wielkopolskie centrum onkologii

Choroba Oligometastatyczna w Raku Gruczołu Krokowego Miejsce Radioterapii i SBRT

Piotr Milecki

Wielkopolskie Centrum Onkologii, Poznań

Katedra Elektroradiologii, UMP, Poznań

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

Solitary Metastases: Philip Rubin and Jerold Green. Springfield, Illinois: Charles C Thomas, 1968. 251 pp. $14.75

Solitary Metastases. Philip Rubin and Jerold Green. Springfield, Illinois: Charles C Thomas, 1968. 251 pp. $14.75

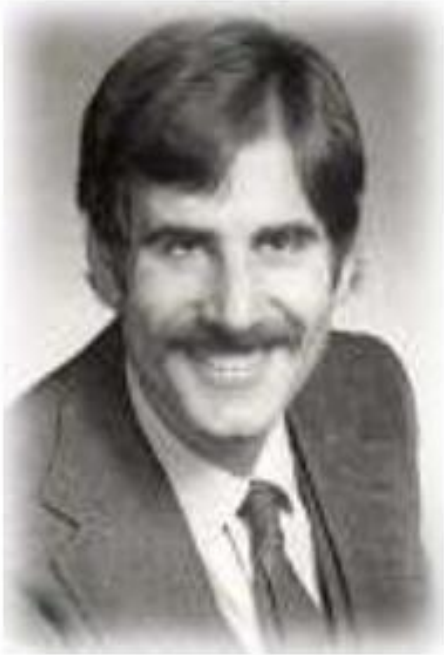
Every physician concerned with the care of patients has been faced with the distressing problem of deciding what to do about a single lesion in the lung, brain, or liver of a patient who has had pr
vious carcinoma elsewhe
and analyzed pertinent
subject and have summ
recommendations in this

While postmortem studies on cancer patients show metastatic disease to be present in the liver in 36% of them and in the lung in 30% of them, successful therapy (long survival after treatment) is accomplished more often in patients with solitary pulmonary metastases than in those patients with solitary metastases of all other sites combined. The longest survival rates occur in patients with solitary pulmonary
metastases from the
genital tract, or larg

occur following therapy for solitary metastases from melanoma, breast, or prostate cancer. The longer the interval (over two years) between treatment for the primary lesion and the discovery of the solitary metastasis, the greater the opportunity for successful therapy.

EDITORIAL

Oligometastases



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

EDITORIAL

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

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

Oligometastatic Disease

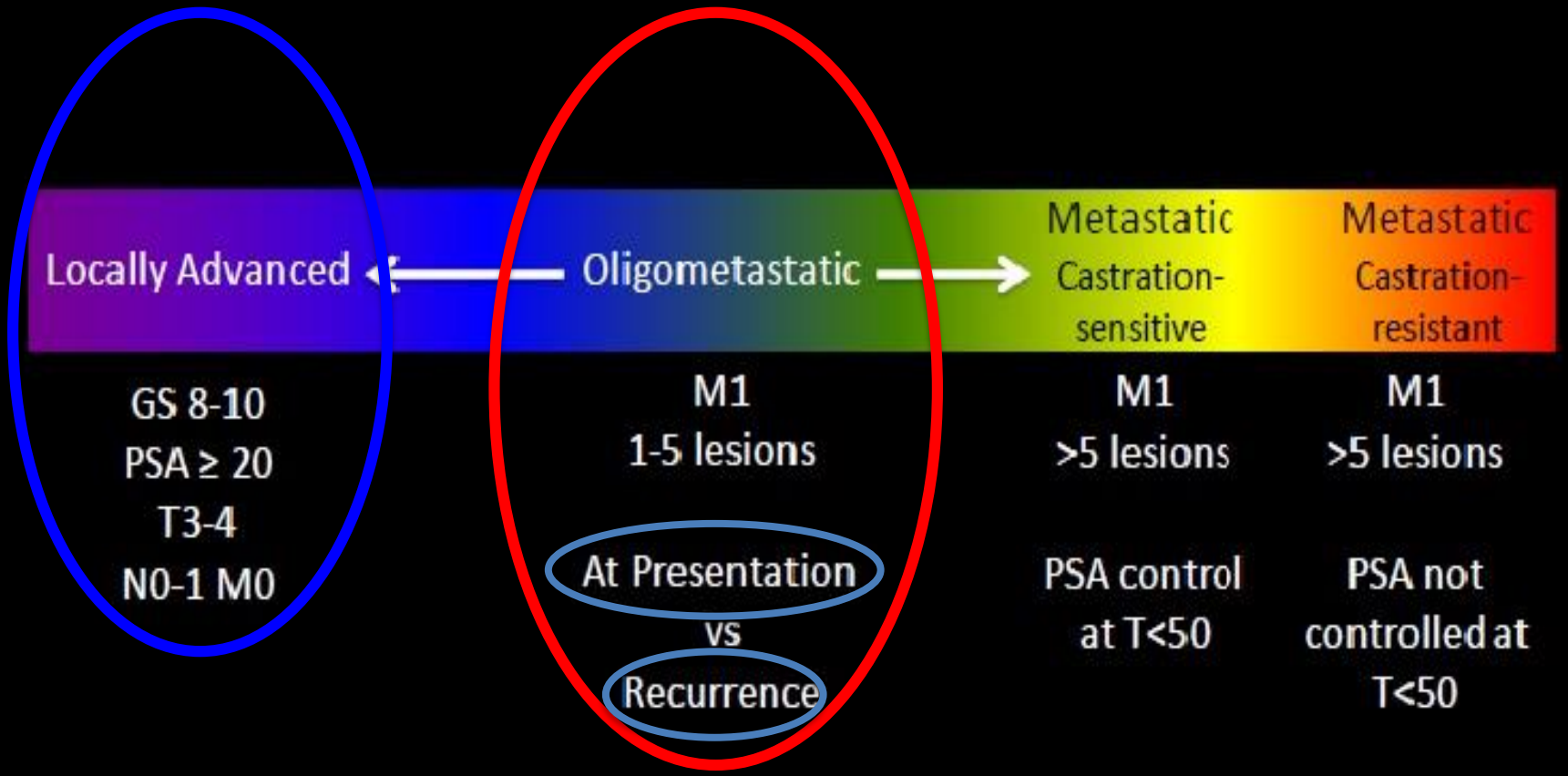
Oligo Latin or Greek = scant or few

Oligometastases = a few metastases

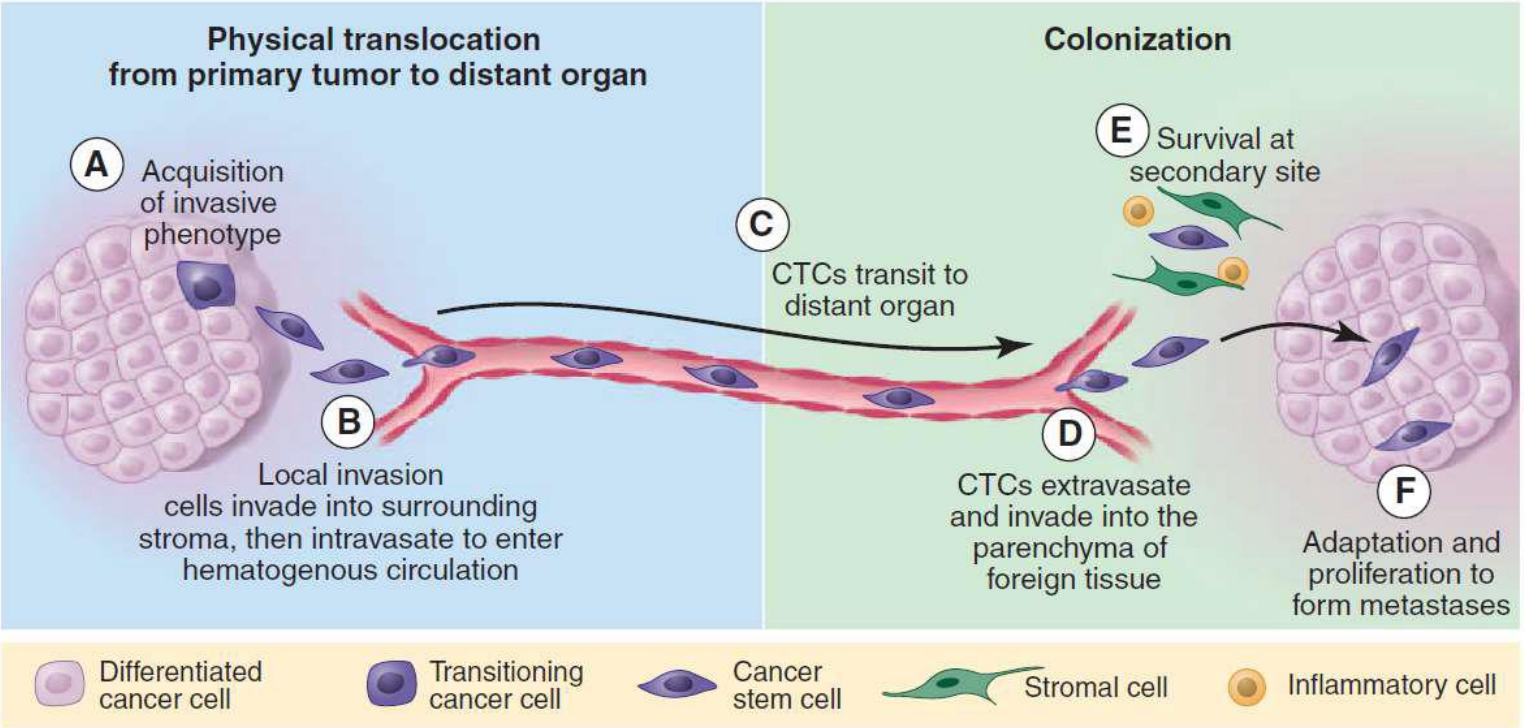
- Hellman S, Weichselbaum RR, *J Clin Oncol 1995, 13:8–10.*
- patient has distant disease in a limited number of regions (less than five), the primary lesion can be controlled,

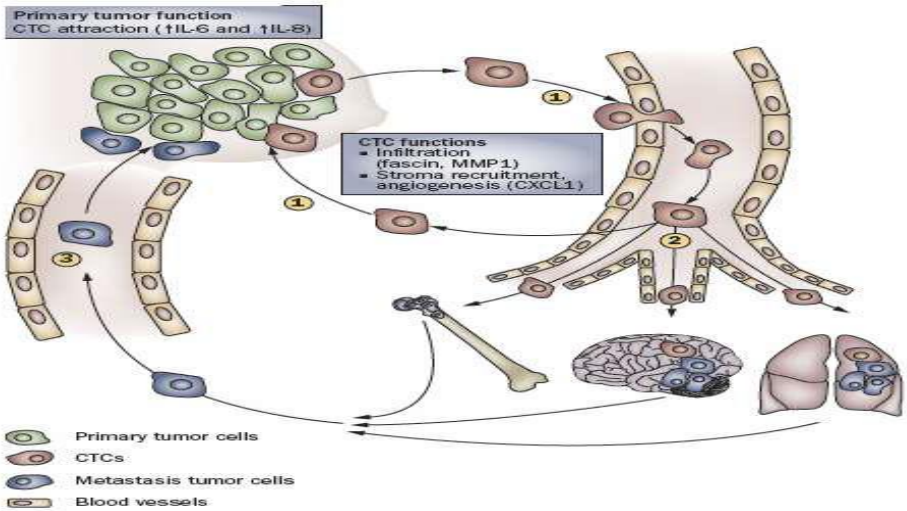
- Niibe Y, Hayakawa K: Oligometastases and oligo-recurrence: the new era of cancer therapy. *Jpn J Clin Oncol 2010, 40:107–111.*
- oligo-recurrence where a patient presents one or more distant metastases or recurrences in one or more organs, and in addition to the primary tumor being under control, these metastases or recurrences may be amenable to local treatment,
- Rubin P, Brasacchio R, Katz A: Solitary metastases: illusion versus reality. *Semin Radiat Oncol 2006, 16:120–130.*
- solitary metastasis (**M1**),
- oligometastases (**M2**),
- multiple metastases (**M3**),

spektrum zaawansowania

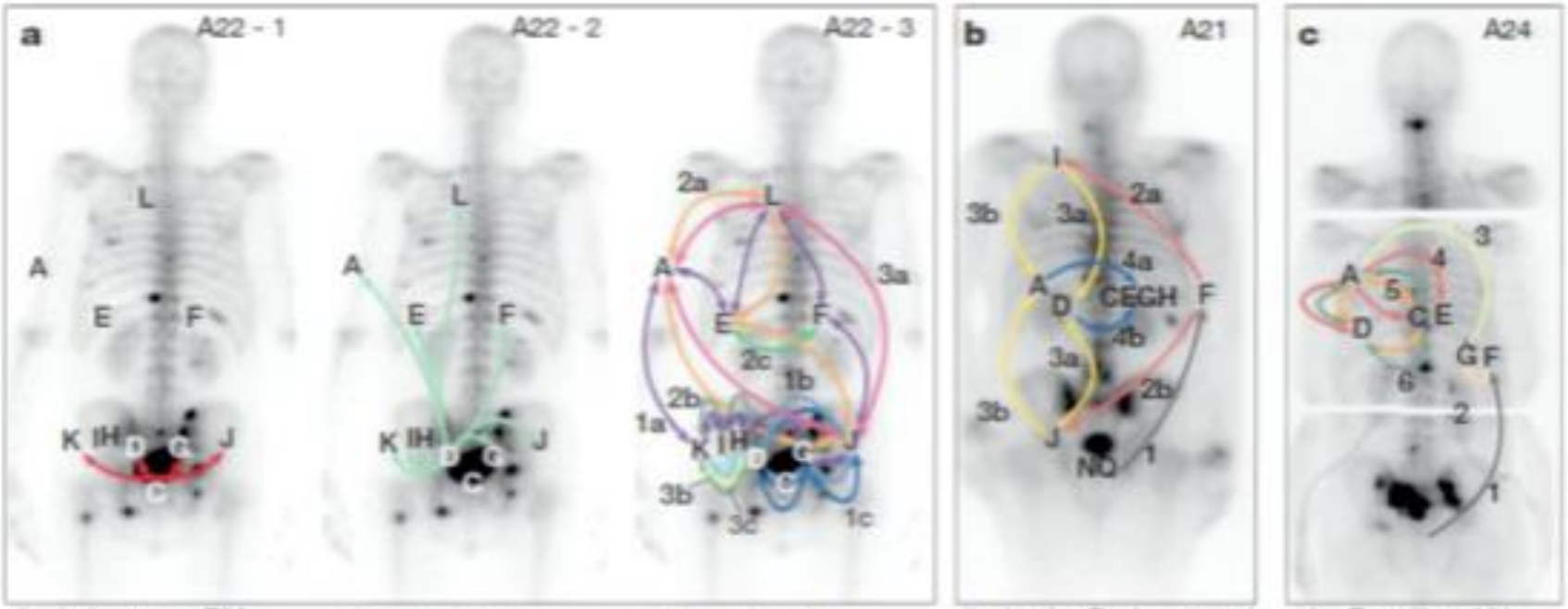


EMT (Epithelial-to-Mesenchymal transition)
Fiziologiczny proces, np. Gojenie się rany





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



A - L. humerus BM
D - Sem. vesicle
C - Prostate
E - L. adrenal

F - R. adrenal
G - Bladder
H - Pelvic LN
I - L. pelvic LN

J - R. pelvic LN
K - L. pelvic LN
L - L. media. LN

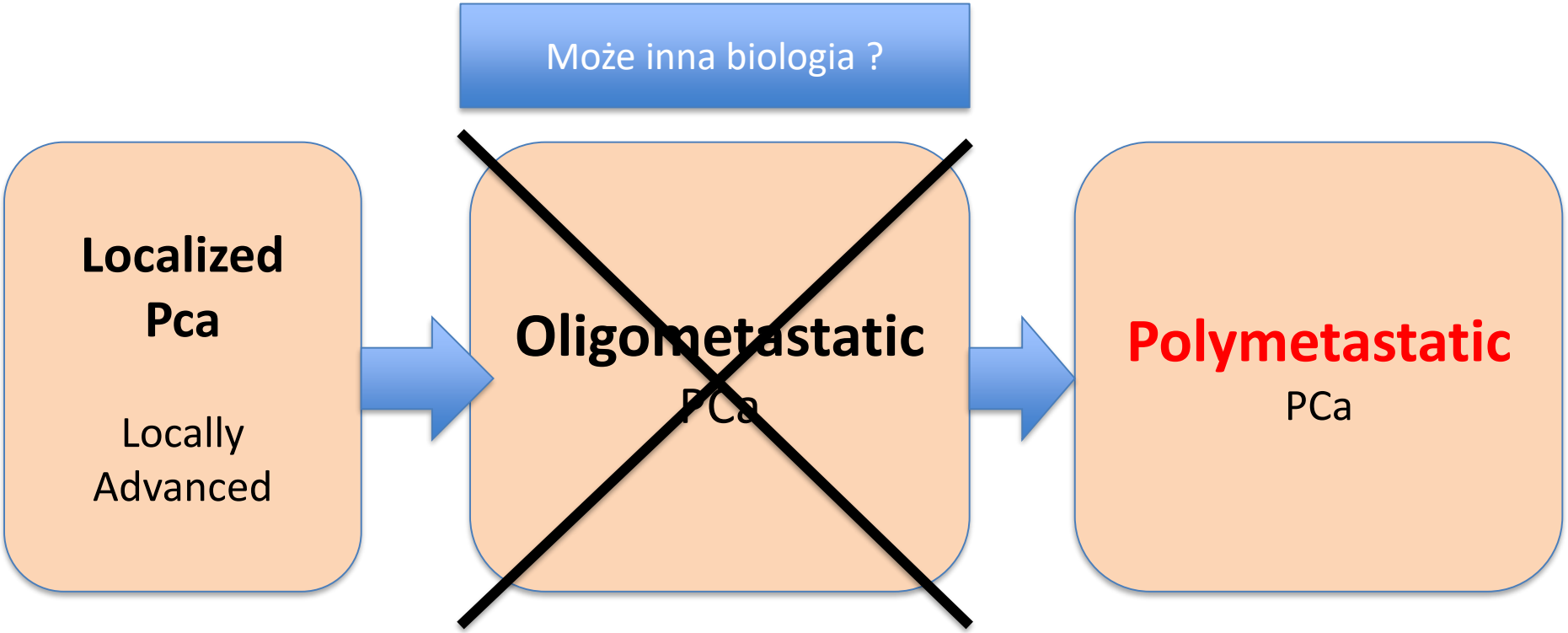
A - L. rib
C - Liver
E - Liver
G - Liver
H - Liver

D - L. adrenal
F - R. rib nod.
I - L. clavicle
J - L. iliac crest
N - GL5 EPE
Q - GL3/5

A - R. axillary LN
C - R. diaphragm
D - R. rib
E - Xiphoid
F - L. lobe liver
G - Falciform ligam.

Bova Nature 2015

Rak Stercza



Przerzuty w węzłach chłonnych bardziej promieniowrażliwe?
Choroba zdiagnozowana na tym poziomie bardziej ograniczona?

Może w tym stadium choroby możliwe jest nawet wyleczenie?

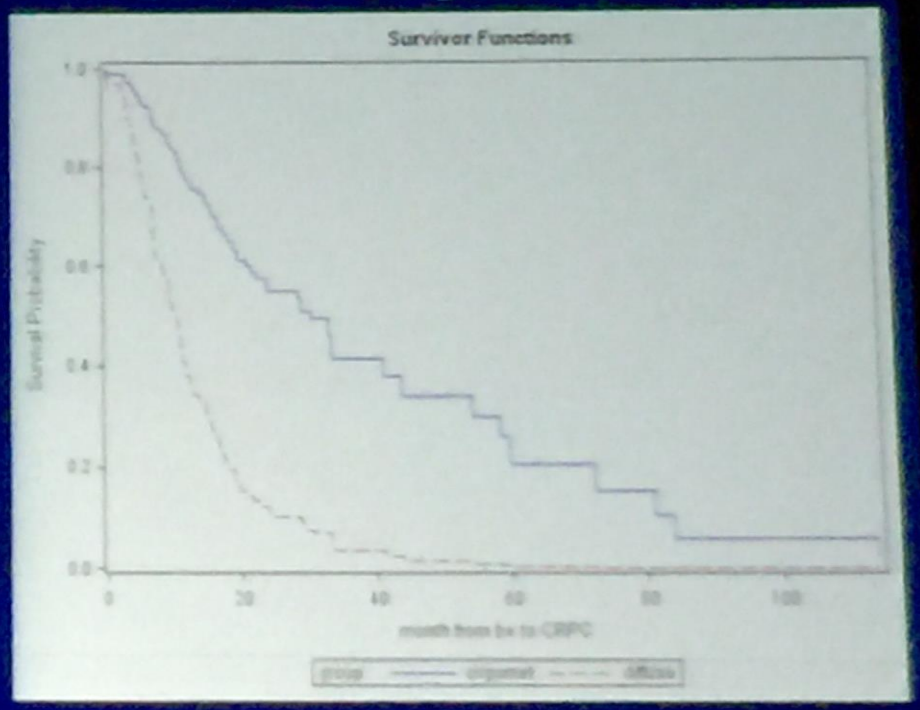
Istotne opóźnienie progresji choroby ?

Choroba Oligometastatyczna przebiega odmiennie od Polimetastatycznej ?

Prostate Cancer-Specific Survival

HR=6.34, CI=2.98-13.49

Time from Diagnosis to CRPC



HR=3.82, CI=2.09-6.56

M1-oligo; N=25

M1-diffuse; N=78

Cox Proportional Hazards Model Controlled for Age and Race

Choroba Oligometastatyczna przebiega odmiennie od Polimetastatycznej ?

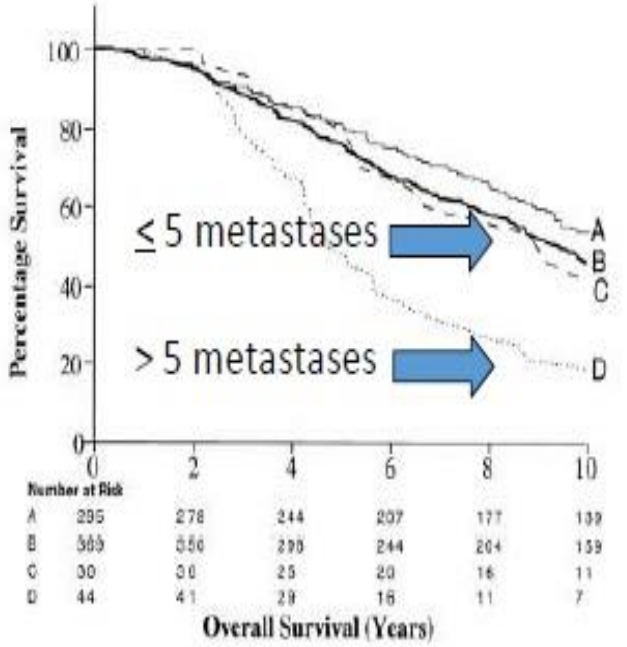
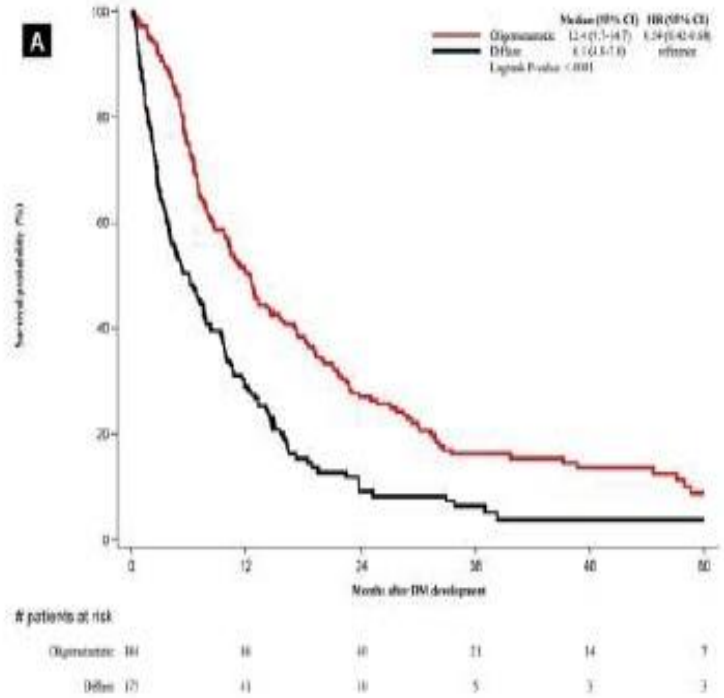


Fig. 3. Overall survival of patients who developed ≤5 metastatic lesions (dashed line [C]) was similar to overall survival of whole group (solid line [B]) and those who developed no metastatic lesions (thin solid line [A]) and significantly better than patients with >5 lesions (dotted line [D], $p = 0.02$). Number of patients at risk shown at bottom.

PROSTATE CANCER

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



NSCLC

Clinical Lung Cancer, Vol. ■, No. ■, 1-10 © 2016

Jeżeli mówimy o Chorobie Oligometastatycznej to kluczowym jest

Definicja grupy chorych

Diagnostyka obrazowa

definicja

DENOVO OLIGOMETASTASES

Primary Tu + Mets

OLIGORECURRENCE

Primary Tu po leczeniu –kontrola a Mets w FU

Choroba Oligometastatyczna rzeczywiście istnieje

Table 1. Lesion site by number

Site	≤5 lesions (*n*)	>5 lesions (*n*)
Bone alone	22 (29.7)	35 (47.3)
Bone + liver	0	2 (2.7)
Bone + lung	0	2 (2.7)
Bone + lymph node	6 (8.1)	3 (4.1)
Bone + multiple sites	2 (2.7)*	2 (2.7)†

Oligometastases

około 10% chorych RGK

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

Oligomets/OligoRecur

Heterogenna groupa chorych

- **Sposób wykrycia:** Bone scan/CT or **PET/CT**
- **Liczba przerzutów**: **1, 3,** 5 ?
- **Lokalizacja**:
  Liver, **Pelvic LNs,** LNs outside Pelvis, **Bone**
- **N1 vs. M1**,
- **Rozmiar/ Objętość przerzutów**
- **Choroba Synchroniczna vs Choroba Metachroniczna**
- **Uprzednie leczenie (ADT); CRPC vs bez uprzedniej terapii**

Diagnostyka

- Wznowa miejscowa - regionalna: MRI
- Przerzuty odległe: PET/CT, WB MRI

Weichselbaum 1995

The limited effectiveness treatments of oligometastases has been primarily the result of an inability to recognize all metastases

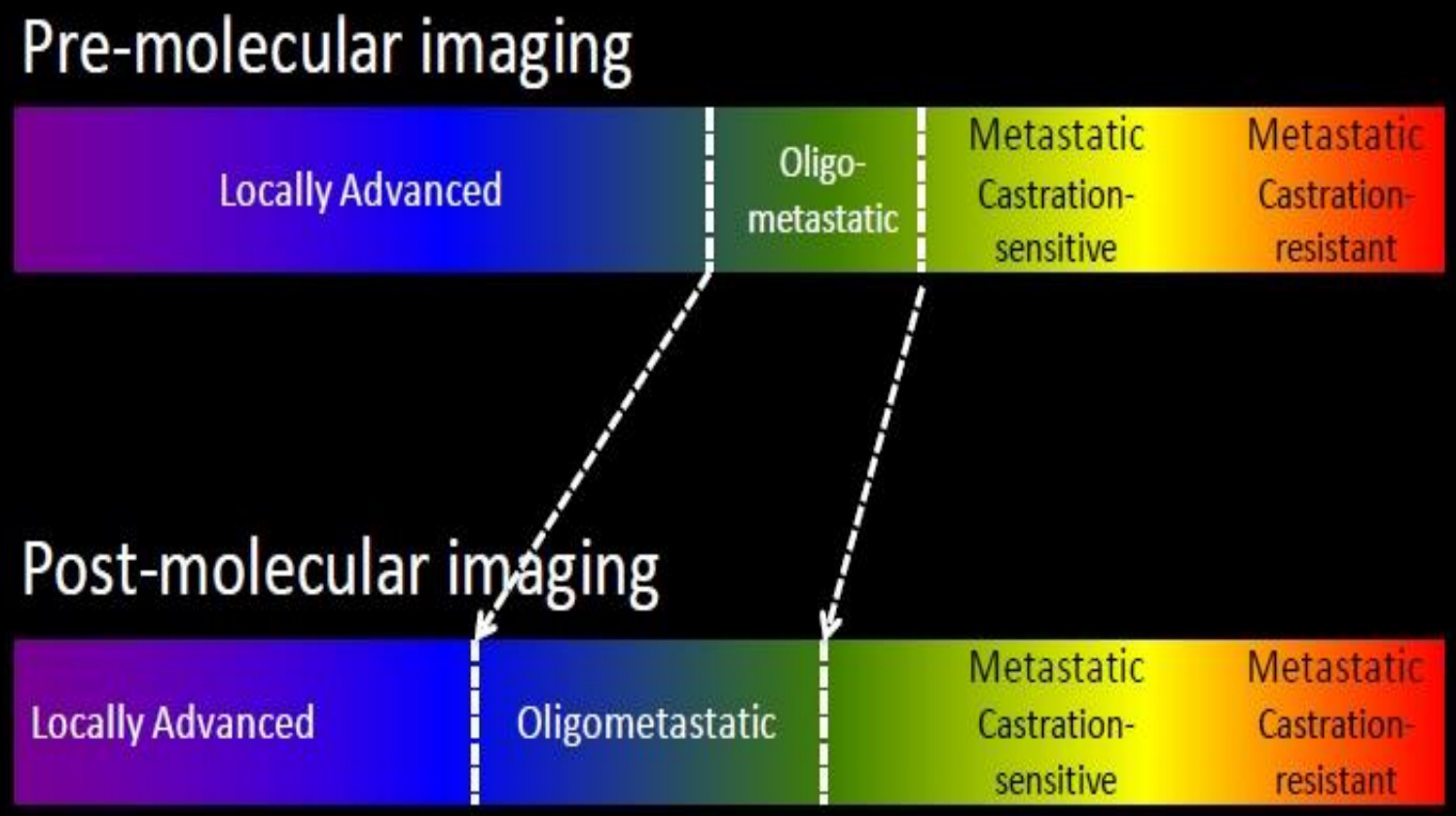
Diagnostyka Oligomets

0.1 g 10^7- 10^8

1.0 g 10^8 - 10^9

10 g $10^9 – 10^{10}$

Migracja zaawansowania spowodowana badaniem PET-CT



Im powszechniej stosujemy badanie PET-CT tym więcej wykrywamy
Oligomets

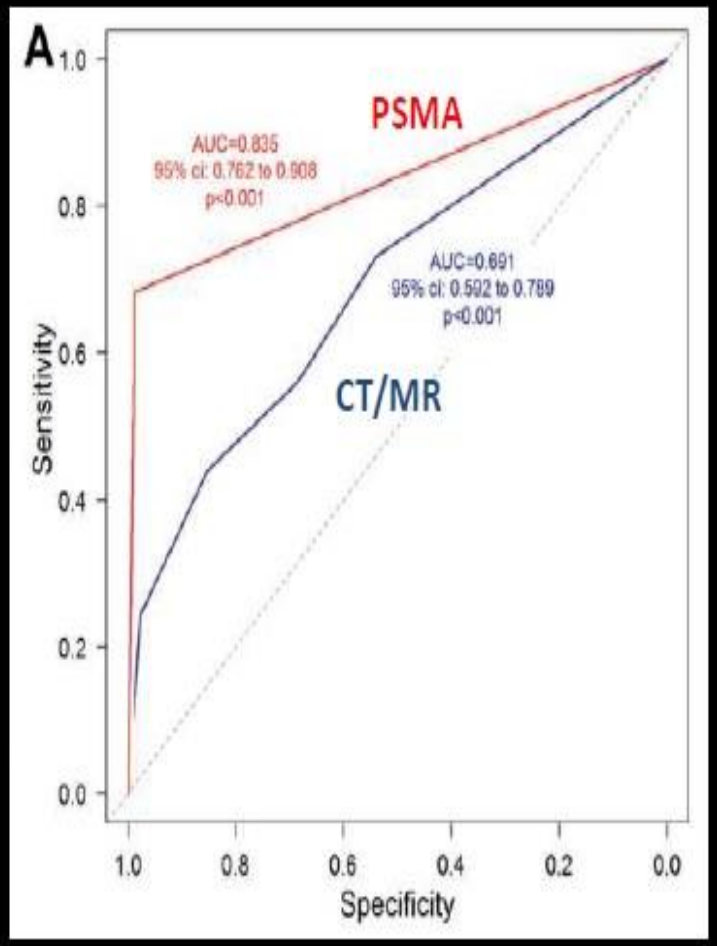
Węzły chłonne: PET PSMA

	PSMA	Cholin
Per Patient	18% false positive	22% false negative
Per LN		
Sensitivity	94%	73%
Specifity	94%	88%
Positve predictive value	80%	76%
Negative predictive value	98%	90%

PET PSMA jest także lepszy w detekcji przerzutów do układu kostnego

Sensitivity	CT/MR/Bone Scan	^{68}Ga-PSMA
Lymph node	43.9%	65.9-94%
Bone mets	86.7-89.3%	98.7-100%

... and may be upstaging patients who would otherwise be considered locally advanced



Hijazi et al. Prostate 2015
Maurer et al. J Urology 2016
Pyka et al. Eur J Nucl Med Mol Imaging 2016

Jak zmienia zaawansowanie choroby badanie PET-CT przed RT

UCSF, ASTRO 2017

High-risk

	Number of patients (%)
Prostate uptake	45 (100%)
Regional nodal involvement	26 (58%)
Detected only by PSMA	21 (47%)
Osseous metastases	6 (13%)
Detected only by PSMA	4 (8.9%)
PSMA-detected N1 or M1 disease	25 (56%)
Total	45 (100%)

Przed pooperac. RT po RP (PSA, 2 ng/ml)

32 pts M1 (16 pts)/N1 na 58 pts

Site	N	Isolated Recurrence
Prostatic fossa	8	5
Pelvic LN	23	13
Retroperitoneal LN	4	0
Inguinal LN	1	0
Bone	11	3

Leczenie Choroby Oligometastatycznej

Radioterapia

Standard of care ????

RT jako standard w leczeniu choroby Oligometastatycznej ?

NCCN:

- RT w przypadku obecnych objawów przerzutu kostnego,
- RT bezobjawowego przerzutu kostnego w kości podporowej – ryzyko złamania patologicznego
- RT przerzutu w układzie chłonnym

- Naive or Metastatic Pca N1; ADT +/- **RT (P + Pelvic LNs)**
- Pca M1; ADT +/- RT for M1 ale **RT for P ??**

Radioterapia

SBRT

SABR

- Sterotactic RT
- Ablative RT
- RadioSurgery

Bardzo wysoka efektywność miejscowa kontroli Oligomets

Radiotherapy and Surgery Techniques are Exportable...

Definitive Stereotactic Body Radiotherapy (SBRT) for Extracranial Oligometastases

An International Survey of >1000 Radiation Oncologists

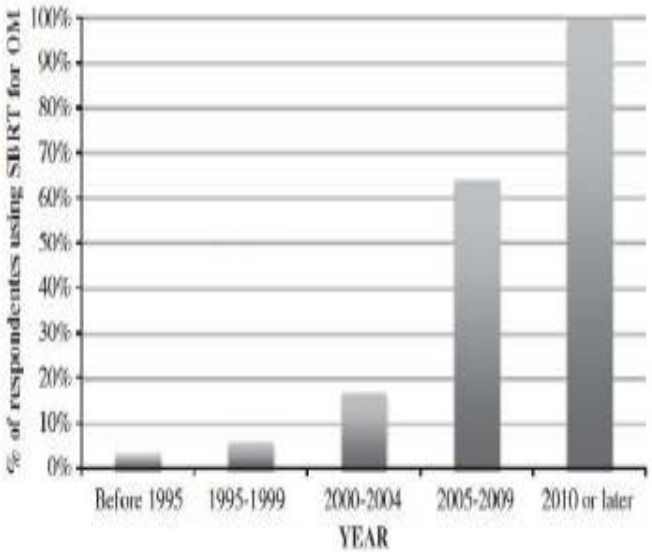


FIGURE 1. Cumulative percentage of respondents using stereotactic body radiotherapy (SBRT) for oligometastases during the defined time intervals.

Definitive SBRT a nie Palliative SBRT !!

(*Am J Clin Oncol* 2015;00:000–000)

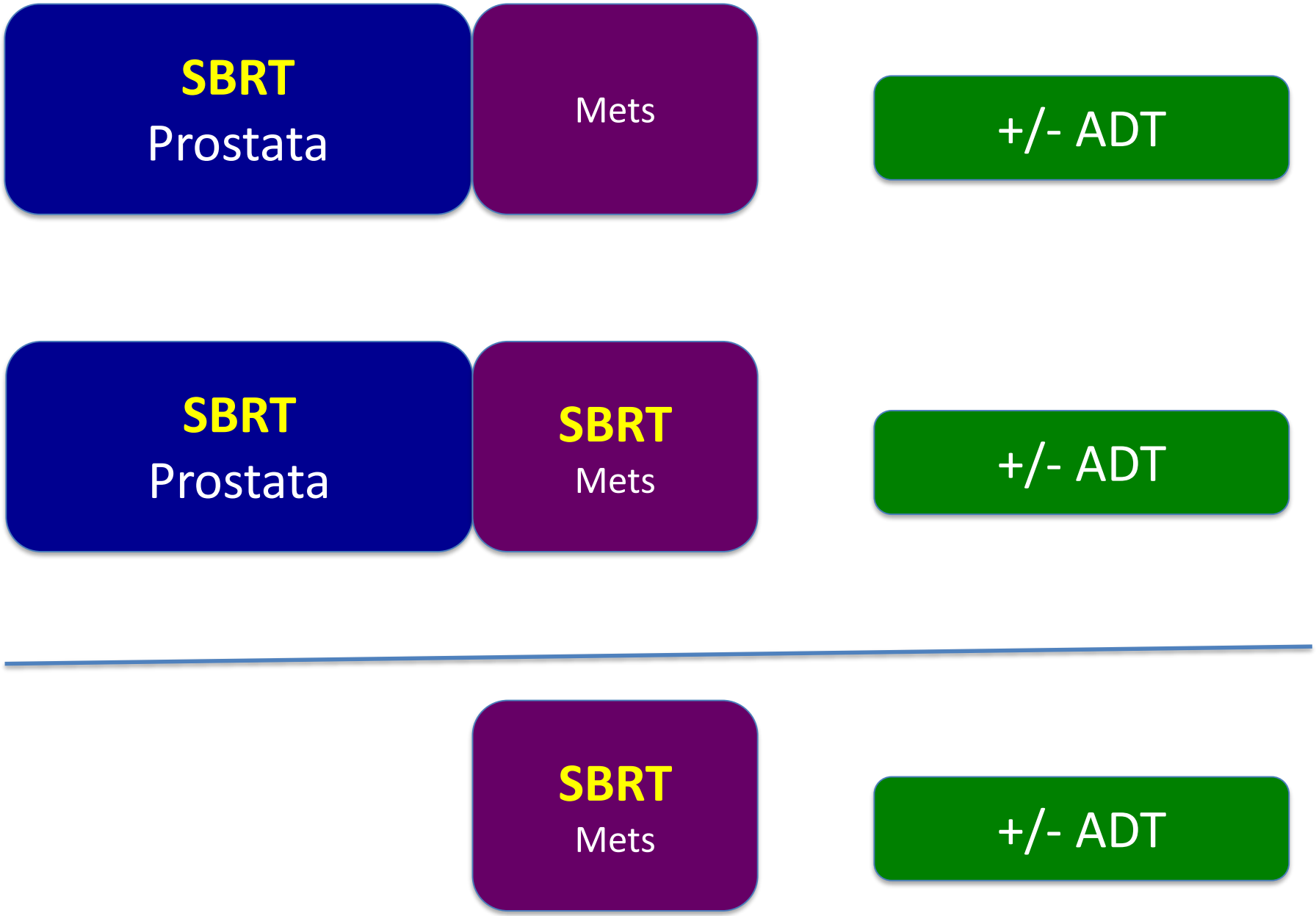
Leczenie Choroby Oligometastatycznej jest coraz popularniejsze

Ale

Czy to pomaga naszym chorym ?

Przesłanki za „radykalną w dawce” RT na Guz Pierwotny w M1

- Wyniki retrospektywnych analiz wskazujących na zysk w przeżyciach,
- Opóźnienie lub istotne ograniczenie wystąpienia powikłań przerzutów/ogniska pierwotnego,
- Opóźnienie rozwoju stadium Polimetastases,
- Opóźnienie wdrożenia leczenia systemowego (ADT, chemioterapii)


SBRT
Prostata
Mets
+/- ADT
SBRT
Prostata
SBRT
Mets
+/- ADT
SBRT
Mets
+/- ADT

Co ma być celem RT ?

- Wydłużenie czasu do włączenia ADT/Chemioterapii ?
  Przeżycie wolne bez ADT

- Wydłużenie czasu:

Przeżycia bez Progresji Choroby & Przeżycia Ogólnego ?

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

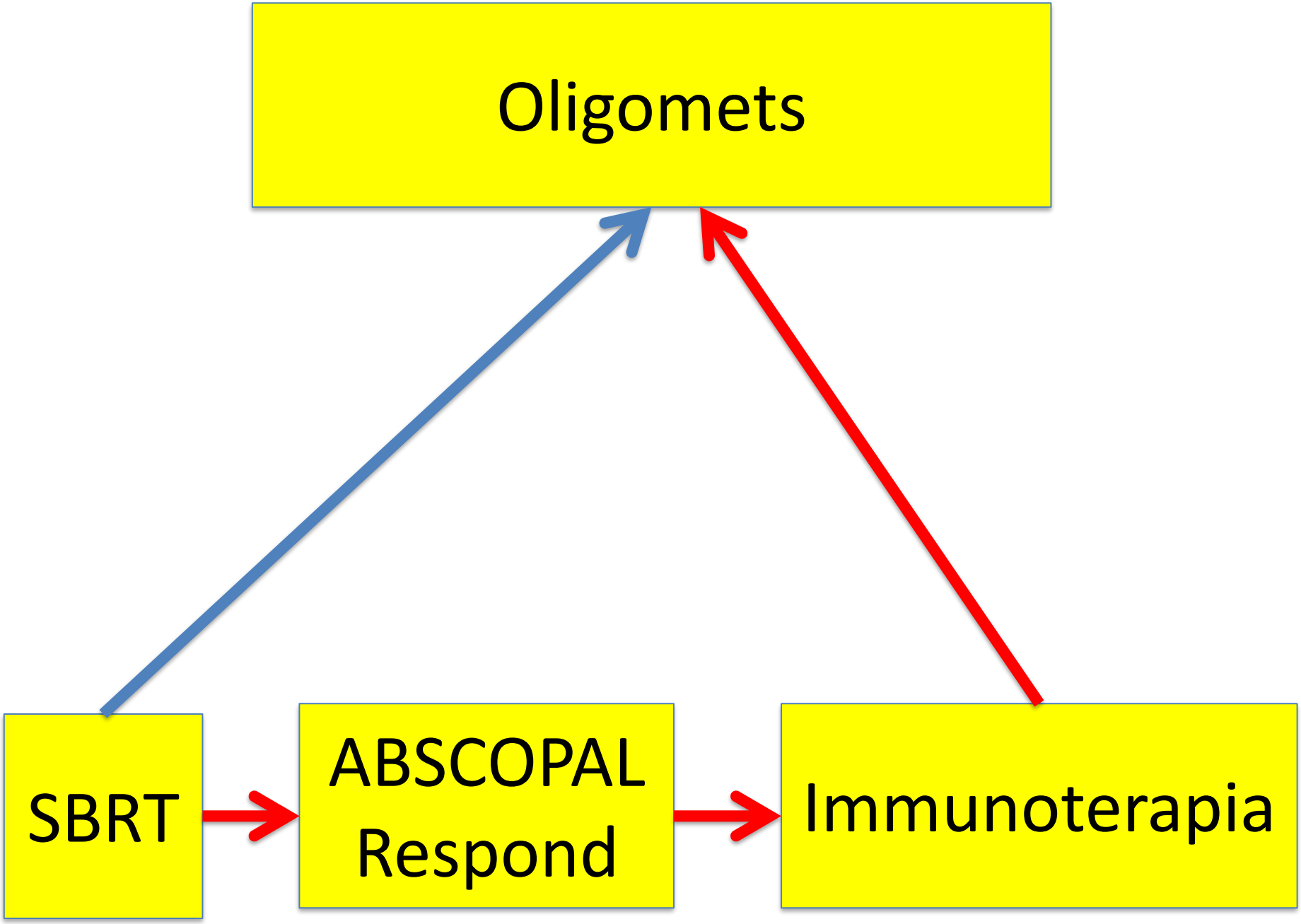
Source	N	Inclusion	Imaging	Intervention	Result
Jereczek-Fossa et al. 2012	34	M1 bone recurrence	11C-choline PET	SBRT (33-36Gy/3 fx)	30mo LC 100% 30mo PFS 0%
Ahmed et al. 2012	17	M1, ≤5 mets	11C-choline PET	SBRT (20 Gy/1 fx) followed by ADT	6 mo LC 100% 53% undetectable PSA
Muacevic et al. 2013	40	M1, ≤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

Czy kojarzyć SBRT z ADT ?
Jeżeli tak to jak długo ?

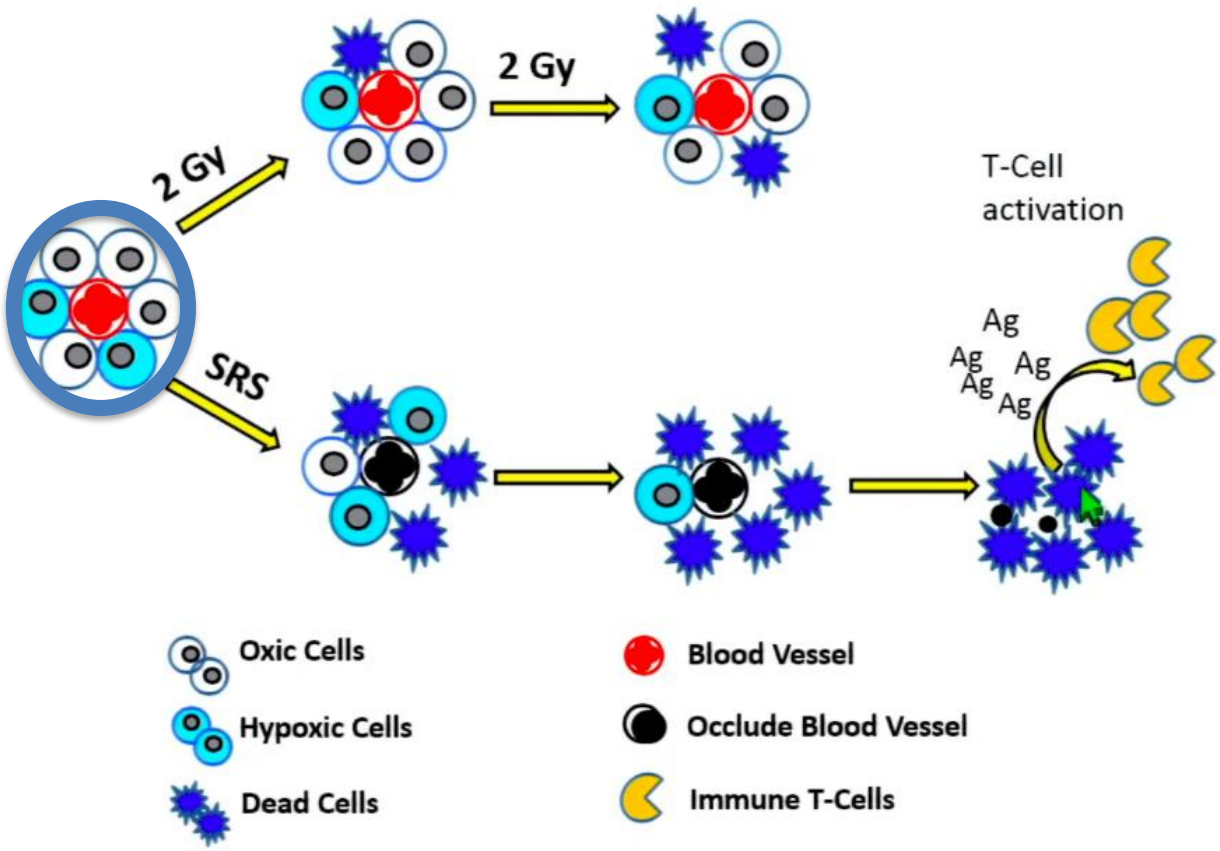
Source	N	Inclusion	Intervention	ADT	Result
Schick et al. 2013	50	≤4 regional LN or mets	EBRT (50.4 Gy pelvic LN, 65Gy LN boost)	STADT, median 12 mo	3y bRFS 55% 3y DMFS 59% 3y OS 92%
Jereczek-Fossa et al. 2017	94	≤5 LN	SBRT (24Gy/3fx)	ADT in 36%, median 16.6 mo	2y LC 84% 2y PFS 30% STADT assoc with longer PFS
Casamassima et al. 2011	25	"Limited" N1 or M1a	SBRT (30Gy/3fx) or Pelvic LN RT (50 Gy/25fx)	None	3y LC 90% 3y DFS 17% 3y OS 92%
Berkovic et al. 2013	24	M1 ≤3 bone or LN mets	SBRT (50Gy/10fx)	None	2y LC 100% 2y cPFS 42% Median ADT-free time: 38mo
Decaestecker et al. 2014	50	M1 ≤3 mets	SBRT (50Gy/10fx or 30Gy/3 fx)	None	2y LC 100% 2y PFS 35% Median ADT-free time: 25mo
Habl et al. 2017	15	M1 ≤2 mets	SBRT 25-35 Gy/5fx	None in 10 pts	2y LC 100% Median distant PFS 7.4 mo Median ADT-free time: 9.3 mo

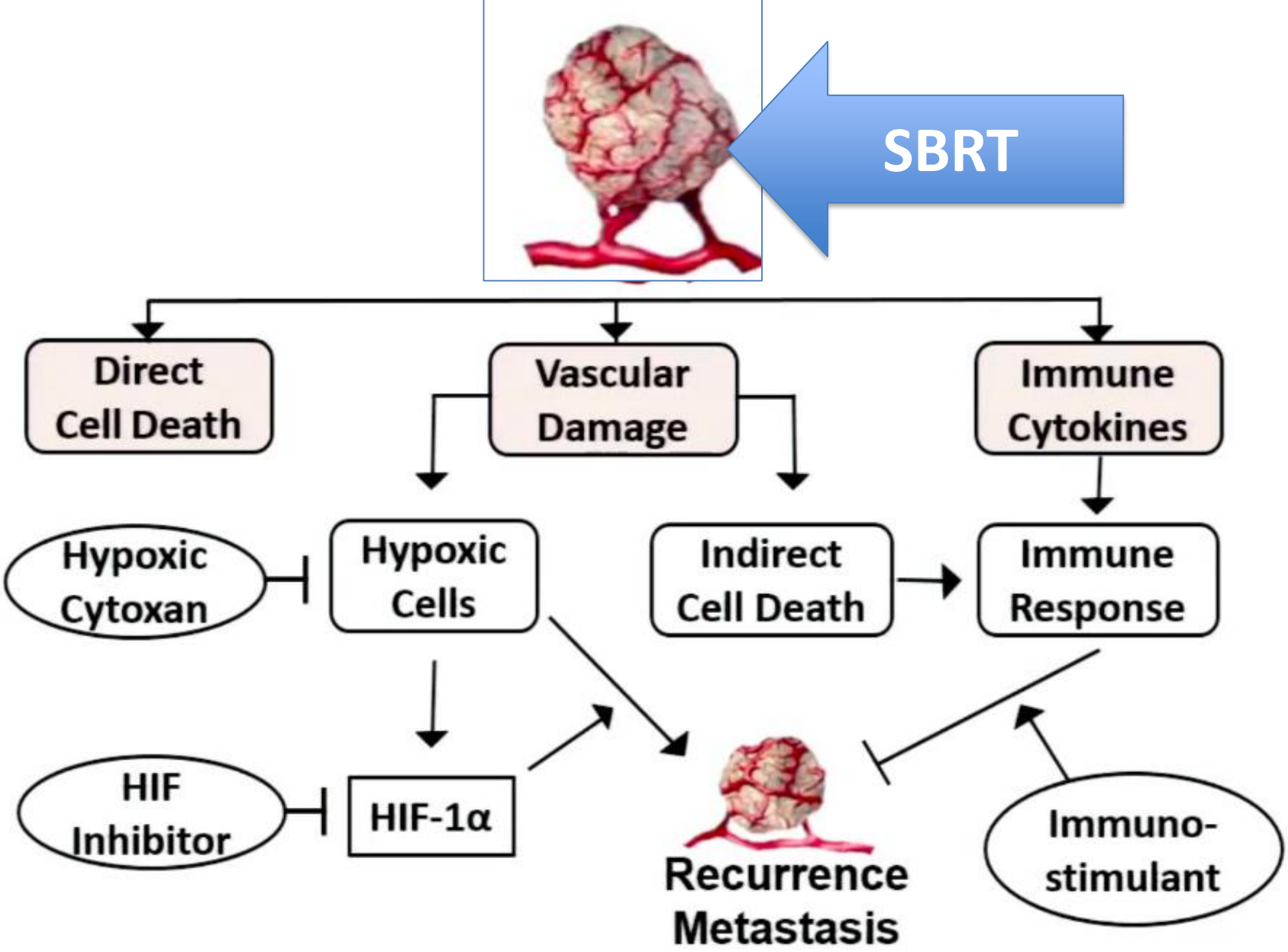
Czy kojarzyć SBRT + ADT z Chemioterapią ?

Source	N	Inclusion	Prostate Tx	Arms	Result
GETUG 12 (Fizazi et al. 2015)	413	GS≥8, T3, PSA≥20, N+	Node neg: RP/RT Node pos: RT or none	3y ADT +/- 4c docetaxel	8y RFS 62% ADT+doce vs 50% ADT alone (HR 0.71, p=0.017)
RTOG 0521 (Sandler et al. 2015)	562	GS≥7, PSA ≥20, any T ≥T2 and GS≥8, PSA <20	WPRT 46.8 Gy + Prostate boost 25.2-28.8 Gy	2y ADT +/- 6c docetaxel + prednisone	5y OS 93% ADT+doce vs 89% ADT alone (HR 0.70, 1-sided p=0.04)
STAMPEDE Docetaxel (James et al. 2016)	2962	New diagnosis high risk, N+ or M1 or high risk relapse (35% N0-1M0)	RT for N0M0 RT optional for N1M0	ADT +/- ZA ADT + Doc +/- ZA	Median OS 81mo ADT + doce vs 71mo ADT alone (HR 0.78, p=0.006)
STAMPEDE Abiraterone (James et al. 2017)	1917	New diagnosis high risk, N+ or M1 or high risk relapse (46% N0-1M0)	RT for N0M0 RT optional for N1M0	ADT +/- abiraterone	3y OS 83% ADT+abi vs 76% ADT alone (HR 0.63, p<0.001)


Oligomets
SBRT
ABSCOPAL
Respond
Immunoterapia

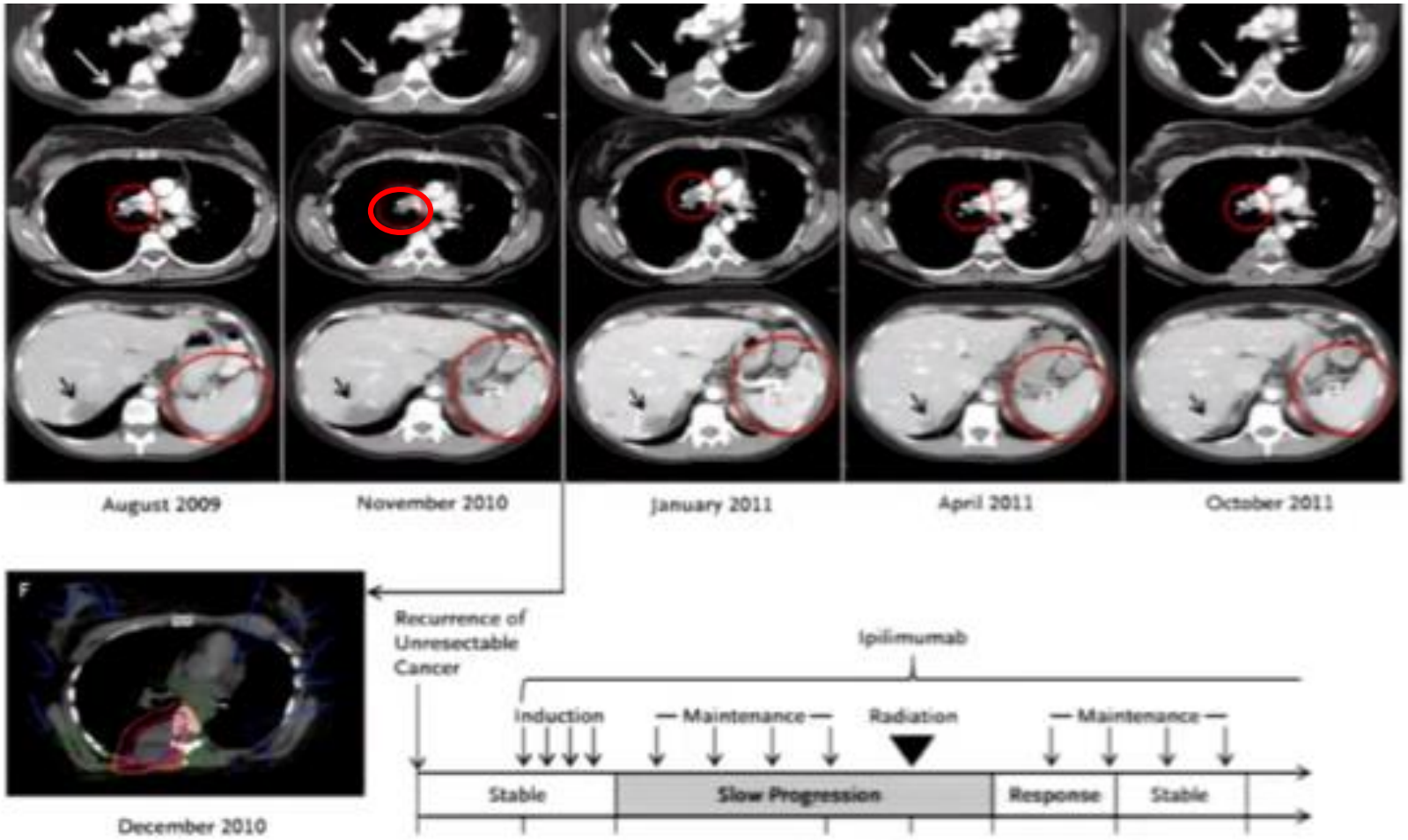
SBRT a RT konwencjonalna



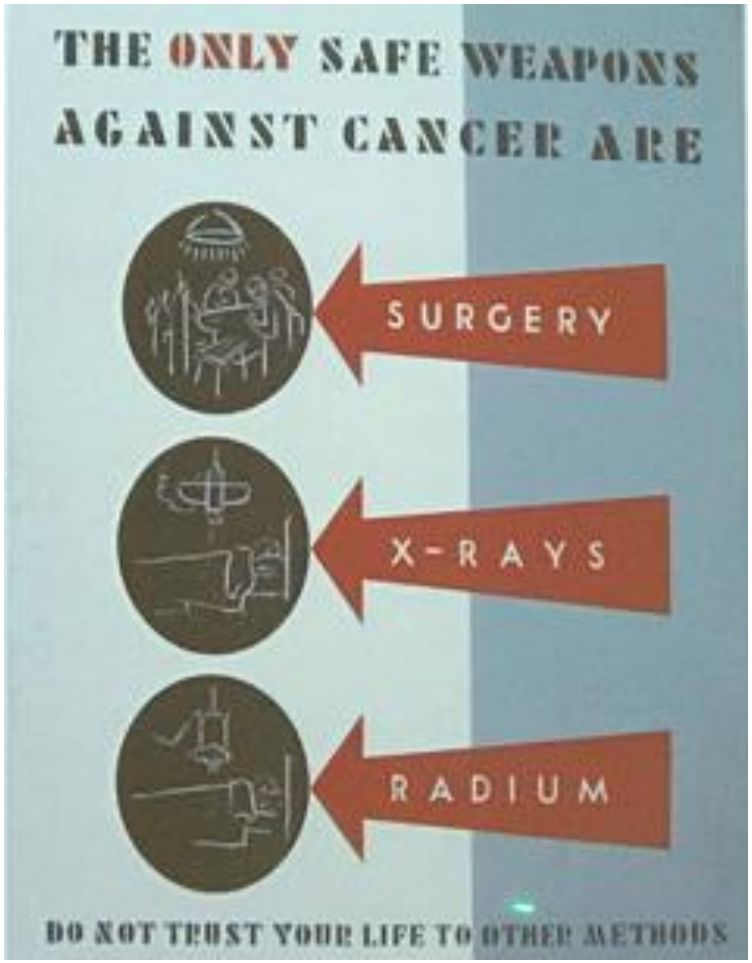

SBRT
Direct Cell Death
Vascular Damage
Immune Cytokines
Hypoxic Cytoxan
Hypoxic Cells
Indirect Cell Death
Immune Response
HIF Inhibitor
HIF-1α
Recurrence Metastasis
Immuno-stimulant

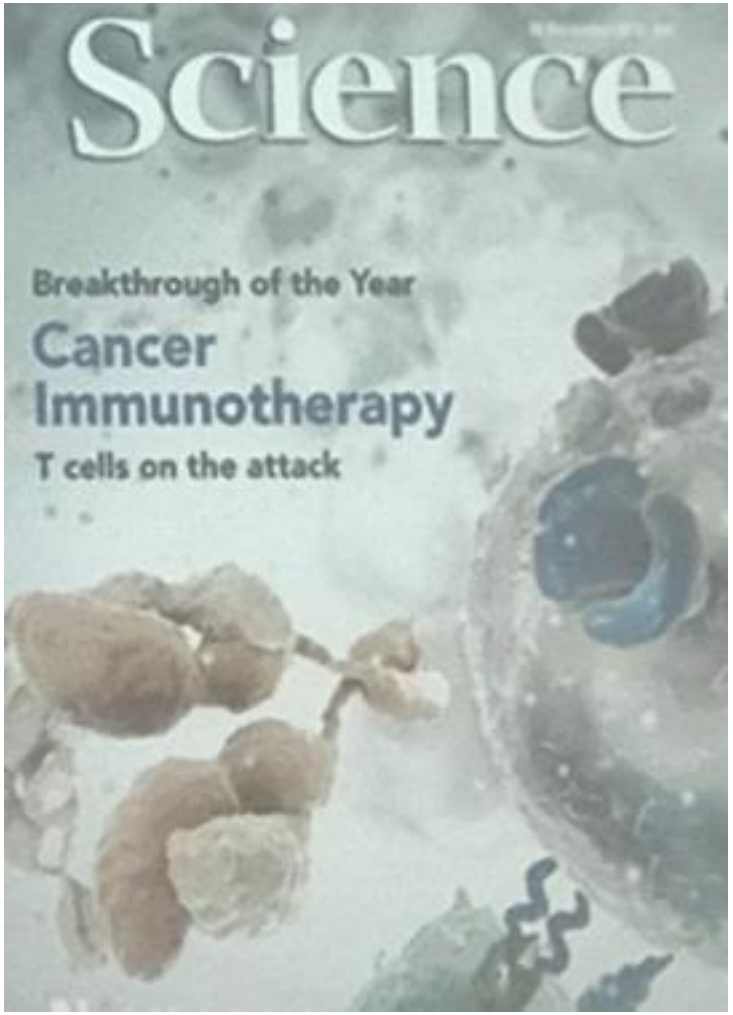
SBRT for metastatic lesions:

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



Postow et al. NEJM 2012


THE ONLY SAFE WEAPONS
AGAINST CANCER ARE
SURGERY
X-RAYS
RADIUM
DO NOT TRUST YOUR LIFE TO OTHER METHODS


Science
Breakthrough of the Year
Cancer
Immunotherapy
T cells on the attack

M1
układ kostny

Oligometastases

RT paliatywna ??? → RT Radykalna ?

SBRT + Immunoterapia

EUROPEAN UROLOGY 69 (2016) 9–12

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

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]*

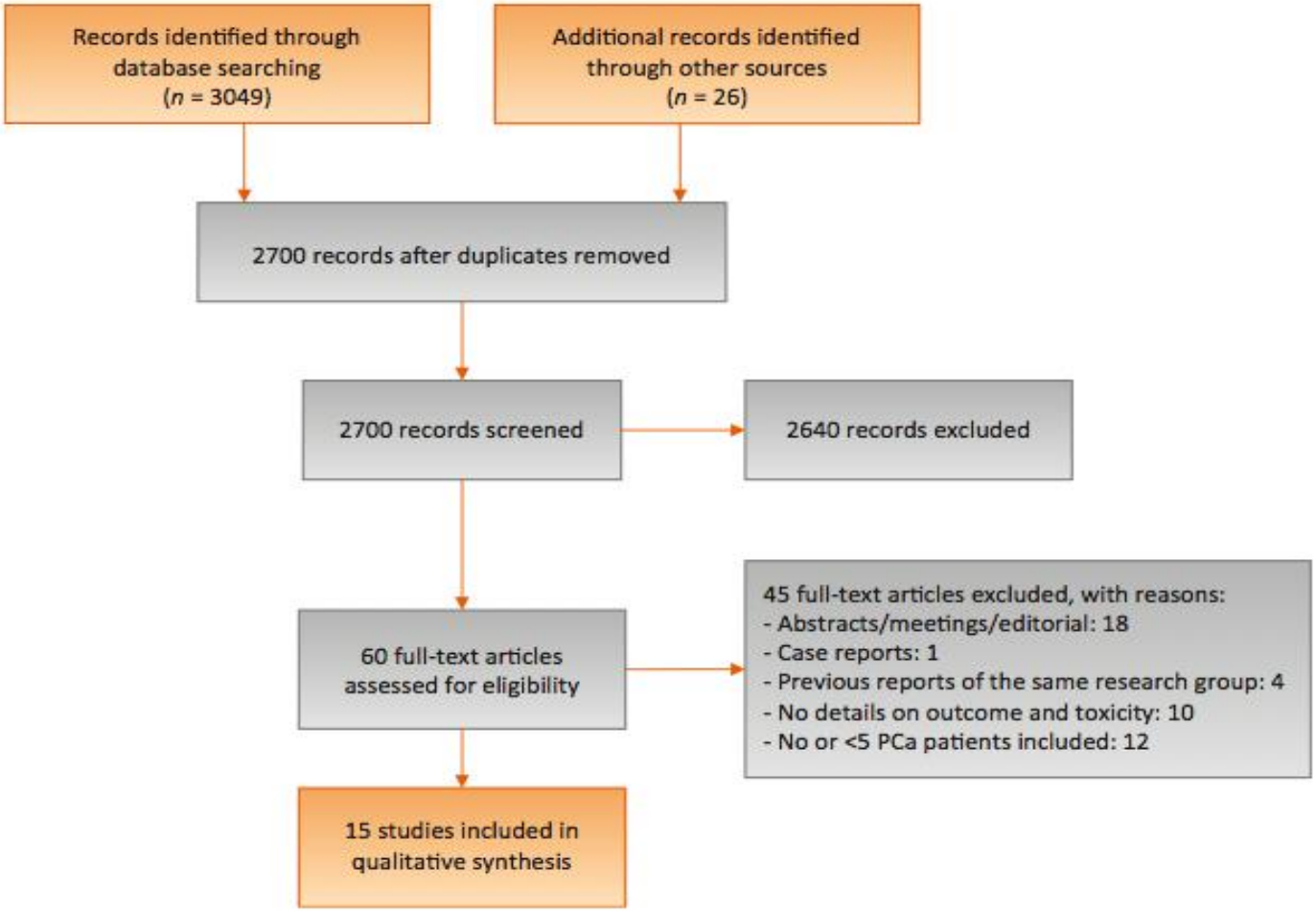


Fig. 1 – Flowchart of the systematic review.
PCa = prostate cancer.

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

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	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.

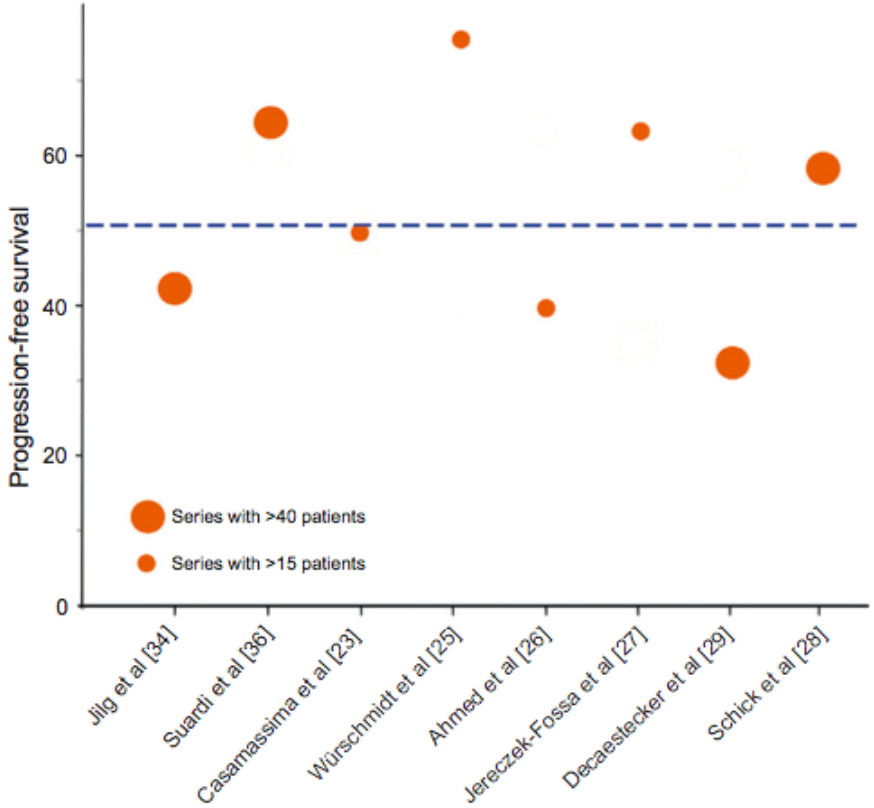


Fig. 2 – Progression-free survival in patients with oligometastatic prostate cancer recurrence at 1–3 yr of follow-up for studies with >15 patients. Dotted line represents mean proportion of patients who were progression free at the reported time point, weighted for the total number of patients.

frontiers in Oncology

ORIGINAL RESEARCH
published: 05 May 2015
doi: 10.3389/fonc.2015.00101

SBRT: an opportunity to improve quality of life for oligometastatic prostate cancer

Gregory Azzam [1], Rachelle Lanciano [1,2*], Steve Arrigo [1,2], John Lamond [1,2], William Ding [3], Jun Yang [1,2], Alexandra Hanlon [3], Michael Good [2] and Luther Brady [1,2]*

Opóźnienie wystąpienia powikłań kostnych

Opóźnienie w zastosowaniu terapii hormonalnej/chemioterapii

Badania kliniczne II fazy anti-CTLA-4 + RT u chorych z przerzutami (mCRPC)

Screening

mCRPC

Po CT (docetaxel) N=799m

1:1

Jednorazowa dawka **RT** na przerzut kostny (8Gy); 1 do 5 zmian meta

N = 399

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

Ipilimumab (10 mg/kg) co 12 tygodni

N= 400

Placebo Tygodnie 1,4,7,10

Placebo co 12 tygodni

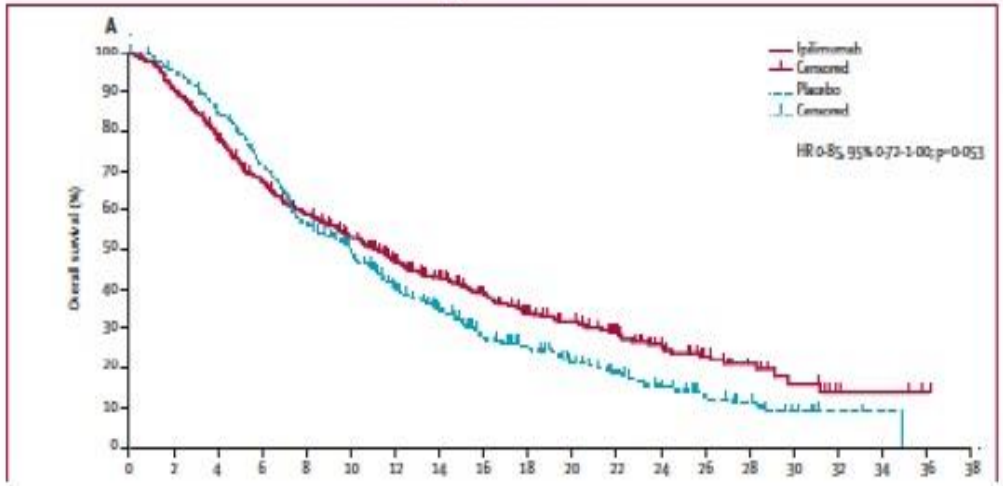
Stratyfikacja:
ALP, Hb, ECOG PS

Kwon et al. Lancet Oncology 2014

Prospective Studies with Radiation + ipilimumab (CTLA-4 inhibitor) *Kwon et al. Lancet Oncol. 2014*

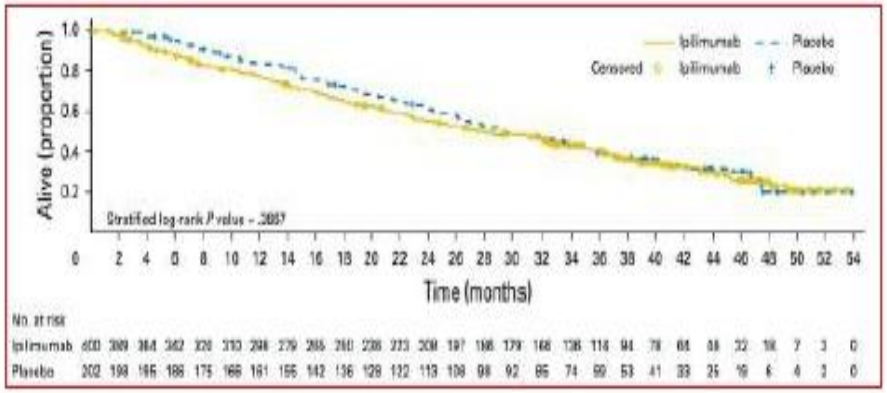
Castrate resistant metastatic prostate cancer patients with >=1 bone metastasis, who received 8 Gy x 1 +/- ipilimumab (n=799)

OS p=0.05

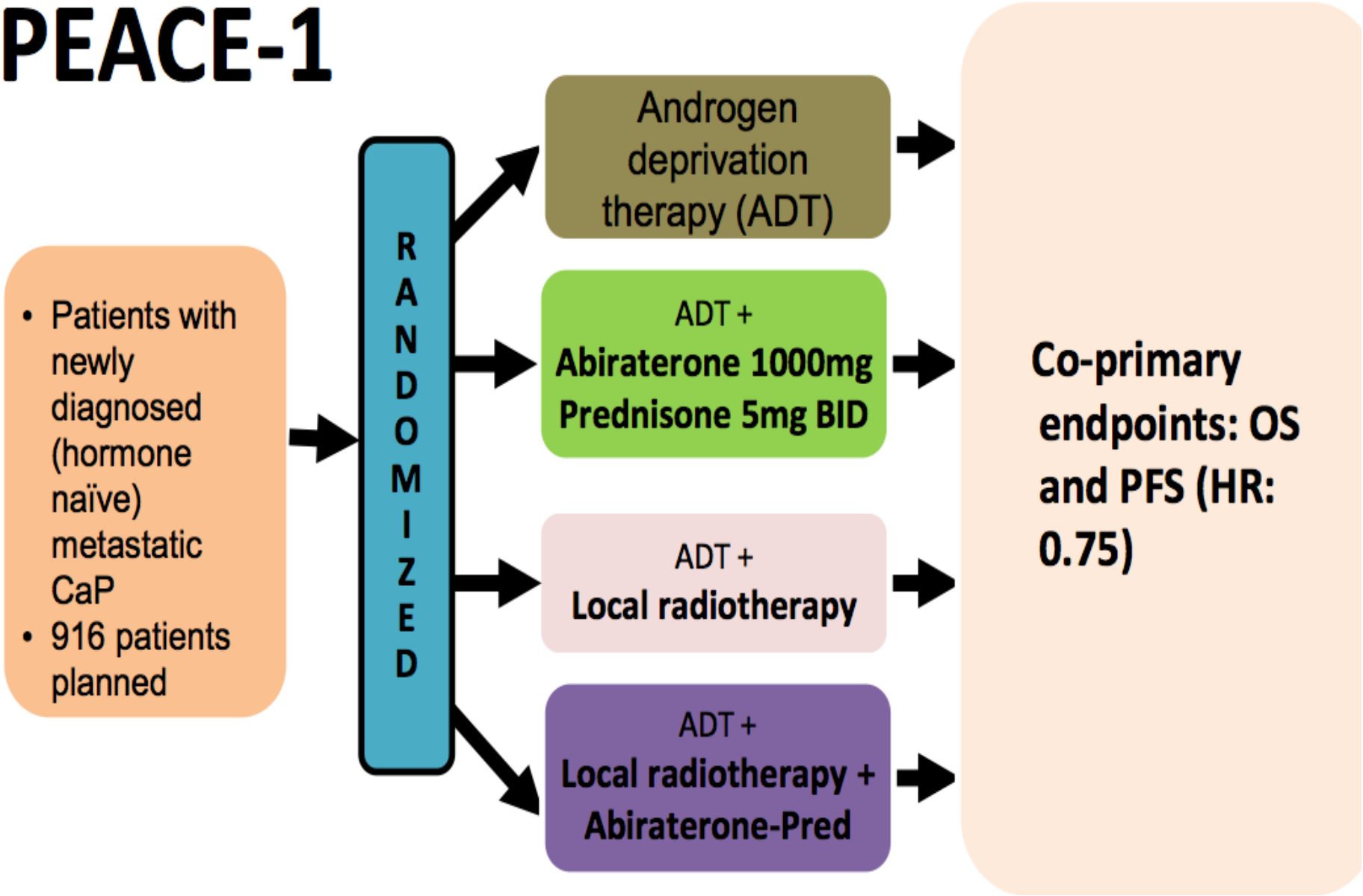


Castrate resistant metastatic prostate cancer patients who received ipilimumab vs. placebo (n=602), Beer et al. *JCO 2016*

OS p=0.37



PEACE-1


• Patients with newly diagnosed (hormone naïve) metastatic CaP
• 916 patients planned
RANDOMIZED
Androgen deprivation therapy (ADT)
ADT + Abiraterone 1000mg Prednisone 5mg BID
ADT + Local radiotherapy
ADT + Local radiotherapy + Abiraterone-Pred
Co-primary endpoints: OS and PFS (HR: 0.75)

MD Anderson Badanie NCT 01751438

Screening:
≥ M1 Pca

Randomizacja:
≥ M1 Pca

Leczenie objawowe
+
RT
lub
Chirurgia

Leczenie objawowe

Stratyfikacja:
- lokalizacja meta
- PSA ≤ 4 ng/ml
- PSA > 4 ng/ml

Wyniki !!!!!
Radioterapia

- ORIOLE
- STOMP
- HORRAD
- STAMPEDE

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

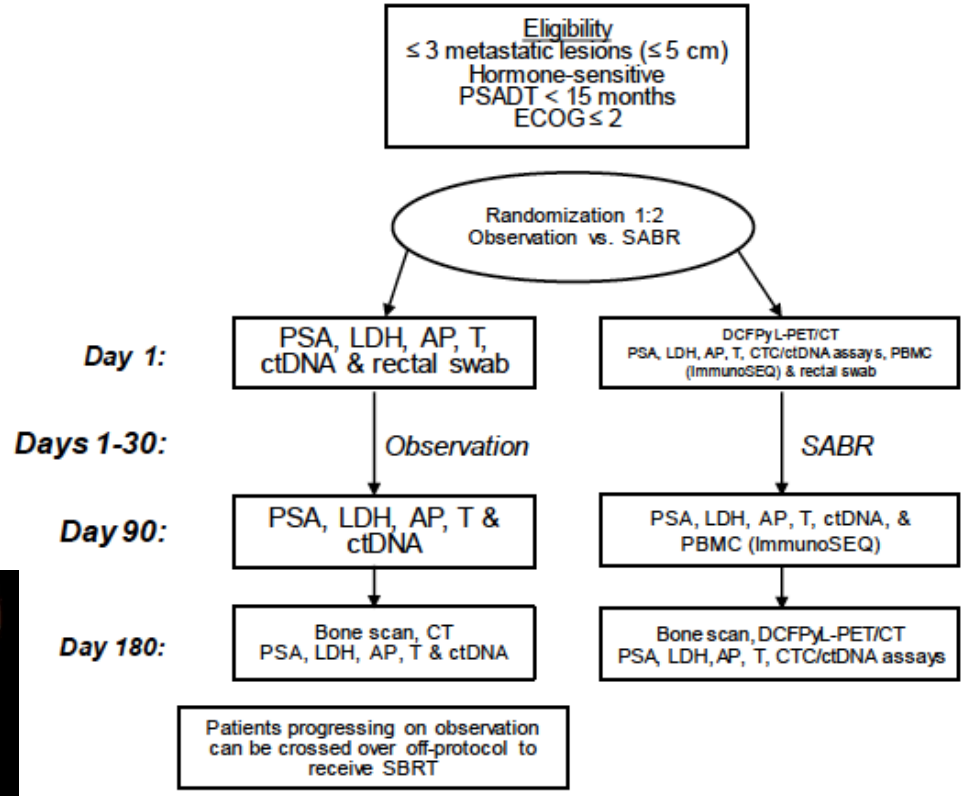
BMC Cancer

STUDY PROTOCOL Open Access

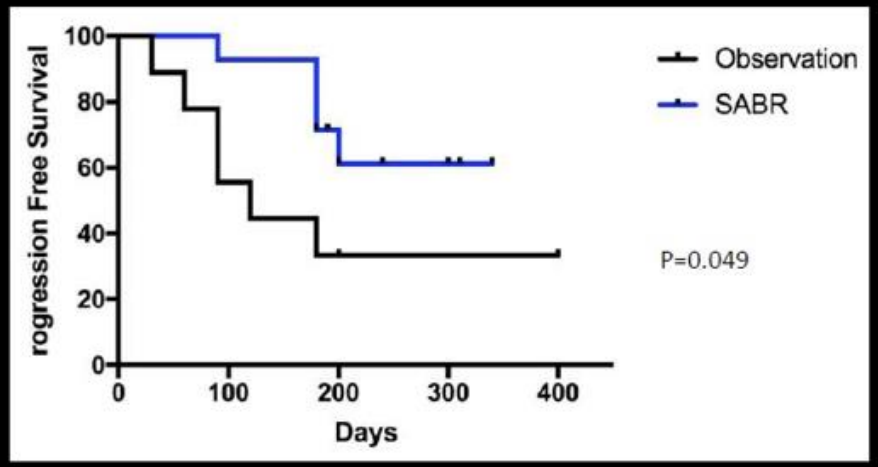
A phase II randomized trial of Observation versus stereotactic ablative RadiatIon for OLigometastatic prostate CancEr (ORIOLE)

Noura Radwan[1†], Ryan Phillips[1†], 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[7], 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*†]

Baltimore ORIOLE Schema



ORIOLE: Biochemical Progression



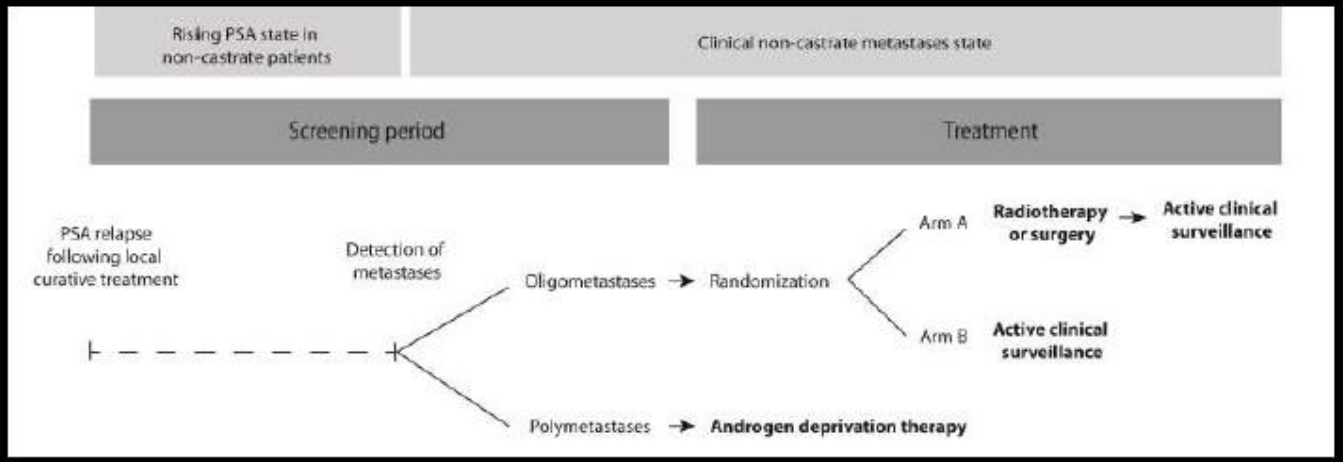
Observation: 67% of pts have progressed @ 6-mos

SABR: 29% of pts have progressed @ 6-mos

STUDY PROTOCOL Open Access

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

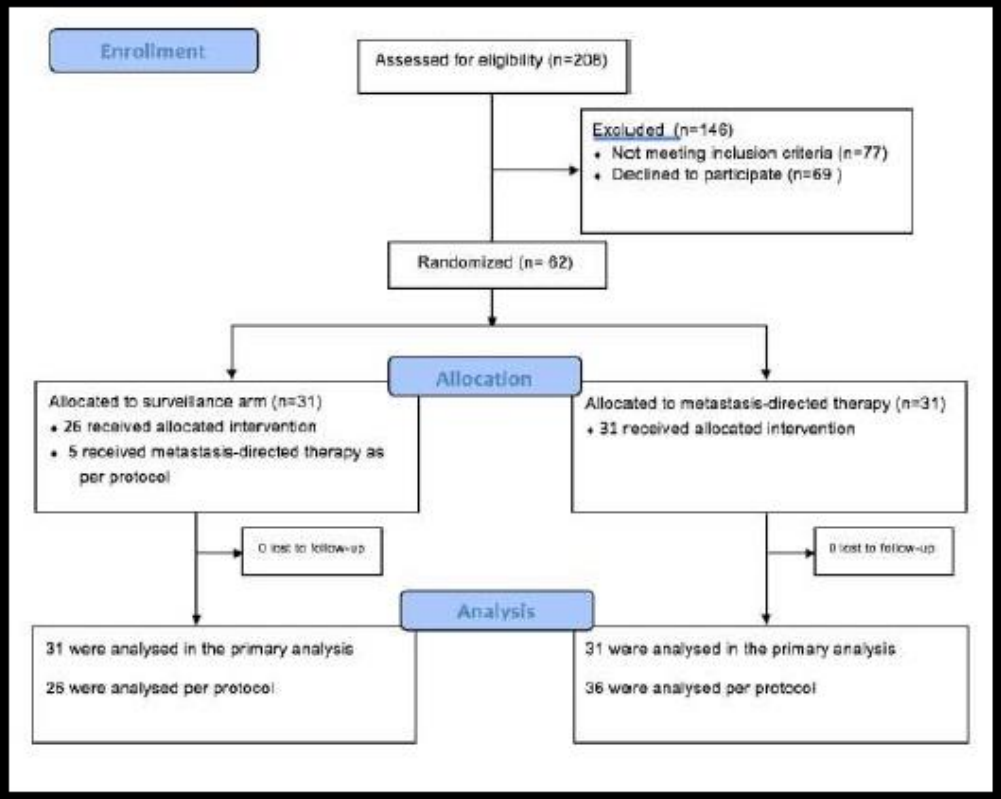
Karel Decaestecker[1], Gert De Meerleer[2], Filip Ameye[3], Valerie Fonteyne[2], Bieke Lambert[4], Steven Joniau[5], Louke Delrue[6], Ignace Billiet[7], Wim Duthoy[8], Sarah Junius[9], Wouter Huysse[6], Nicolaas Lumen[1] and Piet Ost[2*]



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

Ost et al. STOMP-trial
Piet.Ost@UGent.be
Twitter: piet_ost

STOMP: Phase II Randomized Trial



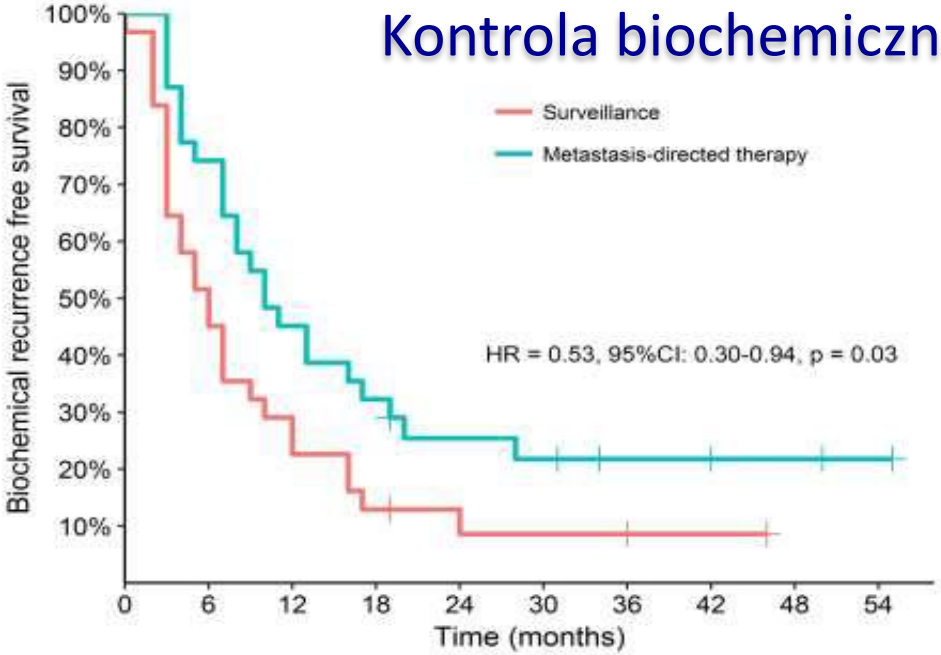
55% Nodal
45% Bone

55% Nodal
45% Bone

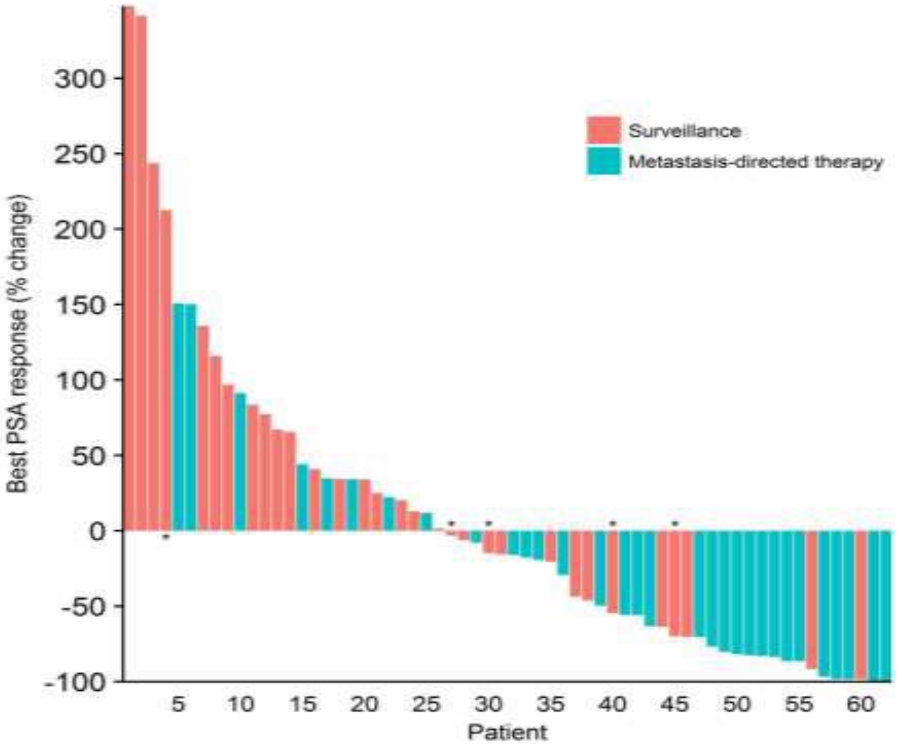
- Primary endpoint: ADT-free survival
- Stratification
  - PSA DT
  - Location of mets
- Reason to start ADT
  - Symptoms
  - Local progression
  - Polymetastatic progression

Ost et al. STOMP-trial
Piet.Ost@UGent.be
Twitter: piet_ost

Kontrola biochemiczna



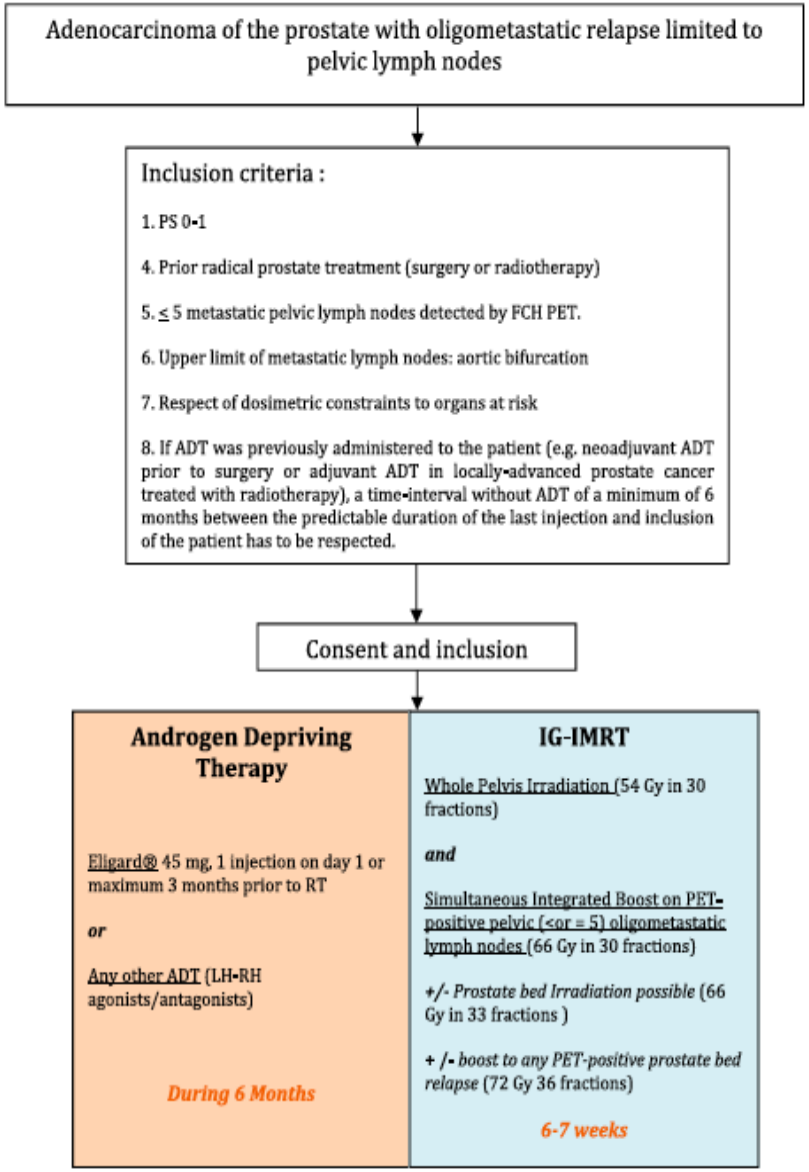
MTD	31	23	14	10	7	6	4	4	2	1
Surv.	31	16	9	4	3	2	2	1	0	0



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]



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

HORRAD

2004 – 2014 r

446 Chorych
Przerzut do kości

Randomizacja

N=223

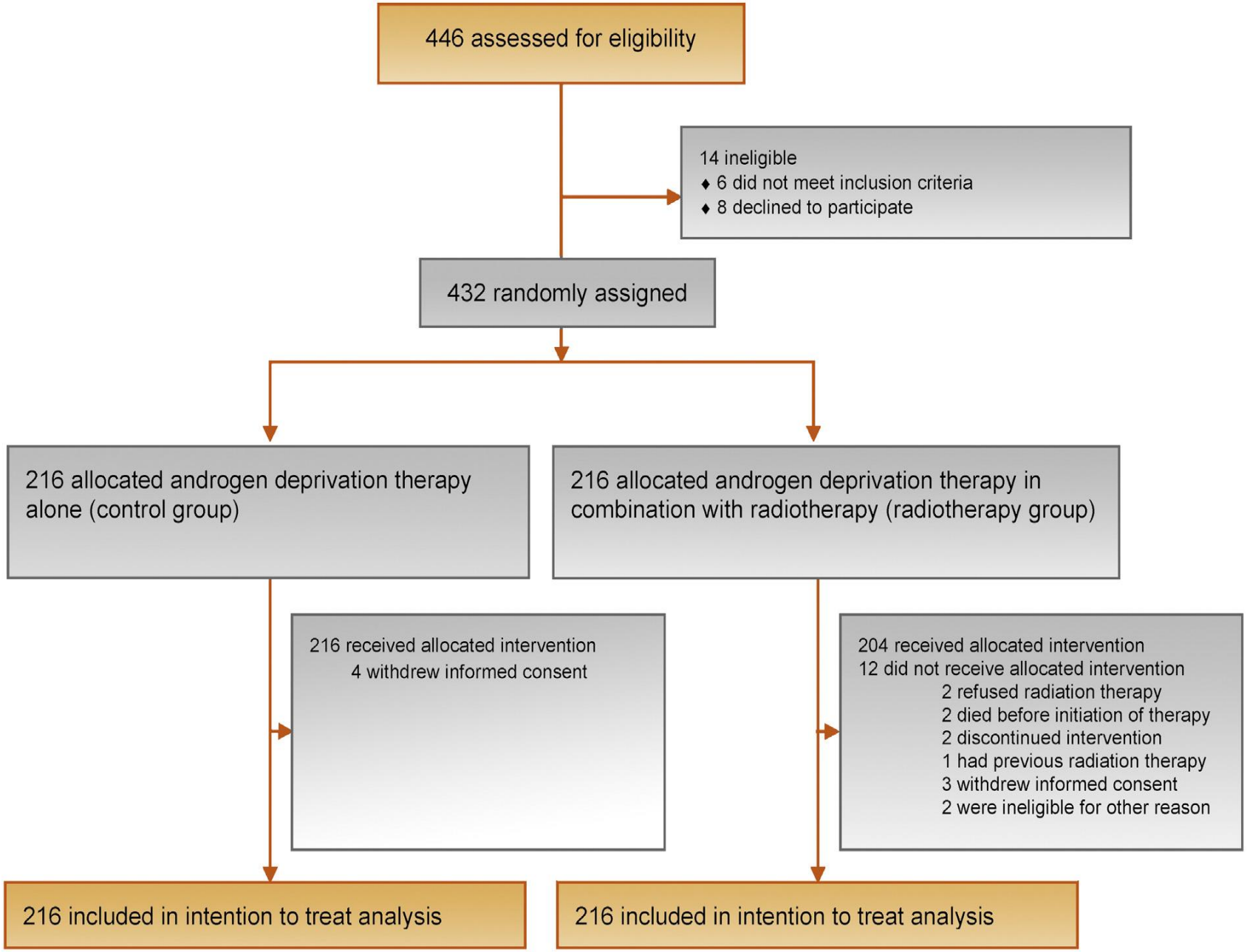
ADT

N= 223

ADT + RT 70 Gy)
na okolicę stercza

Primary Endpoint:

- Przeżycie Całkowite (biopsji- zgon)


446 assessed for eligibility
14 ineligible
♦ 6 did not meet inclusion criteria
♦ 8 declined to participate
432 randomly assigned
216 allocated androgen deprivation therapy alone (control group)
216 allocated androgen deprivation therapy in combination with radiotherapy (radiotherapy group)
216 received allocated intervention
4 withdrew informed consent
204 received allocated intervention
12 did not receive allocated intervention
2 refused radiation therapy
2 died before initiation of therapy
2 discontinued intervention
1 had previous radiation therapy
3 withdrew informed consent
2 were ineligible for other reason
216 included in intention to treat analysis
216 included in intention to treat analysis

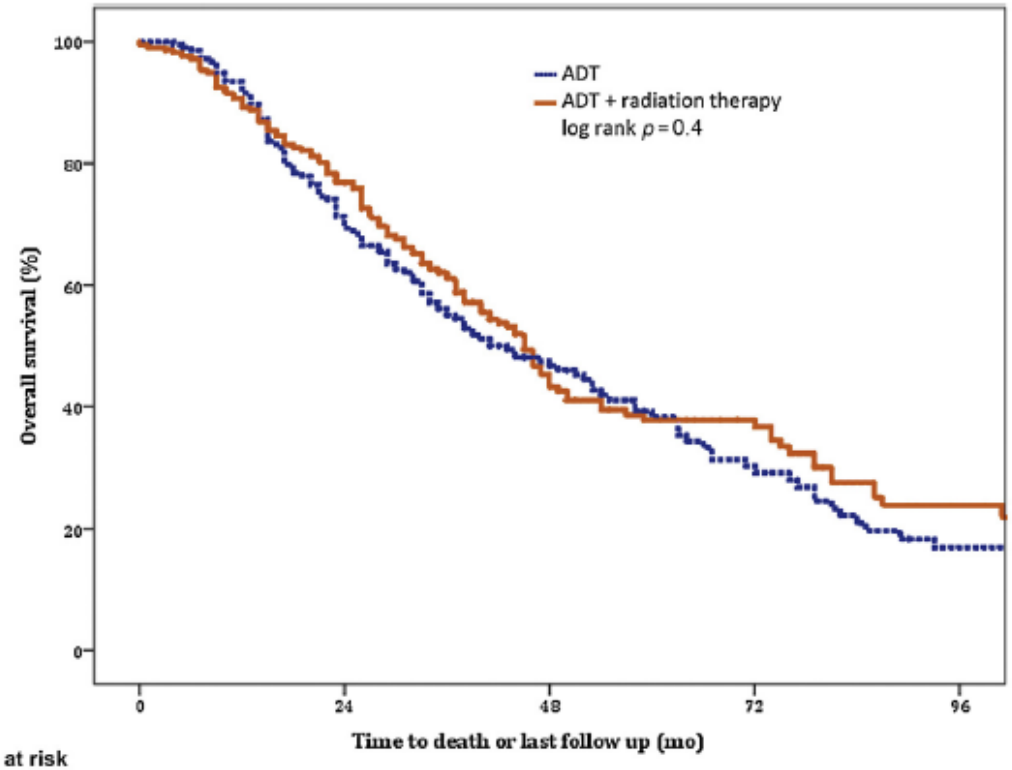
	ADT + radiotherapy (n = 216)[a]	ADT alone (n = 216)[a]
Age (range), yr.	67 (62–71)	67 (61–71)
PSA concentration at start of ADT, ng/ml		
Median (range).	125 (8–14 000)	149 (4–6991)
Q1	48	50
Q3	433	483
Missing data	3 (1)	5 (2)
ALP		
≤ULN	133 (61)	141 (65)
>ULN	51 (24)	54 (25)
Missing data	32 (15)	21 (10)
LDH		
≤ULN	92 (43)	95 (44)
>ULN	65 (30)	69 (32)
Missing data	59 (27)	52 (24)
Gleason sum score[b]		
6	7 (3)	7 (3)
7	66 (31)	64 (30)
8	48 (22)	65 (30)
9	85 (39)	72 (33)
10	9 (4)	7 (3)
Missing data	1 (1)	1 (1)
T stage		
1	7 (3)	5 (3)
2	33 (15)	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)

PSA 130 ng/ml

T4 25%

METS > 5-15 25%
> 15 35%

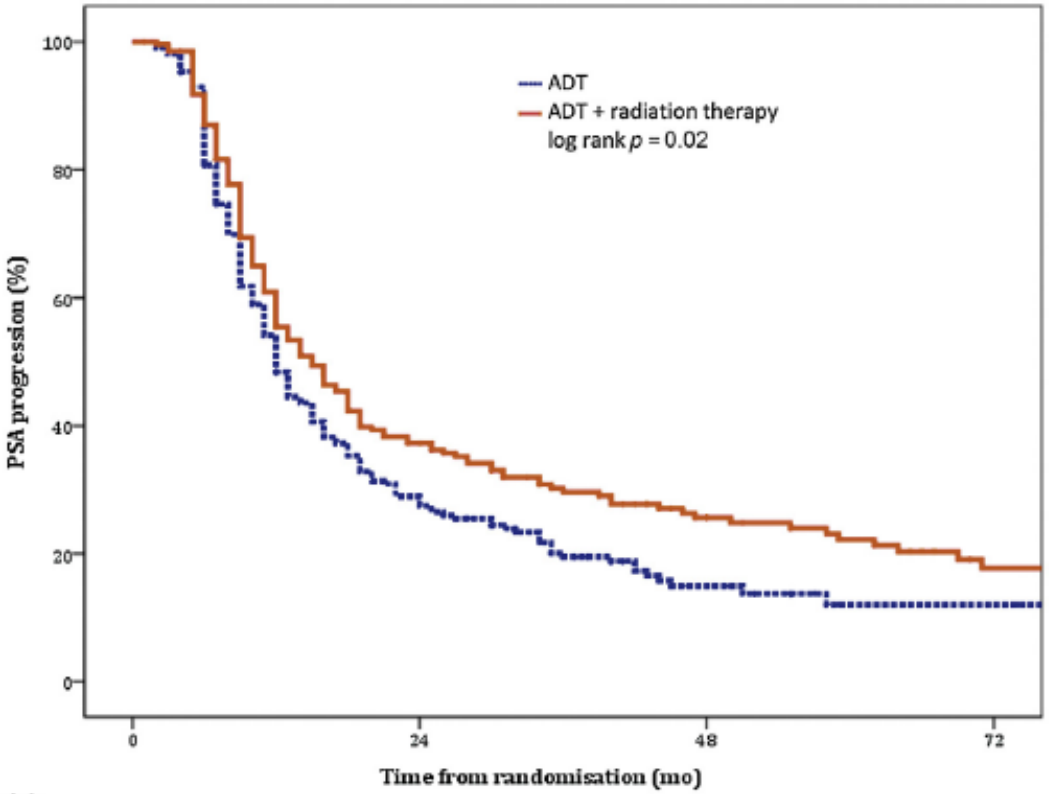
	ADT + radiotherapy (n = 131)[a]	ADT alone (n = 139)[a]
Time (range) to initiation of subsequent therapy, mo.	17 (12–25)	14 (10–30)
Any anticancer therapy	64 (49)	66 (48)
Missing data	2 (1)	2 (1)
Docetaxel	60 (46)	58 (42)
Cabazitaxel	12 (9)	9 (7)
Enzalutamide	11 (8)	18 (13)
Abiraterone	23 (18)	23 (17)
Other systemic treatment	13 (10)	8 (6)
Estracyt	2	2
Mitoxantrone	3	[illegible]
Orteronel	2	
Carboplatin	2	
Denosumab	1	
Ipilimumab	0	
Cabozantinib	0	
Cisplatinum	1	
Olaparib	1	
Pembrolizumab	1	
RA[223]	4 (3)	



No. at risk

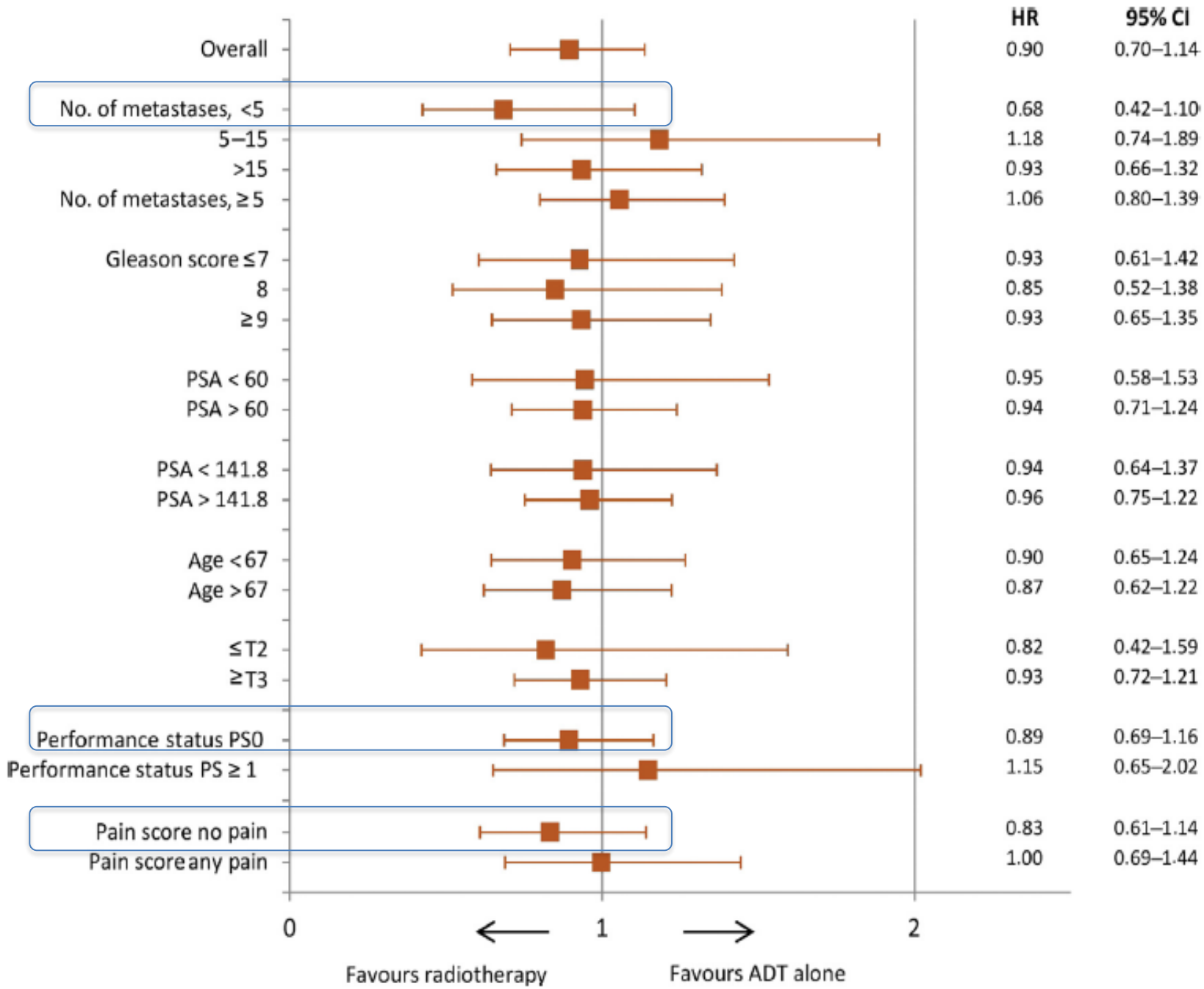
ADT	216	145	65	27	11
ADT + radiation therapy	215	161	61	33	13

Progresja PSA

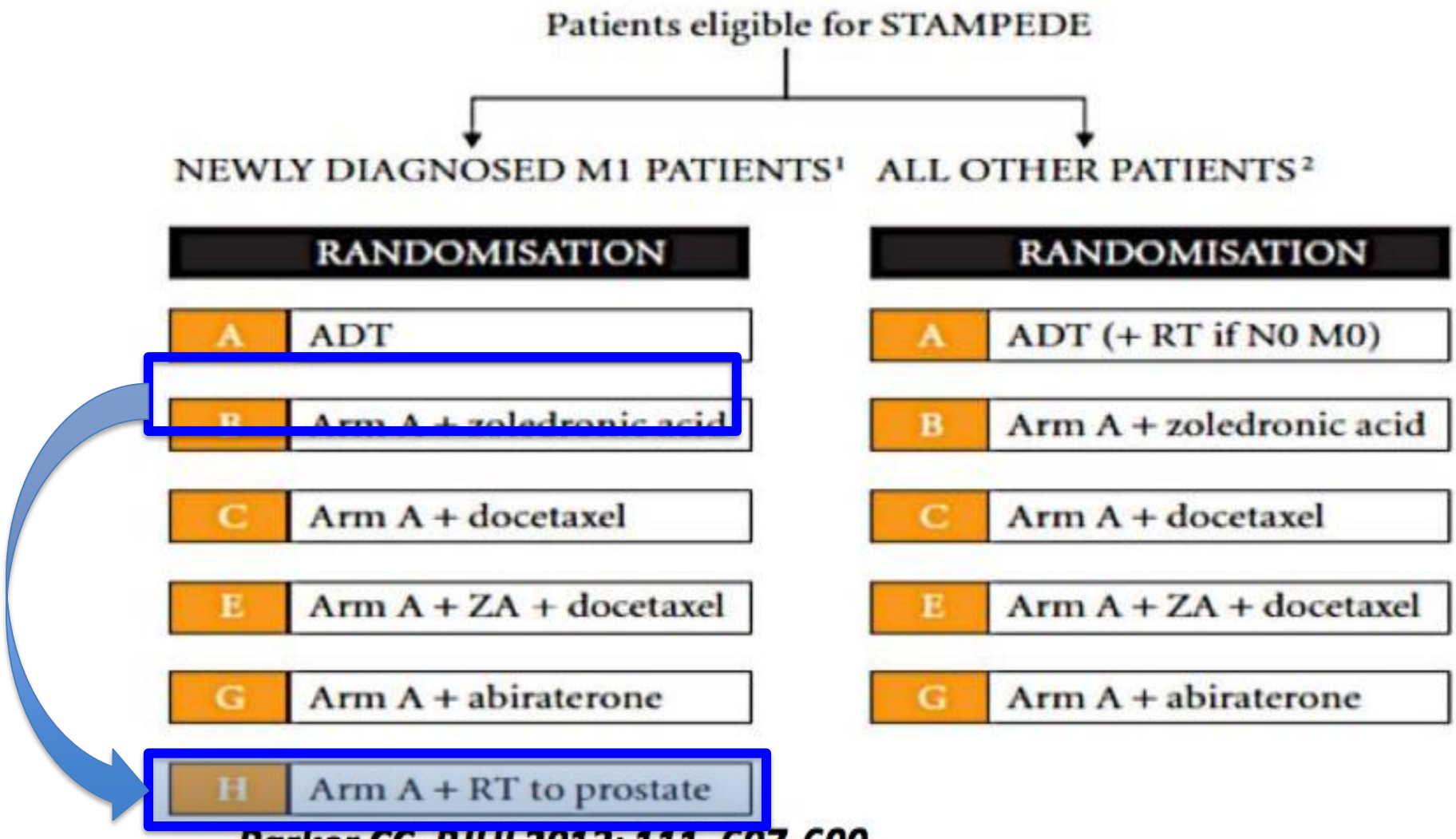


No. at risk

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


HR
95% CI
Overall 0.90 0.70–1.14
No. of metastases, <5 0.68 0.42–1.10
5–15 1.18 0.74–1.89
>15 0.93 0.66–1.32
No. of metastases, ≥5 1.06 0.80–1.39
Gleason score ≤7 0.93 0.61–1.42
8 0.85 0.52–1.38
≥9 0.93 0.65–1.35
PSA < 60 0.95 0.58–1.53
PSA > 60 0.94 0.71–1.24
PSA < 141.8 0.94 0.64–1.37
PSA > 141.8 0.96 0.75–1.22
Age <67 0.90 0.65–1.24
Age >67 0.87 0.62–1.22
≤T2 0.82 0.42–1.59
≥T3 0.93 0.72–1.21
Performance status PS0 0.89 0.69–1.16
Performance status PS ≥ 1 1.15 0.65–2.02
Pain score no pain 0.83 0.61–1.14
Pain score any pain 1.00 0.69–1.44
0
1
2
Favours radiotherapy
Favours ADT alone

STAMPEDE



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,

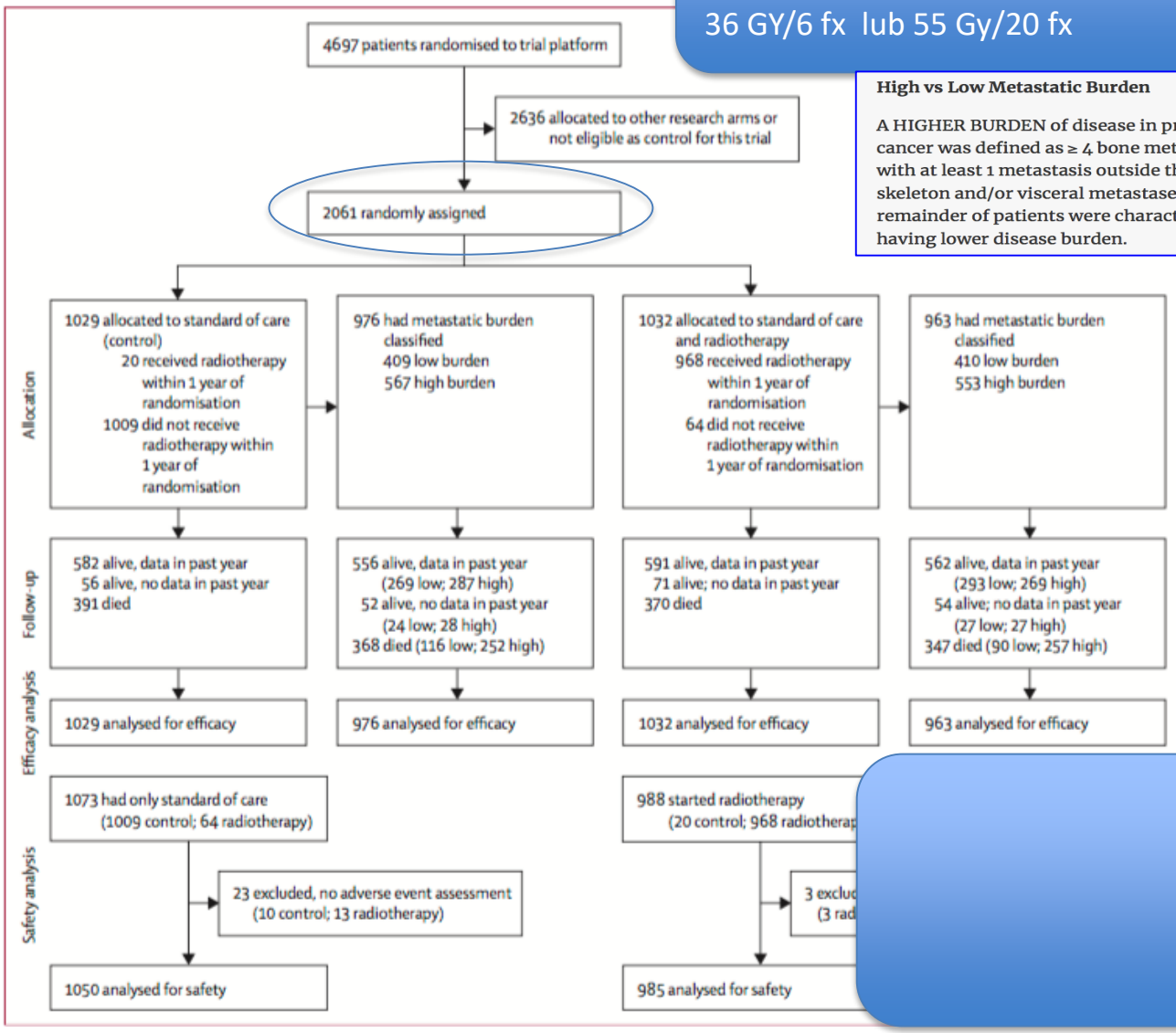
www.thelancet.com Published online October 21, 2018 http://dx.doi.org/10.1016/S0140-6736(18)32486-3

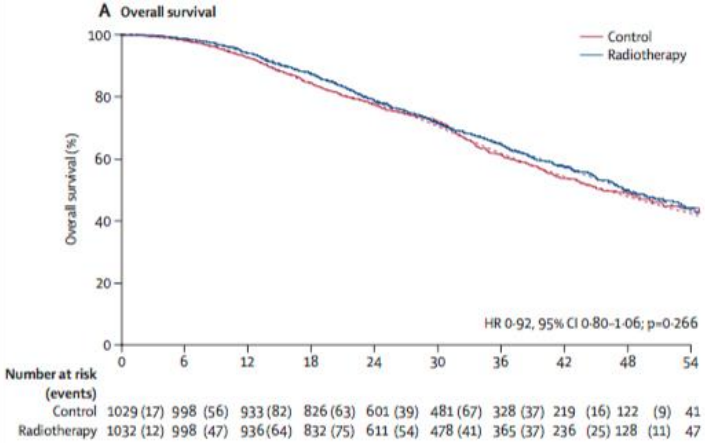
STANDARD OF CARE (ADT +/-CT)

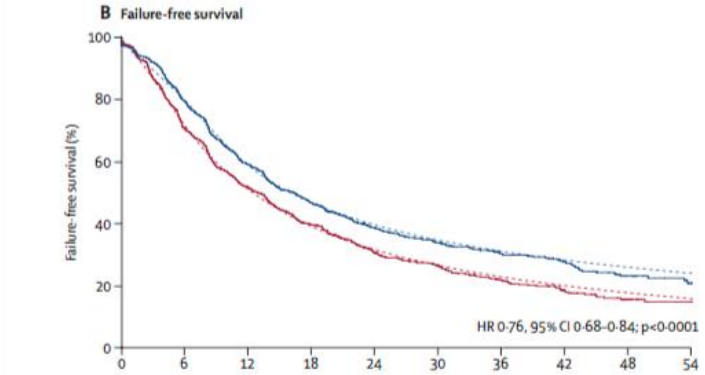
STANDARD OF CARE (ADT +/-CT) + RT PROSTATE
36 GY/6 fx lub 55 Gy/20 fx

High vs Low Metastatic Burden

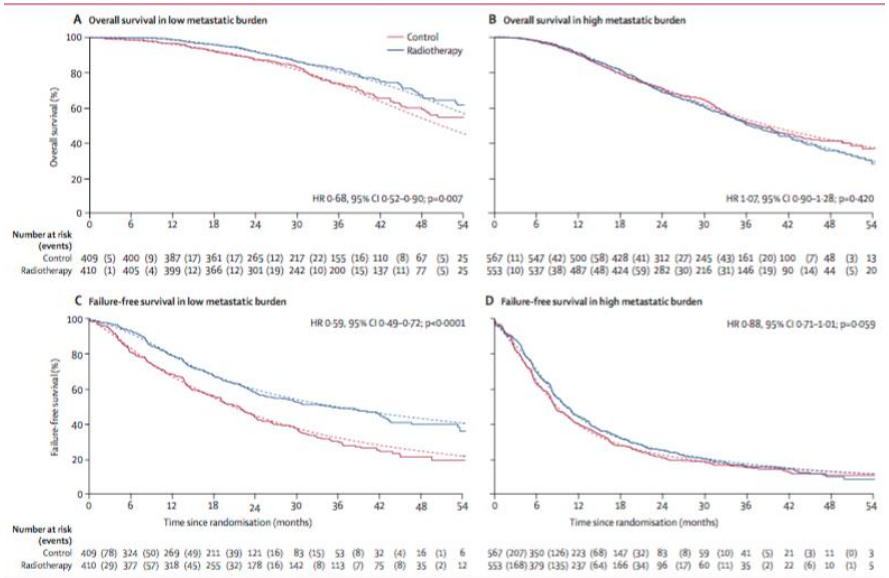
A HIGHER BURDEN of disease in prostate cancer was defined as ≥ 4 bone metastases, with at least 1 metastasis outside the axial skeleton and/or visceral metastases. The remainder of patients were characterized as having lower disease burden.

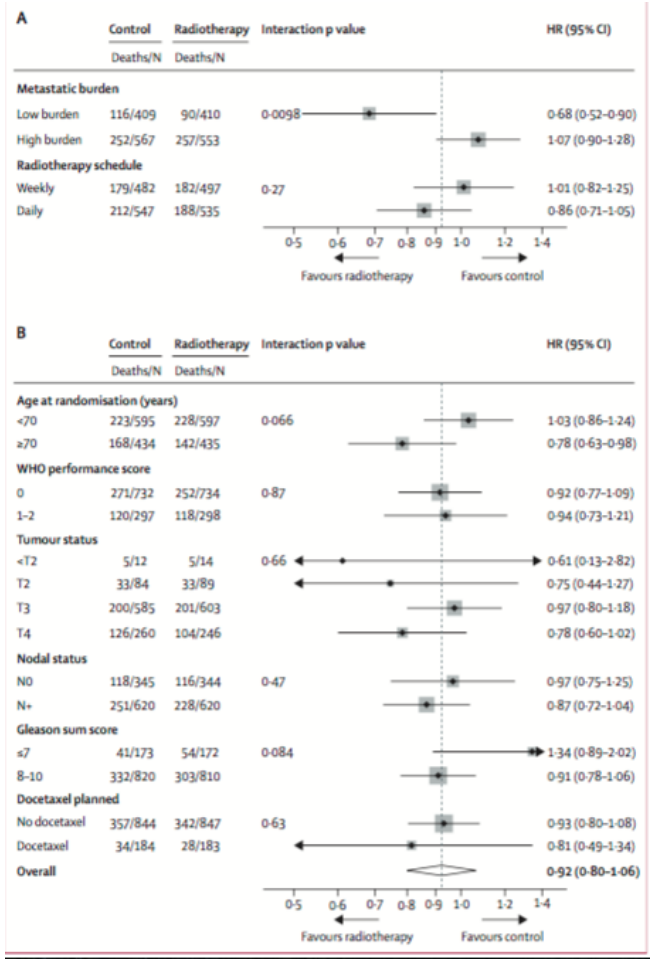






	Adjusted hazard ratio (95% CI)	Survival at 3 years*		Restricted mean survival time (months)*		
		Control	Radiotherapy	Control	Radiotherapy	Difference (95% CI)
Overall survival						
All patients	0·92 (0·80–1·06)	62%	65%	41·6	42·5	1·0 (–0·6 to 2·5)
Low metastatic burden	0·68 (0·52–0·90)	73%	81%	45·4	49·1	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)





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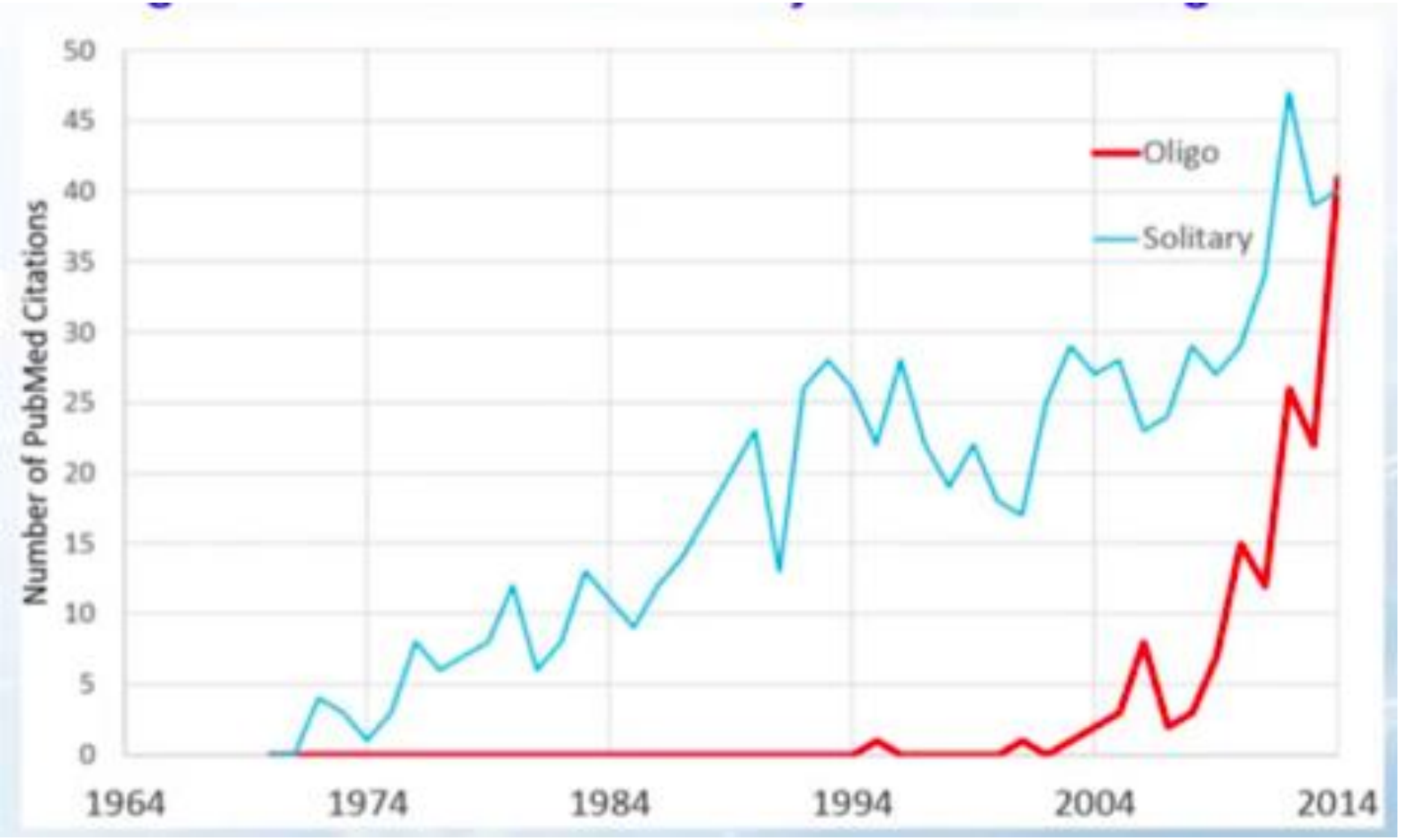
"We think these are robust and reliable findings. Going forward, prostate radiation should be a standard treatment option for men with newly diagnosed metastatic prostate cancer and low metastatic disease burden. Furthermore, we believe the results can be extrapolated to men with pelvic nodal disease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

Oligometastases are defined by new technology



Without Imaging „oligometastases" don't exist

Podsumowanie
Radioterapia w chorobie Oligometastatycznej

- Obiecująca metoda leczenia,
- Wyniki badań z 1-ramieniem wyglądają obiecująco, ale może tylko na wskutek selekcji chorych są tak dobre?
- Konieczna Definicja Choroby w stadium Oligometastatycznym,
- Konieczna definicja panelu diagnostycznego,
- Konieczne badania 3 Fazy: wyniki badania STAMPEDE !!!!
- Decyzja w zespole Interdyscyplinarnym (MDT)

PTRO

Polskie Badanie ?

Prospektywna ocena hipofrakcjonowanej stereotaktycznej radioterapii (SBRT) w skojarzeniu z Deprywacją Androgenową (ADT) u chorych z rakiem stercza z ograniczoną chorobą przerzutową (Oligometastases).