wielkopolskie centrum onkologii

Local Radiotherapy

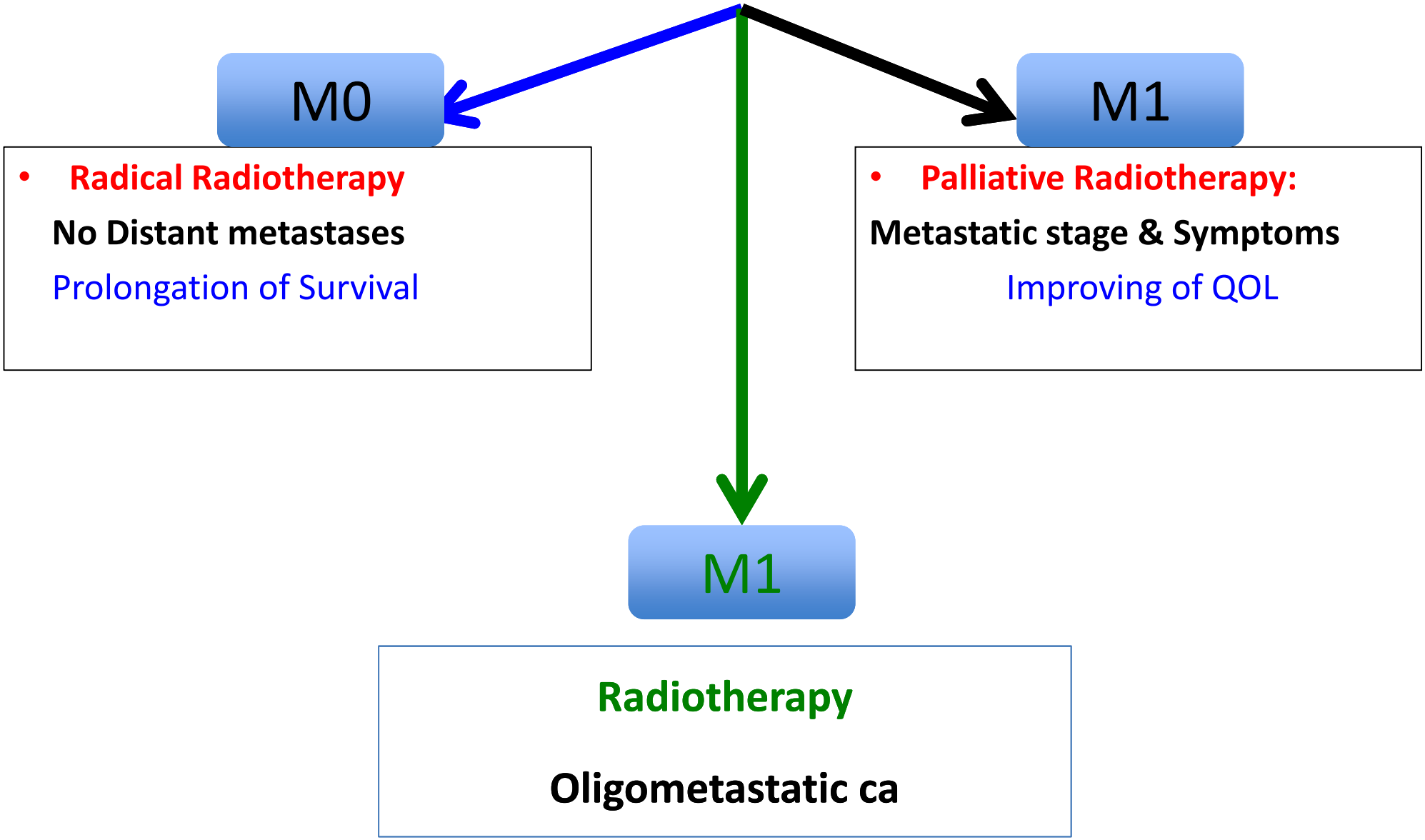
(Stereotactic Body Radiotherapy - SBRT)

in Metastatic Prostate Cancer in 2019

Piotr Milecki

Radiotherapy Department, Greater Poland Cancer Center
Medical University
Poznań, Poland

Radiotherapy



Local Treatment for M1 disease

1855	C. Sédillot	France	1 case
1882	K. Weinlechner	Austria	1 case
1883	U. Krönlein	Switzerland	1 case
1898	F.W. Parham	USA	2 cases, review of 98 cases
1898	Quénu and Longuet	France	34 cases

Early reports of chest wall and lung surgery

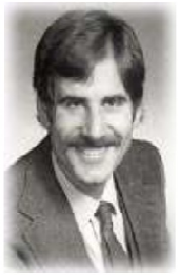
1921/1937	W. Röpke	Germany
1926	G. Divis	Czechoslovakia
1927	A.T. Edwards	United Kingdom
1930	F. Torek	USA
1933	E.D. Churchill	USA

Early reports of pulmonary metastasis resection

Liver metastases M1

- Colo-Rectal cancer

Hellman & Weichselbaum
JCO 1995;13:8.

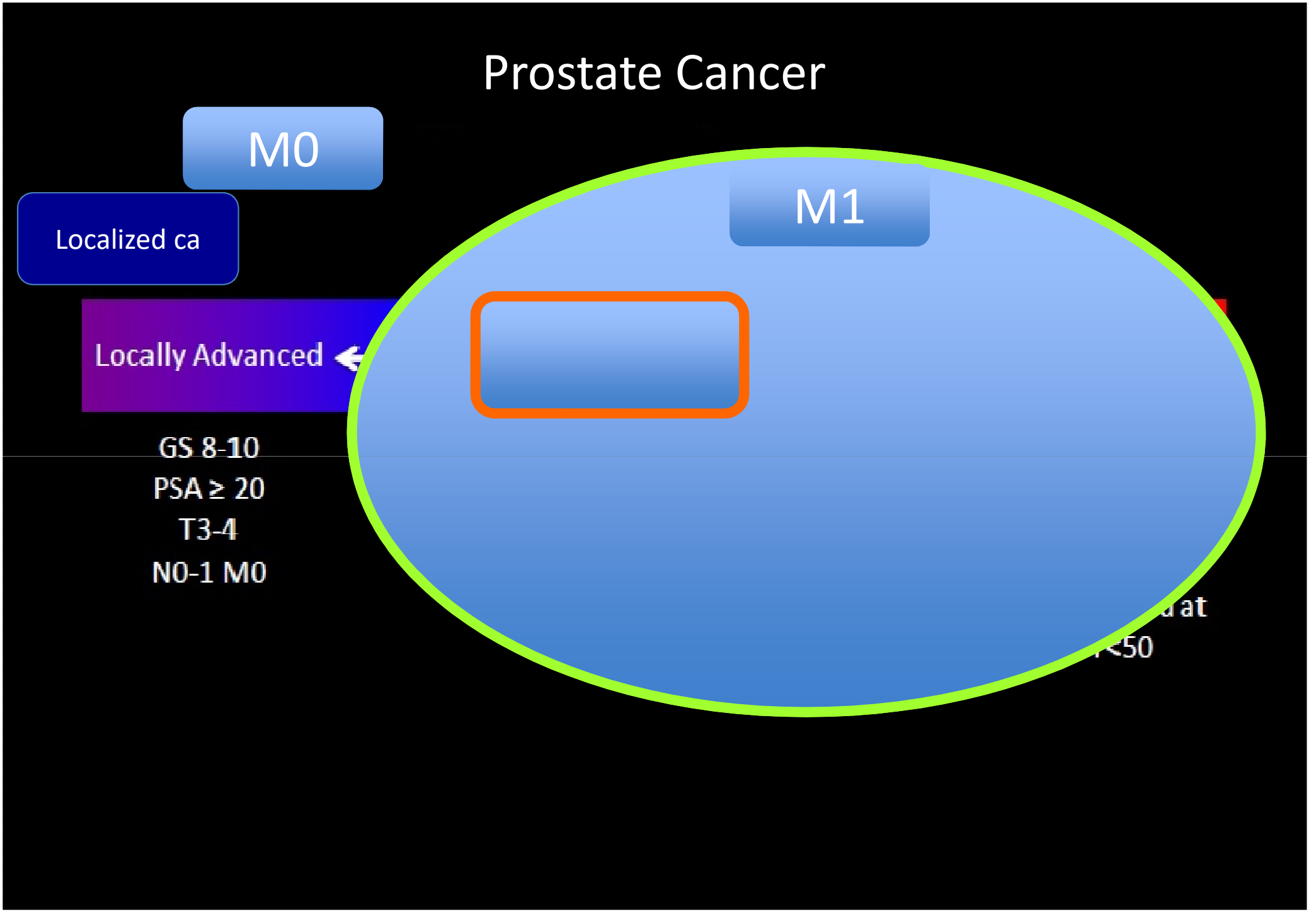


Hellman and Weichselbaum, J Clin Oncol 13:8 (1995)

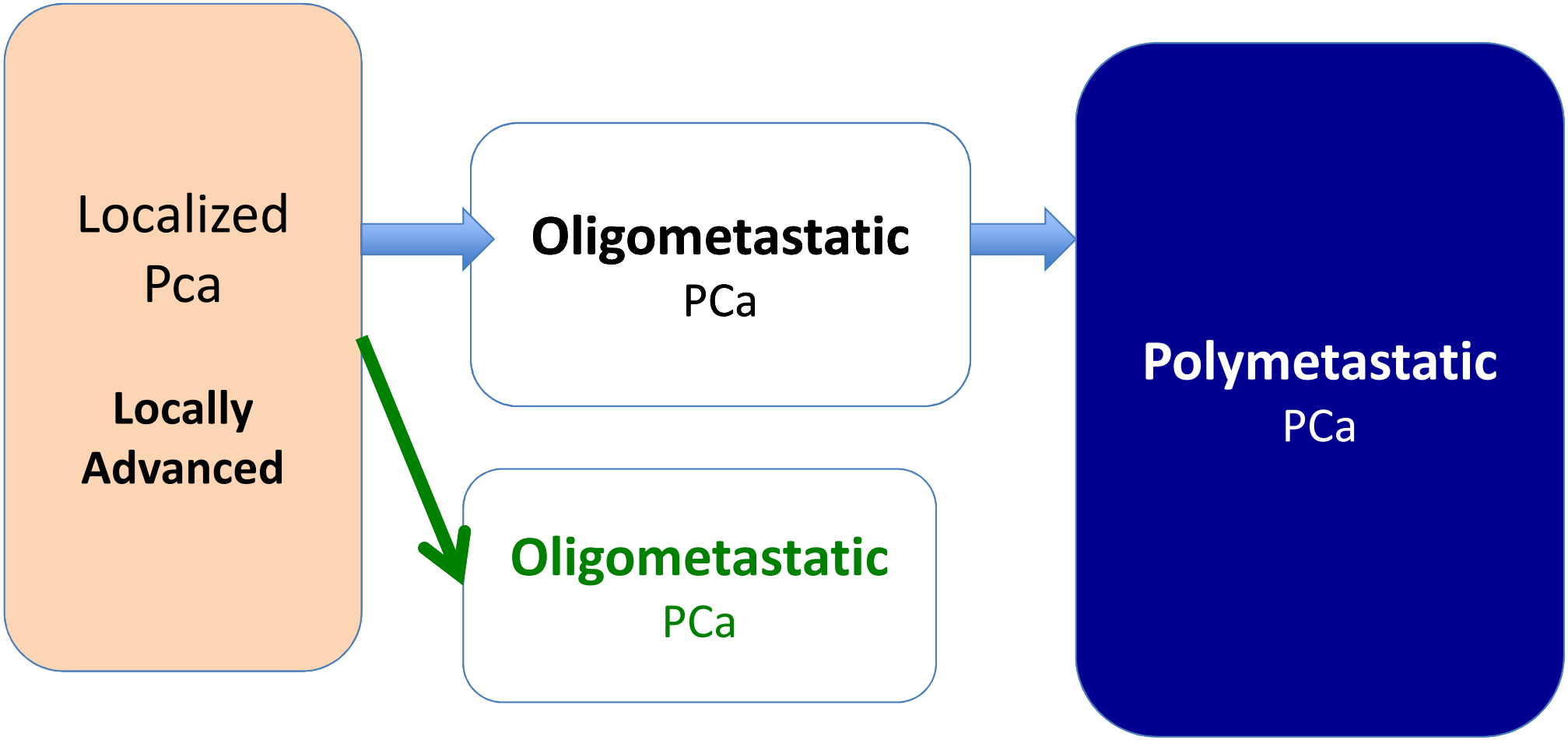
Oligometastases

- Distinct clinical state
- Metastases limited in number/destination organ
- More indolent biology earlier in the metastatic cascade

An attractive consequence of the presence of a clinically significant oligometastatic state is that some patients so affected should be amenable to a curative therapeutic strategy. The occasional success of surgical excision or


Prostate Cancer
M0
Localized ca
Locally Advanced
GS 8-10
PSA ≥ 20
T3-4
N0-1 M0
M1
at
<50

Prostate Ca



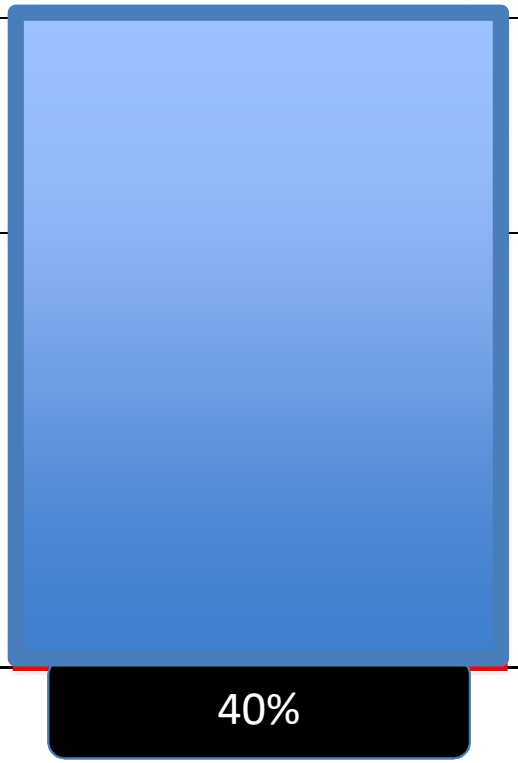
Local therapy

Systemic therapy

No doubt that Oligometastatic disease is present

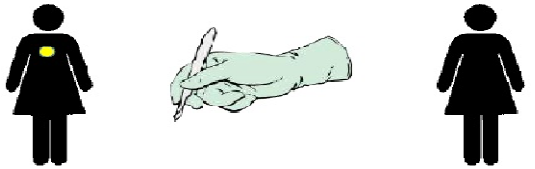
Table 1. Lesion site by number

Site	>5 lesions (*n*)
Bone alone	35 (47.3)
Bone + liver	2 (2.7)
Bone + lung	2 (2.7)
Bone + lymph node	3 (4.1)
Bone + multiple sites	2 (2.7)†



Int. J. Radiation Oncology Biol. Phys., Vol. 58, No. 1, pp. 3–10, 2004

Primary Tu + Mets



Primary Tu post Therapy under control but Mets during FU

De novo metastatic prostate cancer

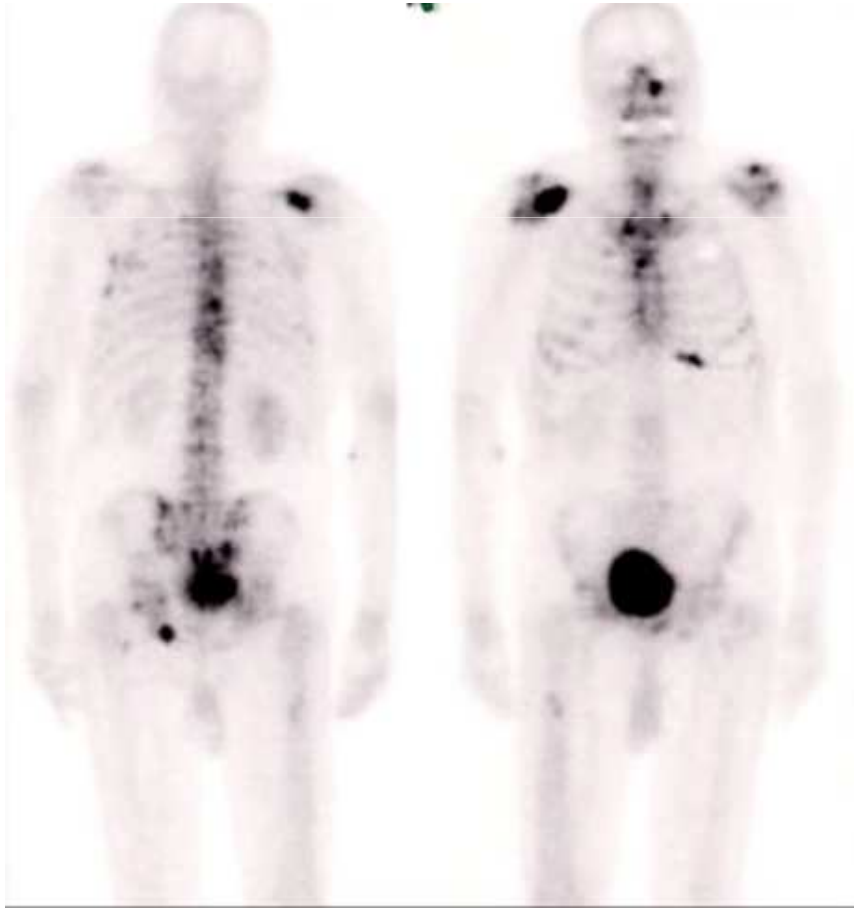
- Metastatic castration-naïve prostate cancer (mCNPC) incidence is[1-5]:
  - ~3% in US and rising;
  - ~6% across Europe
  - ~4-10% in Latin America
  - ~60% in Asia-Pacific

1. Weiner AB, et al. *Prostate Cancer Prostatic Dis*. 2016;19:395-397. 2. Buzzoni C, et al. *Eur Urol*. 2015;68:885-890. 3. Chen R, et al. *Asian J Urol*. 2014;1:15-29. 4. Ito K. *Nat Rev Urol*. 2014;11:15-29. 5. Nardi AC. *Int Braz J Urol*. 2012;38:155-166. 6. Yamaoka M, et al. *Clin Cancer Res*. 2010;16:4319-4324.

Oligomets vs. Polimets ?

Diagnosis !!!

Bone scan	18F –Fluoride PET



RT for Oligomets ?

Author (yr)	Study type	Inclusion criteria	RT modality	No. of patients	Local control rate	Progression-free survival	Overall survival
Zagars, et al. (2001)[66]	Retrospective	Pathologically proven pelvic LN	EBRT to prostate only	RT+ADT (n=72) ADT alone (n=183)	10 yr 89% 49% $p<0.001$	10 yr 85% 56% $p=0.006$	10 yr 67% 46% $p=0.008$
Lawton, et al. (2005)[69]	Prospective	Pathologically proven LN	EBRT to prostate, abdomen and pelvic LN	RT+ADT (n=98) RT alone (n=75)	NR	9 yr 10% 4% $p<0.001$	9 yr 62% 38% $p=0.23$
Widmark, et al. (2009)[67]	Prospective	T3N0M0	Conformal RT	RT+ADT (n=436) ADT	NR	10 yr PSA recurrence 9% 7% 0.001	
Warde, et al. (2011)[68]	Prospective	T3 or T4, N0 or Nx	EBRT to pelvis, prostate, seminal vesicle, iliac LN	RT+ADT (n=803) ADT alone (n=602)	NR	NR	
Rusthoven, et al. (2016)[70]	Retrospective	M1	EBRT to prostate or pelvis	RT+ADT (n=538) ADT (n=5844)	NR	NR	8 yr 33% 13% $p<0.001$

ADT, androgen-deprivation therapy; EBRT, external beam radiation therapy; LN, lymph node; NR, not reported; OM, overall mortality; PSA, prostate-specific antigen; RT, radiation therapy.

How many pts have metastatic cancer ?

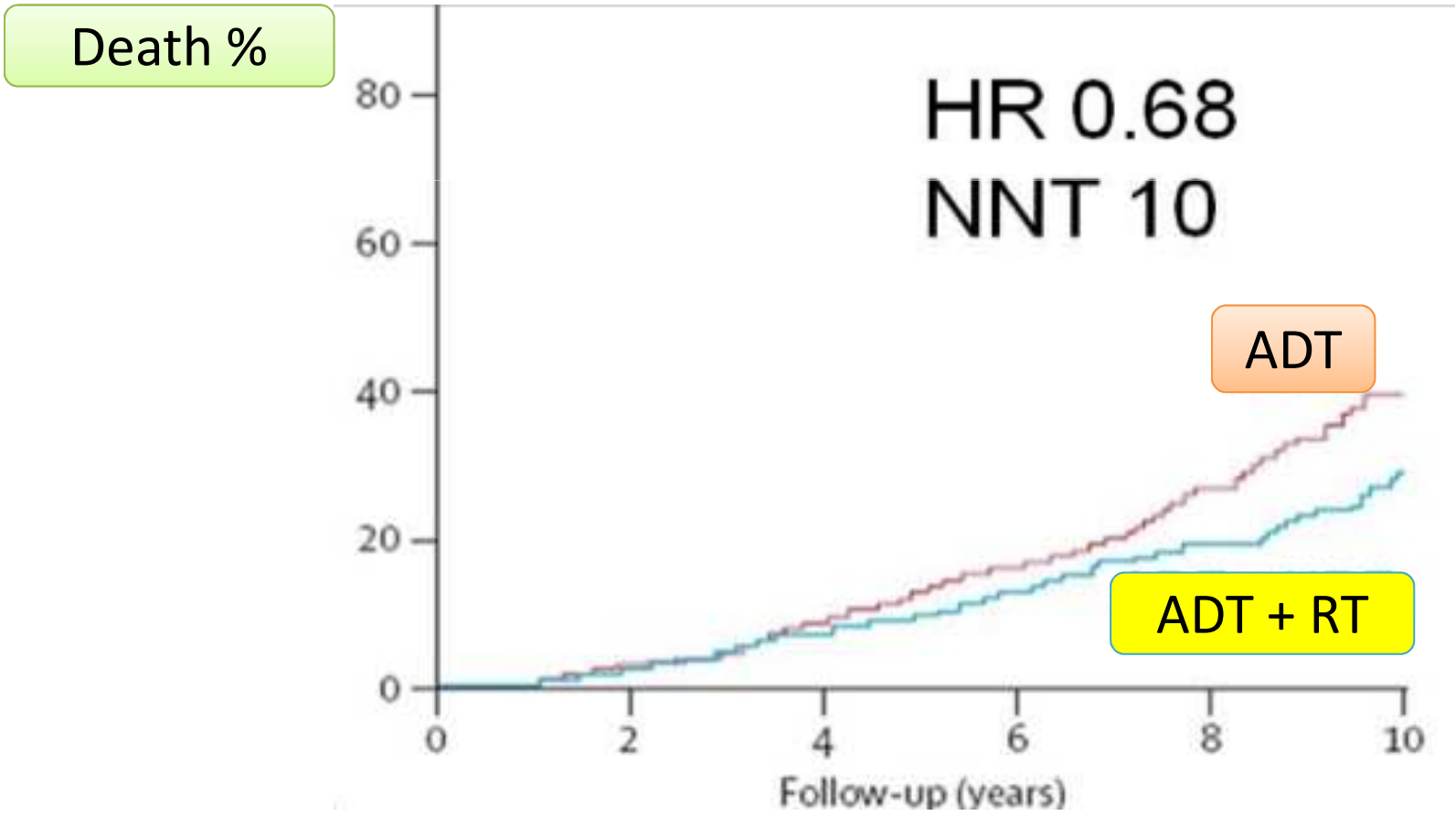
M0/M1

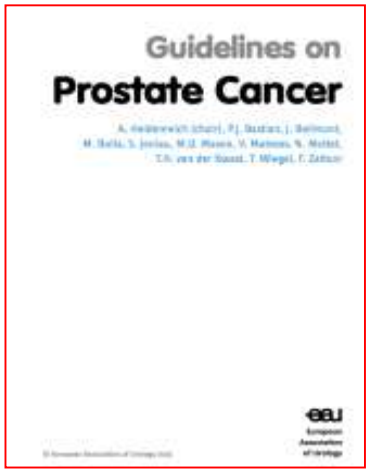
Local RT ?

SPCG 7 Trial

Widmark et al., Lancet 2012

ADT vs. ADT + RT





In patients with locally advanced prostate cancer (T3-4, N0 M0), who are fit enough to receive EBRT, the recommended treatment is EBRT plus long-term ADT and the use of ADT alone is inappropriate.	1b	A

Local therapy (Radiotherapy) plays an important role.

- Milecki, ASTRO Chicago 2009
- Widmark et al. SPCG-7/SFUO-3, Lancet Oncol 2012
- Warde et al. T-94-0110 Trial, Lancet 2012
- Mottet et al. French Trial , Eur Urol 2012

Oligometastatic disease

Low Volume

- 1- 3 bone mets

CHAARTED

High Volume

- >3 bone mets with 1 outside spine or pelvis or visceral mets

Low Volume

- Spine and/or pelvic bone mets and/or Lymphnodes

SWOG

High Volume

- Long bone and/or visceral mets

Low Volume

- > 3 bone mets or GS 9-10 or Visceral mets

LATITUDE

High Volume

- 2 or 3 of the above

Treatment of Oligometastases

Radiotherapy

Standard of Care in 2018 ?

National Comprehensive Cancer Network®

NCCN Guidelines
Prostate Cancer

NCCN Guidelines Index
Table of Contents
Discussion

Orchiectomy
or
LHRH agonist ± antiandrogen[f,jj]
M0 → or
LHRH antagonist[f,jj]
or
Observation[t]

- Physical exam + PSA every 3–6 mo
- Bone imaging[i] for symptoms and as often as every 6–12 mo

→ Progression[dd,ll]

Studies negative for distant metastases → See Systemic Therapy for M0 CRPC (PROS-14) [gg]

Studies positive for distant metastases → See Systemic Therapy for M1 CRPC (PROS-15) [gg]

[f] See Principles of Androgen Deprivation Therapy (PROS-F).

[i] See Principles of Imaging (PROS-B).

[t] Observation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in exam or PSA that suggests symptoms are imminent. See Principles of Active Surveillance and Observation (PROS-C).

[dd] Workup for progression should include chest x-ray or chest CT, bone imaging, and abdominal/pelvic CT or MRI with and without contrast. Consider C-11 choline PET/CT or PET/MRI or F-18 fluciclovine PET/CT or PET/MRI for further soft tissue evaluation or F-18 sodium fluoride PET/CT for further bone evaluation. See Principles of Imaging (PROS-B) and Discussion.

[ff] The term "castration-naive" is used to define patients who are not on ADT at the time of progression. The NCCN Prostate Cancer Panel uses the term "castration-naive" even when patients have had neoadjuvant, concurrent, or adjuvant ADT as part of radiation therapy provided they have recovered testicular function.

[gg] Castration-resistant prostate cancer (CRPC) is prostate cancer that progresses clinically, radiographically, or biochemically despite castrate levels of serum testosterone (<50 ng/dL). Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 2008;26:1148-1159.

[jj] Intermittent ADT can be considered for men with M0 or M1 disease to reduce toxicity. See Principles of Androgen Deprivation Therapy (PROS-F)

[kk] High-volume disease is differentiated from low-volume disease by visceral metastases and/or 4 or more bone metastases, with at least one metastasis beyond the pelvis vertebral column. Patients with low-volume disease have less certain benefit from early treatment with docetaxel combined with ADT.

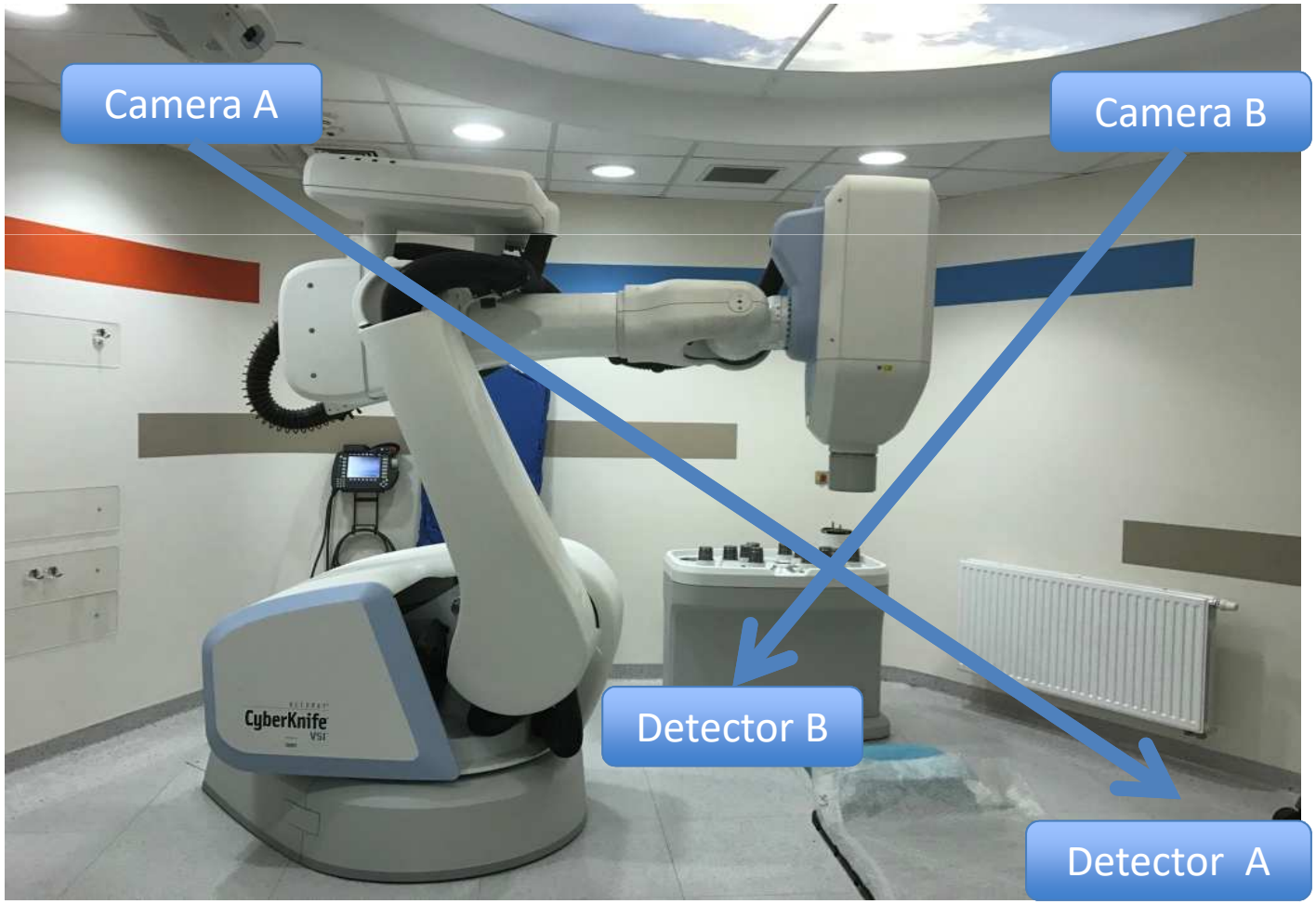
[ll] Assure castrate level of testosterone.

SBRT (SABR)

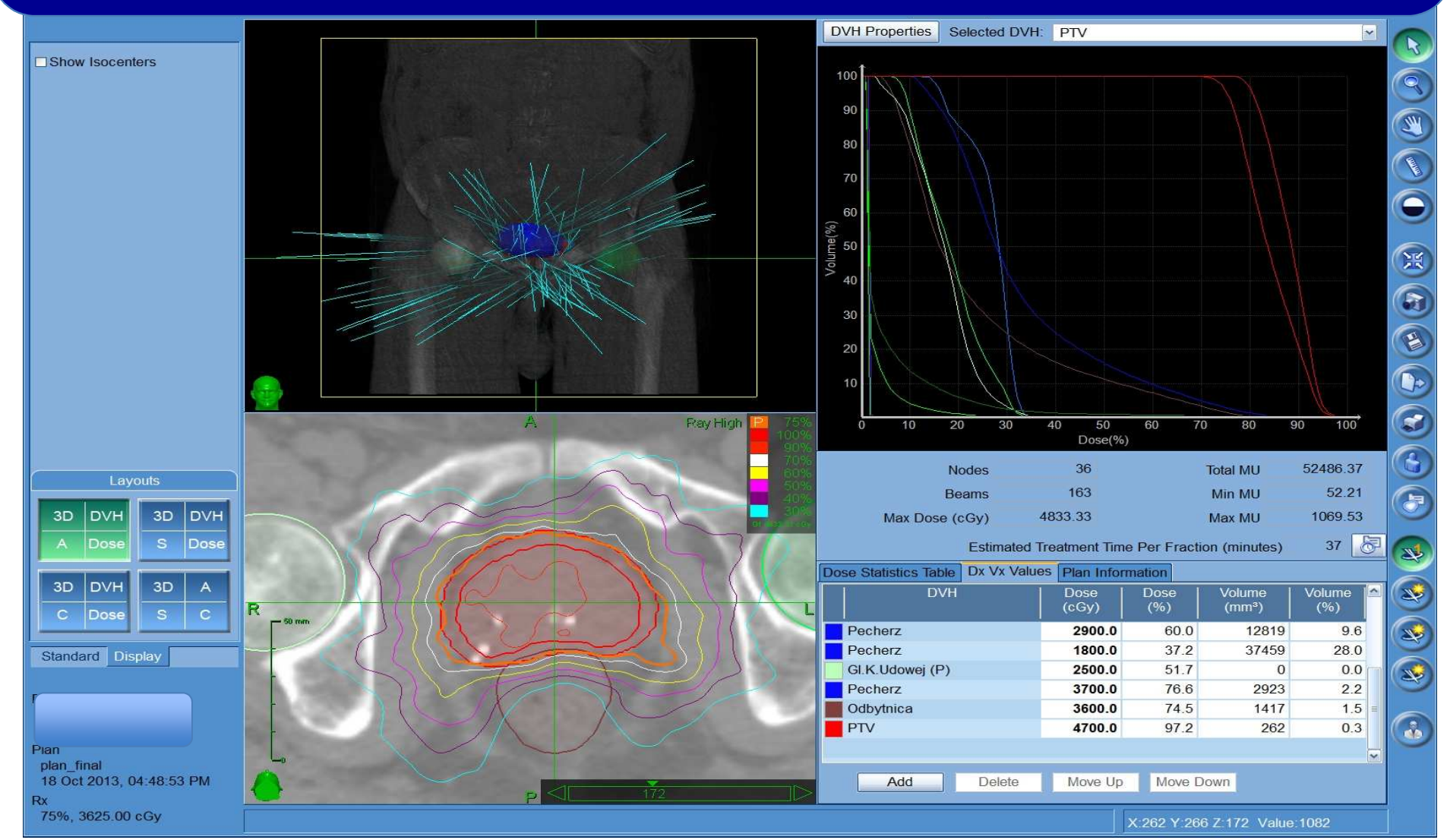
Oligometastatic Disease

Cyberknife Tracking System

- Linac mounted on a robot manipulator
- 6 degrees of freedom
- Fudicial markers

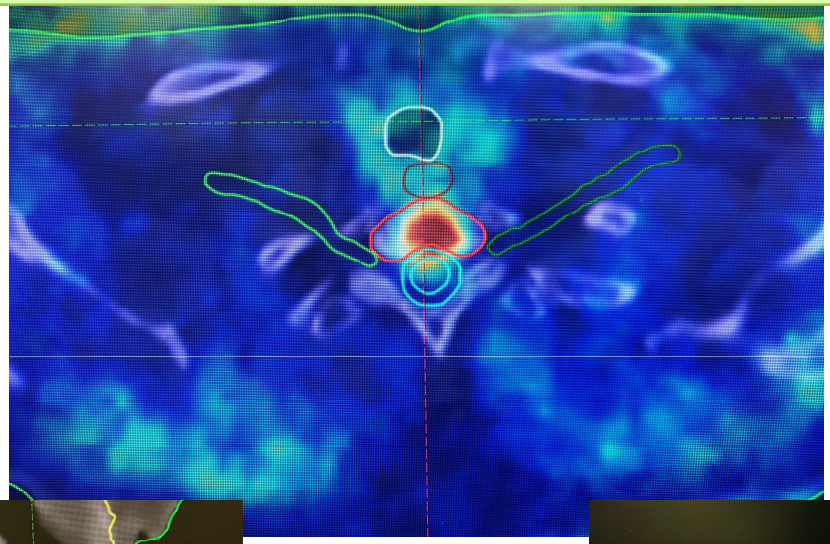


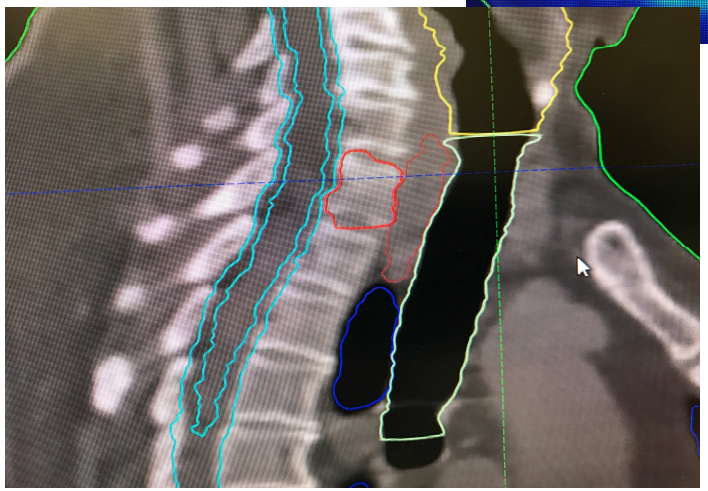
We use very high fraction dose Hypofractionation

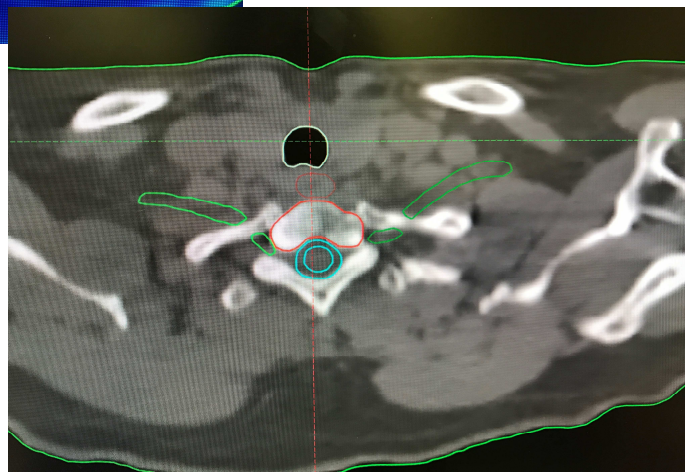


SBRT

TD= 24 Gy, 3 x 8 Gy

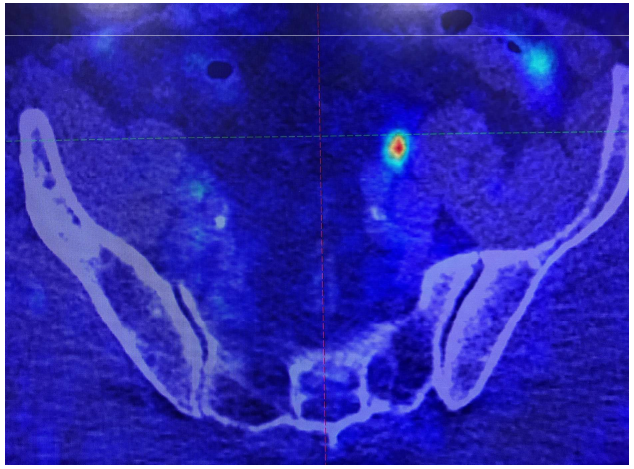






Metastatic Lymph node

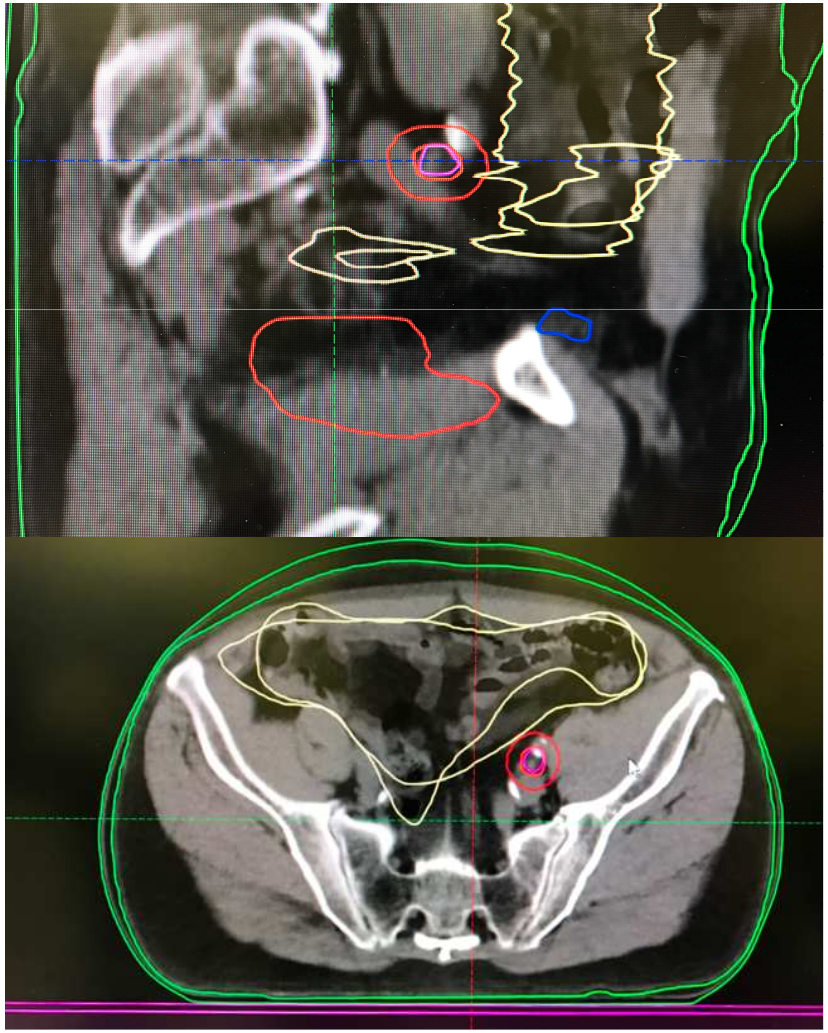
SBRT



SBRT

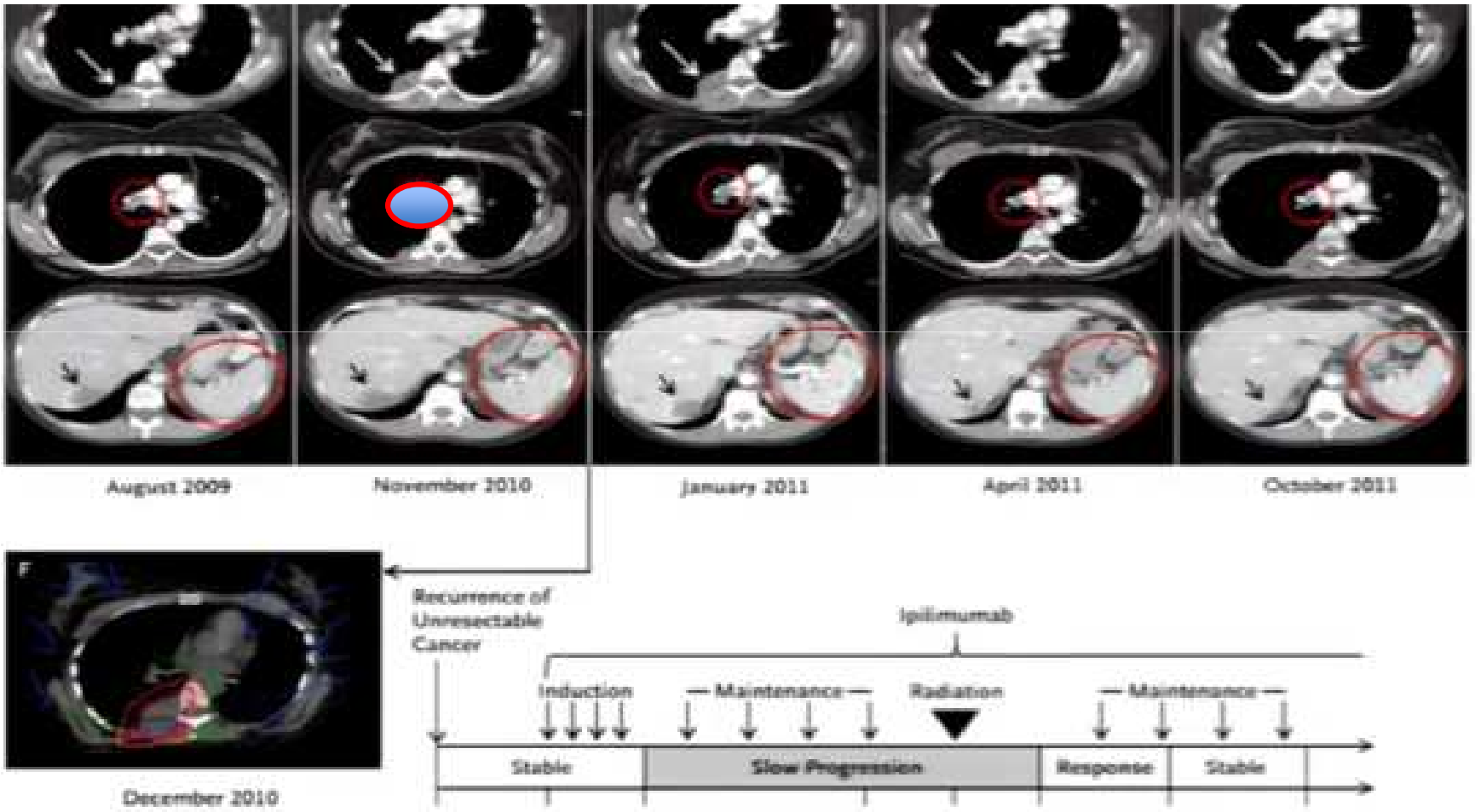
TD= 30 Gy

5 x 6 Gy



SBRT for metastatic lesions:

- **Local effect** of RT
- **Systemic effect of RT** (Augmenting the Immune Response by Radiation)



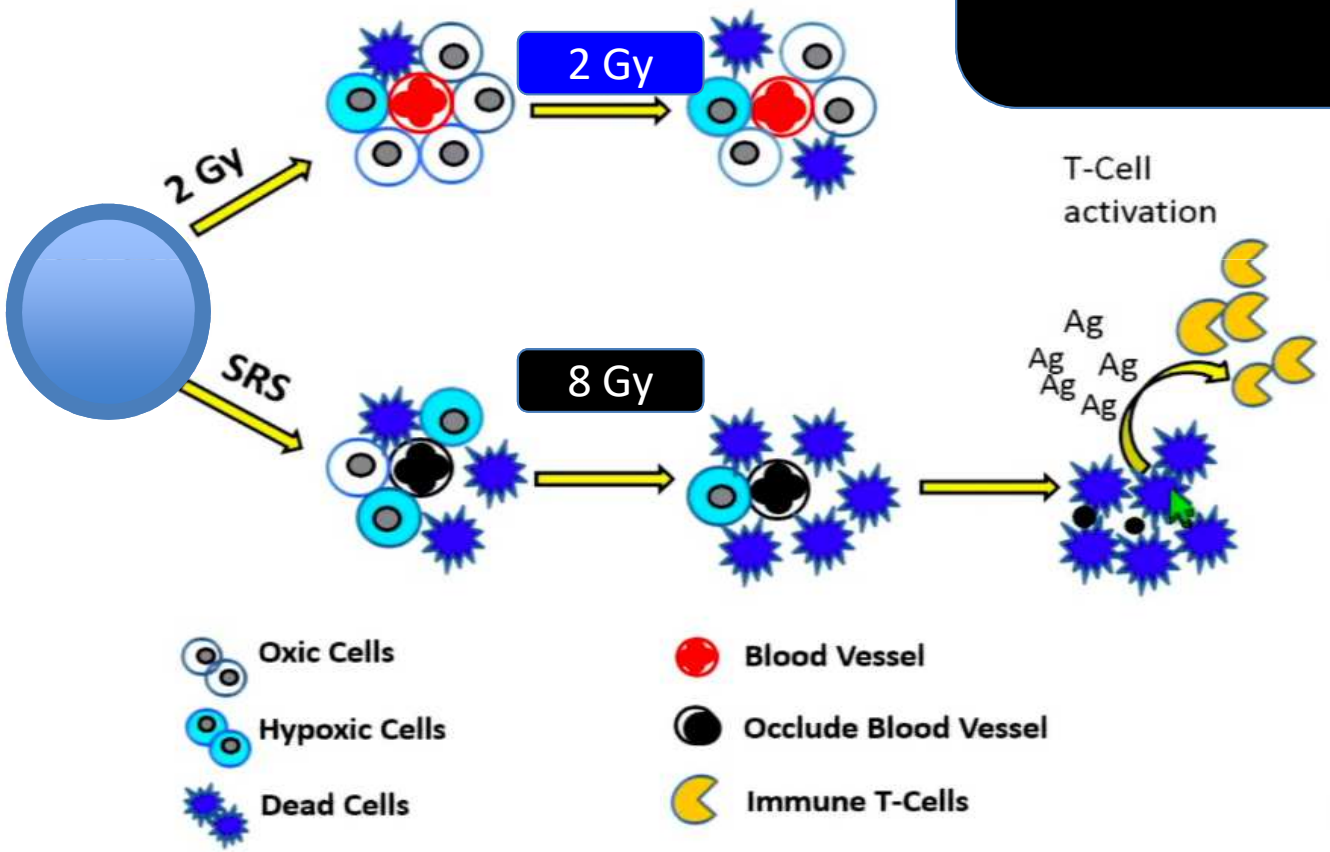
Postow et al. NEJM 2012

Conventional RT vs. Hypofractionated SBRT

Direct cell death

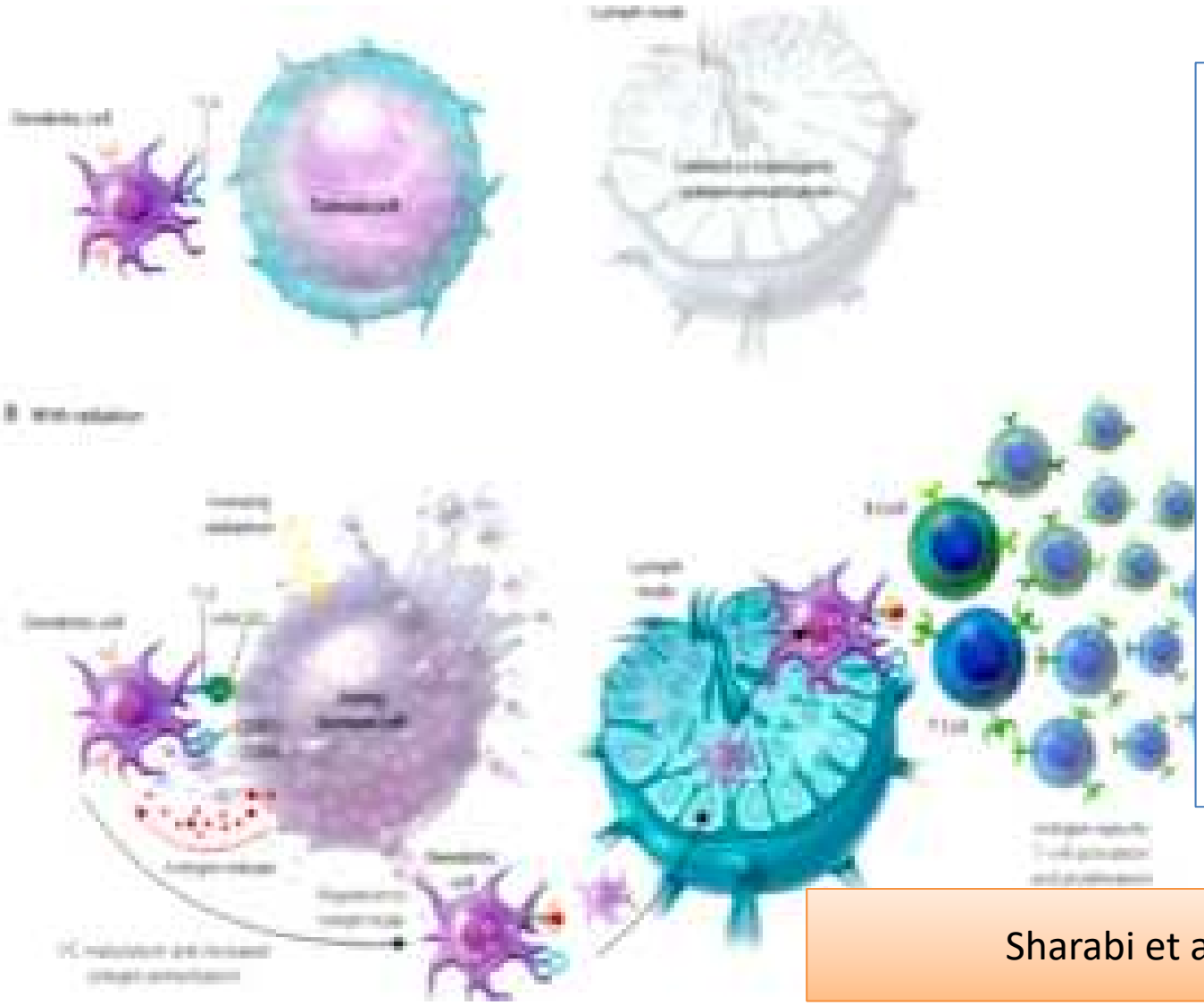
Vascular damage (indirect death)

Immune response



Abscopal Response

RT increases antigen presentation and actives dendritic cells



Death of cancer cells caused by radiation release antigens

Sharabi et al. Lancet Oncol 2015

Clinical Trial Phase II fazy
anti-CTLA-4 + RT for patients M1 (mCRPC)

Screening

mCRPC

Post CT
(docetaxel)
N=799

1:1

RT bone mets
(8Gy); 1 do 5
mets

N = 399

Ipilimumab
(10 mg/kg)
weeks 1,4,7,10

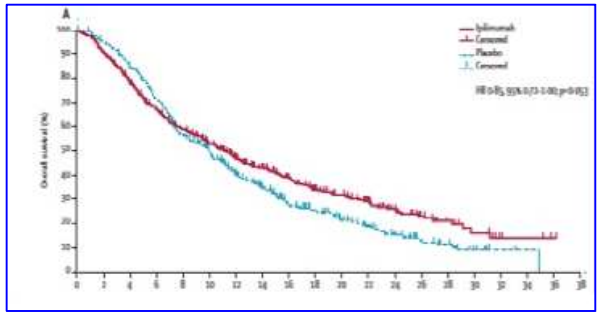
Ipilimumab
(10 mg/kg)
co 12 tygodni

N= 400

Placebo
Weeks 1,4,7,10

Placebo
co 12 tygodni

Stratyfikacja:
ALP, Hb, ECOG PS



Kwon et al. Lancet Oncology 2014

Prostate-Directed Therapy

Adapted from Tosoian et al. Nat Rev Urol 2016

	Design	Inclusion	Intervention	Conclusion
Culp et al. 2014	SEER, n=8185	M1	RP vs BT vs no local therapy	OS and CSS favored RP and BT
Antwi et al. 2014	SEER + propensity score analysis, n=7858	M1	RP vs BT vs no local therapy	CSM favored RP and BT
Gratzke et al. 2014	Munich Cancer Registry Database, n=1538	M1	RP vs no RP (ADT only or RT or other)	OS favored RP
Satkunasivam et al. 2015	SEER + Medicare, n=4069	M1	RP vs IMRT vs 3D CRT vs no local therapy	OS favored RP and IMRT
Heidenreich et al. 2015	Case-control, n=61	M1, ≤3 bone lesions	RP vs no RP	Time to castration resistance, PFS, CSS favored RP
Cho et al. 2016	Case-control, n=140	M1, ≤5 bone lesions	Prostate RT vs palliative RT to M1 vs no local therapy	OS, bFFS favor prostate RT
Rusthoven et al. 2016	NCDB, n= 6382	M1	RT + ADT vs ADT alone	OS favored RT+ADT

Node-Directed RT

Source	N	Inclusion	Imaging	Intervention	Result
Casamassima et al. 2011	25	"Limited" N1 or M1a	11C and 18F-choline PET	SBRT (30Gy/3fx) or Pelvic LN RT (50 Gy/25fx + 24Gy boost)	3y LC 90% 3y DFS 17% 3y OS 92%
Wurschmidt et al. 2011	26	7 primary 19 salvage 16 LN+	18F-choline PET	EBRT 66.6-75.6Gy, 45Gy pelvic LN, boost PET+ LN	28mo bRFS 83% (primary) 28mo bRFS 49% (salvage) 28mo OS 94% 1 G4 GU requiring cystectomy
Schick et al. 2013	50	≤4 regional LN or mets	18F-choline or 11C-acetate PET	EBRT (50.4 Gy pelvic LN, 65Gy LN boost) + STADT	3y bRFS 55% 3y DMFS 59% 3y OS 92%
Jereczek-Fossa et al. 2012	34	LN or bone recurrence	11C-choline PET	SBRT (33-36Gy/3 fx)	30mo LC 100% 30mo PFS 63.5% (LN+); 0% (M1) 2 G3+ acute and late GU AE
Decaestecker et al. 2014	50	M1 ≤3 mets	18F-FDG or 18F-choline PET	SBRT (50Gy/10fx or 30Gy/3 fx)	2y LC 100% 2y PFS 35% If N1, 67% relapses were other LN
Picchio et al. 2014	83	LN recurrence	11C-choline PET	EBRT (36-74Gy/28fx) with simultaneous LN boost	89.4% partial to complete imaging response 2 G3+ acute GU AE
Ost et al. 2016	72	≤3 N1 or M1a	18F-FDG or 18F-choline PET	SBRT (24-30Gy/3fx, 30Gy/5fx, 50Gy/10fx)	3y dPFS 34% Median ADT-free time: 44 mo
Jereczek-Fossa et al. 2017	94	≤5 LN recurrences	11C-choline PET	SBRT (24Gy-30Gy/3fx)	2y LC 84% 2y PFS 30% STADT <12mo assoc with longer PFS

Metastasis-Directed RT

Source	N	Inclusion	Imaging	Intervention	Result
Jereczek-Fossa et al. 2012	34	M1 bone recurrence	11C-choline PET	SBRT (33-36Gy/3 fx)	30mo LC 100% 30mo PFS 0%
Ahmed et al. 2012	17	M1, ≤5 mets	11C-choline PET	SBRT (20 Gy/1 fx) followed by ADT	6 mo LC 100% 53% undetectable PSA
Muacevic et al. 2013	40	M1, ≤2 bone mets	18F-choline PET	SBRT (20.2 Gy/1 fx)	2y LC 95.5%
Schick et al. 2013	50	N1-M1 ≤4 regional LN or mets	18F-choline or 11C-acetate PET	EBRT (50.4 Gy pelvic LN, 65Gy LN boost) + STADT	3y bRFS 55% 3y DMFS 59% 3y OS 92%
Berkovic et al. 2013	24	M1 ≤3 bone or LN mets	BS, 18F-FDG or 11C-choline PET	SBRT (50Gy/10 fx)	2y LC 100% 2y cPFS 42% Median ADT-free time: 38mo
Decaestecker et al. 2014	50	M1 ≤3 mets	18F-FDG or 18F-choline PET	SBRT (50Gy/10fx or 30Gy/3 fx)	2y LC 100% 2y PFS 35% Median ADT-free time: 25mo
Muldermans et al. 2016	66	M1, ≤5 mets, CRPC	11C-choline PET, MRI, CT, BS	SBRT (16Gy/1fx, 18Gy/1fx, 30Gy/3fx, 50Gy/5fx)	2y LC 95% (≥18Gy), 58% (16Gy) 2y bPFS 54% 2y OS 83%
Habl et al. 2017	15	M1 ≤2 mets	11C-choline or 68Ga-PSMA PET	SBRT (25-35Gy/5fx)	2y LC 100% Median distant PFS 7.4 mo Median ADT-free time: 9.3 mo

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European Association of Urology

Platinum Priority – Brief Correspondence

Editorial by Vincent Khoo on pp. 13–14 of this issue

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

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

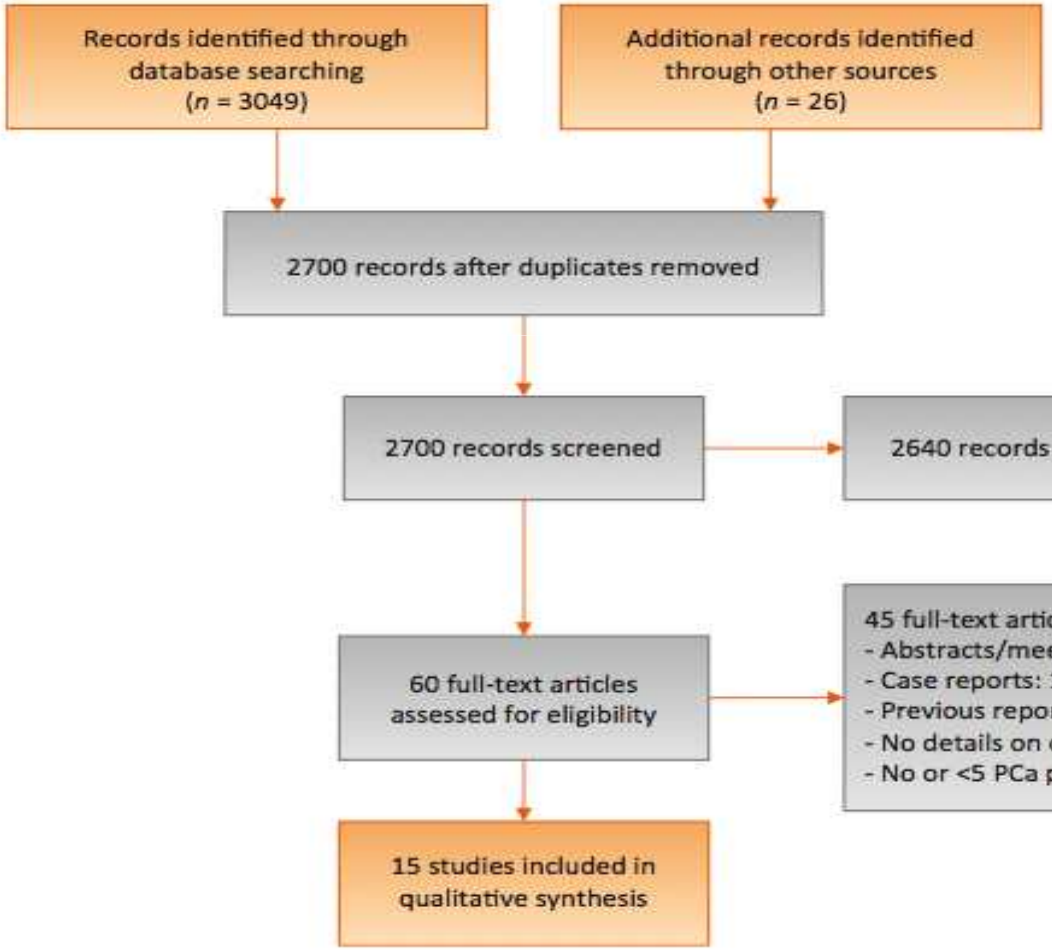


Fig. 1 – Flowchart of the systematic review. PCa = prostate cancer.

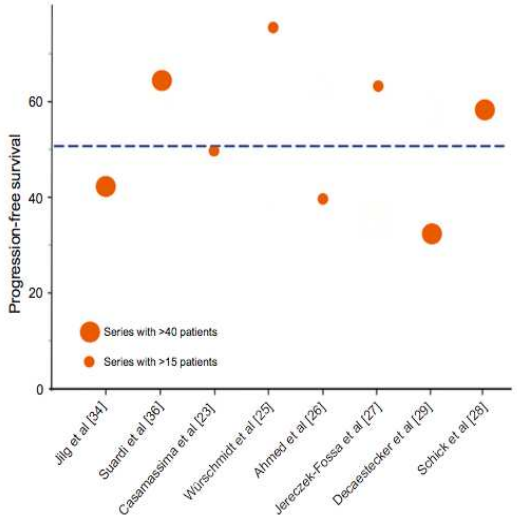


Fig. 2 – Progression-free survival in patients with oligometastatic prostate cancer recurrence at 1–3 yr of follow-up for studies with >15 patients. Dotted line represents mean proportion of patients who were progression free at the reported time point, weighted for the total number of patients.

Table 1 – Full-text publications of metastasis-directed therapy for oligometastatic prostate cancer recurrence included in the systematic review

Study	[redacted]	[redacted]	Median time to metastatic recurrence, mo	Median PSA at time of metastasis	[redacted]	[redacted]	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	Median not reached; 3-yr PFS: 58.6%	49 (98)	12 mo	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	19 mo	35 (70)	1 mo	None
Picchio et al. [30]	83	83/0/0	NR	2.6	Choline PET/CT	HRT	22	NR	58 (70)	NR	77 (93)
Rinnab et al. [31]	15	15/0/0	NR	1.98	Choline PET/CT	LND	13.7*	NR	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)

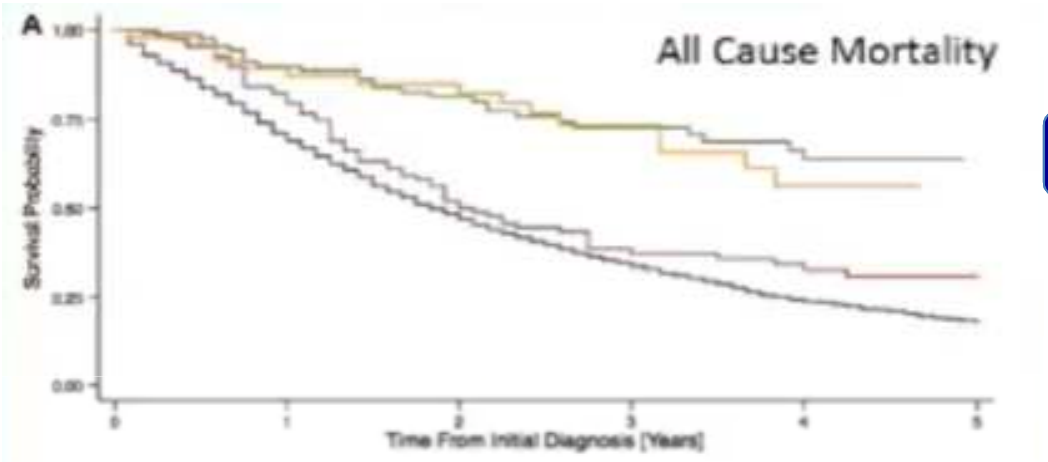
ADT = androgen-deprivation therapy; CT = computed tomography; FDG = fluorodeoxyglucose; HRT = hypofractionated radiotherapy; LND = lymph node dissection; MDT = metastasis-directed therapy; MRI = magnetic resonance imaging; NA = not applicable; NR = not reported; NRT = normofractionated radiotherapy; 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.

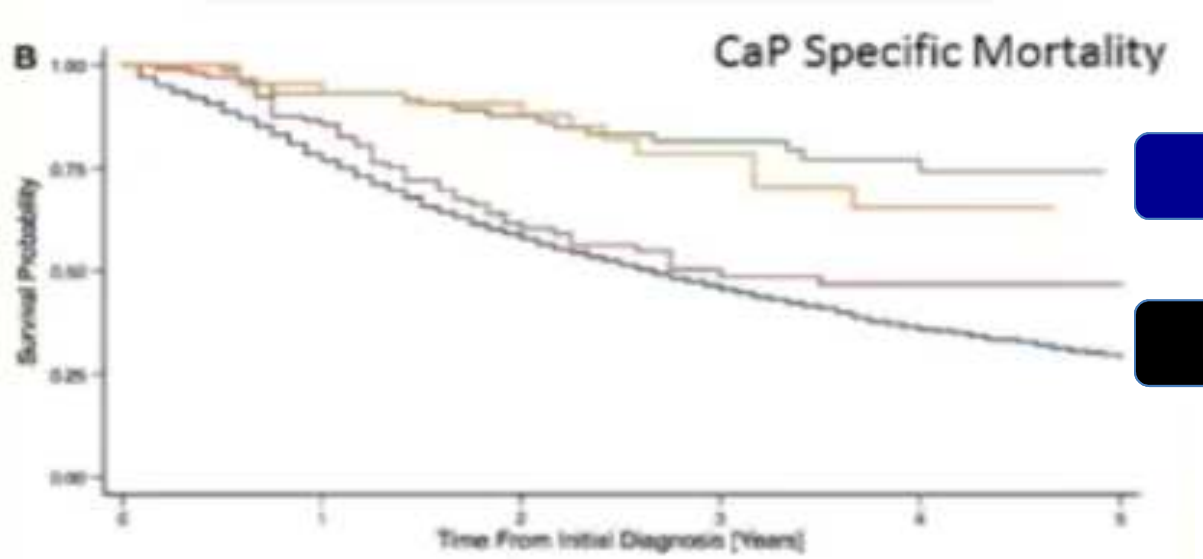
Radical Prostatectomy or External Beam Radiation Therapy vs No Local Therapy for Survival Benefit in Metastatic Prostate Cancer: A SEER-Medicare Analysis

Raj Satkunasivam,* Andre E. Kim, Mihir Desai, Mike M. Nguyen, David I. Quinn, Leslie Ballas, Juan Pablo Lewinger, Mariana C. Stern, Ann S. Hamilton, Monish Aron and Inderbir S. Gill



RP & IMRT

No LT & RT



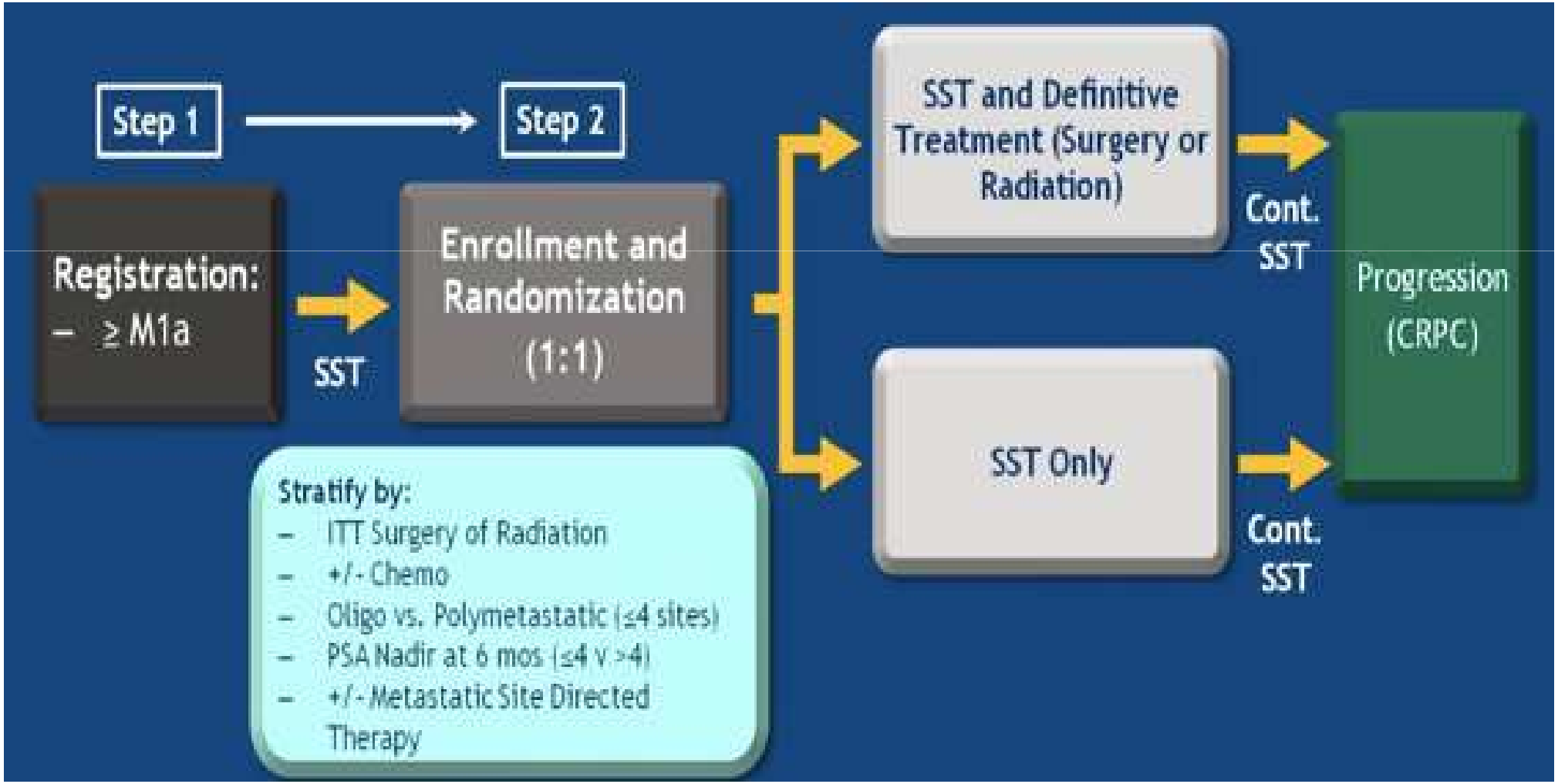
RP & IMRT

52% vs 62%

No LT & RT

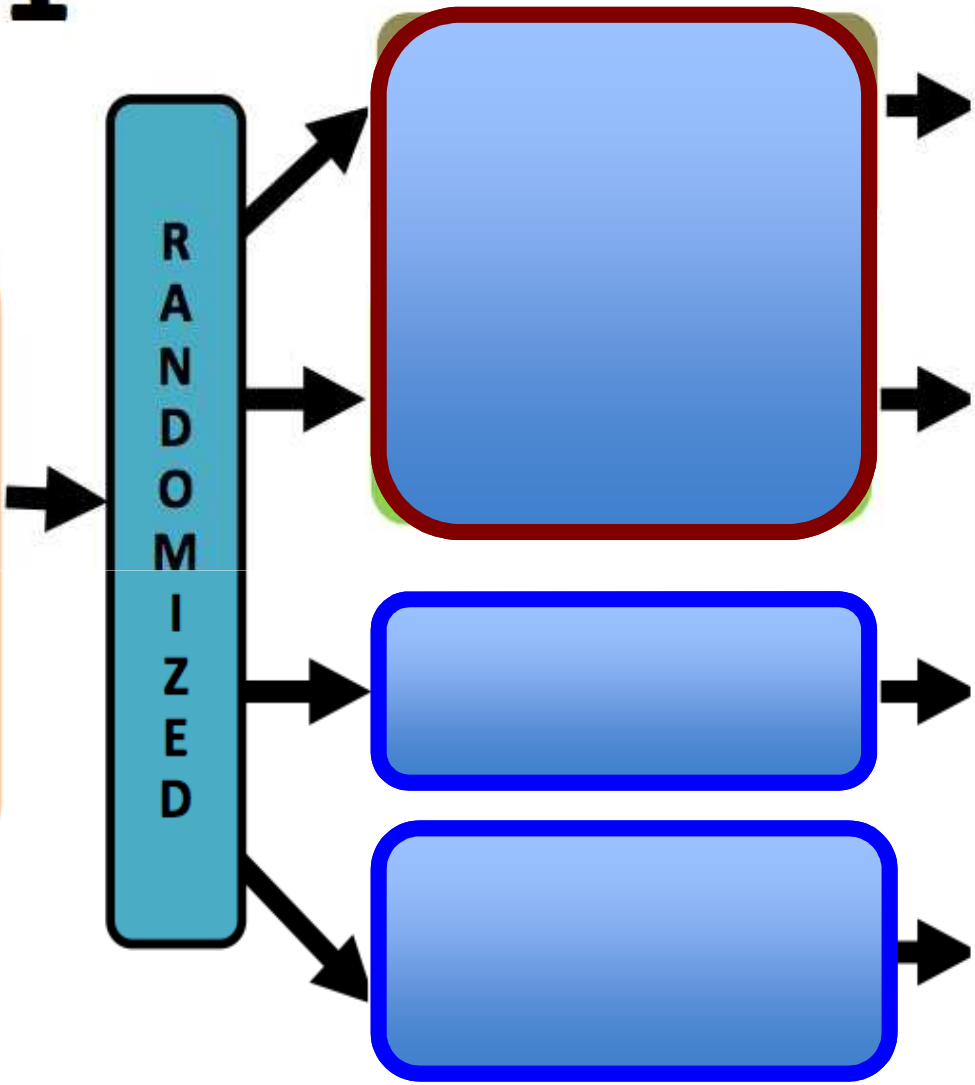
SWOG 1802

Systemic Therapy +/- Local Therapy (RP or RT)



PEACE-1

- Patients with newly diagnosed (hormone naïve) metastatic CaP
- 916 patients planned



Co-primary endpoints: OS and PFS (HR: 0.75)

Results from Phase 2&3 RCTs

- ORIOLE
- STOMP
- GETUG 07
- **COMET**
- **HORRAD**
- **STAMPEDE**

2017/8 Years

Phase 3 RCTs

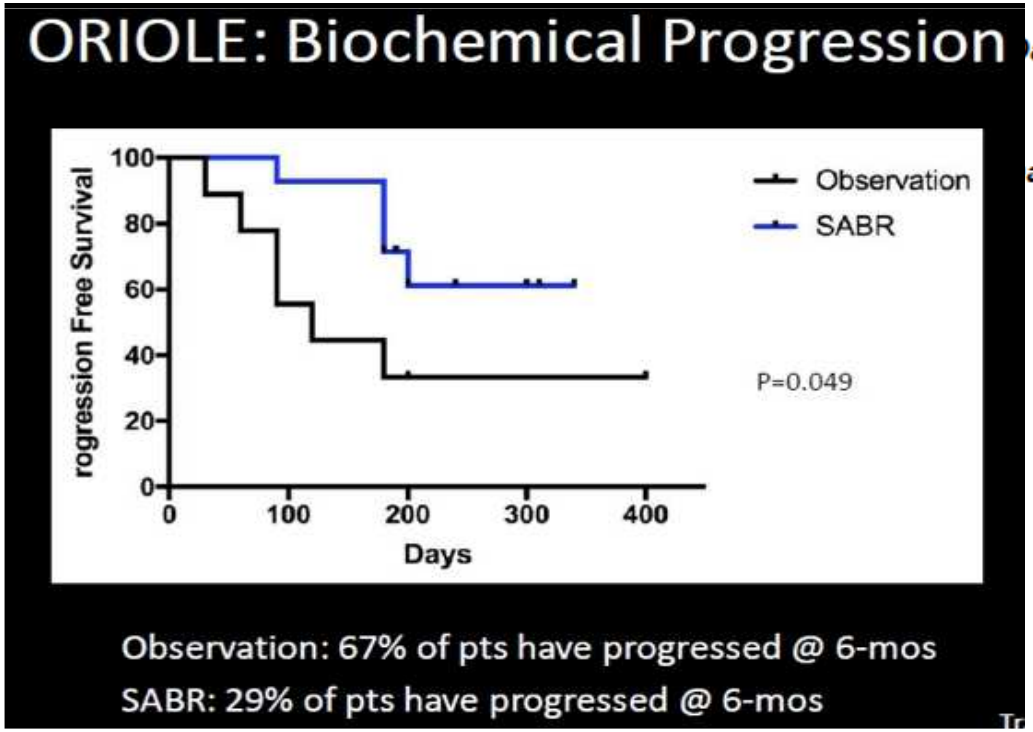
Radwan et al. BMC Cancer (2017) 17:453
DOI 10.1186/s12885-017-3455-6

BMC Cancer

STUDY PROTOCOL Open Access

A phase II randomized trial of Observation versus stereotactic ablative Radiation for OLigometastatic prostate CancEr (ORIOLE)

Noura Radwan[1†], Ryan Phillips[3†], Ashley Ross[2,3], Steven P. Rowe[4], Michael A. Gorin[3], Emmanuel S. Antonarakis[2], Curtiland Deville[1,2], Stephen Greco[1], Samuel Denmeade[2,3], Channing Paller[2], Daniel Y. Song[1,2,3], Maximilian Diehn[5], Hao Wang[3], Michael Carducci[2,3], Kenneth J. Pienta[2,3], Martin G. Pomper[1,2,3,4], Theodore L. DeWeese[1,2,3], Adam Dicker[6], Mario Eisenberger[2,3†] and Phuoc T. Tran[1,2,3*†]



Schema

Eligibility
≤ 3 metastatic lesions (≤ 5 cm)
Hormone-sensitive
PSADT < 15 months
ECOG ≤ 2

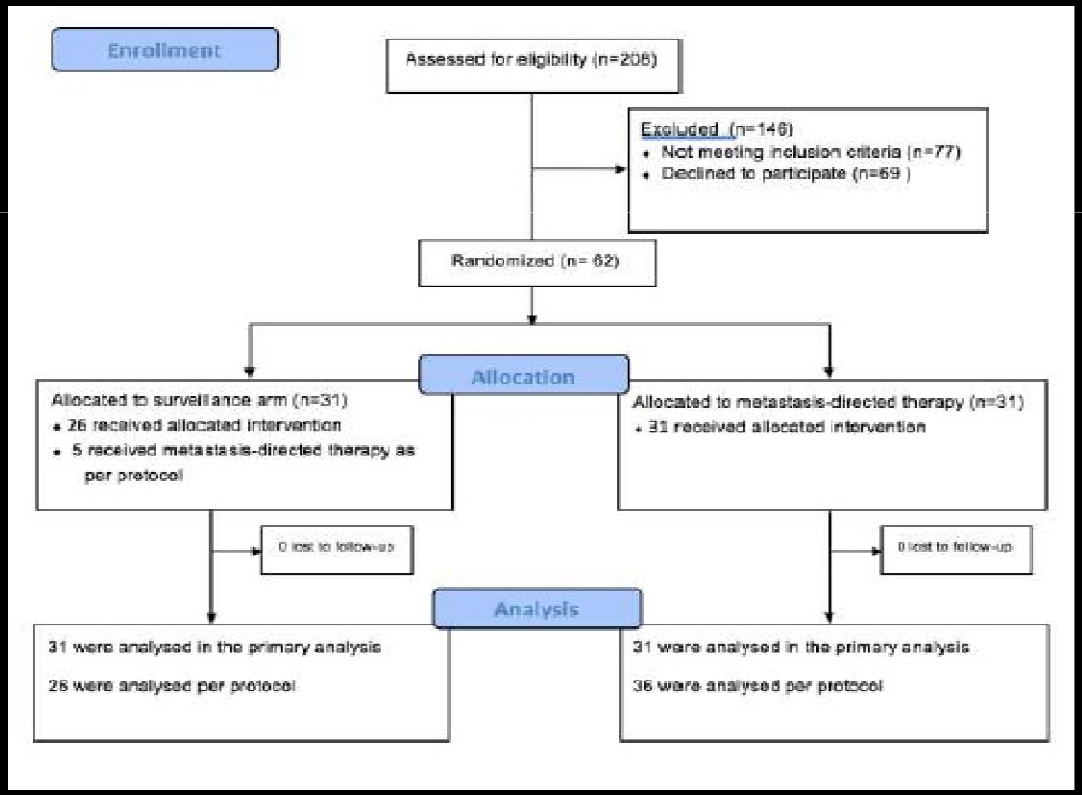
Randomization 1:2
Observation vs. SABR

	Observation	SABR
Day 1:	PSA, LDH, AP, T, ctDNA & rectal swab	DCFPyL-PET/CT PSA, LDH, AP, T, CTC/ctDNA assays, PBMC (ImmunoSEQ) & rectal swab
Days 1-30:	*Observation*	*SABR*
ay 90:	PSA, LDH, AP, T & ctDNA	PSA, LDH, AP, T, ctDNA, & PBMC (ImmunoSEQ)
ay 180:	Bone scan, CT PSA, LDH, AP, T & ctDNA	Bone scan, DCFPyL-PET/CT PSA, LDH, AP, T, CTC/ctDNA assays

Patients progressing on observation can be crossed over off-protocol to receive SBRT

Surveillance or metastasis-directed Therapy for OligoMetastatic Prostate cancer recurrence (SORT): 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[10], Nicolaas Lumen[1] and Piet Ost[2*]



55% Nodal
45% Bone

55% Nodal
45% Bone

Endpoint

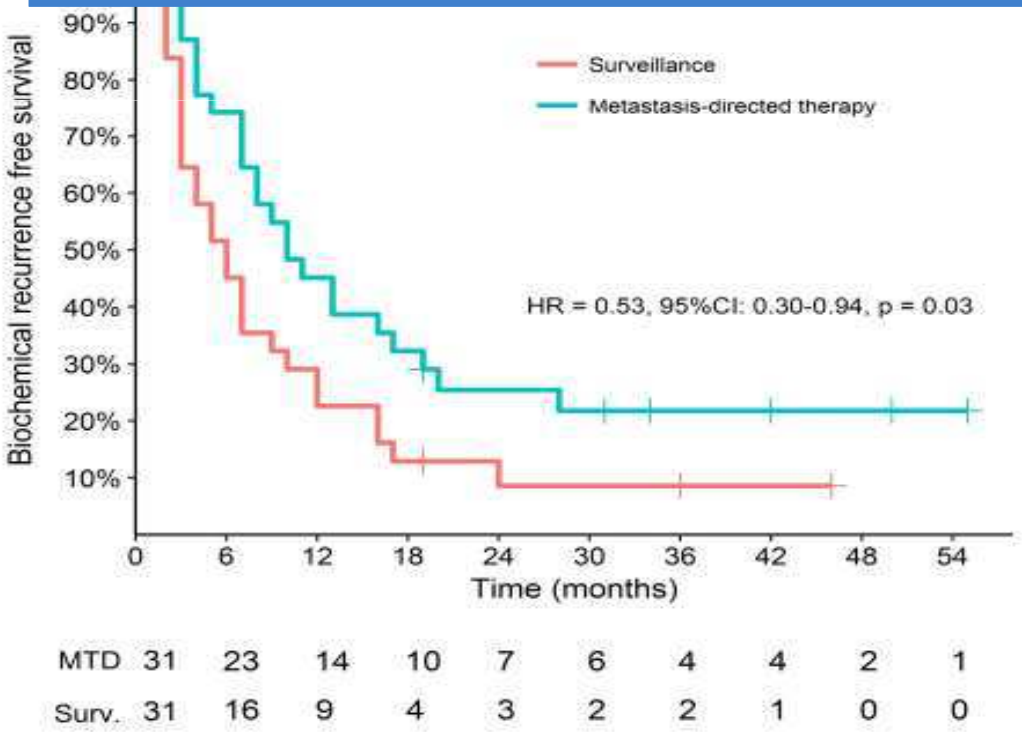
Survival Time without ADT

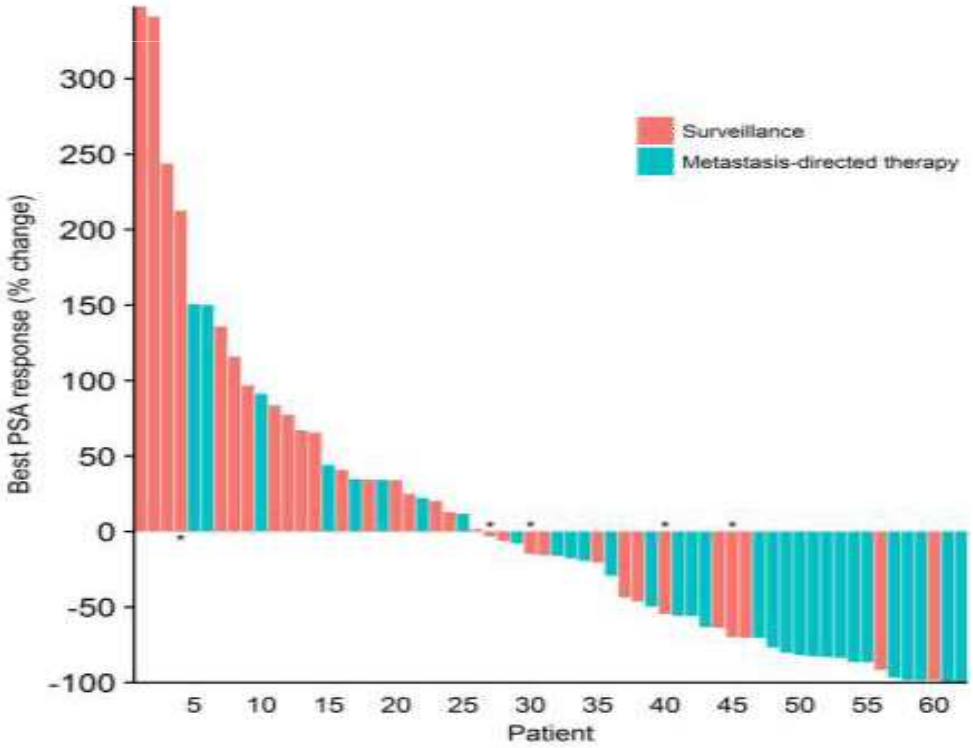
Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial.

Ost P. et J Clin Oncol. 2017 Dec 14:JCO2017754853

ADT Free-Survival

STOMP Trial



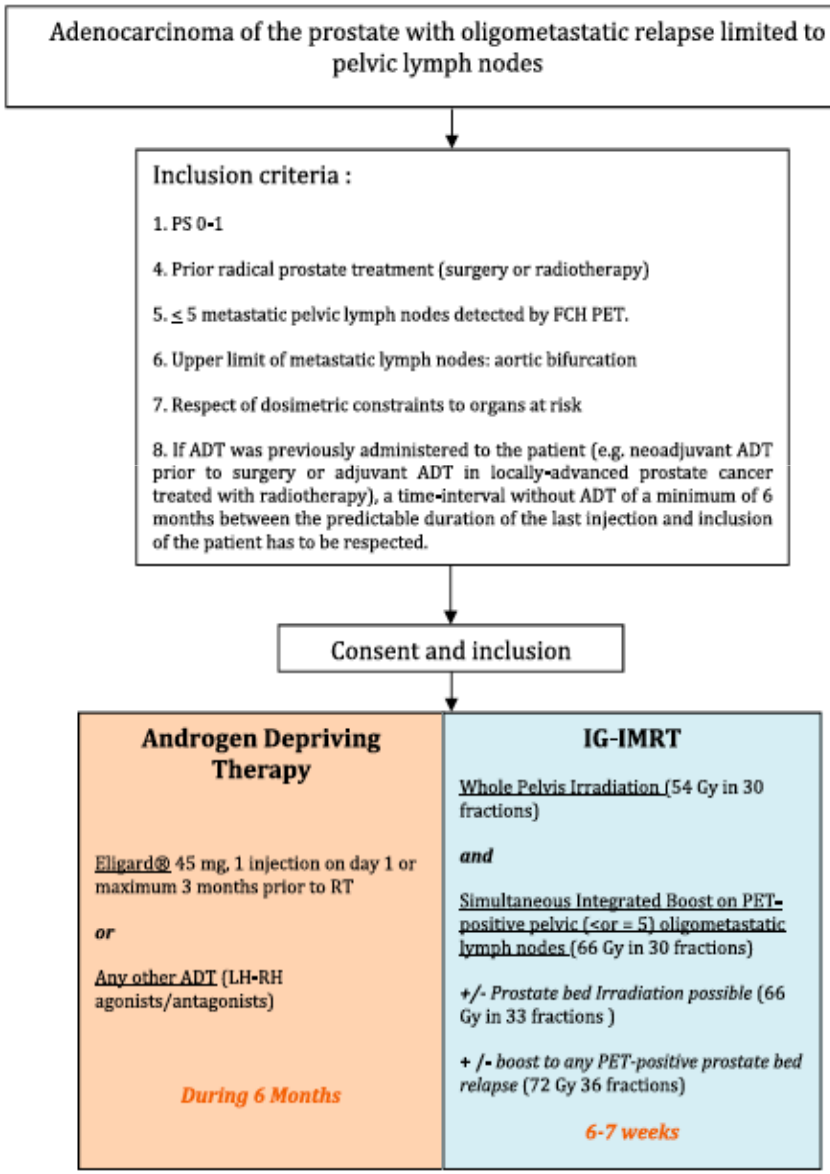


STUDY PROTOCOL Open Access

OLIGOPELVIS – GETUG P07: a multicentre phase II trial of combined salvage radiotherapy and hormone therapy in oligometastatic pelvic node relapses of prostate cancer

Stephane Supiot[1,2*], Emmanuel Rio[1], Valérie Pacteau[3], Marie-Hélène Mauboussin[3], Loïc Campion[2,4] and François Pein[3]

GETUG P 07



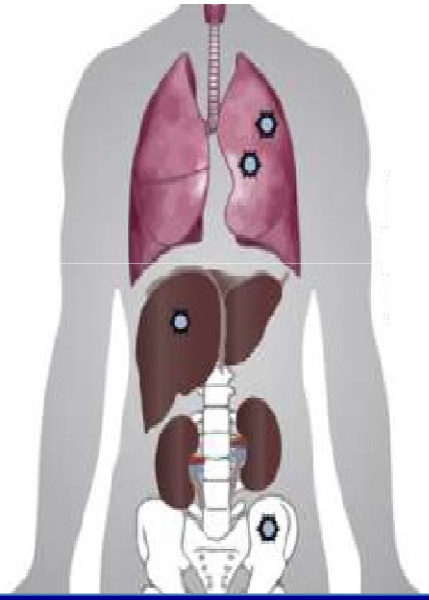
Manuscript

THE LANCET

In Press

RCT 2 Faza; 2012 - 2016

ASTRO 2018



Stereotactic Radiation for the Comprehensive Treatment of Oligometastatic Cancers – Results of a Randomized Study

D. Palma, R. Olson, S. Harrow, S. Gaede, A. Louie, C. Haasbeek, L. Mulroy, M. Lock, G. Rodrigues, B.

1 : 2

Standard of Care vs. Standard of Care + SBRT (METS)

SABR Details

- Number of fractions dependent on tumor size and location
  - Lung: 54/3, 55/5, 60/8
  - Bone: 35/5, 30/3, 16-20/1
  - Brain: SRS (18-24/1) or SABR (40/5), WBRT optional
  - Liver: 45-60 Gy in 3-8
  - Adrenal: 60/8

- Normal tissue tolerances not to be exceeded
  - PTV coverage compromised wherever needed

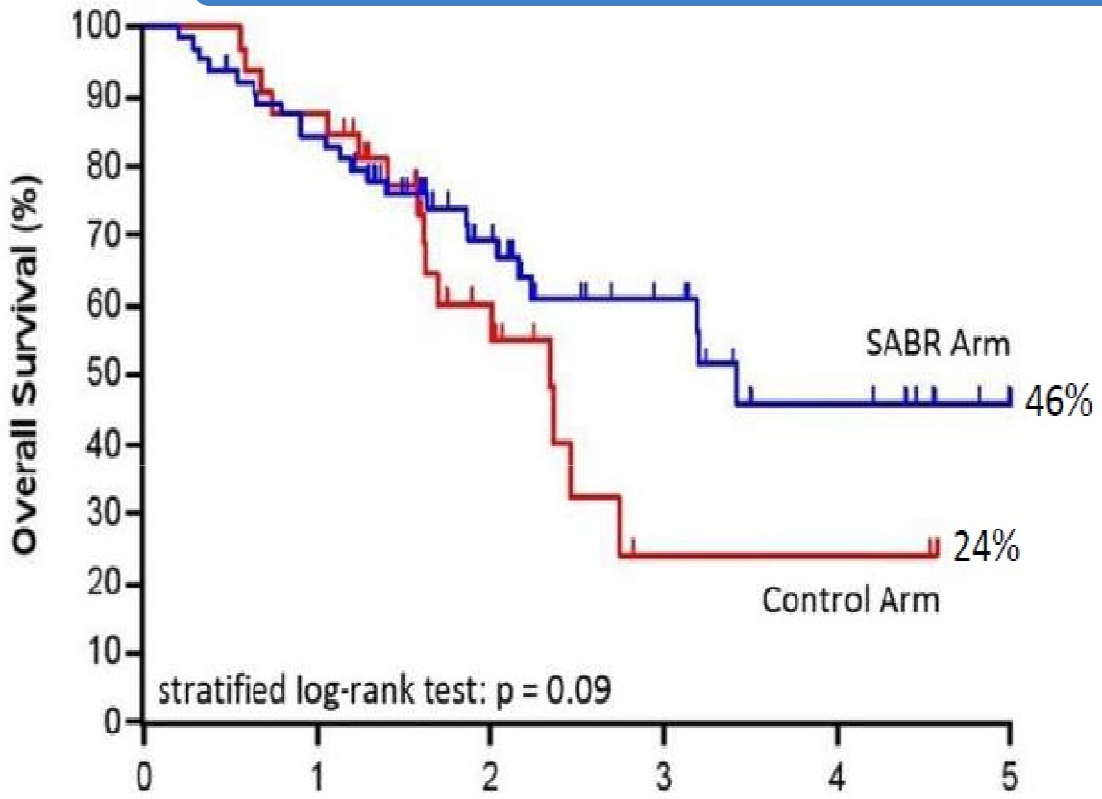
Baseline Characteristics

Between February 2012 and August 2016, 99 patients were randomized at centres in Canada, Scotland, Netherlands and Australia

Characteristic	All Patients (n=99)	Control Arm (n=33)	SABR Arm (n=66)	p-value
Age – median, (min, max)	68 (43, 89)	69 (44, 87)	67 (43, 89)	0.494
Sex – n(%)				0.772
Male	59 (59.6)	19 (57.6)	40 (60.6)	
Female	40 (40.4)	14 (42.4)	26 (39.4)	
Site of Original Primary Tumor – n(%)				0.204
Breast	18 (18.2)	5 (15.2)	13 (19.7)	
Colorectal	18 (18.2)	9 (27.3)	9 (13.6)	
Lung	18 (18.2)	6 (18.2)	12 (18.2)	
Prostate	16 (16.2)	2 (6.1)	14 (21.2)	
Other	29 (29.3)	11 (33.3)	18 (27.3)	

Overall Survival

„we are suprised, we did not expect survival benefit”



Median OS

Control Arm
(95% CI: 19-33 months)

SABR Arm
(95% CI: 26 months to ‘not reached’)

Progression Free Survival

12 msc (SABR) v. 6 msc (No SABR), p=0.001

EURURO-8015; No. of Pages 9
ARTICLE IN PRESS
EUROPEAN UROLOGY XXX (2018) XXX–XXX

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Prostate Cancer
Editorial by XXX on pp. x–y of this issue

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

AUA 2018

2004 – 2014

446 patients
M1 bone

Random

N=223

ADT

N= 223

ADT + **RT 70 Gy**
Prostate Only

	ADT + radiotherapy (n = 216)[a]	ADT alone (n = 216)[a]
Age (range), yr.	67 (62–71)	67 (61–71)
PSA concentration at start of ADT, ng/ml		
Median (range).	125 (8–14 000)	149 (4–6991)
Q1	48	50
Q3	433	483
Missing data	3 (1)	5 (2)
ALP		
≤ULN	133 (61)	141 (65)
>ULN	51 (24)	54 (25)
Missing data	32 (15)	21 (10)
LDH		
		95 (44)
		69 (32)
		52 (24)
		7 (3)
		64 (30)
		65 (30)
		72 (33)
		7 (3)
		1 (1)
		5 (3)
		20 (9)
3	125 (58)	128 (59)
4	51 (24)	59 (27)
Missing data	0	4 (2)
Osseous metastases		
<5 lesions	89 (41)	71 (33)
5–15	53 (25)	65 (30)
>15	74 (34)	80 (37)
WHO performance status[c]		
0	187 (87)	176 (82)
1	22 (10)	31 (14)
2	4 (2)	6 (3)
3	3 (1)	3 (1)
Pain score[d]		
0	140 (65)	139 (65)
1	39 (18)	34 (16)
2	18 (8)	18 (8)
3	3 (1)	3 (1)
4	16 (8)	22 (10)

Polymetatases !!!

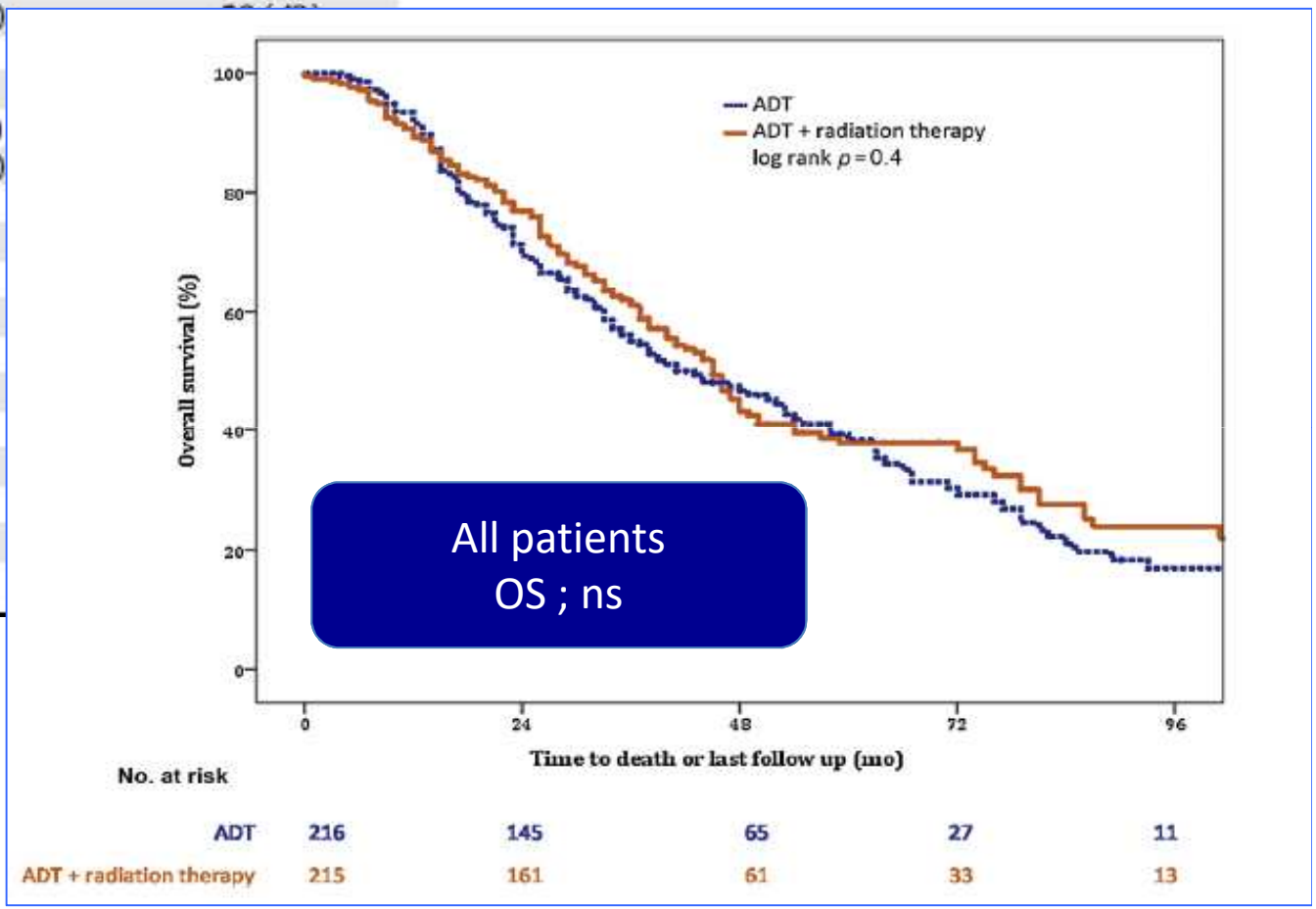
PSA 142 ng/ml

T4 25%

METS > 5-15 25%

> 15 35%

	ADT + radiotherapy (n = 131)[a]	ADT alone (n = 139)[a]
Time (range) to initiation of subsequent therapy, mo.	17 (12–25)	14 (10–30)
Any anticancer therapy	64 (49)	66 (48)
Missing data	2 (1)	2 (1)
Docetaxel	60 (46)	
Cabazitaxel	12 (9)	
Enzalutamide	11 (8)	
Abiraterone	23 (18)	
Other systemic treatment	13 (10)	
Estracyt	2	
Mitoxantrone	3	
Orteronel	2	
Carboplatin	2	
Denosumab	1	
Ipilimumab	0	
Cabozantinib	0	
Cisplatinum	1	
Olaparib	1	
Pembrolizumab	1	
RA[223]	4 (3)	

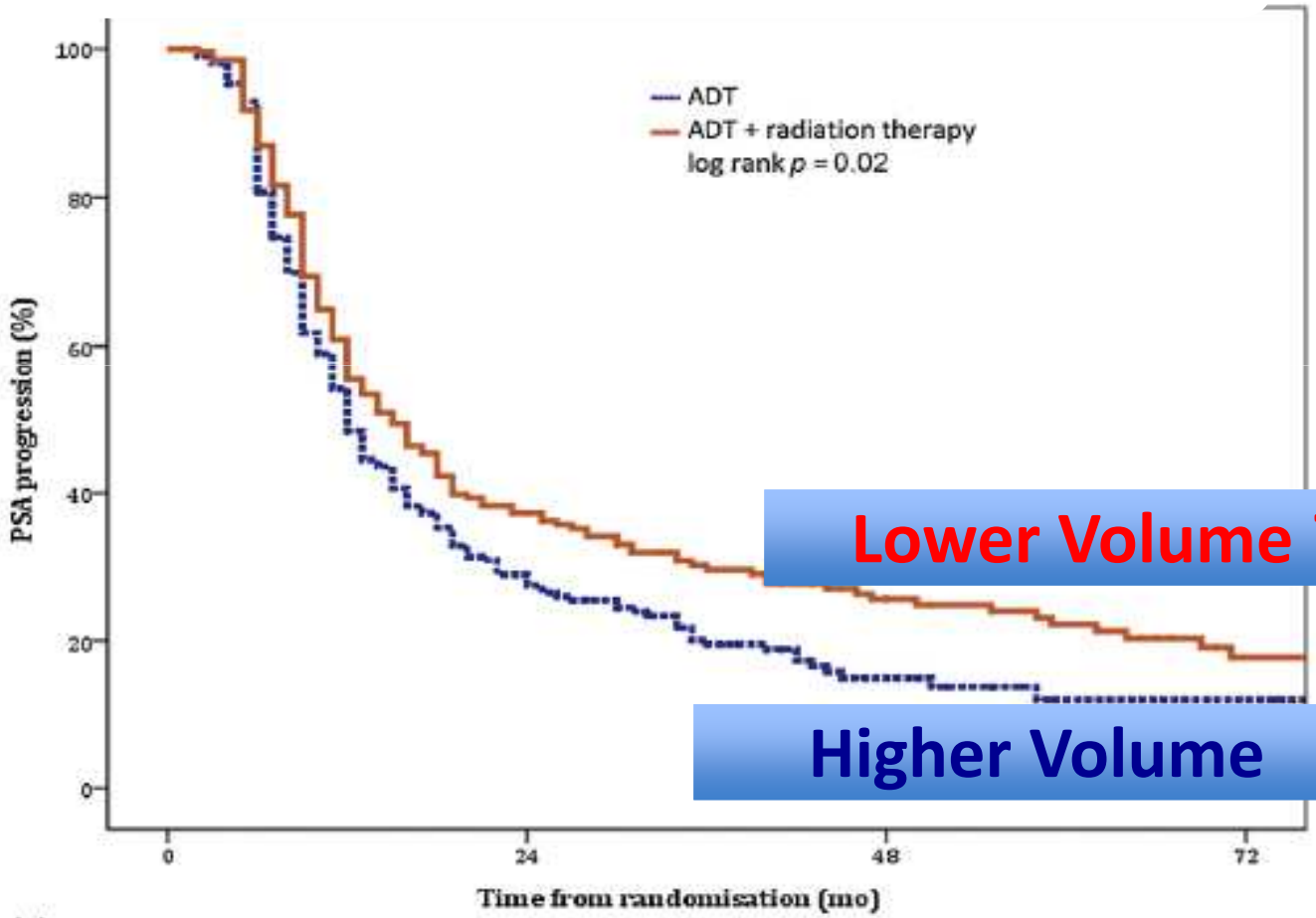


All patients
OS ; ns

Survival Time without PSA Progression

Subgroup Analysis

PSA < 145 ng/ml, GS <=8, Mets < 5

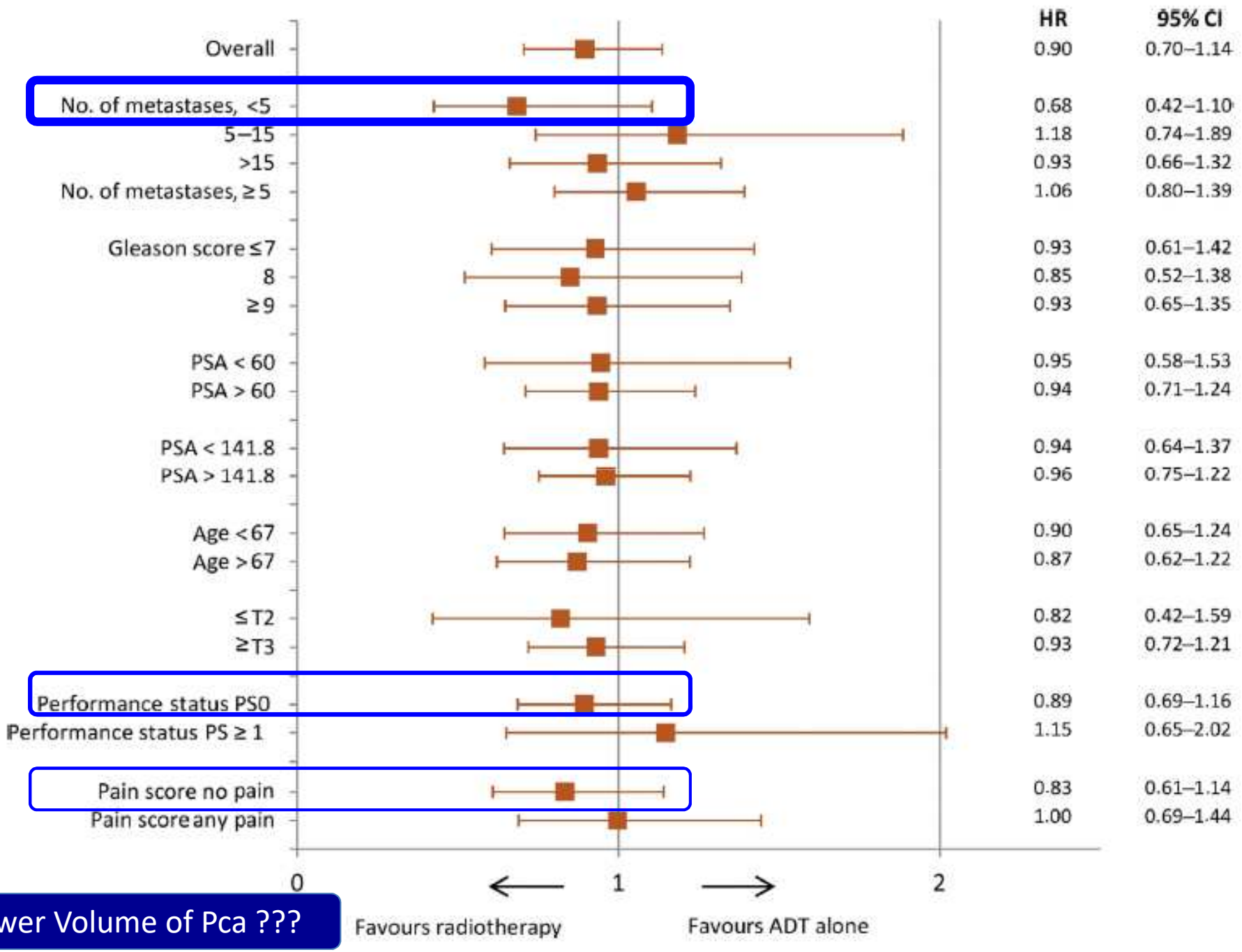


Lower Volume ????

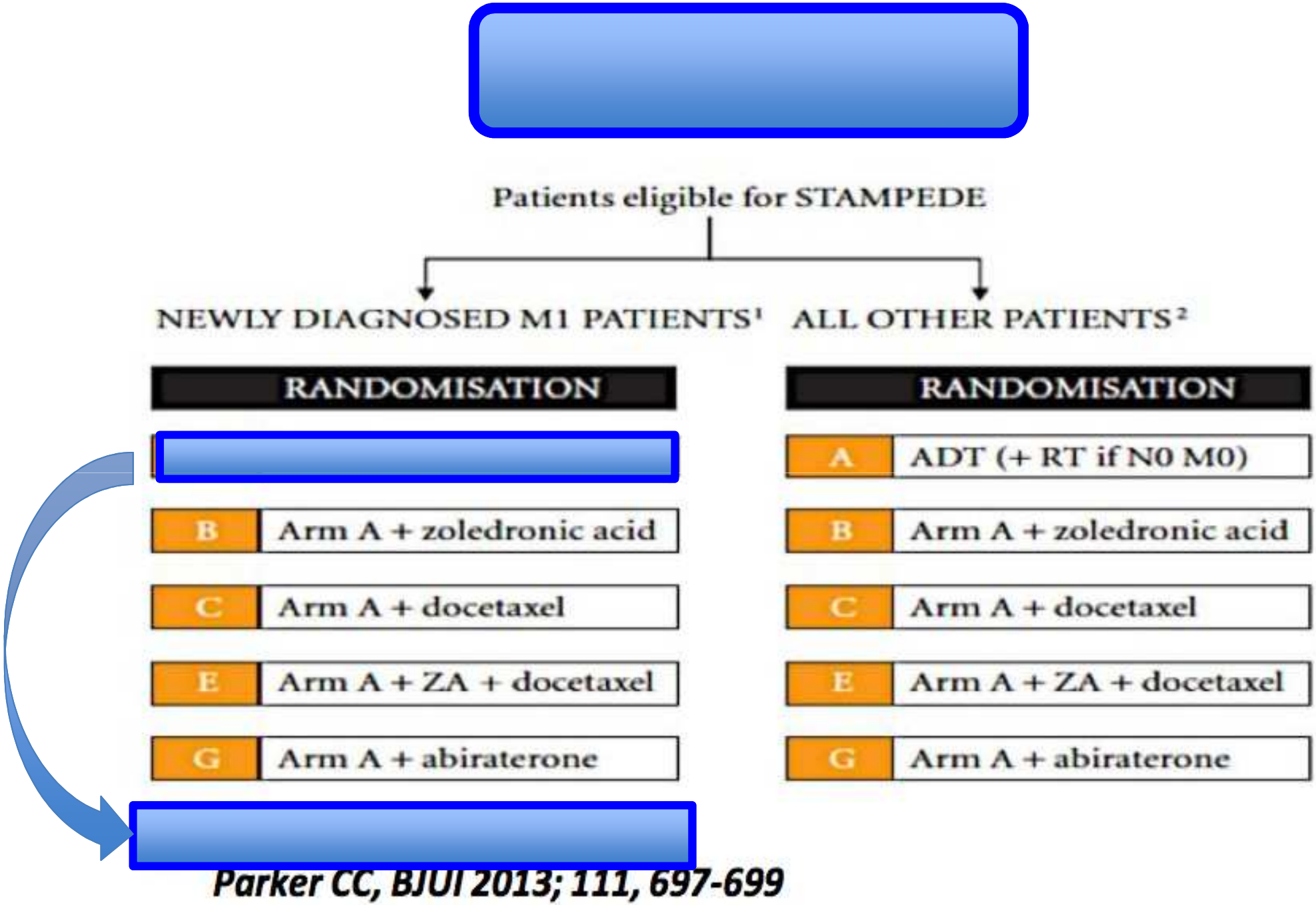
Higher Volume

No. at risk

ADT	214	56	14	5
ADT + radiation therapy	210	72	32	13



Lower Volume of Pca ???



Parker CC, BJUI 2013; 111, 697-699

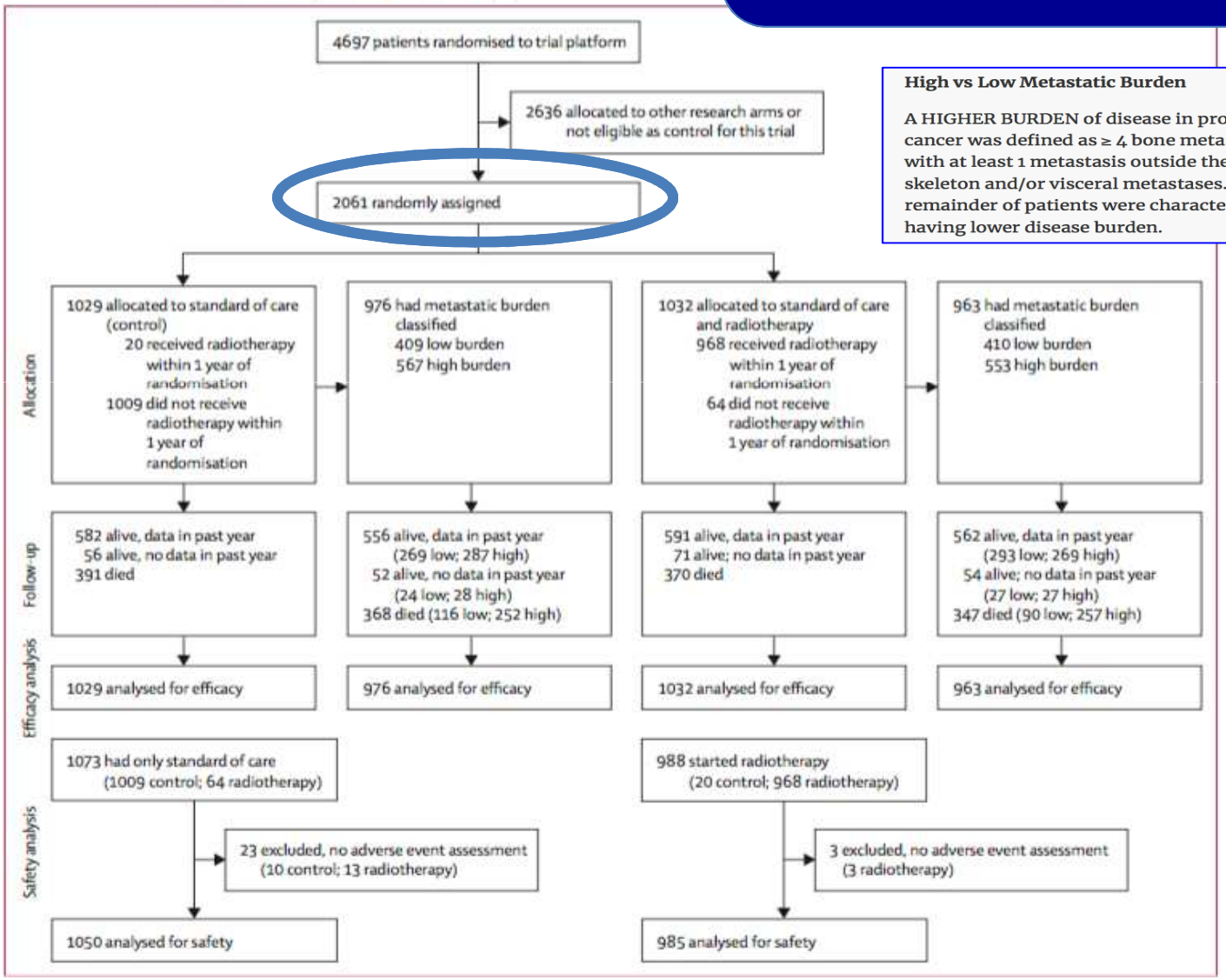
Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial

Christopher C Parker, Nicholas D James, Christopher D Brawley, Noel W Clarke, Alex P Hoyle, Adnan Ali, Alastair W S Ritchie, Gerhardt Attard, Simon Chowdhury, William Cross, David P Dearnaley, Silke Gillessen, Clare Gilson, Robert J Jones, Ruth E Langley, Zafar I Malik, Malcolm D Mason, David Matheson, Robin Millman, J Martin Russell, George N Thalmann, Claire L Amos, Roberto Alonzi, Amit Bahl, Alison Birtle, Omar Din,

www.thelancet.com Published online October 21, 2018 http://dx.doi.org/10.1016/S0140-6736(18)32486-3

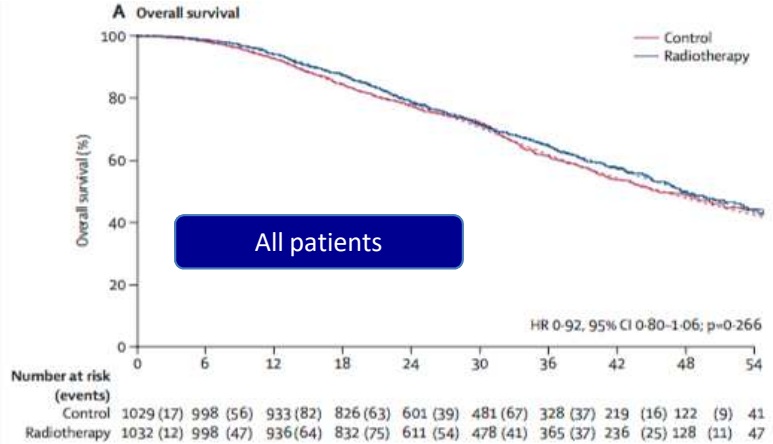
STANDARD OF CARE (ADT +/-CT)

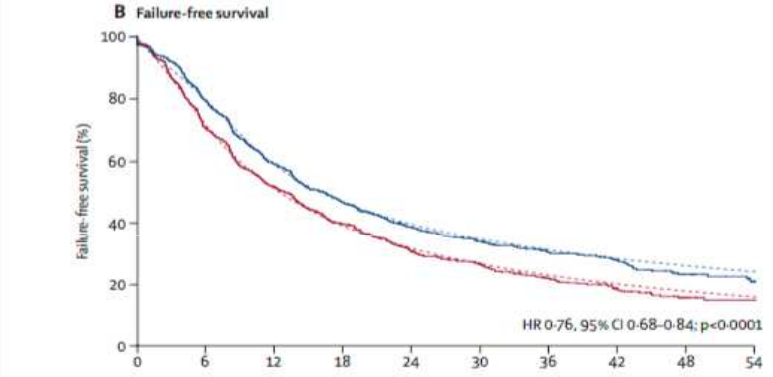
STANDARD OF CARE (ADT +/-CT) + RT PROSTATE
36 GY/6 fx lub 55 Gy/20 fx



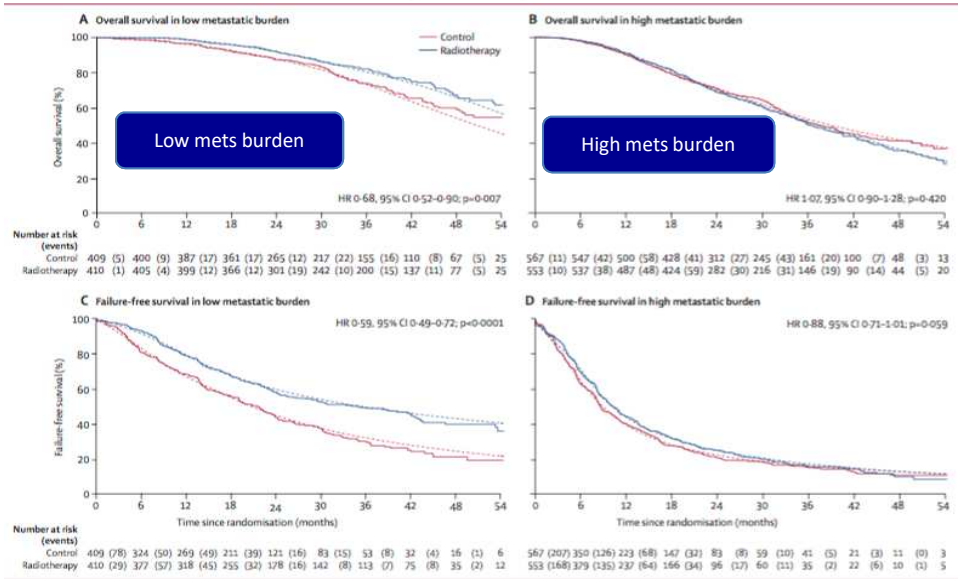
High vs Low Metastatic Burden

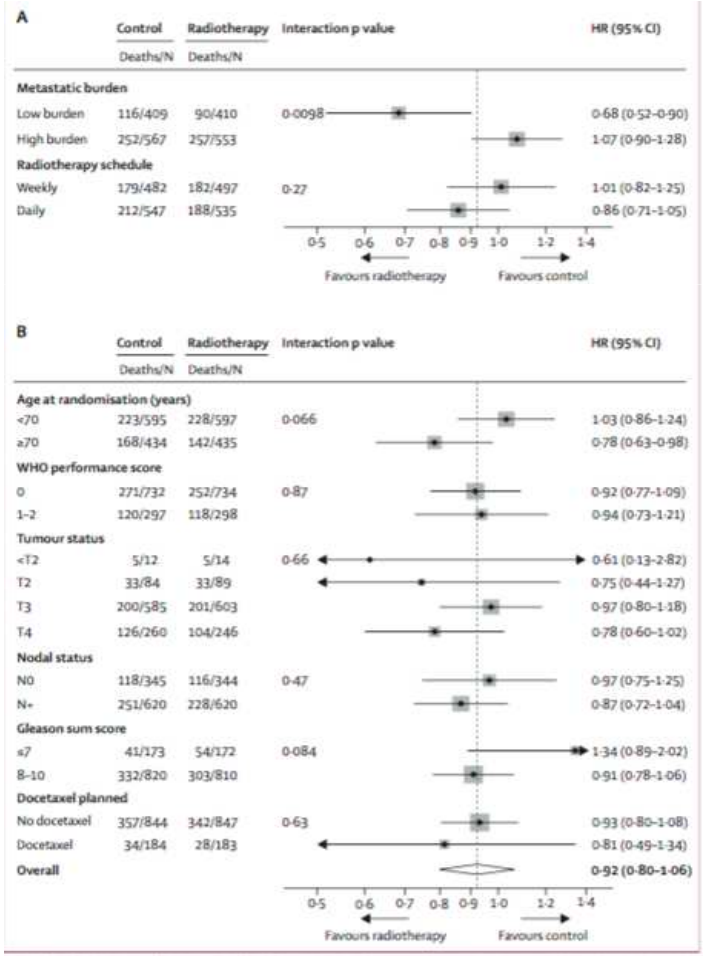
A HIGHER BURDEN of disease in prostate cancer was defined as ≥ 4 bone metastases, with at least 1 metastasis outside the axial skeleton and/or visceral metastases. The remainder of patients were characterized as having lower disease burden.





	Adjusted hazard ratio (95% CI)	Survival at 3 years*		Restricted mean survival time (months)*		
		Control	Radiotherapy	Control	Radiotherapy	Difference (95% CI)
Overall survival						
All patients	0·92 (0·80–1·06)	62%	65%	41·6	42·5	1·0 (−0·6 to 2·5)
Low metastatic burden	0·68 (0·52–0·90)	73%	81%	45·4	49·1	3·6 (1·0 to 6·2)
High metastatic burden	1·07 (0·90–1·28)	54%	53%	38·8	37·6	−1·2 (−3·5 to 1·1)
Failure-free survival						
All patients	0·76 (0·68–0·84)	23%	32%	21·4	26·2	4·8 (2·8 to 6·7)
Low metastatic burden	0·59 (0·49–0·72)	33%	50%	27·4	36·1	8·6 (5·6 to 11·7)
High metastatic burden	0·88 (0·77–1·01)	17%	18%	17·3	18·8	1·5 (−0·7 to 3·6)





ESMO 2018

"We think these are robust and reliable findings. Going forward, prostate radiation should be a standard treatment option for men with newly diagnosed metastatic prostate cancer and low metastatic disease burden. Furthermore, we believe the results can be extrapolated to men with pelvic nodal disease alone, for whom androgen-deprivation therapy alone is no longer adequate treatment."

Table 5. Summary of Clinical Trials Investigating Treatment of Oligometastatic Prostate Cancer

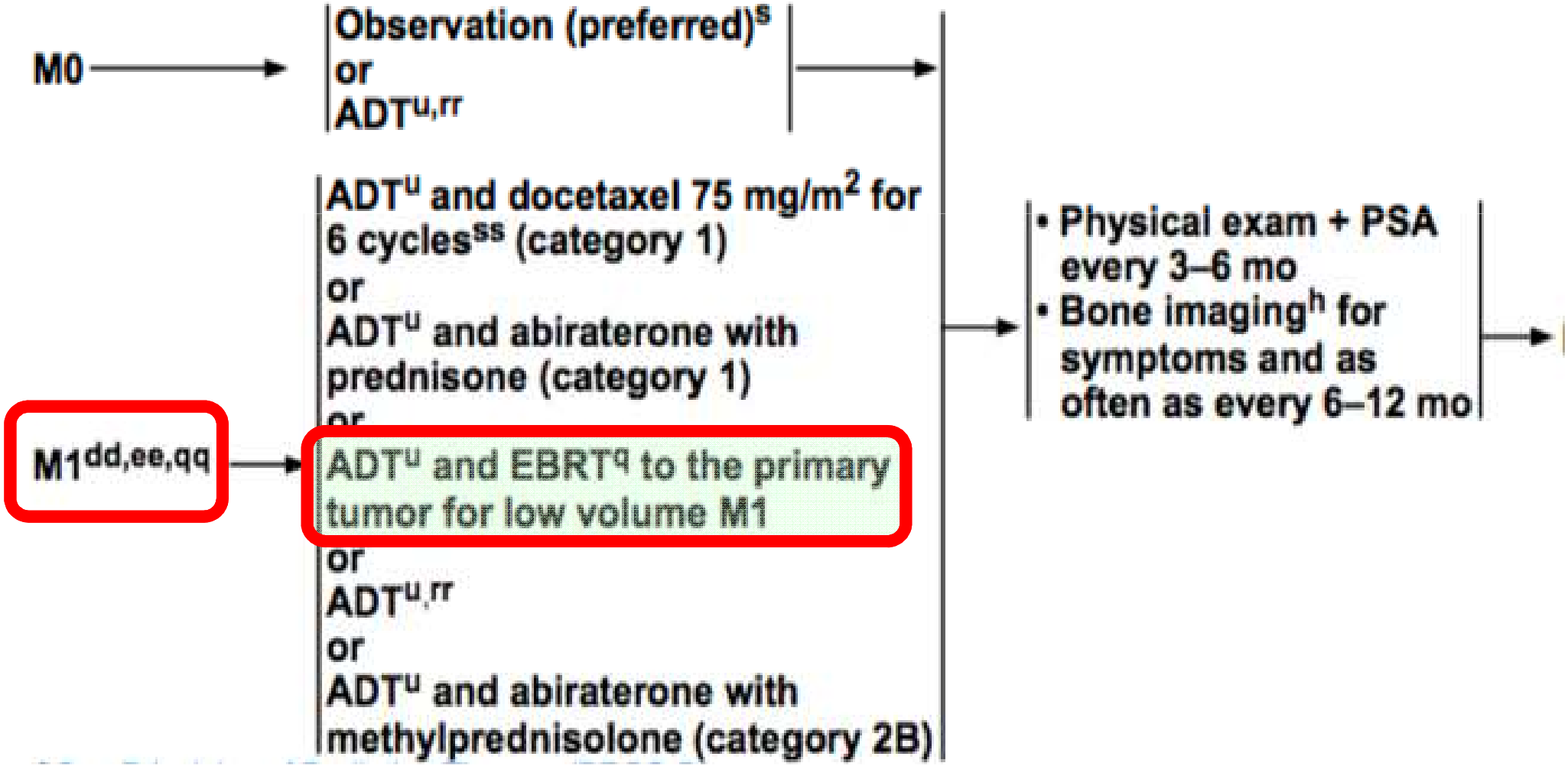
Identifier	Trial title	Number of metastasis	Sites of metastasis
Surgery			
NCT02136721[32]	Local treatment with radical prostatectomy for newly-diagnosed metastatic prostate cancer	NR	N1, M1
NCT02458716[33]	Feasibility of cytoreductive prostatectomy in men newly diagnosed with metastatic prostate cancer	NR	N1, M1
ISRCTN15704862[34]	Testing radical prostatectomy in men with prostate cancer and oligometastases to the bone: a randomized controlled feasibility trial (TRoM/bone)	≤3	Bone
NCT02454543[11]	Multicenter, prospective, randomized controlled trial comparing radical prostatectomy plus best systemic therapy with best systemic therapy alone in the management of men with pauci-metastatic prostate cancer	≤5	Bone, LN
Radiation therapy			
NCT01345539[11]	Phase II study for curative intent treatment for patients with oligometastatic disease at initial presentation	≤5	NR
NCT01345552[11]	Phase II study of stereotactic radiosurgery for patients with oligo-recurrent disease	≤5	NR
NCT01777802[35]	Observational study of immune responses in prostate, lung, melanoma and breast cancer patients following stereotactic body radiotherapy, intensity modulated radiotherapy, or brachytherapy	≤3	NR
NCT01869322[11]	Phase II stereotactic body radiotherapy and stereotactic hypofractionated radiotherapy for oligometastatic prostate cancer	NR	Any except brain or CNS
NCT02192788[11]	Phase II study of SBRT as treatment for oligometastases in prostate cancer	≤4	Bone, LN
NCT02264379[36]	Effectiveness and toxicity of a percutaneous high-dose radiotherapy in patients with oligometastases of prostate carcinoma	≤5	NR
NCT02563691[37]	Comprehensive stereotactic radiotherapy for oligometastatic prostate cancer: A Phase I/II study	≤5	Outside prostate and pelvic LN
NCT02680587[38]	Phase II randomized observation versus stereotactic ablative radiation for oligometastatic prostate cancer (ORIOLE) trial	≤3	Bone, LN
Systemic therapy/combination therapy			
NCT00268476[11]	STAMPEDE: Systemic therapy in advanced or metastatic prostate cancer: Evaluation of drug efficacy - androgen suppression-based therapy alone or combined with zoledronic acid, docetaxel, prednisolone, celecoxib, abiraterone, enzalutamide and/or radiotherapy, metformin and transdermal estradiol in treating patients with locally advanced or metastatic prostate cancer	NR	N1, M1
NCT00544830[11]	Androgen deprivation and localized radiotherapy to metastases in patients with oligometastatic hormone- sensitive prostate cancer	≤5	N1, M1
NCT01568427[39]	Salvage treatment or active clinical surveillance for oligometastatic prostate cancer: a randomized phase II trial	≤3	N1, M1a/b
NCT01751438[40]	A prospective, multi-institutional, randomized, phase II trial of best systemic therapy or best systemic therapy plus definitive treatment (radiation or surgery) of the primary tumor in metastatic (M1) prostate cancer	NR	Any except brain
NCT01957436[11]	A phase III of ADT +/- docetaxel +/- local RT +/- abiraterone acetate in metastatic hormone-naïve prostate cancer	NR	Outside pelvic LN
NCT02489357[41]	A pilot study of MK-3475 with cryotherapy for men with newly diagnosed oligo-metastatic prostate cancer	≤4	Extrapelvis

CNS, central nervous system; LN, lymph node; NR, not reported.

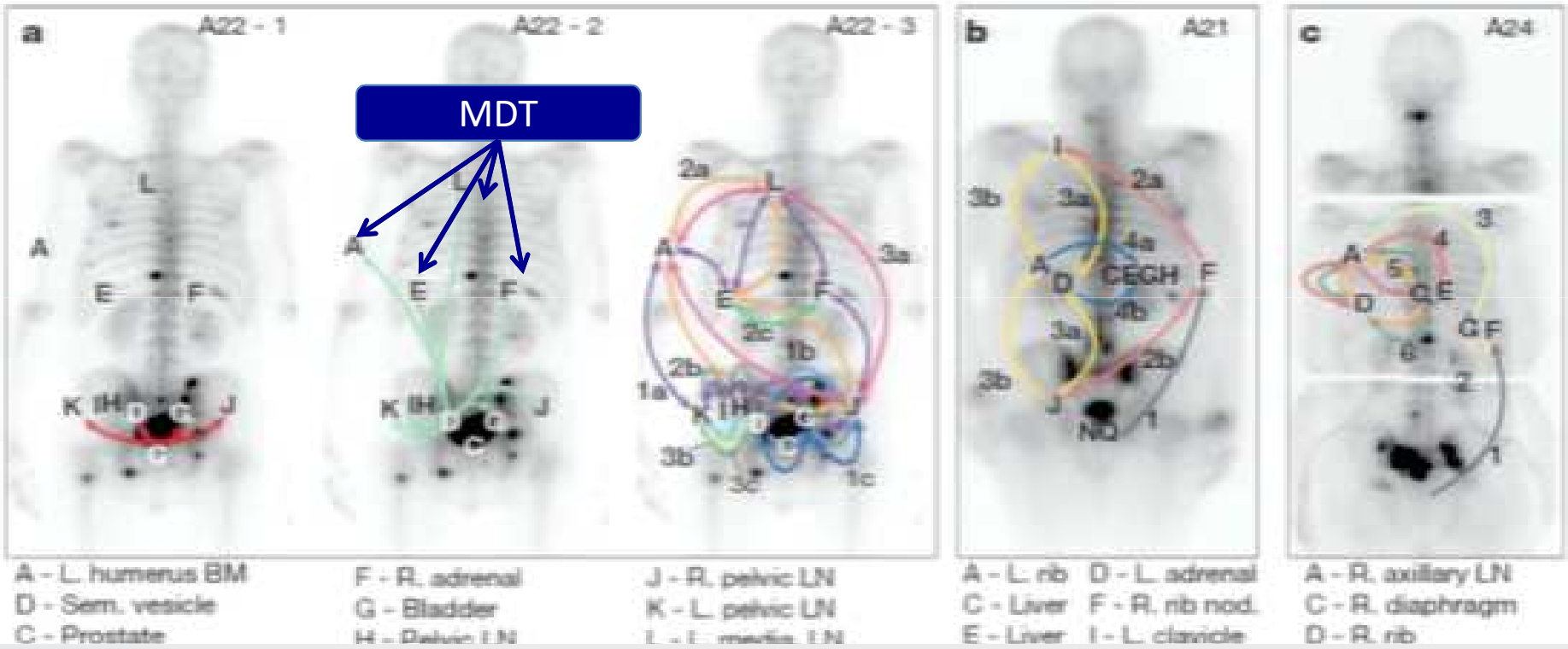
National Comprehensive Cancer Network®

NCCN Guidelines
Prostate Cancer

SYSTEMIC THERAPY FOR CASTRATION-NAIVE DISEASE[jj,pp]



Metastasis to metastasis seeding occur either by linear or by a branching pattern of spread



The evolutionary history of lethal metastatic prostate cancer.
Gundem G. et al. Nature. 2015 Apr 16;520(7547):353-7.

PTRO + PTU + PTO

Polish Study

TROP Trial

ADT + RT/RP of Primary (RTP) only vs. ADT + RTP **+ SBRT to METS**

HSPC with Low Volume Oligomets disease

A Randomized Phase III Trial

comparing Local Ablative Therapy (Surgery or Stereotactic Radiotherapy) plus ADT to Local Ablative Therapy (surgery or stereotactic radiotherapy) plus ADT and Stereotactic Radiotherapy to all sites of metastatic disease for Hormone Sensitive Low volume Oligometastatic Prostate Cancer

Conclusions

- RT of Primary tu plays an important role in Low Volume HSPC – Standard of care

- RT of Distant Mets in Low Volume HSPC

We need RCT

HORRAD TRIAL

- Badano wpływ RT Stercza w grupie Polymets,
- RT na Stercz bardzo niska = mało efektywna,
- Nie stosowano RT Układu chłonnego,
- brak wiedzy o stanie układu chłonnego,
- Przerzuty do kości tylko w oparciu o Sctg,
- Brak wiedzy o przerzutach do narządów trzewnych