

Local Radiotherapy in metastasic prostate cancer

F. Guedea

Prostate Team: F. Ferrer, A. Boladeras, N. Garcia, A. Slocker.

Department of Radiation Oncology Catalan Institute of Oncology (ICO) University of Barcelona (UB)





The context:

"New concept" in Radiation Oncology: Local consolidative therapy of the primary prostate tumour for patients with oligometastasic disease

Local consolidative therapy of the primary prostate tumour with RT

Local consolidative therapy of the primary prostate tumour with Surgery

"New concept" in Radiation Oncology: Metastasis direct therapy with SBRT

From Conventional Imaging (Bone Scan/CT Scan) to Choline PET-CT to PSMA PET-CT:



How many new cancer patients in Europe will require radiotherapy by 2025? An ESTRO-HERO analysis

Based on the projected cancer distributions in 2025, a 16% expected increase in the number of RT treatment courses was estimated.

Borras JM, Lieuvens Y, et al (Spain & other countries)

How many new cancer patients in Europe will require radiotherapy by 2025? An

ESTRO-HERO analysis

Radiother Oncol. 2016;119(1):5-11



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Source	Study design	Inclusion	Intervention	OS*	CSS*	MVA	Additional information
Culp et al.44	Population-based, n=8,185, median follow-up period: 16 months	M1a–M1c	• RP (n = 245) • BT (n = 129) • NLT (n = 7811)	• 67.4% • 52.6% • 22.5% P<0.001	• 75.8% • 61.3% • 48.7% P<0.001	SHR (CSM) • 0.38 (0.27–0.53; RP) • 0.68 (0.49–0.93; BT) • 1.00 (ref; NLT)	MVA includes: Gleason score ≥8, T4, PSA ≥20 ng/ml, AJCC N1 (versus N0), AJCC M stage (versus M1a), year of diagnosis
Antwi et al. ⁴⁵	Population-based, n=7,858, median follow-up period: NR	M1a-M1c	• RP (n = 222) • BT (n = 120) • NSR (n = 7516)	• 82.0% • 66.7% • 43.6% P<0.0001	• 84.7% • 71.7% • 54.6% P<0.0001	aHR (CSM) • 0.22 (0.27–0.28; RP) • 0.40 (0.32–0.51; BT) • 1.00 (ref; NSR)	MVA includes: age, race, marital status, tumour grade, PSA level, and cancer registry
Gratzke et al. ⁴⁶	Population-based, n=1,538, median follow-up period:	M ⁺	• RP (n=74) • RT (n=389) • ADT (n=635) • Other (n=440)	• 55% (RP) • 21% (other therapy) P<0.01	• NR	NR	Overall survival compared between RP patients and non-RP patients (including RT, ADT, and other)
Satkunasivam et al. ⁴⁷	Population-based, n=4,069, median follow-up period: NR	• M⁺ • Age ≥65 years	• RP (n=47) • IMRT (n=88) • CRT (n=107) • NLT (n=3827)	• 73% • 72% • 37% • 34%	• 79% • 82% • 49% • 46%	aHR (CSM) • 0.48 (0.27–0.85; RP) • 0.38 (0.24–0.61; IMRT) • 0.85 (0.64–1.14; CRT) • 1.00 (ref; NLT)	MVA includes: sociodemographics, primary tumour characteristics, CCI, ADT, and bone radiation within 6 months of diagnosis. On CRR: SHR (95% CI) for PCSM versus NLT: RP 0.58 (0.35–0.95), IMRT 0.43 (0.27–0.68)
Heidenreich et al. ⁴⁸	Case-control, n=61, median follow-up period: • 40.6 months (RP) • 44.0 months (no RP)	Limited M1	• RP (n=23) • No RP (n=38)	• 91.3% • 78.9% P=0.048	• 95.6% • 84.2% P=0.043	• NR	Inclusion criteria: ≤3 lesions on bone scan; absence of visceral or extended LN metastases; PSA nadir <1 ng/ ml after 6 months of neoadjuvant ADT
Cho et al. ⁴⁹	Case-control, n=140 (38 cases), median follow-up period: 34 months	M1	• RT (n=38) • No RT (n=102)	• 69% • 43%	• NR	HR (OM) • 0.43 (P=0.015)	MVA includes: ECOG status, site of metastasis

Retrospective data for local consolidative therapy of the primary prostate tumour

Tosoian, J. J. et al. (2016)
Oligometastatic prostate
cancer: definitions, clinical
outcomes, and treatment
considerations
Nat. Rev. Urol.



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EUROPEAN UROLOGY XXX (2018) XXX-XXX

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

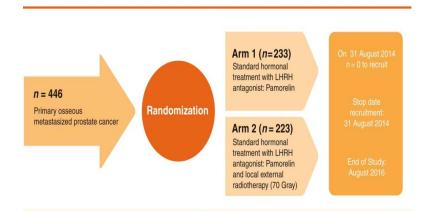


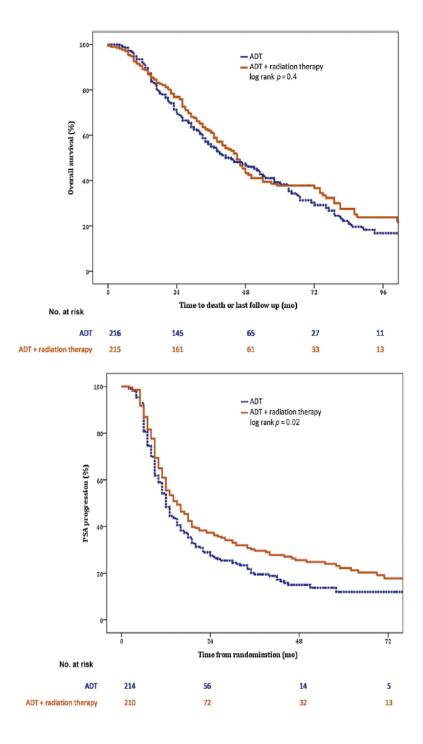


Platinum Priority – Prostate Cancer Editorial by XXX on pp. x-y of this issue

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





The HORRAD Trial

Results and limitations:

- Median PSA level was 142 ng/ml and 67% of pts had more than 5 bone metastases: <u>Patients enrolled were</u> <u>predominately high volume M1.</u>
- No significant difference was found in overall survival.
- Subset analysis within the HORRAD trial, investigators showed an interaction between volume of disease (eg, number of metastatic sites) and benefit of RT, with lowvolume patients trending toward a significant improvement in OS (HR:0,68)

Boevé LMS, et al (The Netherlands)

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 Eur Urol. 2019 Mar;75(3):410-418

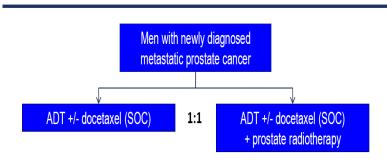
Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial



Local radiotherapy improves survival in metastatic prostate cancer with low disease burden [ESMO 2018 Press Release]

Christopher C Parker, Nicholas D James, Christopher D Brawley, Noel W Clarke, Alex P Hoyle, Adnan Ali, Alastair W S Ritchie, Gerhardt Attan

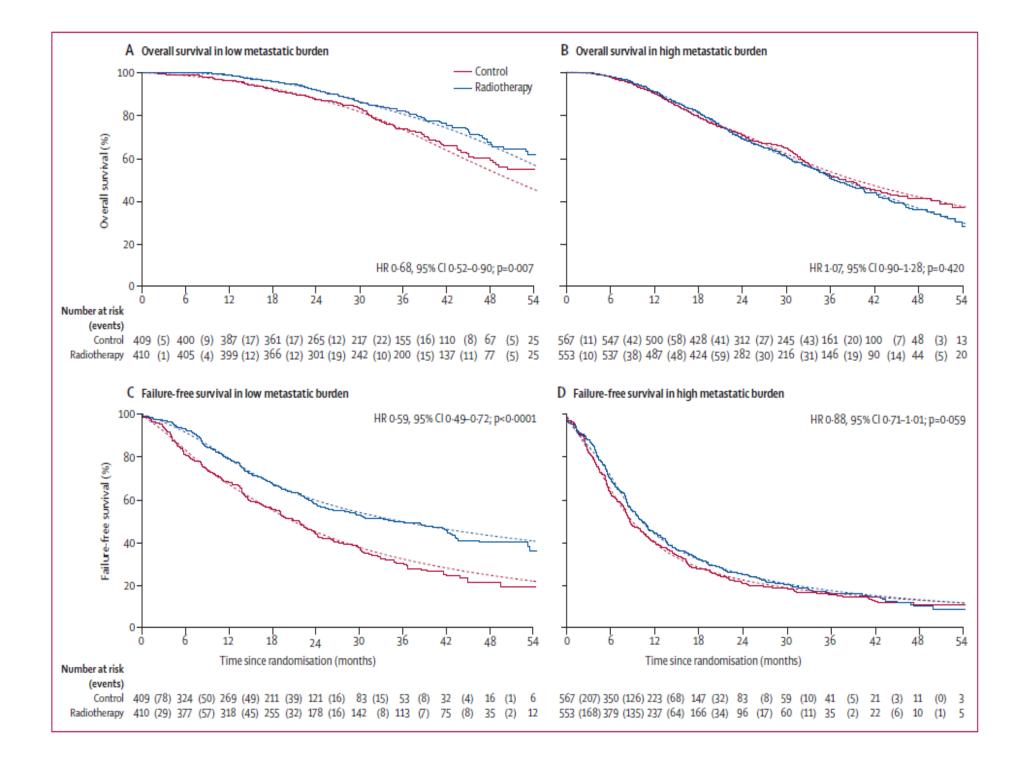
Study design



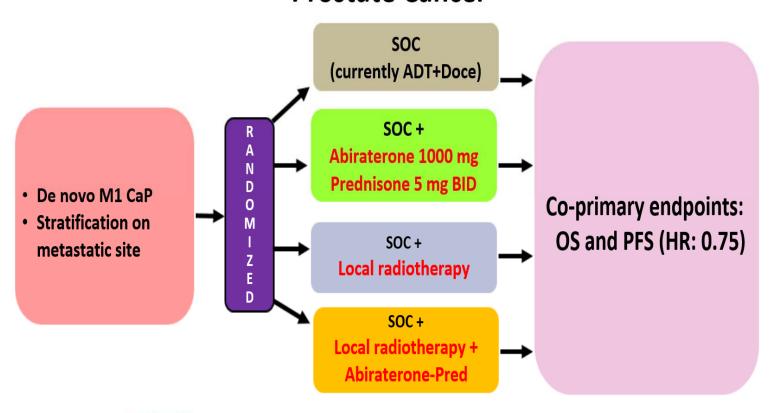
36Gy/6 fractions/6 weeks **or** 55Gy/20 fractions/4 weeks Schedule nominated before randomisation

Parker c. et al. Lancet Oncol 392: 2353-2366, 2018

Characteristic		SOC (n=1029)	SOC+RT (n=1032)
Age (years)	Median (IQR)	68 (63-73)	68 (63-73)
	Range	37-86	45-87
PSA (ng/ml)	Median (IQR)	98 (30-316)	97 (33-313)
	Range	1-20590	1-11156
Metastatic burden	Low	409 (42%)	410 (43%)
	High	567 (58%)	553 (57%)
	Not classified	53	69
Site of metastases	Bone	919 (89%)	917 (89%)
	Liver	23 (2%)	19 (2%)
	Lung	42 (4%)	48 (5%)
	Distant lymph nodes	294 (29%)	304 (29%)
	Other	35 (3%)	33 (3%)
Docetaxel use	No	845 (82%)	849 (82%)
	Yes	184 (18%)	183 (18%)



PEACE-1: European Phase III Trial in *de novo* Metastatic Prostate Cancer





SOC=Standard of Care

ClinicalTrials.gov. Identifier: NCT01957436

Study sponsor: Unicancer

Summary for prospective randomized trials with AD +/- Local Therapy with Prostate Radiotherapy in M1 Disease

Survival benefit when added to ADT	High Volume	Low Volume
Prostate Radiotherapy	X	



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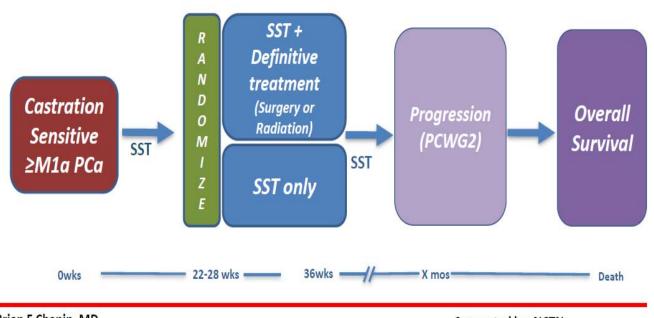
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	Population-based, n=4,069, median follow-up period: NR	• Age ≥65 years	• NLT pr			1st	32 130 Prostate cancer is not primary tumor 1st primary tumor 3829 26 301 Althout distant metastasis (M0) metastasis (M0) 1538
et al. ⁴⁸	Case-control, n=61, median follow-up period: • 40.6 months (RP) • 44.0 months (no RP)	Limited M1	• RP (n=23) • No RP (n=38)	• 91.3% • 78.9% P=0.048	• 95.0 • 84.7 P=0.	90 - 80 - 70 - 60 - 50 - 40 - 30 -	A de la constitución de la const
	Case-control, n=140 (38 cases), median follow-up period: 34 months	M1	• RT (n=38) • No RT (n=102)	• 69% • 43%	• NR	Fig. 1 – Survival of patients in th	0 1 2 3 4 5 e Munich Cancer Registry who did and de cancer patients. apy; RP = radical prostatectomy; RPE = ex

Source	Study design	Inclusion	Intervention	OS* CS	S* MVA		Additional information			
Culp et al.44	Population-based, n=8,185, median follow-up period: 16 months	M1a-M1c	• RP (n=245) • BT (n=129) • NLT (n=300	Cytoreduc		cal Pro	MVAincludes: Distatectomy in Volume Skelet			
Antwi et al.45	Population-based, n=7,858, median follow-up period: NR	M1a-M1c		Avel Heidenreich * David Pfister and Daniel Porres						AL Official Journal of the American Urological Association
Gratzke et al. ⁴⁶ Satkunasivam et al. ⁴⁷	n=1,538, median follow-up period: NR kunasivam Population-based, • M*			Group 23 pt bone M1 (Neoadjuvant AD	21	ik RWTH Aad	Group 2 38 pt bone M1 (≤ 3) AD Median f-up: 37 m (2	B-96),	Vol 193;832-838, March 2015 Criteria for CRP: resectable, ≤ 3 M1, no gross retroperitoneal lymph nodes, no bulky LNM (>3cm), no vissceral M1, informed consent.	
				PSA < 1 ng/ml RP+extended LP 2 years AD 4 +margins; R' Table 2. Oncolog	eg/mi ded LPHN Median f-up: 34,5 m (7-75) • Small nu • Cytoredu related c • Might im • Efffective urinary ti			umber of patients and heterogeneous uctive RP is feasible and does not increase surgery complications prove OS and CSS in selected patients ely prevents complications of the lower and upper ract.		
Heidenreich	C					/	Group 1	Goup 2 (all)	Group 2 (adapted)*	p Value
et al.48	• 44.0 months (no RP)		\	No. pts Median mos followup Median mos to castra Median mos CSS (ran Median mos clinical f Surgery-free survival o Overall survival rate (ation resistant PCA age) PFS (range) rate (%)	(range)	23 40.6 (3-71) 40 (9-65) 47 (9-71) 38.6 (42-52) 100 91.3	38 44.0 (24—96) 29 (16—54) 40.5 (19—75) 26.5 (12—48) 71.1 78.9	26 42.3 (27–89) 35.4 (22–47) 44.3 (21–75) 32.4 (19–48)	Not significant 0.014 Not significant 0.032 <0.01 0.048
Cho et al. ⁴⁹	Case-control, n=140 (38 cases), median follow-up period: 34 months	M1	· No	*Only patients with F	SA less than 1.0 no	g/ml after 6 i	95.6 months of ADT.	84.2		0.043

Randomized, Phase III Trial of Standard Systemic Therapy (SST) or SST Plus Definitive Treatment of the Primary Tumor in Metastatic Prostate Cancer (S1802)



PI: Brian F Chapin, MD Supported by: NCTN

SWOG 1802 (NCT03678025)

Urologe 2015 · 54:1613–1616 DOI 10.1007/s00120-015-4020-z Online publiziert: 11. November 2015 © Springer-Verlag Berlin Heidelberg 2015

H. Rexer

AUO Geschäftsstelle, MeckEvidence – Dienstleistungen für medizinische Dokumentation und Forschung, Schwarz



Interventionelle Studie beim metastasierten, hormonnaiven Prostatakarzinom

Multizentrische prospektive randomisierte Studie zur Evaluierung des Effekts der medikamentösen Standardtherapie mit oder ohne radikale Prostatektomie bei Patienten mit einem begrenzt ossär metastasierten Prostatakarzinom (G-RAMPP-Studie AP 75/13 der AUO)

Metastatic, hormone-naive prostate cancer interventional study:
Multicenter, prospective, randomized study to evaluate the effect of
standard drug therapy with or without radical prostatectomy in
patients with limited bone metastasized prostate cancer
(TRoMbone (ISRCTN15704862). G-RAMPP - the AUO AP 75/13 study)

Summary for prospective randomized trials with AD +/- Local Therapy with Surgery in M1 Disease

Survival benefit when added to ADT	High Volume	Low Volume
Surgery	?	?

STAMPEDE: Is Radiation Therapy to the Primary a New Standard of Care in Men with Metastatic Prostate Cancer?

... Preclinical data suggest that radiation therapy (RT) to the primary can prevent further metastases possibly because of an immunologic effect from RT....

... RT and surgery are also biologically different treatments. It is unknown if the proven synergy of RT with ADT will exist with RP. In fact, in localized prostate cancer that synergy has not been demonstrated when adding ADT to RP....

Choudhury A, et al (UK)

STAMPEDE: Is Radiation Therapy to the Primary a New Standard of Care in Men with Metastatic Prostate Cancer?

Int J Radiat Oncol Biol Phys. 2019 May 1;104(1):33-35



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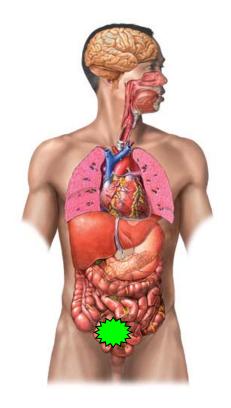
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From Conventional Imaging (Bone Scan/CT Scan) to Choline PET-CT to PSMA PET-CT:



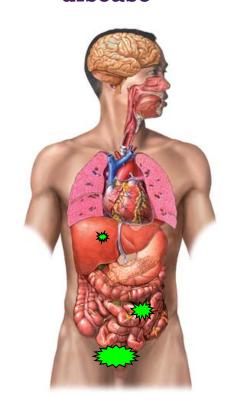
"New Concepts" in Radiation Oncology

Clinically localized disease



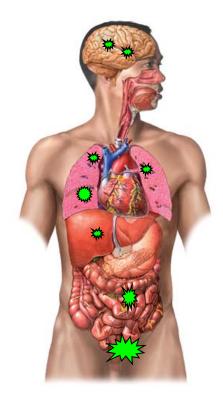
Cure with local treatment

Oligometastatic disease



Cure with local treatment possible

Wide-spread metastatic disease



Local therapy is not curative, Local treatment for symptom control

Hellman S., and Weichselbaum R. (USA, Chicago). Editorial: Oligometastases. JCO 13, 8-10. 1995.

"New Concepts" in Radiation Oncology: SABR-COMET Trial: Stereotactic Ablative Radiation Therapy for Oligometastatic Tumors

In a series of 99 patients with ECOG 0-1 (16 with prostate cancer, 18 with breast cancer, the rest lung and Colorectal cancer) and with 1-3 metastases (93% of cases).

At 5y, 46% of patients in the SBRT arm were alive compared with 24% in the control arm.

SBRT Doubles 5-Year Survival in Oligometastatic Cancer

"New concepts" in Radiation Oncology: Phase II Trials SBRT at ICO using SBRT (On going Trials)

- > 5 fractions of 6,5 Gy in lymph nodes oligometastasis.
- > 1 fraction of 16 Gy (Spine) or 3 fractions of 7,5 Gy (flat bones) in bone oligometastasis.





Radioterapia estereotáctica fraccionada más antiandrógeno de segunda generación para pacientes oligometastáticos con cáncer de próstata resistente a la castración. Estudio español fase II, prospectivo, metacéntrico. (OLIGORESIST)

1. Objetivo

Analizar los resultados obtenidos en supervivencia libre de progresión radiológica (SLPR), seguridad y calidad de vida tras la combinación de radioterapia corporal <u>estereoatáctica /radioterapia ablativa estereoatáctica (SBRT/SART por sus siglas en inglés) más antiandrógeno de</u> segunda generación en pacientes CPRCM1 en situación de oligometástasis (≤5).

2. Hipótesis

El tratamiento combinado sistémico (antiandrógeno de segunda generación) más local ablativo (SBRT) consigue mejorar resultados en SLPR comparado con el tratamiento sistémico aislado.



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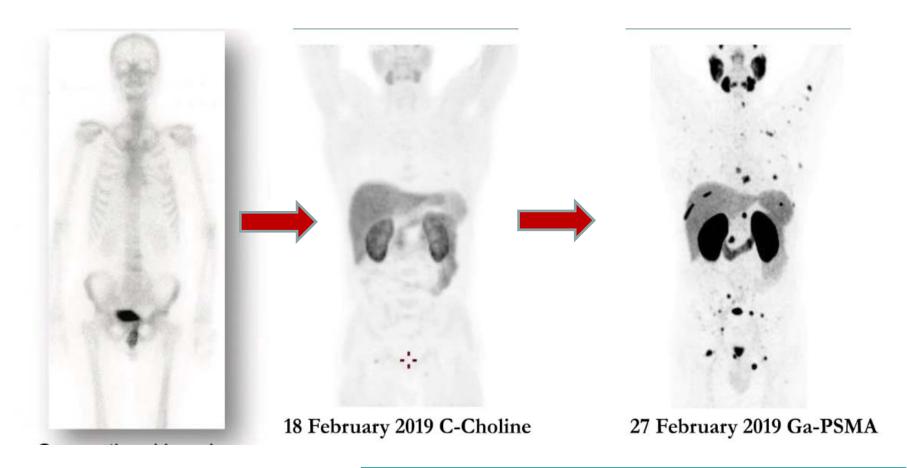
From Conventional Imaging (Bone Scan/CT Scan) to Choline PET-CT to PSMA PET-CT:



Conventional Imaging (Bone Scan/CT Scan) PSA>10 ng/ml

Choline PET-CT PSA>1 ng/ml

PSMA PET-CT PSA <0,5 ng/ml



Images from S. Fanti at Advanced Prostate Cancer Consensus Conference (APCCC 2021), Lugano, Switzerland.

Can PSMA PET-CT replace conventional imaging modalities?

Table 1 – Sensitivity and specificity of different imaging modalities for detection of lymph node metastasis.

Imaging modality	Study	Patients (n)	Sensitivity (%)	Specificity (%)
СТ	Hövels et al [2]	1024 (18 studies)	42	82
MRI	Hövels et al [2]	628 (10 studies)	39	82
WB-MRI	Johnston et al [6]	56	100	96
Choline PET/CT	von Eyben et al [7]	609 (11 studies)	62	92
	Johnston et al [6]	33	100	82
⁶⁸ Ga-PSMA PET/CT	Perera et al [9]	244 (5 studies)	77 (per patient)	97 (per patient)
			75 (per lesion)	99 (per lesion)
	Kim et al [11]	298 (6 studies)	71 (per patient)	95 (per patient)

CT = computed tomography; MRI = magnetic resonance imaging; WB-MRI = whole-body MRI; PET = positron emission tomography; PSMA = prostate-specific

Table 2 - Sensitivity and specificity of different imaging modalities for detection of bone metastasis.

Imaging modality	Study	Patients (n)	Sensitivity (%)	Specificity (%)
Nuclear bone scan	Shen et al [3]	901 (13 studies)	79 (per patient)	82 (per patient)
	Shen et al [3]	1077 (6 studies)	59 (per lesion)	75 (per lesion)
	Johnston et al [6]	56	60	100
	Lengana et al [14]	113	73.1	84.1
WB-MRI	Johnston et al [6]	56	90	88
NaF PET	Sheikhbahaei et al [5]	507 (12 studies)	98 (per patient)	90 (per patient)
	Sheikhbahaei et al [5]	1812 (7 studies)	97 (per lesion)	84 (per lesion)
Choline PET/CT	Johnston et al [6]	33	80	92
⁶⁸ Ga-PSMA PET/CT	Lengana et al [14]	113	96.2	99.1

WB-MRI = whole-body magnetic resonance imaging; PET/CT = positron emission tomography/computed tomography; PSMA = prostate-specific membrane antigen.

Can PSMA PET-CT replace conventional imaging for primary lymph node &bone staging of prostate cancer.

Esen T., et al. Eur Urol Focus 2019.



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Is RT to the primary a new standard of care for M1 prostate cancer patients?

- 1. Yes, for low-volume patients who have no contraindications to RT. In these patients, RT to the primary provides no increase in grade 3 toxicity, and an impressive OS benefit within the first 3 years after treatment.
- 2. For men with high-volume disease, RT to the primary does not appear to improve OS.
- 3. PSMA PET-CT offers news possibilities for Metastasis direct therapy with SBRT