Martini-Klinik
Prostatakrebszentrum

Bedeutung der radikalen Prostatektomie bei Patienten mit einem begrenzt ossär metastasierten Prostatakarzinom

Markus Graefen, Martini-Klinik
Hamburg

Universitätsklinikum Hamburg-Eppendorf

UKE
HAMBURG

Lokale Therapie des mPCa bereits Therapiestandard...?

...bei N+ **ja**!

...bei M+ **ja** aber nur bei geringer Metastasenlast!

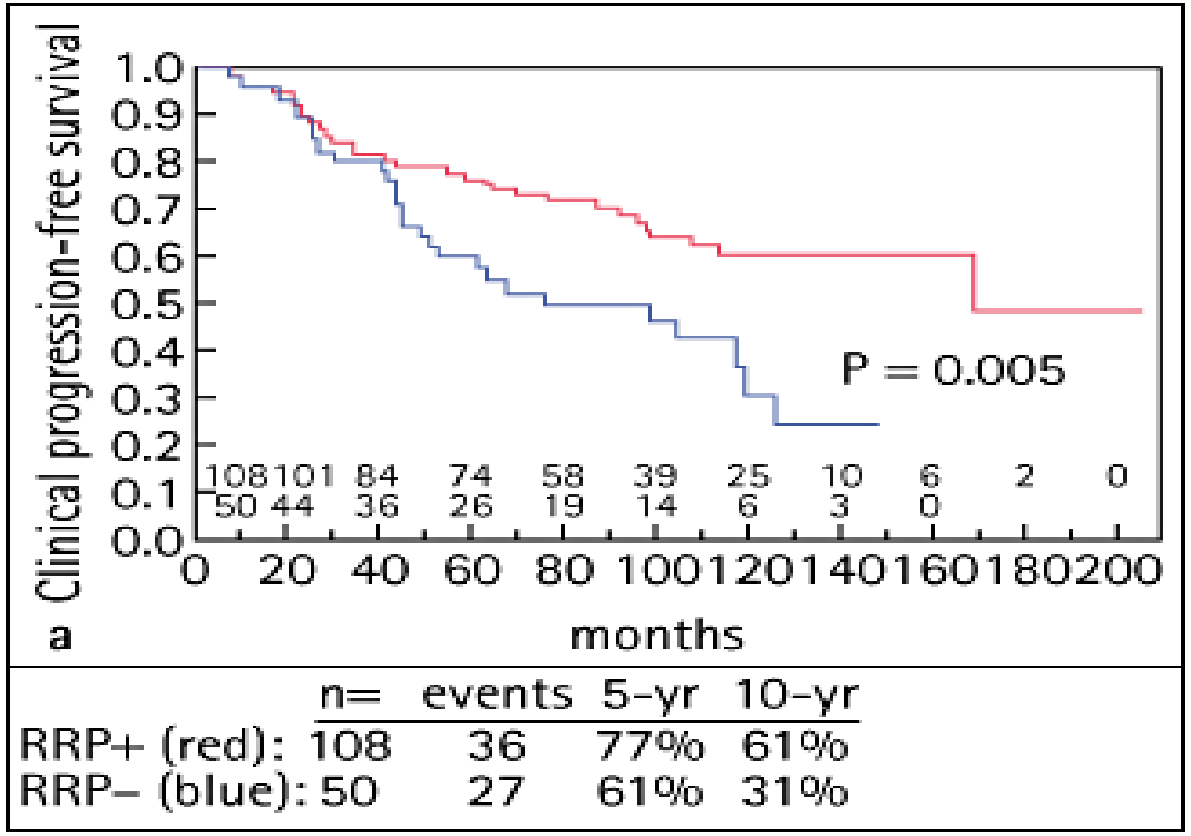
Paradigmenwechsel bei N+ Patienten...

...bei LN+ kein Abbruch der RP wegen “dramatischem Überlebensvorteil“

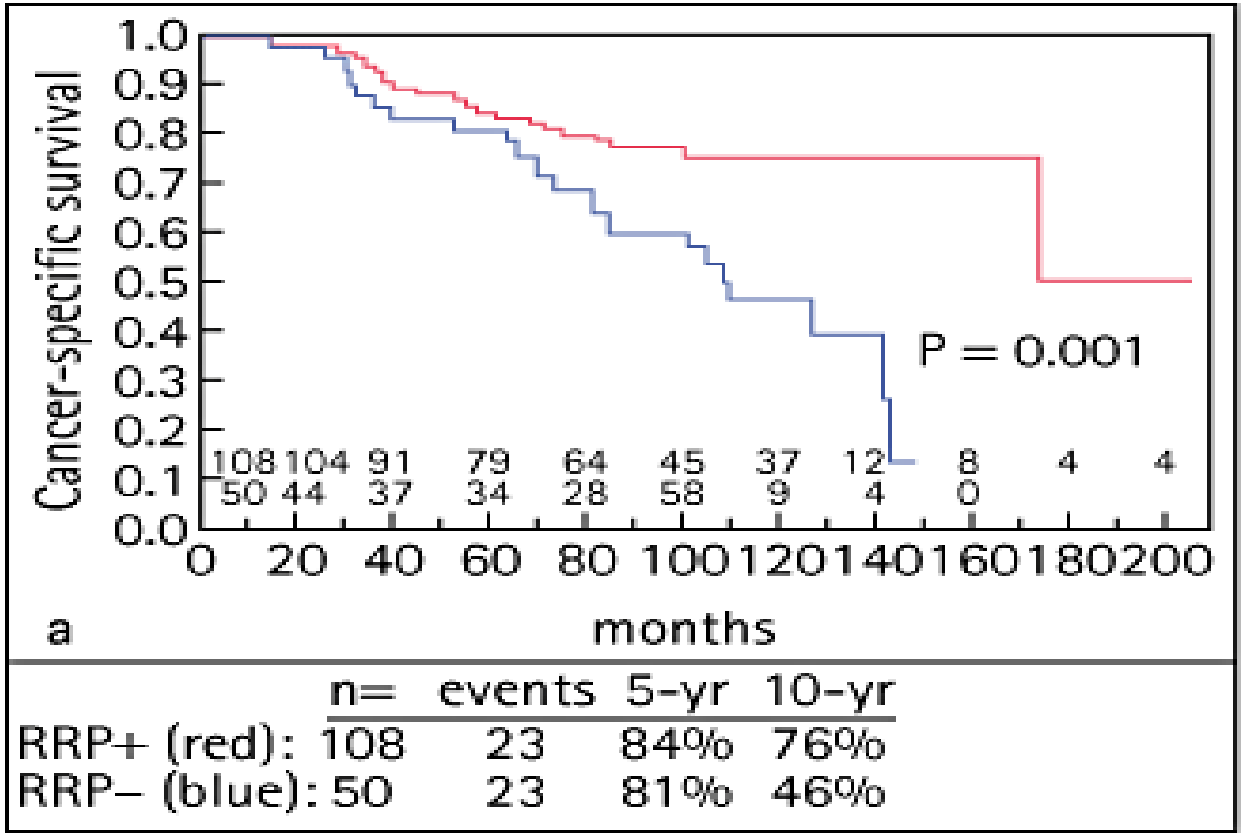
BJUI

Radical prostatectomy improves progression-free and cancer-specific survival in men with lymph node positive prostate cancer in the prostate-specific antigen era: a confirmatory study

Thomas Steuber*[1], Lars Budäus*[1], Jochen Walz[†], Kevin C. Zorn[†], Thorsten Schlomm*, Felix Chun[§], Sascha Ahyai[§], Margit Fisch[§], Guido Sauter[¶], Hartwig Huland*, Markus Graefen* and Alexander Haese*

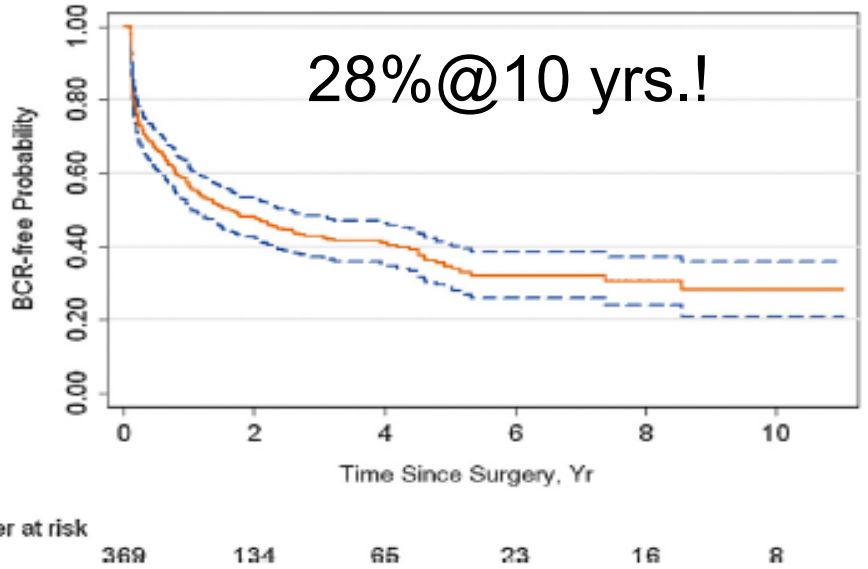


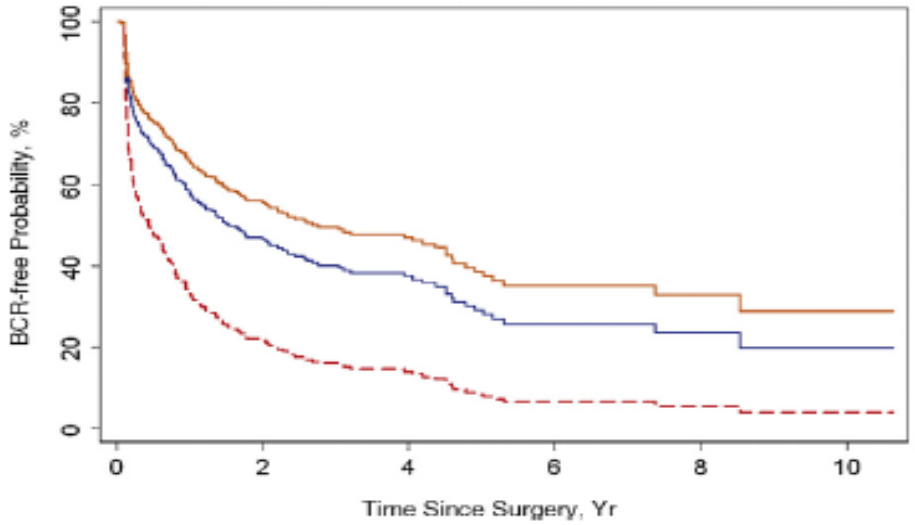
	n=	events	5-yr	10-yr
RRP+ (red):	108	36	77%	61%
RRP– (blue):	50	27	61%	31%



	n=	events	5-yr	10-yr
RRP+ (red):	108	23	84%	76%
RRP– (blue):	50	23	81%	46%

LN+ können durch alleinige RP + PLND geheilt werden!





Risk factor	HR	95% CI	*p* value
PSA	1.00	0.99–1.02	0.6
Pathologic Gleason score >7	4.05	1.94–8.45	0.0002
Extraprostatic extension	3.77	0.91–15.73	0.068
Seminal vesicle invasion	2.67	1.34–5.32	0.005
Positive surgical margin	1.32	0.68–2.53	0.4
Positive nodes, no.			
1	ref	ref	–
2	0.31	0.07–1.32	0.11
≥3	1.96	0.96–4.02	0.065

HR = hazard ratio; CI = confidence interval; PSA = prostate-specific antigen; ref = reference.

Toujier et al, Eur Urol 2014

...lokale in M+ PCa?

European Association of Urology

Guidelines for the first-line treatment of metastatic prostate cancer

Treatment type	Modality	Recommendation	LE	GR
Castration combined with chemotherapy	Docetaxel combined with castration	Offer castration combined with chemotherapy to all patients whose first presentation is M1 disease and who are fit enough for chemotherapy.	1a	A
Castration alone	Surgical, LHRH agonist, OR LHRH antagonist	Offer castration alone with or without an anti-androgen to patients unfit for, or unwilling to consider, castration combined with chemotherapy.	1b	A
		Do not prescribe abiraterone acetate or enzalutamide outside of a clinical trial.	3	A
Castration combined with any local treatment	Radiotherapy/Surgery	Use castration combined with local treatment in an investigational setting only.	3	A

Evidenzlage der radikalen Prostatektomie...

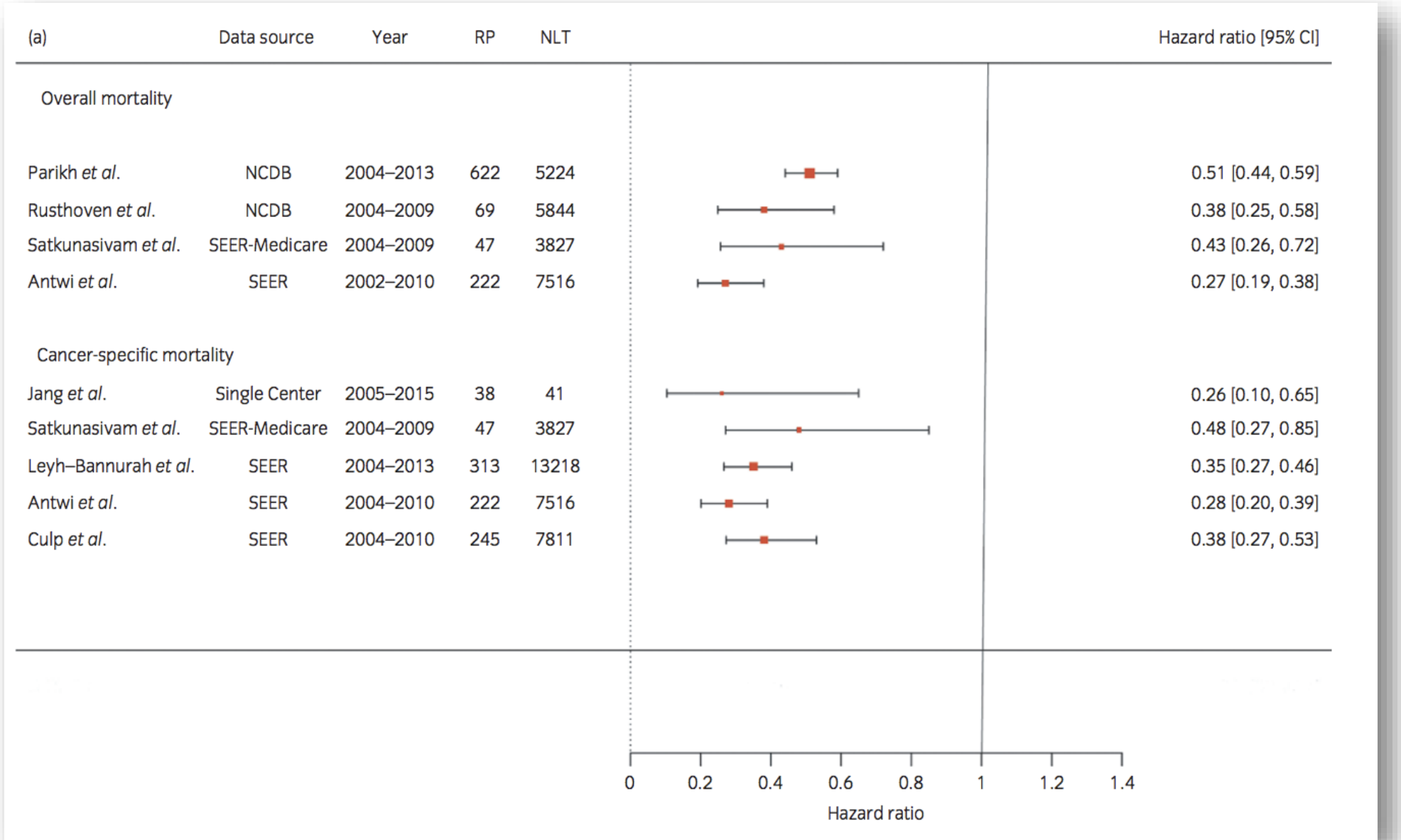
- Keine randomisierten Studien oder prospektive Daten

16 Original Paper:

-12 Full articles, 3 Brief Correspondences, and 1 Letter to the Editor

- 4 SEER Database, 1 SEER-Medicare
- 3 National Cancer Database
- 7 Institutional data (2/7 multi-institutional)
- 1 Munich registry

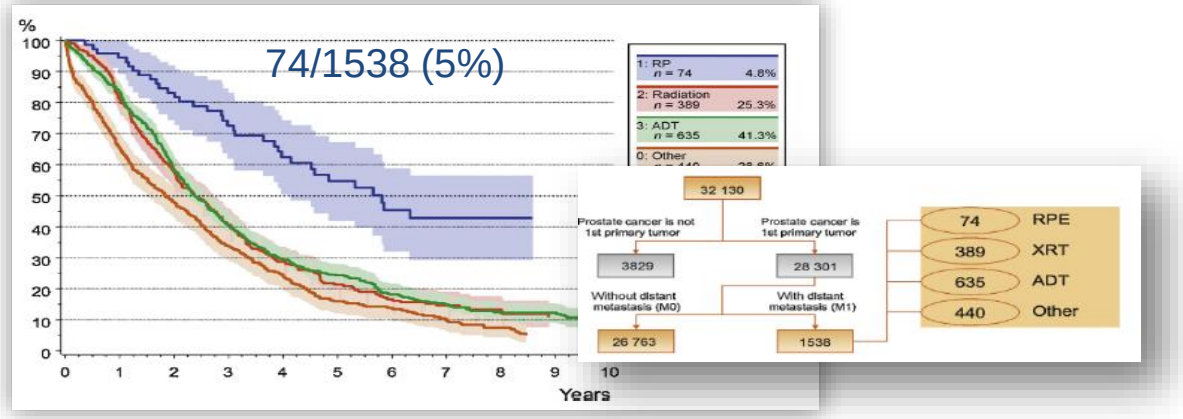
Tilki et al., Int J of Urol, 2018



Tilki et al., International Journal of Urology, 2018

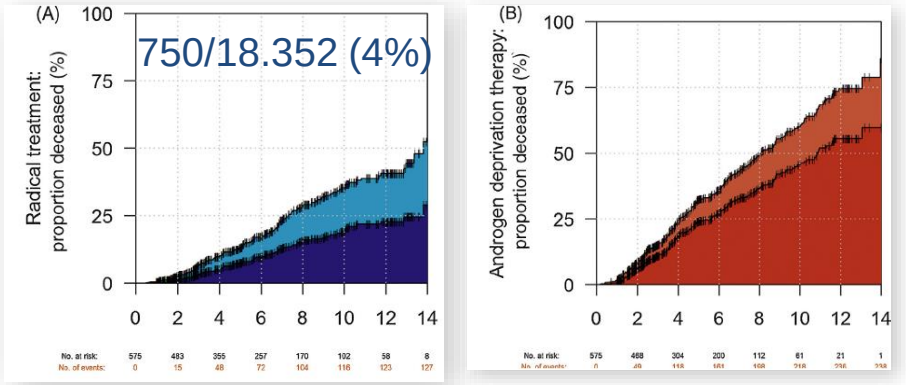
Retrospektive Analysen nach RP bei M+ PCa

Münchner Tumorregister



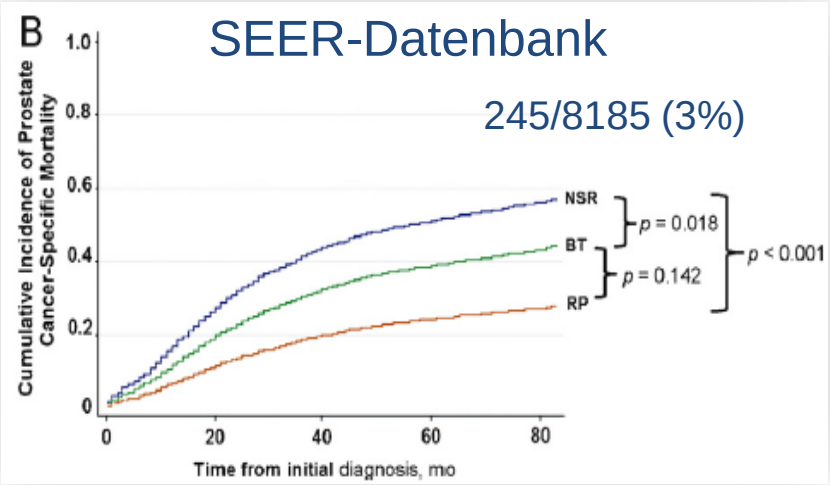
Gratzke et al., Eur Urol 2014

Prostate Cancer Register Schweden (RP)



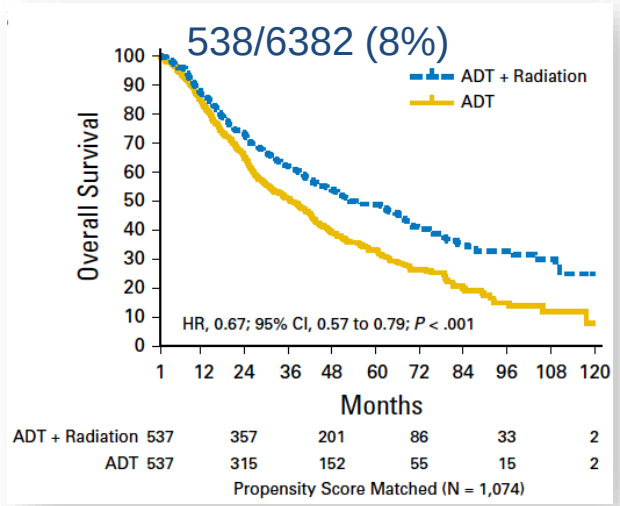
Sooriakumaran et al., Eur Urol 2017

SEER-Datenbank



Culp et al., Eur Urol 2014

National Cancer Database (RT)



Rusthoven et al., J Clin Oncol 2017

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

European Association of Urology

Brief Correspondence

Identifying Optimal Candidates for Local Treatment of the Primary Tumor Among Patients Diagnosed with Metastatic Prostate Cancer: A SEER-based Study

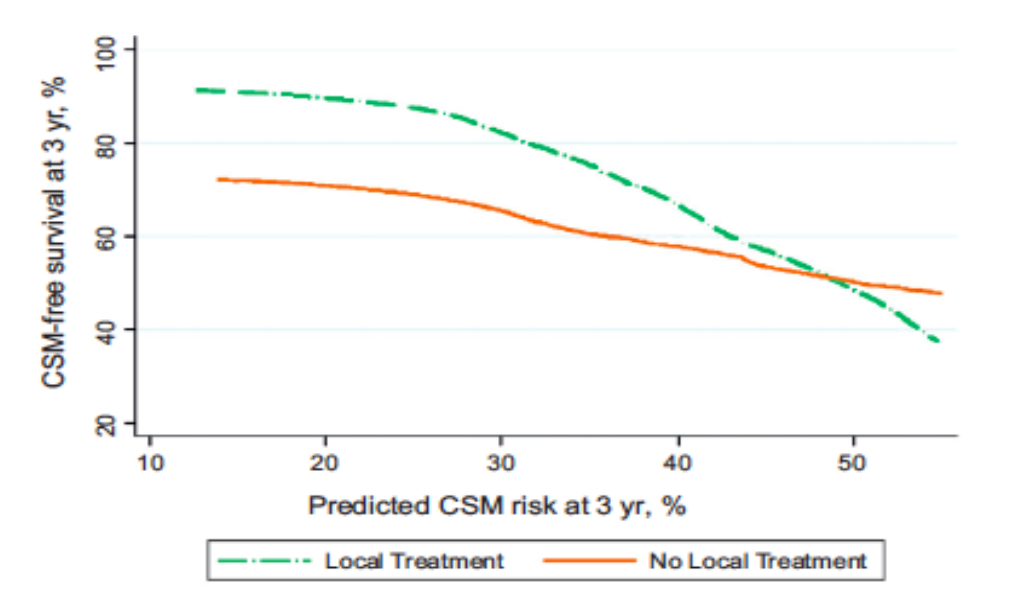
Nicola Fossati [a,b], Quoc-Dien Trinh [c], Jesse Sammon [d], Akshay Sood [d], Alessandro Larcher [b,e], Maxine Sun [e], Pierre Karakiewicz [e], Giorgio Guazzoni [b], Francesco Montorsi [b], Alberto Briganti [b], Mani Menon [d], Firas Abdollah [d,]*

Eur Urol 2015

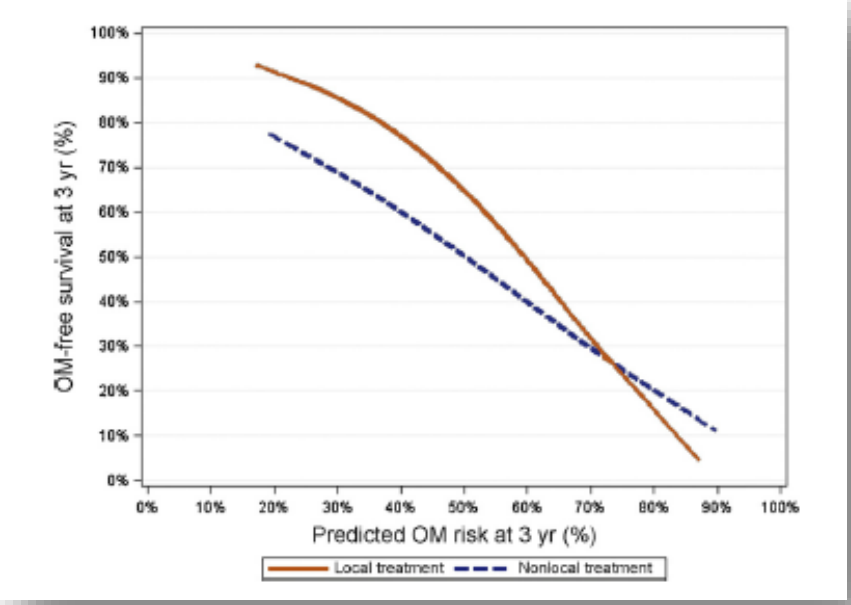
The Impact of Local Treatment on Overall Survival in Patients with Metastatic Prostate Cancer on Diagnosis: A National Cancer Data Base Analysis

Björn Löppenberg [a,b,†], Deepansh Dalela [a,†], Patrick Karabon [a,c], Akshay Sood [a], Jesse D. Sammon [a], Christian P. Meyer [d], Maxine Sun [d], Joachim Noldus [b], James O. Peabody [a], Quoc-Dien Trinh [d], Mani Menon [a], Firas Abdollah [a,]*

Eur Urol 2017



SEER data



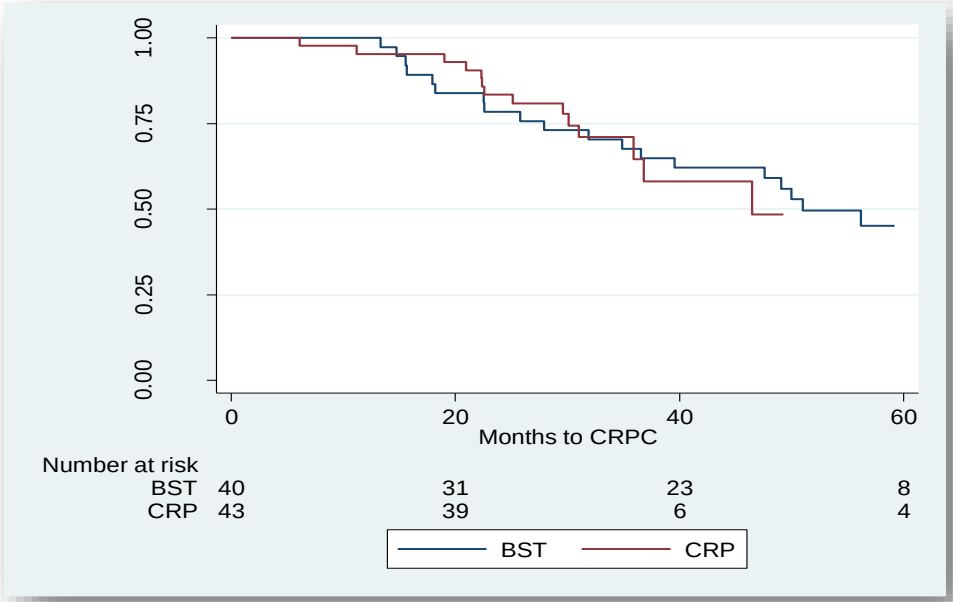
National Cancer Database

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

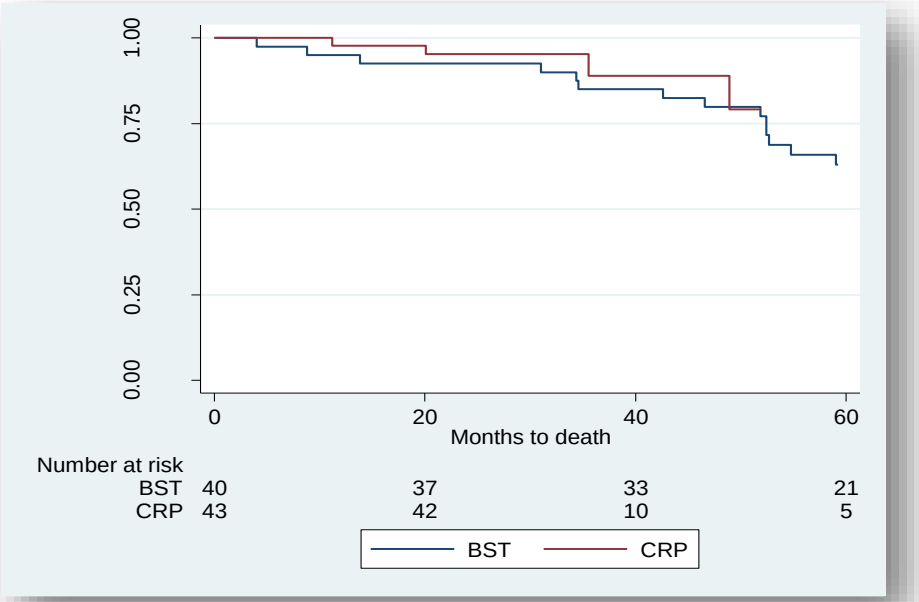
Thomas Steuber[a,†,*], *Kasper D. Berg*[b,†], *Martin A. Røder*[b], *Klaus Brasso*[b], *Peter Iversen*[b], *Hartwig Huland*[a], *Anne Tiebel*[a], *Thorsten Schlomm*[a], *Alexander Haese*[a], *Georg Salomon*[a], *Lars Budäus*[a], *Derya Tilki*[a], *Hans Heinzer*[a], *Markus Graefen*[a], *Philipp Mandel*[a]

EUROPEAN UROLOGY FOCUS

Eur Urol Focus, 2017

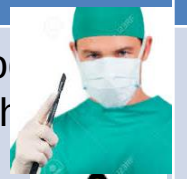


CRPC-freies Überleben

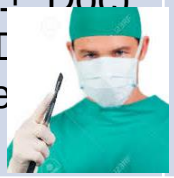


Gesamtüberleben

Studientitel	Institution und Details	Intervention	Studienendpunkte
Best Systematic Therapy or Best Sytematic Therapy (BST) Plus Definitive Treatment (Radiation or Surgery) [22]	M.D. Anderson, USA Phase II N=120 NCT01751438	Rad. Prostatektomie o Radiatio plus Systemth vs. Systemtherapie	Progressionsfreies Überleben Lebensqualität
Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy. **STAMPEDE** Trial, Arm H [23]	Multiinstitutional, England und Schweiz 2005–2017 Phase III NCT00268476	Standard of care (ADT) vs. Standard of care plus Radiatio	Gesamtüberleben Progressionsfreies Überleben
HORRAD Study [24] Radiatio vs.keine Radiatio	Multiinstitutional, Niederlande N=446, 2004–2011 Rekrutierung komplettiert ISRCTN06890529	ADT vs. ADT und Radiatio	Gesamtüberleben Progressionsfreies Überleben Lebensqualität
EORTC-1201-GUCG-ROG.**(PEACE-1)** [25]	Multiinstitutional, Europa N=15501, 2004–2012 NCT01957436	Arm A: ADT (± Doc) vs. Arm B: ADT (± Doc) plus Abirateron vs. Arm C: Arr plus Radiatio vs. Arm D: B plus Radiatio	Gesamtüberleben Progressionsfreies Überleben, QoL
AP 75/**G_RAMPP** – Multizentrische prospektive randomisierte Studie zur [26]	Multiinstitutional, Deutschland N=452,, 2015–2025 NCT02454543	Systemtherapie (ADT ± Doc) vs. Systemtherapie (AD Doc) plus rad. Prostate	Gesamtüberleben Progressionsfreies Überleben





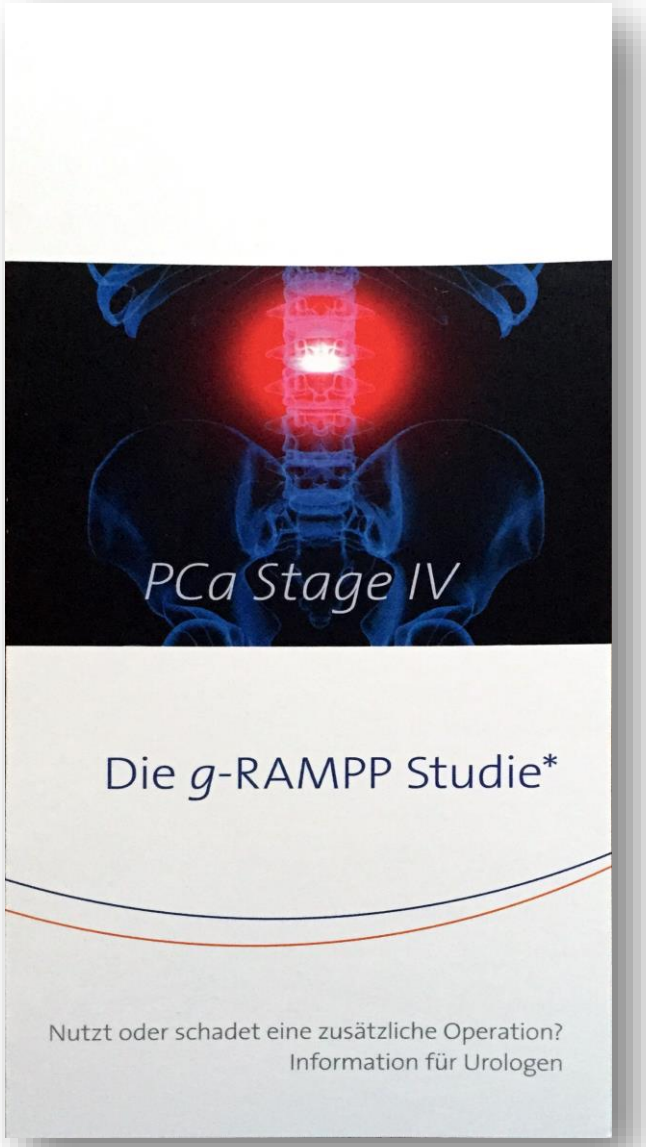



RAMPP Studie

A randomized controlled trial comparing ***R***adical prostatectomy plus neoadjuvant hormones with ***A***ndrogen deprivation therapy alone in the ***M***anagement of men with ***P***auci-metastatic ***P***rostate cancer

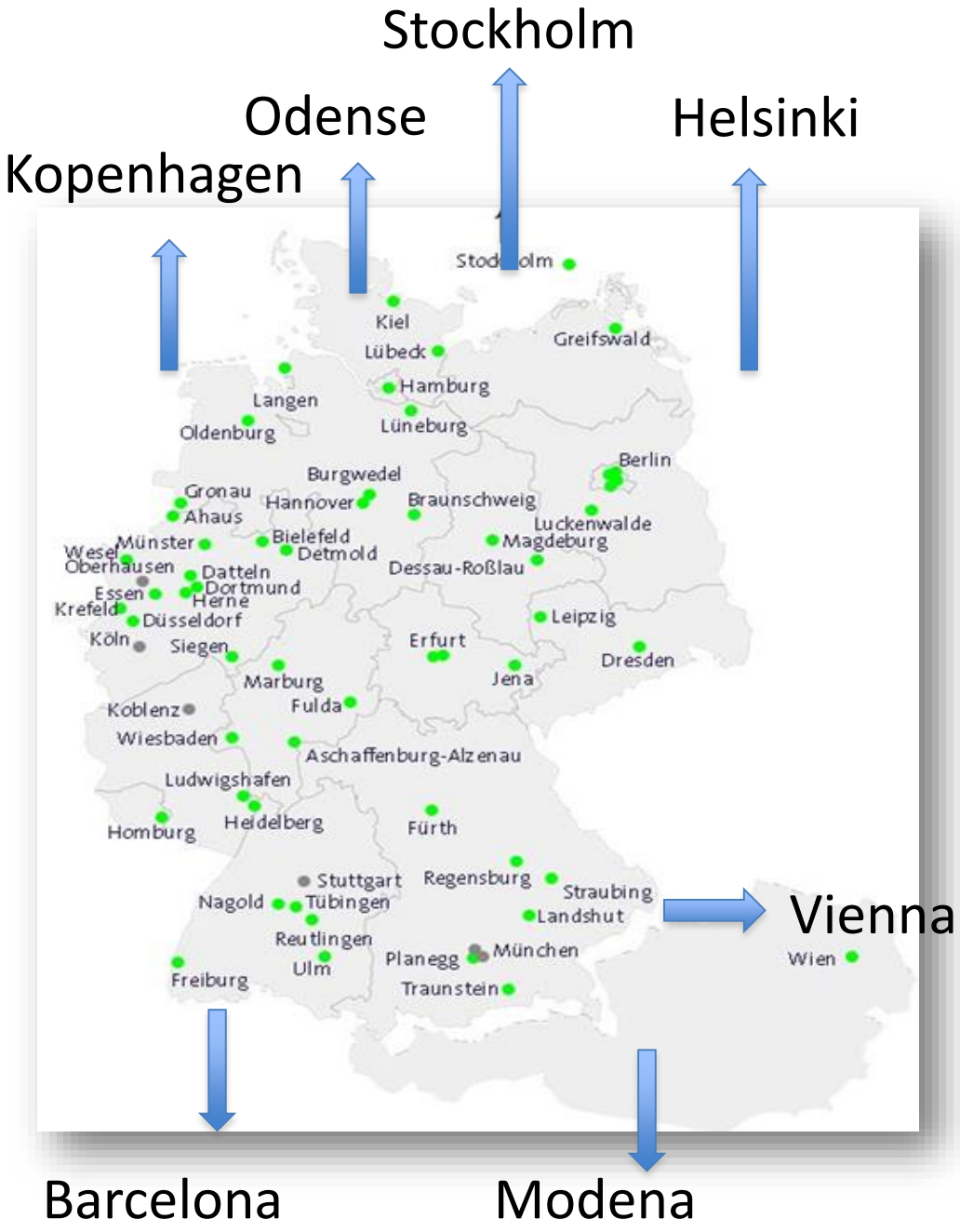
Histologisch gesichertes Prostata-Ca
(innerhalb von ≤6 Monaten)

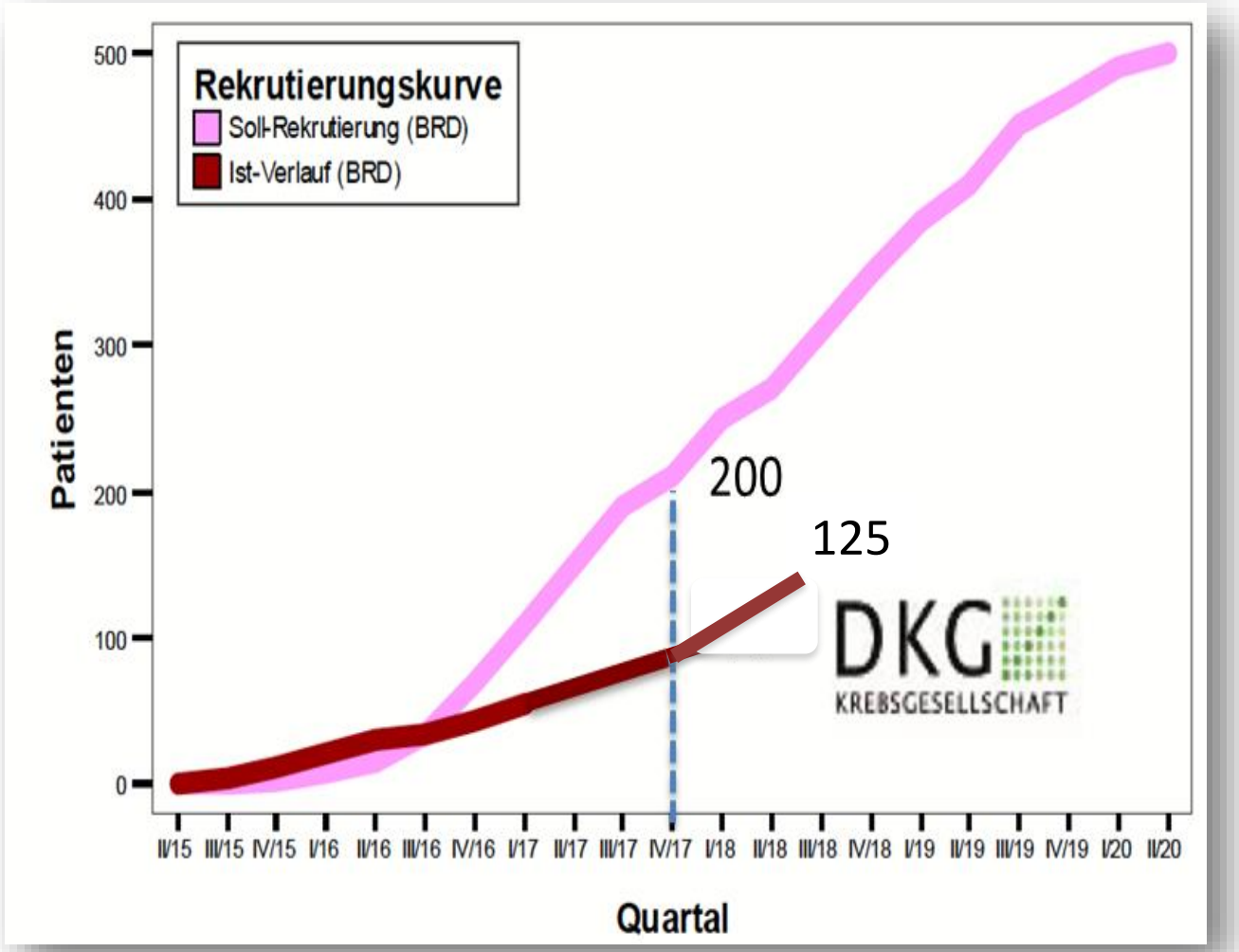
- 1-5 Knochenmetastasen
  (Knochenscan, CT/MRT, PET-CT)
- PSA bei Diagnose < 200 ng/ml
- asymptomatisch oder mild symptomatisch
- Lokal rektabel(klinisch ≤T3)
- ECOG Performance Status 0-1
- Alter≥ 18 -≤ 75 Jahre



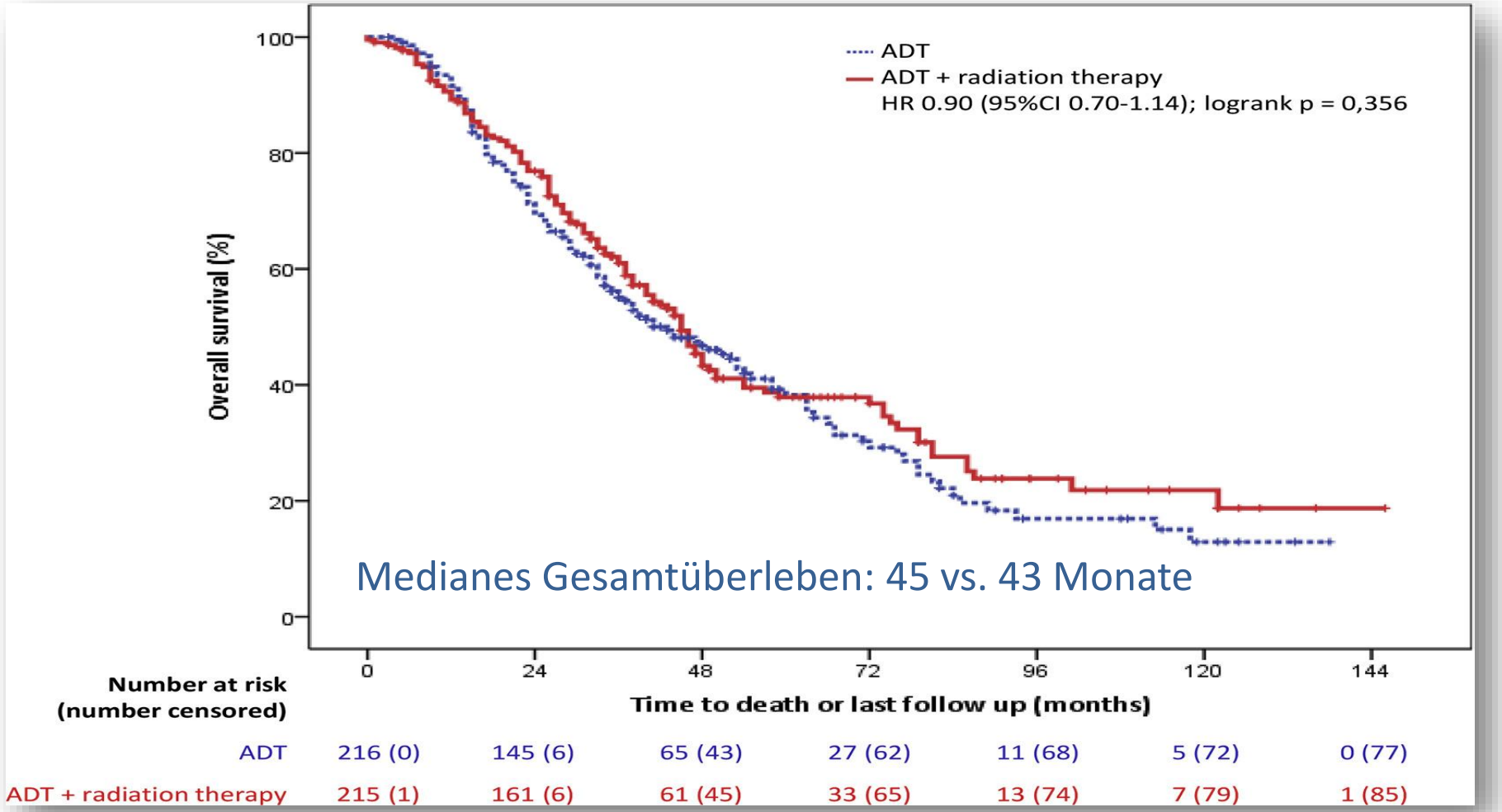
- Primärer Endpunkt: CSS @ 5 Jahren

130 Patienten rekrutiert...



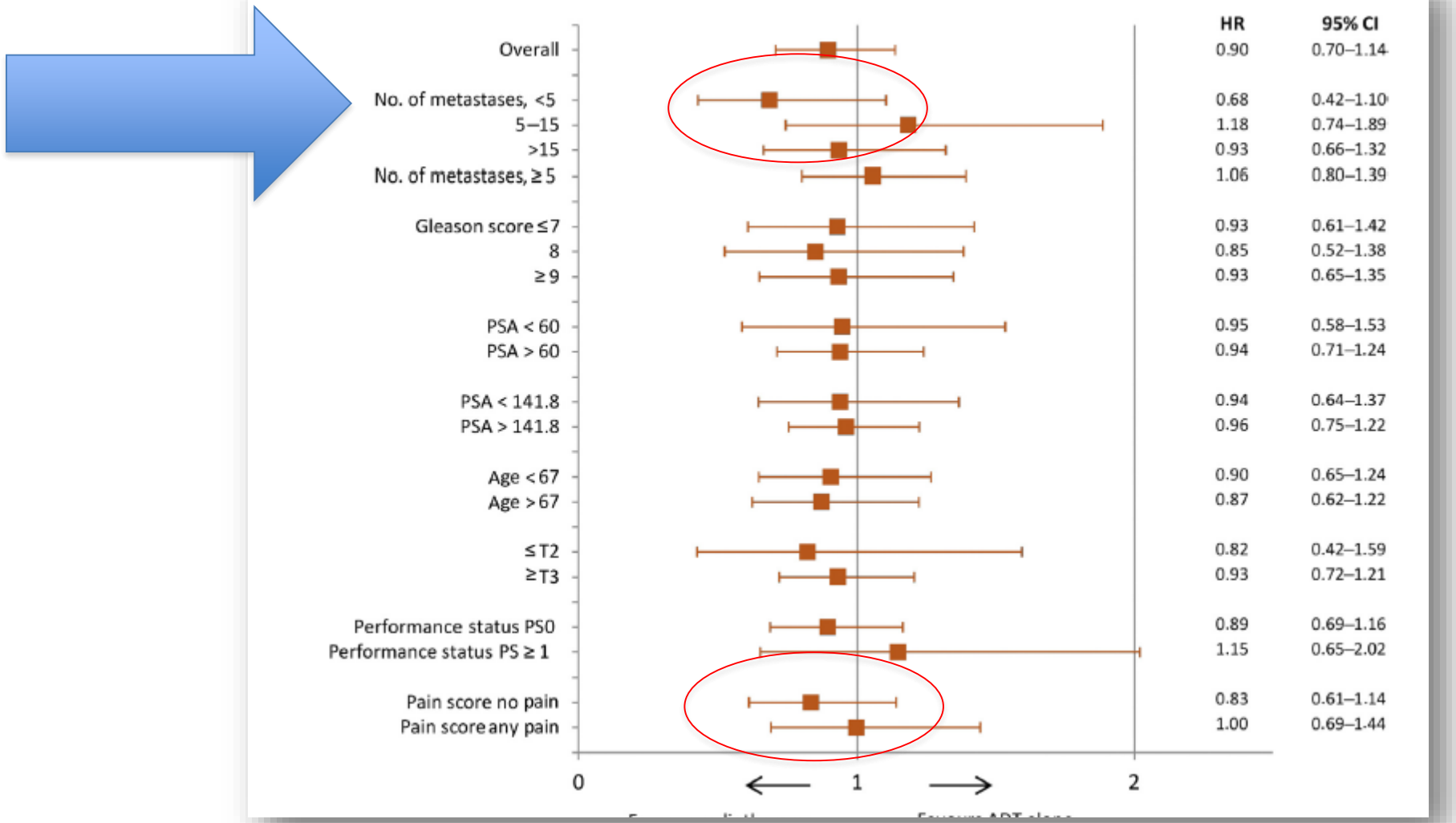


HORRAD Studie



The Journal of Urology 2018 199, e231-e232DOI: (10.1016/j.juro.2018.02.620)

HORRAD Studie



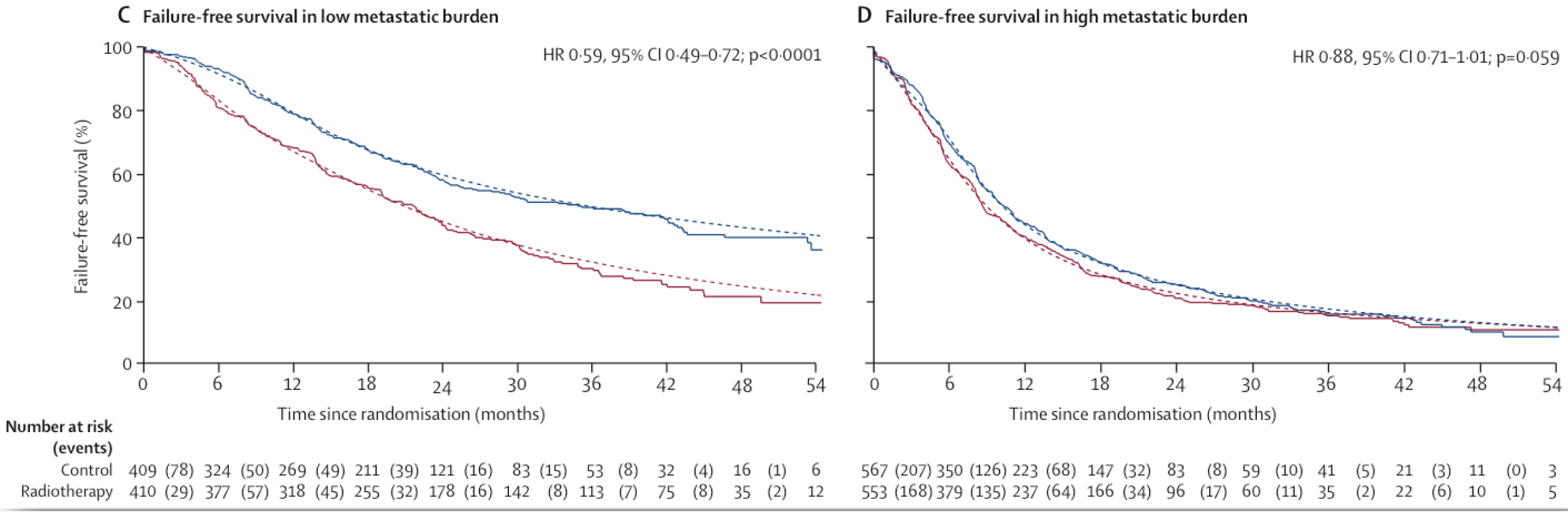
Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial

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, Hassan Douis, Chinnamani Eswar, Joanna Gale, Melissa R Gannon, Sai Jonnada, Sara Khaksar, Jason F Lester, Joe M O'Sullivan, Omi A Parikh, Ian D Pedley, Delia M Pudney, Denise J Sheehan, Narayanan Nair Srihari, Anna T H Tran, Mahesh K B Parmar, Matthew R Sydes*, on behalf of the Systemic Therapy for Advanced or Metastatic Prostate cancer: Evaluation of Drug Efficacy (STAMPEDE) investigators†*

The Lancet
21.10.2018

- Rolle der lokalen Strahlentherapie beim metastasierten PCa
- RCT 117 Krankenhäuser in UK und Schweiz
- Rekrutierung 1/2013 – 9/2016
- n=2016
- Bestrahlung hypofraktioniert (6 x 6 Gy (48%) oder 20 x 2.75 Gy (52%))
- Kontrollgruppe: alleinige Hormontherapie (82%) und ab 12/2015 zusätzlich Docetaxel (18%)

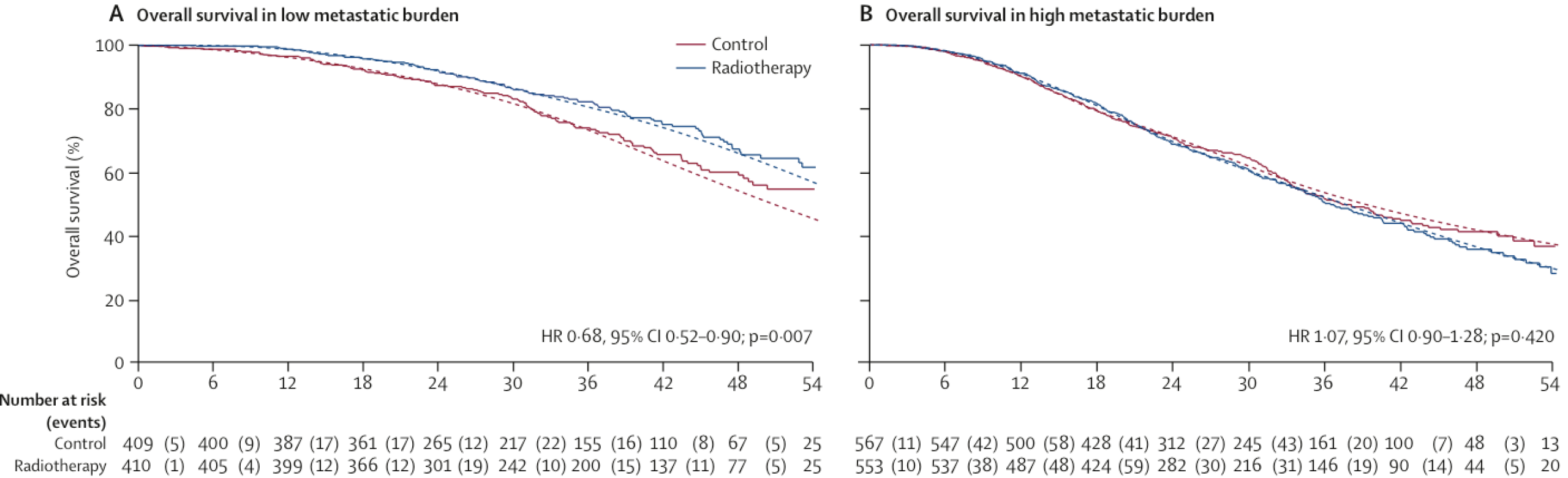
Rezidiv-freies Überleben



Geringe Metastasenlast

Hohe Metastasenlast

Gesamtüberleben



Geringe Metastasenlast

Hohe Metastasenlast

Interpretation: Radiotherapy to the prostate did not improve overall survival for unselected patients with newly diagnosed metastatic prostate cancer

Aber:

Implications of all the available evidence

Evidence suggests that prostate radiotherapy improves overall survival for men with metastatic prostate cancer who have a **low metastatic burden**, but not for unselected patients.

Prostate radiotherapy should be a **standard treatment option** for men with newly diagnosed disease with a **low metastatic burden**.

Role of Abiraterone Acetate + Prednisolone + ADT in High and Low Risk Metastatic Hormone Naïve Prostate Cancer

Mr Alex Hoyle MBChB MRCS

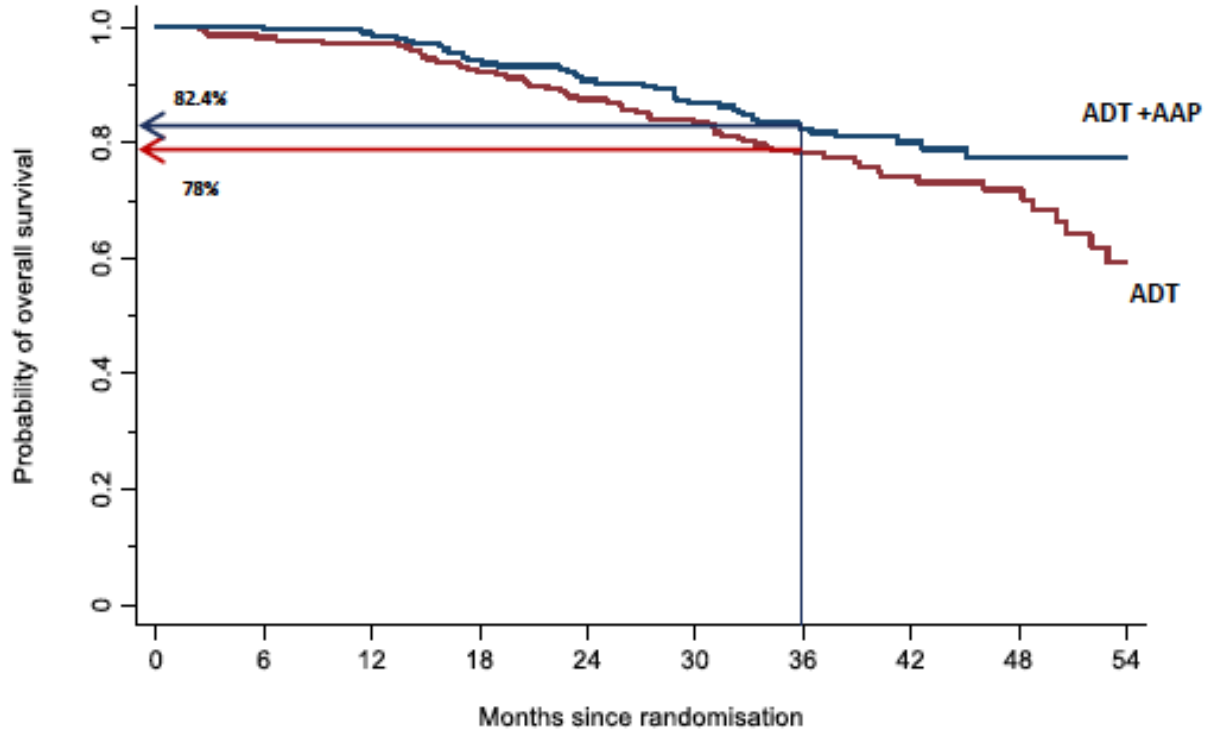
(Christie GenitoUrinary Research Group Fellow, UK)

Adnan Ali, Nick James, Chris Parker, Adrian Cook, Gert Attard, Simon Chowdhury, Bill Cross, David Dearnaley, Johann de Bono, Clare Gilson, Silke Gillessen, Rob Jones, David Matheson, Malcolm Mason, Alastair Ritchie, Martin Russell, Max Parmar, Matt Sydes, Noel Clarke;

for the STAMPEDE trial

RESULTS: OVERALL SURVIVAL

Low Risk

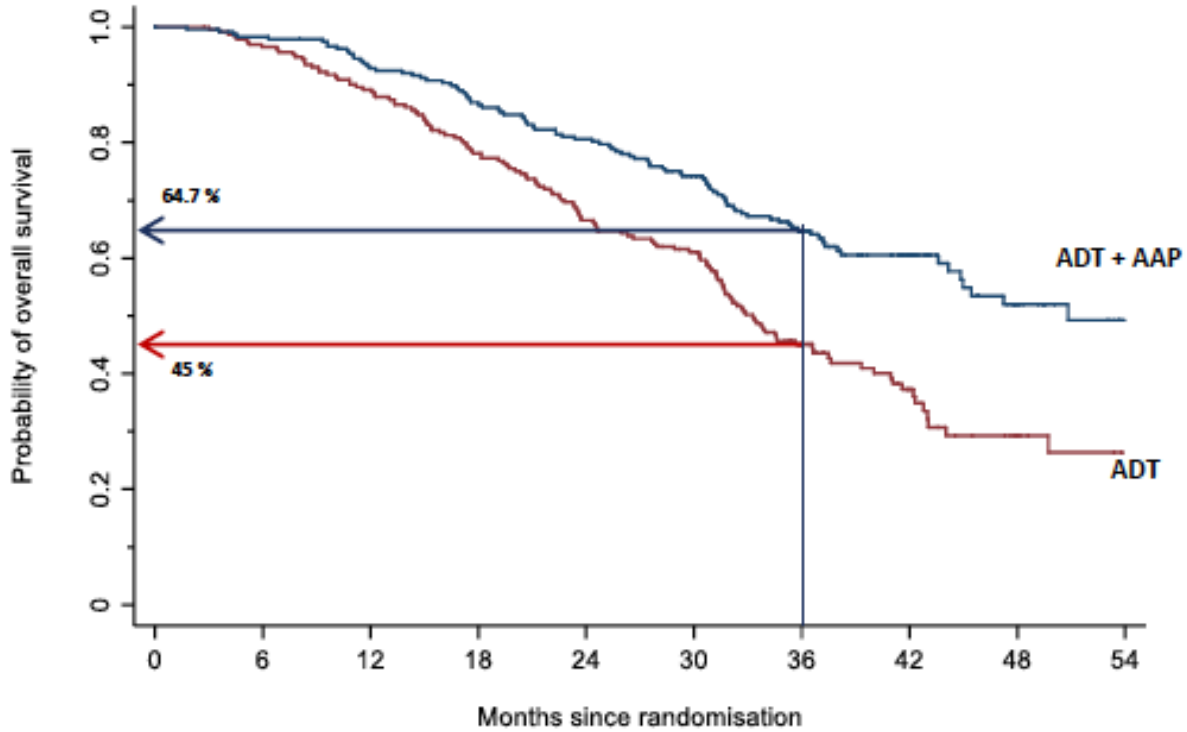


No. of patients (Events)

AAP	208	(2)	205	(17)	186	(16)	131	(5)	45
ADT alone	220	(6)	210	(21)	186	(19)	125	(7)	43

OS - 4.4%
HR 0.66 (0.44-0.98)
p=0.041

High Risk



No. of patients (Events)

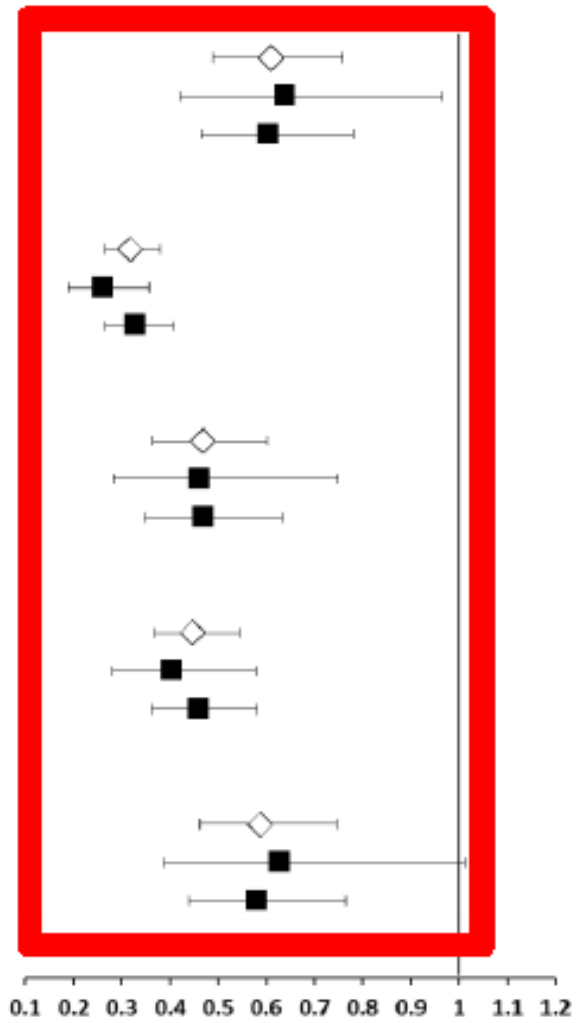
AAP	241	(17)	220	(29)	190	(35)	106	(12)	28
ADT alone	232	(25)	204	(51)	148	(44)	71	(15)	13

OS – 19.7%
HR 0.54 (0.41-0.70)
p<0.001

MUNICH 2018 ESMO congress

CHAARTED VOLUME CRITERIA

	ADT alone	AAP	Adjusted HR[a] (95%CI)	p-value	Interaction by metastatic volume p-value
	No. of events/No. of patients				
Overall survival					
All patients	195/452	135/449	0.609 (0.488-0.789)	<0.001	
Low volume	53/196	39/206	0.637 (0.420-0.966)	0.034	0.771
High volume	142/256	96/243	0.601 (0.463-0.779)	<0.001	
Failure free survival					
All patients	354/452	191/449	0.316 (0.264-0.378)	<0.001	
Low volume	133/196	57/206	0.259 (0.189-0.356)	<0.001	0.472
High volume	221/256	134/243	0.327 (0.263-0.408)	<0.001	
Skeletal related events					
All patients	164/452	93/449	0.467 (0.362-0.602)	<0.001	
Low volume	46/196	25/206	0.459 (0.282-0.749)	0.002	0.981
High volume	118/256	68/243	0.468 (0.347-0.632)	<0.001	
Progression free survival					
All patients	267/452	158/449	0.446 (0.366-0.544)	<0.001	
Low volume	86/196	45/206	0.401 (0.279-0.577)	<0.001	0.670
High volume	181/256	113/243	0.457 (0.360-0.579)	<0.001	
Prostate cancer specific death*					
All patients	172/452	114/449	0.587 (0.462-0.746)	<0.001	
Low volume	43/196	31/206	0.627 (0.388-1.013)	0.057	0.740
High volume	129/256	83/243	0.579 (0.439-0.764)	<0.001	



MUNICH 2018 ESMO congress

S3-Leitlinie, Version 0.5.0. (Konsultationsfassung), Sept. 2017

6.19	Empfehlung	modifiziert 2017
Empfehlungsgrad B	Patienten in gutem Allgemeinzustand (ECOG 0-1) mit metastasiertem (M1), hormonsensitiven Prostatakarzinom sollte zusätzlich zur Androgendeprivation eine Chemotherapie mit Docetaxel oder eine ergänzende antihormonelle Therapie mit Abirateron (plus Prednison / Prednisolon) empfohlen werden.	
Level of Evidence 1+	Literatur: [736-740]	
	Gesamtabstimmung: 100 %	

Low metastatic burden = Abiraterone

http://www.leitlinienprogramm onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/

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

- Patients with newly diagnosed (castration-naïve) metastatic CaP
- 1156 pts planned

RANDOMIZED

- SOC
- SOC + Abiraterone 1000 mg Prednisone 5 mg BID
- SOC + Local radiotherapy
- SOC + Local radiotherapy + Abiraterone-Pred

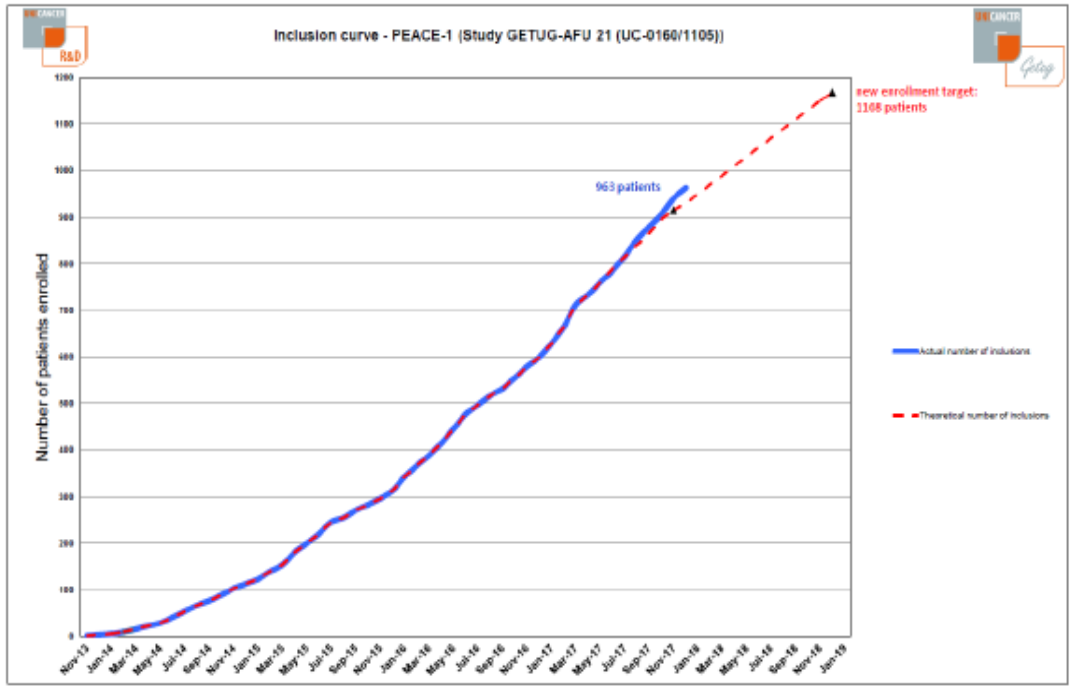
Co-primary endpoints: OS and PFS (HR: 0.75)

Standard of Care (SOC)= Androgen deprivation therapy (ADT) +/- docetaxel (Stratification)

Study sponsor: Unicancer

ClinicalTrials.gov Identifier: NCT01957436

Current accrual in PEACE-1



VOLUME 34 · NUMBER 24 · AUGUST 20, 2016

JOURNAL OF CLINICAL ONCOLOGY

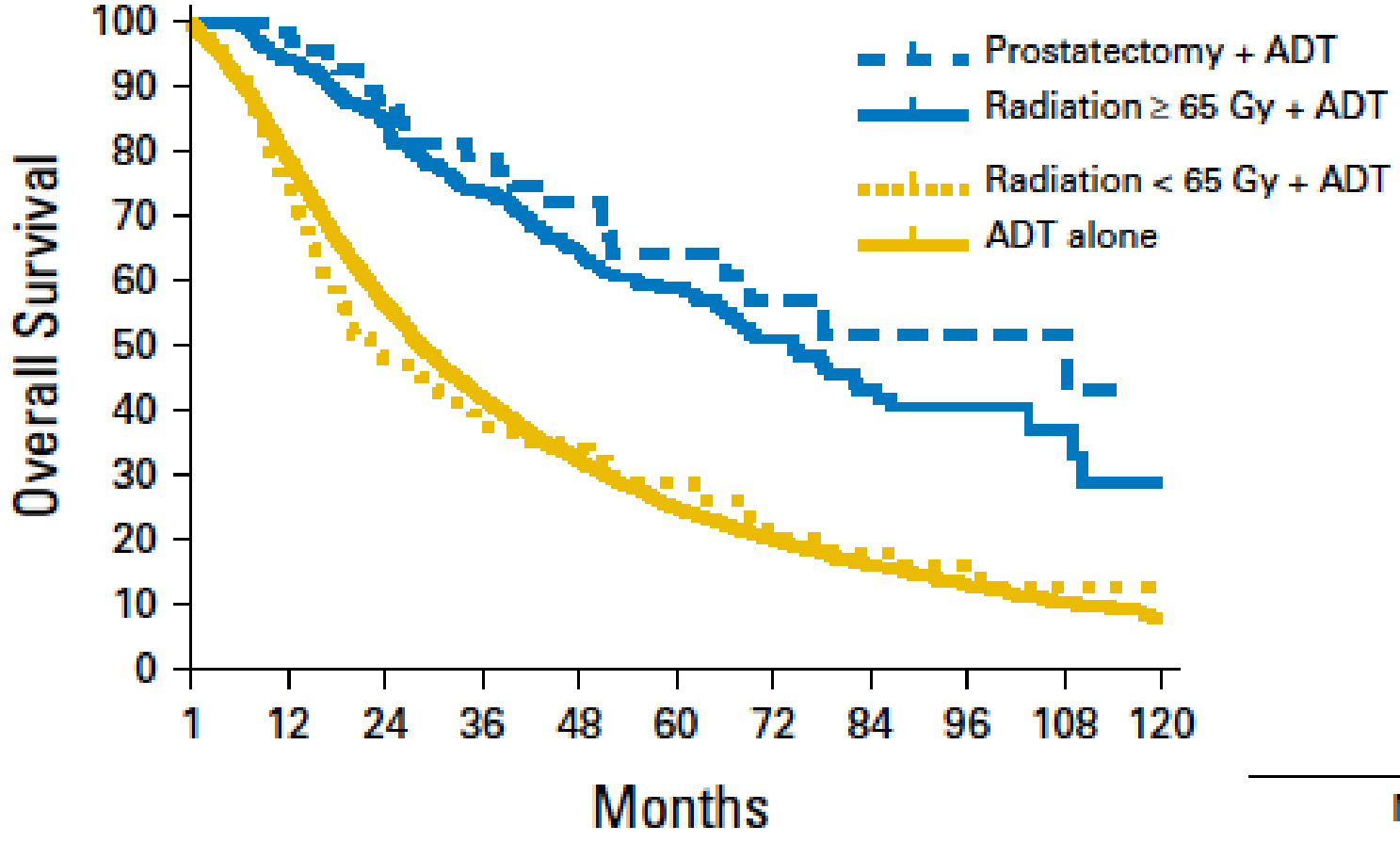
ORIGINAL REPORT

Improved Survival With Prostate Radiation in Addition to Androgen Deprivation Therapy for Men With Newly Diagnosed Metastatic Prostate Cancer

Chad G. Rusthoven, Bernard L. Jones, Thomas W. Flaig, E. David Crawford, Matthew Koshy, David J. Sher, Usama Mahmood, Ronald C. Chen, Brian F. Chapin, Brian D. Kavanagh, and Thomas J. Pugh

- National Cancer Database
- n=6382 ADT vs 538 (8.5%) ADT + RTX

- Subgruppenvergleich RTX vs. RP



							Multivariate		
							HR	95% CI	*P*
ADT alone	5,844	3,034	1,277	472	155	13	Ref	–	–
Radiation < 65 Gy + ADT	163	73	41	15	7	1	1.02	0.84 to 1.23	.874
Radiation ≥ 65 Gy + ADT	324	254	146	61	21	1	0.45	0.38 to 0.54	< .001
Prostatectomy + ADT	69	56	30	13	7	0	0.38	0.25 to 0.58	< .001

Local Therapy Improves Survival in Metastatic Prostate Cancer

Sami-Ramzi Leyh-Bannurah [a,b,c,1,], Stéphanie Gazdovich [a,d,1], Lars Budäus [b], Emanuele Zaffuto [a,e], Alberto Briganti [e], Firas Abdollah [e,f], Francesco Montorsi [e], Jonas Schiffmann [g], Mani Menon [f], Shahrokh F. Shariat [h], Margit Fisch [c], Felix Chun [c], Thomas Steuber [b], Hartwig Huland [b], Markus Graefen [b], Pierre I. Karakiewicz [a,d]*

Variables	Local treatment versus no local treatment	
	SHR (95% CI)	*p* value
Type of treatment		
No local therapy	Ref.	
Radiotherapy	0.48 (0.35–0.66)	<0.001
Radical prostatectomy	0.35 (0.26–0.46)	<0.001
Biopsy Gleason score		
≤7	Ref.	
≥8	1.84 (1.59–2.13)	<0.001
Unknown	1.72 (1.28–2.31)	<0.001
Clinical T stage		
T1/T2	Ref.	
T3	1.10 (0.87–1.40)	0.4
T4	1.85 (1.39–2.46)	<0.001
Clinical N stage		
N0/Nx	Ref.	
N1	1.18 (0.91–1.52)	0.20
AJCC M stage		
M1a	Ref.	
M1b	1.65 (1.31–2.08)	<0.001
M1c	1.98 (1.52–2.58)	<0.001
Age (yr)	1.00 (0.99–1.01)	0.4
Race		
Caucasian	Ref.	
African American	0.91 (0.76–1.09)	0.3
Other/unknown	0.77 (0.58–1.02)	0.07
Marital status		
Married	Ref.	
Divorced/widowed	1.25 (1.03–1.51)	0.024
Single	1.23 (0.97–1.57)	0.092
Unknown	0.75 (0.54–1.03)	0.074

CI = confidence interval; SHR = subhazard ratio; Ref. = reference; AJCC = American Joint Committee on Cancer.

Type of treatment		
No local therapy	Ref.	
Radiotherapy	0.48 (0.35–0.66)	<0.001
Radical prostatectomy	0.35 (0.26–0.46)	<0.001

Variables	Radical prostatectomy versus radiotherapy	
	SHR (95% CI)	*p* value
Type of treatment		
Radiotherapy	Ref.	
Radical prostatectomy	0.59 (0.35–0.99)	0.048
Biopsy Gleason score		
≤7	Ref.	
≥8	3.67 (2.03–6.66)	<0.001
Unknown	0.80 (0.14–4.72)	0.8
Clinical T stage		
T1/T2	Ref.	
T3	1.01 (0.39–2.61)	>0.9
T4	5.48 (2.64–11.4)	<0.001
Clinical N stage		
N0/Nx	Ref.	
N1	1.01 (0.34–2.99)	>0.9
AJCC M stage		
M1a	Ref.	
M1b	3.48 (1.51–8.04)	0.01
M1c	4.70 (1.88–11.7)	<0.001
Age (yr)	1.02 (0.98–1.05)	0.3

Martini-Klinik

Zusammenfassung:

- Eine lokale Therapie beim fortgeschrittenen PCa N0/N1M0 ist Standard
- Eine lokale Therapie bei M1 wird/ist Standard bei geringer Metastasenlast
- Vergleich RP vs RTx steht aus

- Die systemische Therapie bei M1 = Hormontherapie plus Arbiraterone bei geringer Metastasenlast

Vielen Dank!