Surgery for metastatic prostate cancer

Rational Strategy or Foolish Optimism?

The issues:

- Imaging/staging
- Patient selection
  - Definition of ‘oligometastases’
  - Role of molecular biomarkers
- Nodal disease vs bone mets
- Primary vs salvage
- Surgery vs radiation—which is optimal?
- Role of ADT, AR targeted therapy, chemotherapy

The puzzles of advanced prostate cancer

- Until recently: SOC ADT alone until CRPC
- Now: multiple strategies
- But: optimal care pathways not clear, many questions remain.
- Drug portfolio limited:
  - 2-3 similar AR pathway inhibitors with +++ cross-resistance (2 more in pipeline)
  - two taxane chemotherapy agents;
  - one radionuclide;
  - one vaccine, (USA only)
  - two bone protection therapies
- Precision medicine still on horizon
- No combination trials have succeeded so far.

Current state of evidence for radical prostatectomy for M1c PCa

- No level one evidence
- Pre-clinical evidence in both directions
- Recent case series

Celsus, 30 BC-30 AD: First cancer staging system

- "First there is the cacoetheses, then carcinoma without ulceration, then the fungating ulcer… None of these can be removed but the cacoetheses; the rest are irritated by every method of cure. The more violent the operations the more angry they grow. Some use caustics, some burning irons, others remove the growth with the scalpel. After excision, it recurs, bringing with it the cause of death, whereas at the same time, most people, by using no violent methods to attempt the extirpation of the disease but only applying mild medications to soothe it, protract their lives, notwithstanding the disorder, to an extreme old age."

Is cure possible when it is necessary?

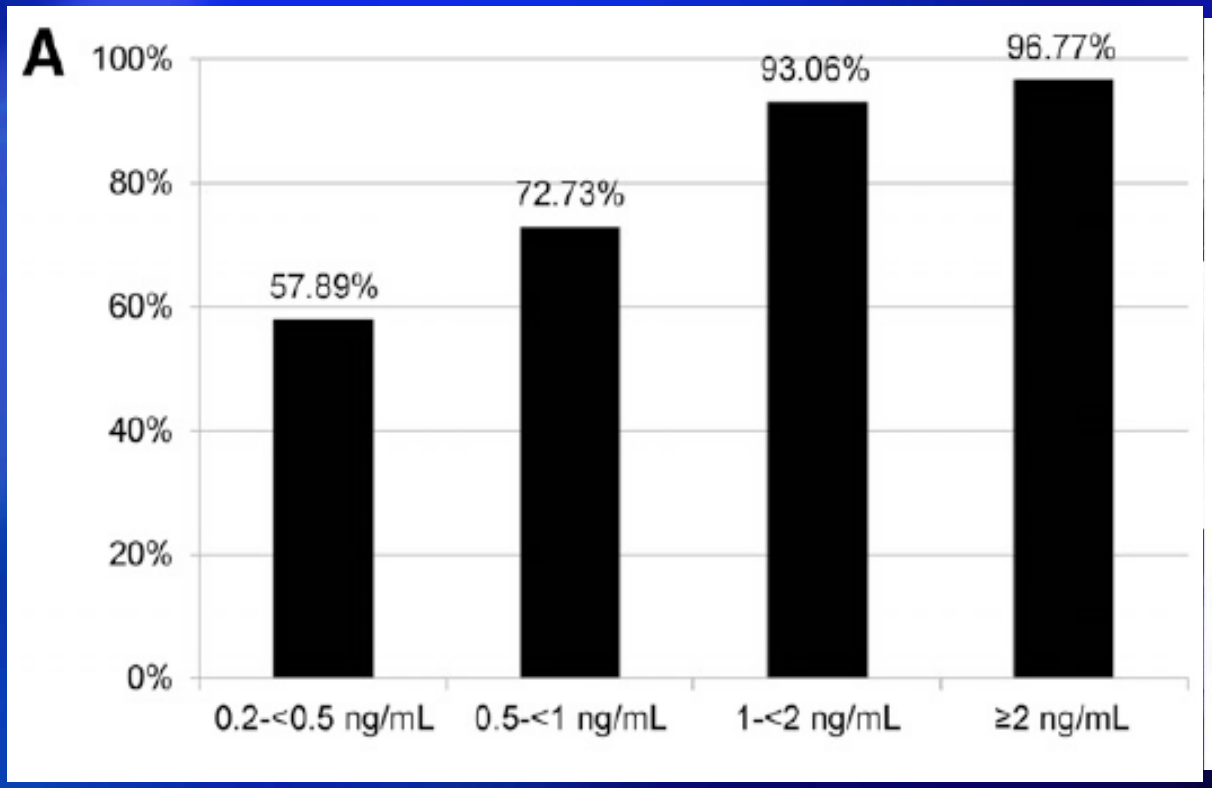
Is it necessary when it is possible?

W. Whitmore, MSKCC

The message: Be realistic about the modest impact of treatment on outcome

Evaluation of Hybrid ^{68}Ga-PSMA Ligand PET/CT in 248 Patients with Biochemical Recurrence After Radical Prostatectomy

As staging tests improve, the ‘oligomets’ space will increase



J Nucl Med 2015 56:668-674

First, salvage lymphadenectomy

- More straight forward
- Rising PSA post local therapy
- Imaging (PSMA-PET) identifies solitary lymph node
- Resection or SBRT appealing

74 year old pat. , Prostate cancer Gleason 4+4 3 years post RP, salvage XRT, now rising PSA (4.1)

Choline-PET:

1 lymph node metastasis

Salvage Lymph Node Dissection for Nodal Recurrent Prostate Cancer: A Systematic Review. Ploussard G, Eur Urol. 2018 Oct 31.

- 27 series, mean follow-up 29 mo.
- PSMA or Choline PET
- Complete biochemical response in 13–79.5%of cases
- 5-yr biochemical PFS rates 6% to 31%,
- Five-year overall survival 84%.
- Limitations:
  - retrospective design, single-center series, short F/U,
  - heterogeneity between series in terms of adjuvant treatment, endpoints, definitions of progression and study population

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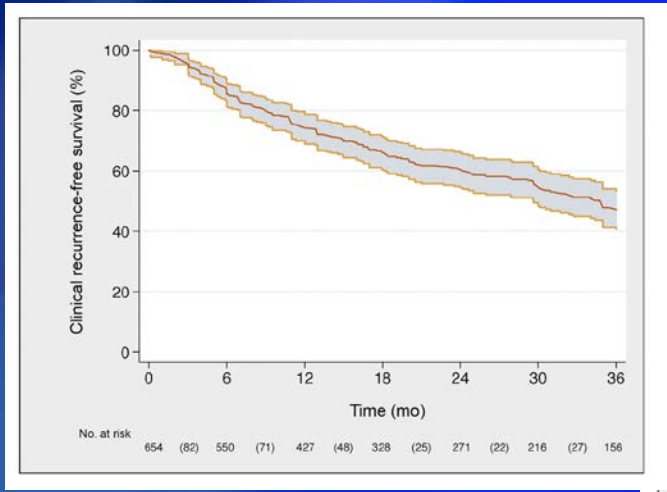
Identifying the Optimal Candidate for Salvage Lymph Node Dissection for Nodal Recurrence of Prostate Cancer: Results from a Large, Multi-institutional Analysis.

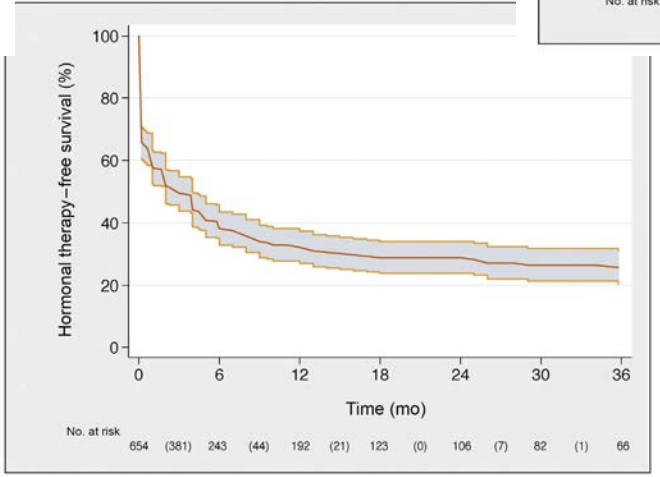
Fossati N. Eur Urol. 2019 Jan;75(1):176-183

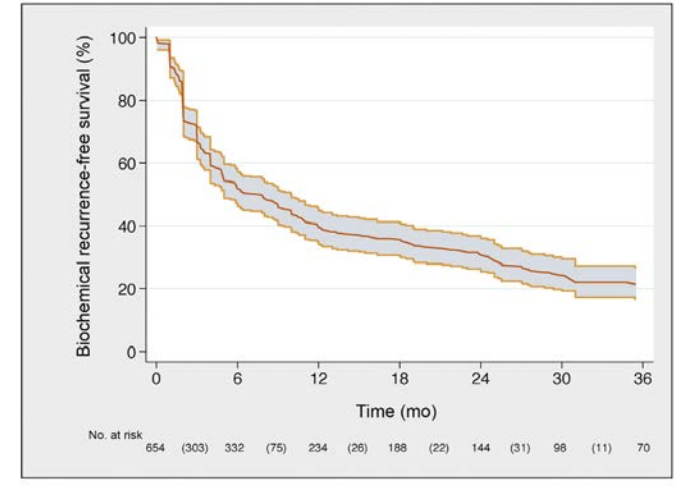
N=654



Clinical recurrence free survival

ADT free





bNED

Identifying the Optimal Candidate for Salvage Lymph Node Dissection for Nodal Recurrence of Prostate Cancer: Results from a Large, Multi-institutional Analysis

Multivariable Cox regression analysis predicting clinical recurrence after SLND

Gleason grade group			
≤4	1.00	Ref.	–
5	2.04	1.66–2.50	<0.0001
Time from RP to PSA rising, per 6 mo	0.98	0.96–0.99	0.025
HT administration at the time of PET/CT scan			
No	1.00	Ref.	–
Yes	1.47	1.19–1.82	0.0005
Retroperitoneum involvement at PET/CT scan			
No	1.00	Ref.	–
Yes	1.24	1.01–1.52	0.038
Positive spots at PET/CT scan			
≤2	1.00	Ref.	–
>3	1.26	1.05–1.61	0.019
PSA at SLND, ng/ml	1.05	1.04–1.07	<0.0001

EUROPEAN UROLOGY 75 (2019) 176–183

The harder problem is the patient with oligomets to bone

- Worse outcome
- Shorter survival
- Less benefit of local therapy

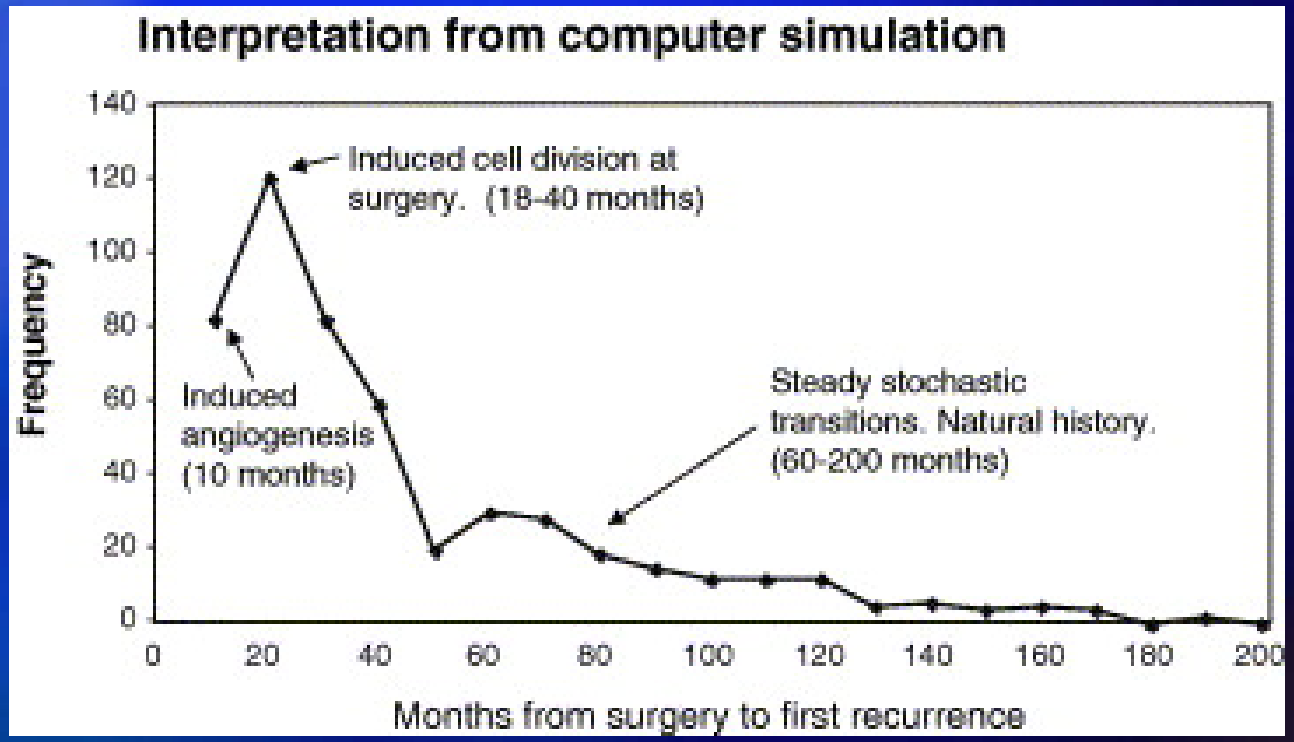
Local therapy may promote metastasis

- Growth factors, chemokines, and cytokines orchestrating surgical wound healing promote tumour growth, invasion, and angiogenesis[1]
- Breast cancer: Removal of primary may increase progression of mets.
- Radiation can exert local and distant effects on the movement of tumor cells and inhibit immune response

[1]Ceelen Crit Rev Oncol Hematol 2014;
[2]Vilalta Cell Mol Life Sci 2016

Does surgery unfavourably perturb the “natural history” of early breast cancer by accelerating the appearance of distant metastases?

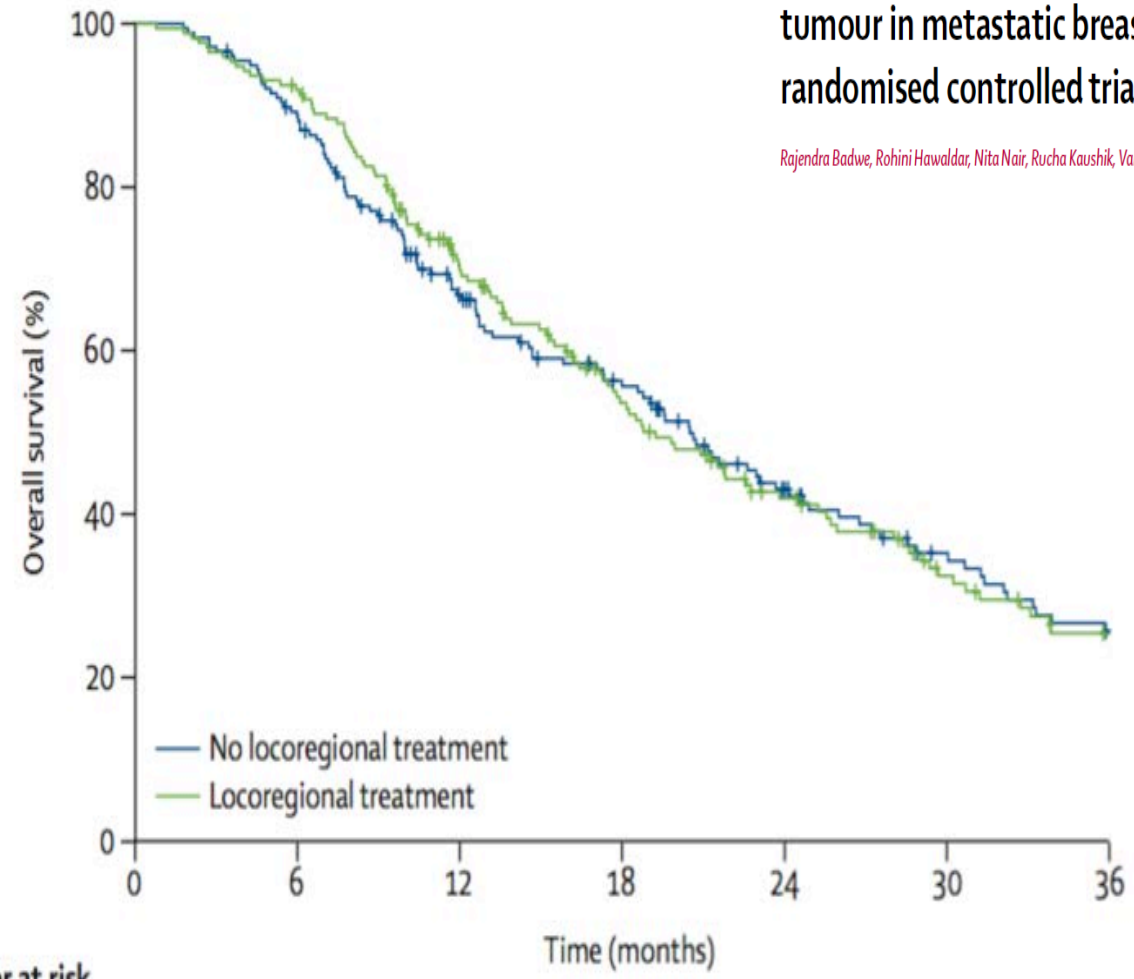
Baum M European Journal of Cancer, Volume 41, Issue 4, 2005, 508–515



Breast cancer: Cautionary tale

Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial

Rajendra Badwe, Rohini Hawaldar, Nita Nair, Rucha Kaushik, Vani Parmar, Shabina Siddique, Ashwini Budrukkar, Indraneel Mittra, Sudeep Gupta



Number at risk							
No locoregional treatment	177	148	101	75	50	36	24
Locoregional treatment	173	152	105	73	49	32	21

Badwe Lancet Oncol 2015

What is the biology of ‘oligomets’?

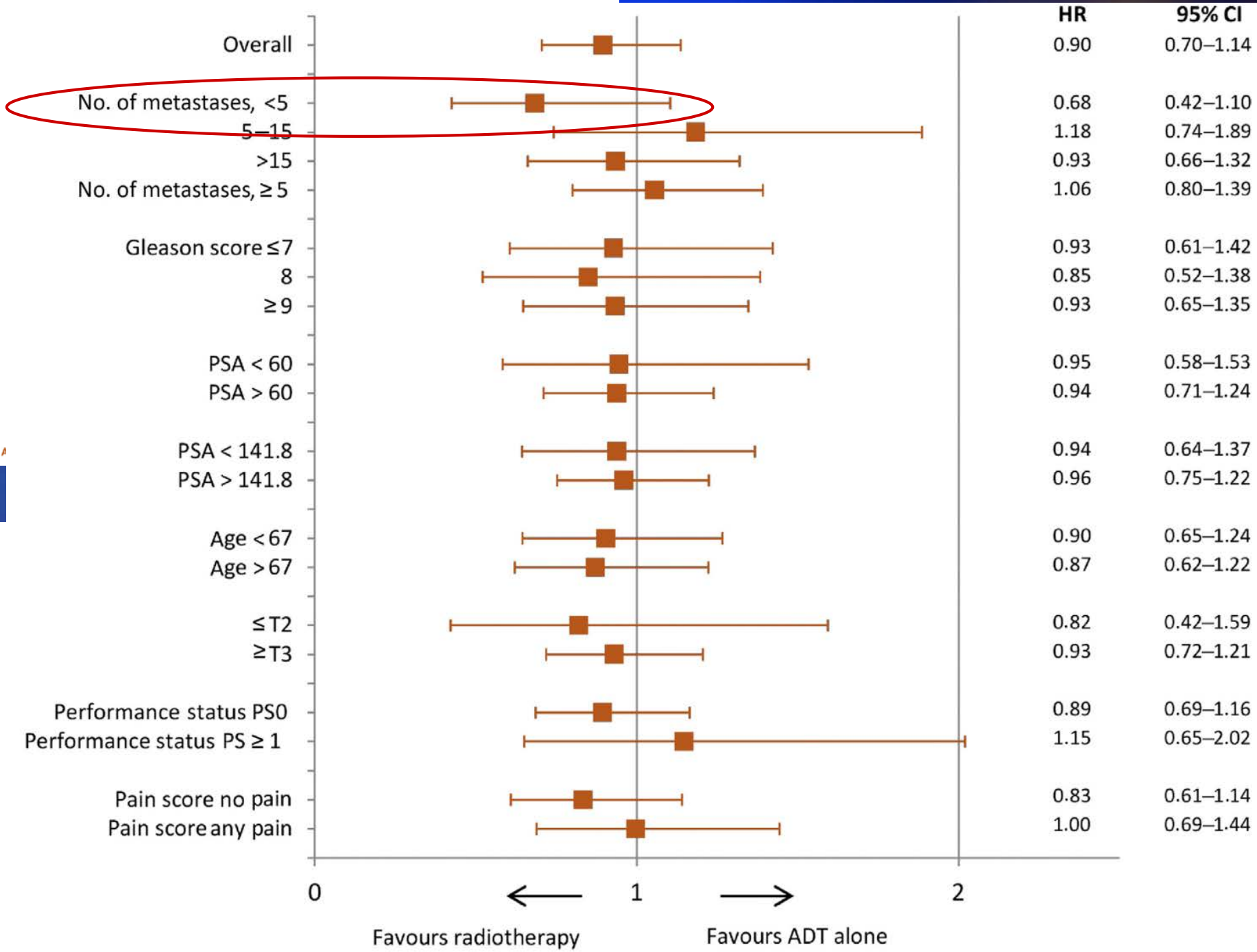
Is it:

A stable disease amenable to local therapy

Or is it:

A snapshot of an exploding condition

Answer: Unknown in any one patient



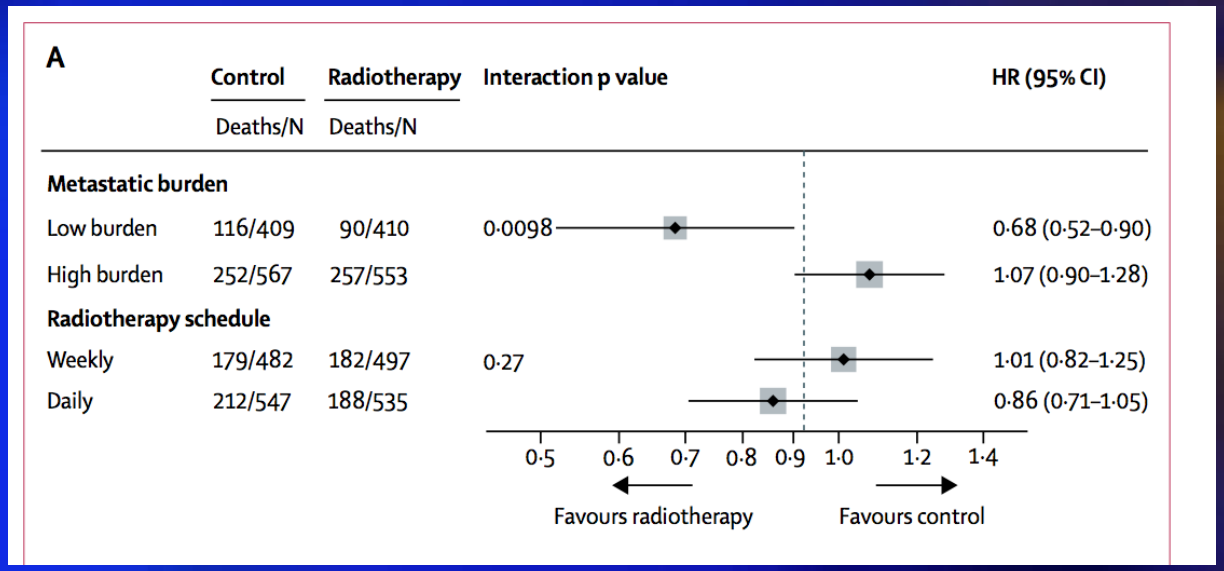
ADT + radiation therapy 210 72 32 13

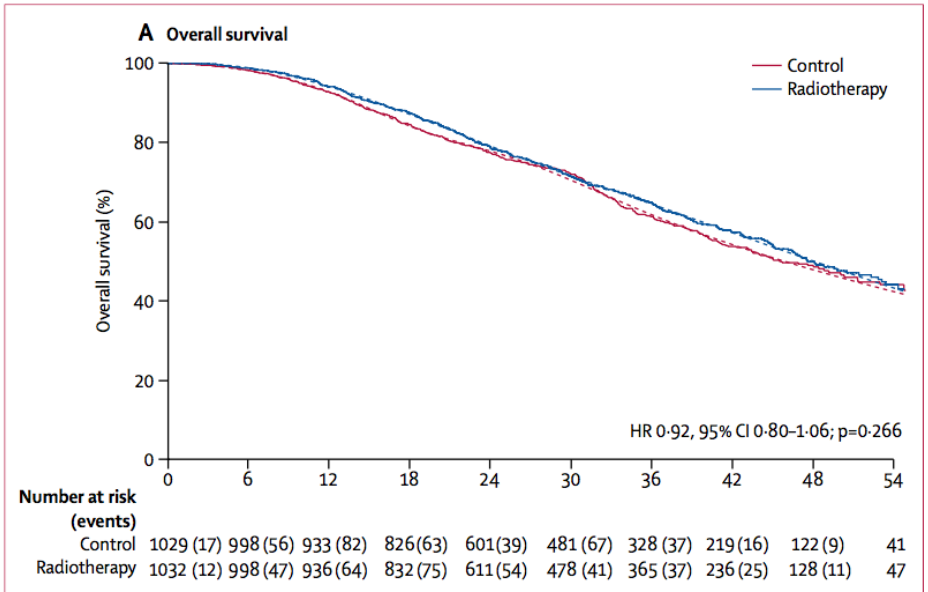
Favours radiotherapy Favours ADT alone

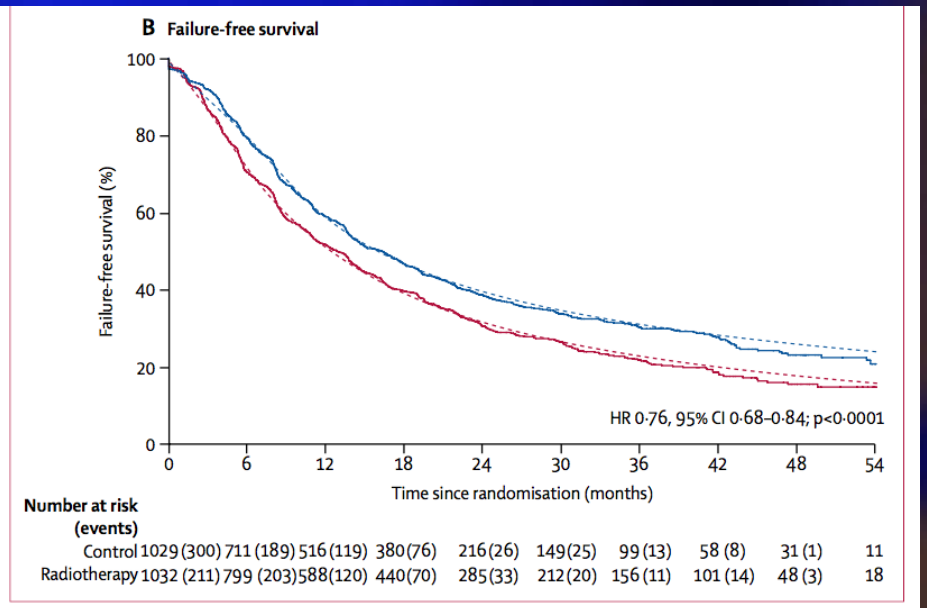
Radiotherapy to the primary for newly diagnosed, metastatic **prostate** cancer (**STAMPEDE**):

Parker CC,et al Lancet. 2018 Dec 1;392(10162):2353-2366.

- N=2061
- Median PSA 92
- 40% 'low burden' (Chaarted)







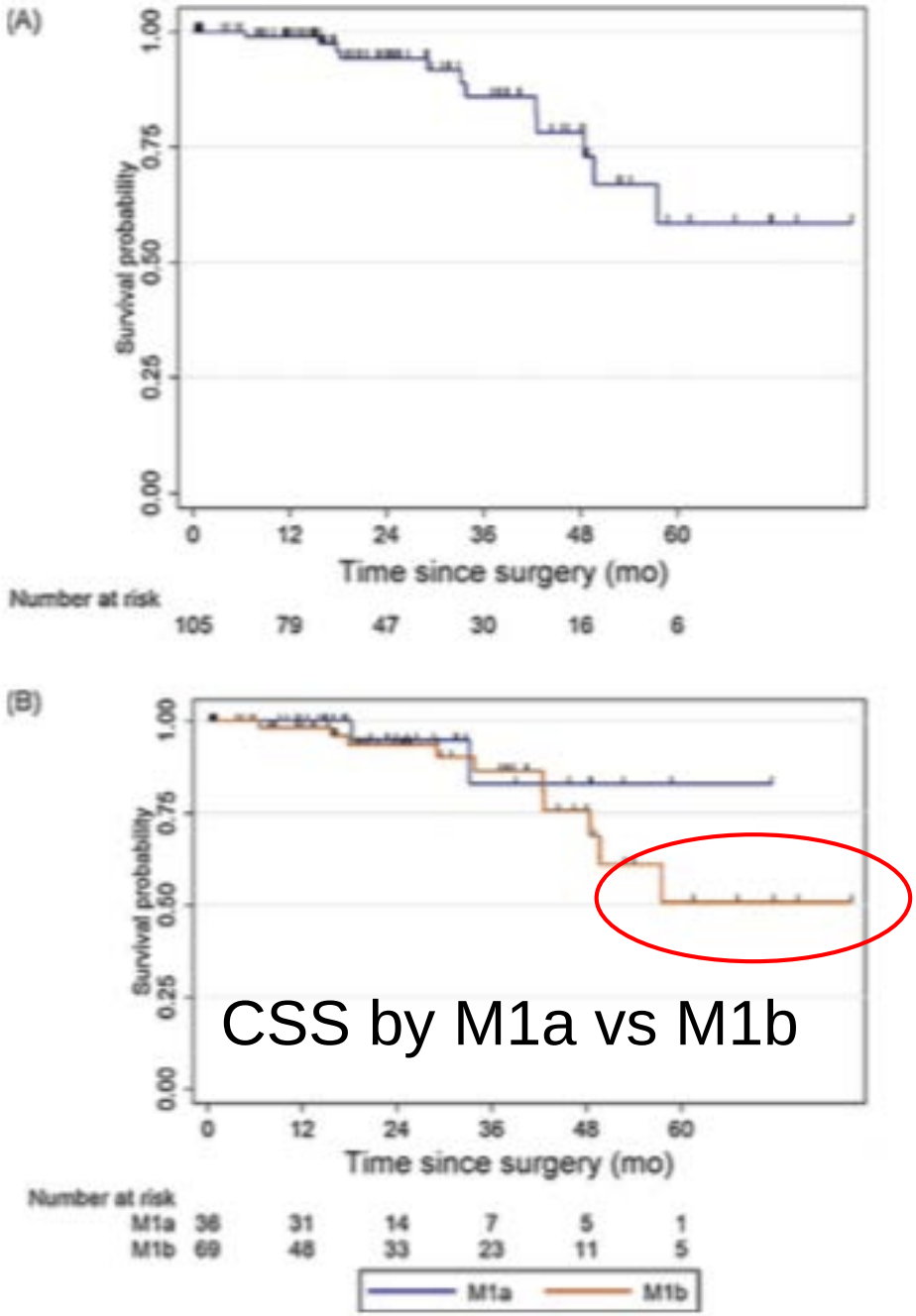
Local Therapy Improves Survival in Metastatic PCa. Leyh-Bannurah S et al, Euro Urol 72 (2017) 118–124

- SEER analysis of 13,692 mPCa patients
- 313 RP, 161 RT, 13,218 no local Rx
- Propensity adjustment
- Local therapy HR for CSM 0.40
- Lower CSM for RP than XRT

  HR 0.59

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

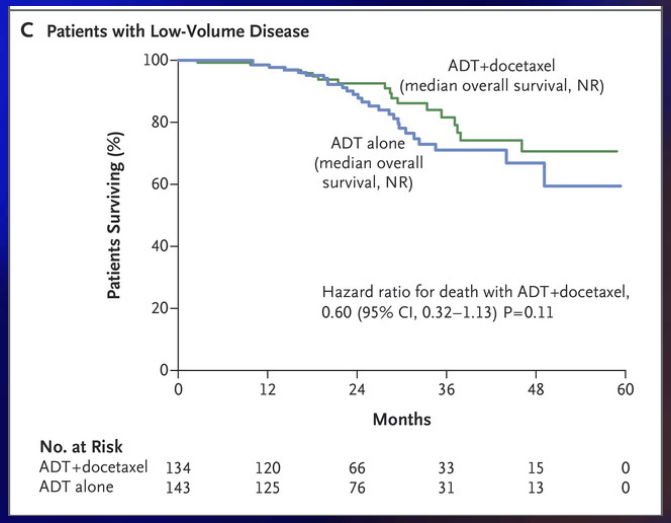
Overall Pca survival



CSS by M1a vs M1b

Perioperative Outcomes in 106 Men Who Underwent Radical Prostatectomy for Distant Metastatic Prostate Cancer at Presentation
Sooriakumaran P, European Urology 2015

N=106



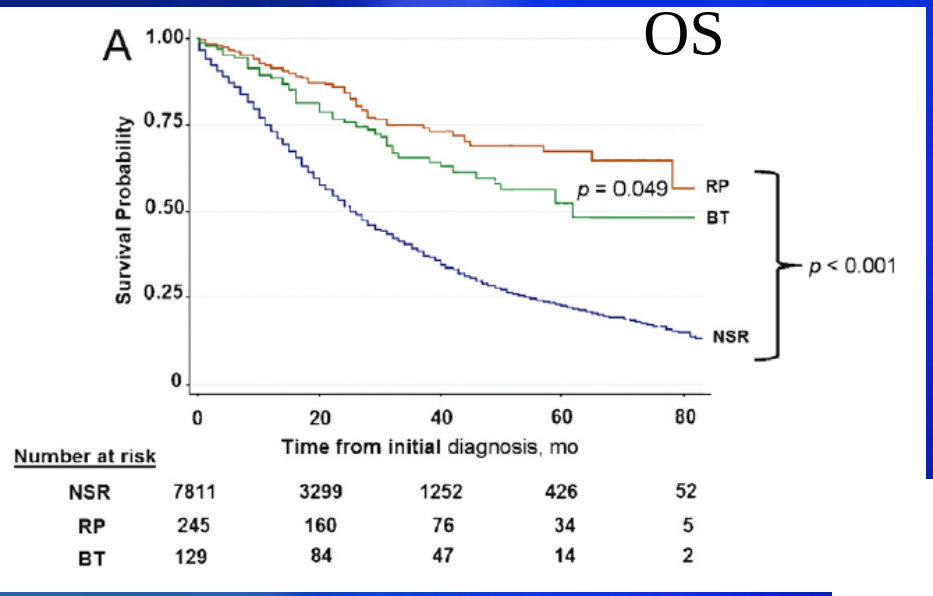
Chaarted:
low volume group

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

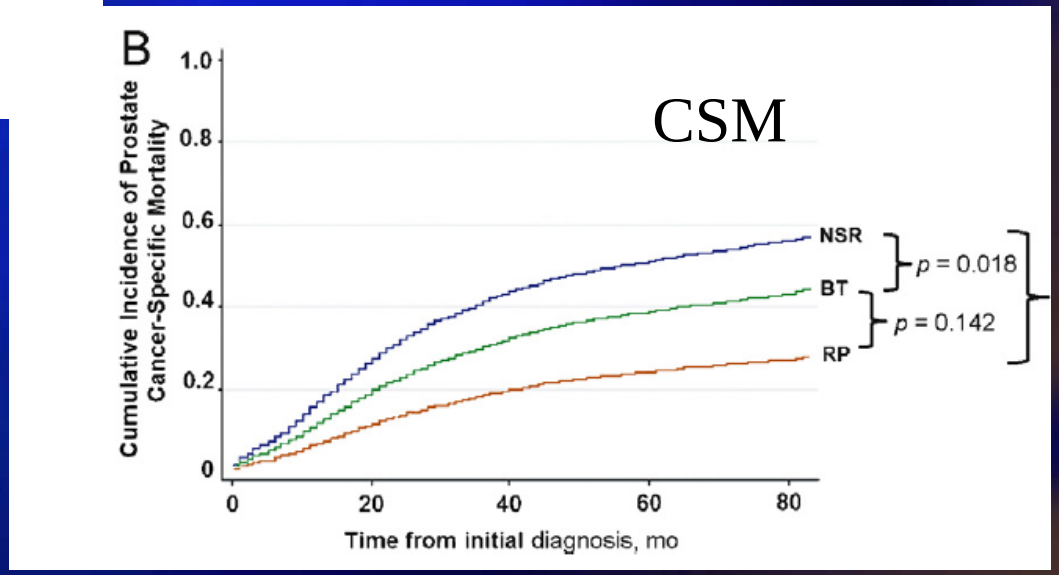
Satkunasivam R J Urol.2015 Aug;194(2):378-85

- 4069 men in SEER with Met CaP
- 47 RP, 88 IMRT, 107 cRT
- HR for CSM 0.48 for RP, 0.38 for IMRT

Might men diagnosed with metastatic prostate cancer benefit from definitive treatment of the primary tumor? A SEER-based study S.H. Culp Eur Urol, 65 (2014) 1058–10



8185 SEER patients
245 RPs (3%)
129 Brachy (1.5%)



Conclusion:
‘Prospective trials needed’

The key question from registry studies:

- Does receiving local therapy
- a) select patients with more favorable disease,

  Or
- b) does it favourably affect natural history?
- Answer:
  - almost certainly (a).
  - (b) is possible but uncertain
- Further: There is a real possibility of harm to patients

What about local control?

- In men with bone mets, death usually occurs before local progression
- Aus et al, J Urol 1995
  - 12% of men with bone mets treated with ADT only required nephrostomy tubes/stents before death
  - 25% required TURP

Prospective randomized ADT+/– local therapy in M1 PCa

Study	Status	Patients	Maneuver	OS
Horrad	Completed N=432	Newly Dx M1	ADT +/- XRT to prostate	No diff but HR 0.90, TTP 0.78
Stampede	Completed N=2061	Newly Dx M1	ADT +/- XRT to prostate	OS no diff but low risk HR 0.68 FFS HR 0.76
PEACE-1	Ongoing	Newly Dx M1	ADT vs ADT+ Abi vs ADT + XRT vs ADT + XRT + Abi	
MDACC BST	Ongoing N = 120	Newly Dx M1	Best Supportive Care vs BST + XRT or RP	Time to CRPC
G-RAMPP	Ongoing	M1b limited bone mets	ADT vs ADT + RP	OS
S1802	Ongoing	≥ M1a PCa	ADT +/- XRT or RP	TTP and OS

Unanswered Questions

- What is the target: prostate only, +/- nodes, +/- distant metastases?
- What is the best local strategy: surgery, radiation, or the combination of the two?
- Who are the patients most likely to benefit?
- Does the type of systemic therapy influence the need for control of the primary tumour?
  - Does use of chemotherapy influence benefit of local treatment?

Conclusion

- Salvage lymphadenectomy or SBRT for solitary nodal mets in selected patients
- Surgery for primary with oligo bone mets not ready for prime time—confine to clinical trials
  - ?Exception: Very young patient with solitary met
- 2 studies suggest benefit of XRT in low volume mets
- Radiation likely preferable for most--less invasive, long term side effects not an issue, usually good local control