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Best Systemic Therapy +/- Radical Prostatectomy in the Management of Men with Oligometastatic PCa: The RAMPP Randomized Controlled Trial

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Original Article

Best Systemic Therapy With or Without Radical Prostatectomy in the Management of Men With Oligometastatic Prostate Cancer: The RAMPP Randomised Controlled Trial

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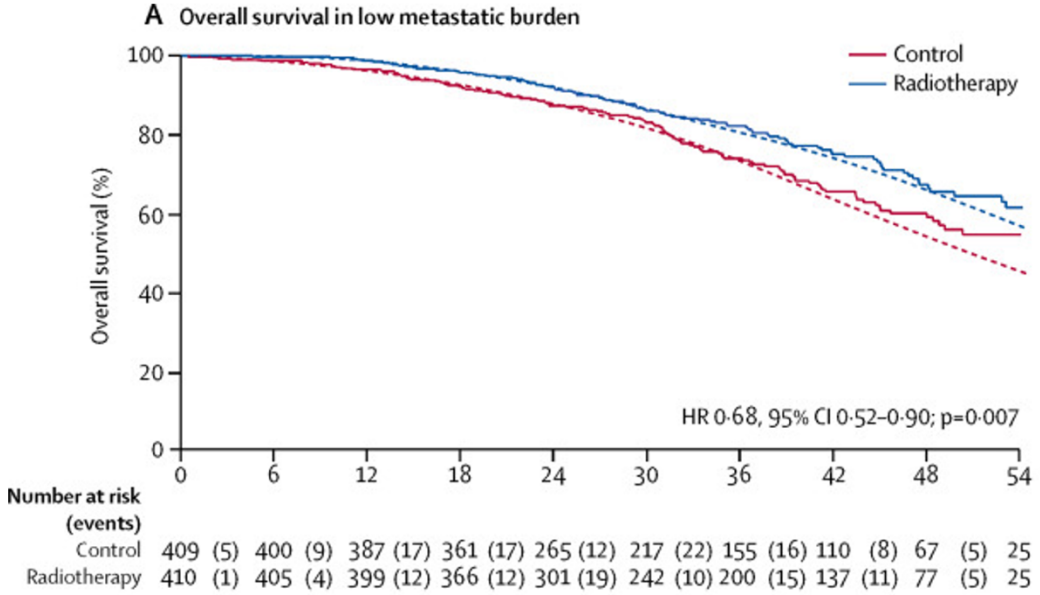
What is the existing evidence for primary local therapy in the low-volume mHSPC setting?

STAMPEDE Arm H
PEACE-1

STAMPEDE Arm H: Prostate XRT

- Phase III trial randomized 2,061 men with de novo mHSPC (2013-2016) to either:
  - SOC + prostate XRT
  - SOC alone
- Median PSA: 97 ng/ml
- Prior docetaxel: 18%
- Overall cohort: No OS benefit (HR: 0.92, 95% CI: 0.80-1.06)
- LV group: OS benefit (median OS: 49 vs 45 months; HR: 0.68, 95% CI: 0.52-0.90)



Parker et al. Lancet, 2018

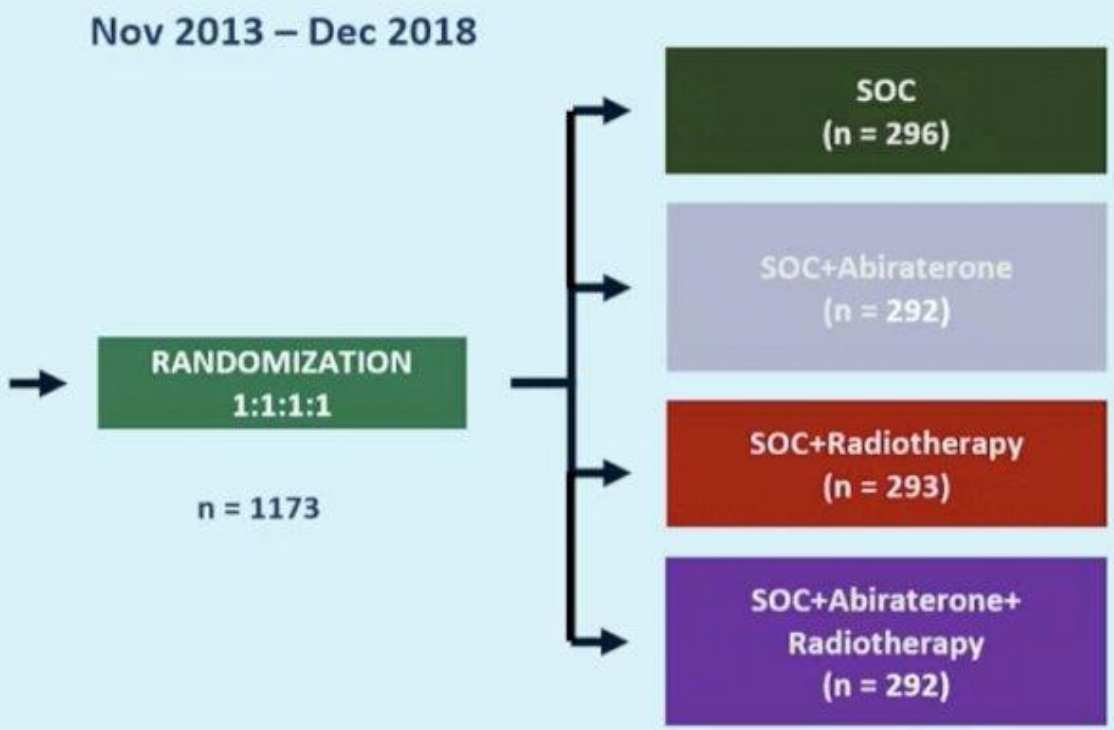
Design of PEACE-1 (2x2)

Key Eligibility Criteria
De novo mCSPC
Distant metastatic disease by ≥ 1 lesion on bone scan and/or CT scan
ECOG PS 0 -2

On-Study Requirement
Continuous ADT

Permitted
ADT ≤ 3 months

Stratification
ECOG PS (0 vs 1-2)
Metastatic sites (LN vs bone vs visceral)
Type of castration (orchidectomy vs LHRH agonist vs LHRH antagonist)
Docetaxel (yes vs no)



ECOG PS, Eastern Cooperative Oncology Group performance status

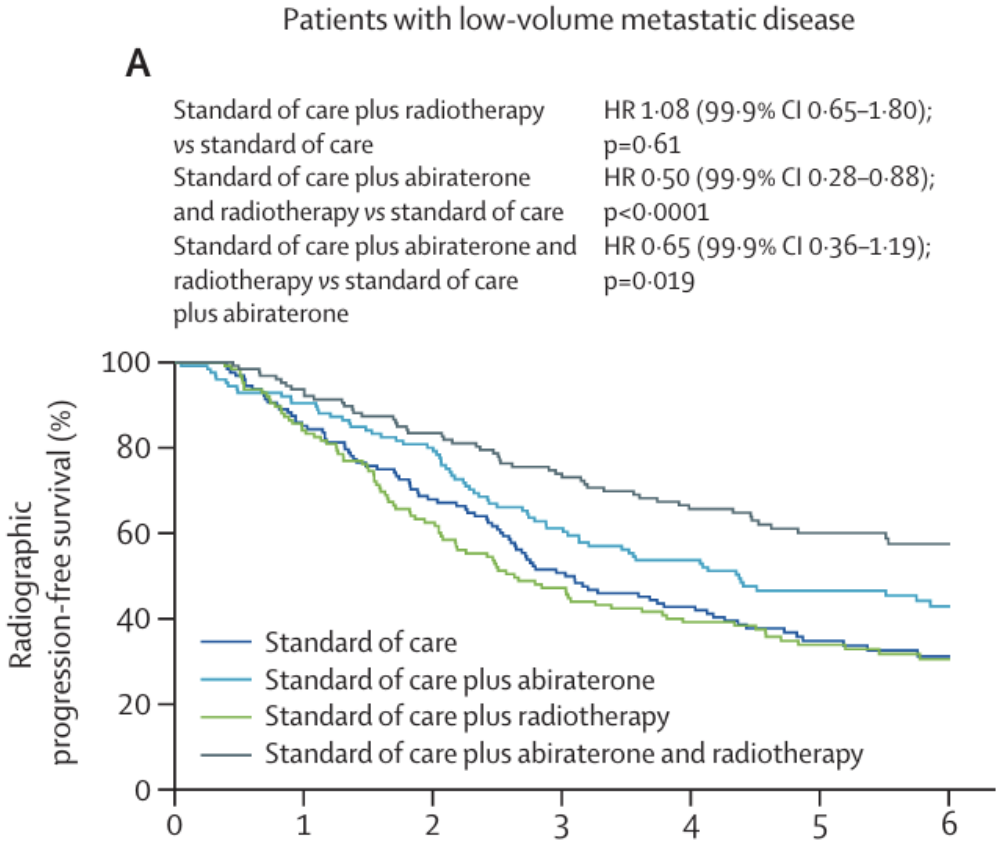
2021 ESMO congress

Karim Fizazi

Bossi et al. Lancet, 2024

PEACE-1: Low-Volume Group

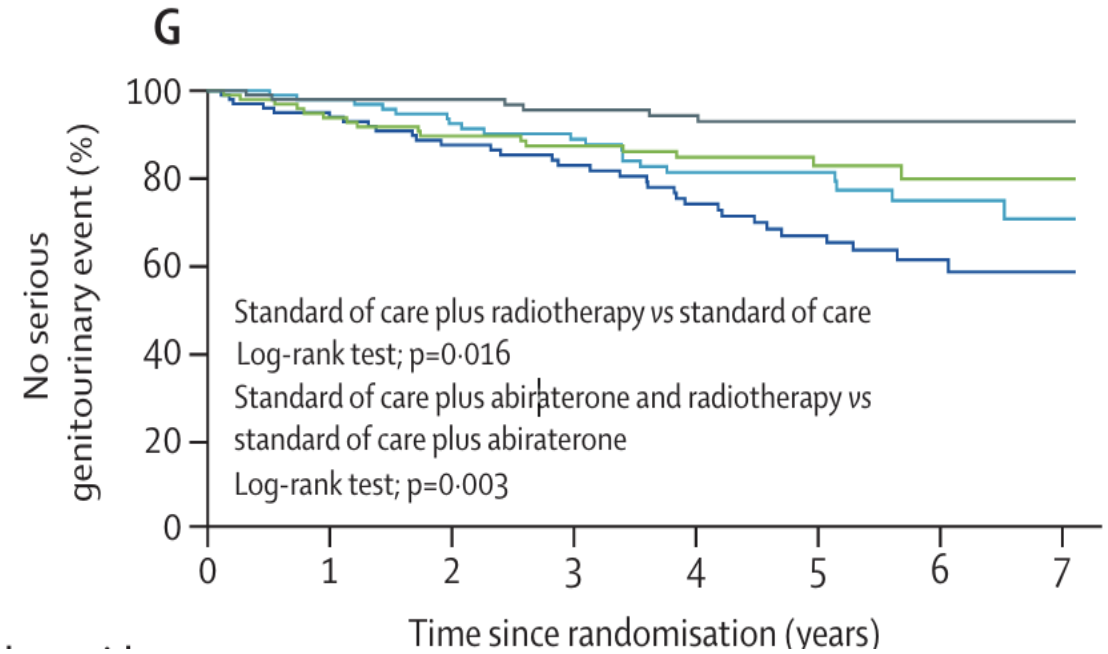
- rPFS:
  - SOC + AAP: XRT improved rPFS (7.5 vs 4.4 yrs; HR: 0.65, p=0.02)
  - SOC alone: No survival benefit (3 vs 2.6 yrs; HR: 1.08, p=0.61)
- No OS benefit w/ prostate XRT (6.9 vs 7.5 yrs; p=0.86)



Bossi et al. Lancet, 2024

Prostate XRT: Improved Time to Serious GU Events

	Patients with low-volume metastatic disease		Overall study population	
	Standard of care with or without abiraterone (n=200)	Standard of care plus radiotherapy with or without abiraterone (n=198)	Standard of care with or without abiraterone (n=458)	Standard of care plus radiotherapy with or without abiraterone (n=451)
Missing data	53/253 (20·9%)	54/252 (21·4%)	130/588 (22·1%)	133/584 (22·8%)
Total events	52 (26·0%)	22 (11·1%)	102 (22·3%)	55 (12·2%)
Urinary catheter	9 (4·5%)	7 (3·5%)	22 (4·8%)	23 (5·1%)
Suprapubic catheter	0	0	0	2 (0·4%)
Double J ureteric stent	13 (6·5%)	12 (6·1%)	28 (6·1%)	20 (4·4%)
Nephrostomy	2 (1·0%)	1 (0·5%)	6 (1·3%)	5 (1·1%)
Prostate radiotherapy	17 (8·5%)	0	27 (5·9%)	1 (0·2%)
Transurethral resection of the prostate	10 (5·0%)	1 (0·5%)	18 (3·9%)	2 (0·4%)
Radical prostatectomy	1 (0·5%)	1 (0·5%)	1 (0·2%)	2 (0·4%)



What about radical prostatectomy in the omHSPC setting?

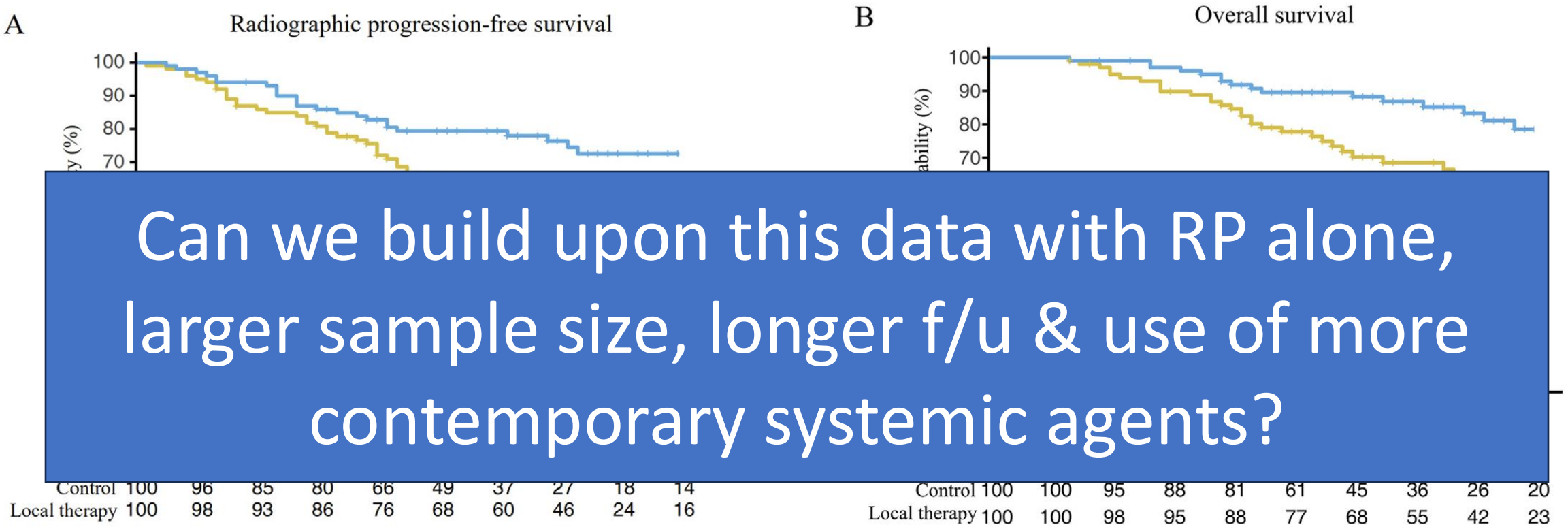
EUROPEAN UROLOGY ONCOLOGY 5 (2022) 519–525

Combination of Androgen Deprivation Therapy with Radical Local Therapy Versus Androgen Deprivation Therapy Alone for Newly Diagnosed Oligometastatic Prostate Cancer: A Phase II Randomized Controlled Trial

Bo Dai [a,b,c,d,*,†], *Sheng Zhang* [b,c,d,e,†], *Fang-Ning Wan* [a,b,c,d,†], *Hong-Kai Wang* [a,b,c,d,†], *Jun-Yu Zhang* [a,b,c,d], *Qi-Feng Wang* [b,c,d,f], *Yun-Yi Kong* [b,c,d,f], *Xue-Jun Ma* [b,c,d,g], *Miao Mo* [b,h], *Yao Zhu* [a,b,c,d], *Xiao-Jian Qin* [a,b,c,d], *Guo-Wen Lin* [a,b,c,d], *Ding-Wei Ye* [a,b,c,d,*]

- Open-label RCT randomized 200 pts w/ omPCA (≤5 bone mets or extra-pelvic LN mets on conv imaging) to **ADT** vs **ADT + RLT** (2015-2019)
- Median PSA: 99 ng/ml
- Intervention: 96 pts underwent RLT (RP: 85, RT: 11)
- Control: 17 eventually underwent RLT (RP: 15, RT: 2)

Dai et al. Eur Urol Oncol, 2022



Can we build upon this data with RP alone, larger sample size, longer f/u & use of more contemporary systemic agents?

Median rPFS: NR vs vs 40 mo
(HR: 0.43, p=0.001)

3-year OS: 88% vs 70%
(HR: 0.44, p=0.008)

Dai et al. Eur Urol Oncol, 2022

RAMPP Trial

- International RCT across 39 sites in Germany, Sweden, Denmark, Australia, Finland, and Spain
- Trial eligibility:
  - Newly diagnosed (<6 mo) PCa (D'Amico IR or HR)
  - PSA <200 ng/ml
  - 1-5 bone mets (PET or conv imaging)
  - No brain or visceral mets
- Randomized 1:1 to:
  - BST alone (ADT +/- NSAA, ARPI, docetaxel)
  - RP + ePLND + BST

Study Outcomes

- Primary: Cancer-specific mortality (CSM)
  - Study designed for 80% power to detect 14% difference in 5-yr CSM
  - Required sample size: 500 pts (250/arm) & 106 primary outcome events over 5-yr f/u
- Secondary:
  - Clinical progression: New bone or soft tissue mets on imaging or CSM
  - OS
  - Surgery-specific complications: Bleeding, anastomotic leak, thromboembolic or cardiac events, lymphocele, impaired wound healing

Early Study Accrual Closure – STAMPEDE Arm H

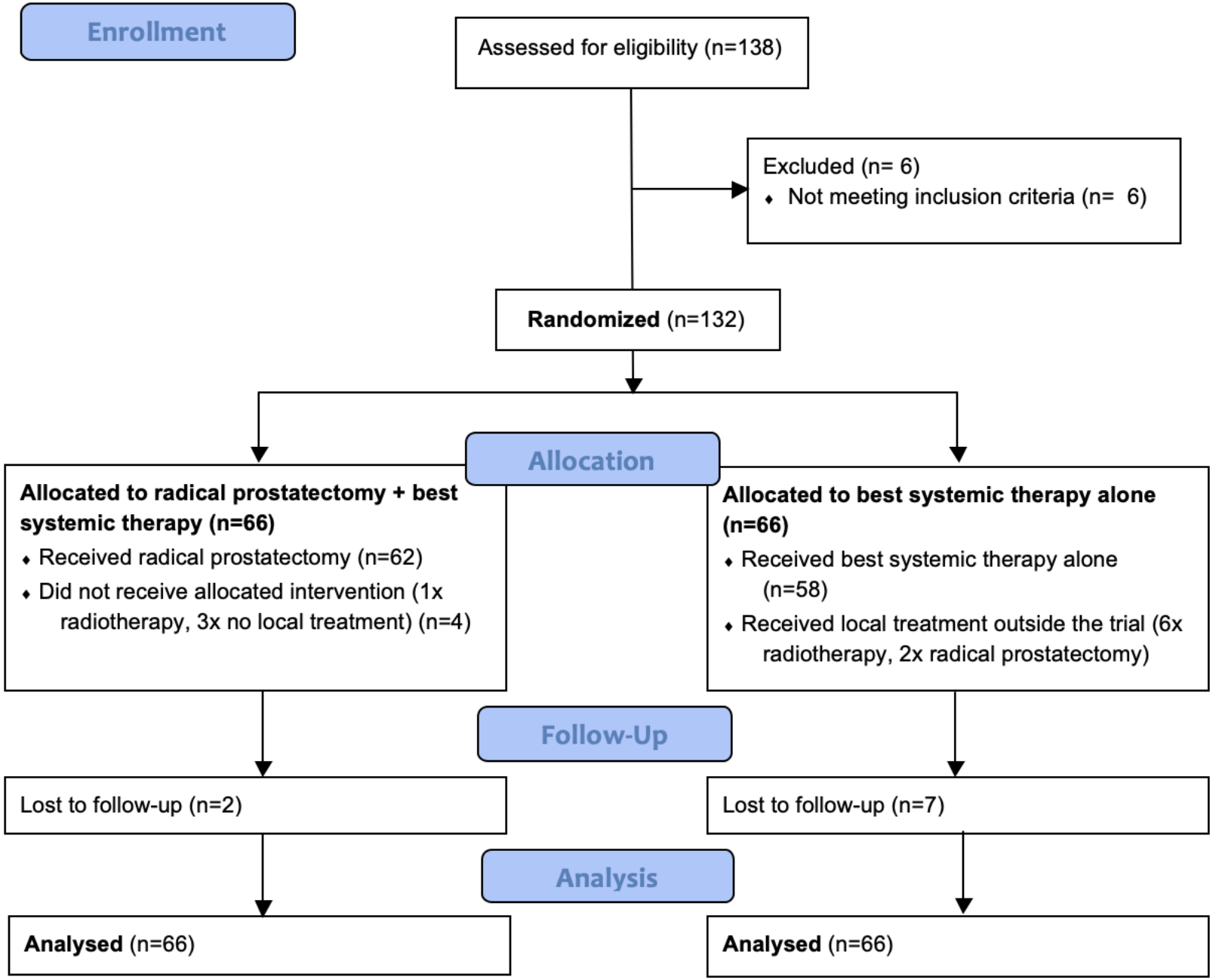
- Following publication of STAMPEDE Arm H results demonstrating OS benefit for prostate XRT in LV mHSPC & low recruitment rate → Steering committee decision to stop study accrual early for ethical reasons

- Available resources in smaller sample size used to extend planned f/u from 5→10 years

Statistical Methods

- Intent-to-treat analyses
- Differences between study arms: Wilcoxon rank-sum and Pearson's chi-square tests
- CSM and clinical progression: Other-cause death is a competing event → Competing risks analyses with cumulative incidence curves used
  - Comparisons: Gray test
  - Regression analysis used to evaluate effect of RP addition on CSM
- OS: KM curves
  - Comparisons: Log-rank test

Consort Flow Diagram



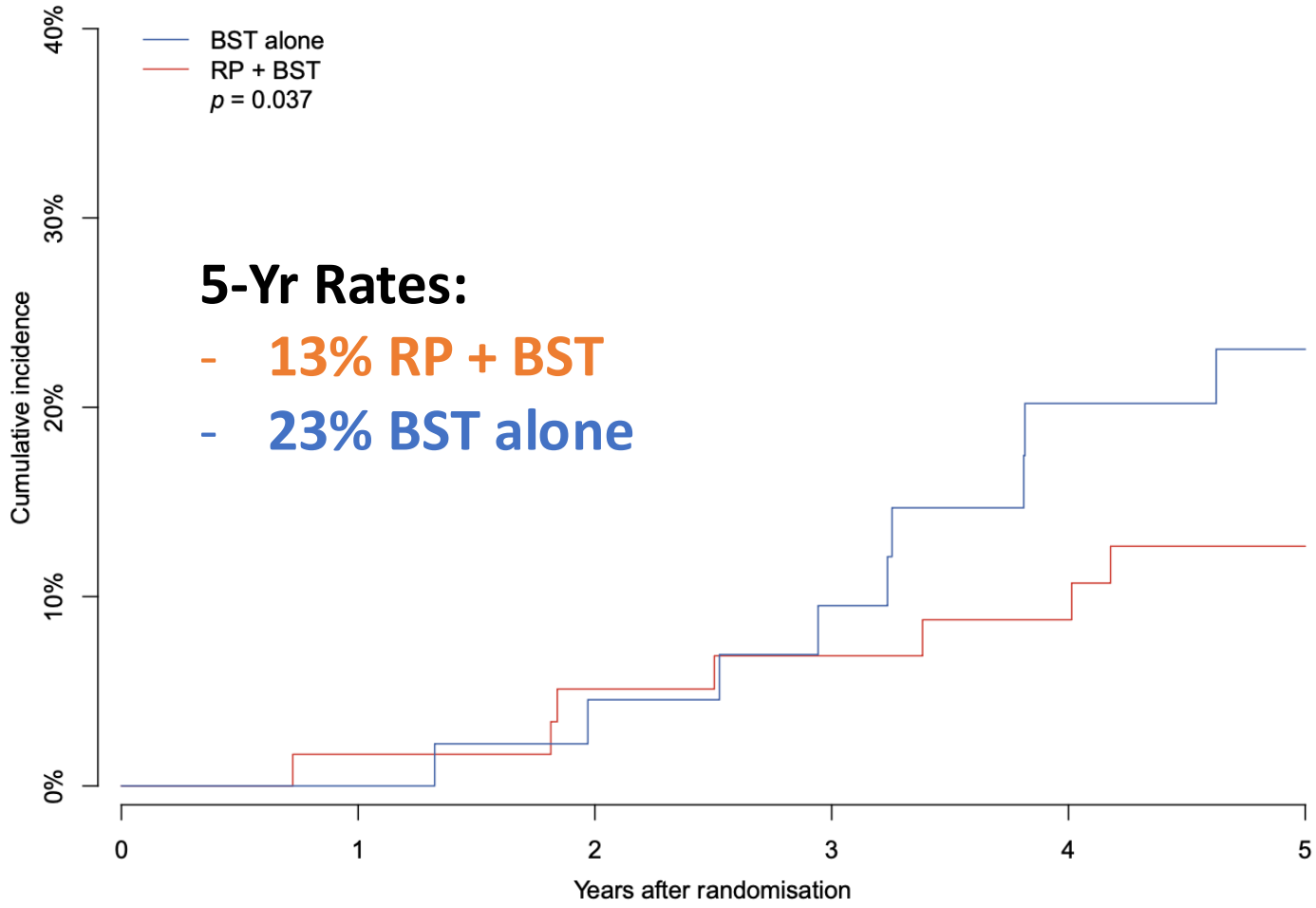
Descriptive Characteristics at Randomization (2015-2018)

Parameter	RP + BST (n = 66)	BST alone (n = 66)
Median age, yr (IQR)	67 (63–70)	67 (62–71)
Median PSA, ng/ml (IQR)	20 (12–43)	22 (10–35)
ECOG performance score, n (%)		
0	58 (88)	61 (92)
1	8 (12)	5 (8)
Median TDR, mo (IQR)	2 (1–3)	2 (1–3)
Gleason sum score at biopsy, n (%)		
≤7	19 (29)	20 (30)
8–10	46 (70)	44 (67)
Data not available	1 (2)	2 (3)
cT stage, n (%)		
≤cT2	35 (53)	41 (62)
cT3–4	27 (41)	19 (29)
cTx	4 (6)	6 (9)
cN stage, n (%)		
cN0/x	49 (74)	44 (67)
cN1	17 (26)	22 (33)
PET used for initial staging, n (%)	22 (37)	18 (30)
Number of bone metastases, n (%)		
1–3 metastases	60 (91)	62 (94)
4–5 metastases	6 (9)	4 (6)
Location of bone metastases, n (%) [a]		
Spine	18 (27)	16 (24)
Rib	13 (20)	22 (33)
Pelvis	44 (67)	44 (67)
Shoulder	2 (3)	9 (14)
Extremities	5 (8)	6 (9)
Skull	1 (2)	2 (3)
Local treatment received, n (%)		
No local treatment	3 (5)	58 (88)
Received RP within the trial	62 (94)	0 (0)
Received RP outside the trial	0 (0)	2 (3)
Received definitive radiotherapy	1 (2)	6 (9)
Initial best systemic therapy, n (%)		
ADT alone	56 (85)	42 (64)
ADT + chemotherapy	3 (5)	7 (11)
ADT + androgen receptor pathway inhibitor	0 (0)	4 (6)
Started after 3 mo/data not available	7 (11)	13 (20)
Type of ADT used, n (%)		
Nonsteroidal androgen receptor antagonist	12 (18)	2 (3)
GnRH agonist	17 (26)	15 (23)
Combination	30 (46)	36 (55)
Data not reported	8 (12)	13 (20)
Initial metastases-directed therapy, n (%) [b]	1 (2)	3 (5)

Clinicopathological Characteristics and Outcomes Among Patients Undergoing RP (n=66)

Parameter	Result
Gleason sum at RP, *n* (%)	
≤7	17 (26)
8–10	44 (67)
Data not available	5 (8)
Margin status at RP, *n* (%)	
R0/X	25 (38)
R1	41 (62)
pT stage at RP, *n* (%)	
≤pT2	10 (15)
pT3–4	52 (79)
pTx	4 (6)
pN stage at RP, *n* (%)	
pN0/x	28 (42)
pN1	38 (58)
First PSA after RP (ng/ml) [a]	0.10 (0.03–0.50)

Cumulative Incidence of CSM



5-Yr Rates:

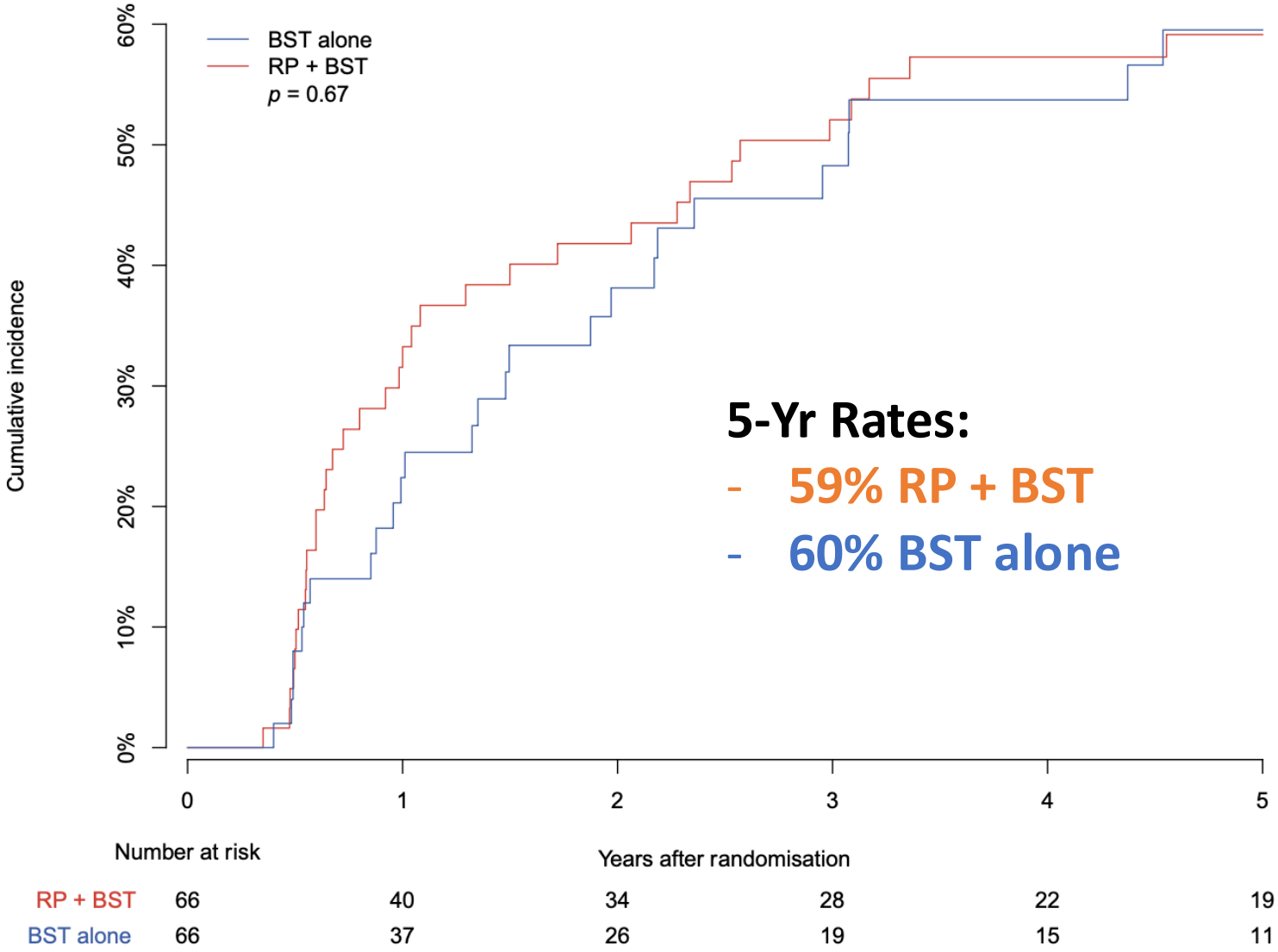
- **13% RP + BST**
- **23% BST alone**

HR 0.39, 95% CI 0.16-0.98

Number at risk

RP + BST	66	57	55	52	45	35
BST alone	66	47	41	35	28	21

Cumulative Incidence of Clinical Progression

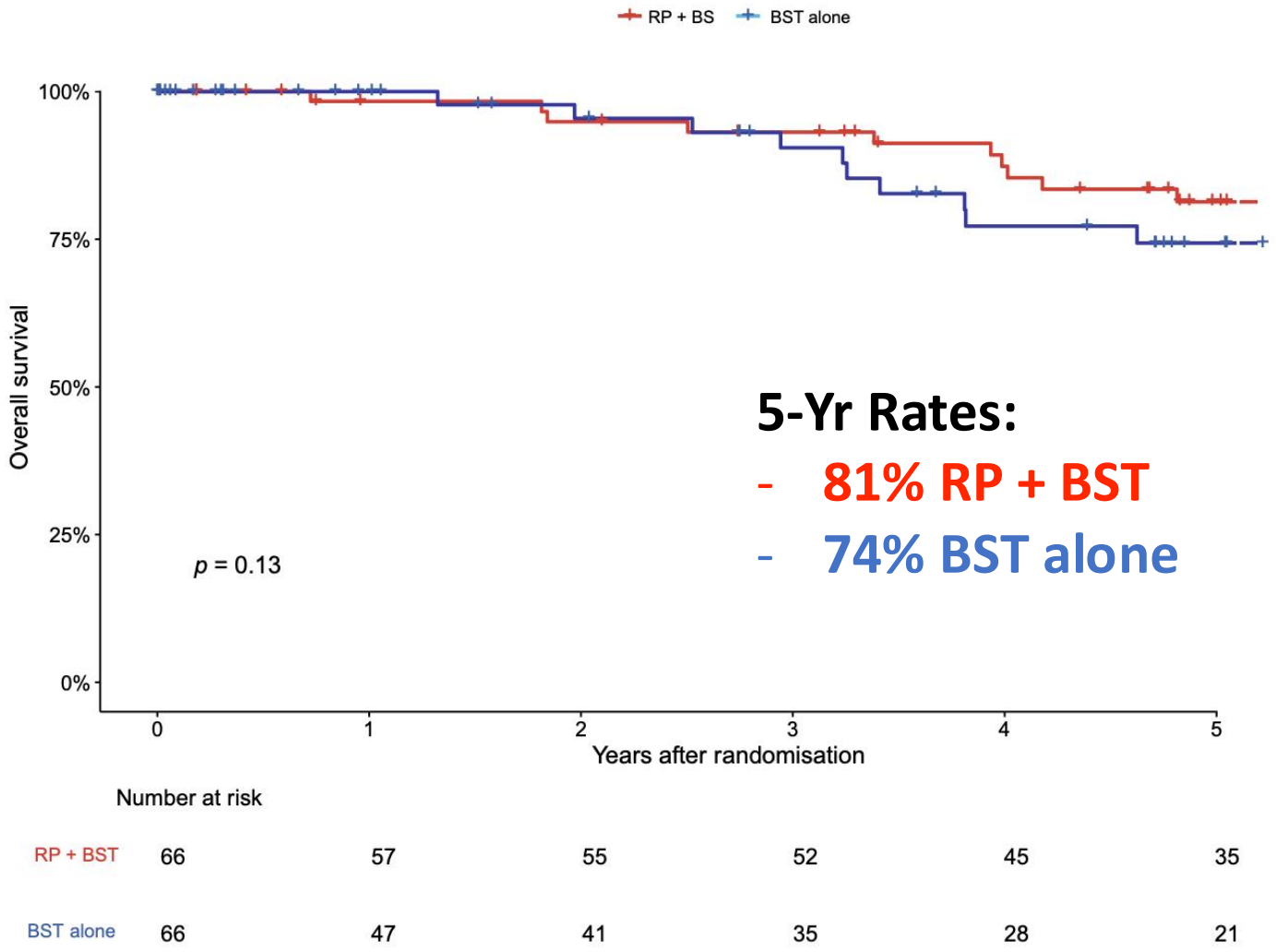


5-Yr Rates:

- **59% RP + BST**
- **60% BST alone**

HR 1.11, 95% CI 0.67-1.84

Kaplan-Meier Estimates of OS



5-Yr Rates:

- **81% RP + BST**
- **74% BST alone**

HR 0.55, 95% CI 0.25-1.22

AEs and Surgery-Specific Complications

Parameter	RP + BST (n = 66)	BST alone (n = 66)
Adverse events, n (%)	33 (50)	29 (44)
Serious adverse events, n (%)	16 (24)	12 (18)
Surgery-specific complications overall, n (%)		
Clavien-Dindo grade <III	19 (29)	–
Clavien-Dindo grade ≥III	9 (14)	–
Bowel injury	1 (2)	–
Bleeding	3 (5)	–
Anastomotic leakage	3 (5)	–
Lymphocele	2 (3)	–
Thromboembolic/cardiac event	0	–
Impaired wound healing	0	–

Limitations

1. The study was stopped early:

- 3 other major trials incorporating RP in omPC are ongoing: TRoMbone, SIMCAP, SWOG S1802
- Pooled analyses of these trials with RAMPP may provide more robust estimates

2. Patient enrolment was slow

3. Eligibility criteria mainly relied on conventional bone scans (~1/3 had PSMA PET)

4. Results for the secondary endpoint of clinical progression failed to validate the findings of improved CSM:

- It remains unclear if the CSM benefit of RP addition is direct (by reducing the primary cancer volume) or indirect (by prompting earlier use of salvage therapies)

5. RAMPP was not powered to show a sufficient OS benefit

Discussion

- This randomized trial showed a significant CSM benefit from addition of RP to BST in omPC:
  - Local therapy (either RP or RT) should be considered

- The CSM cumulative incidence rate at 5 yrs was significantly lower in the RP arm: 13% vs 23%; p = 0.037. Comparable to:
  - The 5-yr OS benefit of RT addition in STAMPEDE was 12% (65% vs 53%)[1]
  - The STOPCAP meta-analysis of 3 prospective studies (HORRAD, STAMPEDE, PEACE-1) showed a consistent pattern of better cancer control with RT addition to BST for men with <5 bone mets (pooled 7% OS improvement at 3 yrs)[2]

- RP was a safe treatment modality that resulted in excellent biochemical response and local cancer control:
  - However, 14% in the RP + BST arm experienced severe surgery-specific complications during follow-up
  - In the RT arm in STAMPEDE[1] 5% of patients reported at least 1 RTOG grade 3/4 acute toxicity, and 39% experienced a CTCAE grade 3+ AE

1. Parker et al., *PLoS Med*, 2022.
2. Burdett et al., *Eur Urol*, 2019.

Take Home Message

Although this trial has substantial limitations, the results support the addition of radical prostatectomy as local therapy to best systemic therapy in oligometastatic PCa