Role of radical prostatectomy in oligometastatic prostate cancer: Cons

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Role of Cytoreductive Radical Prostatectomy (CRP)

- Potential benefits of CRP
 - Removal of the primary tumor source
 - : Molecular mediators from the primary tumor may enable and promote metastatic disease
 - : Patients with mPCa continue to have aggressive and active tumor cells even after adequate chemo-hormonal treatment
 - Reduction in the local tumor complications
- Concerns about CRP
 - Randomized prospective clinical trial
 - : Therapeutic benefits vs Complications

Oncologic outcomes

Radical CRP in Men with Prostate Cancer and Oligometastatic disease (Retrospective studies)

Author	Type of study	cRP	Control group	Complications	Follow-up (months)	PFS (months)	OS	CSS
Heidenreich	Case-control	23	23	13%	34.5 vs. 47.1	38.6 vs. 26.5, P=0.032	95.6 vs. 84.2%, P=0.043	
Culp	SEER data, retrospective	245	7811	No data	16.0	No data	67.4 vs. 22.5%, P<0.001	75.8% vs. 48.7%, P<0.001
Sooriakumaran	Retrospective, multiinstitutional	106	None	20.8%	22.8	No data	88.7%	88.7%
Gratzke	Cancer registry	74	None	No data	No data	No data	55 vs. 21% at 5 years, P<0.01	
Steuber	Case-control	43	40	7 vs. 35%	32.7 vs. 82.2			
Leyh-Bannurah	SEER data, retrospective		None	No data	43.5 vs. 31.0	No data	-	65 vs. 52%, P<0.001
Heidenreich	Retrospective, multiinstitutional	113	None	9.7%	53.6	72.3	85.6	

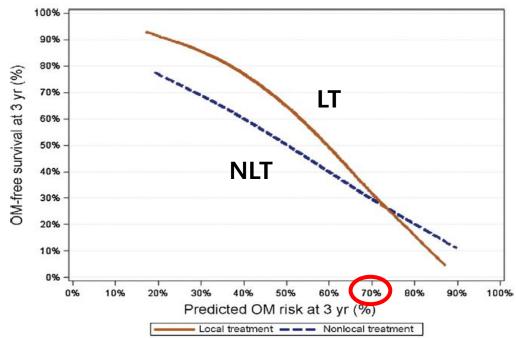
CRP, cytoreductive radical prostatectomy; CSS, cancer specific survival; OS, overall survival; PFS, progression-free survival; SEER, surveillance, epidemiology, and end results.

multiinstitutional

CRP, cytoreductive radical prostatectomy; CSS, cancer specific survival; OS, overall survival; PFS, progression-free survival; SEER, surveillance, epidemiology, and end results.

The impact of local treatment on survival in patients with metastatic prostate cancer on diagnosis : A national cancer data base analysis

- Overall, 9.5% (n=1470) of pts received LT.
 - EBRT targeted to the prostate : 77%
 - RP : 20%
 - Brachytherapy : 3%
- 3 yr-survival probability based on Tx. type
 - Brachytherapy : 80%
 - RP : 78%
 - EBRT : 60%
 - NLT : 48%



Pts. with a predicted OM risk ≥ 70% had a similar observed survival rate whether they received LT or not.
This implies that these patients did not benefit from LT.

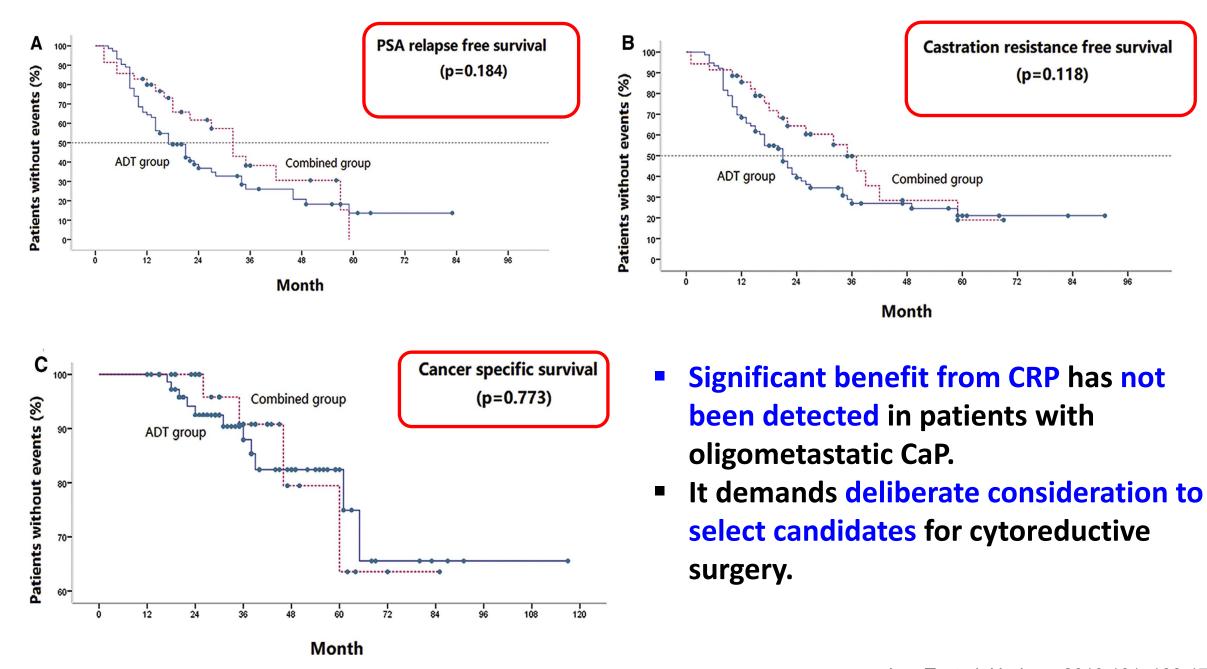
Oncological Outcome of CRP in Prostate Cancer Patients with Bone Oligometastases

Characteristics of 111 patients	35 pts. : CRP + ADT	76 pts. : ADT alone	
	Combined Group N (%)	Control Group N (%)	P Value
Baseline Characteristics			
Ν	35 (100%)	76 (100%)	
Follow-up (mean, month)	36.86 ± 16.55	39.21 ± 20.62	.555
Age (mean, y)	67.83 ± 7.19	71.17 ± 7.73	.030
<u>≤</u> 59	5 (14.3%)	6(7.9%)	.284
60-69	14 (40.0%)	26 (34.2%)	
70-79	15 (42.9%)	34 (44.7%)	
≥80	1 (2.9%)	10 (13.2%)	
ECOG performance status score*			
0	33 (94.3%)	64 (84.2%)	.137
1	2 (5.7%)	12 (15.8%)	
Charlson comorbidity score			
<5	32 (91.4%)	60 (78.9%)	.105
6-10	3 (8.6%)	16 (21.1%)	

Oncological Outcome of CRP in Prostate Cancer Patients with Bone Oligometastases

	Combined Group N (%)	Control Group N (%)	P Value
Diagnostic characteristics			
Serum PSA value (ng/mL)	90.4 ± 152.8	502.9 ± 806.0	.003
≤20	13(37.1%)	13 (17.1%)	.000
20-100	16 (45.7%)	15 (19.7%)	
100-500	5 (14.3%)	26 (34.2%)	
≥500	1 (2.9%)	22 (28.9%)	
Volume of Prostate (cc)	54.45 ± 27.68	50.55 ± 26.58	.480
PSA density (ng/mL/cc)	1.68 ± 2.92	11.10 ± 22.49	.015
Positive cores of biopsy			
<u>≤</u> 50 %	5 (14.3%)	5 (6.6%)	.016
>50 %	29 (82.9%)	53 (69.7%)	
Missed	1 (2.9%)	18 (23.7%)	
Biopsy Gleason grade group [†]			
1	8 (22.9%)	10 (13.2%)	.001
2	14 (40.0%)	9 (11.8%)	
3	5 (14.3%)	8 (10.5%)	
4	6 (17.1%)	27 (35.5%)	
5	2 (5.7%)	21 (27.6%)	
Missed	0	1 (1.3%)	
Clinical TNM stage			
Clinical T stage			
cT1	1 (2.9%)	2 (2.6%)	.000
cT2	23 (65.7%)	12 (15.8%)	
cT3	6 (17.1%)	11 (14.5%)	
cT4	2 (5.7%)	21 (27.6%)	
Missed	3 (8.6%)	30 (39.5%)	
Radiological N stage	· · ·	· · ·	
cNO	25 (71.4%)	24 (31.6%)	.015
cN1	7 (20.0%)	23 (30.3%)	
Missed	3 (8.6%)	30 (39.5%)	
Number of bone metastases (mean)	2.37 ± 1.22	2.93 ± 1.12	.019
1	9 (25.7%)	6 (7.9%)	.068
2	13 (37.1%)	24 (31.6%)	

Lan T, et al. Urology, 2019;131: 166-175



Does CRP really have an impact on prognosis in Prostate cancer patients with low-volume bone metastasis ? Results from a prospective case-control study

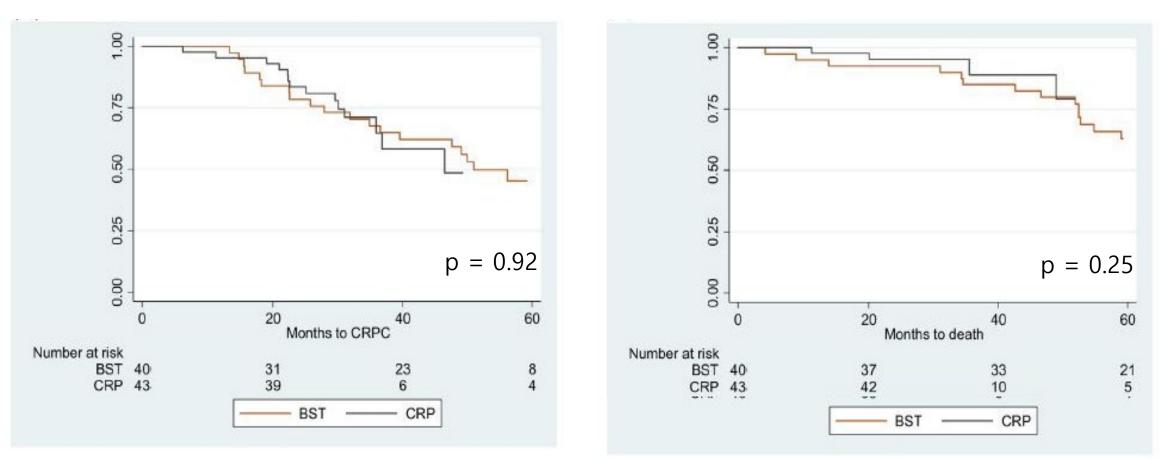
- Using prospective institutional data
 - 43 PCa patients with low-volume bone metastases (1–3 lesions) : CRP (median follow-up 32.7 mo)
 - 40 PCa patients receiving best systemic therapy (BST) (median follow-up 82.2 mo)

Characteristics for patients with oligometastatic prostate cancer

	No CRP (<i>n</i> = 40)	CRP (<i>n</i> = 43)	p value ^a
Median age at diagnosis (yr)	70	65	<0.01
Median prostate-specific antigen at diagnosis (ng/ml)	42.5	29	0.02
Number of bone metastases (%)			0.04
1	41	67.4	
2	30.8	20.9	
3	28.2	11.6	
cT stage (%)			<0.01
≤2c	22.5	46.5	
T3a/b	77.5	53.5	
Biopsy Gleason score (%)			0.22
6	2.5	0	
7	12.5	30.2	
8	32.5	30.2	
9	40	34.9	
10	12.5	4.7	

Castration resistance-free survival

Overall survival



No significant difference in castration resistant— free survival (p = 0.92) or overall survival (p = 0.25) has been detected.

Does CRP really have an impact on prognosis in Prostate cancer patients with low-volume bone metastasis ? Results from a prospective case-control study

- Compared to recent reports, the outcomes for our control group are more favorable, indicating a potential selection bias in the previous retrospective studies.
- Therefore, the unclear oncological effect has to be weighed against the potential risks of CRP.

Effect on survival of ADT alone compared to ADT combined with concurrent RT to the prostate in patients with primary bone metastatic prostatic cancer in a prospective randomized clinical trial: Data from the HORRAD Trial

- HORRAD Trial
 - Multicenter RCT recruiting 432 patients with PSA > 20 ng/ml and primary bone mPCa on bone scan.

Median overall survival

- ADT with **RT Group** : 216 pts. 45 mos.
- ADT only Group (control) : 216 pts. 43 mos.
 - No significant difference was found in overall survival.

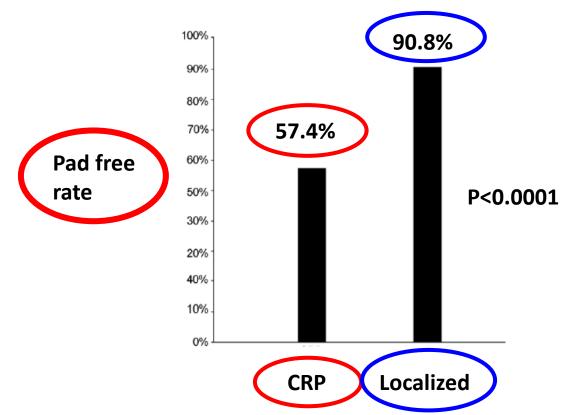
Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE) : a randomized controlled phase 3 trial

- **RCT** 2,061 pts.
 - **RT** 1,032
 - Control (SoC) 1,029
- RT improved failure-free survival, but not overall survival.

Complications and functional outcomes

Risk of complications and urinary incontinence following cytoreductive prostatectomy: a multi-institutional study

- CRP : **68** pts.
- RP for clinically localized prostate cancer : 598 pts.



Urinary incontinence (use of any pad)

Complication grades and descriptions

Cla	vien-Dindo complications	CRP	Control
		<mark>62</mark>	563
1	Obturator neuropraxia	1	
2	Deep vein thrombosis	1	
3b	Rectal injury	2	

Kim DK, et al. Asian Journal of Andrology, 2018; 20: 9-14

Bertram E. Yuh ^a, Young Suk Kwon ^b, Brian M. Shinder ^b, Eric A. Singer ^b, Thomas L. Jang ^b, Sinae Kim ^c, Mark N. Stein ^d, Tina Mayer ^d, Anna Ferrari ^d, Nara Lee ^d, Rahul R. Parikh ^e, Nora Ruel ^a, Wun-Jae Kim ^f, Shigeo Horie ^g, Seok-Soo Byun ^h, Thomas E. Ahlering ⁱ, Isaac Yi Kim ^{b, *}

- 32 men with newly diagnosed clinical mPCa to lymph nodes or bones were eligible
- The primary endpoint
 - rate of major perioperative complications (Clavien-Dindo Grade 3 or higher) occurring within 90 days of surgery

12 (37.5%)

Sample size	32
Age (yr), mean (range)	64.0 (50-73)
PSA diagnosis (ng/ml), mean (range)	75.5 (5-418)
Biopsy Gleason score, n (%)	
6	1 (3.2%)
7	10 (32.3%)
8	7 (22.6%)
9	12 (38.7%)
10	1 (3.2%)
Clinical T stage, n (%)	
cT1	6 (18.7%)
cT2	13 (40.6%)
cT3	13 (40.6%)
Clinical N and M stage, n (%)	
N1M0	7 (21.9%)
N1M1a	3 (9.4%)
N1M1b	7 (21.9%)
N0M1a	0 (0%)
N0M1b	15 (46.9%)
Neoadjuvant treatment, n (%)	
Orchiectomy	1
Leuprolide	4
Leuprolide + bicalutamide	2
Leuprolide + docetaxel	4
Leuprolide + paclitaxel	1

Total

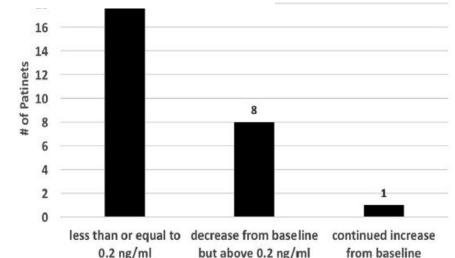
Preoperative patient characteristics

Clavien-Dindo Grade 1, symptom (n)	Urinary anastomotic leak (4)
	Severe abdominal pain (1)
Clavien-Dindo Grade 2, symptom (n)	Paralytic ileus (1)
	DVT/PE(1)
	Postop bleeding, anemia (1)
Clavien-Dindo Grade 3	0
Clavien-Dindo Grade 4, symptom (n)	ATN of kidney requiring dialysis (1)
Clavien-Dindo Grade 5, symptom (n)	Death (1)
Minor (<3), n (%)	8 (25.0%)
Major (>3), n (%)	2 (6.25%)
Total complication rates, $n(\%)$	10 (31.25%)

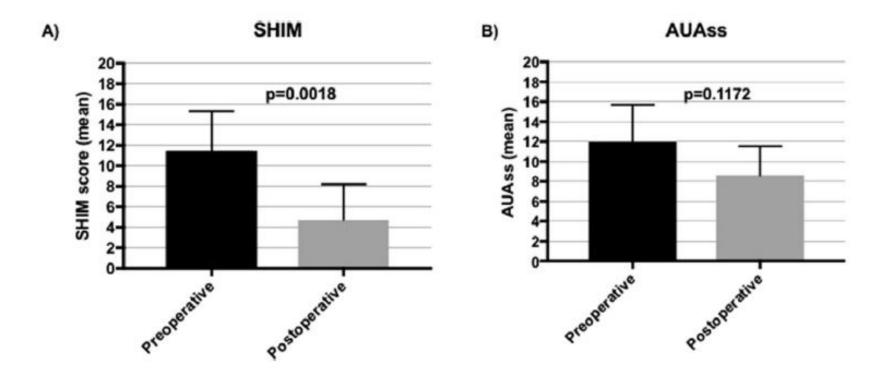
32 pts.

- The 90-day overall complication rate was 31.2% (n = 10), of which two (6.25%) were considered major complications
 - one acute tubular necrosis requiring temporary dialysis
 - one death

In men with more than 6 months of follow-up,
 67.9% had prostate specific antigen nadir 0.2 ng/mL



- while one patient experienced a rapid rise in prostate specific antigen and another a widely disseminated disease that resulted in death 5 months after surgery.
- Altogether, these results demonstrate that cytoreductive radical prostatectomy is safe and surgically feasible in selected patients who present with mPCa, yet, there may be a small subset of patients in whom surgery may cause a significant harm.



Conclusion: Therefore, cytoreductive surgery in men with mPCa should be limited to clinical trials until robust data are available.

Does robot-assisted radical prostatectomy benefit patients with prostate cancer and bone oligometastases?

Patient characteristics		Adjuvant RT : 7 pts. (18.4%) Salvage RT : 15 pts. (39.5%)	
Characteristic	ADT (<i>N</i> = 41)	RARP (<i>N</i> = 38)	Р
Median (IQR) age, years	71 (67-76)	65 (62-69)	< 0.001
Median (IQR) PSA, ng/mL	50.0 (23.8-162.8)	39.0 (15.0-84.5)	0.206
Charlson comorbidity index, n (%)			0.462
0	28 (68.3)	29 (76.3)	
≥1	13 (31.7)	9 (23.7)	
Biopsy Gleason score, n (%)			0.484
≤8	24 (58.5)	26 (68.4)	
≥9	17 (41.5)	12 (31.6)	
Clinical T stage, n (%)			0.252
≤cT2	2 (4.9)	5 (13.2)	
≥cT3	39 (95.1)	33 (86.8)	
Clinical N stage, n (%)			0.117
cN0	15 (36.6)	21 (55.3)	
cN1	26 (63.4)	17 (44.7)	
Neoadjuvant ADT, n (%)			
No	NA	16 (42.1)	
Yes	NA	22 (57.9)	

Jang WS, et al. Transl Androl Urol, 2018; 121: 225-231

Adjuvant ADT : 28 pts. (73.7%)

Does robot-assisted radical prostatectomy benefit patients with prostate cancer and bone oligometastases?

RARP 38 pts.

- Median EBL : 300 (200-500) ml
- Blood transfusion : 3 pts. (7.9%)
- Median length of catheraization : 10 (10-12) days
- Grade III postoperative complications : 2 pts. (5.3%)
- Reoperation as a result of rectal injury : 1 pt. (2.6%)
- Overall anti-incontinence surgery rate : 7.9%

Does robot-assisted radical prostatectomy benefit patients with prostate cancer and bone oligometastases?

RARP 38 pts.

- RARP in the setting of oligometastatic PCa is a safe and feasible procedure which improve oncological outcomes in terms of PFS and CSS.

- The study highlights results from expert surgeons and highly selected patients that cannot be extrapolated to all patients with oligometastatic PCa.

Comparison of Peri-operative outcomes between CRP and RP for non-metastatic PCa

- National Inpatient Sample database (2008–2013)
- Of 76 378 patients, 1.2% (n = 953) underwent Cytoreductive RP

	CRP (<i>n</i> = 953, 1.2%)	nmRP (<i>n</i> = 75 425, 98.8%)	p value ^a
Overall complication	142 (14.9)	9247 (12.3)	0.02
In-hospital mortality	1 (0.1)	23 (0.03)	0.7
Intraoperative complication	15 (1.6)	639 (0.8)	0.02
Genitourinary complication	18 (1.9)	735 (1.0)	0.01
Blood transfusion	60 (6.3)	3660 (4.9)	0.048
Miscellaneous surgical complication	32 (3.4)	1512 (2.0)	0.01
Cardiac complication	13 (1.4)	770 (1.0)	0.4
Pulmonary complication	16 (1.7)	989 (1.3)	0.4
Vascular complication	5 (0.5)	292 (0.4)	0.7
Wound complication	4 (0.4)	175 (0.2)	0.4
Bowel obstruction	39 (4.1)	2736 (3.6)	0.5
Miscellaneous medical complication	57 (6.0)	3803 (5.0)	0.2
Parenteral nutrition	0 (0)	109 (0.1)	0.5

CRP for mPCa : First lessons from Multicentric Prospective Local Treatment of Metastatic Prostate Cancer (LoMP) Trial

	Total (n = 46)	Group A (n = 17)	Group B (n = 29)	P value
Patient/tumor				
Age, y	69 ± 10	64 ± 8	72 ± 10	.005
Initial PSA, μg/L	45 (4.6-3092)	16 (4.6-75)	156 (5.2-3092)	.002
cT stage, n (%)				<.001
T1-T2	11 (24)	8 (47)	3 (10)	
ТЗа	12 (26)	2 (12)	10 (35)	
T3b	10 (22)	7 (41)	3 (10)	
T4	13 (28)	O (O)	13 (45)	
cN positive, n (%)	34 (74)	12 (71)	22 (76)	.7
cM stage, n (%)				.01
1a	13 (28)	9 (53)	4 (14)	
1b	29 (63)	8 (47)	21 (72)	
1c	4 (8.7)	O (O)	4 (14)	
Grade group, n (%)				.2
1	1 (2.2)	O (O)	1 (3.4)	
2 3	2 (4.3)	2 (12)	0 (0)	
3	3 (6.5)	2 (12)	1 (3.4)	
4	13 (28)	5 (29)	8 (28)	
5	27 (59)	8 (47)	19 (66)	
Metastatic burden				
Low volume, n (%)	25 (54)	16 (94)	9 (31)	<.001
Median no. bone lesions	8 (1-63)	2 (1-9)	13 (1-63)	<.001
Follow-up, mo	15 ± 9	13 ± 8	16 ± 10	.292

Poelaert F, et al. Urology, 2017; 106: 146-152

CRP for mPCa : First lessons from Multicentric Prospective Local Treatment of Metastatic Prostate Cancer (LoMP) Trial

Local symptoms assessed at 3 mos F/U of patients (group A : CRP + SoC, group B : only SoC)

	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 (<u>71</u>)	13 (45)	
Urinary incontinence	7 (15)	5(29) 0(0)	2 (6.9) 8 (28)	
Obstructive voiding (>medication)	8 (17)	0 (0)	8 (28)	
Obstructive voiding (>SPS/CIC)	3 (6.5)	O (O)	3 (10)	
Ureteric obstruction (>observation)	1 (2.2)	O (O)	1 (3.4)	
Ureteric obstruction (>JJ-stent)	1 (2.2)	0 (0)	1 (3.4)	

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Parameter Value Age (yr) 64.5 (58.0–70.0) Body mass index (kg/m²) a 26.9 (24.7–28.7) Prostate volume (cm³) b 40 (29.6–58.2) PSA (ng/ml) 23.5 (8.1–55.1) Gleason score 8.5 (8.0–9.0)

n (%)

Charlson comorbidity index	
0	58 (77.3)
1	17 (22.7)
Preoperative T stage	
T0/Tx	42 (39.6)
T2	25 (23.6)
T3a	17 (16.0)
T3b	13 (12.3
T4	9 (8.5)
Preoperative N stage	
N0/Nx	61 (57.5
N1	45 (42.5
Preoperative M stage	
M1a	36 (34.0)
M1b, 1 bone lesion	20 (18.9)
M1b, 2 bone lesions	7 (6.6)
M1b, \geq 3 bone lesions	9 (8.5)
M1b, number not recorded	34 (32.1)

Sooriakumaran P, et al. European Urology, 2016; 69: 788-794

Platinum Priority – Prostate Cancer Editorials on pp. 795–796 and on pp. 797–799 of this issue

A Multi-institutional Analysis of Perioperative Outcomes in 106 Men Who Underwent Radical Prostatectomy for Distant Metastatic Prostate Cancer at Presentation

Center	Patients (n)	and the second		Operative time (min)	Length of stay (d)	Complications at 90 d, n (%)
		Open, <i>n</i> (%)	Robotic (n)			
1	31	31 (100)	0	190 (164-247)	3 (3-5)	4 (12.9)
2	31	27 (87.1)	4	79.5 (67-140)	11 (9-13)	4 (12.9)
3	25	25 (100)	0	180 (156-212.5)	7 (6-8)	6 (24.0)
4	11	11 (100)	0	170 (160-380)	13 (7-19)	6 (54.5)
5	5	0(0)	5	147 (130-180)	3 (3-3)	2 (40.0)
6	3	3 (100)	0	159 (147-170)	9 (7-10)	0 (0)

	n (%)
Margin status	
Positive	57 (54.3)
Negative	48 (45.7)
Postoperative T stage	
T0/Tx	2 (1.9)
T2	21 (19.8)
T3a	14 (13.2)
T3b	57 (53.8)
T4	12 (11.3)
Postoperative N stage	
Nx	4 (3.8)
NO	26 (24.5)
N1	76 (71.7)
Postoperative continence at 90 d	
0-1 pad (for security)	38 (64.4)
1-2 pads (mild incontinence)	10 (17.0)
≥3 pads (moderate/severe incontinence)	11 (18.6)

	n (%)
Reoperation	2 (1.9)
Readmission	4 (3.8)
Blood transfusion	15 (14.2)
latrogenic injury	
Vessel	0 (0)
Obturator nerve	0 (0)
Ureteral	1 (0.9)
Bladder	0 (0)
Rectal	0 (0)
Other bowel	0 (0)
Need for ileostomy	0 (0)
lleus	1 (0.9)
Deep vein thrombosis	1 (0.9)
Pulmonary embolism	0 (0)
Pneumonia	0 (0)
Myocardial infarction	0 (0)
Symptomatic hematoma	2 (1.9)
Symptomatic lymphocele	9 (8.5)
Anastomotic leak	7 (6.6)
Anastomotic stricture	1 (0.9)
Sepsis	1 (0.9)
Wound infection	5 (4.7)
Wound dehiscence	0 (0)

Sooriakumaran P, et al. European Urology, 2016; 69: 788-794

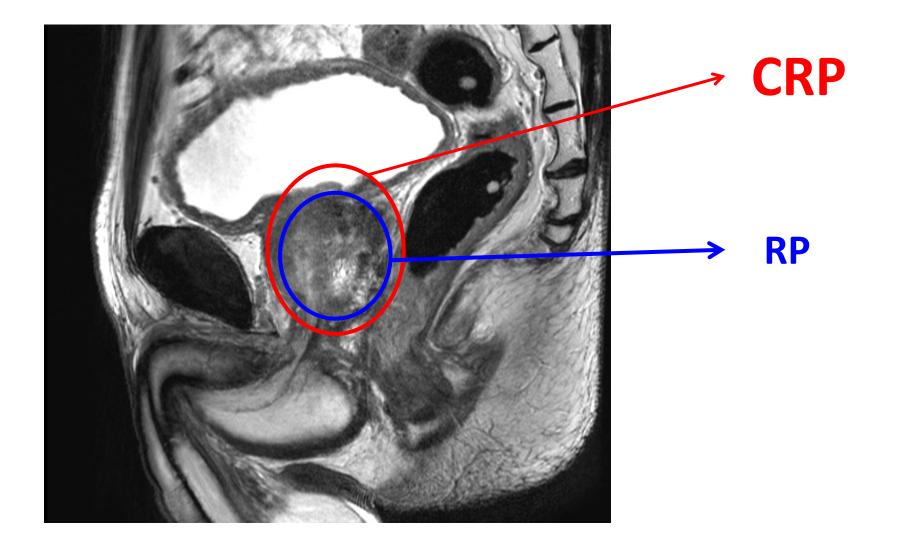
Cytoreductive Radical Prostatectomy in Men with Prostate Cancer and Skeletal Metastases

- Retrospective, multi-institutional study of 113 patients with biopsy-proven mPCA (1) completely resectable PCA
 - (2) osseous metastases
 - (3) absence of gross retroperitoneal lymph node metastases
 - (4) absence of bulky pelvic lymph node metastases >3 cm
 - (5) no or minimal visceral metastases
 - (6) ECOG performance status of 0–1
 - (7) written informed consent
- CRP with extended pelvic lymphadenectomy
- Eighty patients (70.8%) received neoadjuvant ADT and 91 (86.5%) adjuvant ADT and/or radiation therapy.

Cytoreductive Radical Prostatectomy in Men with Prostate Cancer and Skeletal Metastases

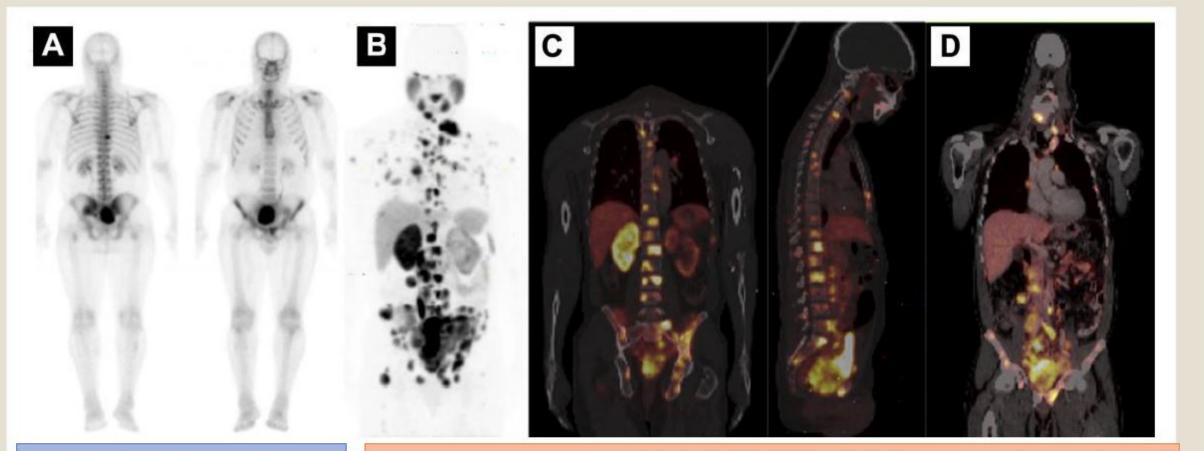
	Patients (n)	Patients Complications, n (Complications, n (%)		p value
		Overall	Low-grade ^a	High-grade ^b	
Low-volume metastases	85	26 (30.6)	20 (23.5)	6 (7.1)	<0.036
High-volume metastases	28	14 (50.0)	5 (17.8)	9 (32.1)	
PSA <4 ng/ml	66	17 (25.7)	13 (19.7)	4 (6.1)	< 0.045
PSA >4 ng/ml	47	23 (48.9)	12 (25.5)	11 (47.8)	
Neoadjuvant ADT	80	21 (26.3)	14 (17.5)	7 (8.75)	< 0.032
No neoadjuvant ADT	33	19 (57.6)	11 (33.3)	8 (24.2)	

Cytoreductive Radical Prostatectomy (CRP)



Patient selection

Figure 1 Patient With Single Osteoblastic Skeletal Lesion in Thoracic Vertebrae. (A) Bone Scan of 58-Year-Old Man With Gleason 4 + 5 Disease Demonstrated Single Osteoblastic Skeletal Lesion in Thoracic Vertebrae. ⁶⁸Ga-PSMA-11 PET/CT Maximum Intensity Projection (B) and Fused Coronal and Sagittal Images (C, D) Demonstrated Widespread Skeletal and Nodal Lesions, Which Were Not Visualized on Bone Scan, Which is Why ⁶⁸Ga-PSMA PET/CT Should Replace Bone Scan



^{99m}Tc-MDP Bone Scan

68Ga-PSMA PET/CT

Lengana T, et al. Clinical Genitourinary Cancer, 2018;16:392-401

Inherent selection bias from a retrospective cohort study

CRP Group

Relatively good general health General anesthesia (healthy) Pts. with a predicted OM risk < 70%

Relatively low tumor risk Relatively lower PSA, GS, TNM stage No visceral metastasis

Control Group

Relatively poor general health Pts. with a predicted OM risk \ge 70%

Relatively high tumor risk Relatively higher PSA, GS, TNM stage

Prospective RCT

Prospective RCT

Survival benefits

VS

Complications

Perioperative

Prolonged operative time Increased blood loss & Transfusion DVT Rectal injury Lymphocele Death

Functional

Urinary incontinence

ED

Conclusions

- Despite evidence to suggest CRP might be beneficial, an absence of prospective data has limited its implement into routine clinical practice.
- CRP is never justified when the potential perioperative risks outweigh the benefit of enhancing oncologic control and symptomatic relief.
- A randomized prospective clinical trial will be necessary to determine whether there is a therapeutic benefit of CRP that justifies the 40~50% urinary incontinence risk.
- CRP might be an individualized treatment option in the multimodality management of mPCa.

Thank you for your attention

삼성서울병원

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