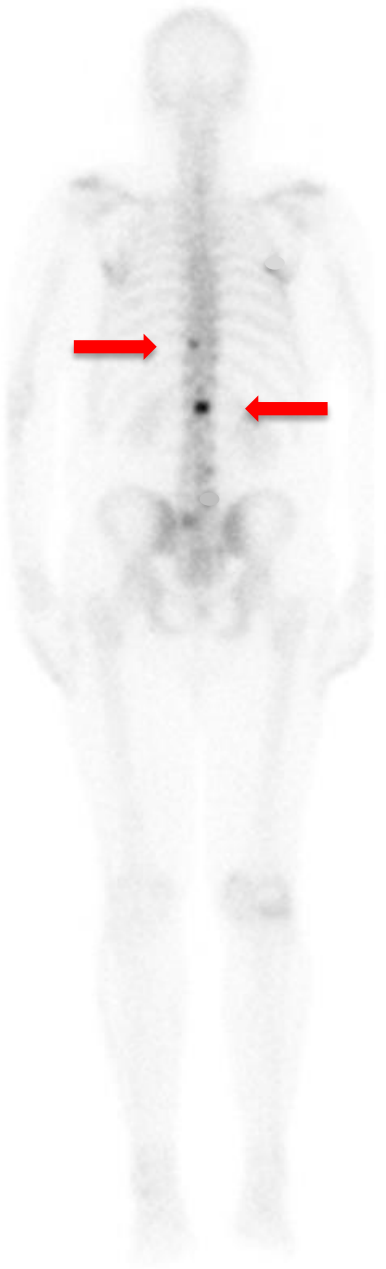
PSA 40 ng/ml
ALP 450 UI/L
Biopsy: PC - GS 7 (3+4)

First-line treatment: LH-RHa

De novo Oligometastatic

Low Volume (CHAARTED)

Low Risk (LATITUDE)



Any other option?

1. Nothing
2. Abiraterone/Prednisone
3. Apalutamide
4. Enzalutamide
5. Docetaxel

70 years old

PSA 40 ng/ml
ALP 450 UI/L
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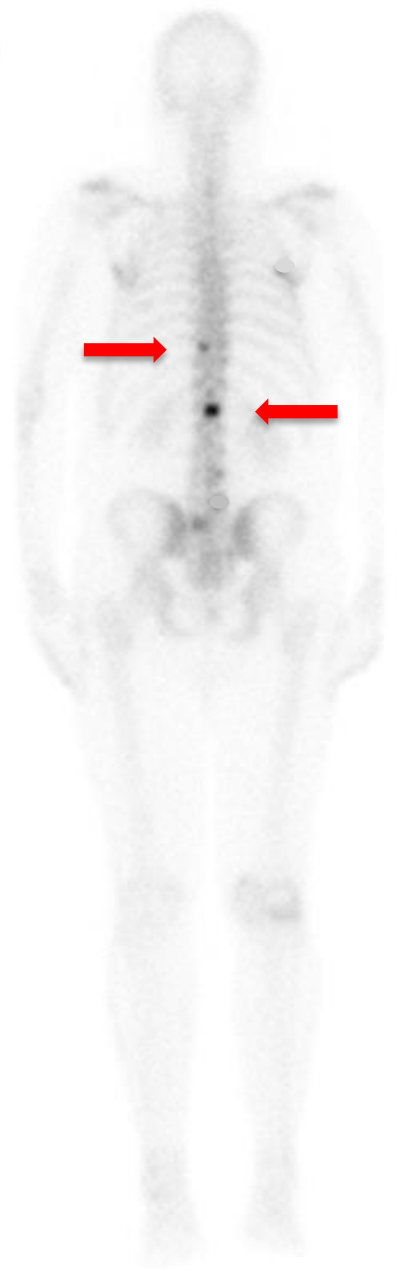


Recommendation	Level
Offer castration alone, with or without an anti-androgen, to patients unfit for, or unwilling to consider, castration combined with docetaxel or abiraterone acetate plus prednisone or prostate radiotherapy.	Strong
Offer castration combined with chemotherapy (docetaxel) to all patients whose first presentation is M1 disease and who are fit enough for chemotherapy.	Strong
Offer castration combined with abiraterone acetate + prednisone to all patients whose first presentation is M1 disease and who are fit enough for the regimen	Strong

EAU – ESTRO – ESUR – SIOG Guidelines on **Prostate Cancer**

Combination strategies for mHSPC
Phase III trials

Agent	Study	HR OS, CI 95%
Docetaxel	**CHAARTED** *Kyriakoupulos , JCO 2018*	0.72 (0.59 -0.89)
Docetaxel	**GETUG-15** *Gravis, Eur Urol 2015*	0.88 (0.68-1.14)
Docetaxel	**STAMPEDE** *Clarke, Ann Onc 2019*	0.81 (0.69-0.95)
Abiraterone	**STAMPEDE** *James, NEJM 2017*	0.61 (0.49-0.75)
Enzalutamide	**ARCHES** *Armstrong, JCO 2019*	NR
Enzalutamide	**ENZAMET** *Davis, NEJM 2019*	0.67 (0.52-0.86)
Apalutamide	**TITAN** *Chi, NEJM 2019*	0.67 (0.51-1.89)

70 years old

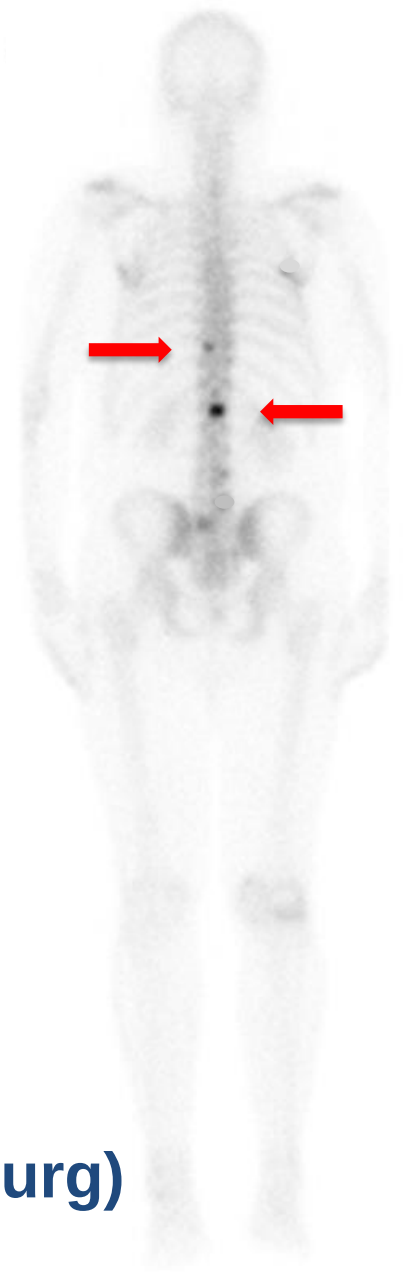
PSA 40 ng/ml
ALP 450 UI/L
Biopsy: PC - GS 7 (3+4)

First line treatment: Degarelix

De novo Oligometastatic

Low Volume (CHAARTED)

Low Risk (LATITUDE)



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1. Nothing
2. Abiraterone/Prednisone
3. Apalutamide
4. Enzalutamide
5. Docetaxel
6. Local treatment to the primary (RT or Surg)

Local treatment to the primary tumor (Rt or Surg)

Rationale

Evidences

- Radiotherapy
- Surgery

Metastasis-directed therapy in oligometastatic disease

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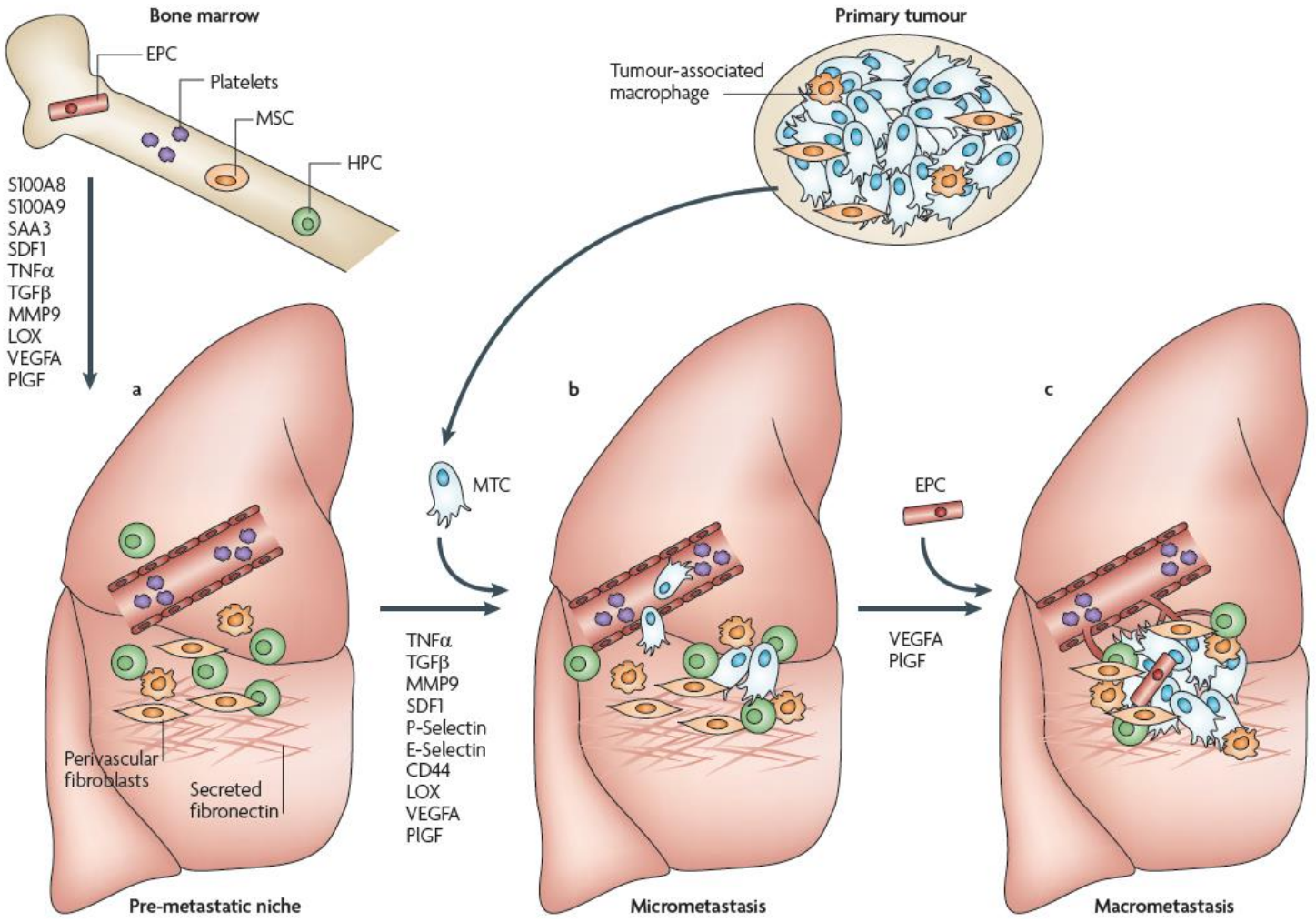
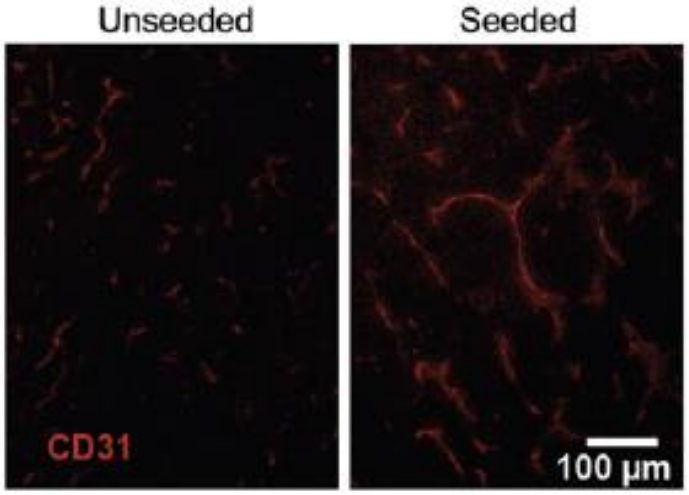
The metastatic niche: adapting the foreign soil



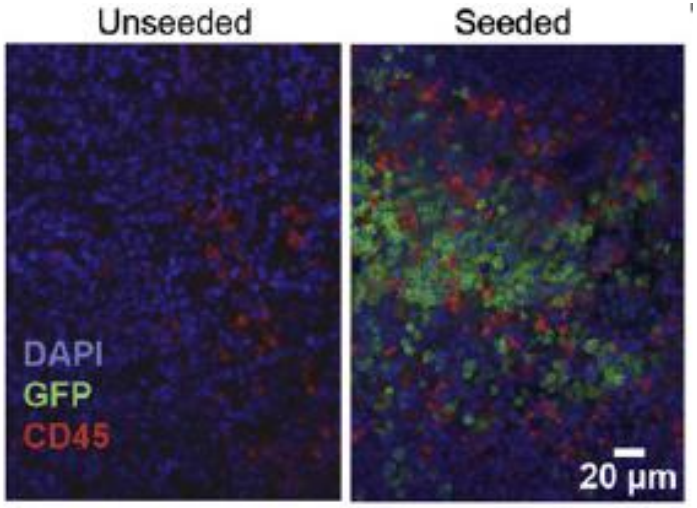
Psaila et Al. Nat Rew 2009

Tumor Self-Seeding by Circulating Cancer Cells

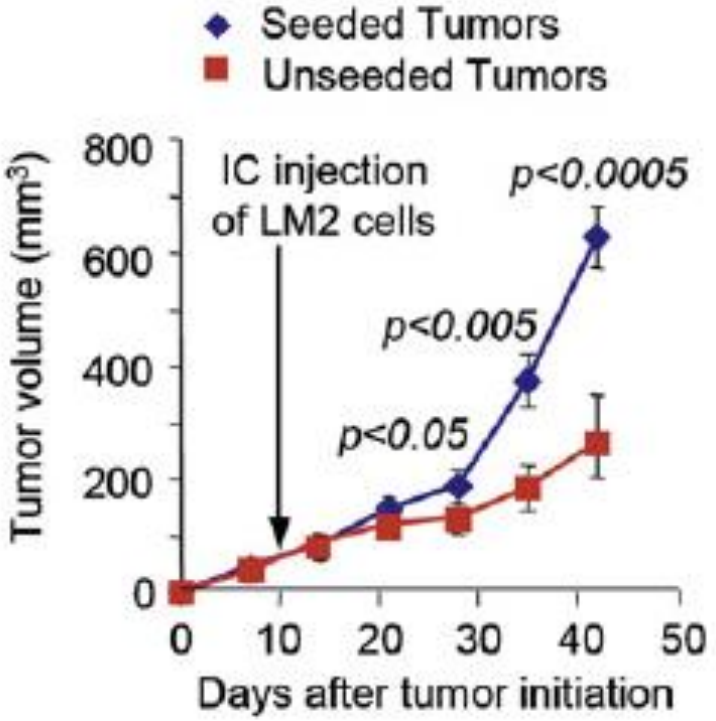
Increased Vascular Tumor branching



Increased lymphocytes recruitment

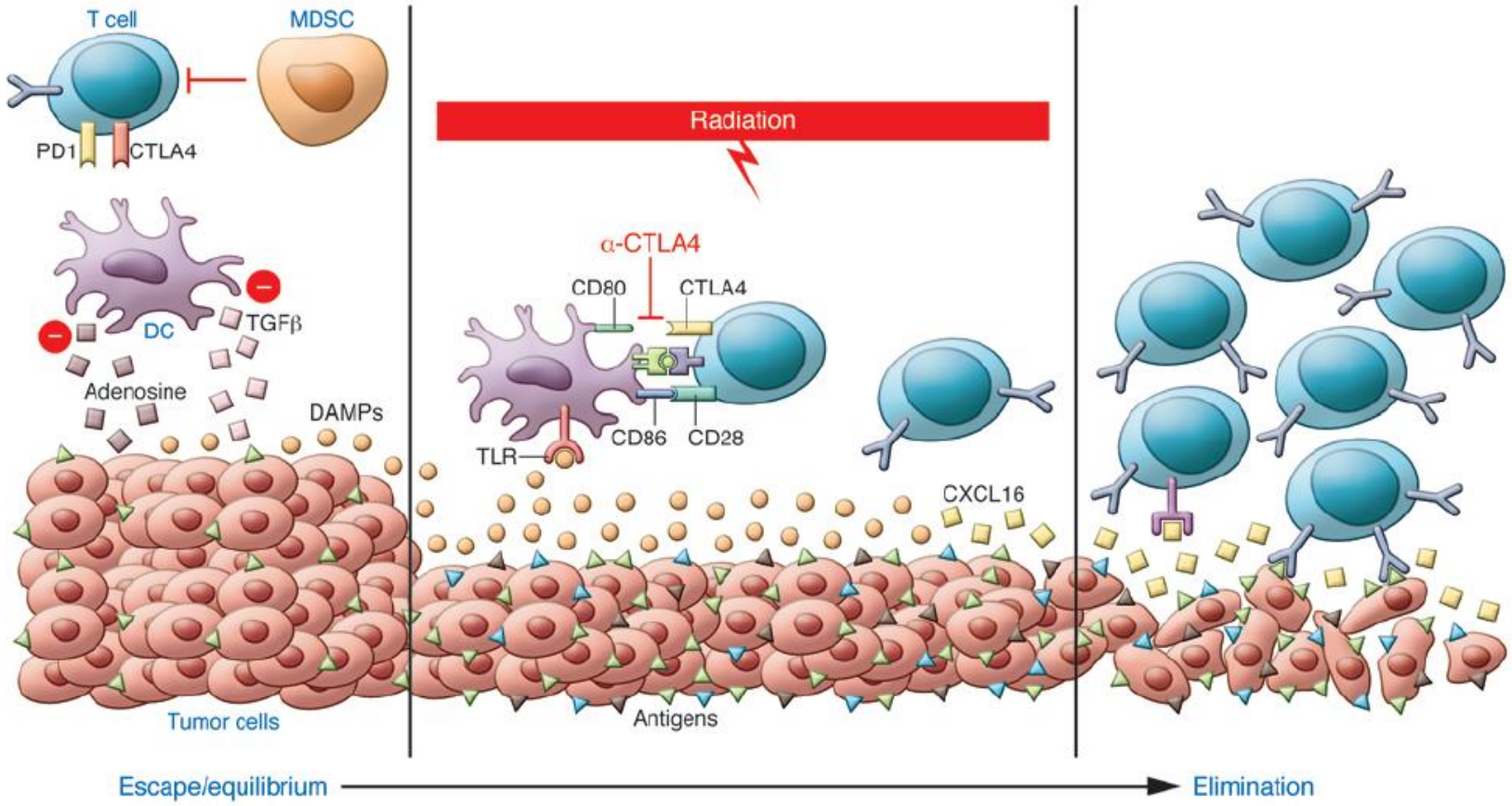


Change in Tumor Volume



kim et Al. Cell 2009

Imnomodulatory properties of Radiotherapy



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Local treatment to the primary tumor (Rt or Surg)

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Retrospective data for Local Therapy in metastatic Prostate Cancer

Author	Data Source	Patients	Intervention	Outcome
Parikh 2017	NCDB 2004-2013	6.051	LT vs No-LT	5yOS: 45.7% vs 17.1% p=0.01
Loppenberg 2017	NCDB 2004-2012	15.501	LT vs No-LT	Cancer specific Mortality HR 0.57
Bannurah 2017	SEER 2004-2013	13.692	LT vs No-LT	Cancer specific Mortality HR 0.40
Pompe 2018	SEER 2004-2014	13.906	LT vs No-LT	Cancer specific Mortality HR 0.57
Culp 2014	SEER 2004-2010	8185	LT vs No-LT	5yOS p<0.001
Satkunasivam 2015	SEER 2004-2009	4.069	LT vs No-LT	Cancer specific Mortality HR 0.38-0.48

LT: Local Therapy (*Radiotherapy and/or Radical Prostatectomy)*

Limitations

Retrospective
Selection bias
Eterogeneity of interventions
No informations about subsequent treatments
Different outcomes and reporting

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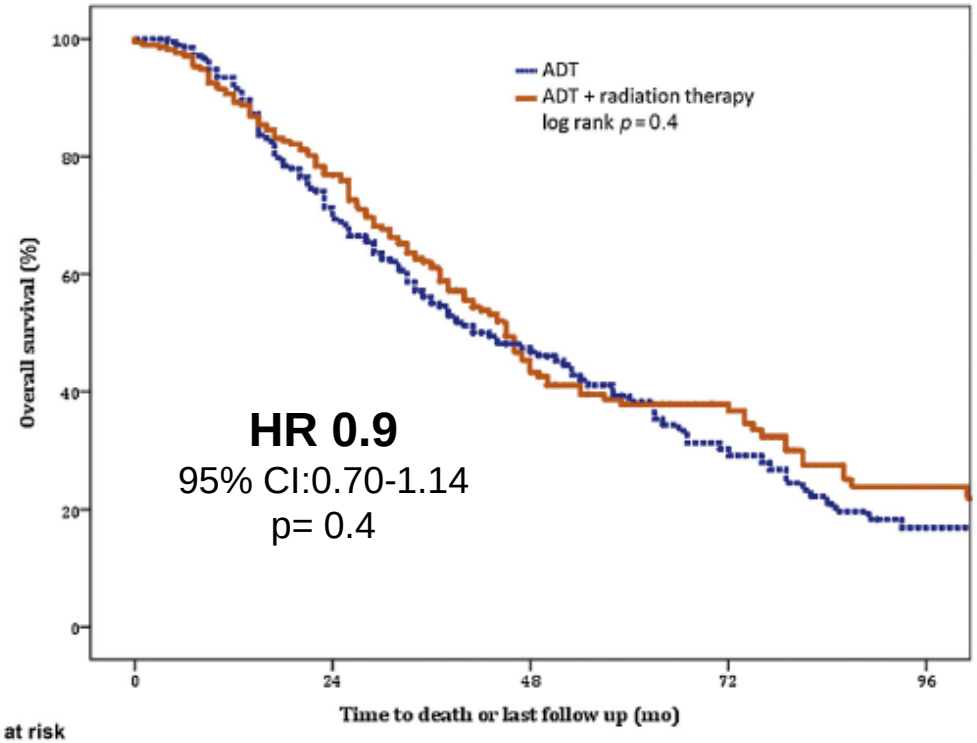
Effect on Survival of Androgen Deprivation Therapy Alone Compared to Androgen Deprivation Therapy Combined with Concurrent Radiation Therapy to the Prostate in Patients with Primary Bone Metastatic Prostate Cancer in a Prospective Randomised Clinical Trial: Data from the HORRAD Trial

- Multicentre RCT recruiting 432 pts with PSA>20 on bone scan between 2004 and 2014

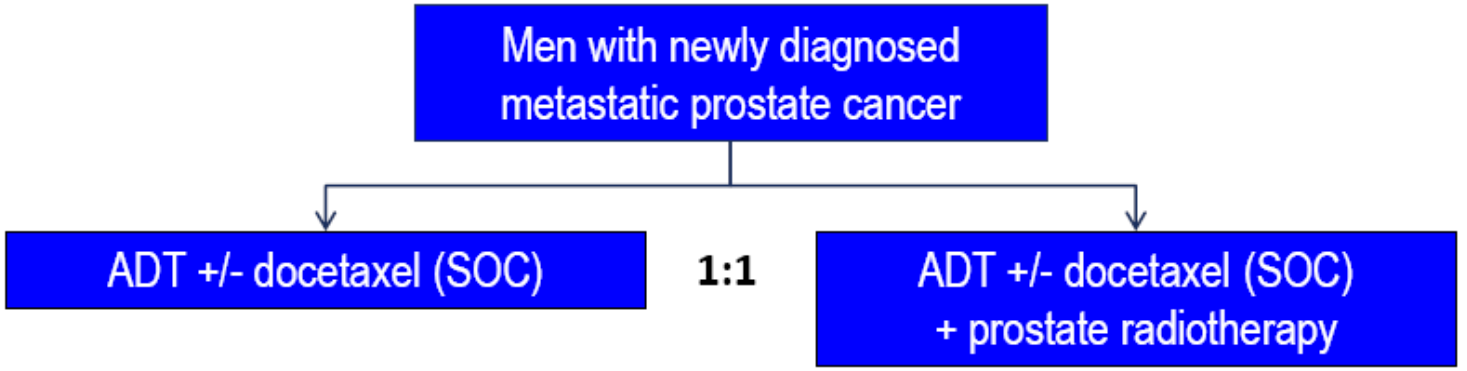
- Randomised to either ADT with EBRT (70Gy/35 or 57.76Gy/19, pelvic nodes not included) or ADT alone (control group)

Overall Survival



Boevè et Al. Eur Urol 2018

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



- Main outcome measure: **Overall survival**
- Secondary outcome measures:
  - **Failure-free survival**
  - **Symptomatic local events (SLE)**
  - **Toxicity**
  - Progression-free survival
  - Metastatic progression-free survival
  - Cause specific survival
  - Symptomatic skeletal events
  - Quality of life

- Pre-specified subgroup analyses
  - Radiotherapy schedule (daily vs weekly)
  - Metastatic burden (low vs high)

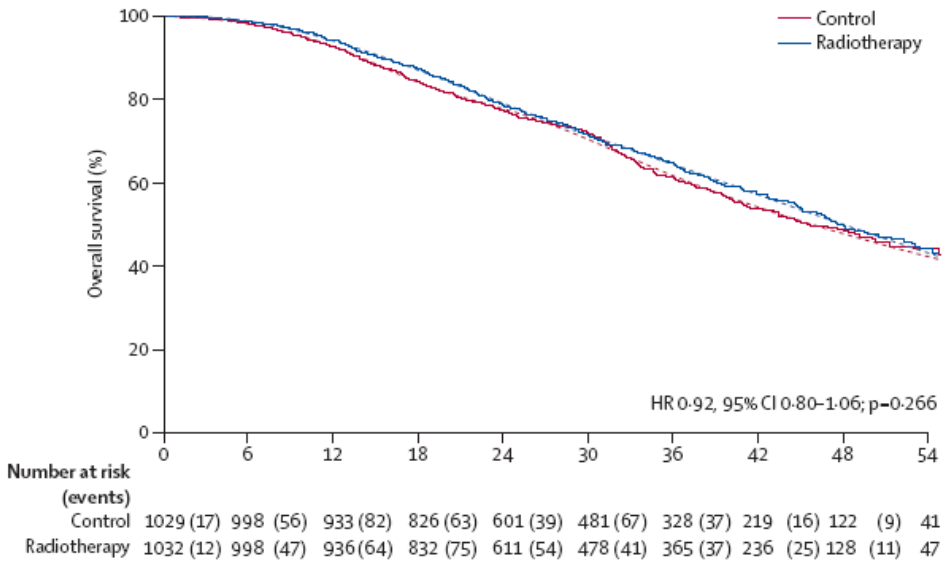
Parker et Al. Lancet Onc 2018

RESULTS: Baseline characteristics

Characteristic		SOC (n=1029)	SOC+RT (n=1032)
Age (years)	Median (IQR) Range	68 (63-73) 37-86	68 (63-73) 45-87
PSA (ng/ml)	Median (IQR) Range	98 (30-316) 1-20590	97 (33-313) 1-11156
Metastatic burden	Low High Not classified	409 (42%) 567 (58%) 53	410 (43%) 553 (57%) 69
Site of metastases	Bone Liver Lung Distant lymph nodes Other	919 (89%) 23 (2%) 42 (4%) 294 (29%) 35 (3%)	917 (89%) 19 (2%) 48 (5%) 304 (29%) 33 (3%)
Docetaxel use	No Yes	845 (82%) 184 (18%)	849 (82%) 183 (18%)

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

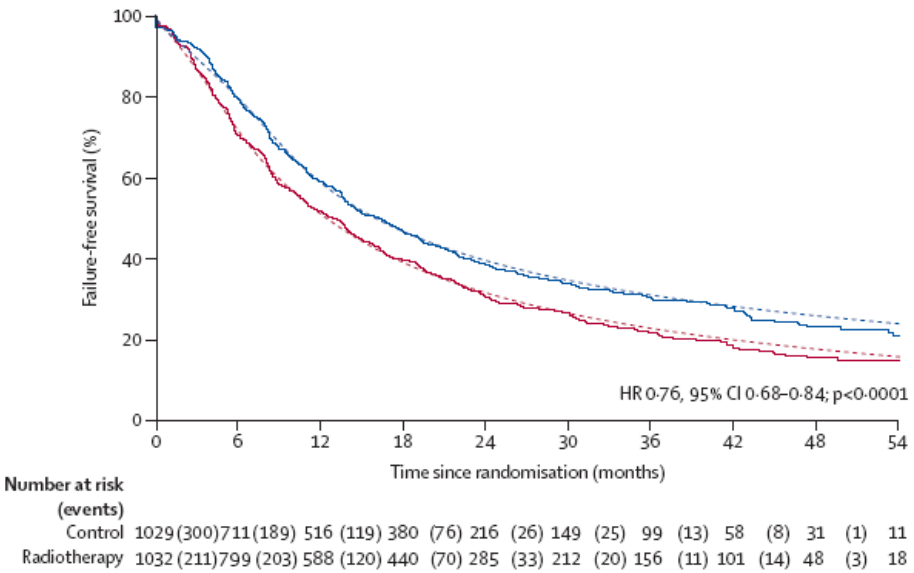
Overall Survival



Number at risk (events)

Control	1029	(17)	998	(56)	933	(82)	826	(63)	601	(39)	481	(67)	328	(37)	219	(16)	122	(9)	41
Radiotherapy	1032	(12)	998	(47)	936	(64)	832	(75)	611	(54)	478	(41)	365	(37)	236	(25)	128	(11)	47

Failure free Survival



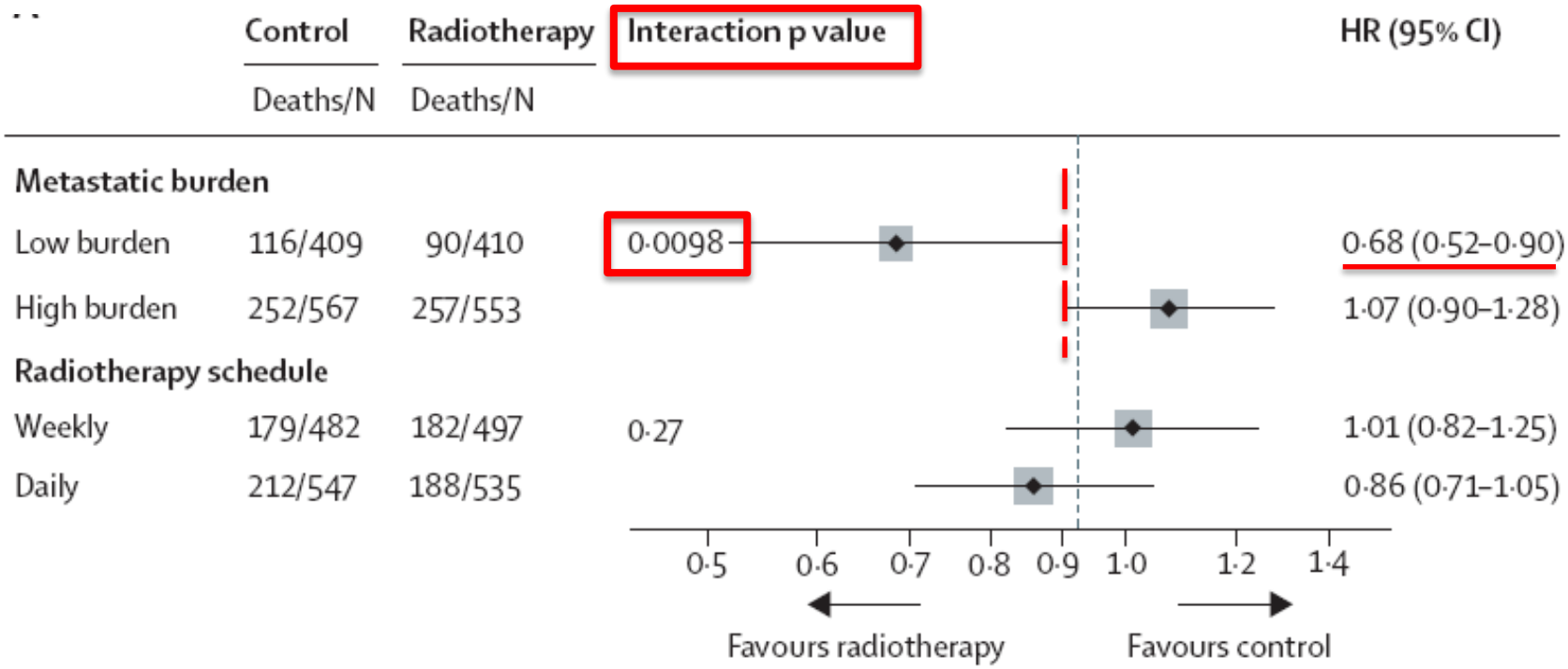
Number at risk (events)

Control	1029	(300)	711	(189)	516	(119)	380	(76)	216	(26)	149	(25)	99	(13)	58	(8)	31	(1)	11
Radiotherapy	1032	(211)	799	(203)	588	(120)	440	(70)	285	(33)	212	(20)	156	(11)	101	(14)	48	(3)	18

Parker et Al. Lancet Onc 2018

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

Overall Survival: subgroup analysis

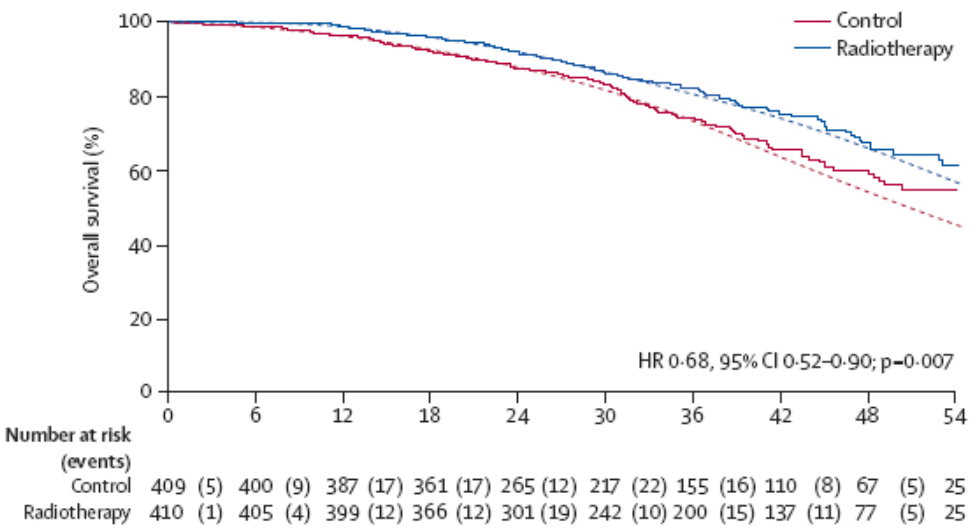


Parker et Al. Lancet Onc 2018

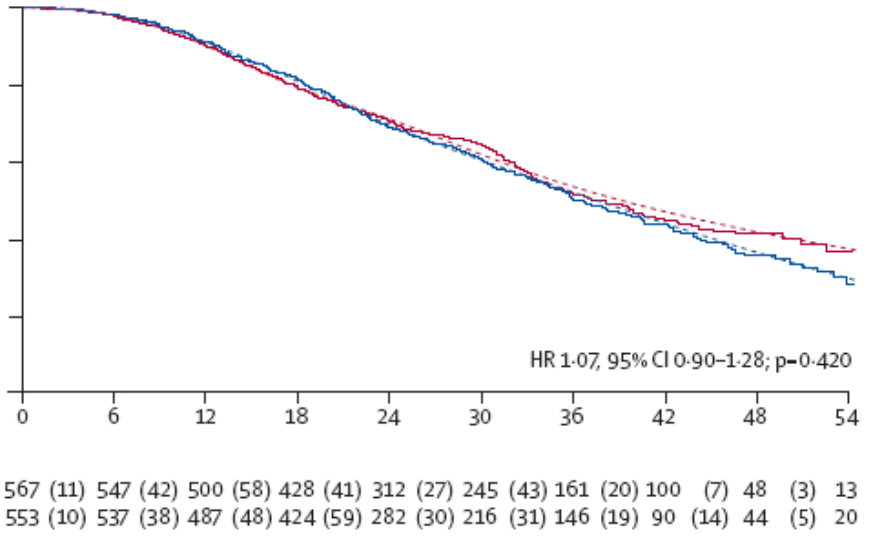
Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial

Overall Survival: subgroup analysis

Low metastatic burden



High metastatic burden



Parker et Al. Lancet Onc 2018

Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses

- Was the subgroup variable a baseline characteristic? ✓
- Was the subgroup variable a stratification factor? X explicitly; ✓
- Was the subgroup hypothesis specified a priori? ✓
- Was the analysis one of a small number of subgroups tested? ✓
- Was the test of interaction significant? ✓
- Was the significant interaction effect independent? ✓
- Was the direction of the subgroup effect correctly pre-specified? ✓
- Was the effect consistent with previous studies? ✓
- Was the effect consistent across related outcomes? ✓
- Indirect supportive evidence eg. biological rationale? ✓

Sun et Al. BMJ 2010

Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses

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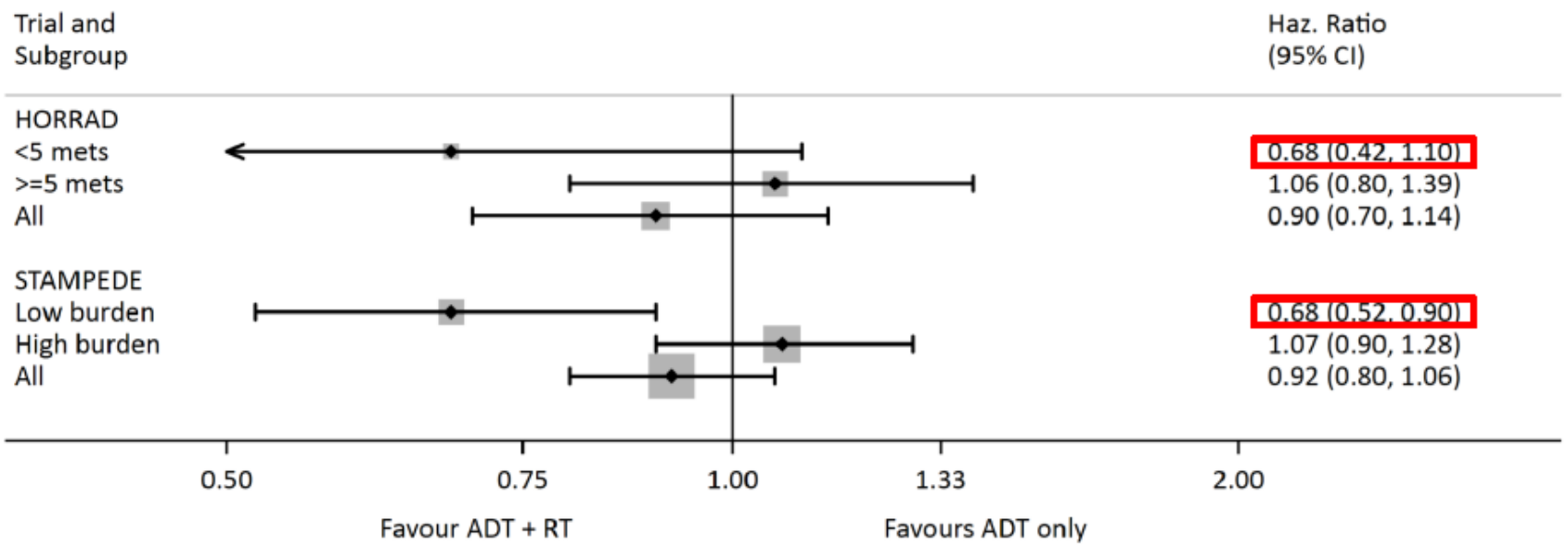
Sun et Al. BMJ 2010

The effect is consistent with HORRAD



MUNICH 2018 ESMO congress

Boeve et al. Eur Urol (2018)

MRC CTU at UCL

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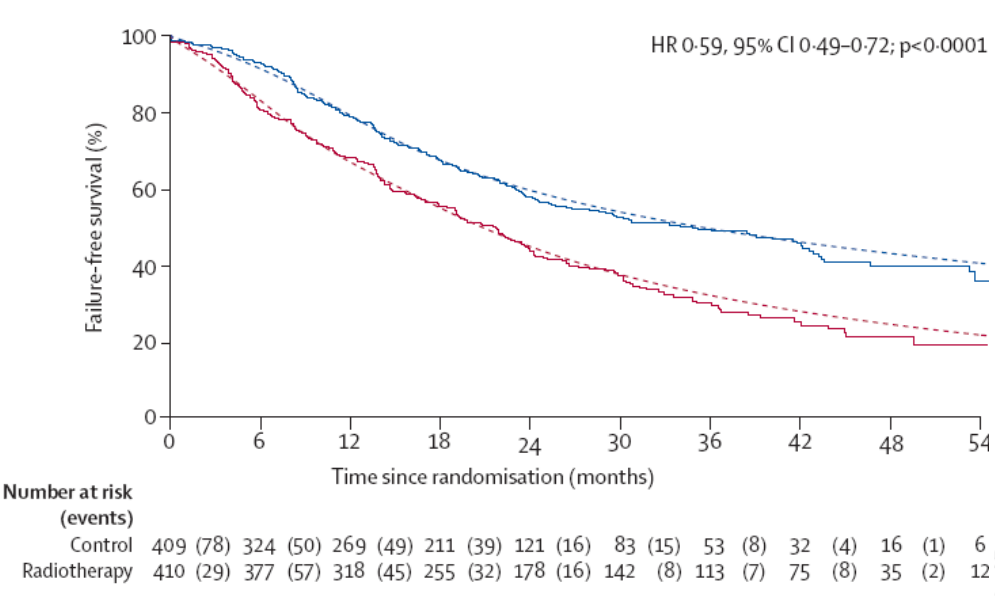
Sun et Al. BMJ 2010

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

Failure-free Survival: subgroup analysis

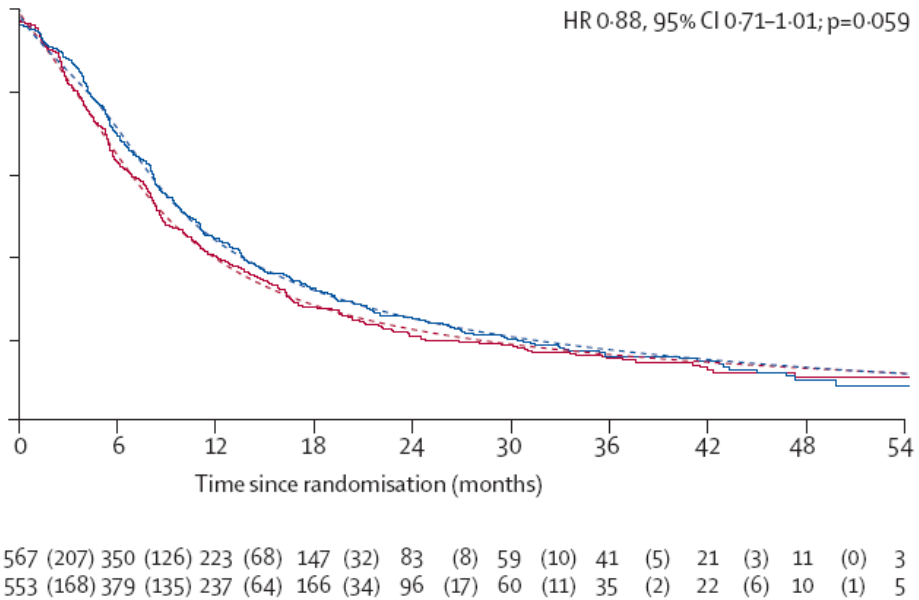
Low metastatic burden



Number at risk (events)

Control	409	(78)	324	(50)	269	(49)	211	(39)	121	(16)	83	(15)	53	(8)	32	(4)	16	(1)	6
Radiotherapy	410	(29)	377	(57)	318	(45)	255	(32)	178	(16)	142	(8)	113	(7)	75	(8)	35	(2)	12

High metastatic burden

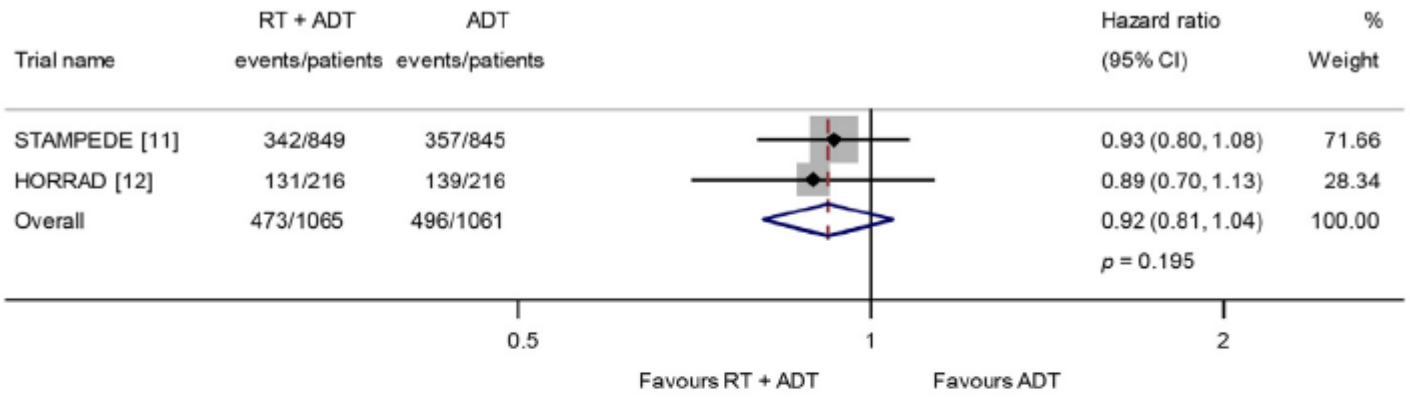


567	(207)	350	(126)	223	(68)	147	(32)	83	(8)	59	(10)	41	(5)	21	(3)	11	(0)	3
553	(168)	379	(135)	237	(64)	166	(34)	96	(17)	60	(11)	35	(2)	22	(6)	10	(1)	5

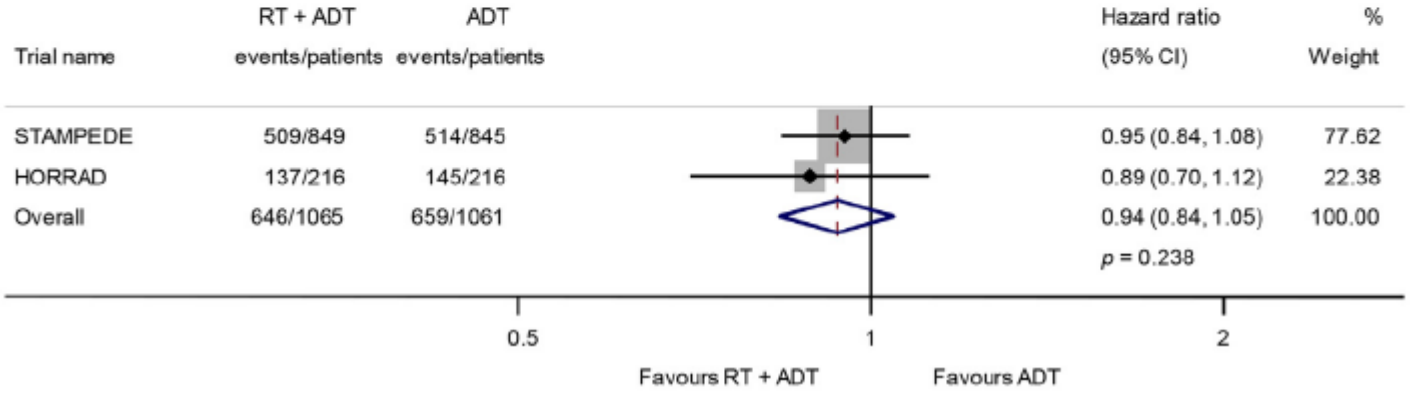
Parker et Al. Lancet Onc 2018

Prostate Radiotherapy for Metastatic Hormone-sensitive Prostate Cancer: A STOPCAP Systematic Review and Meta-analysis

Overall Survival



Progr.-free Survival



Burdett et Al. Eur Urol 2019

Prostate Radiotherapy for Metastatic Hormone-sensitive Prostate Cancer: A STOPCAP Systematic Review and Meta-analysis

Overall Survival by number of metastases (<5 vs ≥5)

Benefit is limited to Low Volume disease or patients with <5 metastases

Burdett et Al. Eur Urol 2019

70 years old

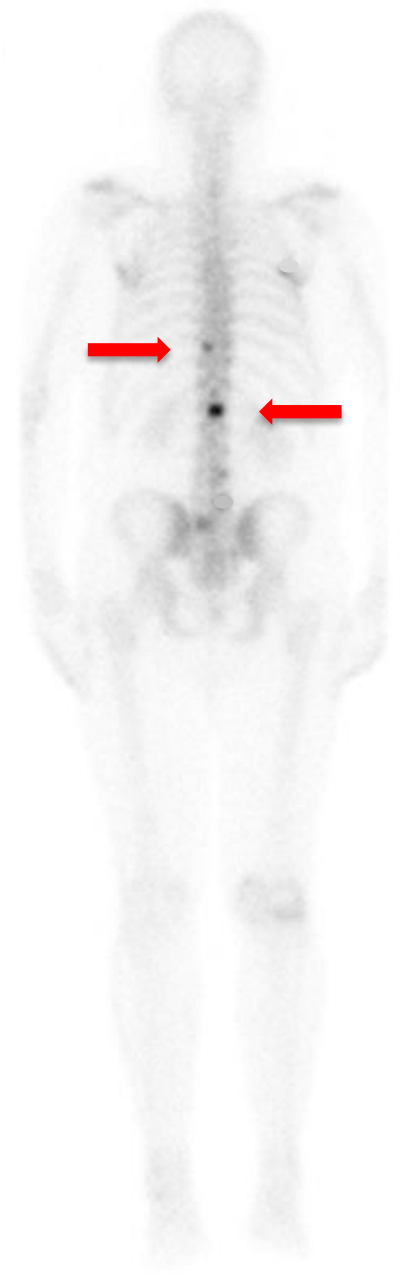
PSA 40 ng/ml
ALP 450 UI/L
Biopsy: PC - GS 7 (3+4)

First line treatment: Degarelix

De novo Oligometastatic

Low Volume (CHAARTED)

Low Risk (LATITUDE)



Recommendation	Level
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Offer castration combined with chemotherapy (docetaxel) to all patients whose first presentation is M1 disease and who are fit enough for chemotherapy.	Strong
Offer castration combined with abiraterone acetate + prednisone to all patients whose first presentation is M1 disease and who are fit enough for the regimen	Strong
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

EAU – ESTRO – ESUR – SIOG Guidelines on
Prostate Cancer

Treatment options for Low Volume mHSPC

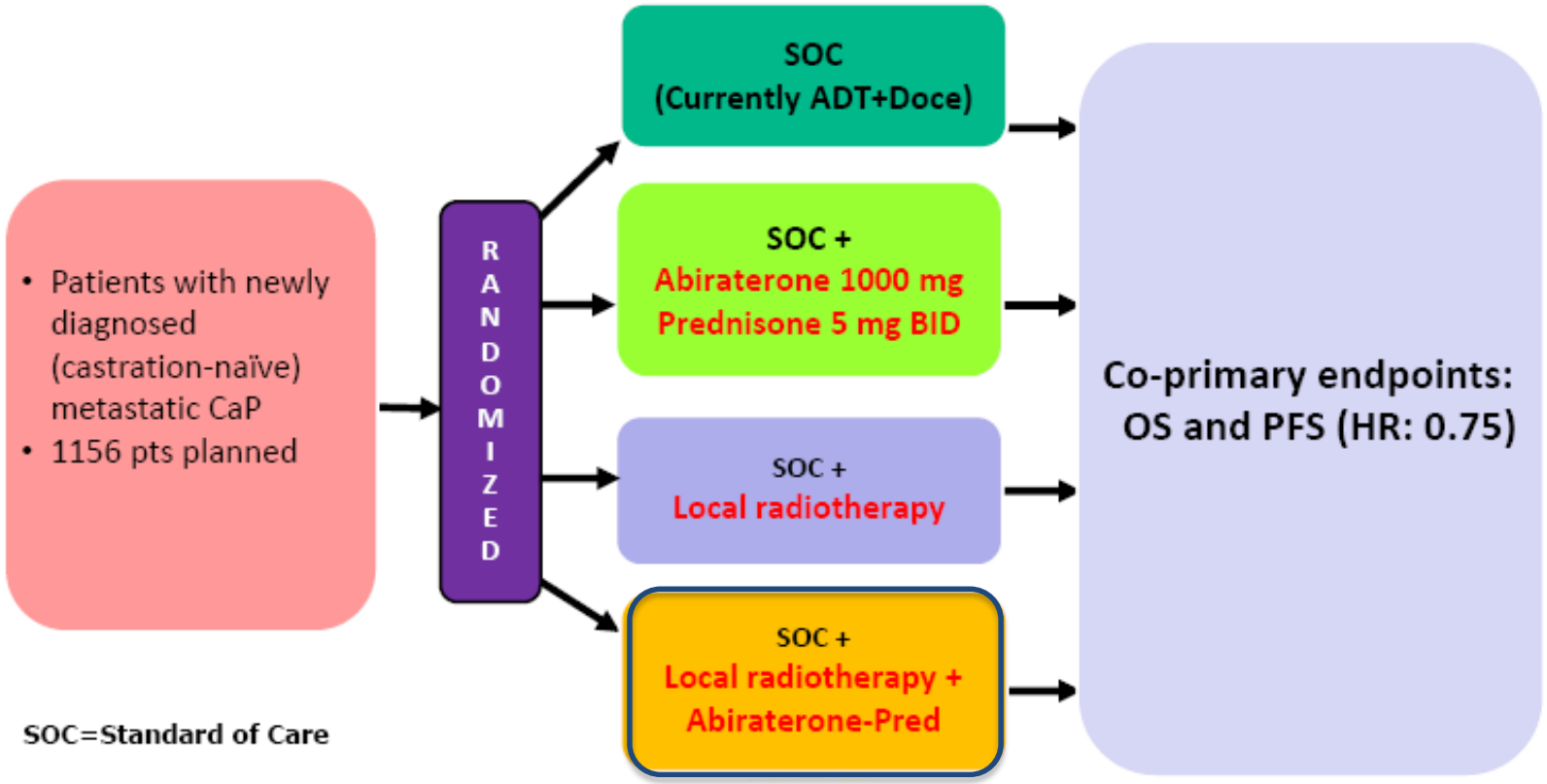
Agent	Study (rep. for Low Volume Subgroup)	HR OS, CI 95%	% Toxicity Grade≥3
Docetaxel	**CHAARTED** *Kyriakoupulos , JCO 2018*	1.02 (0.70-1.55)	42
Docetaxel	**GETUG-15** *Gravis, Eur Urol 2015*	1.02 (0.67-1.55)	
Docetaxel	**STAMPEDE** *Clarke, Ann Onc 2019*	0.76 (0.54-1.07)	52
Abiraterone	**STAMPEDE** *Hoyle, Ann Onc 2019*	0.63 (0.42-0.96)	47
Enzalutamide	**ARCHES** *Armstrong, JCO 2019*	NR	24
Enzalutamide	**ENZAMET** *Davis, NEJM 2019*	0.43 (0.26-0.72)	49
Apalutamide	**TITAN** *Chi, NEJM 2019*	0.67 (0.34-1.32)	42
Radiotherapy	**STAMPEDE** *Parker, Lancet Onc 2018*	0.68 (0.52-0.90)	5

Other considerations:

- **Treatment duration**
- **Costs**

Open Issue:
any benefit combining RT and AARTA?

PEACE-1: European Phase III Trial in de novo Metastatic Prostate Cancer (revised design)



ClinicalTrials.gov. Identifier: NCT01957436.

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- **Surgery**

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Retrospetive data for Radical Prostatectomy in metastatic Prostate Cancer

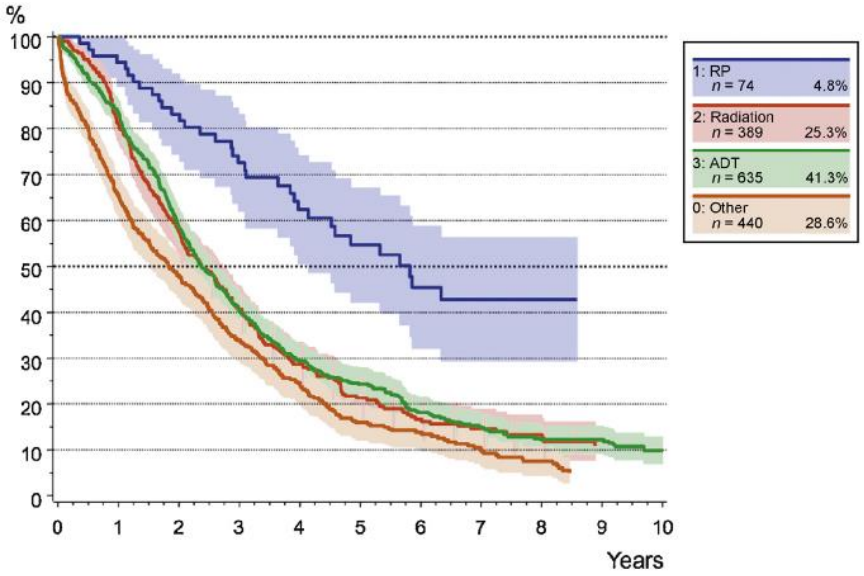
Author	Data Source	Patients	Intervention	Outcome
Bannurah 2017	SEER 2004-2013	13.692	RP vs RT	Cancer specific Mortality HR 0.59
Pompe 2018	SEER 2004-2014	13.906	RP vs No-LT	Cancer specific Mortality HR 0.55
Culp 2014	SEER 2004-2010	8185	LT vs No-LT	5yOS 67% vs 22.5% p<0.001
Satkunasivam 2015	SEER 2004-2009	4.069	LT vs No-LT	Cancer specific Mortality HR 0.48
Gratzke 2014	Munich Canc. Registry 1998-2010	1538	RP vs No-RP	5yOS 55% vs 21% p<0.01
Jang 2018	Single Center 2005-2015	91	RP-Robot vs No-LT	Cancer specific Survival NR vs 40 mo p=0.002

RP: Radical Prostatectomy **- LT:** Local Therapy

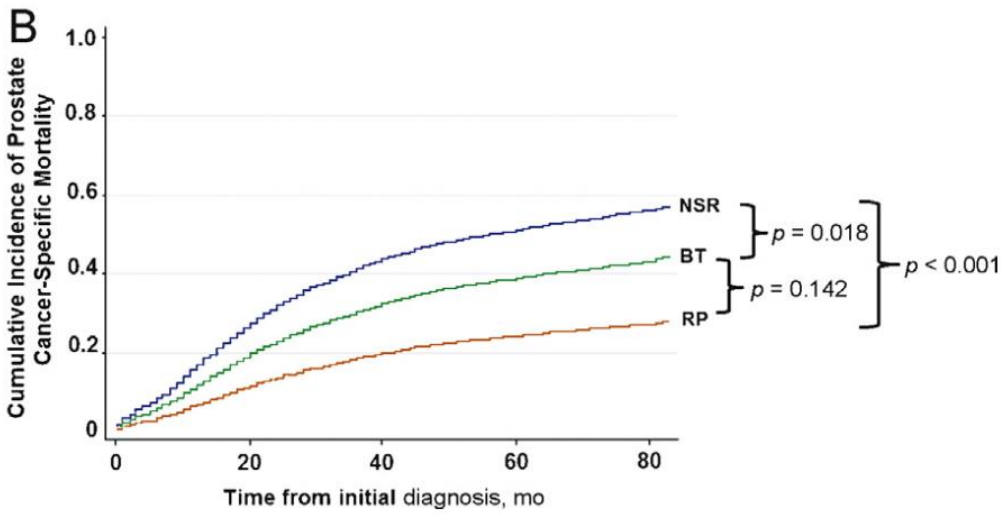
Role of Radical Prostatectomy in Metastatic Prostate Cancer: Data from the Munich Cancer Registry

Might Men Diagnosed with Metastatic Prostate Cancer Benefit from Definitive Treatment of the Primary Tumor? A SEER-Based Study

Overall Survival



Prostate Cancer Specific Mortality

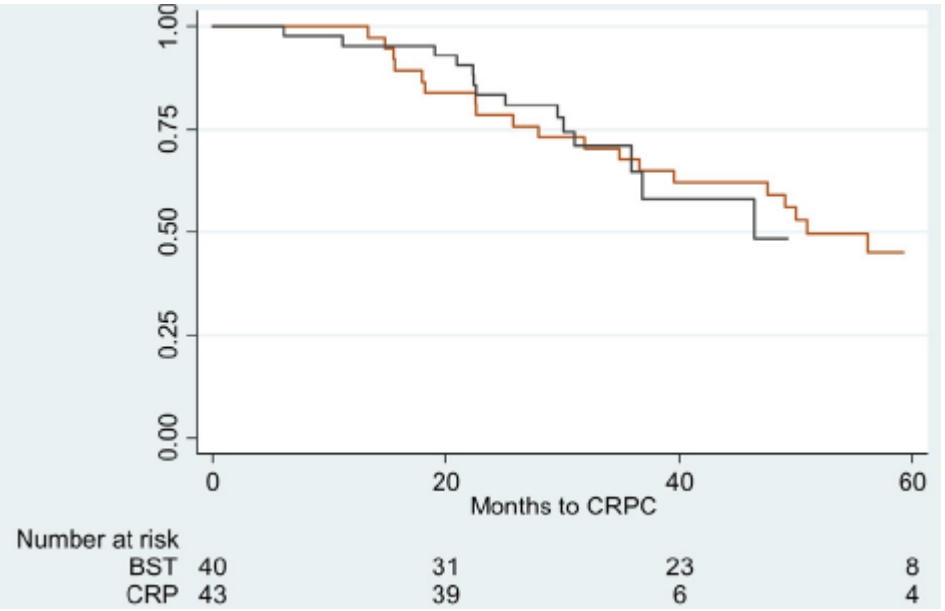


Gratzke et Al. Eur Urol 2014

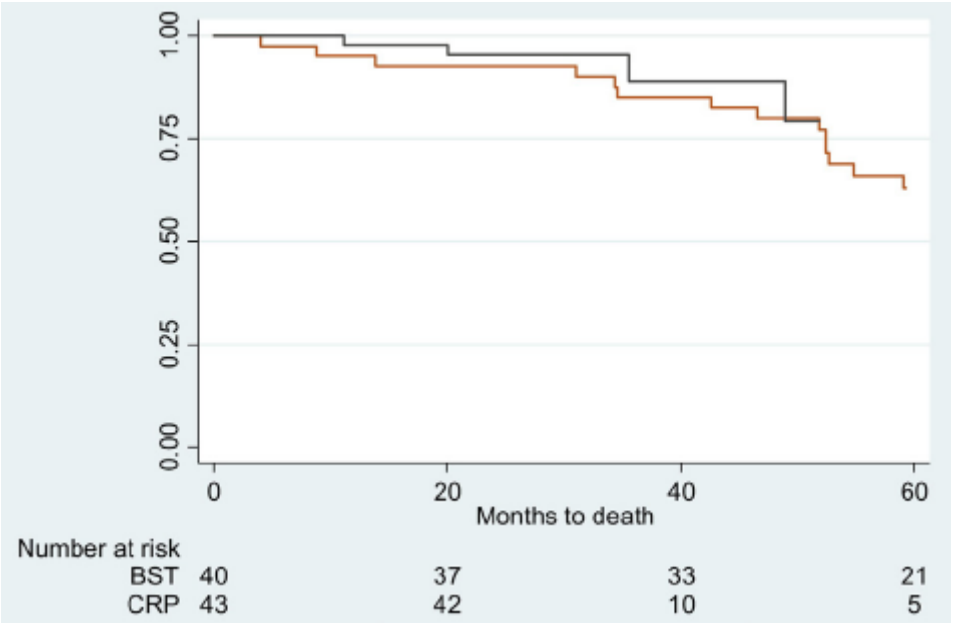
Culp et Al. Eur Urol 2014

Does Cytoreductive Prostatectomy Really Have an Impact on Prognosis in Prostate Cancer Patients with Low-volume Bone Metastasis? Results from a Prospective Case-Control Study

Castration resistance-free Interval



Overall Survival



BST CRP

83 low-volume mHSPC (1-3 lesions)

Parker et Al. Lancet Onc 2018

Ongoing randomised trials surgery for primary tumor in mHSPC

ISRCTN15704862 (TRoMbone)

mHSPC (n.50)

Primary endpoint

- Time to CRPC
- Quality of Life

R

ADT

ADT+RP
with extended lymphadenectomy

NCT02454543 (SIMCAP)

mHSPC (n.190)

Primary endpoint

- Failure-free Survival

R

ADT +/- Doce

ADT + RP +/- Doce

NCT02454543 (g-RAMMP)

mHSPC (n.452)

Primary endpoint

- Cancer Specific Survival

R

BST

BST + RP
with extended lymphadenectomy

Local treatment to the primary tumor (Rt or Surg)

Basing on 2 RCT and 1 meta-analysis RT should not be recommended for the ITT population….but it can be considered for patients with *low volume M1 disease* *(OS sig. improved)*

Surgery is not yet validated and should be considered experimental

Metastasis-directed therapy in oligometastatic disease

Local treatment to the primary tumor (Rt or Surg)

Rationale

Evidences

- **Radiotherapy**
- **Surgery**

Metastasis-directed therapy in oligometastatic disease

Definition of the *'oligo-state'*

Evidences

- **Castration naive**
- **Castration resistant**
  - ✓**Oligoprogression on ADT**
  - ✓**Oligoprogression on ARTA**

70 years old

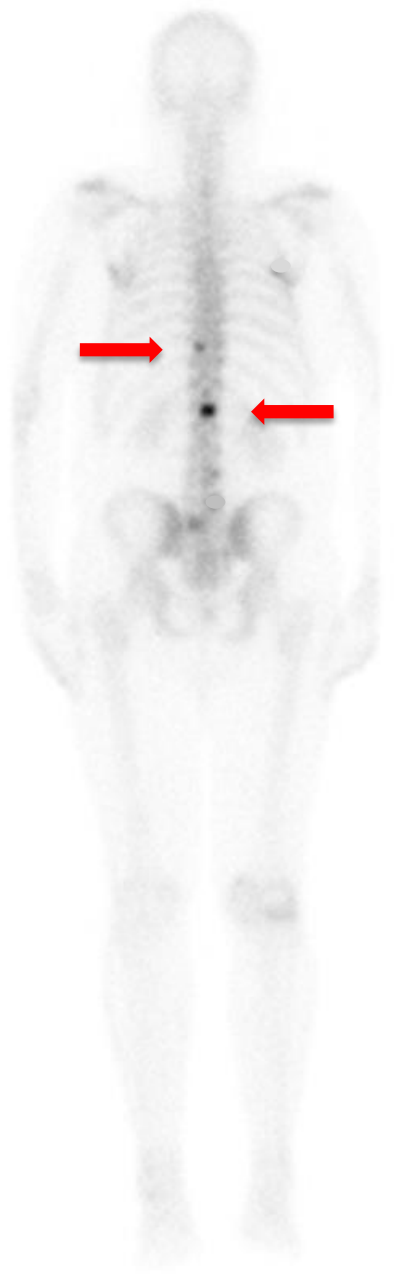
PSA 40 ng/ml
ALP 450 UI/L
Biopsy: PC - GS 7 (3+4)

First line treatment: LH-RHa

De novo Oligometastatic

Low Volume (CHAARTED)

Low Risk (LATITUDE)



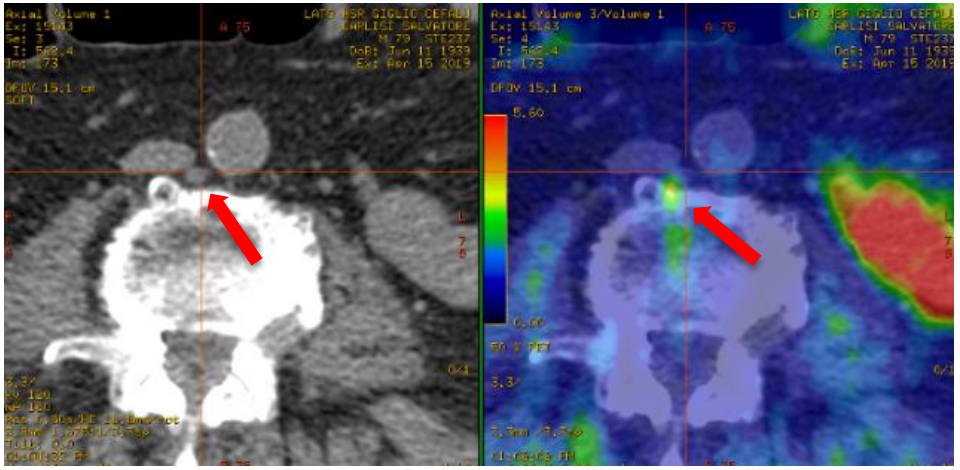
Any other option?

1. Nothing
2. Abiraterone/Prednisone
3. Apalutamide
4. Enzalutamide
5. Docetaxel
6. Local treatment to the primary (RT or Surg)
7. Metastasis directed treatment

75 years old

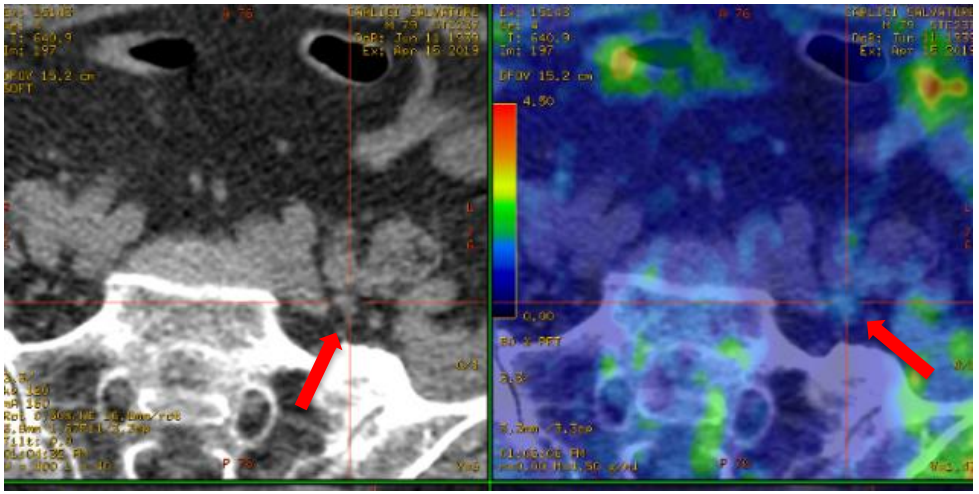
Oligoprogression on ADT

2014 - PSA 8 ng/ml
Radical prostatectomy for Adenocarcinoma GS 7 (3+4) pT3b pN0 M0.
Adjuvant Radiotherapy



2017 - PSA 1,5 ng/ml
Abd. MRI and C-PET Neg.
LH-RHa

2019 – PSA 3,9 ng/ml (Doubl. T.8 mo)
C-PET: 2 lymph nodes mets
Metastasis-directed Radiotherapy (37.5 Gy)

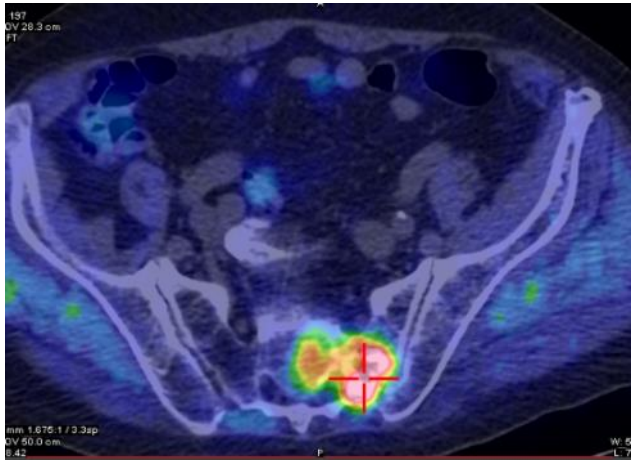


PSA – PFS 9 months

78 years old

Oligoprogression on ARTA

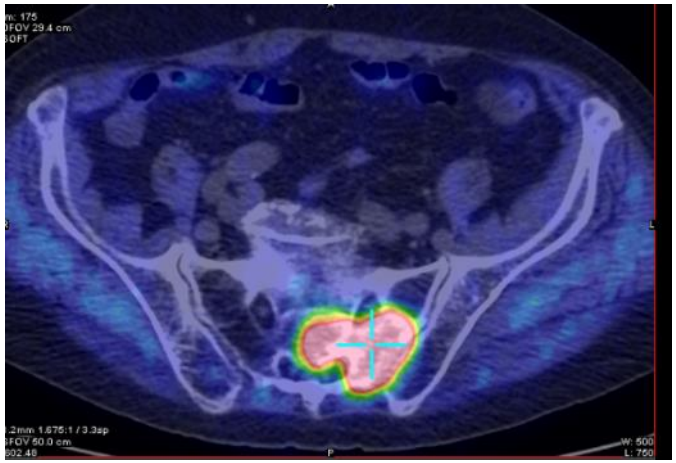
2015 - PSA 98 ng/ml
Biopsy: Adenocarcinoma GS 7 (3+4)
CT and Bone scan: lymph nodes and Bone metastases
LH-RHa



2017 – PSA 42 ng/ml
C-PET: bone progression
Enzalutamide (PSA nadir 5 ng/ml)

2019 – PSA 22 ng/ml
C-PET: single site of bone progression

Metastasis-directed Radiotherapy (30 Gy)



PSA – PFS 8 months (PSA 3 ng/ml)

Local treatment to the primary tumor (Rt or Surg)

Rationale

Evidences

- **Radiotherapy**
- **Surgery**

Metastasis-directed therapy in oligometastatic disease

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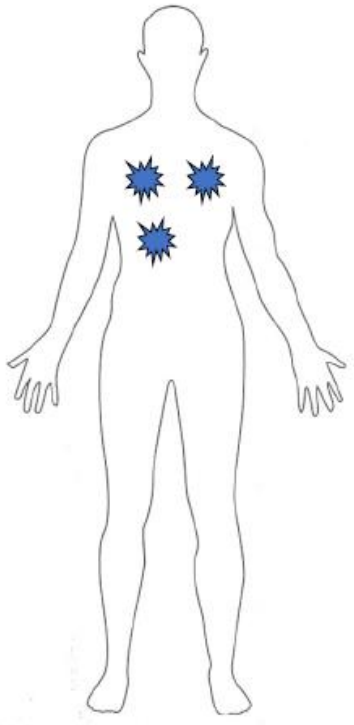
Oligometastatic Concept

'Disease stage with a limited number of clinically detectable metastases'

Implicit in this concept:

- unique biologic characteristics
- potentially less aggressive disease course



'…subgroup of patients with an intermediate phase of metastatic disease, that presents a potential for disease control with the ablation of the few metastases'

Hellmann and Weichselbaum, J Clin Onc 1995

Oligometastatic prostate cancer

No clear definition

'…limited number of of bone and/or lymph nodes metastases'

(61% consensus)

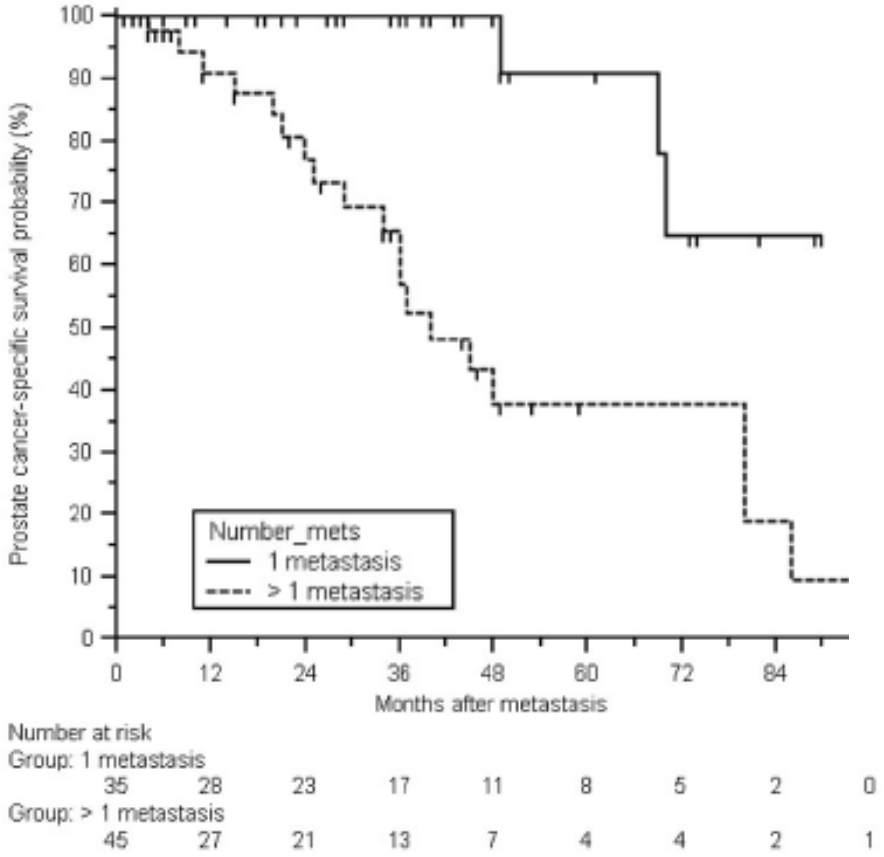
No formal cut-off for the number of metastases to define the 'Oligo-state'

- ***≤2 metastases*** ***(14% consensus)***
- ***≤3 metastases*** ***(66% consensus)***
- ***≤5 metastases*** ***(20% consensus)***

Gillessen et Al. Eur Urol 2018

Prognostic Factors Influencing Prostate Cancer-Specific Survival in Non-Castrate Patients with Metastatic Prostate Cancer

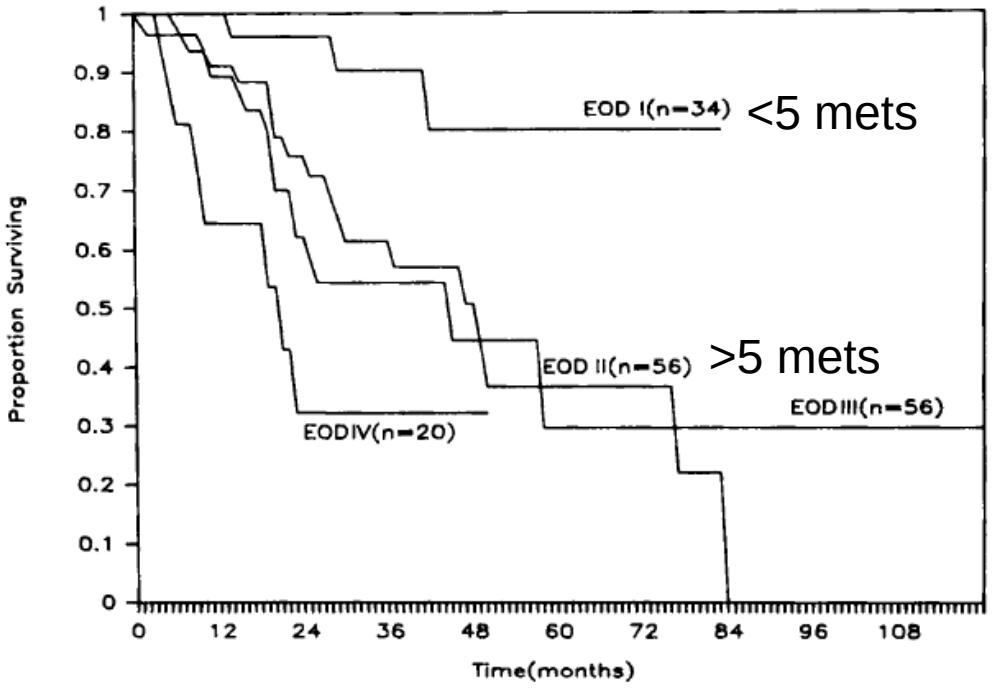
Survival by number of metastases



Gundem, Prostate 2014

Stratification of Patients With Metastatic Prostate Cancer Based on Extent of Disease on Initial Bone Scan

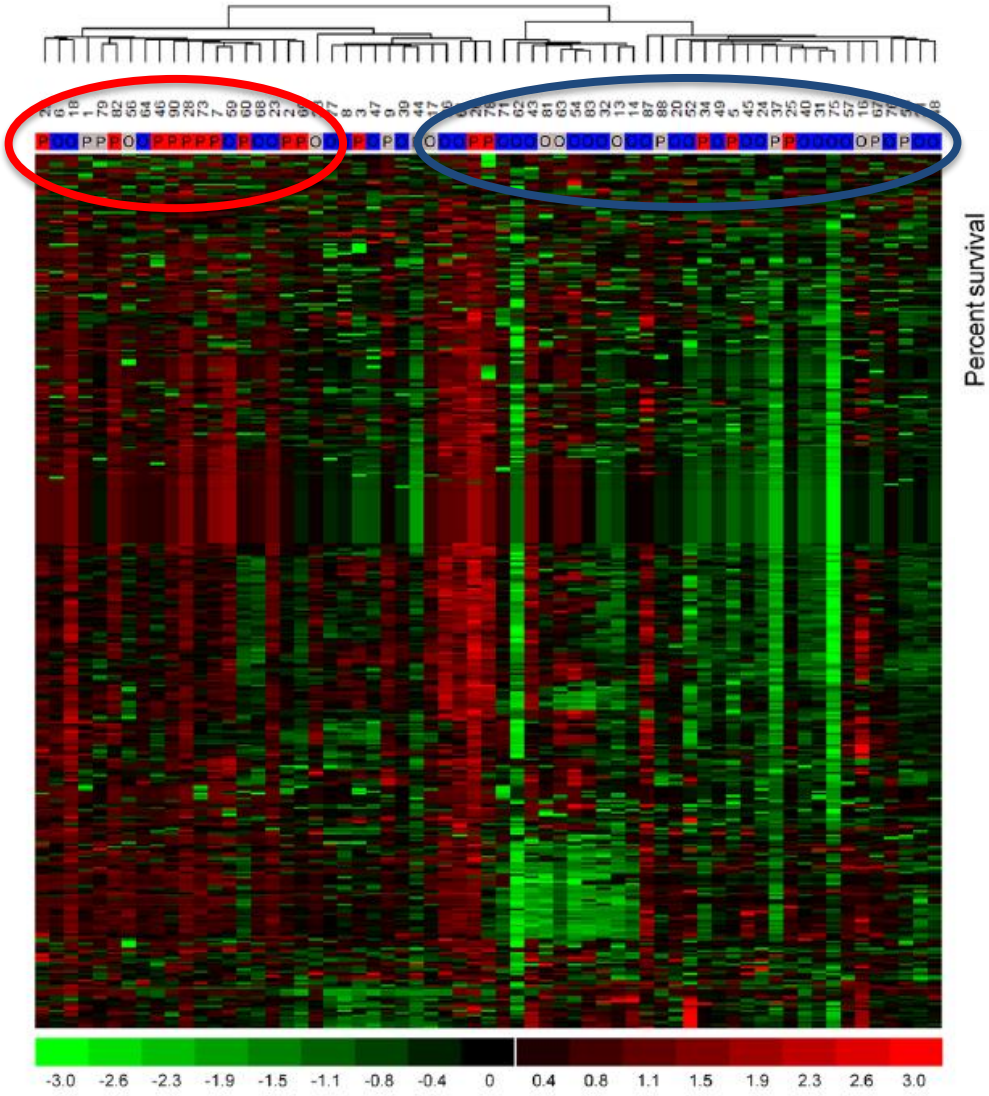
Survival by extent of disease



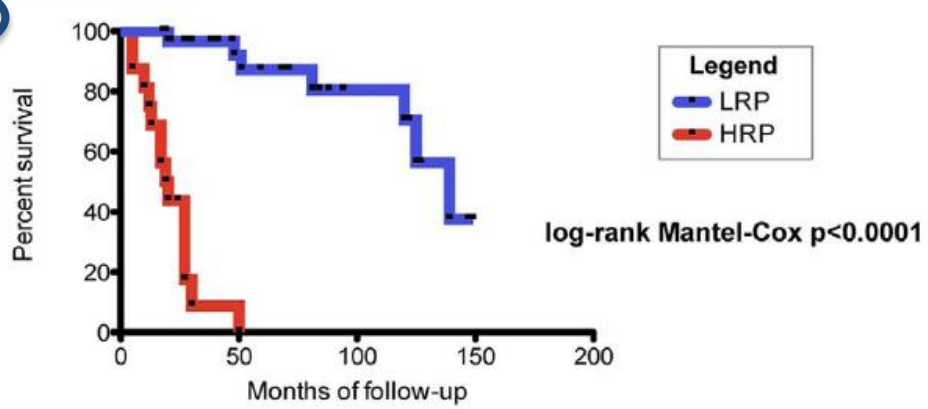
Soloway, Cancer 1988

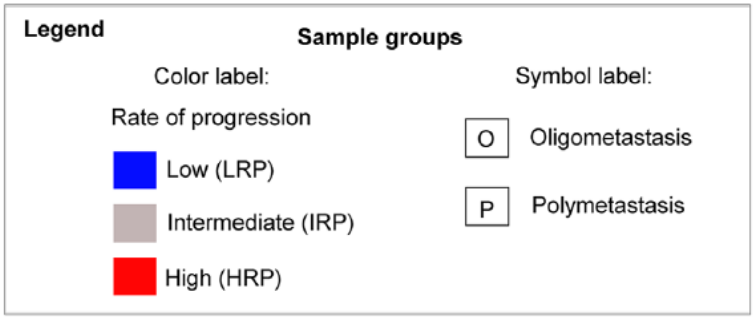
Oligo- and Polymetastatic Progression in Lung Metastasis(es) Patients Is Associated with Specific MicroRNAs

MicroRNAs distribution



Survival by progression rate

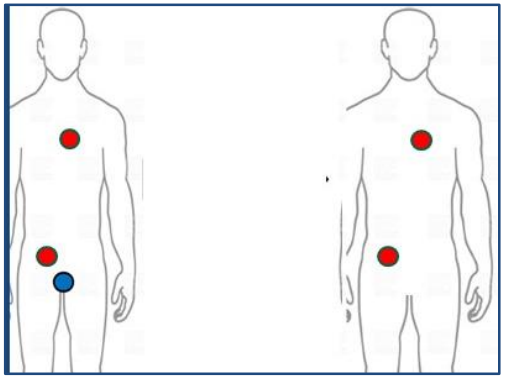




Lussier et Al PLOSone 2012

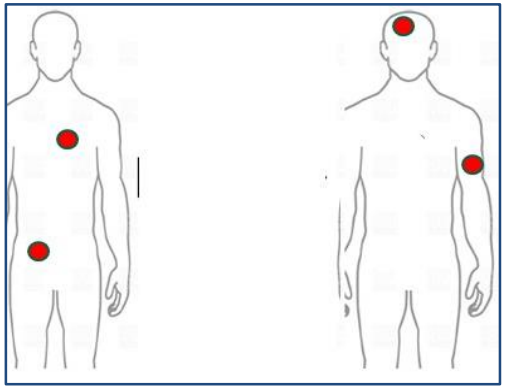
Oligometastatic prostate cancer considerations for consensus definition

Timing



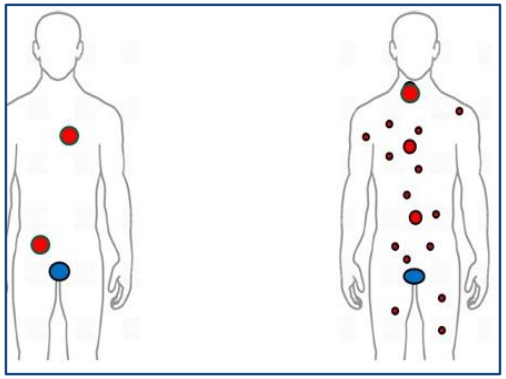
Syncronous vs Metachronous

Location



Bony vs Visceral

Imaging



Conventional vs Advanced

Castration State

Naive
vs
Resistant

Syncronous Oligometastatic Castration-naive

Metachronous Oligometastatic Castration-naive

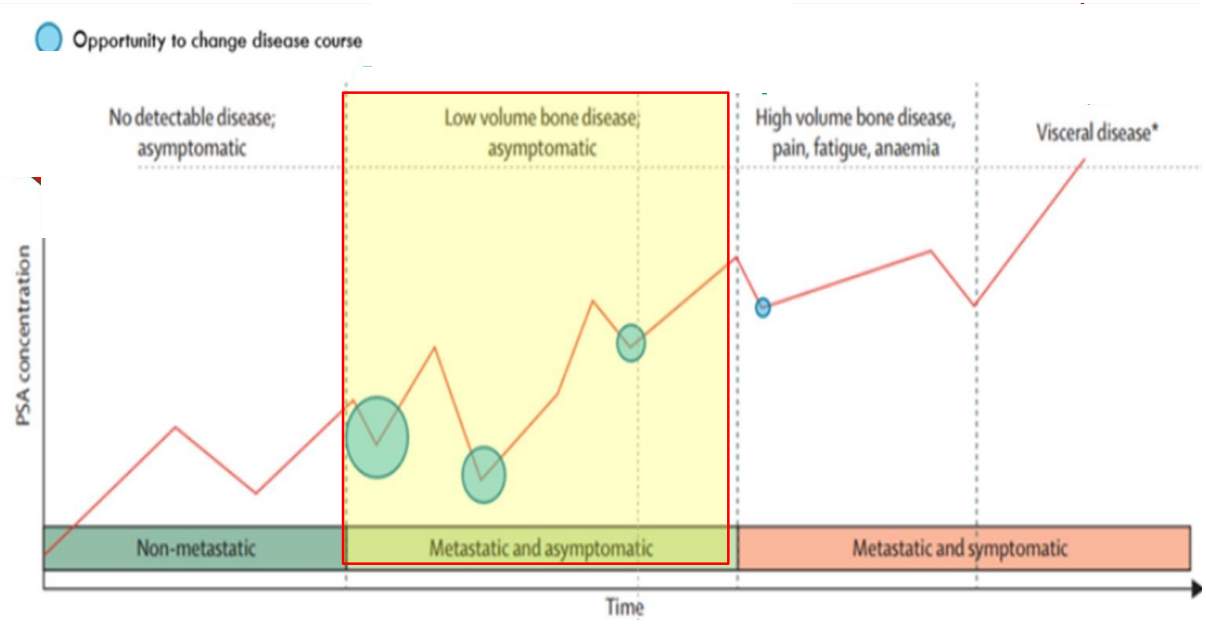
Oligometastatic rising PSA on ADT (mCRPC)

APCCC 2017

Gillessen, Eur Urol 2018

Goals of metastasis-directed therapies in oligometastatic prostate cancer

Dont’t miss the window of opportunity



Treatment goals

- **Progression-free survival**
- **Avoid/delay systemic treatment**
- **Quality of life**
- **Overall Survival**

Adapted from Kamperis et Al, J Canc Prevent 2017

Local treatment to the primary tumor (Rt or Surg)

Rationale

Evidences

- **Radiotherapy**
- **Surgery**

Metastasis-directed therapy in oligometastatic disease

Definition of the *'oligo-state'*

Evidences

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- **Castration resistant**
  - ✓**Oligoprogression on ADT**
  - ✓**Oligoprogression on ARTA**

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

Single-arm case series

Study	No. of patients	Site of metastasis: node/bone/visceral	Median time to metastatic recurrence, mo	Median PSA at time of metastasis	Staging method	Type of MDT	Median follow-up, mo	Median PFS	Adjuvant ADT (%)	Median duration ADT	Prophylactic nodal radiotherapy (%)
Casamassima et al. [23]	25	25/0/0	11.8–36.7	5.65	Choline PET/CT	SBRT	29	24 mo	None	NA	7 (28)
Muacevic et al. [24]	40	0/40/0	NR	5.4	Choline PET/CT	SBRT	14*	NR	27 (68)	NR	NA
Würschmidt et al. [25]	15	15/0/0	NR	1.79	Choline PET/CT	NRT	28	Median not reached: 3-yr PFS: 75%	NR	NR	15 (100)
Ahmed et al. [26]	17	1/15/1	50.4	2.1	Choline PET/CT (n = 9), MRI (n = 6), CT (n = 1), and biopsy (n = 1)	SBRT	6	12 mo	15 (88)	NR	NA
Jereczek-Fossa et al. [27]	19	18/1/0	66	1.77 (pelvic nodes); 10.7 (M1)	Choline PET/CT	SBRT	17	Median not reached; 30-mo PFS: 63.5%	19 (100)	12–17 mo	None
Schick et al. [28]	50	33/15/2	15.6	6.7	Choline PET/CT and bone scintigraphy	SBRT (n = 14) NRT (n = 36)	31	Medi			25 (50)
Decaestecker et al. [29]	50	27/22/1	57.6	3.8	Choline (n = 18) or FDG (n = 32) PET/CT	SBRT	25				None
Picchio et al. [30]	83	83/0/0	NR	2.6	Choline PET/CT	HRT	22				77 (93)
Rinnab et al. [31]	15	15/0/0	NR	1.98	Choline PET/CT	LND	13.7*		11 (73)	NR	1 (7)
Schilling et al. [32]	10	10/0/0	NR	8.75	Choline PET/CT	LND	11*	NR	6 (60)	NR	None
Winter et al. [33]	6	6/0/0	NR	2.04	Choline PET/CT	LND	24 mo	NR	None	NA	None
Busch et al. [37]	6	6/0/0	Mean: 79.9	37.6*	Choline (n = 3), MRI (n = 1), CT (n = 2)	LND	NR	15.5 mo	6 (100)	Lifelong ADT	None
Jilg et al. [34]	47	47/0/0	62	11.1*	Choline PET/CT	LND	35.5	27 mo**	34 (65)	NR	27 (52)
Martini et al. [35]	8	8/0/0	NR	1.62	Choline PET/CT	LND	NR	NR	None	NA	None
Suardi et al. [36]	59	59/0/0	NR	2.0	Choline PET/CT	LND	76.6	60 mo**	24 (41)	24 mo	21 (36)

ADT = androgen-deprivation therapy; CT = computed tomography; FDG = fluorodeoxyglucose; HRT = hypofractionated radiotherapy; LND = lymph node dissection; MDT = metastasis-directed therapy; MRI = magnetic resonance imaging; NA = not applicable; NR = not reported; NRT = normofractionated radiotherapy; PET/CT = positron emission tomography with coregistered computed tomography; PFS = progression-free survival; PSA = prostate-specific antigen; SBRT = stereotactic body radiotherapy.

* Mean numbers reported instead of median.

** Median estimated from curves.

1-3 years PFS 51%

Ost et Al. Eu Urol 2015

Toxicities associated to radiotherapy

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)

Toxicities associated to surgery

Complication type	Rinnab et al. [31] (n = 15), no. (%)	Busch et al. [37] (n = 6), no. (%)	Jilg et al. [34] (n = 47), no. (%)	Suardi et al. [36] (n = 59), no. (%)	Total (n = 127), no. (%)
Grade 1					
Lymphorrhea	0 (0)	0 (0)	4 (7.7)	12 (20.3)	16 (12.5)
Fever	0 (0)	0 (0)	3 (5.8)	18 (30.5)	21 (16.5)
Temporary weakness of the hip flexor	0 (0)	0 (0)	1 (1.9)	0 (0)	1 (0.8)
Wound dehiscence	0 (0)	0 (0)	3 (5.8)	0 (0)	3 (2.3)
Grade 2					
Deep vein thrombosis	0 (0)	0 (0)	0 (0)	1 (1.7)	1 (0.8)
Ileus	1 (7)	0 (0)	0 (0)	12 (20.3)	13 (10.2)
Grade 3a					
Lymphocele requiring drainage	1 (7)	0 (0)	2 (3.9)	7 (11.2)	10 (7.8)
Wound dehiscence	0 (0)	0 (0)	0 (0)	3 (5.1)	3 (2.3)
Hydronephrosis requiring stenting	1 (7)	0 (0)	0 (0)	0 (0)	1 (0.8)
Grade 3b					
Lymphocele requiring surgical drainage	0 (0)	0 (0)	0 (0)	1 (1.7)	1 (0.8)

Ost et Al. Eu Urol 2015

Local treatment to the primary tumor (Rt or Surg)

Rationale

Evidences

- Radiotherapy
- Surgery

Metastasis-directed therapy in oligometastatic disease

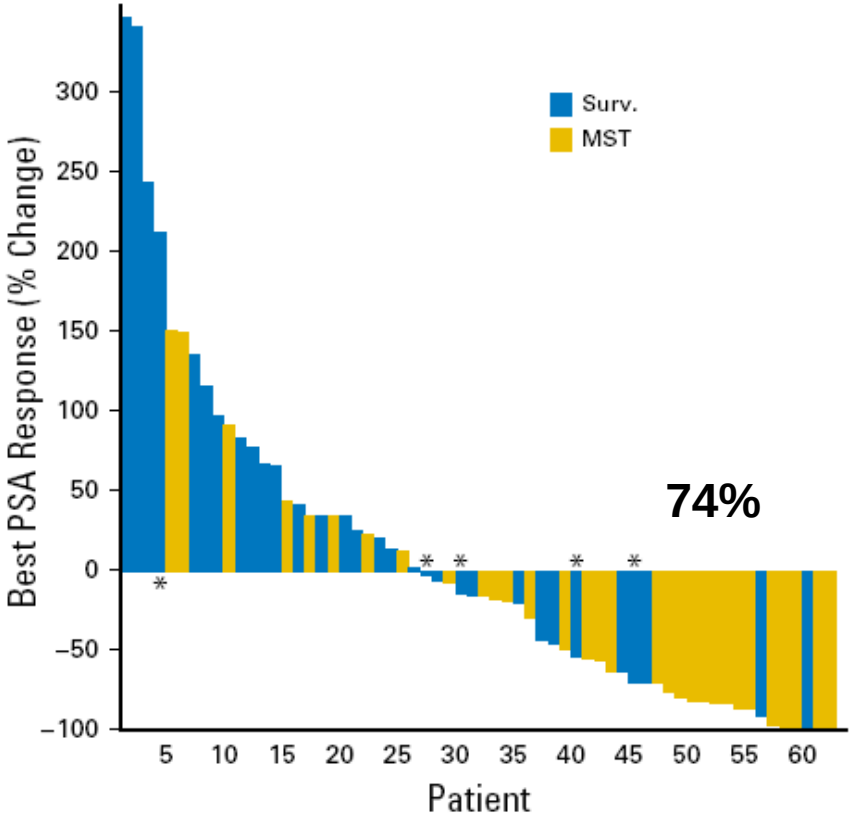
Definition of the *'oligo-state'*

Evidences

- **Castration naive**
- Castration resistant
  - ✓Oligoprogression on ADT
  - ✓Oligoprogression on ARTA

Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial

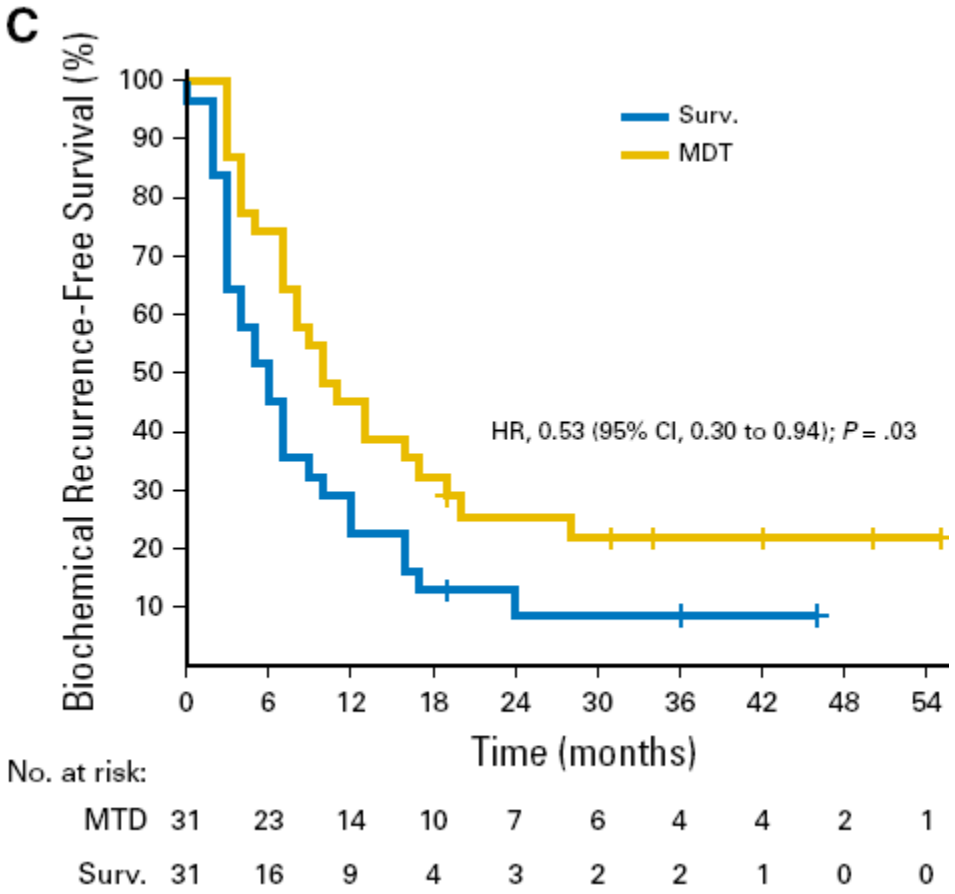
Best PSA Response



62 Oligorecurrent pts

- Biochemical progression
- Testosterone > 50 ng/ml
- ≤3 metastatic lesions

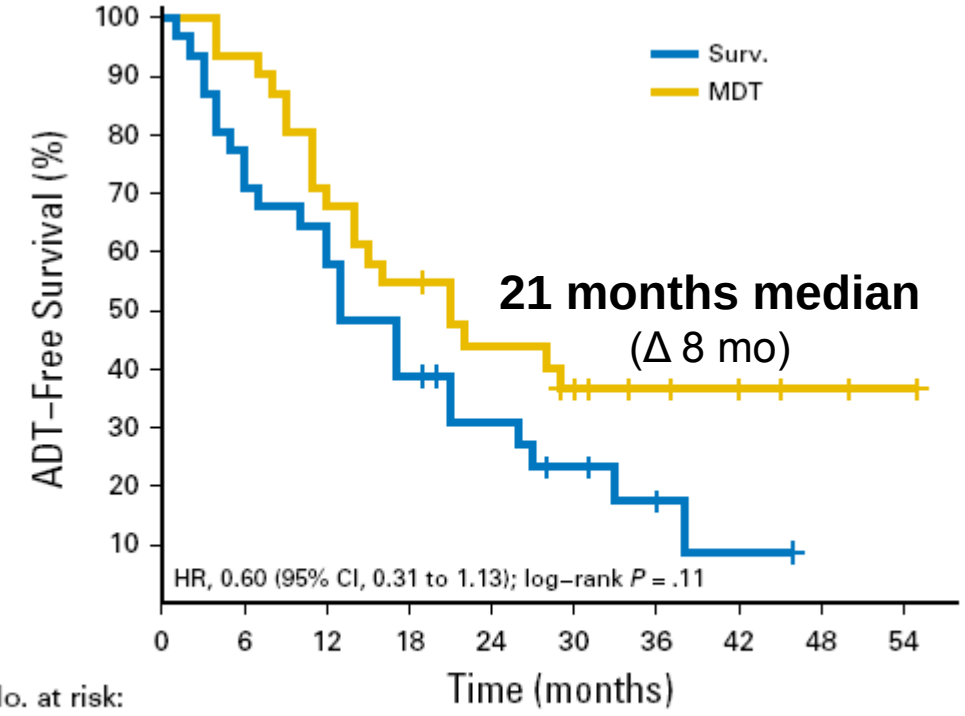
PSA Recurrence-Free Survival



Ost et Al. J Clin Onc 2017

Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial

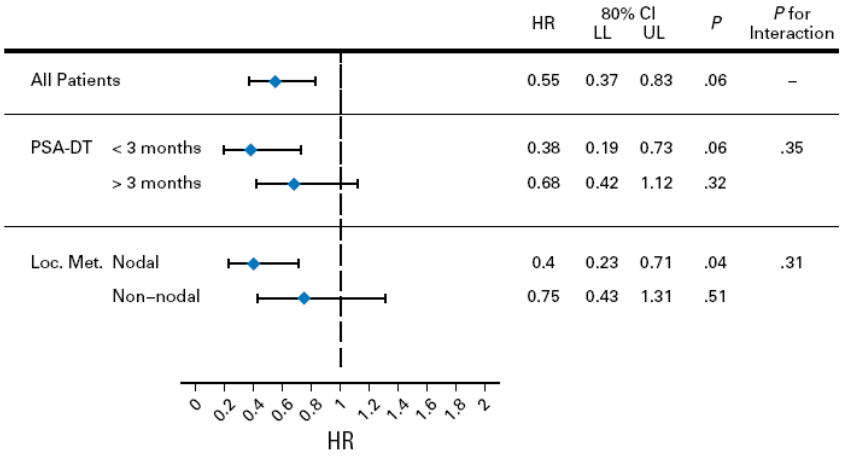
ADT-Free Survival



No. at risk:

MTD	31	29	22	17	12	9	6	5	2	1
Surv.	31	24	20	12	8	5	3	1	0	0

Subgroup Analysis



Ost et Al. J Clin Onc 2017

Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial

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.

Should we combine ADT to MDT for castration-sensitive oligometastatic disease?

……how long?

Is ADT-free survival a relevant end point for MDT-radomised trials?

Ost et Al. J Clin Onc 2017

Local treatment to the primary tumor (Rt or Surg)

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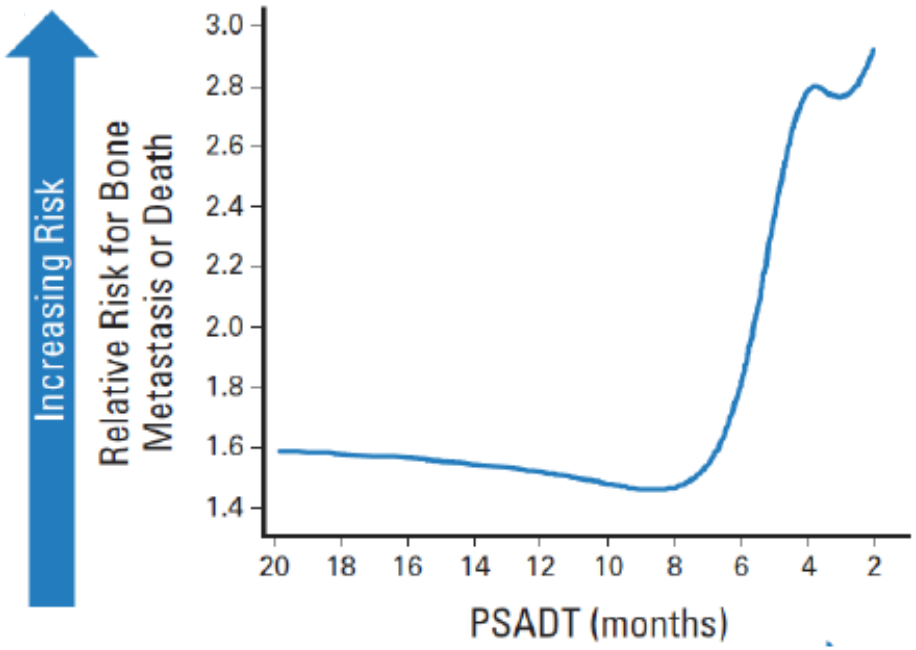
Treatment options for minimally- asymptomatic mCRPC

Randomised phase III trials

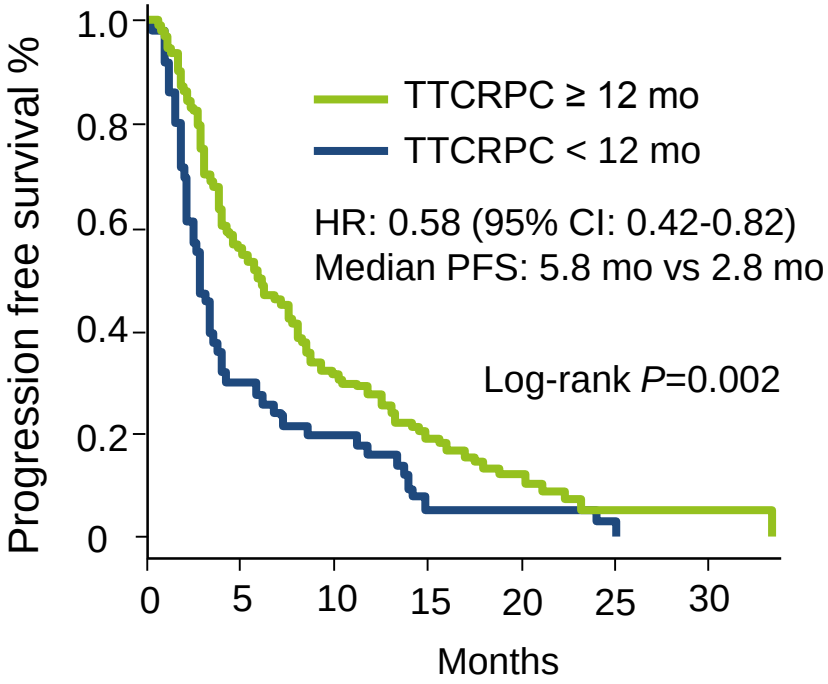
Study	n.pts.	Comparison	Overall Survival HR, CI 95%
TAX 327 *Berthold, JCO 2008*	*1006*	**Docetaxel +P** vs Mitoxantrone+P	0.76 (0.62-0.94)
COUAA 202 *Ryan, NEJM 2012*	*1088*	**Abitaterone + P** vs Placebo	0.75 (0.61-0.93)
PREVAIL *Armstrong, NEJM 2014*	*1077*	**Enzalutamide** VS Placebo	0.71 (0.60-0.84)

Eterogeneity of mCRPC

PSA Doubling Time and risk or progression or death



Progression-free Survival by time to CRPC



PFS: progression-free survival;
TTCRPC: time to castration resistant prostate cancer

Smith at Al. J Clin Onc 2013

Loriot et al. Eur J Cancer. 2015

Metastasis-directed therpy for oligoprogressive mCRPC

Retrospective series

Rference	n.pts.	Treatment	% 2-years Distant PFS	Median systemic therapy–free surv
Muldermans, *2016*	*50*	**SBRT** (BED 30-50 Gy)	45	NR
Triggiani, *2019*	*86*	**SBRT** (BED 80 Gy)	33.7	21.8 months

	% Grading	
Toxicity	**G1**	**G2**
Pain flare	9	3
Gastrointestinal	3	-
Genitourinary	1	3

Consensus statements on ablative radiotherapy for oligometastatic prostate cancer: A position paper of Italian Association of Radiotherapy and Clinical Oncology (AIRO)

In an asymptomatic or minimally symptomatic mCRPC patient with a PSA doubling time > 6 months, time to castration-resistant phenotipe > 12 months, and oligometastases up to three nodal or bone lesions detected by metabolic imaging, RT with radical intent to metastatic sites could be offered as alternative to ARTA to delay systemic treatment

D'Angelillo at Al. Crit. Rev Oncol Hematol 2019

Local treatment to the primary tumor (Rt or Surg)

Rationale

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Metastasis-directed therapy in oligometastatic disease

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JOURNAL OF CLINICAL ONCOLOGY SPECIAL ARTICLE

Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3

in cases in which multiple sites of disease continue to respond but one to two sites grow, focal therapy such as radiation or surgery could be administered to the resistant site(s) and systemic therapy continued.

Sher et Al. J Clin Oncol 2016

Combining Abiraterone and Radiotherapy in Prostate Cancer Patients Who Progressed During Abiraterone Therapy

32 patients affected by mCRPC showing oligoprogression on treatment with Abiraterone Acetate

mPFS from abiraterone initiation **12.6 months**

mPFS from radiotherapy administration **9.6 months**

No safety signals identified

Detti et Al. Anticanc Res 2016

Consensus statements on ablative radiotherapy for oligometastatic prostate cancer: A position paper of Italian Association of Radiotherapy and Clinical Oncology (AIRO)

In an asymptomatic or minimally symptomatic oligoprogressive mCRPC patient, with up to two nodal or bone lesions, in treatment with ARTA from at least 6 months, RT with radical intent to sites of metastases of progressive disease could be offered as an alternative to the change of systemic treatment

D'Angelillo at Al. Crit. Rev Oncol Hematol 2019

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

Patients characteristics

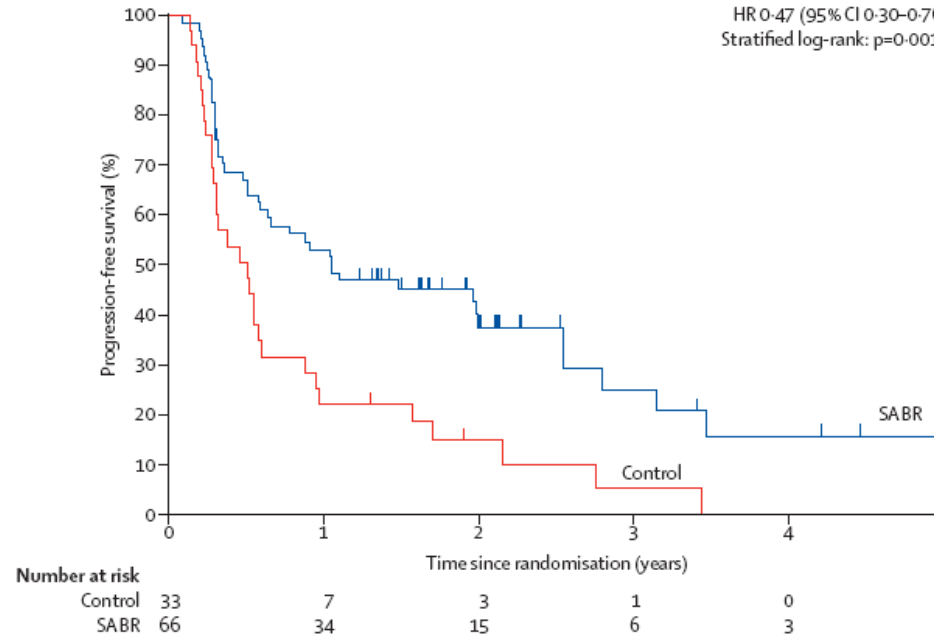
	Control group (n=33)	SABR group (n=66)
Site of original primary tumour		
Breast	5 (15%)	13 (20%)
Colorectal	9 (27%)	9 (14%)
Lung	6 (18%)	12 (18%)
Prostate	2 (6 %)	14 (21%)
Other	11 (33%)	18 (27%)
Time from diagnosis of primary tumour to randomisation (years)	2·3 (1·3–4·5)	2·4 (1·6–5·3)
Number of metastases		
1	12 (36 %)	30 (46%)
2	13 (40%)	19 (29%)
3	6 (18%)	12 (18%)
4	2 (6%)	2 (3%)
5	0 (0%)	3 (5%)

	Control group (n=33)	SABR group (n=66)
Location of metastases		
Adrenal	2/64 (3%)	7/127 (6%)
Bone	20/64 (31%)	45/127 (35%)
Liver	3/64 (5%)	16/127 (13%)
Lung	34/64 (53%)	55/127 (43%)
Other*	5/64 (8%)	4/127 (3%)

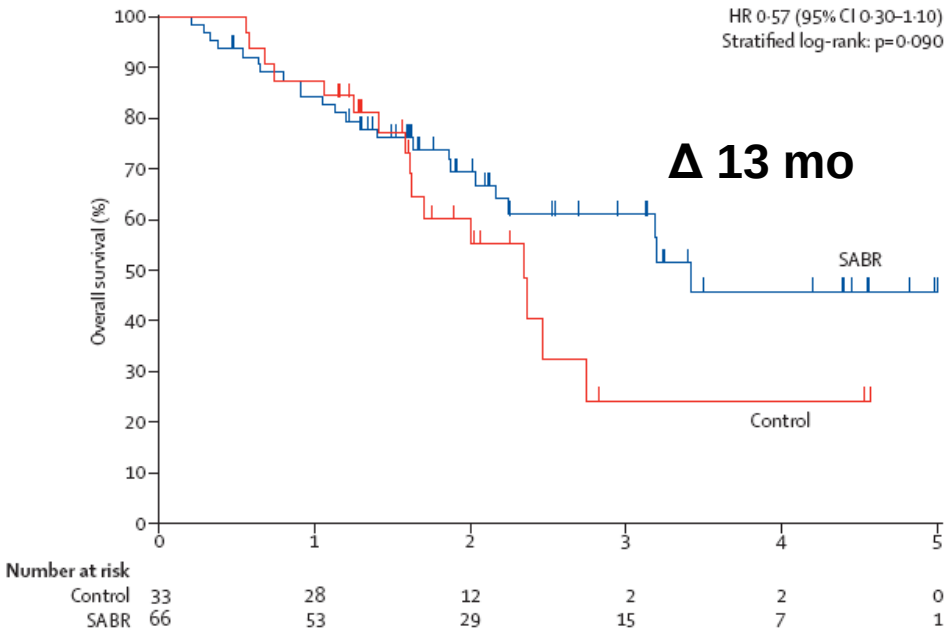
Palma et Al. Lancet Onc 2019

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

Progression-Free Survival



Overall Survival



Palma et Al. Lancet Onc 2019

Ongoing randomised trials of metastases directed therapy for mPC

NCT03449719 (ARTO phase II)

mCRPC (n.174)

≤3 mets; mildly/asymptomatic

R

Abiraterone + Prednisone

Abiraterone + Prednisone + SBRT to all metastases

Primary endpoint

- PSA Response

NCT03784755 (PLATON phase III)

mHSPC (n.410)

≤5 mets; de novo or oligorecur.

R

SST

SST + SBRT

To all mets and untreated primary

Primary endpoint

- Failure-free Survival

Definition

Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation

Panel: Characteristics of oligometastatic disease

Descriptive tumour characteristics

- Primary tumour characteristics: primary tumour site, histology, stage according to TNM Classification of Malignant Tumours, mutational status, tumour marker
- History of cancer progression: time interval since first diagnosis, disease-free interval, treatment-free interval
- History of treatment of primary tumour: method of local treatment, radical or palliative intent, controlled primary tumour
- History of systemic therapy before diagnosis of oligometastatic disease: types of systemic therapy, number of lines of systemic therapy
- Oligometastatic disease staging: imaging method, anatomical areas covered, invasive staging
- Involved organs of oligometastatic disease

Quantitative characteristics

- Number of metastatic lesions
- Number of involved organs
- Number of lesions per organ
- Maximum size or volume of individual metastasis

Quantitative characteristics

- Number of metastatic lesions
- Number of involved organs
- Number of lesions per organ
- Maximum size or volume of individual metastasis

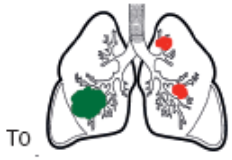
Developmental characteristics

- Does the patient have a history of polymetastatic disease before oligometastatic disease diagnosis?
- Does the patient have a history of oligometastatic disease before current diagnosis?
- Is oligometastatic disease diagnosed within 6 months after diagnosis of the primary tumour?
- Is the patient under active systemic therapy at the time of oligometastatic disease diagnosis?
- Are any oligometastatic lesions progressive on current imaging?

Guckemberger et Al. Lancet Onc 2020

A De-novo oligometastatic disease

Synchronous oligometastatic disease

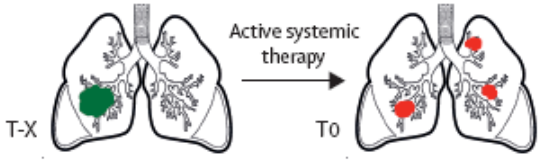


- T0: first time diagnosis of primary cancer (green) and oligometastases (red) within 6 months

Metachronous oligorecurrence

- T-X: diagnosis and treatment of primary cancer (green) in a non-metastatic state
- Systemic therapy-free interval
- T0: First time diagnosis of new oligometastases (red) >6 months after diagnosis of cancer

Metachronous oligoprogression



- T-X: diagnosis and treatment of primary cancer (green) in a non-metastatic state
- Under treatment with active systemic therapy
- T0: first time diagnosis of new oligometastases (red) >6 months after diagnosis of cancer

B Repeat oligometastatic disease

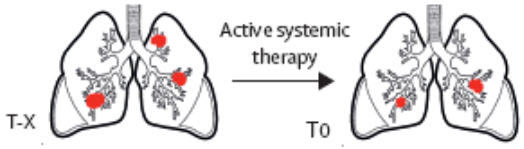
Repeat oligorecurrence

- T-X: diagnosis of oligometastases followed by local treatment or systemic treatment or both
- Systemic therapy-free interval
- T0: diagnosis of new (blue) and growing or regrowing (red) oligometastases

Repeat oligoprogression

- T-X: diagnosis of oligometastases followed by local treatment or systemic treatment or both
- Under treatment with active systemic therapy
- T0: diagnosis of new (blue) and growing or regrowing (red) oligometastases

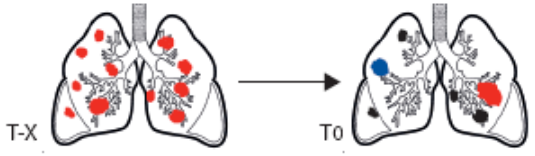
Repeat oligopersistence



- T-X: diagnosis of oligometastases followed by local treatment or systemic treatment or both
- Under treatment with active systemic therapy
- T0: diagnosis of persistent non-progressive (red) oligometastases

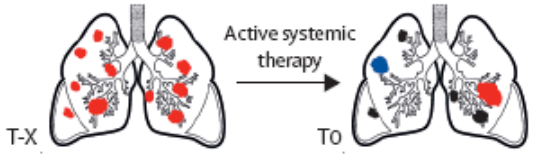
C Induced oligometastatic disease

Induced oligorecurrence



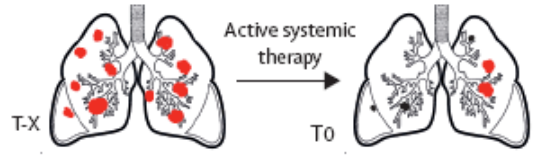
- T-X: diagnosis of polymetastatic metastatic disease followed by systemic treatment with or without local treatment
- Systemic therapy-free interval
- T0: diagnosis of new (blue) and growing or regrowing (red) oligometastases, possible residual non-progressive metastases (black)

Induced oligoprogression



- T-X: diagnosis of polymetastatic metastatic disease followed by systemic treatment with or without local treatment
- Under treatment with active systemic therapy
- T0: diagnosis of new (blue) and growing or regrowing (red) oligometastases, possible residual non-progressive metastases (black)

Induced oligopersistence



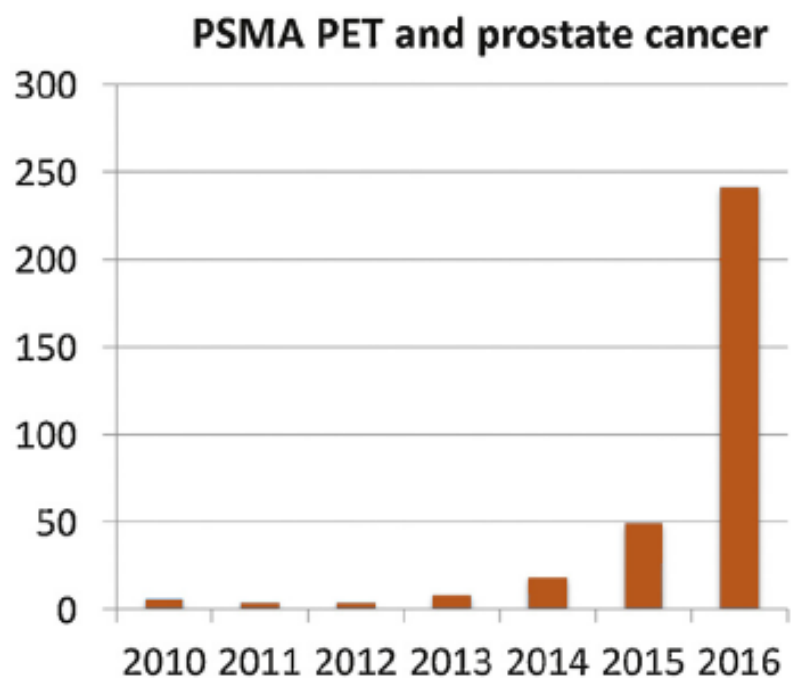
- T-X: diagnosis of polymetastatic metastatic disease followed by systemic treatment with or without local treatment
- Under treatment with active systemic therapy
- T0: diagnosis of persistent non-progressive oligometastases (red), where response is worse compared with other residual metastases (black)

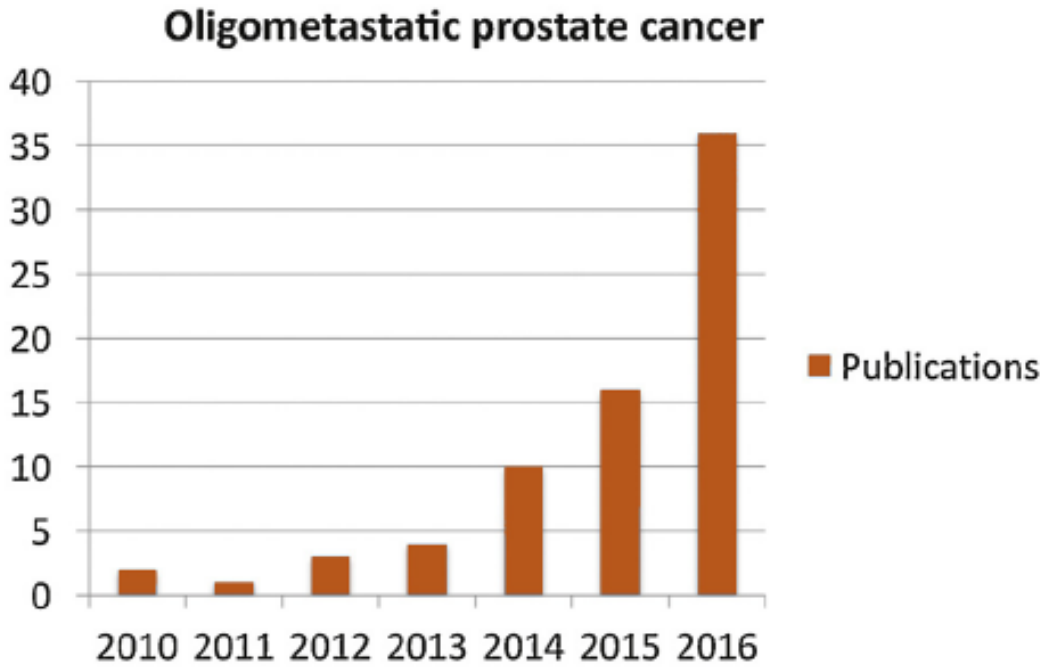
Guckemberger et Al. Lancet Onc 2020

Platinum Opinion

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

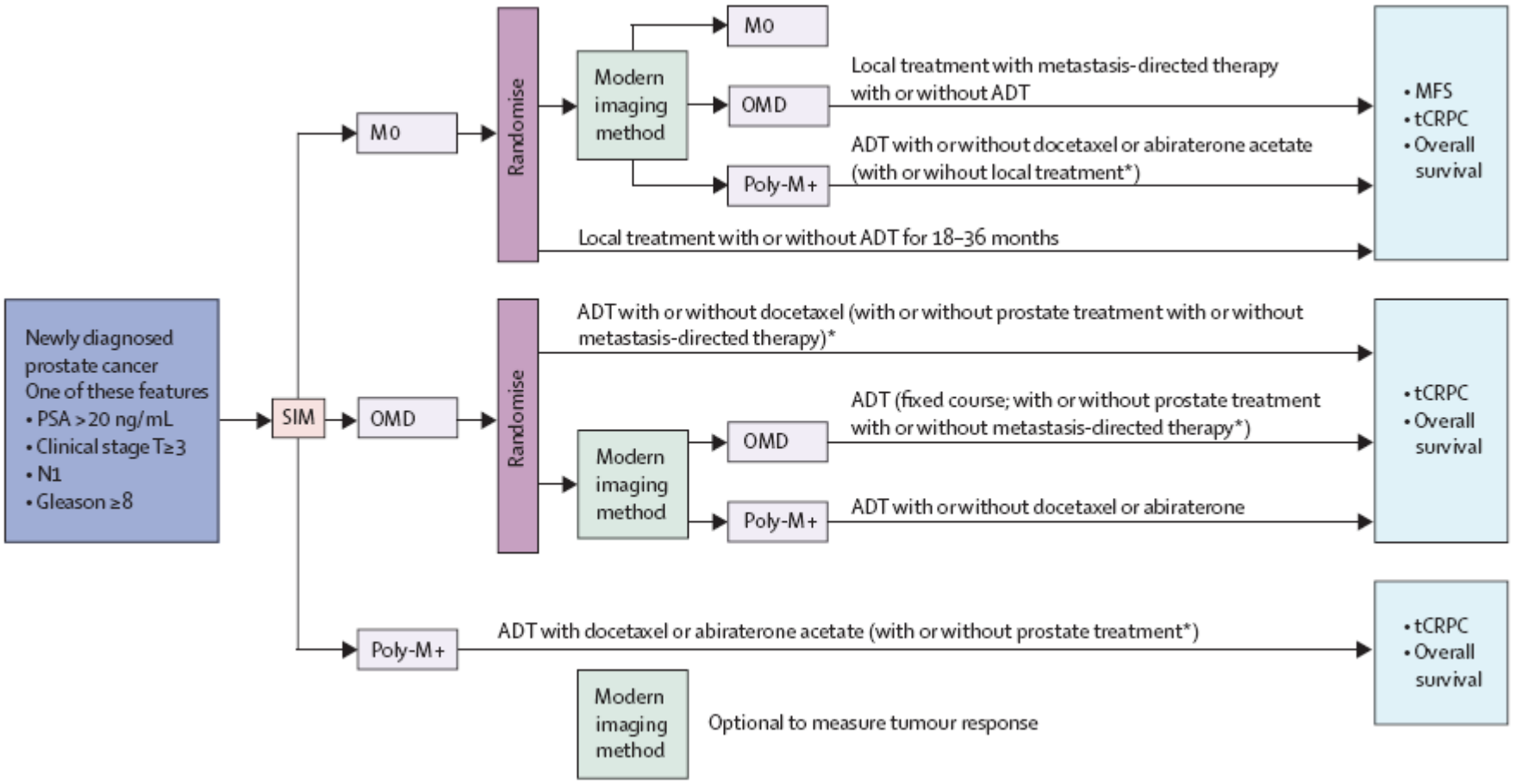
Declan G. Murphy [a,b,c,*], *Christopher J. Sweeney* [d], *Bertrand Tombal* [e]





Use of modern imaging methods to facilitate trials of metastasis-directed therapy for oligometastatic disease in prostate cancer: a consensus recommendation from the EORTC Imaging Group

Proposed clinical trial for newly diagnosed prostate cancer



Lecouvet et Al. Lancet Onc 2018

….modern imagning is just the peak of the iceberg

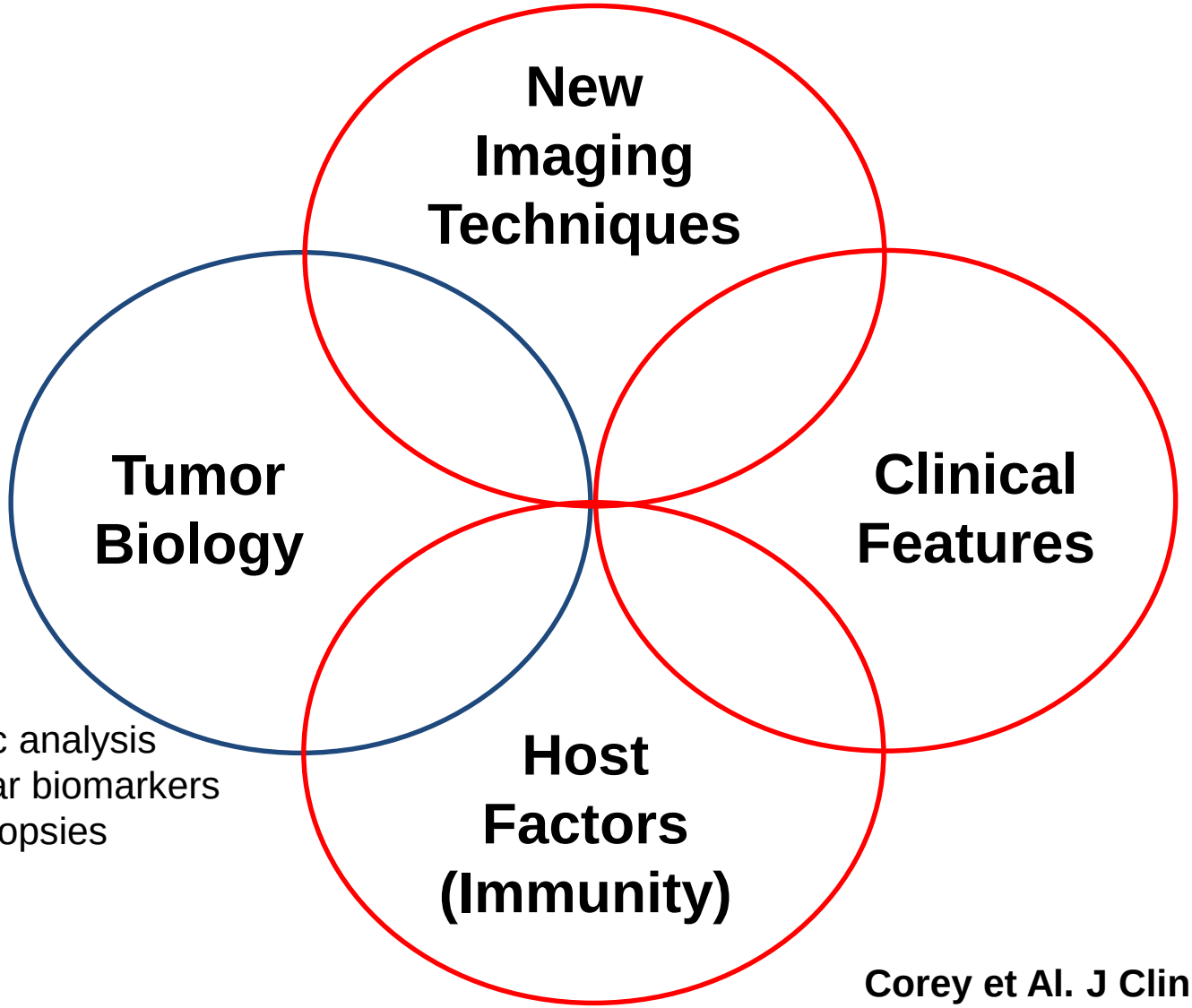
Any image taken of a cancer is a snapshot of an ongoing process that does not inform on the kinetics of the progression.

If some patients indeed harbour slow-growing metastatic deposits, others may be rapidly progressive disease wrongly frozen in an oligometastatic state by a still image.

will need more biomarkers to ascertain the natural history of the disease and, more importantly, to distinguish who needs MDT instead of systemic treatment and who needs MDT on top of systemic therapy.

Murphy et Al. Eur Urol 2019

Staging the Metastatic Spectrum Through Integration of Clinical and Molecular Features



- miRNA
- Genomic analysis
- Molecular biomarkers
- Liquid biopsies
- CTCs

Corey et Al. J Clin Oncol 2019

Local treatment to the primary tumor (Rt or Surg)

Basing on 2 RCT and 1 meta-analysis RT should not be recommended for the ITT population….but it can be considered for patients with *low volume M1 disease* *(OS sig. improved)*

Surgery is not yet validated and should be considered experimental

Metastasis-directed therapy in oligometastatic disease

The oligometastatic state defines an *‘intermediate stage of disease’* that might benefit from local treatment

There is growing evidence about the offect of MDT on clinical outcomes in oligometastatic prostate cancer

Level of evidence is low *(mainly retrospective)* and need further validation in prospective randomised trials

Understandig the role of new imaging and the biology of oligomtastatic disease is essential for future developements