Surgery in High Risk Prostate Cancer

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GU Oncology Retreat 2019

Disclosures

Honoraria- Tersera, Janssen

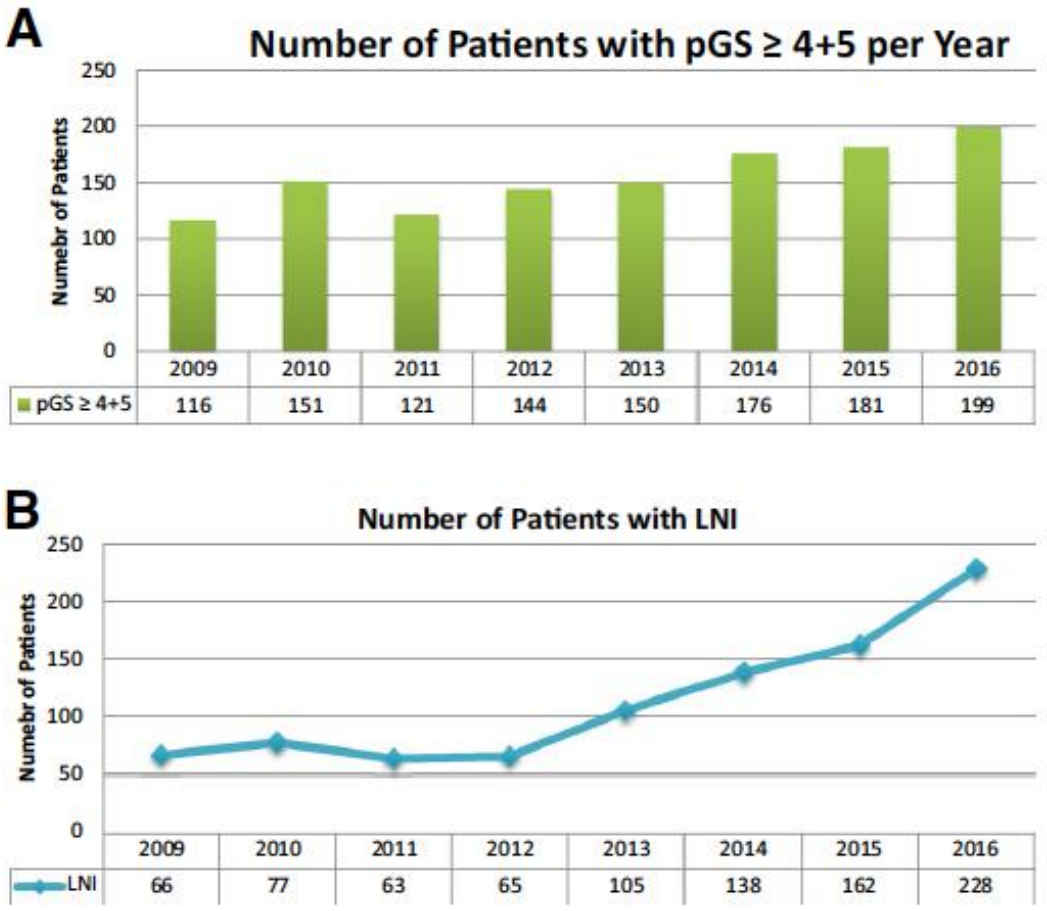
Defining "high risk"

Rationale for surgery in high risk disease

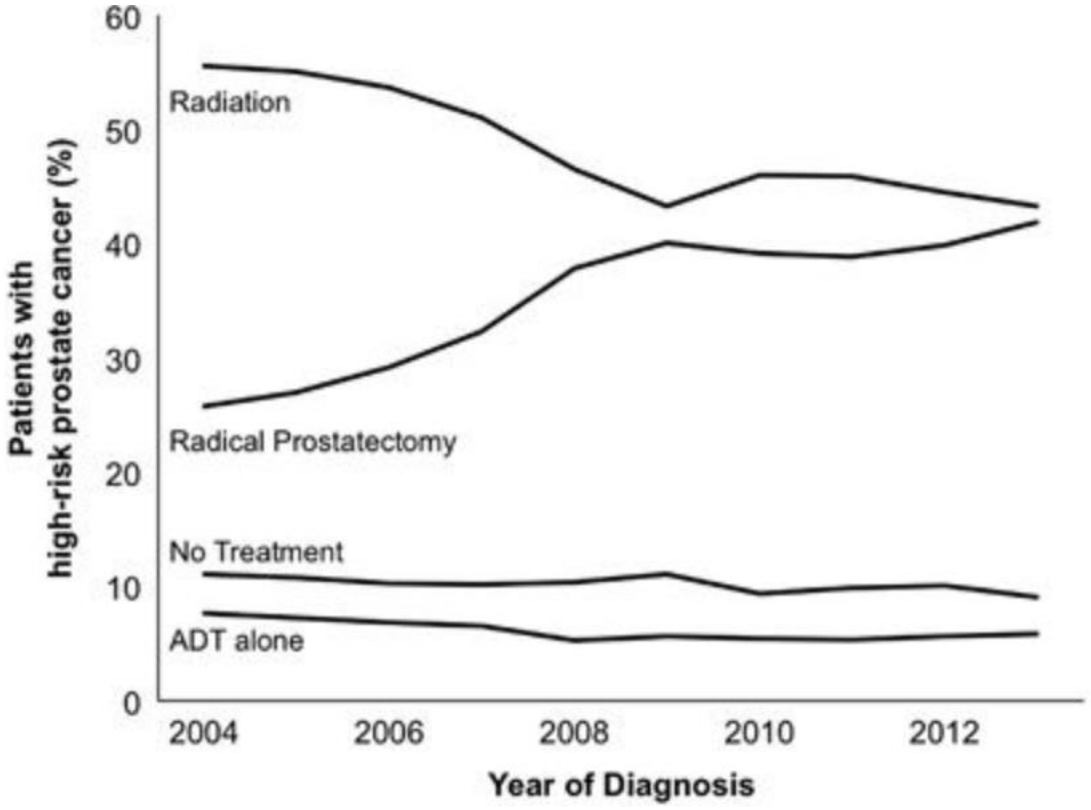
RP in clinically localized high risk PCa

Surgery in metastatic PCa

High Risk prostate cancer is increasing



We are operating on more high risk men



WEINER ET AL 2017

Defining “High Risk”

Multiple definitions of high risk PCa exist

- NCCN
- D’Amico
- Kattan nomogram
- PSA > 20 alone
- ≥ cT3 alone
- ≥ Gleason 8 alone

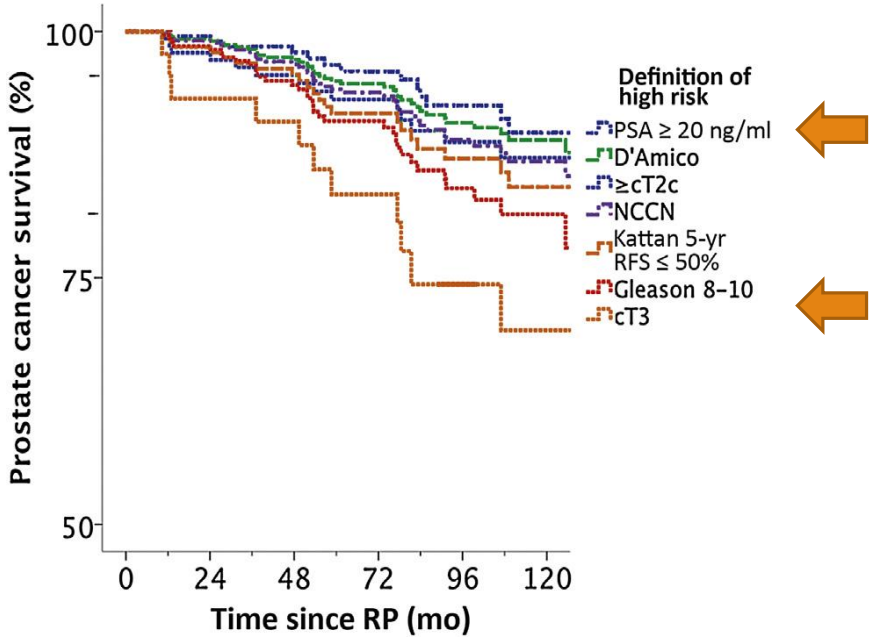
NCCN

High	• T3a OR • Gleason score 8/grade group 4 or Gleason score 4+5=9/grade group 5 OR • PSA >20 ng/mL
Very high	• T3b-T4 OR • Primary Gleason pattern 5 OR • >4 cores with Gleason score 8–10/ grade group 4 or 5
Regional	Any T, N1, M0

How do these definitions compare?

Heterogeneity in Definitions of High-risk Prostate Cancer and Varying Impact on Mortality Rates after Radical Prostatectomy

Matthew Mossanen [a,b,*], Kenneth G. Nepple [c], Robert L. Grubb 3rd [d], Gerald L. Androile [d], Dorina Kallogjeri [d], Eric A. Klein [e], Andrew J. Stephenson [e], Adam S. Kibel [a,b]



Definition of high-risk prostate cancer	HR (95% CI)*
Prostate-specific antigen ≥20 ng/ml	4.38 (2.40–8.00)
Clinical stage ≥T2c	7.43 (4.20–13.15)
Kattan nomogram 5-yr recurrence-free survival ≤50%	9.72 (5.89–16.04)
D'Amico high risk	10.12 (6.42–15.96)
National Comprehensive Cancer Network high risk	12.36 (7.84–19.50)
Biopsy Gleason score 8-10	17.88 (11.34–28.20)
Clinical stage T3	19.97 (10.67–37.39)

HR = hazard ratio; CI = confidence interval.
* All p 0.001.

Limitations of current definitions

Based on clinical/histologic factors alone

- Significant inaccuracies

Large heterogeneity in who is ‘high risk’

- cT1c with PSA > 20 ≠ cT3b with PSA 12

Were not developed using mpMRI features

MRI

Guidelines	Overall Recommendation	Early detection (screening)	Localisation and targeted biopsies	Staging & Treatment Planning	Active Surveillance/Focal therapy	Recurrence post treatment
European Association Urology [1] 2011	MRI is now of a high technical standard, but not sufficiently reliable to make use	No comment	If suspicion for PCa persists despite negative biopsies, MRI may be used to investigate a possible anterior PCa, followed	MRI demonstrates higher accuracy than DRE, TRUS & CT for the assessment of uni/bilobar disease (T2), ECE/	No comment	Pelvic MRI or CT may be used to detect metastases post-treatment,
National Comprehensive Cancer Network (North America)[3,4]	Not accepted as essential in the workup of all patients. Optional in specific instances	No comment	Multi-parametric MRI can aid in cancer detection in patients with persistent PSA elevation but negative TRUS-biopsy	MRI has yet to be accepted as essential in tumour staging MRI is indicated for nodal staging if cT3-4, PSA >20–25 or if the nomogram-derived probability of nodal metastases is >20%	No comment	No comment

It is possible that **routine MRI** in **higher-risk** patients may identify those with evidence of **extensive T3 disease**

MRI could be added to **existing nomograms** for prediction of **organ-confined disease in high-risk men**

Thompson et al. BJU Int, 2014

Historical perspective

RP not offered for “higher risk” disease

Concerns regarding morbidity of RP in high-risk

Likely need for adjuvant treatments

Won’t “cure” patient with surgery, so best to avoid

- Therapeutic nihilism

So why should we consider RP in men with high risk disease?

Accurate histopathologic diagnosis

Monotherapy possible in some men

Advantage of multi-modal therapy in others

Durable survival is possible

Morbidity is acceptable

Accurate Histopathology

Downgrading is common

- 30 – 50% with ‘high grade’ disease will be downgraded
- Dohahue et al – 238 men with biopsy Gleason 8-10, 45% had G $\leq$ 7 on final path

Down staging is also common

- Up to 30%

Effect of mpMRI on downgrading/downstaging unknown

RP as Monotherapy in HR PCa

Not all patients with high risk disease will require adjuvant therapy after RP

- Up to 68% BCR free at 5 years

Study	N	BCR FS	CSS
Gerber	242	29% at 5-year	57% at 10-years
Yossepowitch	957	68% at 5-year	-
Stephenson	1962	-	92% at 10-years
Loeb		68% at 10-years	92% at 10-years

RP as monotherapy in HR PCa

Factors most predictive of failure are pT3b or margin positive disease (non-organ confined).

Joniau (2011)

- RP as monotherapy in 612 patients
- Non-organ confined – 10 y CSS = 97.1%
- Organ confined – 10 y CSS = 87.1%

Durable long-term survival possible

Regardless of criteria defining high-risk, RP has shown high long-term survival

- pT3 disease
- Gleason 8-10
- ”High” PSA

Often in combination with adjuvant/salvage treatments

BJUI
BJU INTERNATIONAL

20-year survival after radical prostatectomy as initial treatment for cT3 prostate cancer

Christopher R. Mitchell, Stephen A. Boorjian, Eric C. Umbreit, Laureano J. Rangel*, Rachel E. Carlson* and R. Jeffrey Karnes

Retrospective, single institution study

N = 843

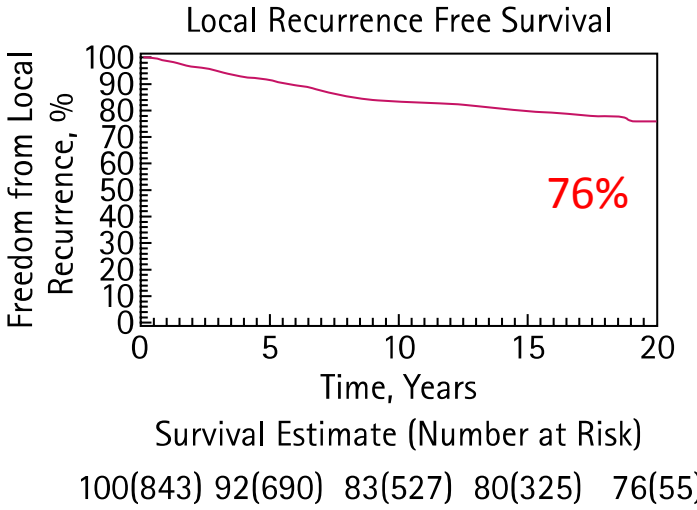
Clinical over-staging of cT3 disease occurred in 26% (223/843)

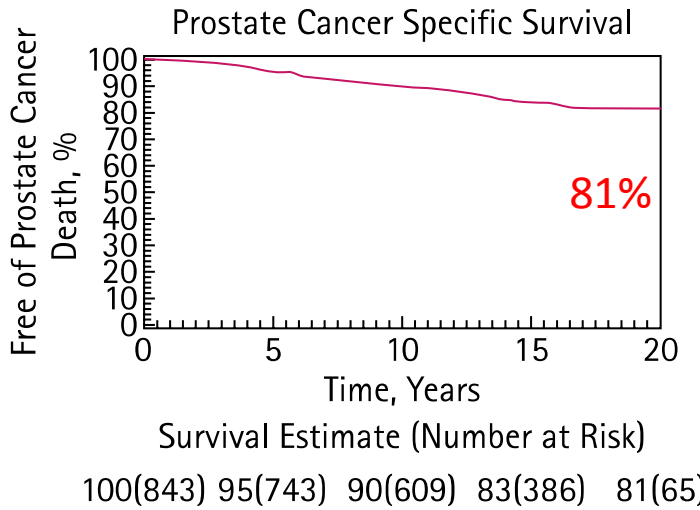
BJUI
BJU INTERNATIONAL

20-year survival after radical prostatectomy as initial treatment for cT3 prostate cancer

Christopher R. Mitchell, Stephen A. Boorjian, Eric C. Umbreit, Laureano J. Rangel*, Rachel E. Carlson* and R. Jeffrey Karnes

20 year f/u





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42% of patients did not receive adjuvant ADT and/or RT

No differences in post-operative complications between cT2 and cT3 patients

Long-term Outcomes of Radical Prostatectomy With Multimodal Adjuvant Therapy in Men With a Preoperative Serum Prostate-Specific Antigen Level ≥50 ng/mL

Cancer

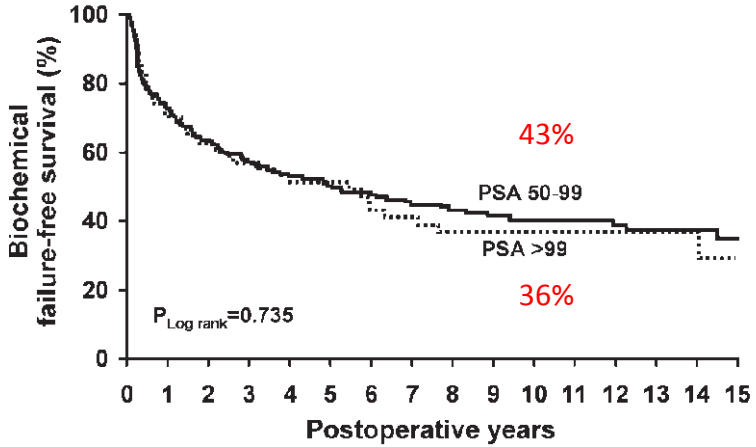
Observational study

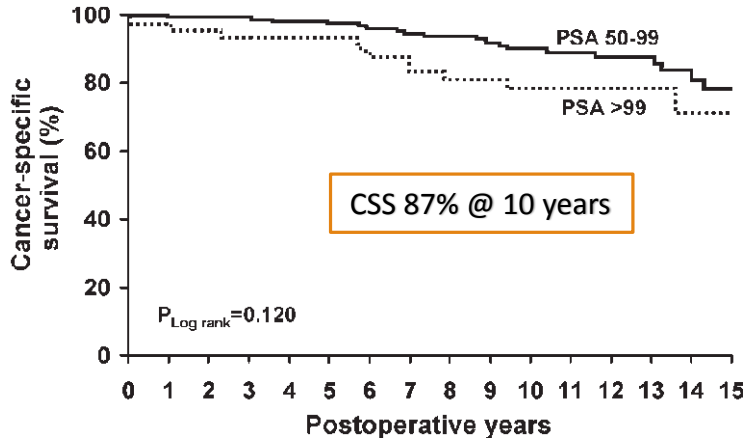
N = 234

80% had pT3+ disease

Long-term Outcomes of Radical Prostatectomy With Multimodal Adjuvant Therapy in Men With a Preoperative Serum Prostate-Specific Antigen Level ≥50 ng/mL

Cancer





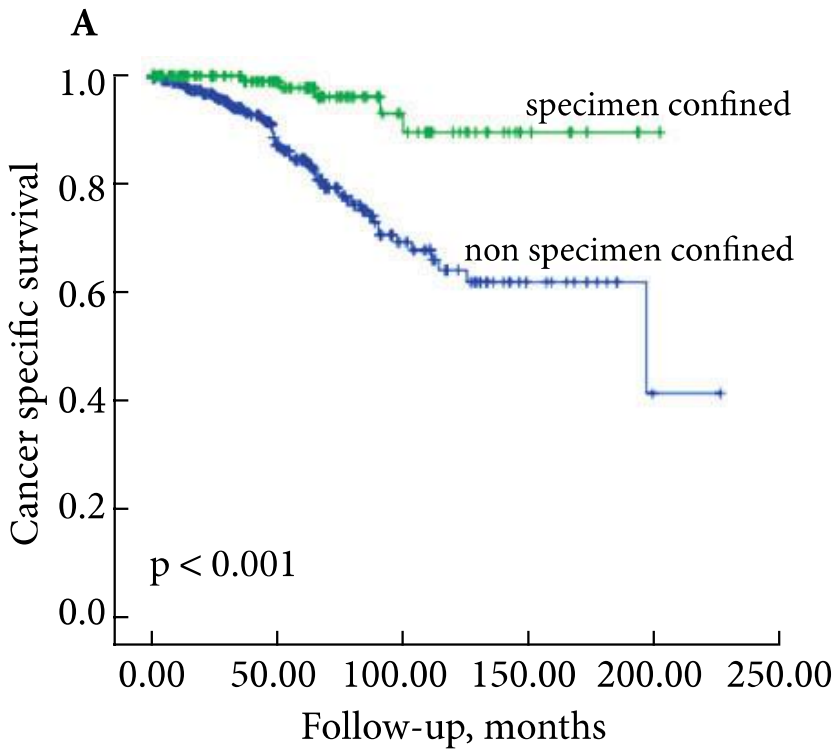
Radical prostatectomy represents an effective treatment in patients with specimen-confined high pathological Gleason score prostate cancer

BJUI
BJU International

- Single European institution
- N = 580, Gleason 8-10 disease
- 25% had “specimen confined” disease
  - Negative margins
  - No SVI
  - Negative LN

Radical prostatectomy represents an effective treatment in patients with specimen-confined high pathological Gleason score prostate cancer

BJUI
BJU International



Specimen confined disease

5-year CSS 97.8%

10-year CSS 89.6%

LUGHEZZHANI ET AL 2013

Morbidity is acceptable

Return of continence after RP for high risk disease appears to be similar according to risk category

- Data very limited

Surgical complications may be higher but not substantially so

Multimodal therapy does increase chance of incontinence and possibly worsens quality of life

- Patient counselling paramount

Current Management of pT3b Prostate Cancer After Robot-assisted Laparoscopic Prostatectomy

Filip Poelaert [a,*], Steven Joniau [b], Thierry Roumeguère [c], Filip Ameye [d], Greet De Coster [e], Peter Dekuyper [d], Thierry Quackels [c], Ben Van Cleynenbreugel [b], Nancy Van Damme [e], Elizabeth Van Eycken [e], Alexander Mottrie [f], Nicolaas Lumen [a], on behalf of the Belgian RALP Consortium [1]

EUROPEAN UROLOGY ONCOLOGY 2 (2019) 110–117

798 patients- pT3b

92% No complications- Clavein 0

Table 2 – Early (0–30 d) grade 1 complications were more frequent in patients receiving PLND

Clavien-Dindo grade, *n* (%)	Total (*n* = 68)	RALP + PLND (*n* = 58)	RALP (*n* = 10)	*p* value
0	728 (92)	488 (89)	240 (96)	0.002
I	46 (5.8)	42 (7.7)	4 (1.6)	<0.001
II	11 (1.4)	7 (1.3)	4 (1.6)	0.7
III	9 (1.1)	8 (1.5)	1 (0.4)	0.3
IV	–	–	–	–
V	2 (0.3)	1 (0.2)	1 (0.4)	0.5

RALP = robot-assisted laparoscopic radical prostatectomy; PLND = pelvic lymph node dissection.

Incontinence after RP for high-risk disease

Original Article

A match-pair analysis of continence in intermediate and high-risk prostate cancer patients after robot-assisted radical prostatectomy: the role of urine loss ratio and predictive analysis

Prostate International

Matched cohort study comparing continence at 12 months

N = 295 patients

Incontinence (>1ppd)

Intermediate risk	High risk
8.2%	10.8%

Functional Outcomes and Quality of Life After Radical Prostatectomy Only Versus a Combination of Prostatectomy with Radiation and Hormonal Therapy

EUROPEAN UROLOGY 71 (2017) 330–336

13,150 patients who underwent RP

- RP alone
- RP + RT
- RP + RT + ADT

Compared functional outcomes at 3 years

Functional Outcomes and Quality of Life After Radical Prostatectomy Only Versus a Combination of Prostatectomy with Radiation and Hormonal Therapy

EUROPEAN UROLOGY 71 (2017) 330–336

3 yrs after surgery

	RP	RP + RT	RP + RT + ADT
Severe incontinence	2%	4%	6%
Sexual function	58%	40%	24%

Adjuvant/salvage therapies result in worse functional outcomes BUT not drastically so

Take-home for RP in high-risk disease

Can be offered as initial treatment choice

Many will require adjuvant/salvage treatments

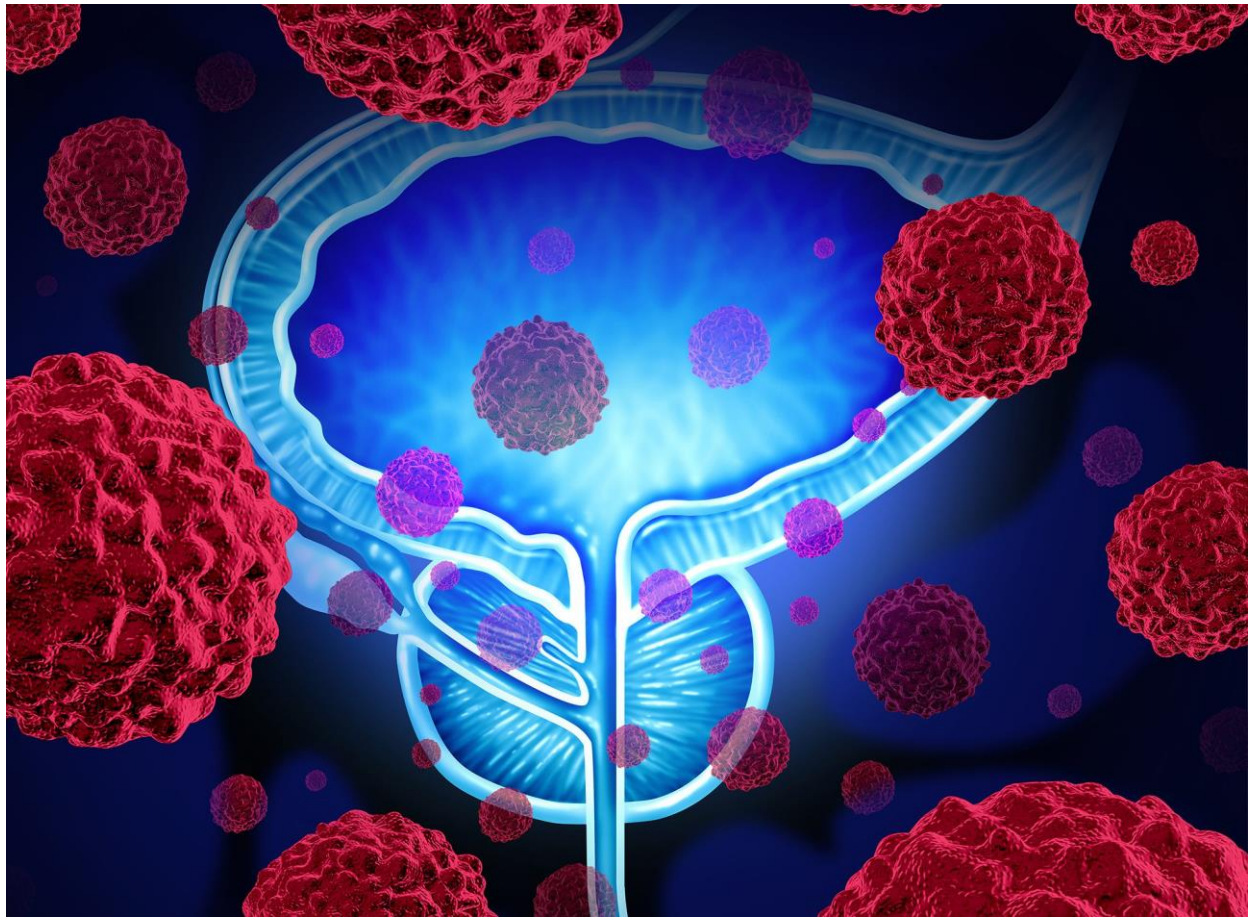
- Some won't

Durable long-term control possible

- Particularly if pT3a or less

Functional price to pay

- But not huge



Is There a Role for Radical Prostatectomy in Metastatic Prostate Cancer?

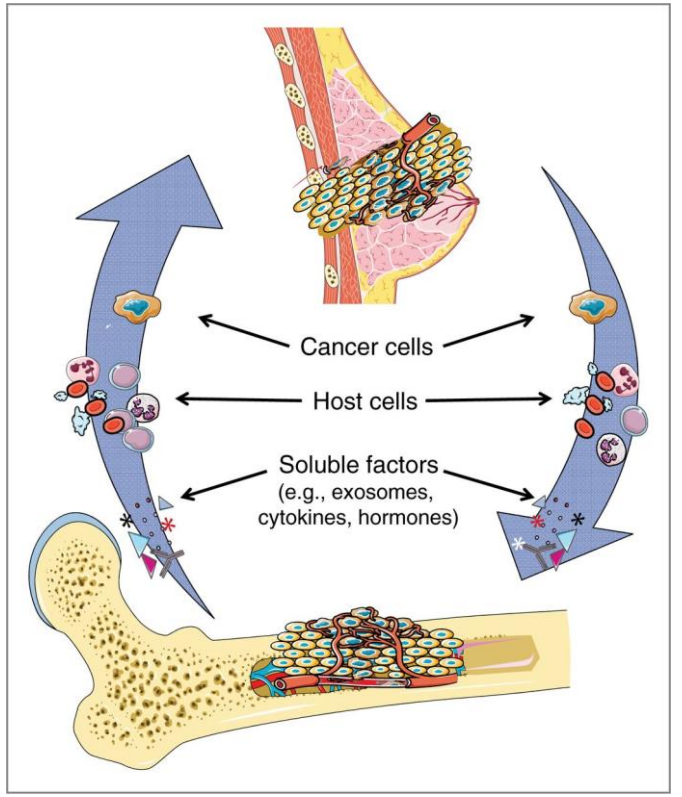
Theoretical rationale for Cytoreductive Prostatectomy

Removing source of metastases
(*seed and soil hypothesis*)

Decreased # of cells to develop resistance

Improved immune function/Cytokine signaling

Decreased growth factors



Pienta et al. 2013

Cytoreductive Radical Prostatectomy in Patients with Prostate Cancer and Low Volume Skeletal Metastases: Results of a Feasibility and Case-Control Study

Axel Heidenreich,* David Pfister and Daniel Porres

From the Department of Urology, Uniklinik RWTH Aachen, Aachen, Germany

THE JOURNAL OF UROLOGY®

23 Men with metastatic prostate cancer:

oligometastasis (≲ 3 bone mets)

Absence of bulky pelvic or RP LN (>3cm)

No visceral metastases

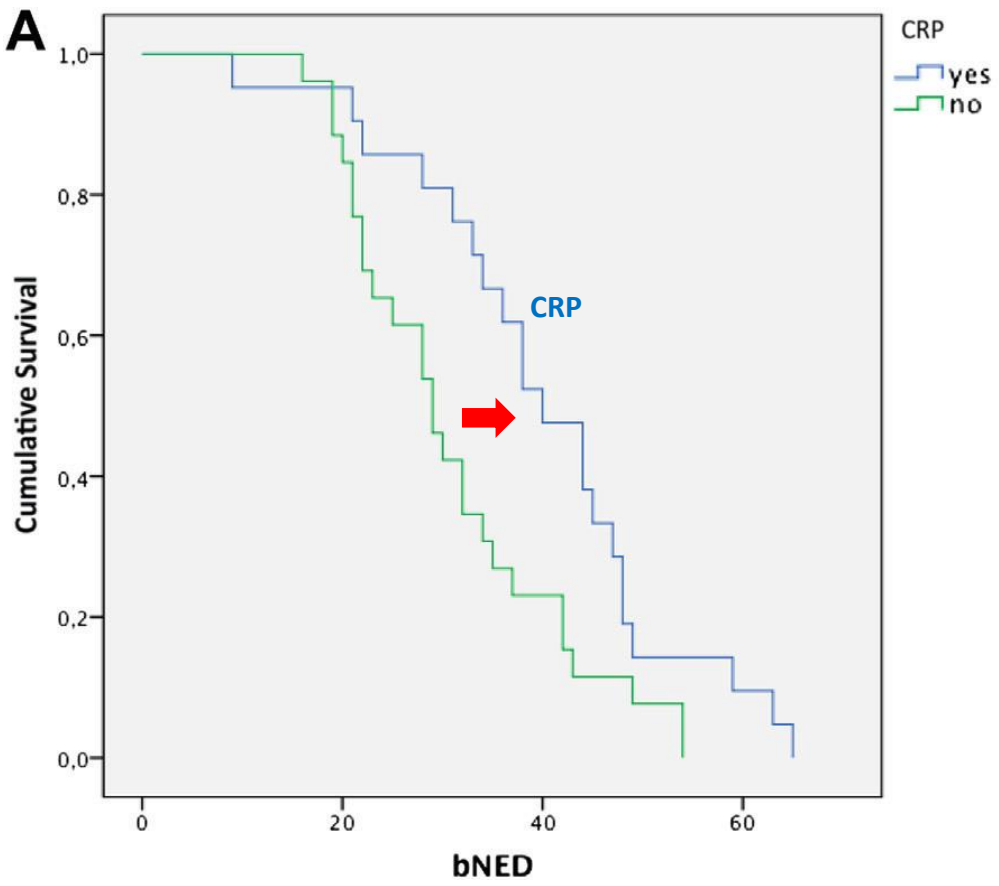
ADT x 6 months

PSA <1.0
Radiographic disease stability

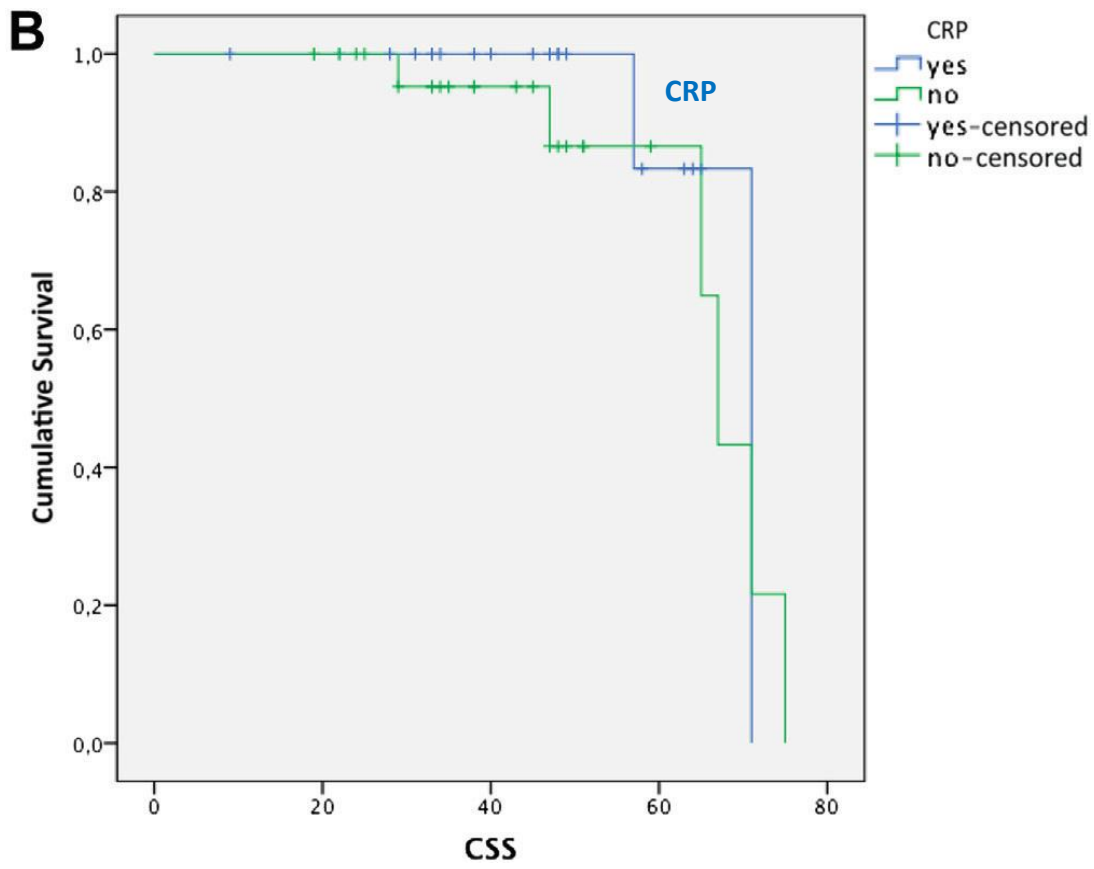
Cytoreductive RP + LND

	CRP (group 1)		Control (group 2)	
Mean age (range)	61	(42–69)	63.9	(47–83)
No. age (%):				
Less than 60	7	(30.4)	9	(23.7)
61–70	10	(43.5)	18	(47.4)
Greater than 70	6	(26.1)	11	(28.9)
Mean Eastern Cooperative Oncology Group performance status (range)	0.6	(0–2)	0.71	(0–2)
Mean Charlson comorbidity score (range)	6.6	(6–9)	7.1	(6–11)
Mean ng/ml PSA (range)	135.2	(3.5–150.4)	105.9	(45–195)
Median ng/ml 6-mo PSA (range)	0.42	(less than 0.01–2.2)	1.25	(less than 0.01–9.8)
Mean U/l baseline lactate dehydrogenase (range)	194	(165–294)	201	(153–286)
Mean U/l baseline alkaline phosphatase (range)	105	(67–145)	108	(71–155)
Mean mg/l baseline CRP (range)	3.6	(0.5–7.8)	3.8	(0.5–8.1)
No. clinical stage (%):				
cT2c	7	(30.4)	10	(26.3)
cT3a/b	16	(69.6)	24	(63.1)
cT4	0		4	(10.5)
Mean biopsy Gleason score	7.6		7.9	
No. biopsy Gleason score (%):				
6	0		4	(10.5)
7 (3+4, 4+3)	5	(21.7)	11	(28.9)
8	7	(30.4)	11	(28.9)
9	7	(30.4)	8	(21.1)
10	4	(17.4)	4	(10.5)
No. skeletal metastases (%)	23	(100)	38	(100)
Mean bone metastases (range)	2.1	(1–3)	2.5	(1–5)
No. pelvic lymph nodes (%):	4	(17.4)*	8	(21.1)*
Less than 2 cm	3	(13.1)	6	(15.8)
2–3 cm	1	(4.3)	2	(5.3)
No. suspicious retroperitoneal lymph nodes (%)	3	(13.1)	4	(10.5)

Median f/u ~40 months



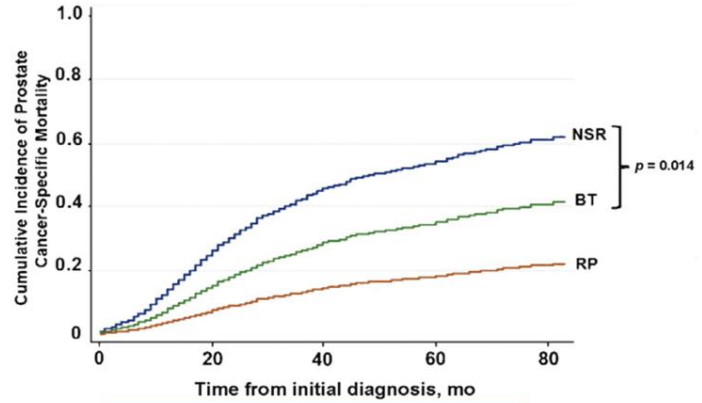
Time to castrate resistant disease

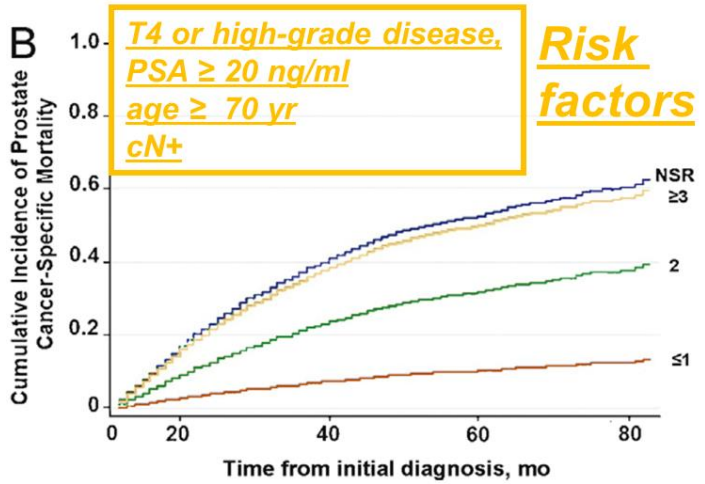


Cancer Specific Survival

Survival advantage to RP in M1 patients?

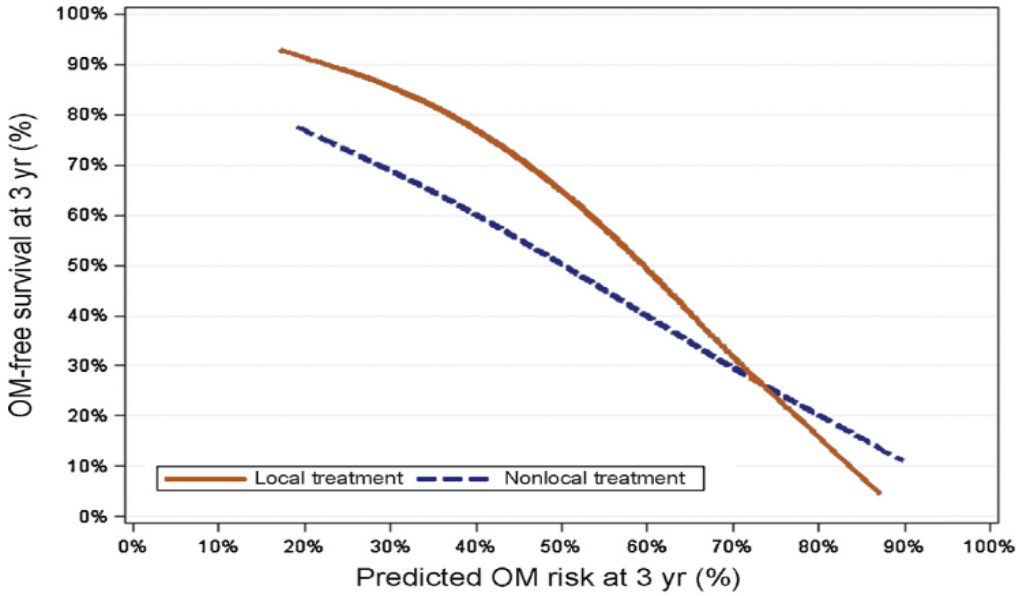
- 8185 SEER pts with M1 disease
  - 245 (3%) underwent RP
- Survival outcomes at 5 yrs
  - RP CSS 75.8%
  - Brachytherapy CSS 61.3%
  - No local therapy CSS 48.7%
- Limitations: Limited patient level data, no info of other treatments





Culp et al. Eur Urol 2016

Survival advantage to RP in M1 patients?



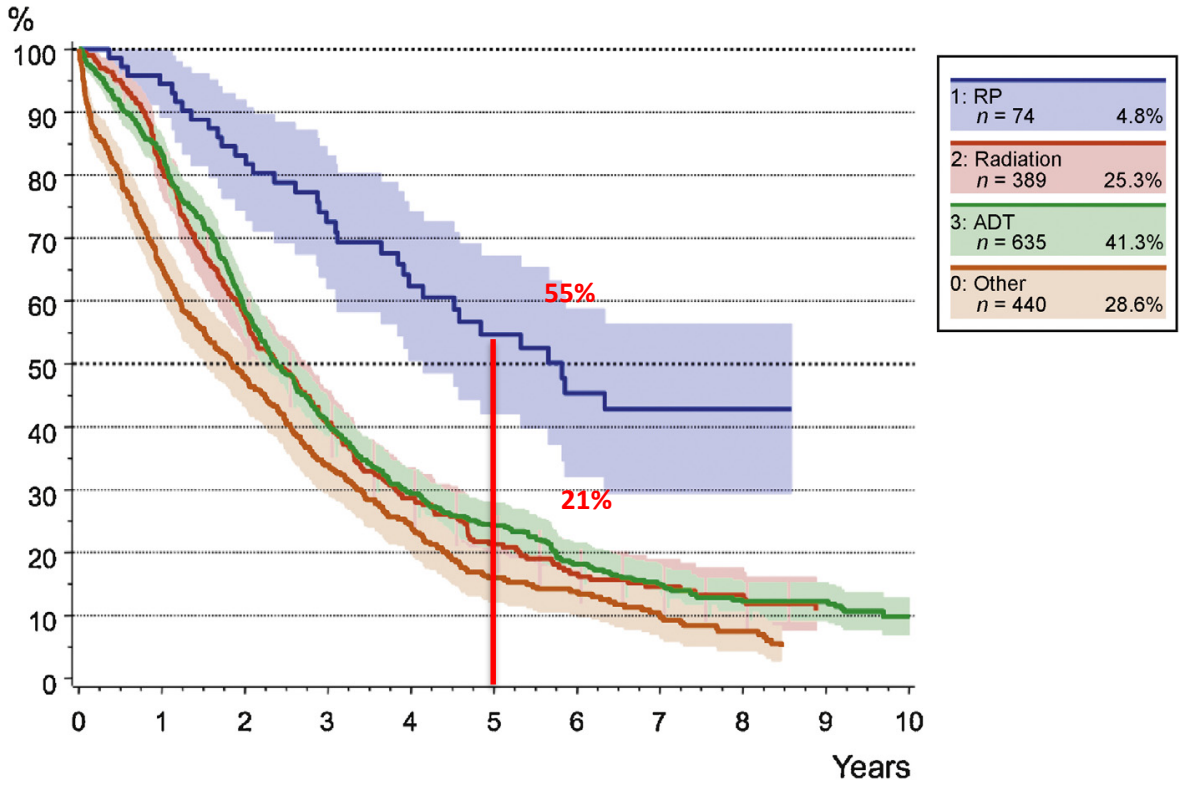
15,501 patients with the National Cancer Database →

3-yr OM-free survival higher in local therapy group
(69% vs 54%)

Löppenberg et al. Eur Urol 2017

Survival advantage to RP in M1 patients?

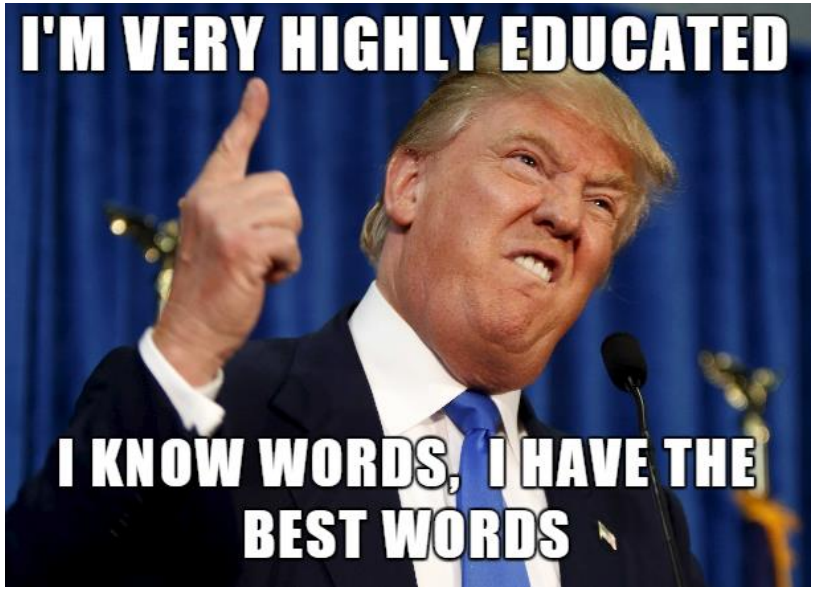
Munich Cancer Registry (1998-2010)
N= 1538



Gratzke C et al. European Urology (2014)

Survival advantage to RP in M1 patients?

Overall, may benefit some…. But not beneficial in everyone



Major limitations to this data:

- All retrospective
- Subject to selection bias & confounding factors
- Lack adequate characterization of patient population undergoing RP

Ongoing trials in M1 PCa patients

	Intervention	Outcome
TROMBONE	RP + SOC versus SOC alone	Feasibility
g-RAMPP	RP + SOC versus SOC alone	CSS
SWOG 1802	RP/RT + systemic therapy versus systemic therapy alone	OS
PEACE-1	RT+ADT | RT +Abi + ADT| Abi + ADT | ADT alone	OS

Symptomatic progression in common in de Novo Metastatic PC

Symptoms	
Any local Symptoms	**65.4%**
Pelvic Pain	44.8%
Dysuria	38.8%
Acute Urinary Retention	28.5%
Hematuria	13.7%
Renal Failure	9.9%

(Patrikiduo A et al, Urol Onc. 2015)

Reduced Local Symptoms

Cytoreductive Prostatectomy for Metastatic Prostate Cancer: First Lessons Learned From the Multicentric Prospective Local Treatment of Metastatic Prostate Cancer (LoMP) Trial

Cytoreductive prostatectomy (n=17)
Standard care (n=29)

		RP	No RP	
	Total (n = 46)	Group A (n = 17)	Group B (n = 29)	*P* value
Local symptom, n (%)				.014
Continent and no local symptoms	25 (54)	12 (71)	13 (45)	
Urinary incontinence	7 (15)	5 (29)	2 (6.9)	
Obstructive voiding (>medication)	8 (17)	0 (0)	8 (28)	
Obstructive voiding (>SPS/CIC)	3 (6.5)	0 (0)	3 (10)	
Ureteric obstruction (>observation)	1 (2.2)	0 (0)	1 (3.4)	
Ureteric obstruction (>JJ-stent)	1 (2.2)	0 (0)	1 (3.4)	

Poelaert et al. Urology 2017

Surgery in M1 Prostate Cancer

Still needs prospective evaluation

Overall, may benefit some…. But not beneficial in everyone

Surgery should be done as part of a clinical trial !!

Need to understand the mechanism of underlying potential benefit:

- How to integrate multimodal therapy
- Identify the appropriate patient population

Radiotherapy in M1 Prostate Cancer

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†*

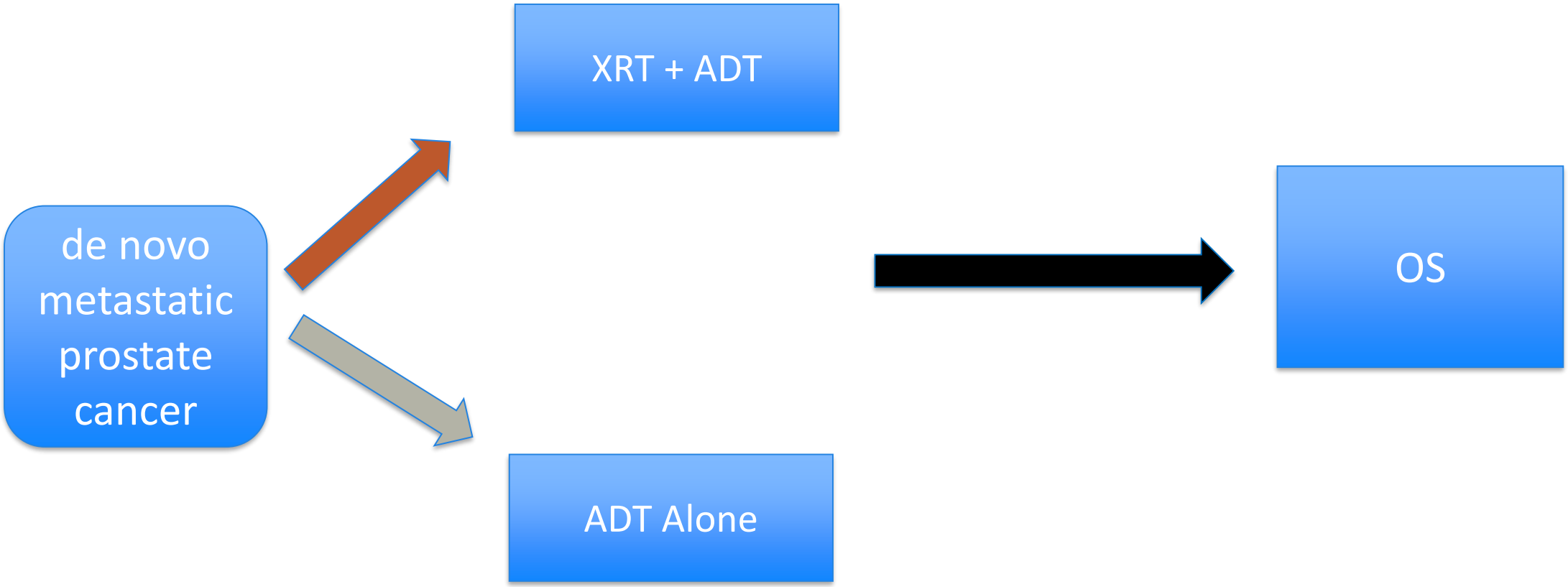
Lancet 2018

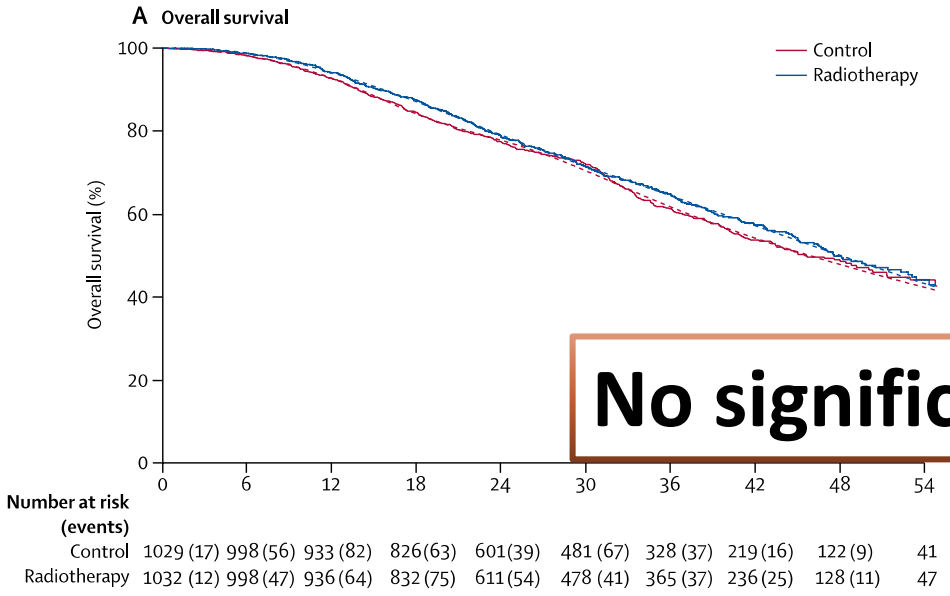
Effect on Survival of Androgen Deprivation Therapy Alone Compared to Androgen Deprivation Therapy Combined with Concurrent Radiation Therapy to the Prostate in Patients with Primary Bone Metastatic Prostate Cancer in a Prospective Randomised Clinical Trial: Data from the HORRAD Trial

Liselotte M.S. Boevé [a,b,*], Maarten C.C.M. Hulshof [c], André N. Vis [b], Aeilko H. Zwinderman [d], Jos W.R. Twisk [e], Wim P.J. Witjes [f], Karl P.J. Delaere [g], R. Jeroen A. van Moorselaar [b], Paul C.M.S. Verhagen [h], George van Andel [a]

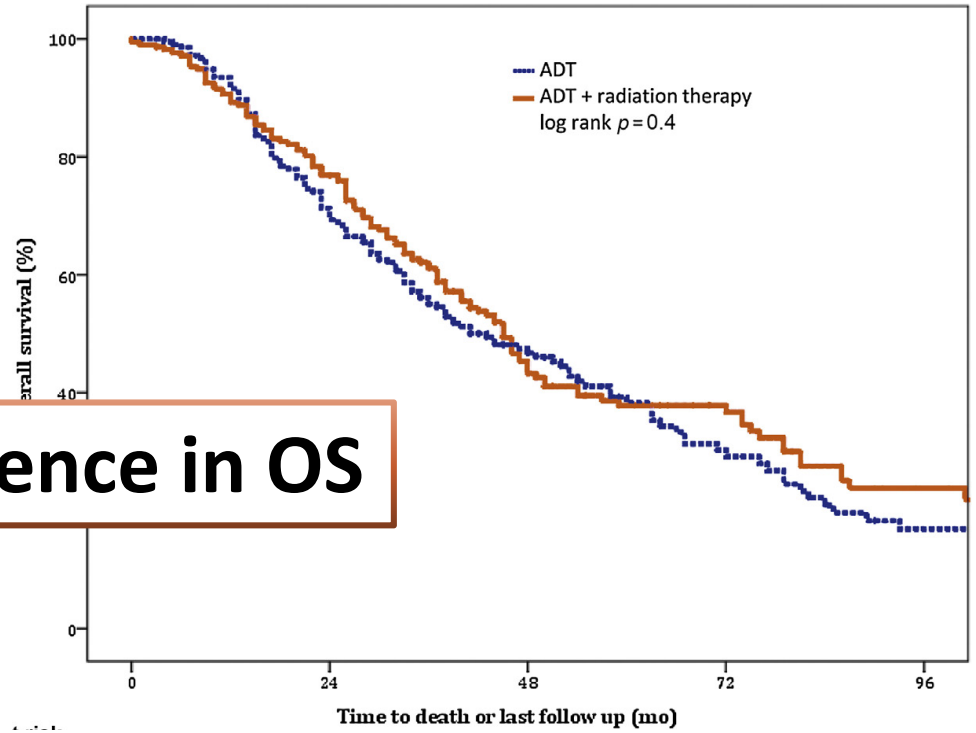
European Urology 2018

Local RT to the prostate in metastatic disease





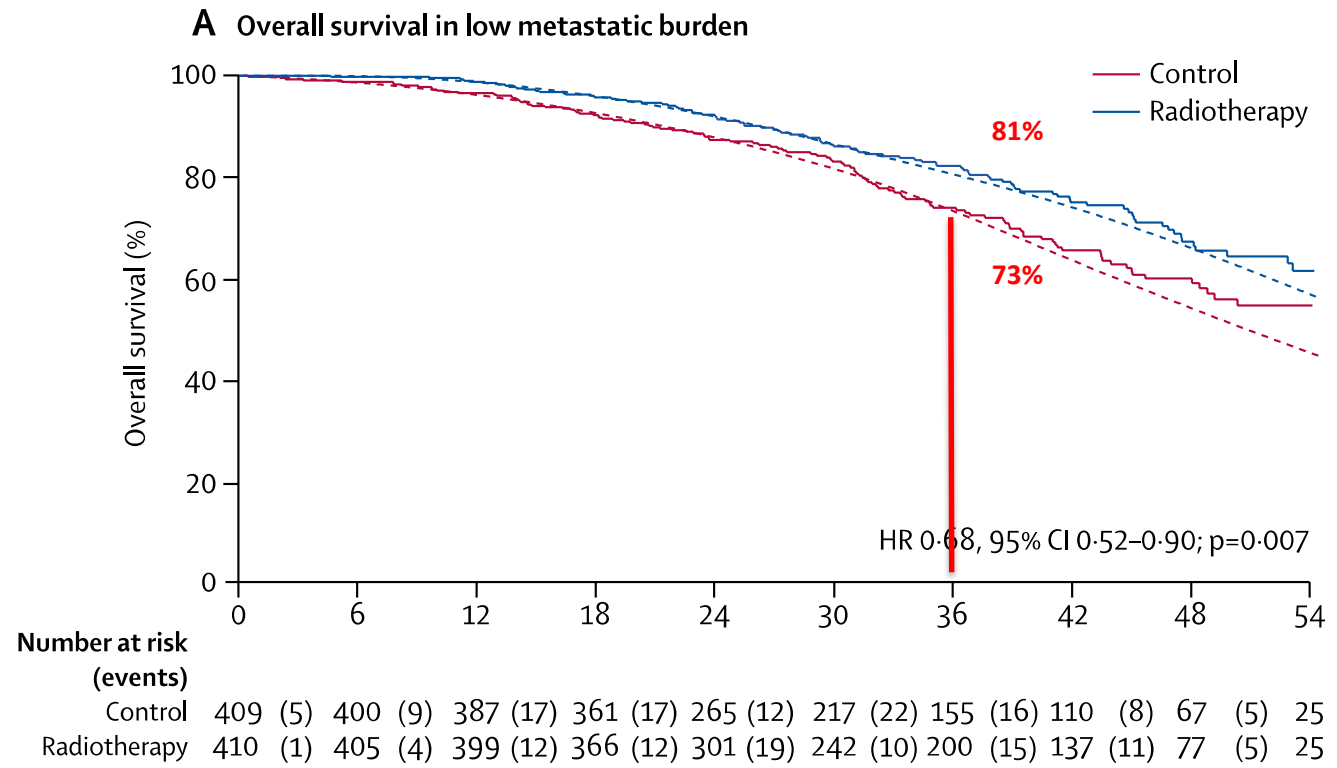
(Lancet 2018)



(Eur Urol 2018)

No significant difference in OS

OS Benefit in low metastatic burden



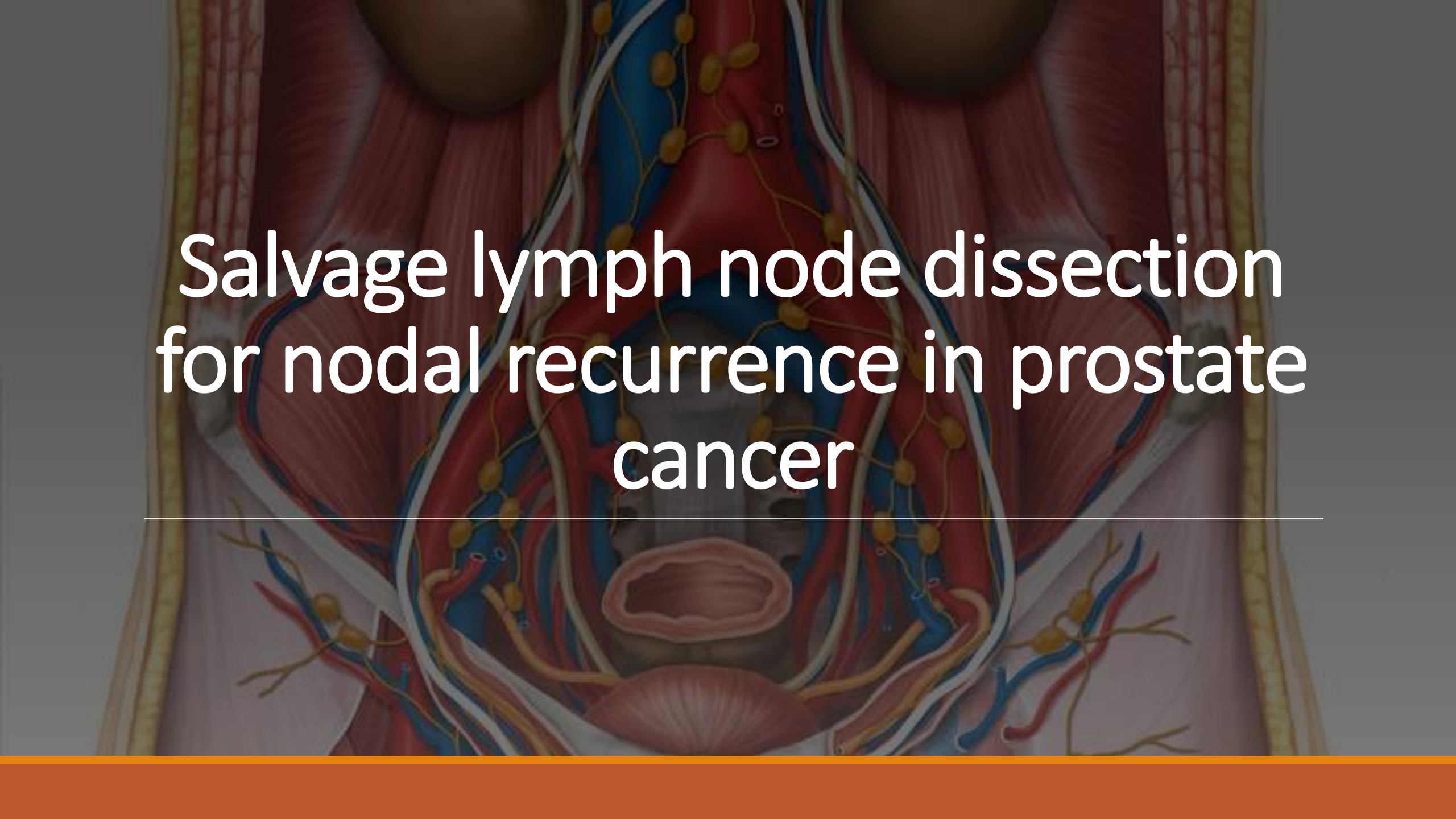
Low mets criteria:

- <5 bone mets
- No visceral disease

Parker et al. Lancet 2018

Ongoing trials in M1 PCa patients

	Intervention	Outcome
TROMBONE	RP + SOC versus SOC alone	Feasibility
g-RAMPP	RP + SOC versus SOC alone	CSS
SWOG 1802	RP/RT + systemic therapy versus systemic therapy alone	OS
PEACE-1	RT+ADT | RT +Abi + ADT| Abi + ADT | ADT alone	OS



Salvage lymph node dissection for nodal recurrence in prostate cancer

Rationale for sLND in prostate cancer

Optimize loco-regional control (node-only recurrence)

Limit the risk of distant progression

Avoid/delay the use of ADT

Improve Cancer specific survival

Advances in functional imaging (PSMA)

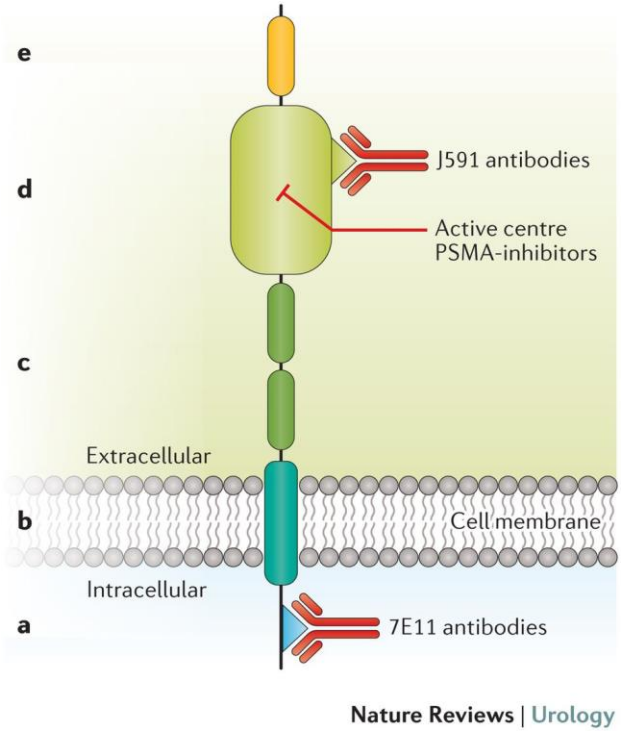
Prostate Specific Membrane Antigen (PSMA)

Type 2 transmembrane glycoprotein

Altered expression & transformation in Prostate Cancer – amenable to binding

Expression of PSMA increases with grade and stage of malignancy

Gallium-68 (^{68}Ga-PSMA) developed in Heidelberg, Germany



Maurer et el. Nat Rev Urol. 2016

PSMA vs Choline PET

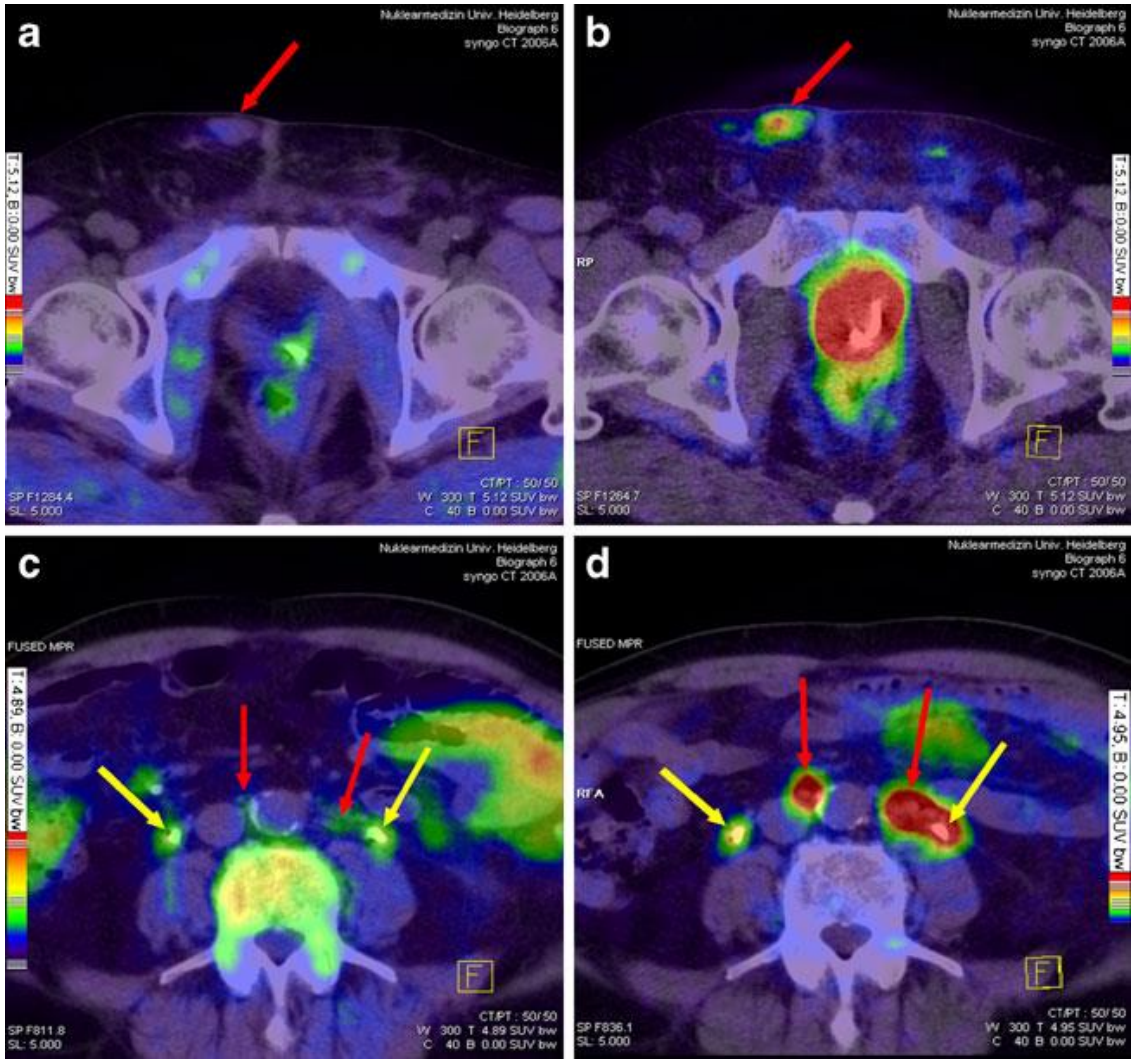
Statistically superior detection with PSMA vs Choline PET

	PSMA	Choline PET
Overall Accuracy	92%	83%
Accuracy BCR (PSADT<6 months)	90%	65%
Accuracy BCR (PSA <1.0 ng/dl)	58%	30%
Negative Predictive Value	97%	89%

(Afshar-Oromieh et al. Eur J Nuc Med. 2014,Herlman et al. Eur Urol. 2016, Maurer et al. J Urol 2016)

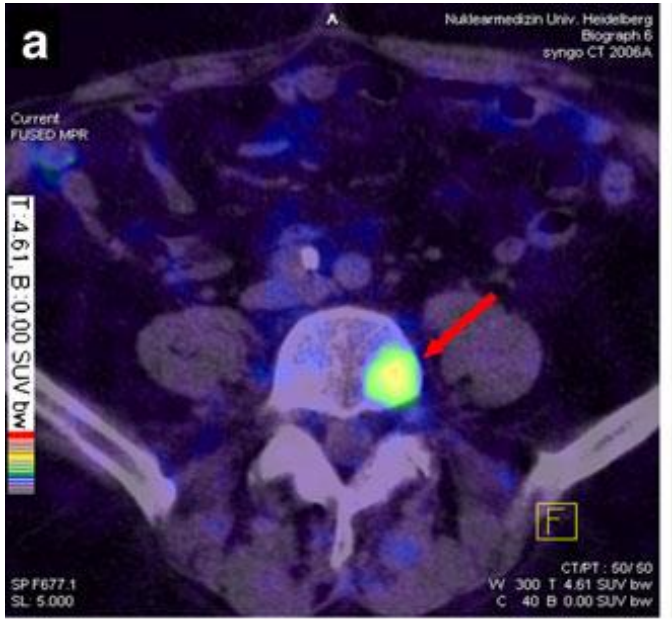
(PSA 0.01ng/dl)

Choline PET **PSMA PET**

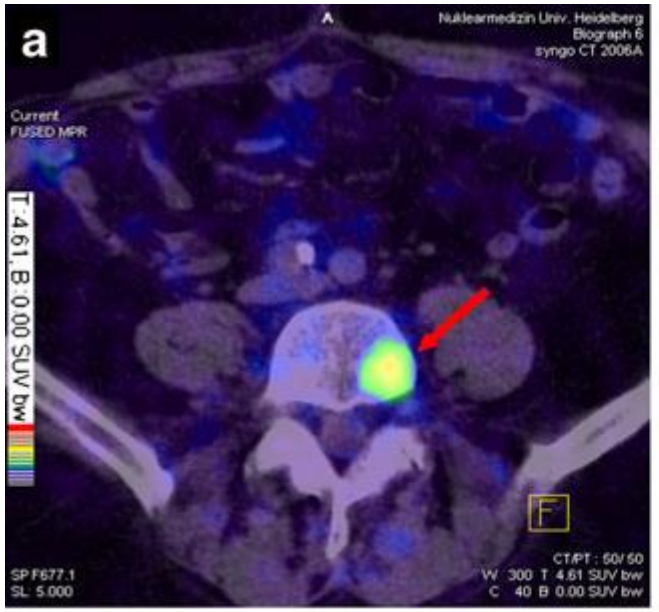


(Afshar-Oromieh et al. Eur J Nuc Med. 2014)

Choline PET



PSMA PET



(Afshar-Oromieh et al. Eur J Nuc Med. 2014)

Prostate Specific Membrane Antigen (PSMA)

Can now detect disease earlier vs. CT/MRI, bone scan, Choline PET

Imaging modality of choice for men with high risk disease and BCR ?

Can this help identify which patients are appropriate candidates for sLND ?

Overall, sLND for prostate cancer…..

Variable outcomes…

Early biochemical response, **but most will eventually progress**

Morphological imaging (ie; CT,MRI) under-evaluate extent nodal involvement

Use of functional imaging (PSMA) to guide sLND is still under investigation

Overall, sLND for prostate cancer……

What still needs to be defined:

- Appropriate patient selection (PSMA??)
- Timing & extent of surgery
- Meaningful improvement in QOL
- Improved CSS

Dramatization- Dr. Raj Goel during sLND