Caratteristiche cliniche del paziente nmcrpc

- Definizione del paziente
- Benefici in outcome dai diversi trattamenti disponibili

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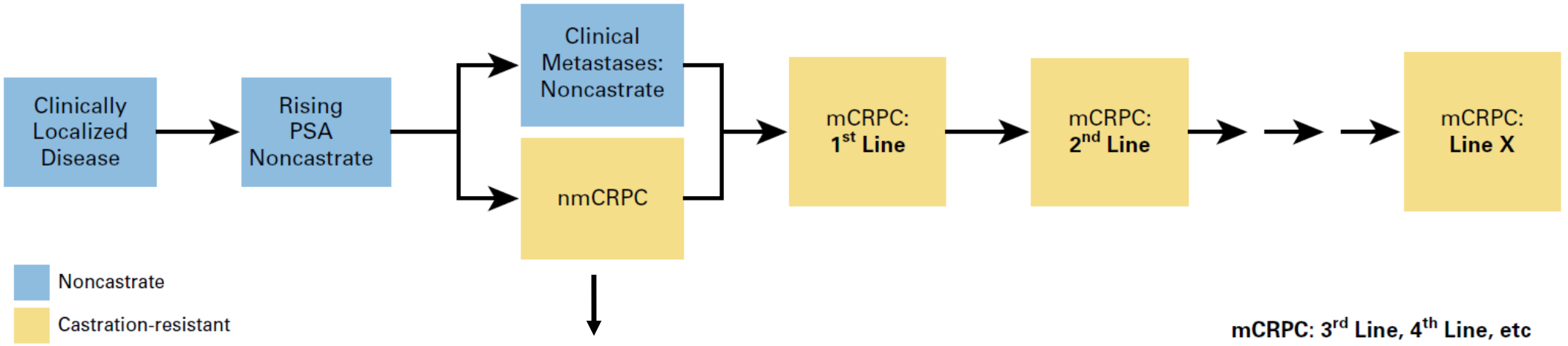
Prostate cancer progression is a continuous process despite discrete clinical states defined to subclassify the disease with pragmatic delineated biological and clinical miletones marking these transitions.



serum testosterone < 50 ng/dl, rising PSA, no evidence of metastasis on conventional imaging

Heterogeneous population
dynamic disease that changes in function of
tumor biology, patient factors, previous therapies to which the tumor has been exposed

PSA to define CRPC

European Association of Urology

EANM

ESTRO

SIOG

6.5.1 Definition of CRPC

Castrate serum testosterone < 50 ng/dL or 1.7 nmol/L plus either:

a. Biochemical progression: Three consecutive rises in PSA at least one week apart resulting in two 50% increases over the nadir, and a PSA > 2 ng/mL

Clinical subtypes of CRPC that are based on pattern of spread. The five clinical subtypes defined in PCWG2 on the basis of the pattern of spread in individual patients are retained with modifications: (1) locally recurrent CRPC after radical prostatectomy or persistent disease in the prostate or prostate bed after radiation therapy on ADT, with no evidence of metastases on imaging; (2) nonmetastatic (nmCRPC): a rising PSA with no detectable disease in the primary site, in lymph nodes beyond the true pelvis by CT/MRI (lymph nodes ≤ 1.5 cm in the short axis in the pelvis are eligible), in bone by radionuclide bone scan or CT, or in visceral organs; (3) nodal spread within the pelvis (lymph nodes > 1.0 cm) and/or beyond the pelvis (specify) and no evidence of bone or visceral disease[43]; (4) bone disease with or without nodal disease and no evidence of visceral spread; (5) visceral disease with or without spread to other sites; includes spread to lung, liver, or adrenal and CNS sites, each reported separately. It is recommended that research

VOLUME 34 · NUMBER 12 · APRIL 20, 2016

JOURNAL OF CLINICAL ONCOLOGY SPECIAL ARTICLE

Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3

THE JOURNAL of UROLOGY®

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Advanced Prostate Cancer: AUA/ASTRO/SUO Guideline PART II

William T. Lowrance,* Rodney H. Breau, Roger Chou, Brian F. Chapin, Tony Crispino,

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Vol. 205, 22-29, January 2021
Printed in U.S.A.

Non-metastatic Castration-Resistant Prostate Cancer (nmCRPC)

Men with a rising prostate specific antigen (PSA) but no visible metastatic disease on conventional imaging despite medical or surgical castration represent a uniquely distinct disease state.

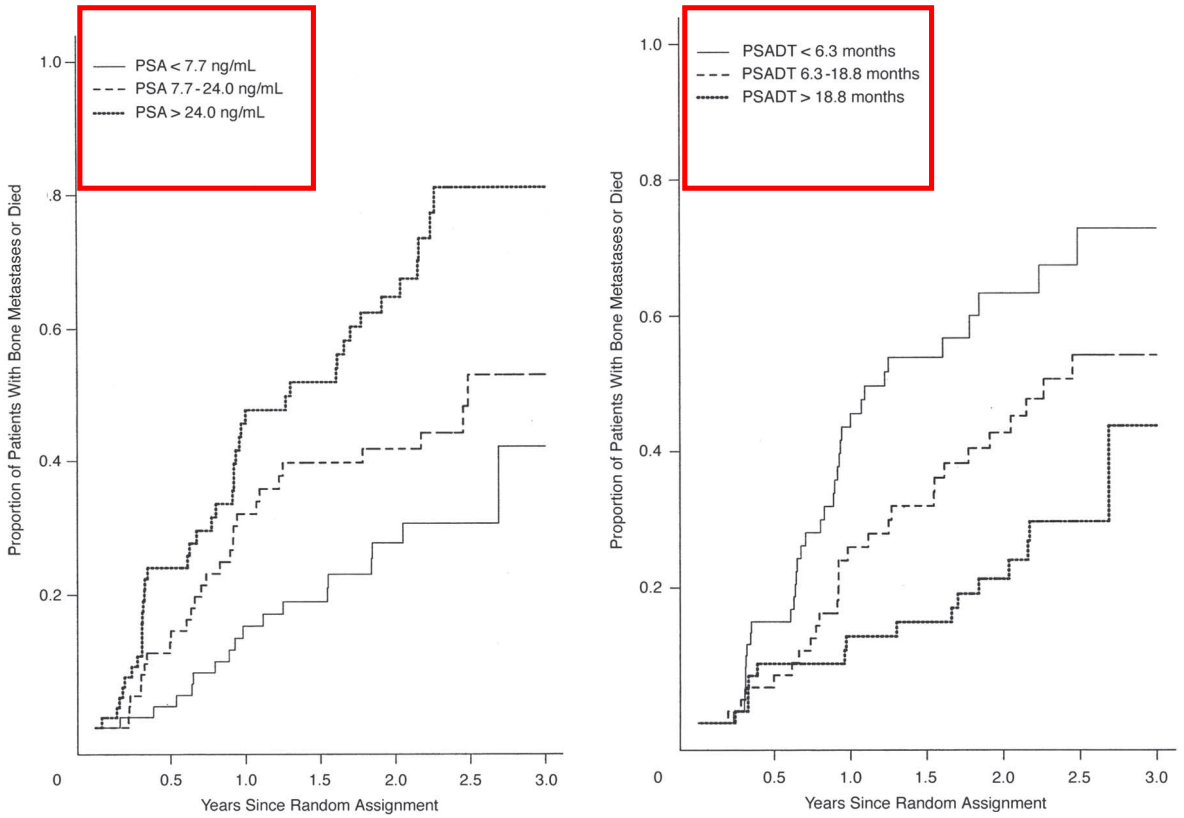
PSA to define CRPC

VOLUME 23 · NUMBER 13 · MAY 1 2005

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Natural History of Rising Serum Prostate-Specific Antigen in Men With Castrate Nonmetastatic Prostate Cancer

Matthew R. Smith, Fairooz Kabbinavar, Fred Saad, Arif Hussain, Marc C. Gittelman, David L. Bilhartz, Chris Wynne, Robin Murray, Norman R. Zinner, Claude Schulman, Ronald Linnartz, Ming Zheng, Carsten Goessl, Yong-Jiang Hei, Eric J. Small, Richard Cook, and Celestia S. Higano



Negative prognostic factors:
Baseline PSA > 10 ng/ml
PSADT < 10 mo

At 2 y 33% had developed bone mets, 21% had died

PSA to define CRPC

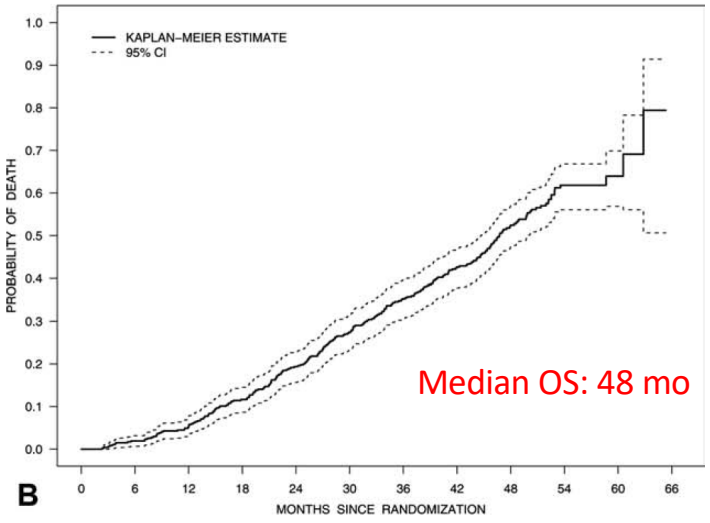
Disease and Host Characteristics as Predictors of Time to First Bone Metastasis and Death in Men With Progressive Castration-Resistant Nonmetastatic Prostate Cancer

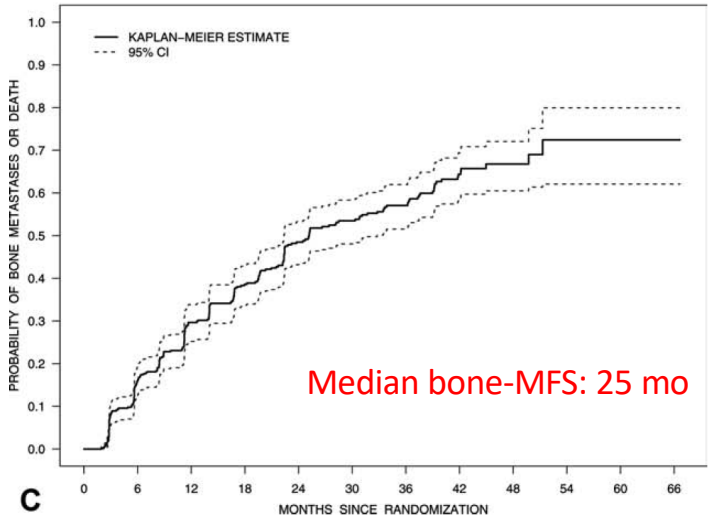
Matthew R. Smith, MD, PhD[1]; Richard Cook, PhD[2]; Ker-Ai Lee, PhD[2]; and Joel B. Nelson, MD[3]

Cancer May 15, 2011

Negative prognostic factors:
Baseline PSA > 13 ng/ml
PSADT < 8 mo

At 2 y 46% had developed bone metastasis, 20% had died





Conventional imaging to define nmCRPC

Table 1 Current guideline and consensus recommendations regarding imaging for patients with castration-resistant prostate cancer

Guideline	Recommended imaging modality
EAU/ESTRO/ESUR/SIOG 2018	Bone scan and CT of chest abdomen and pelvis
NCCN 2018	Chest CT, bone imaging, and abdominal CT or MRI with or without contrast. Consider C-11 choline PET/CT or PET/MRI or F-18 fluciclovine PET/CT or PET/MRI for further soft tissue evaluation or F-18 sodium fluoride PET/CT for further bone evaluation
APCCCP 2017	Regarding imaging modality for staging and monitoring in men with mCRPC, 74% of the panel voted for CT and bone scintigraphy and 24% of the panellists voted for one of the next-generation imaging methods
	For monitoring of patients with a diagnosis of aggressive variant mCRPC, 62% of the panellists voted for standard imaging by CT and bone scintigraphy, 2% voted for CT alone, and 36% voted for next-generation imaging modalities

World Journal of Urology (2019) 37:457–467

Conventional imaging to define nmCRPC

EAU – EANM – ESTRO – ESUR – ISUP – SIOG Guidelines on Prostate Cancer

6.5.4 ***Non-metastatic CRPC***

Frequent PSA testing in men treated with ADT has resulted in earlier detection of biochemical progression. Of these men approximately one-third will develop bone metastases within two years, detected by conventional imaging [207].

In men with CRPC and no detectable clinical metastases using bone scan and CT-scan, baseline PSA level, PSA velocity and PSA-DT have been associated with time to first bone metastasis, bone metastasis-free survival and OS [207, 1200]. These factors may be used when deciding which patients should be evaluated for metastatic disease. A consensus statement by the PCa Radiographic Assessments for Detection of Advanced Recurrence (RADAR) group suggested a bone scan and a CT scan when the PSA reached 2 ng/mL and if this was negative, it should be repeated when the PSA reached 5 ng/mL, and again after every doubling of the PSA based on PSA testing every three months in asymptomatic men [1201]. Symptomatic patients should undergo relevant investigations regardless of PSA level. With more sensitive imaging techniques like PSMA PET/CT or whole-body MRI, more patients are diagnosed with early mCRPC [1202]. It remains unclear if the use of PSMA PET/CT in this setting improves outcome.

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European Association of Urology

Urothelial Cancer

Management of Patients with Advanced Prostate Cancer: Report of the Advanced Prostate Cancer Consensus Conference 2019

Silke Gillessen[a,b,c,d,e,*], *Gerhardt Attard*[f], *Tomasz M. Beer*[g], *Himisha Beltran*[h,i], *Anders Bjartell*[j],

Q63: Regarding imaging, for the majority of patients with CRPC and rising PSA with no metastatic disease documented on past imaging, 58% of panellists voted for PSMA PET/CT, 39% voted for CT and/or bone

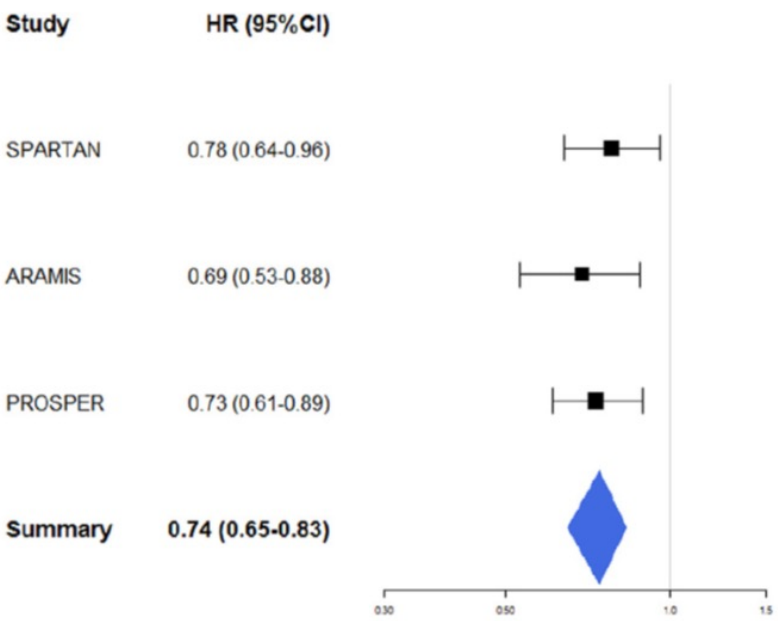
Caratteristiche cliniche del paziente nmcrpc

- Definizione del paziente
- Benefici in outcome dai diversi trattamenti disponibili

Outcome

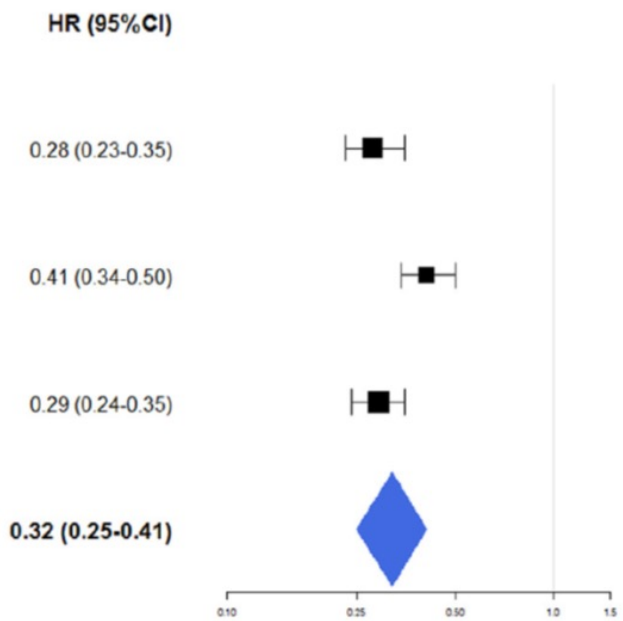
	SPARTAN	ARAMIS	PROSPER
N° patients	1207 (806 Apalutamide; 401 Placebo)	1509 (955 Darolutamide; 554 Placebo)	1401 (933 Enzalutamide; 468 Placebo)
Primary endpoint	MFS	MFS	MFS
Secondary endpoint	OS, TTM, PFS, TTCHT	OS, TTPP, TTCHT, TTFSE	OS, TTPP, PRR, TTCHT, CHTFS, TTPP
Type of Analysis	Intention to treat	Intention to treat	Intention to treat
Median Follow-Up (months)	52	29	48
Median treatment duration (months)			
Median MFS (months)			
Drug	40.5	40.4	36.6
Placebo	16.2	18.4	14.7
Median OS (months)			
Drug	73.9	NR	67
Placebo	59.9	NR	56.3

Outcome



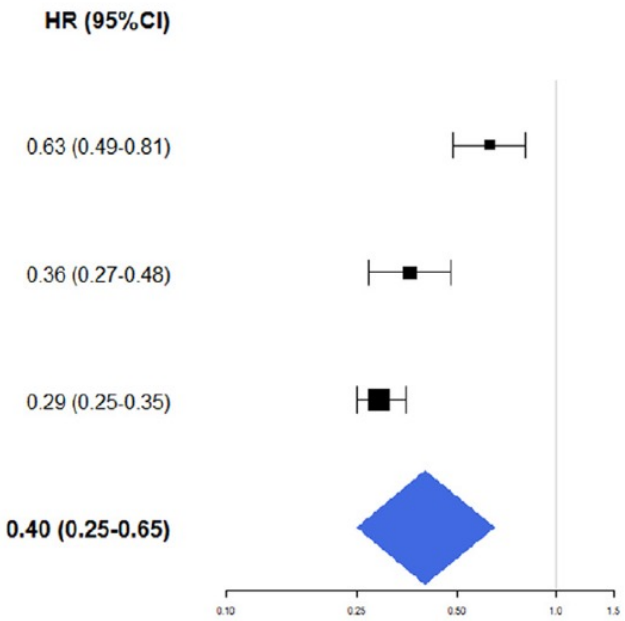
Overall survival

26%



Metastasis-free survival

68%



Subs. antineoplastic-free survival

60%

Quando fare la PSMA-PET

Come le caratteristiche cliniche possono guidare la scelta della diagnostica

Clinical determinants in CRPC

5.4.5 *Guidelines for evaluating health status and life expectancy*

Recommendations	Strength rating
Use individual life expectancy, health status, and co-morbidity in PCa management.	Strong
Use the Geriatric-8, mini-COG and Clinical Frailty Scale tools for health status screening.	Strong
Perform a full specialist geriatric evaluation in patients with a G8 score ≤ 14.	Strong
Consider standard treatment in vulnerable patients with reversible impairments (after resolution of geriatric problems) similar to fit patients, if life expectancy is > 10 years.	Weak
Offer adapted treatment to patients with irreversible impairment.	Weak
Offer symptom-directed therapy alone to frail patients.	Strong

Figure 5.3: Decision tree for health status screening (men > 70 years)** [134]

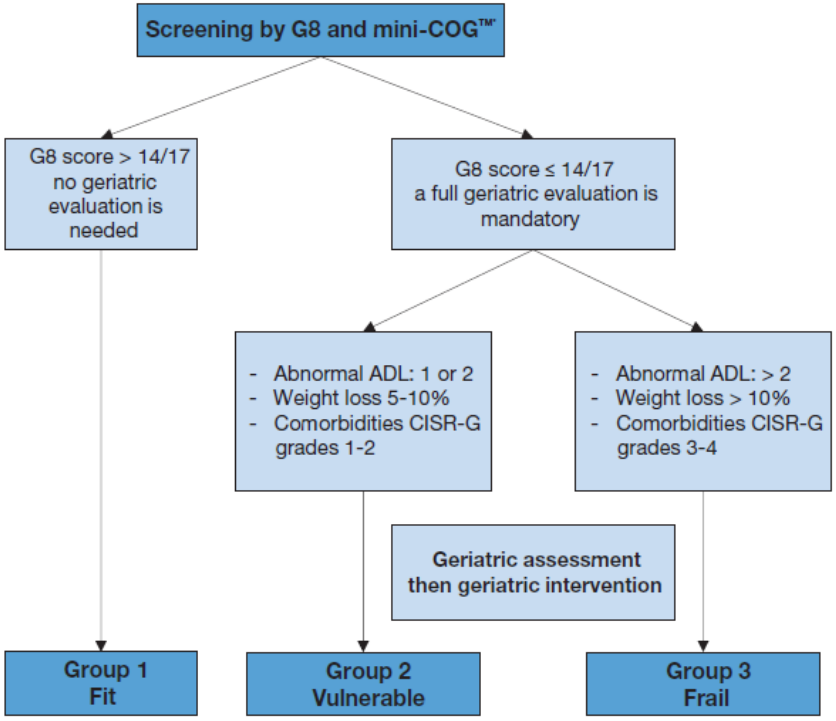
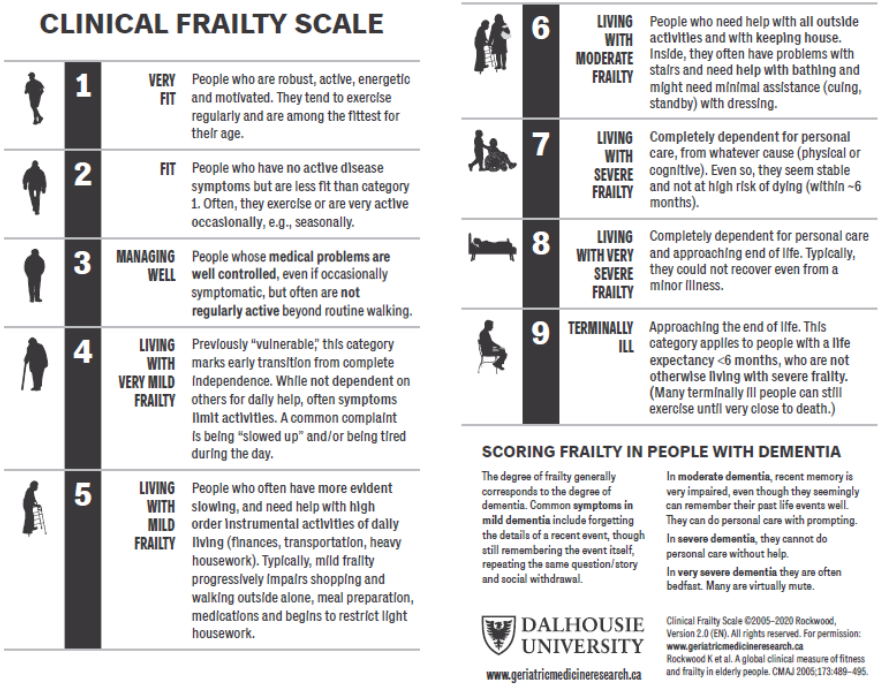


Figure 5.4: The Clinical Frailty Scale version 2.0 [437]*

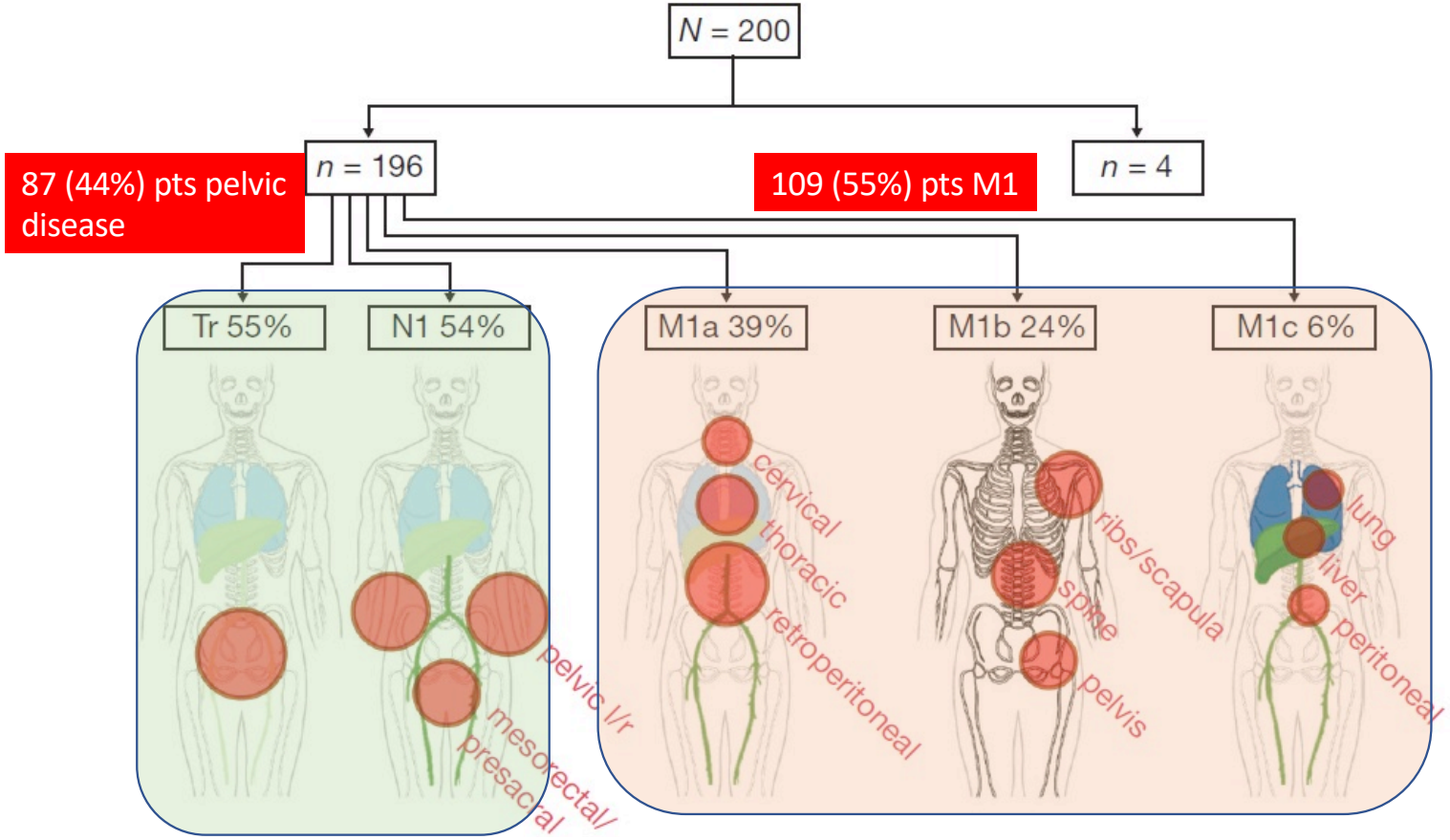


PSMA-PET to define nmCRPC

Fendler WP, Clin Ca Research 2019

200 pts [ARAMIS, PROSPER, AND SPARTAN INCLUSION CRITERIA]
Documented CRPC state with PSA > 2 ng/ml, PSADT≤ 10 mo, and/or Gleason ≥ 8, N0 and M0 on conventional imaging
PSMA findings categorized by Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE) criteria

116 PSMA+ regions from 75 pts validated by histopathology



N/M disease
(number of metastases)

1, 29 (15%)
2-3, 28 (14%)
≥ 4, 91 (46%)

Prostate bed recurr. 48 (24%)

PSMA-PET to define nmCRPC

EUROPEAN UROLOGY FOCUS XXX (2019) XXX–XXX

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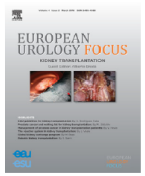
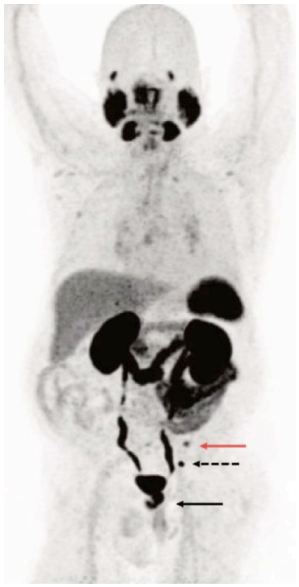
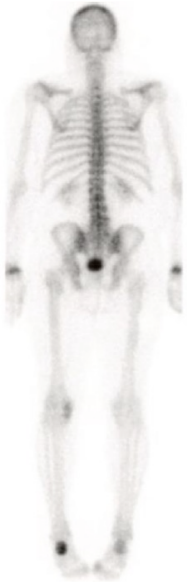


Review – Prostate Cancer

Prostate-specific Membrane Antigen–based Imaging of Castration-resistant Prostate Cancer

Manuel Weber[a,b,*], *Boris Hadaschik*[b,c], *Justin Ferdinandus*[a,b], *Kambiz Rahbar*[b,d],





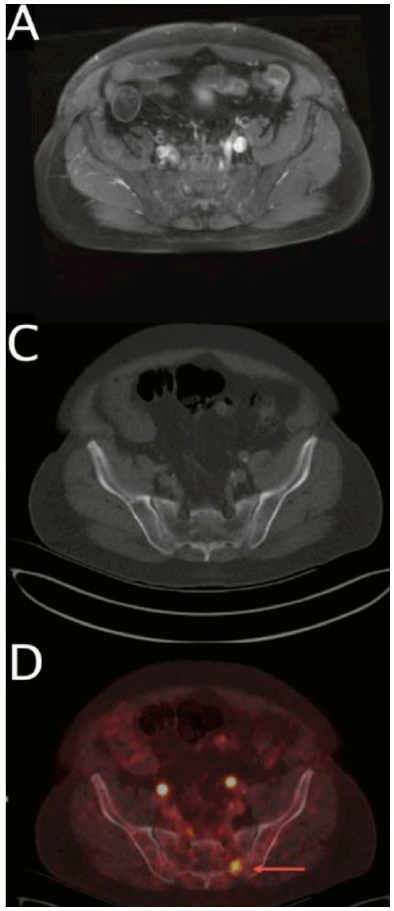


Table 1 – Studies on PSMA-PET in nonmetastatic castration-resistant prostate cancer.

Parameter	Fendler et al [12]	Wang et al [14]	Weber et al [15]	Fourquet et al [13]
Study design	Retrospective, multicenter	Prospective, single-center	Retrospective, single-center	Retrospective, single-center
Patients (*n*)	200[a]	37	55[a]	30
Median PSA (ng/ml)	5	0.57	1.5	3
Patients with PSADT ≤ 10 mo (*n*)	115	37	n/a	n/a
Patients with PSADT ≤ 6 mo (*n*)	85	25	27	15
PSMA-PET positivity (*n*)	196 98%	26 70%	41 75%	27 90%
M1 disease (*n*)	109	21	25	N/A
Extrapelvic nodes (M1a)	77	8	15	N/A
Bone (M1b)	47	16	13	9
Soft tissue/visceral organs (M1c)	12	2	2	4
Oligometastatic disease (*n*) [definition]	28 14% [2–3 lesions]	17 46% [LNMs and/or <3 BMs]	17 31% [2–5 lesions]	6 20% [<3 lesions]
M1 disease on conventional imaging (*n*)	0	0	N/A	N/A

PSMA-PET to define sites of metastasis for MDT

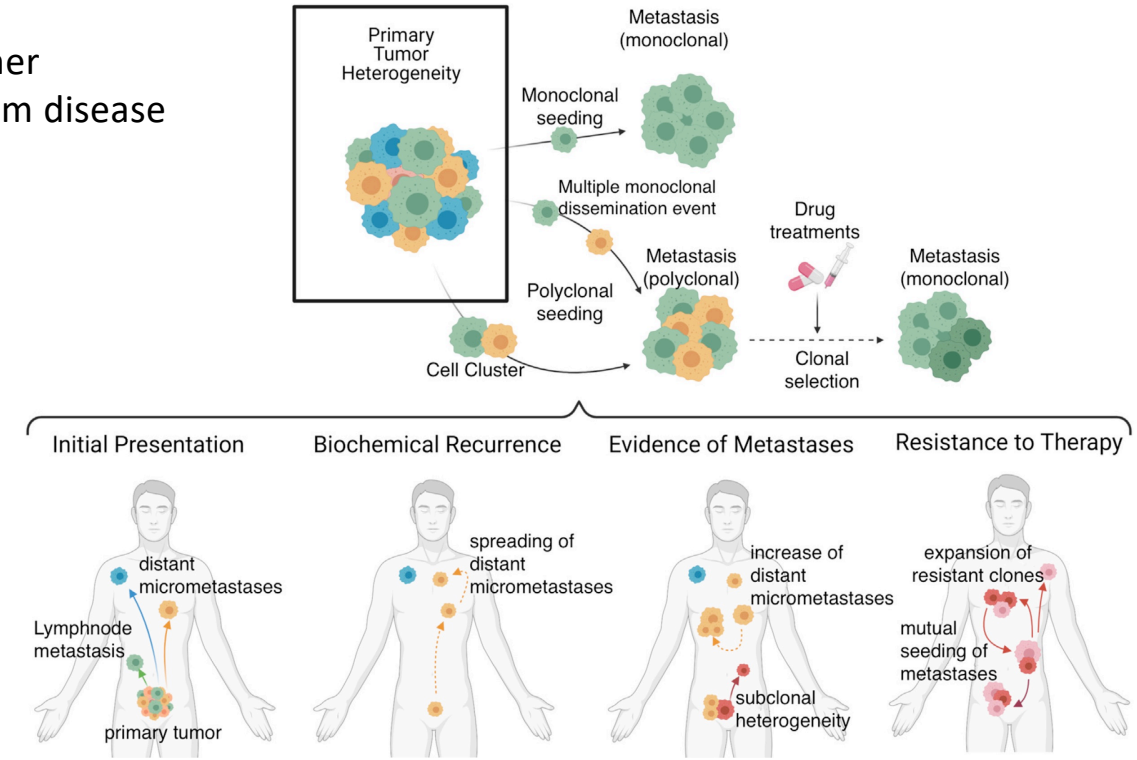
1. Clonal heterogeneity studies have shown that tumor clones are seeded from metastases to new metastatic sites.

2. Systemic treatment might pressure individual metastatic clones, giving rise to more heterogeneous, resistant, and aggressive metastases

3. Early ablation of metastatic disease may prevent further metastatic seeding, and result in long-term freedom from disease

4. Positive impact on metastatic cross-talk

5. Trigger immune-response



Clinical trials investigating the role of stereotactic body radiotherapy (SBRT) in combination with androgen receptor inhibitors.

Trial	Title	Phase	Design	Patients	Estimated completion date	Primary outcome	Secondary outcome
PILLAR (NCT03503344)	Apalutamide With or Without SBRT in Treating Participants With CRCP	II	Randomized, open label	60	December 2023	Proportion of pts with undetectable serum PSA (<0.2 ng/mL) at 6 months following completion of apalutamide (18 months from date of randomization)	Time to PSA progression according to PCWG criteria; rPFS according to PCWG criteria; frequency of treatment-emergent AEs
PCS IX TRIAL (NCT02685397)	Management of CRCP With Oligometastases. LHRH + Enzalutamide versus LHRH + Enzalutamide + SBRT	II/III	Randomized, open label	130	April 2025	rPFS	QoL; Toxicity; PCSS; Time to Skeletal-related Event. OS; LC; Time to Systemic Antineoplastic Therapy; PSA response
PCS X (NCT04070209)	SBRT With or Without Darolutamide for Oligo/Recurrent PC: a Randomized Phase II Trial (DART)	II	Randomized, open label	66	November 2027	rPFS	FACT-P; QoL; Toxicity of ODM-201; Time to Subsequent Systemic Antineoplastic Therapy; PSA response; OS; Disease Specific Survival. Time to Skeletal-related Event; LC
DECREASE (NCT04319783)	Darolutamide and SBRT consolidation in PSMA-detected lesions.	II	Randomized, open label	87	June 2026	Undetectable PSA at 12 months	rPFS; Distribution of disease on baseline PSMA-PET/CT imaging; Biochemical progression free survival; Treatment related AEs (CTCAE-5); OS; Patterns of disease on PSMA PET/CT after 12 wk of commencing darolutamide, and at time of disease progression
TRAP (NCT03644303)	Targeted Radiotherapy in Androgen-suppressed Prostate Cancer Patients. (TRAP)	-	Single arm, prospective interven-tional cohort study	84	October 2021	Median PFS	LC following SBRT; Treatment related AEs (CTCAE/RTOG); HRQoL (EQ-5D-5L); Time to administration of next line of therapy; Association between selected WB DW MRI characteristics at baseline and prognosis after SBRT