

Management of Men with PSA Recurrence after Radical Local Radiation Therapy

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Disclosures

- I have consulted for Astellas, Dendreon, EMD Serono, Ferring, Genentech, Bayer, Clovis, Janssen, Sanofi, and Blue Earth Diagnostics.
- I am co-founder of PFS Genomics, a molecular diagnostics company in the breast cancer space.
- I am on the Scientific Advisory Board for Nutcracker Therapeutics and SerImmune.

Overview

- Over 1.2 million patients are diagnosed with prostate cancer worldwide each year¹.
- In the United States, over one third of patients with localized prostate cancer are treated with radiation therapy (RT)².
- Depending on the disease characteristics, 15-70% of prostate cancer patients recur after definitive RT.
- These figures suggest that over 100,000 men may present with recurrent disease after upfront RT.

¹Bray F et al, CA CANCER J CLIN 2018; 68: 394-424, ²Chen J et al, Prostate 2018; 78(7): 512-520.

How do we define a PSA recurrence after RT?

- RTOG-ASTRO Phoenix Consensus Definition¹:
PSA increase by 2 ng/mL or more above the nadir PSA
- Many clinicians do not wait for Phoenix criteria to be achieved before evaluating for recurrence.
- NCCN Guidelines: “A recurrence evaluation should be considered when PSA has been confirmed to be increasing after radiation even if the increase above nadir is not yet 2 ng/mL, especially in candidates for salvage local therapy who are young and healthy.”

¹Roach M et al, IJROBP 65(4): 965-974.

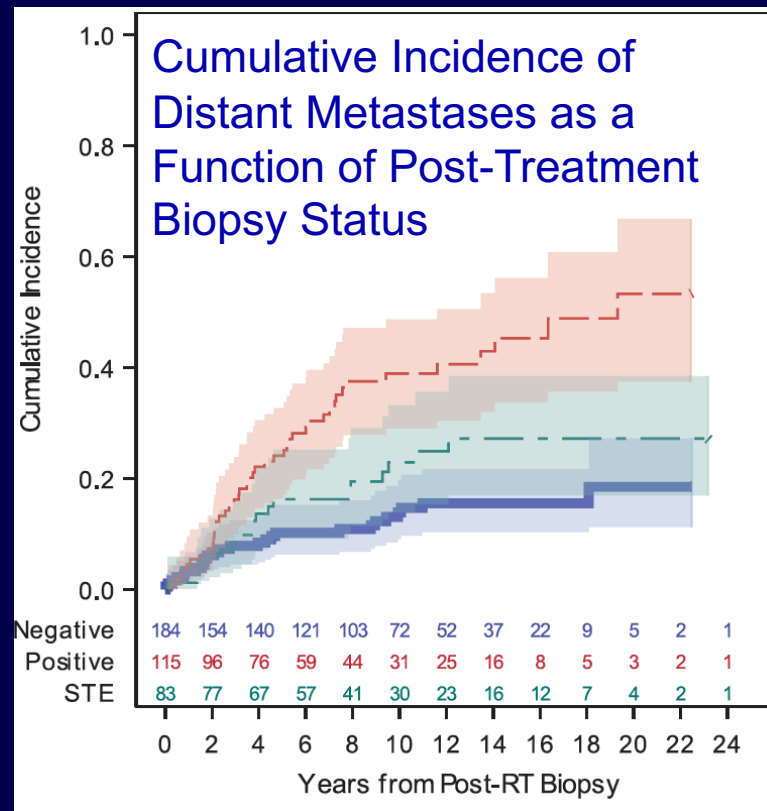
Management of a PSA recurrence after definitive RT

- Work-up
 - Imaging
 - Potential biopsy
 - Local Therapy for Local Recurrences
 - Local Therapy for Regional or Distant Recurrences
 - Systemic Therapy
- } Focus of my talk
- } Focus of subsequent talks at APCCC

What is the significance of a local recurrence after RT?

382 patients with post-treatment biopsies after definitive RT for prostate cancer:

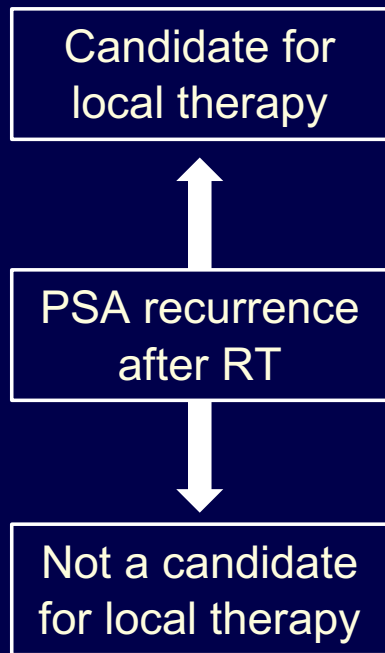
- 30% positive (red)
- 22% w/ significant treatment effect (green)
- 48% negative (blue)



Positive post-treatment biopsies are associated with increased incidence of distant metastases

Zelevsky M et al, *J Urology* 2019, 201 (1127-1133)

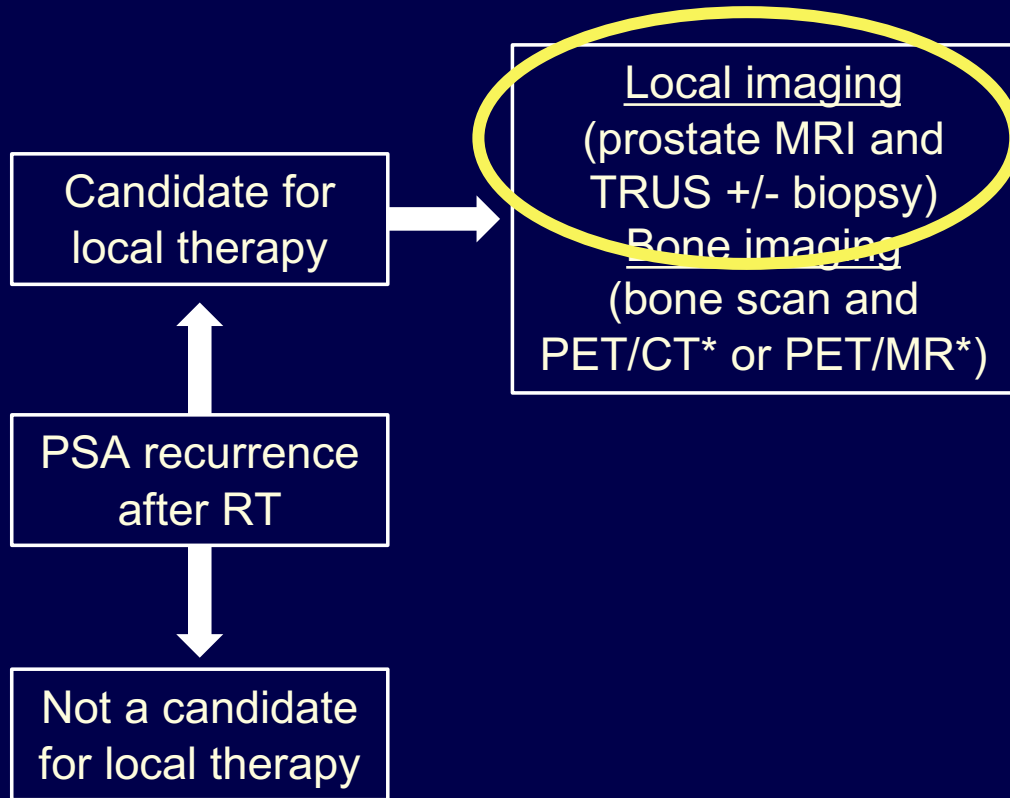
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Who are the best candidates for local therapy?

- Original clinical stage T1-2, NX or N0
- Life expectancy > 10 yrs
- PSA now < 10 ng/mL
- Long interval to recurrence (>3 years)
- Long PSA doubling time (>12 months)
- Organ-Confined at Recurrence (i.e., MRI)

Management of a PSA recurrence after definitive RT



*PET can be PSMA or fluciclovine or C-11 choline PET

Detection of a local recurrence

Cancer Detection Rates:

	TPM n (%)	MRI-TB n (%)
Total	77 (100.0)	77 (100.0)
No cancer	8 (10.4)	14 (18.2)
Clinical insignificant (Gleason 3+3 and ≤ 3 mm)	3 (3.9)	3 (3.9)
UCL/Ahmed definition 2 (Gleason $\geq 3+4$ and/or MCCL ≥ 4 mm)	11 (14.3)	8 (10.4)
UCL/Ahmed definition 1 (Gleason $\geq 4+3$ and/or MCCL ≥ 6 mm)	55 (71.4)	52 (67.5)

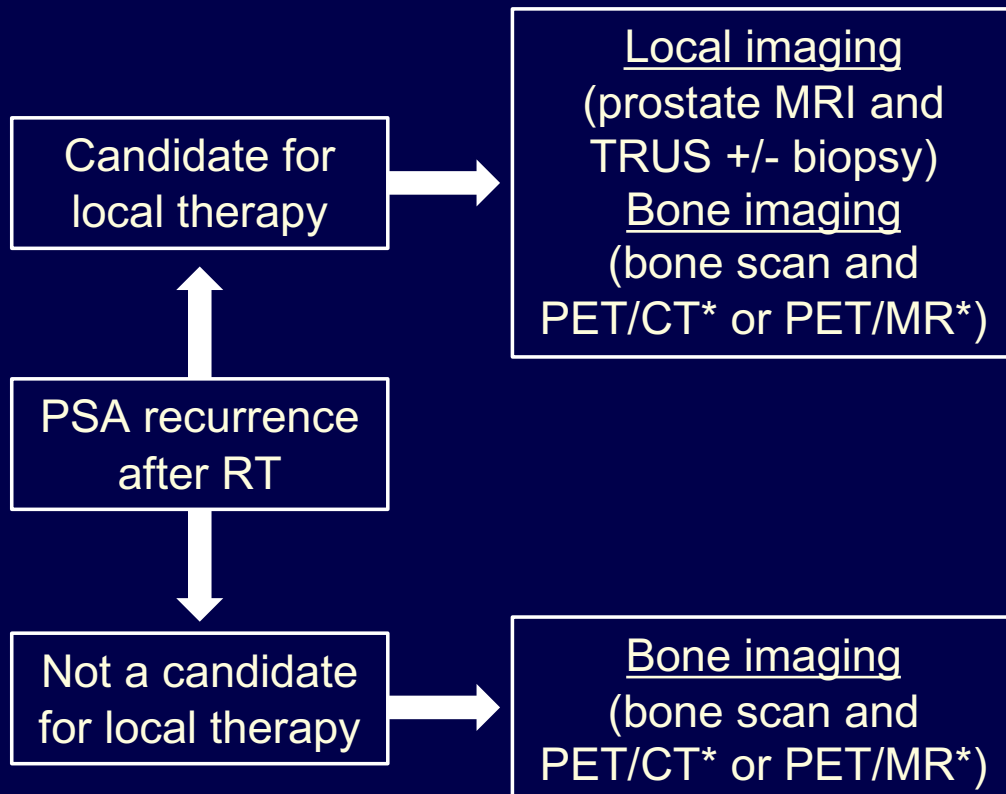
MCCL, maximum cancer core length.

Core-Based Comparison:

	TPM (%)	MRI-TB (%)
Total number of cores	2392 (100)	380 (100)
Any cancer	428 (17.9)	203 (53.4)
UCL/Ahmed definition 2 or UCL/Ahmed definition 1	425 (17.8)	190 (50.0)
Gleason score ≥ 7	419 (17.5)	181 (47.6)
UCL/Ahmed definition 1	379 (15.8)	177 (46.6)

Data from 77 patients who underwent Transperineal Prostate Mapping (TPM) with 5 mm sampling as well as MRI-Targeted Biopsies (MRI-TB) with multi-parametric MRI

Management of a PSA recurrence after definitive RT

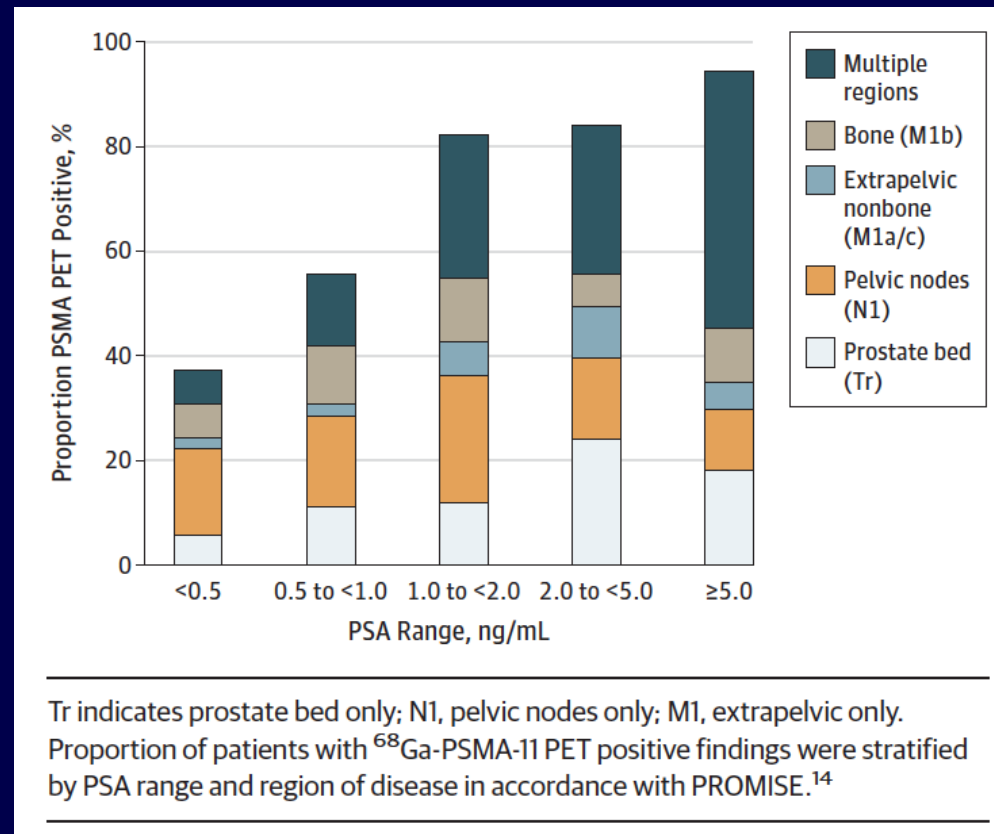


*PET can be PSMA or fluciclovine or C-11 choline PET

Advanced imaging has changed our ability to detect disease at low PSA levels

Prospective study:
PSMA PET imaging
performed on 635
patients, including 169
treated with definitive
radiation therapy

All PET-detected
lesions validated with
histopathological
assessment or a
composite endpoint
based on imaging and
PSA follow-up



Fendler W et al, *JAMA Oncology* 2019, 5(6): 856-863

Advanced imaging has changed our ability to detect disease at low PSA levels

Retrospective study:
Detection rates of
 ^{68}Ga -PSMA PET in
276 patients treated
with definitive
radiation therapy

PSA	Total patients	Number of patients with positive scan	Detection rate
0.0–<0.5	12	8	66.7%
0.5–<1.0	18	14	77.8%
1–<2.0	43	33	76.7%
>2.0	203	184	90.6%
Overall detection	276	239	86.3%

15-30% have isolated local failures

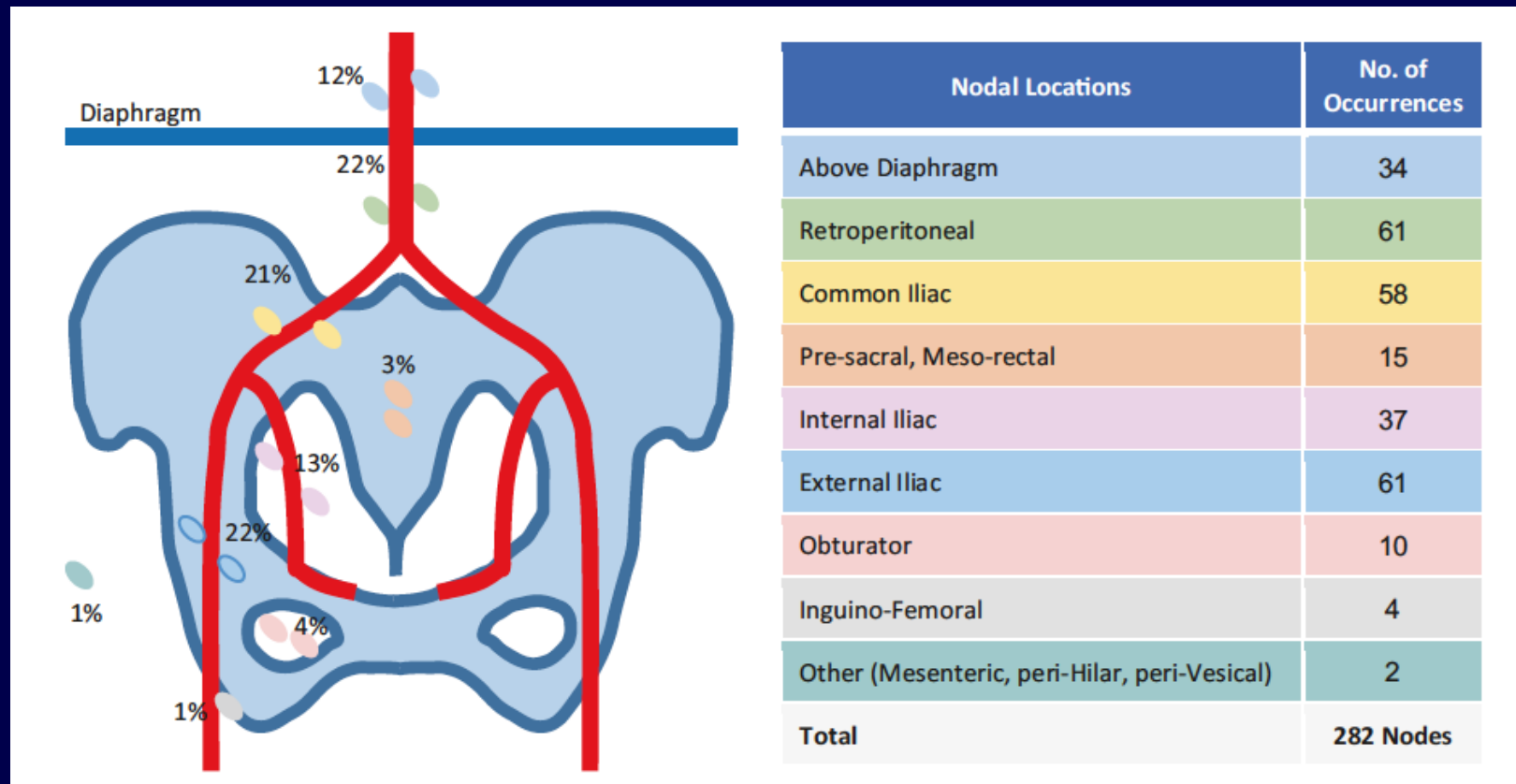
Not biopsy proven

Patterns of recurrence in this cohort:

PSA	Total patients	Local recurrence	Lymph nodes	Skeletal	Visceral
0.0–<0.5	12	5	6	4	0
0.5–<1.0	18	8	7	3	0
1–<2.0	43	22	14	4	1
>2.0	203	122	95	47	5
Total	276	157 (56.9%)	122 (44.2%)	57 (20.7%)	6 (2.2%)

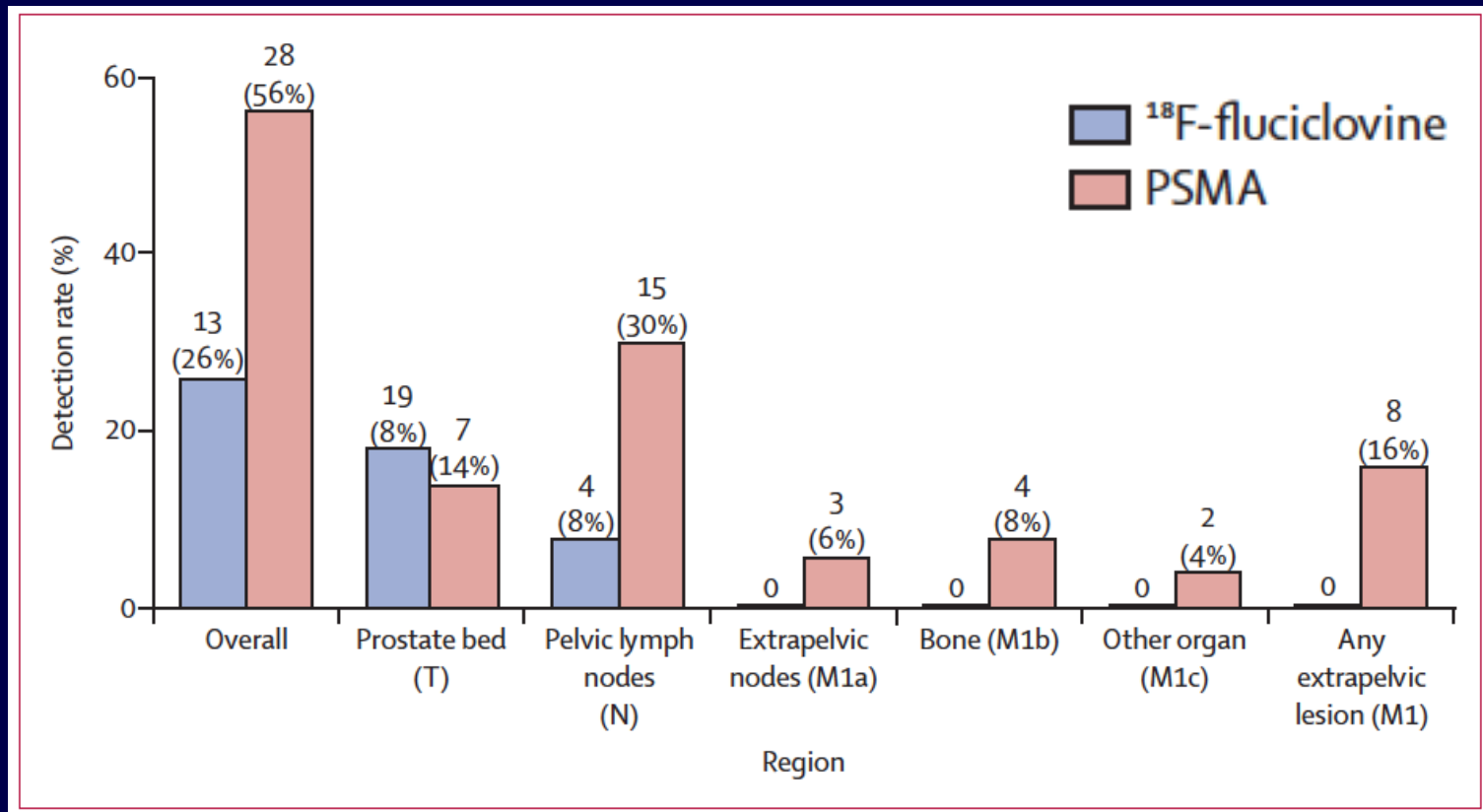
Raveenthiran S et al, Prostate Cancer and Prostatic Diseases, 2019, 22: 385-390

Using PSMA PET to determine patterns of disease recurrence following primary radiotherapy



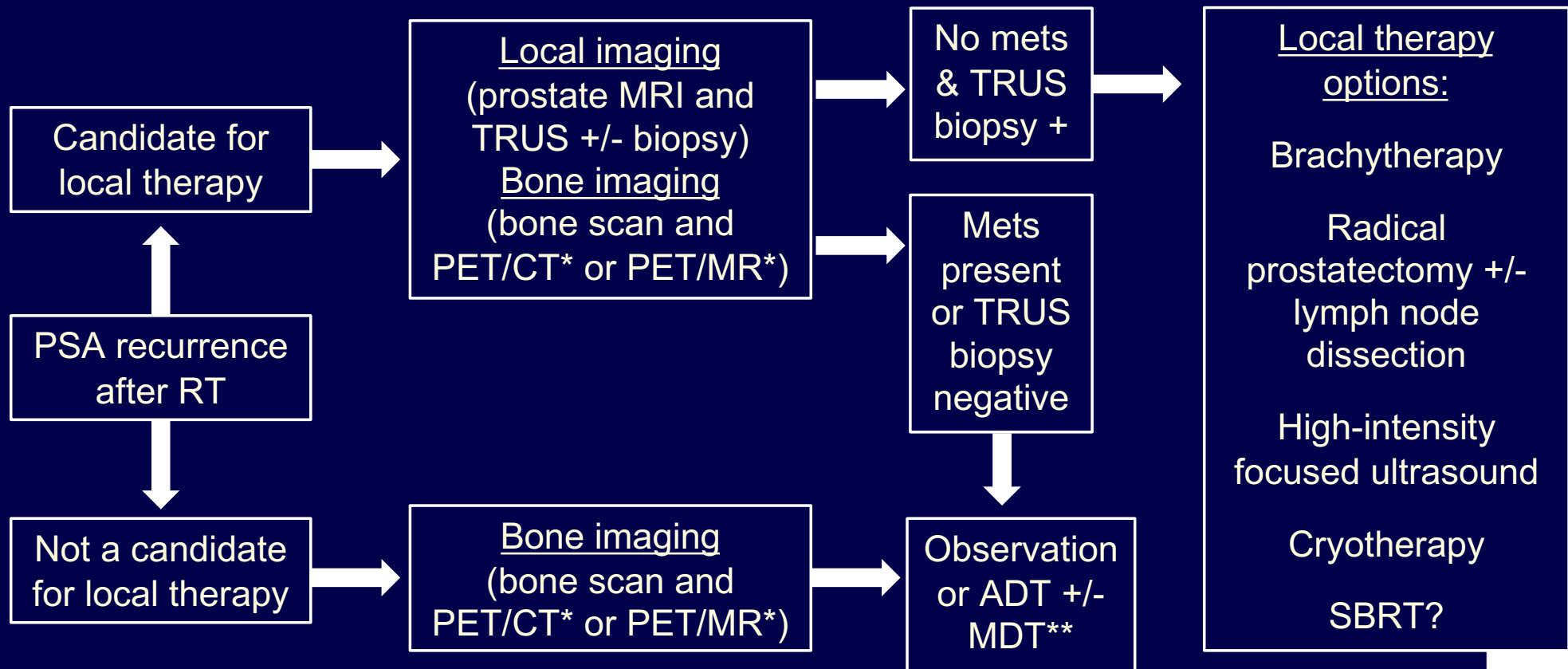
Raveenthiran S et al, Prostate Cancer and Prostatic Diseases, 2019, 22: 385-390

PSMA PET detects more lesions than Axumin PET



Calais J et al, *Lancet Oncology* 2019

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**MDT = Metastases-directed therapy

European Guidelines



European Association of Urology



Guidelines

EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part II: Treatment of Relapsing, Metastatic, and Castration-Resistant Prostate Cancer

Philip Cornford^{a,*}, Joaquim Bellmunt^{b,c}, Michel Bolla^d, Erik Briers^e, Maria De Santis^f,
Tobias Gross^g, Ann M. Henry^h, Steven Joniauⁱ, Thomas B. Lam^{j,k}, Malcolm D. Mason^l,
Henk G. van der Poel^m, Theo H. van der Kwastⁿ, Olivier Rouvière^o, Thomas Wiegel^p,
Nicolas Mottet^q

Table 1 = Guidelines for ... second-line therapy after txt with curative intent

Local salvage treatment	LE	GR
• Treat highly selected pts with localized PC & histologically proven local recurrence with salvage RP	3	B
• Due to the increased rate of side effects, perform salvage RP in experienced centres	3	A
• Offer or discuss HiFu, Cryo and salvage brachy with pts without mets ... inform pts about the experiential nature of these approaches	3	B

Approaches for treatment of a local recurrence

Table 5 Toxicity and 5-year FFS by Salvage Therapy Type

Salvage Therapy	Incontinence	Bladder Neck Stricture	Fistula
Brachytherapy	6.16%	7.48%	3.09%
Prostatectomy	49.69%	26.09%	2.43%
Cryotherapy	16.40%	4.15%	1.61%
HiFU	36.94%	17.22%	3.61%

	Number of studies reviewed with 5-year FFS	Total number of patients	5-year FFS
Brachytherapy	9	223	55.63%
Prostatectomy	16	980	52.18%
Cryotherapy	2	335	56.07%
HiFU	1	22	52.00%

Almost all studies of salvage therapies for post-RT local recurrences are retrospective
5 year FFS rates are approximately the same for all modalities (52-56%)

RTOG 0526: A Prospective Phase 2 Trial of Transperineal Ultrasound-Guided Brachytherapy for Locally Recurrent Prostate Cancer After External Beam Radiation Therapy

- 92 patients received salvage LDR brachytherapy from 2007-2014
- Prescribed minimum target dose: I-125 (140 Gy), Pd-103 (120 Gy)
- Primary endpoint (late GI/GU adverse events): 13.8% of patients had late treatment-related GI/GU AE's (hypothesis was that <10% of patients would have these AE's, but >20% was considered unacceptable)
- MVA logistic regression: No pre treatment characteristics predicted occurrence of late treatment-related GI/GU AE's

Conclusions

- There is a significant subset of prostate cancer patients with PSA recurrences after definitive RT.
- Positive post-treatment biopsies are associated with metastatic progression.
- Advanced imaging approaches allow detection of recurrences at PSA levels lower than the nadir + 2 (phoenix) definition.
- Treatment approaches for biopsy-proven local recurrences (in the absence of metastases) include salvage brachytherapy, RP, HiFU, and cryotherapy.