Oligometastatic Disease: Definitions and Concepts

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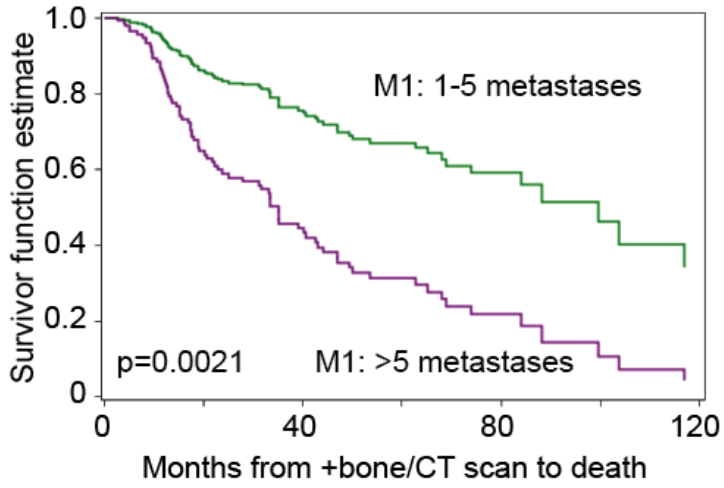
What is Oligometastatic Prostate Cancer?

- What is it? An intermediate/transitional disease state characterized by *limited metastasis* proposed by Hellman and Weichselbaum (1995)
  - The "spectrum" theory argues that there is a spectrum of disease ranging from indolent to widespread metastasis
  - Concept combines elements of Halsted's step-wise and Fisher's systemic pattern of metastasis
- Why does it matter? The existence of an intermediate (limited) metastatic state implies that there is a window of opportunity in which local treatment (the primary +/- the oligometastatic sites) can impact outcome meaningfully
  - Well established in colon cancer where liver resection reduces mortality by as much as 40%

Evidence of an Oligometastatic Disease State:



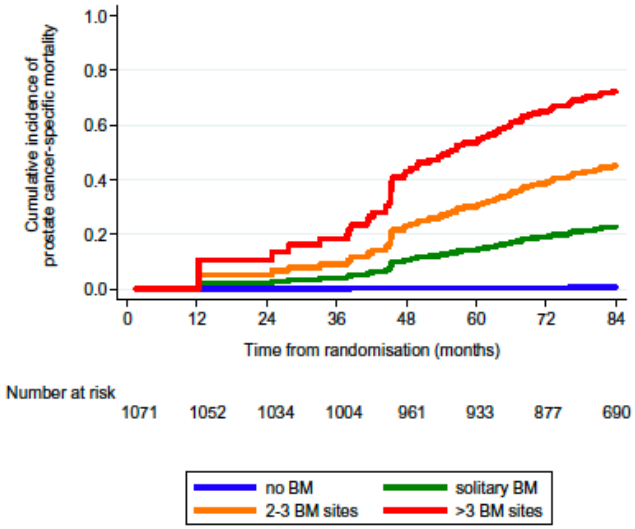


Fig. 1. Evidence of a prostate cancer-specific mortality gradient in men with solitary, two or three, and more than three bony metastatic presentations ($n = 1071$). *Abbreviations:* BM, bony metastasis.

Sridharan et al. Oligometastatic bone disease in prostate cancer patients treated on the TROG 03.04 RADAR trial

De novo prostate cancer

Garraway et al. Unpublished. VA Greater LA.

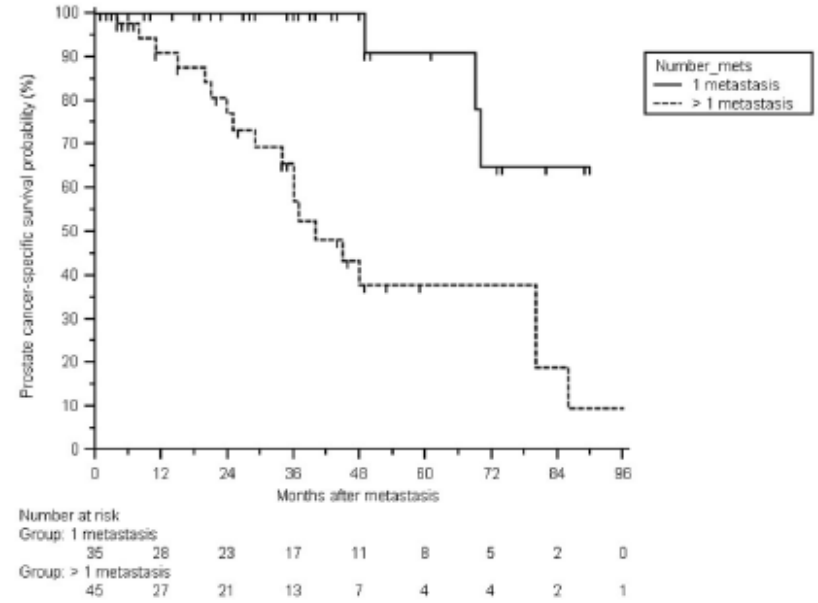
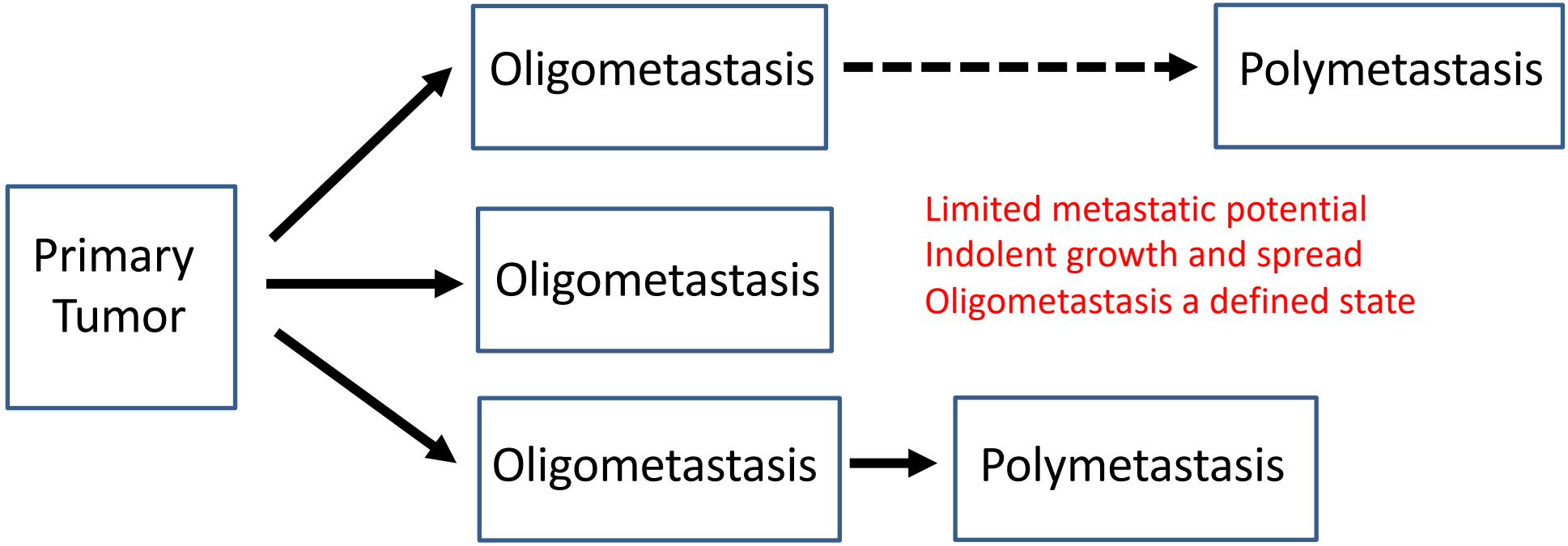


Fig. 4. Prostate cancer-specific survival following diagnosis of metastatic disease stratified according to the number of metastases (1 vs. >1).

Ost et al , Prognostic Factors Influencing Survival In Non-Castrate Patients with Metastatic PC

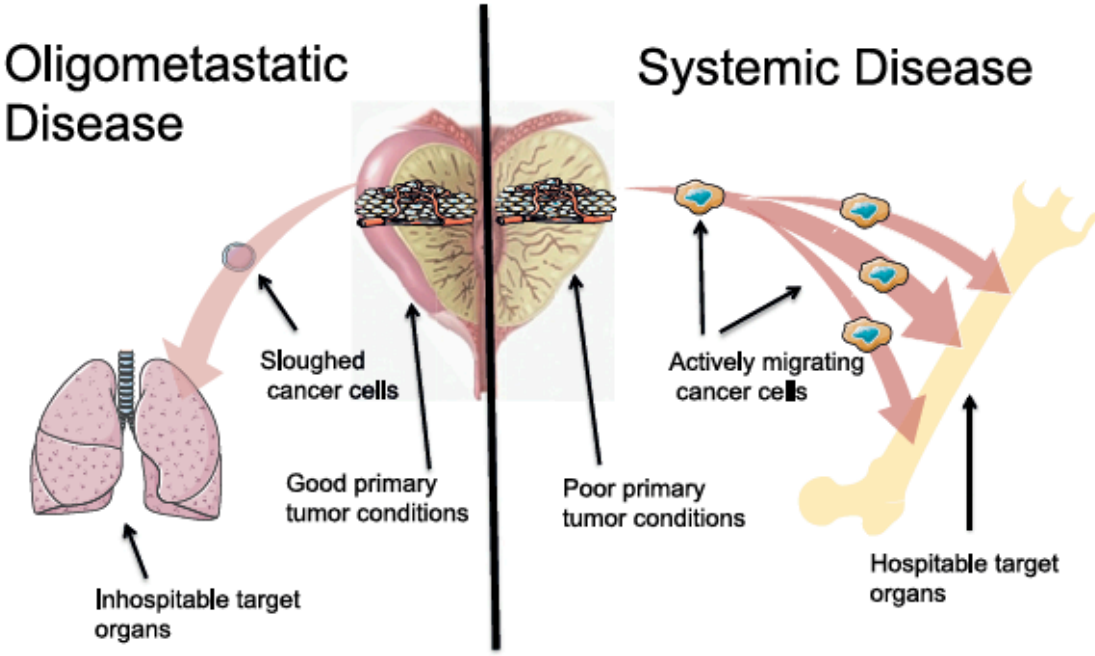
BUT DO THESE DATA PROVE THAT OLIGOMETASTASIS IS A UNIQUE DISEASE STATE or JUST a FUNCTION OF TIME?

Potential Pathways of Metastasis



Can biomarkers/genomics classify patients into these alternative models? What impact does imaging technique have on classification?

Biologic Models of (Oligo)Metastasis



Pienta et al.

- Oligometastasis hypothesized to represent a state in which a tumor lacks all necessary "hallmarks of cancer" to metastasize to specific sites, grow rapidly, or metastasize secondarily
- However, NO genomic data to define or classify the oligometastatic state yet available (GAP6)

Definitions of Oligometastasis

- Site of disease
  - Bone only
  - Any site (bone, node and/or soft tissue)
  - Bone and other site (node and/or soft tissue)
- Number of lesions
  - 1-5 in general
- Temporal pattern
  - Synchronous (de novo)- primary in place
  - Metachronous (recurrent)- primary treated previously
  - Progressive - induced by prior systemic treatment
- Castration status
  - Hormone Sensitive (Naïve) - mostly common
  - Castration Resistant

Variable Definitions of Oligometastatic Disease in Representative Trials

TABLE 1. Definition of Oligometastatic Disease and Imaging Modalities Used in Representative Studies of Oligometastatic Prostate Cancer

Study	Type	Sample Size, No.	Cutoff for Oligometastases, No.	Location of Metastases	Imaging Modality
Singh et al[5]	R; NA	369	≤ 5	Any	^{99m}Tc bone scan
Berkovic et al[14]	P; SA	24	≤ 3	Bone or LN	^{99m}Tc bone scan, ^{18}F-FDG PET/CT, ^{11}C-choline PET/CT
Schick et al[15]	P; SA	50	≤ 4	NR	^{99m}Tc bone scan, ^{18}F-choline PET/CT, ^{11}C-acetate PET/CT
Decaestecker et al[16]	P; SA	50	≤ 3	Bone or LN	^{18}F-FDG PET/CT, ^{18}F-choline PET/CT
Jereczek-Fossa et al[17]	P; SA	69	≤ 1	LN	^{18}F-FDG PET/CT, ^{11}C-choline PET/CT, CT
Ost et al[18]	P; SA	119	≤ 3	Any	^{18}F-FDG PET/CT, ^{18}F-choline PET/CT
Ost et al[19]	P; RA	62	≤ 3	Any	^{18}F-choline PET/CT

Abbreviations: FDG, 18-fluorodeoxyglucose; LN, lymph node; NA, not applicable; NR, not reported; P, prospective; R, retrospective; RA, randomized; SA, single arm.

Related Definitions and "Disease Burden"

- The oligometastatic state may be related to other measures of disease burden
- "Low-volume" (CHAARTED)
  - Exclusion: Either of the following: (a) ≥4 bone metastases on bone scan, with ≥1 outside the vertebral bodies or pelvis or (b) visceral metastases
  - OS benefits shown for abiraterone acetate, enzalutamide, apalutamide, and prostate-directed RT in *de novo* disease
- "Low-risk" (LATITUDE)
  - Exclusion: Any two of the following: (a) ≥3 bone metastases on bone scan, (b) Gleason score ≥8, or (c) Visceral metastases
  - OS benefits shown for abiraterone acetate in *de novo* disease
- Are "low volume" or "low risk" metastasis akin to oligometastatis?

Kyriakopolous et al. JCO 2018 36:1080-1087; Hoyle et al. Eur Urol (2019) *in press*

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

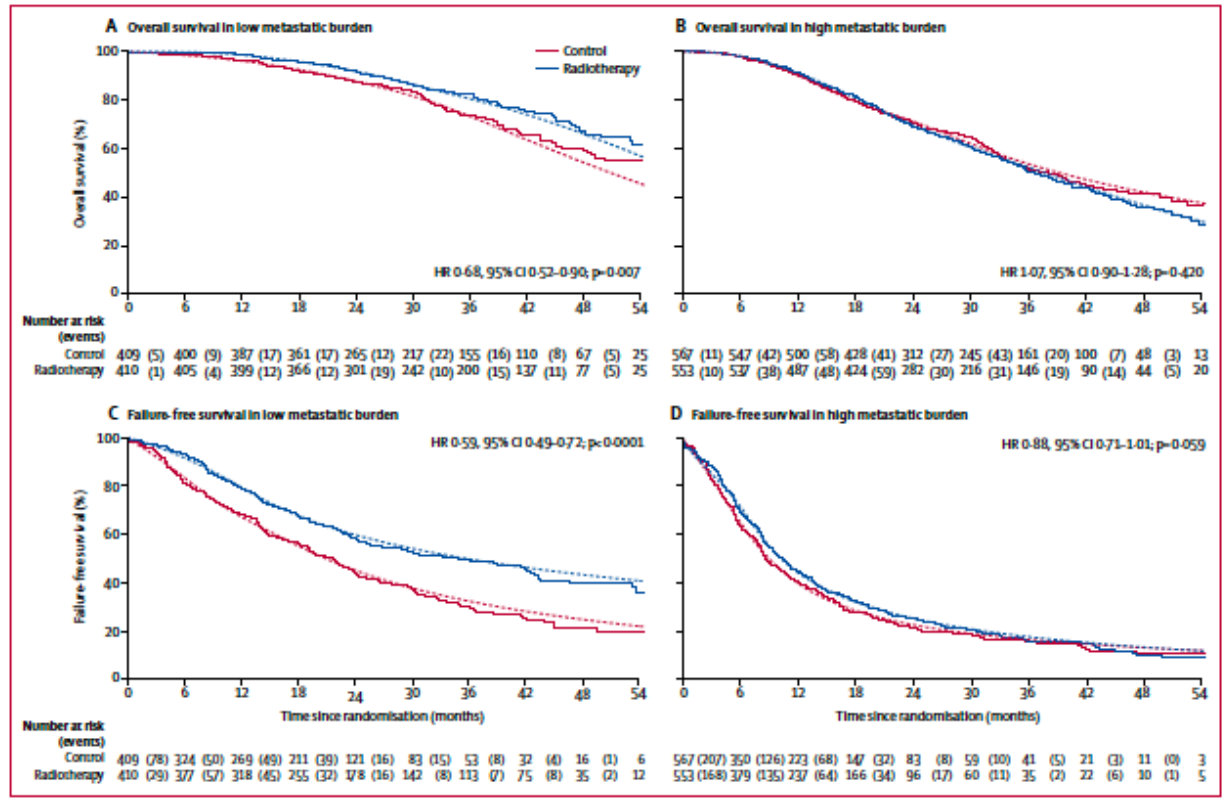


Figure 4: **Overall survival and failure-free survival by treatment and metastatic burden**
HR=hazard ratio. Solid lines show the Kaplan-Meier analysis and dotted lines show the flexible parametric model.

Low metastatic burden defined as per CHAARTED = axial only metastases and no visceral

Parker et al. Lancet 2018

Can we extrapolate these data to oligometastatic disease?

Impact of Imaging on Defining Metastatic State

- Most published studies based on conventional imaging (MRI, CT, bone scan) and first generation molecular (NaF, choline, acetate)
- Definition and diagnosis of oligometastasis will depend on staging modality
- Significant reclassification (upstaging) clearly occurs with molecular imaging (PSMA, axumin)
  - non-metastatic to oligometastatic
  - oligometastatic to polymetastatic
  - Extrapolation of clinical data obtained with CI to that obtained with PSMA may NOT be warranted
- Also remember, even the best molecular imaging tool will miss (understage) a significant percentage of metastases (< 5mm, low PSMA)
  - In high risk patients, Ga-PSMA has a 30-40% sensitivity on per patient basis for nodes and a 24% sensitivity on a per node basis (Yaxly et. Al Journal of Urology 2019)

Upstaging when imaged by PSMA PET/CT: UCLA and UCLA/German pooled data

Intact prostate, no prior treatment, M0 by conventional

^{68}Ga-PSMA-11 PET/CT Findings and Patterns

Parameter	Total population (n = 73)	Patients without radiographic N1 disease (n = 66)
PSMA-positive findings*		
N1	25 (34%)	19 (29%)
M1	7 (9.5%)	7 (10.5%)
M1a	4 (5.5%)	4 (6%)
M1b	4 (5.5%)	4 (6%)
M1c	1 (1.5%)	1 (1.5%)
PSMA patterns		
N0M0	46 (63%)	45 (68%)
N1M0	20 (27.5%)	14 (21%)
N1M1a	3 (4%)	3 (4.5%)
N0M1b	2 (2.5%)	2 (3%)
N1M1aM1b	1 (1.5%)	1 (1.5%)
N1M1bM1c	1 (1.5%)	1 (1.5%)

*Percentages do not add up to 100 because multiple disease locations per patient were possible.
Data are number of patients.

J Nucl Med. 2018;59(11):1714-1721.

PSA rising post surgery, PSA 0.01-1.0, median 0.4

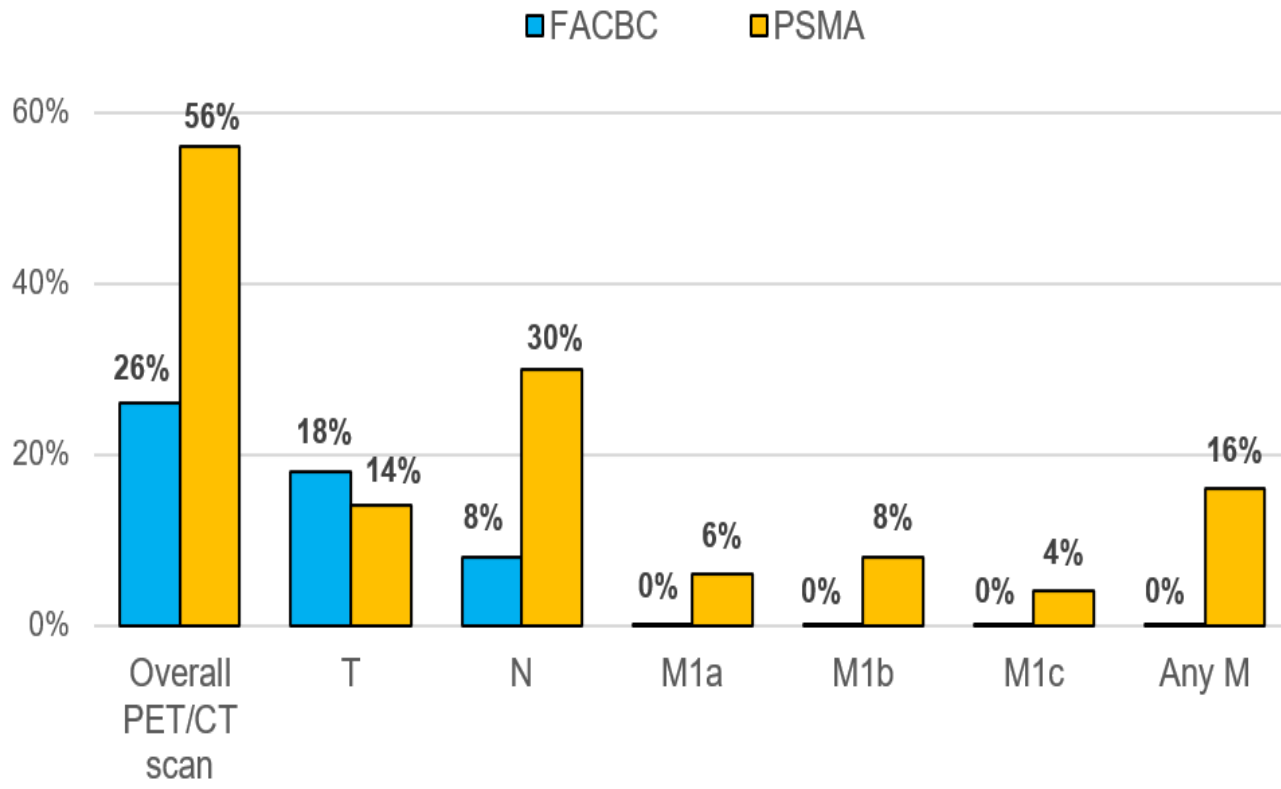
^{68}Ga-PSMA-11 PET/CT Patterns of Relapse

Pattern	Number of patients
PSMA-11 PET/CT+	132 (49%)
Prostate bed (T+)	47 (17.5%)
Pelvic LN (N1)	83 (30.5%)
Extrapelvic LN (M1a)	9 (3.5%)
Bone (M1b)	23 (8.5%)
Visceral (M1c)	3 (1%)
PSMA-11 T+ N0 M0	32 (12%)
PSMA-11 T0 N1 M0	59 (22%)
PSMA-11 T+ N1 M0	8 (3%)
PSMA-11 T+ N0 M1	2 (0.7%)
PSMA-11 T0 N0 M1	15 (5.5%)
PSMA-11 T0 N1 M1	11 (4%)
PSMA-11 T+ N1 M1	5 (2%)

Total population = 270. Percentages do not add up to 100 because multiple disease localizations per patient were possible.

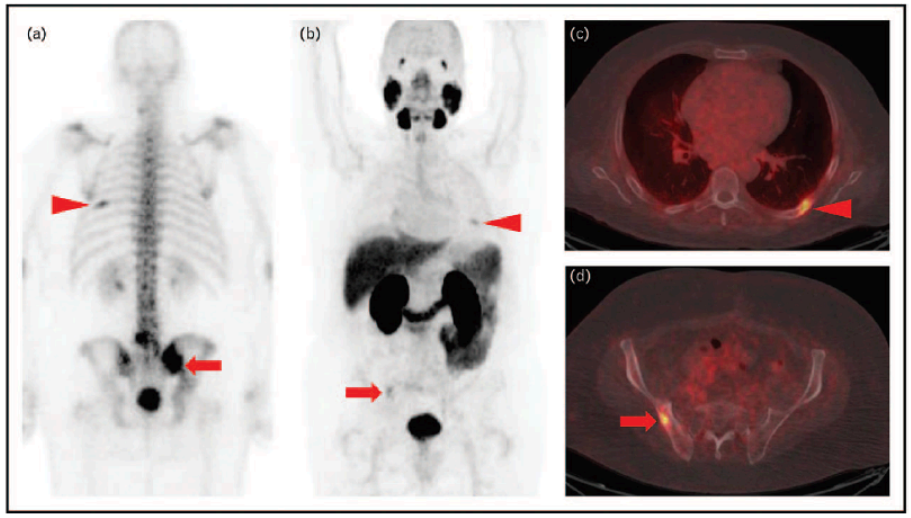
J Nucl Med. 2018;59(2):230-237.

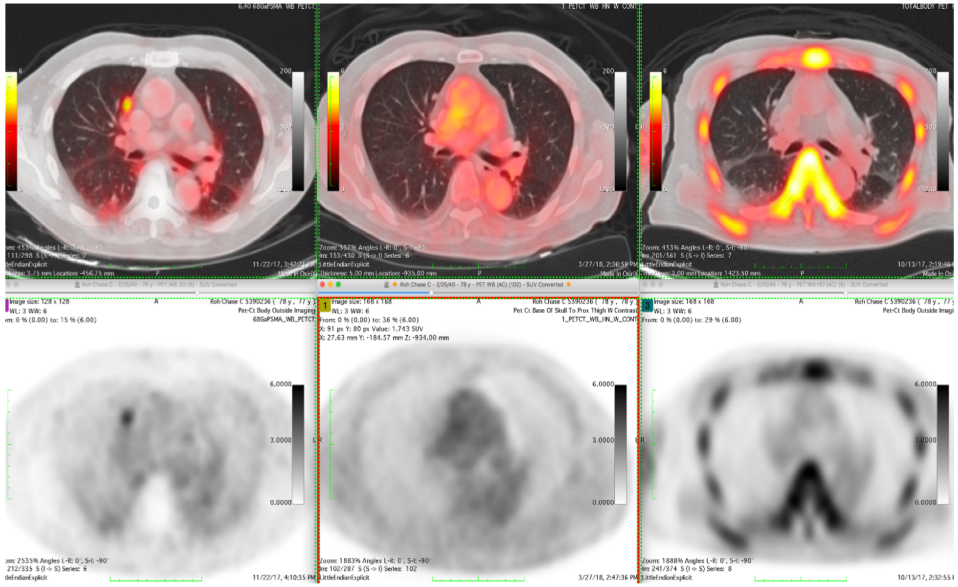
Choice of Tracer Influences Detection Rates: per-patient comparison of FACBC and PSMA



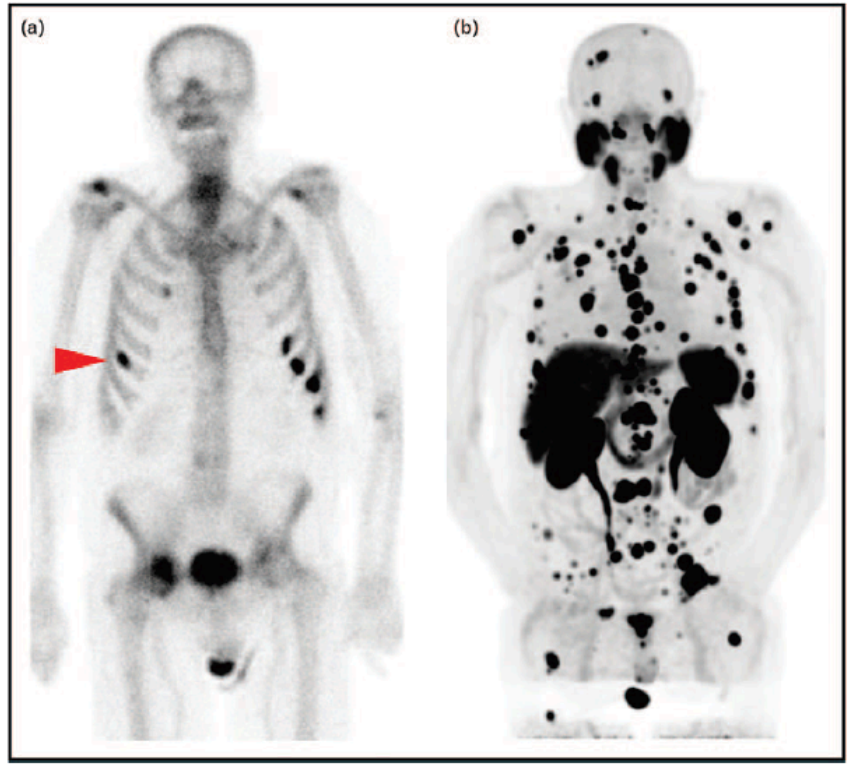
Calais et al Lancet Oncology 2019

Potential of PSMA PET to Distinguish True Oligometastatic Disease?





PSMA PET FDG PET Na-F PET

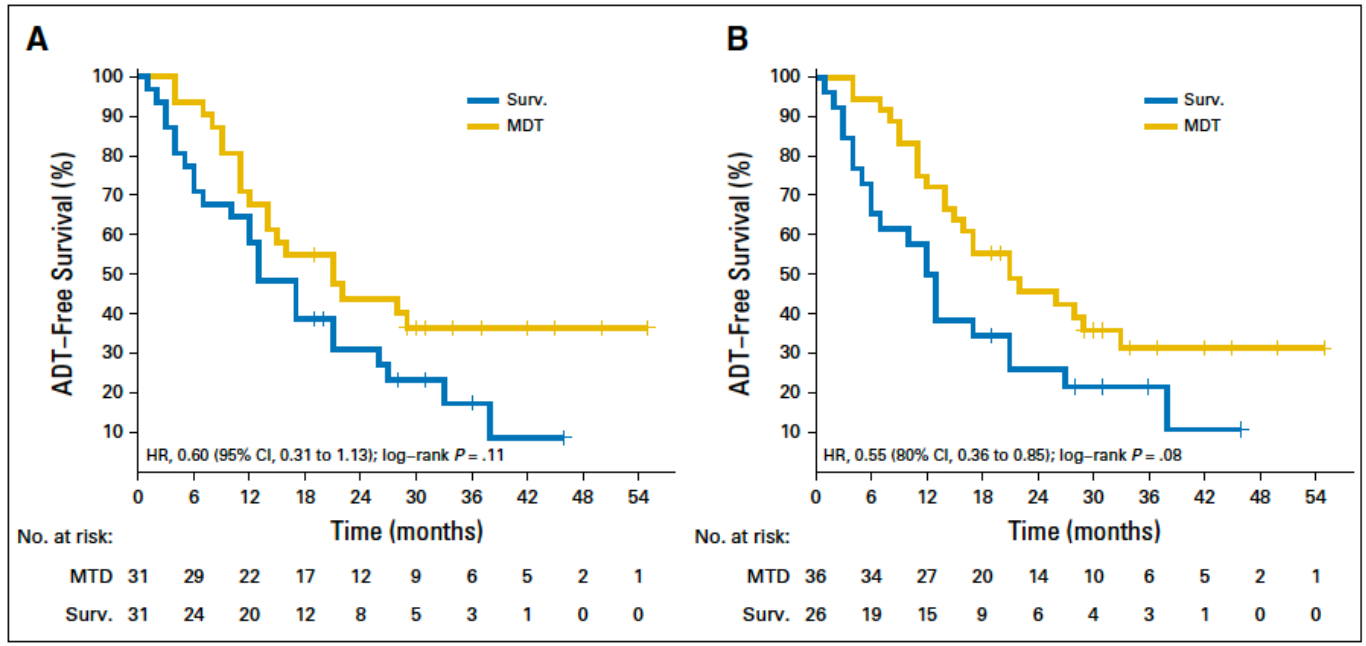


Bone scan PSMA PET

Clinical Trials in Oligometastatic Disease

- Two central clinical questions
  - Synchronous disease: Does "local" treatment of ALL visualized disease impact patient or disease related outcomes?
  - Metachronous or progressive disease: Does metastasis directed therapy impact patient or disease related outcomes?
- What are valid(ated) endpoints?
  - Survival
  - Time to polymetastatic progression
  - Time to systemic therapy

STOMP: Metastasis Directed Therapy Delays Time to ADT



BUT is this a valid endpoint?

Could MDT delay in ADT but reduce overall survival?

Conclusions

- This is a consensus conference but:
  - No clear consensus on its existence as a discrete entity or its prevalence
    - Is it a distinct biological/disease state or simply an earlier stage in progression?
    - Is it a measure of indolent vs aggressive disease, clonal or polyclonal disease etc. ?
    - Genomic and other classifiers needed
  - No consensus on definition
  - No consensus on role of imaging to definine or manage
    - Trials must consider inclusion of PSMA imaging
  - No consensus on appropriate clinical trial endpoints