Key advances in genito-urinary tumors: What we learned in the last 10 years

Prostate cancer

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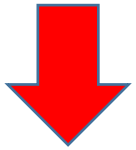
Key advances in genito-urinary tumors in the last 10 years

- ✓ The revolution of Imaging (diagnosis, staging and recurrence)
- ✓ Treatment intensification in localized prostate cancer
- ✓ Treatment of metastatic prostate cancer

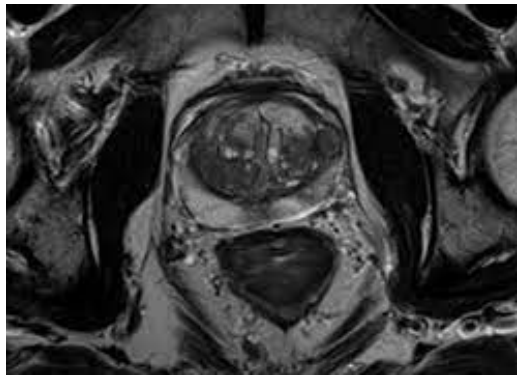


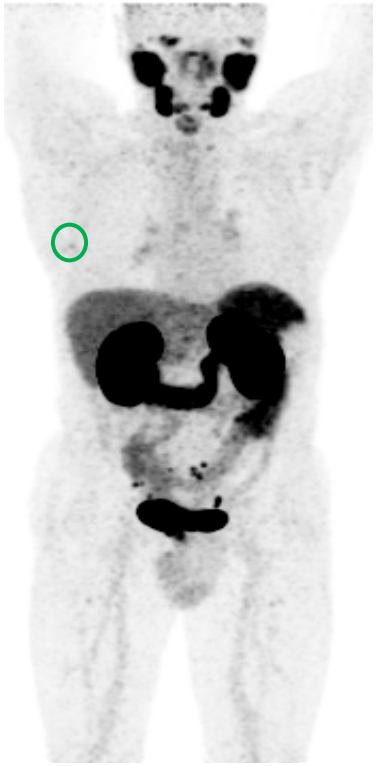
High level of evidence – significant steps forward
However, many answers but also many new questions...

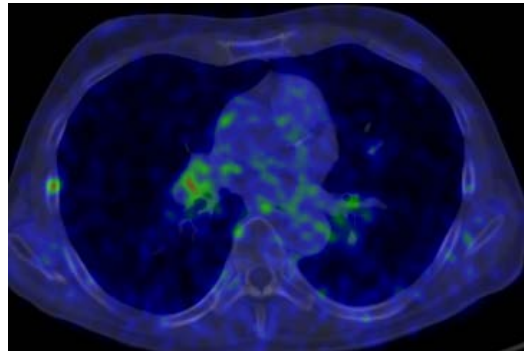
Role of Imaging for Clinical Diagnosis and Staging in prostate cancer

1) **MRI: Diagnosis**

2) PSMA/PET-CT/MRI : Local and distant Staging







Key advances in genito-urinary tumors in the last 10 years

Not reported until 2014

	LE	GR
When available, mMRI of the prostate can be used to trigger a (targeted) repeat prostate biopsy.	2b	B

2014

	LE	GR
When clinical suspicion of PCa persists in spite of negative biopsies, MRI-targeted biopsies are recommended.	2b	B

2015

Recommendation	LE	GR
Before repeat biopsy, perform mpMRI when clinical suspicion of PCa persists in spite of negative biopsies.	1a	A
During repeat biopsy include systematic biopsies and targeting of any mpMRI lesions seen.	2a	B

2016

From repeat

To first biopsy

Recommendations in biopsy-naïve patients	LE	Strength rating
Perform mpMRI before prostate biopsy.	1a	Weak
When mpMRI is positive (i.e. PI-RADS ≥ 3), combine targeted and systematic biopsy.	2a	Strong
When mpMRI is negative (i.e. PI-RADS ≤ 2), and clinical suspicion of prostate cancer is low, omit biopsy based on shared decision making with the patient.	2a	Weak

Strong

Recommendations in patients with prior negative biopsy	LE	Strength rating
Perform mpMRI before prostate biopsy.	1a	Strong
When mpMRI is positive (i.e. PI-RADS ≥ 3), perform targeted biopsy only.	2a	Weak
When mpMRI is negative (i.e. PI-RADS ≤ 2), and clinical suspicion of prostate cancer is high, perform systematic biopsy based on shared decision making with the patient.	2a	Strong

2019-22

EAU guideines in prostate cancer

Role of MRI for Clinical Diagnosis

1) MRI: Diagnosis - CERTAINTIES

Reduction in the number of biopsies performed and in the rates of ciPCa detected

High negative predictive values in experienced hands

Negative predictive value maintained over time

At (initial) biopsy combine targeted + systematic biopsies

Biopsy-naive

Recommendations for biopsy-naïve patients	Strength rating
Perform MRI before prostate biopsy.	Strong
When MRI is positive (i.e. PI-RADS ≥ 3), combine targeted and systematic biopsy.	Strong
When MRI is negative (i.e., PI-RADS ≤ 2), and clinical suspicion of PCa is low (e.g. PSA density < 0.15 ng/mL), omit biopsy based on shared decision-making with the patient.	Weak

Prior negative biopsy

Recommendations for patients with prior negative biopsy	Strength rating
Perform MRI before prostate biopsy.	Strong
When MRI is positive (i.e. PI-RADS ≥ 3), perform targeted biopsy only.	Weak
When MRI is negative (i.e., PI-RADS ≤ 2), and clinical suspicion of PCa is high, perform systematic biopsy based on shared decision-making with the patient.	Strong

EAU Guidelines on prostate cancer, 2022

Role of MRI for Clinical Diagnosis

1) MRI: Diagnosis - GREY ZONES

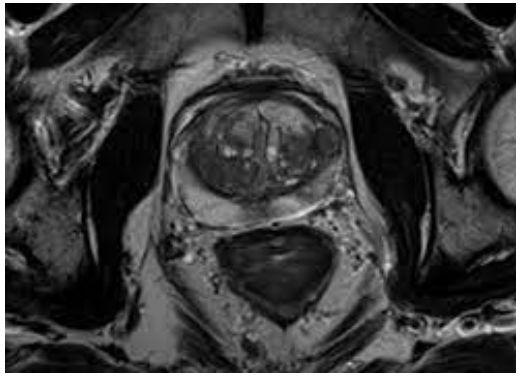
Sub-optimal specificity and PPV

High inter-reader variability

Experience matters: need for images revision (?)

Need for quality assessment

How to include biomarkers in the MRI pathway?



Has MRI improved the outcomes of men wth Pca?

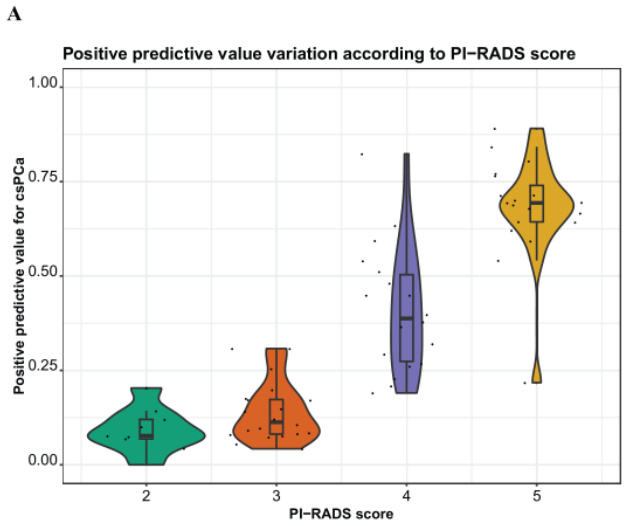
EAU Guidelines on prostate cancer, 2022

Role of MRI for Clinical Diagnosis

1) MRI: Diagnosis

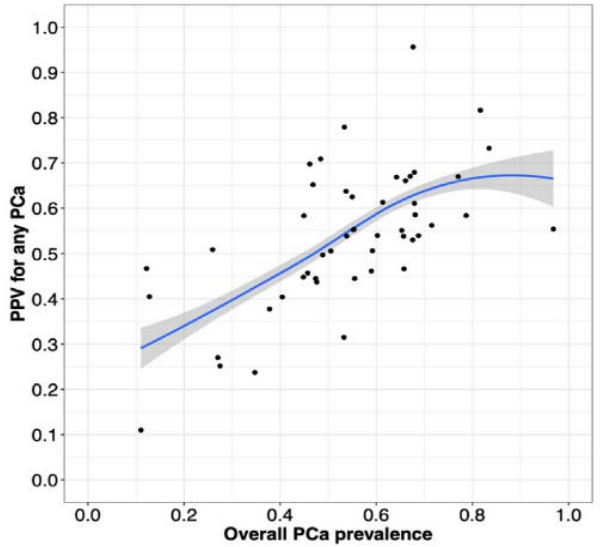
Sub-optimal specificity and PPV

Overall, 56 studies, with a total of 16, 537 participants, were included.
The PPV of suspicious mpMRI for csPCa was **40%** (95% CI: 36-43%), with large heterogeneity between studies (I^2 94%, $p < 0.01$).



PPVs for csPCa

- ✓ PI-RADS 3: 13%
- ✓ PI-RADS 4: 40%
- ✓ PI-RADS 5: 69%



Mazzone et al Eur Urol Oncol, 2021;4:697-713

Role of MRI for Clinical Diagnosis

1) MRI: Diagnosis

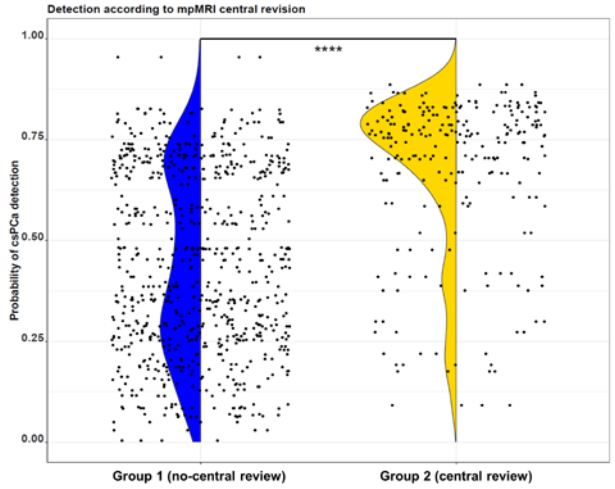
Experience matters: need for images revision

- ✓ 319 consecutive men with a positive mpMRI (PI-RADS≥3) who underwent a targeted biopsy (TBx) and a concomitant systematic biopsy at a single tertiary referral centre between 2018 and 2020
- ✓ All mpMRIs performed externally:116 (n=36%-Group 2) were reviewed by an experienced Radiologist

Initial PI-RADS Score	Revised PI-RADS Score				Total
	≤2	3	4	5	
≤2	0	0	0	0	0
3	29 (67%)	9 (21%)	5 (12%)	0 (0%)	43
4	15 (28%)	2 (4%)	36 (67%)	1 (2%)	54
5	1 (5%)	0 (0%)	0 (0%)	18 (95%)	19
Total	45	11	41	19	116

csPCa detection in Group 1 vs Group 2:

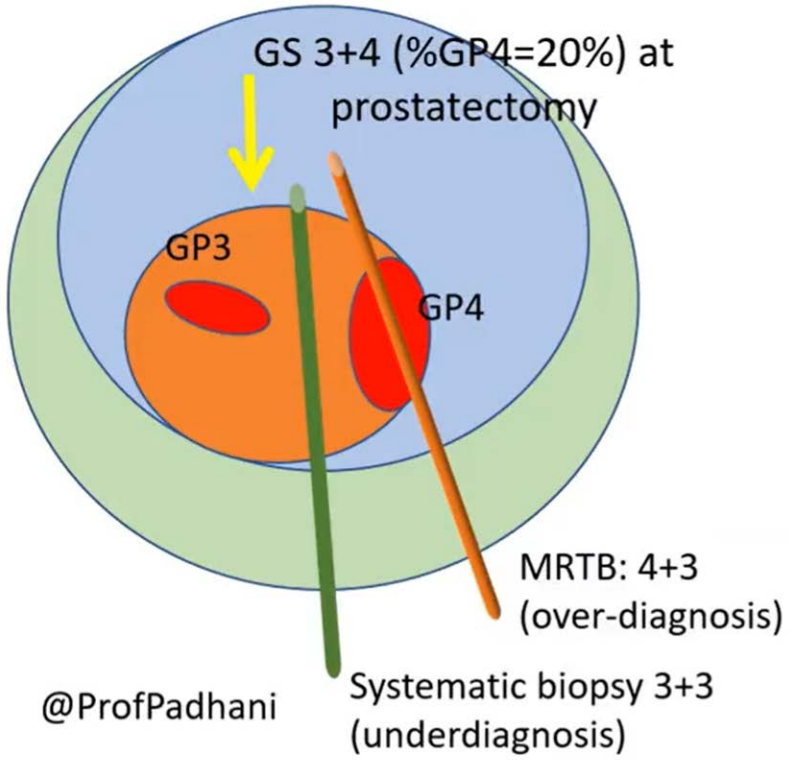
41% vs 63% (p=0.006).



Stabile et al, EAU Meeting 2021

MRI : reduced detection of ciPCa but... still issue of overgrading

Will-Rogers effect



Regional targeted biopsy (RTB) is a viable alternative to overcome grade migration bias

Regional targeted biopsies overcomes grade migration bias of targeted biopsies

RTB increases cores numbers but preserves the benefits of fewer -ve cores & GG1 detection

ISUP 2019: do not report highest GP in the target cores. Instead, aggregate GP for all +ve targeted cores (%GP4) to further mitigate grade migration

- Vickers A, et al. Routine Use of MRI for Early Detection of Prostate Cancer Is Not Justified by the Clinical Trial Evidence. Eur Urol. 2020 Sep;78(3):304-306.
- Padhani AR, et al. Platinum Opinion Counterview: The Evidence Base for the Benefit of MRI-directed Prostate Cancer Diagnosis is Sound. Eur Urol. 2020 Sep;78(3):307-309.
- van den Bergh RCN, & EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guidelines Panel. Prebiopsy MRI: Through the Looking Glass. Eur Urol. 2020 Sep;78(3):310-313.
- van Leenders GJLH, et al. The 2019 ISUP Consensus Conference on Grading of Prostatic Carcinoma. Am J Surg Pathol. 2020 Aug;44(8):e87-e99

Has MRI solved overdiagnosis?

- ✓ Data from 2 groups:
  - ✓ 999 men with negative systematic biopsy and concurrent MRI-targeted biopsy in the National Cancer Institute MRI study.
  - ✓ 3056 men followed for 11 yr after negative sextant biopsy in the European Randomized Trial of Screening for Prostate Cancer (ERSPC).

NND and NNT following targeted biopsy to prevent 1 Pca death at 11 year

	Base case with favorable assumptions for MRI	NAS for MRI properties and Tx effects	Extreme case of MP MRI properties and Tx effects	NAS for MRI properties, CAS for Tx effects
(A) Proportion of subsequent diagnoses avoided (%) [a]	75	67	100	67
Additional diagnoses associated with MRI [b]	1378	1453	1143	1453
(B) Proportion of cases subject to treatment (%) [a]	64	75	50	75
Additional treatments [c]	882	1090	571	1090
(C) Proportion of cancers detected by MRI in patients destined to die of prostate cancer (%) [a]	90	75	100	75
(D) Relative risk reduction for immediate Tx (%) [a]	75	50	100	25
Proportion of deaths avoided using MRI (%) [d]	68	37.5	100	18.8
Deaths avoided [e]	15.5	8.6	22.9	4.3
Number needed to diagnose [f]	89.1	169.1	49.9	338.3
Number needed to treat [g]	57.0	126.9	24.9	253.7

Vickers A, 80:567-72,2020

Imaging and prostate cancer staging : PSMA

Currently, PSMA PET-CT remains experimental

2015

5.3.5 Summary of evidence and guidelines for staging of prostate cancer

For patients with clinically localised high-risk prostate cancer, 77% of panellists voted to recommend PSMA PET and 23% voted not to recommend it. (Consensus for PSMA PET for high-risk disease).

2022

Recommendations	Strength rating
High-risk localised disease/locally advanced disease	
Perform metastatic screening including at least cross-sectional abdominopelvic imaging and a bone-scan.	Strong
When using PSMA PET or whole body MRI to increase sensitivity, be aware of the lack of outcome data of subsequent treatment changes.	Strong

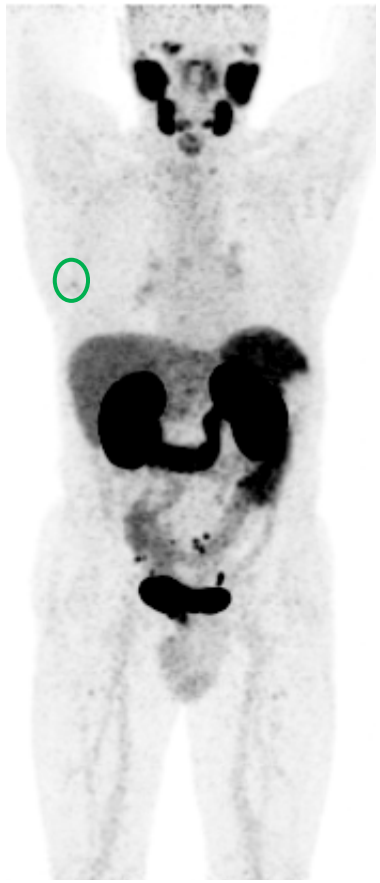
EAU Guidelines on prostate cancer
APCCC meeting, 2022

The real question is : what to do with a positive test?

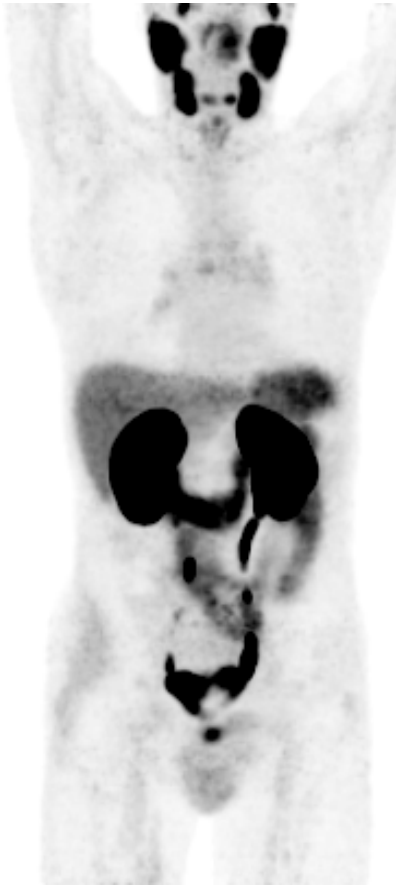
Do not undertreat the primary

	EVIDENCE (cN1)	EVIDENCE (oligo M+)
Treatment of the primary	Yes	Yes
Treatment of metastatic sites	Yes (?)	Not supported by level 1 evidence
Concomitant systemic treatment ADT alone ADT + ARTA ADT + chemotherapy	Offer RT + ADT +/- abiraterone Offer RP + long-term ADT	Offer ADT combined with prostate radiotherapy (RT) (using the doses and template from the STAMPEDE study) to patients whose first presentation is M1 disease and who have low volume of disease by CHAARTED criteria.

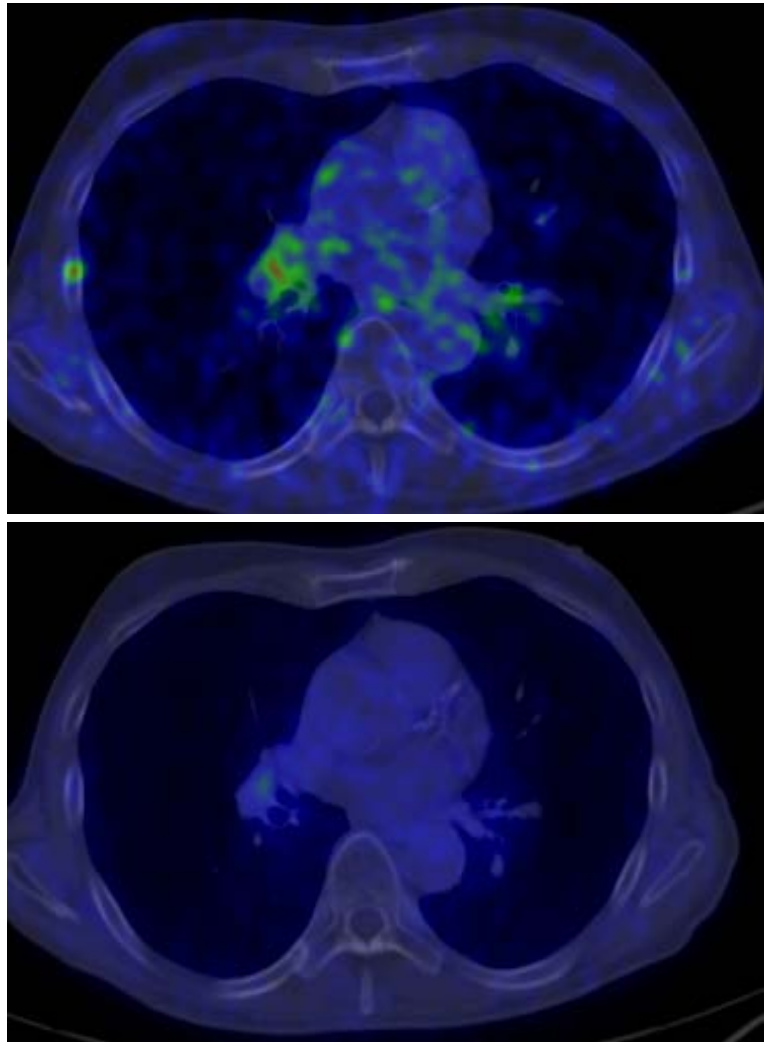
Role of PSMA PET for Staging in prostate cancer



STAGING PET



FOLLOW UP PET



By the courtesy of Prof. Fanti

Imaging and prostate cancer staging: recurrence

Currently, PSMA PET-CT remains experimental

2015

Recommendations	Strength rating
Prostate-specific antigen (PSA) recurrence after radical prostatectomy	
Perform prostate-specific membrane antigen (PSMA) positron emission tomography (PET) computed tomography (CT) if the PSA level is > 0.2 ng/mL and if the results will influence subsequent treatment decisions.	Weak
In case PSMA PET/CT is not available, and the PSA level is ≥ 1 ng/mL, perform fluciclovine PET/CT or choline PET/CT imaging if the results will influence subsequent treatment decisions.	Weak
PSA recurrence after radiotherapy	
Perform prostate magnetic resonance imaging to localise abnormal areas and guide biopsies in patients fit for local salvage therapy.	Weak
Perform PSMA PET/CT (if available) or fluciclovine PET/CT or choline PET/CT in patients fit for curative salvage treatment.	Strong

2022

EAU Guidelines on prostate cancer

The real question is : what to do with a positive test?

Study	N.	Nodal recurrence	Number of mets	Treatment arms	Type of treatment	Type of imaging	Median follow-up	Results
STOMP	62	55%	<3 extracranial	Observation vs. metastases-directed therapies	SBRT (n=25) sLND (n=6)	Choline PET/CT	5.3 years	Improved ADT-free survival (HR: 0.53; p<0.05)
ORIOLE	54	61%	≤3	Observation vs. metastases-directed therapies	SBRT	Conventional imaging (for study inclusion) + PSMA PET/CT	18.8 months	SBRT improved 6-month progression-free survival
SABR-COMET	16	NA	1-5	SOC vs. SOC + SABR	SBRT	Conventional imaging + PET	51 months	SBRT improved overall survival

ARE THESE ENDPOINTS STRONG ENOUGH FOR MEN WITH OVERALL LONG MEDIAN SURVIVAL ?

Only offer metastasis-directed therapy to M1 patients within a clinical trial setting or well-designed prospective cohort study.	Strong

Ost et al. GU-ASCO 2020
Phillips et al. JAMA Oncology 2020;6:650-9
Palma et al. J Clin Oncol 2020;38:2830-2838
EAU guidelines on prostate cancer, 2022

Combination treatments… what do the experts think? Results of the APCCC Meeting

For metachronous mHSPC that is low volume on NGI and nonmetastatic on conventional imaging:

67% of panel lists voted for MDT plus systemic therapy

15% for MDT only (without systemic therapy)

} Roughly 82% voted for MDT alone or in combination

18% for systemic therapy alone (including ADT). (No consensus for any answer option)

Gillessen et al, Eur Urol, in press 2022

Treatment (de) intensification in localized, high risk prostate cancer

RADIOTHERAPY → *TREATMENT INTENSIFICATION*

RT + 2/3 YEARS OF ADT

ADT + 3 YEARS OF ADT + 2 YEARS OF ABIRATERONE

Bolla M, et al. Lancet 2002;360:103-8
Hanks GE, et al. J Clin Oncol 2003;21:3972-78
Roach M, et al. J Clin Oncol 2003;21:1904-11
Attard et al. Lancet 2022;399:447.460

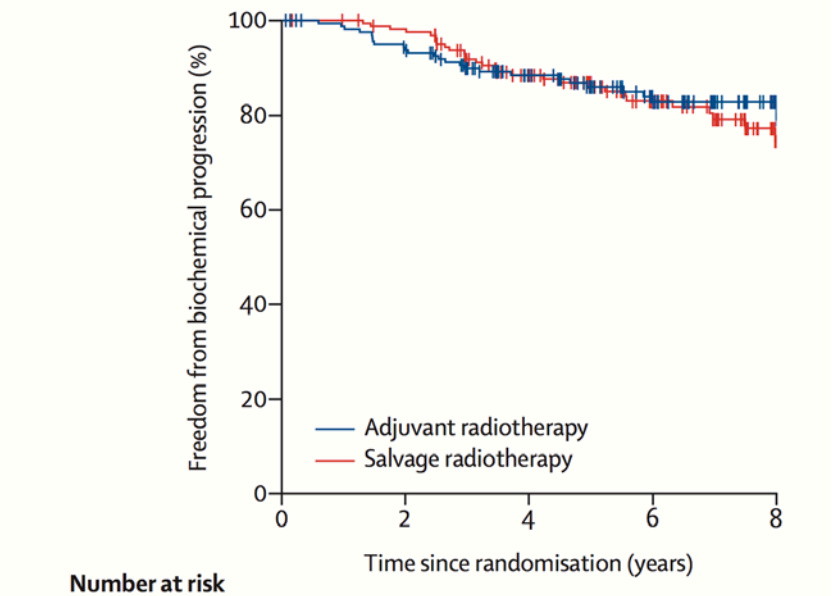
SURGERY → *TREATMENT DE-INTENSIFICATION*

NO INDICATION FOR PERI-OPERATIVE SYSTEMIC TREATMENT (EXCEPT FOR NODE POSITIVE DISEASE)

EARLY SALVAGE FAVOURED OVER ART

Is the era of aRT over?

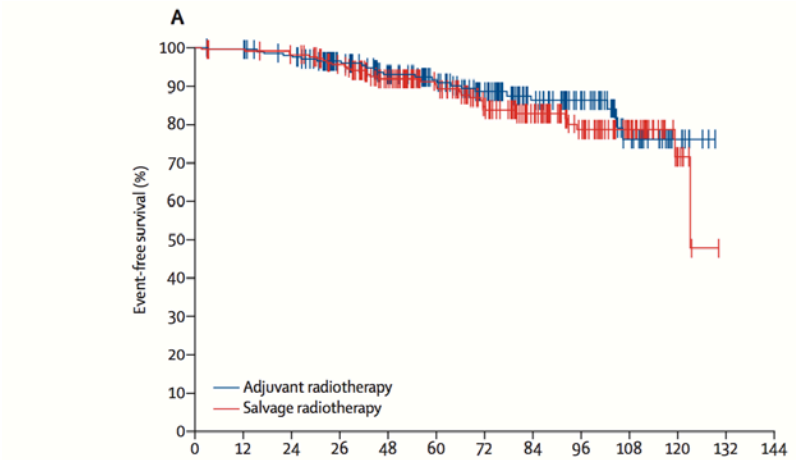
RAVES



Number at risk (number censored)					
Adjuvant radiotherapy	166 (0)	151 (5)	111 (37)	73 (71)	21 (120)
Salvage radiotherapy	167 (0)	160 (4)	119 (30)	76 (68)	21 (117)

Kneebone et al.
Lancet Oncol 2020;21:1331-40

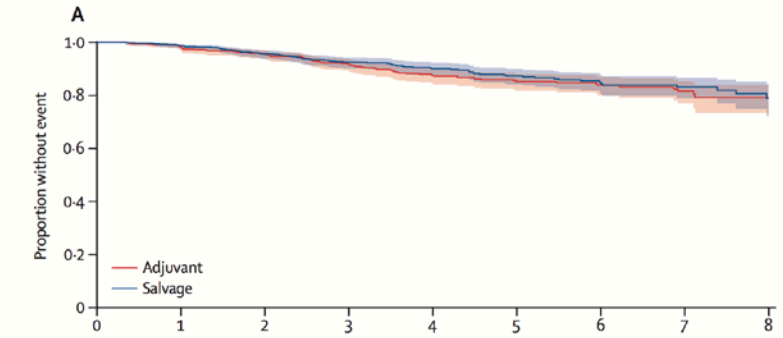
GETUG 17



Number at risk (number censored)							
Adjuvant radiotherapy	212 (0)	196 (12)	148 (51)	101 (92)	52 (139)	8 (179)	..
Salvage radiotherapy	212 (0)	203 (5)	158 (38)	105 (81)	54 (127)	8 (172)	..

Sargos et al.
Lancet Oncol 2020;21:1341-52

RADICALS-RT



Adjuvant									
At risk	697	650	596	470	361	239	154	82	36
Censored	0	35	73	176	266	380	462	531	575
Event	0	12	28	51	70	78	81	84	86
Salvage									
At risk	699	665	601	477	378	263	165	95	42
Censored	0	26	69	175	263	368	459	527	577
Event	0	8	29	47	58	68	75	77	80

Paker et al
Lancet. 2020;396:1413-1421

Is the era of aRT over? Patient Characteristics

	RADICALS-RT		GETUG-AFU 17		RAVES	
	Adjuvant radiotherapy	**Early salvage radiotherapy**	**Adjuvant radiotherapy**	**Early salvage radiotherapy**	**Adjuvant radiotherapy**	**Early salvage radiotherapy**
Patients randomised	697	699	212	212	166	167
Median follow-up, months	60 (range 2–132)	..	75 (range 0–130)	..	78 (range 1– 122)	..
Median age, years	65 (60–68)	65 (60–68)	64 (60–68)	64 (59–68)	64 (60–68)	64 (59–68)
Median preoperative PSA	7·8 (5·8–11·4)	8·0 (5·6–11·6)	Not available	Not available	7·4 (5·5–10·2)	7·4 (5·3–10·4)
Stage						
pT2	163 (23%)	176 (25%)	0	0	37 (22%)	39 (23%)
pT stage 3a/b	529 (76%)	519 (74%)	208 (99%)	206 (98%)	129 (78%)	128 (77%)
pT4	5 (1%)	4 (1%)	3 (1%)	5 (2%)	0	0
Gleason score						
≤6	48 (7%)	48 (7%)	21 (10%)	22 (10%)	8 (5%)	8 (5%)
7	537 (77%)	528 (76%)	173 (82%)	167 (78%)	132 (80%)	134 (80%)
≥8	112 (16%)	123 (17%)	17 (8%)	23 (11%)	26 (16%)	25 (15%)
Positive margins	439 (63%)	443 (63%)	211 (100%)	210 (100%)	110 (66%)	113 (68%)
Seminal vesicle involvement						
Yes	129 (19%)	132 (19%)	44 (21%)	46 (22%)	31 (19%)	33 (20%)
No	568 (81%)	567 (81%)	167 (79%)	165 (78%)	135 (81%)	134 (80%)
Unknown	0	0	1 (<1%)	1 (<1%)	0	0
Extracapsular extension						
Yes	492 (71%)	483 (69%)	212 (100%)	212 (100%)	129 (78%)	128 (77%)
No	205 (29%)	215 (31%)	0	0	37 (22%)	39 (23%)
Unknown	0	1 (<1%)	0	0	0	0
Lymph node involvement						
Involved	38 (5%)	28 (4%)	0	0	1 (1%)	0
Not involved	335 (48%)	374 (54%)	212 (100%)	212 (100%)	165 (99%)	167 (100%)
Nx	324 (47%)	297 (43%)	0	0	0	0

Only 1 out of 5 pts in RCTs have aggressive features!!

Vale et al. Lancet 2020, 396:1422-1431

Metastatic prostate cancer: 2012

12.12 Conclusions and guidelines for hormonal therapy in prostate cancer	LE
In advanced PCa, androgen deprivation therapy (ADT) delays progression, prevents potentially catastrophic complications, and palliates symptoms effectively, but does not prolong survival.	1b
In advanced PCa, all forms of castration used as monotherapy (e.g. orchiectomy, LHRH and DES) have equivalent efficacy.	1b
Non-steroidal anti-androgen monotherapy (e.g. bicalutamide) is an alternative to castration in patients with locally advanced disease.	2a
In metastatic PCa, the addition of a non-steroidal anti-androgen to castration (CAB) results in a small advantage in OS over castration alone, but is associated with increased adverse events, reduced QoL, and high costs.	1a
In metastatic PCa, ADT should only be offered to carefully selected patients.	2a
In advanced PCa, immediate ADT (given at diagnosis) significantly reduces disease progression, as well as the complication rate due to progression itself, compared with deferred ADT (delivered at symptomatic progression). However, the survival benefit is at best marginal and not related to cancer-specific survival.	1b
Bilateral orchiectomy might be the most cost-effective form of ADT, especially if initiated after the occurrence of symptoms from metastatic disease.	3

M1 asymptomatic	Immediate castration to defer progression to a symptomatic stage and prevent serious disease progression-related complications.	1b
	An active clinical surveillance protocol may be an acceptable option in clearly informed patients if survival is the main objective.	3

EAU guidelines on prostate cancer, 2012

Metastatic prostate cancer: 2022

Recomendations	Strength rating
Offer immediate systemic treatment with androgen deprivation therapy (ADT) to palliate symptoms and reduce the risk for potentially serious sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction) to M1 symptomatic patients.	Strong
Offer ADT combined with chemotherapy (docetaxel) to patients whose first presentation is M1 disease and who are fit for docetaxel.	Strong
Offer ADT combined with abiraterone acetate plus prednisone or apalutamide or enzalutamide to patients whose first presentation is M1 disease and who are fit enough for the regimen.	Strong
Offer ADT combined with prostate RT to patients whose first presentation is M1 disease and who have low volume by CHARTEED criteria.	Strong

De novo HSmPCA: new standards of care in 2022

De novo Hormone Sensitive mPCa^

ADT + Docetaxel^
ADT+ Abiraterone^^
ADT + Enzalutamide^^
ADT + Apalutamide^^
ADT + Docetaxel + Abiraterone ^^
ADT + Docetaxel + Darolutamide ^^
ADT+ Docetaxel + Enzalutamide ^^

^ All diagnosed by conventional imaging only !

^^ Pending approval in several countries

Proposed mHSPC Treatment Plans

Prognosis ADT Alone	Presentation of Metastases	Metastases Distribution	Main Plan Testo suppression +	Trials
Intermediate (4.5 yrs)	Synchronous	≤ 3 bone mets (+/- NRLN)	Abi/Enza/Apa plus Radiate Prostate	SBRT as MDT if oligometastatic
Poor (3 yrs)	Synchronous	≥ 4 bone mets and/or visceral mets	Abi/Daro/Enza + docetaxel or Abi/Enza/Apa	Trials with new agents
Good (8 yrs)	Metachronous	≤ 3 bone mets (+/- NRLN)	Abi/Enza/Apa	Add on SBRT New agents
Intermediate (4.5 yrs)	Metachronous	≥ 4 bone mets (visc mets: rare)	Abi/Enza/Apa	New agents (consider docetaxel)

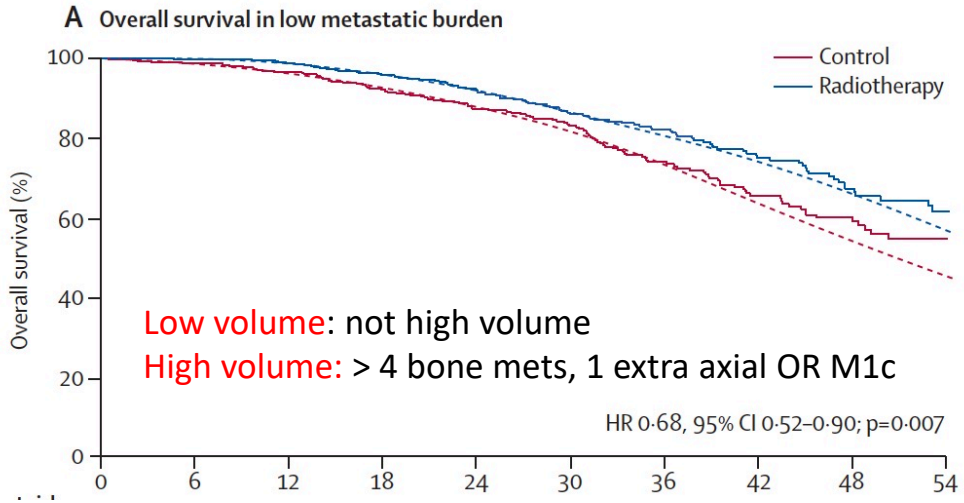
Dr Sweeney, EAU meeting 2022

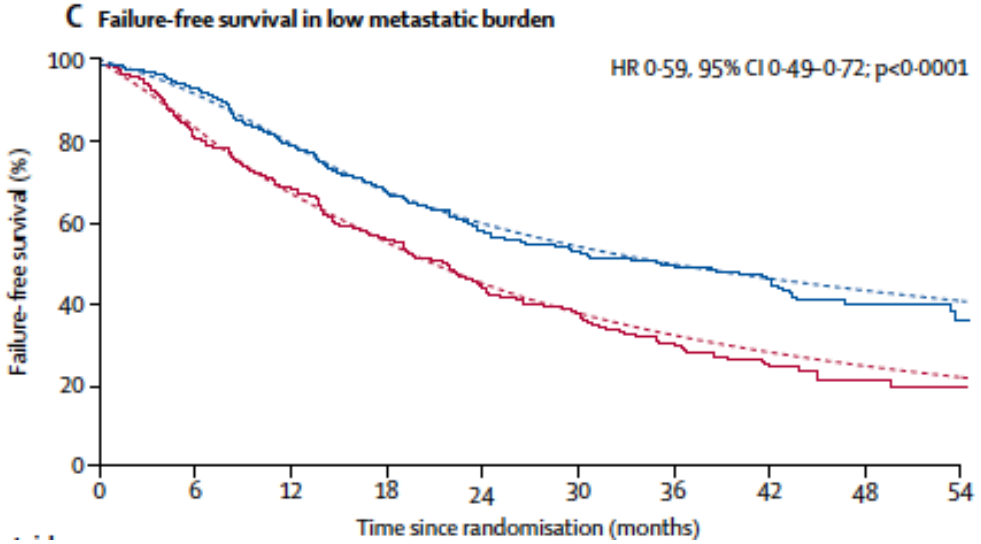
Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial

- ✓ Randomised controlled phase 3 trial: ADT / ADT + EBRT (prostate only) in 20161 men with de novo M+ disease at bone scan and soft tissue imaging done within 12 weeks of starting ADT.
  Overall, 18% received ADT + docetaxel and 89% were M1b

- ✓ RT was given with either 36 Gy in 6 weekly fractions or 55 Gy in 20 daily fractions

- ✓ Two pre-specified subgroup analyses tested the effects of RT by baseline M+ burden and RT schedule





Parker et al. Lancet 2018;392:2353-66

Surgery for oligo-M+ Pca - OSR

- ✓ First patient treated with cytoreductive RP on Oct 29th 2006 (I was there!)
- ✓ PSA: 36 ng/ml, Gleason 4-4, cT3, 4 positive spots at bone scan
- ✓ Recurred within 1 year after surgery

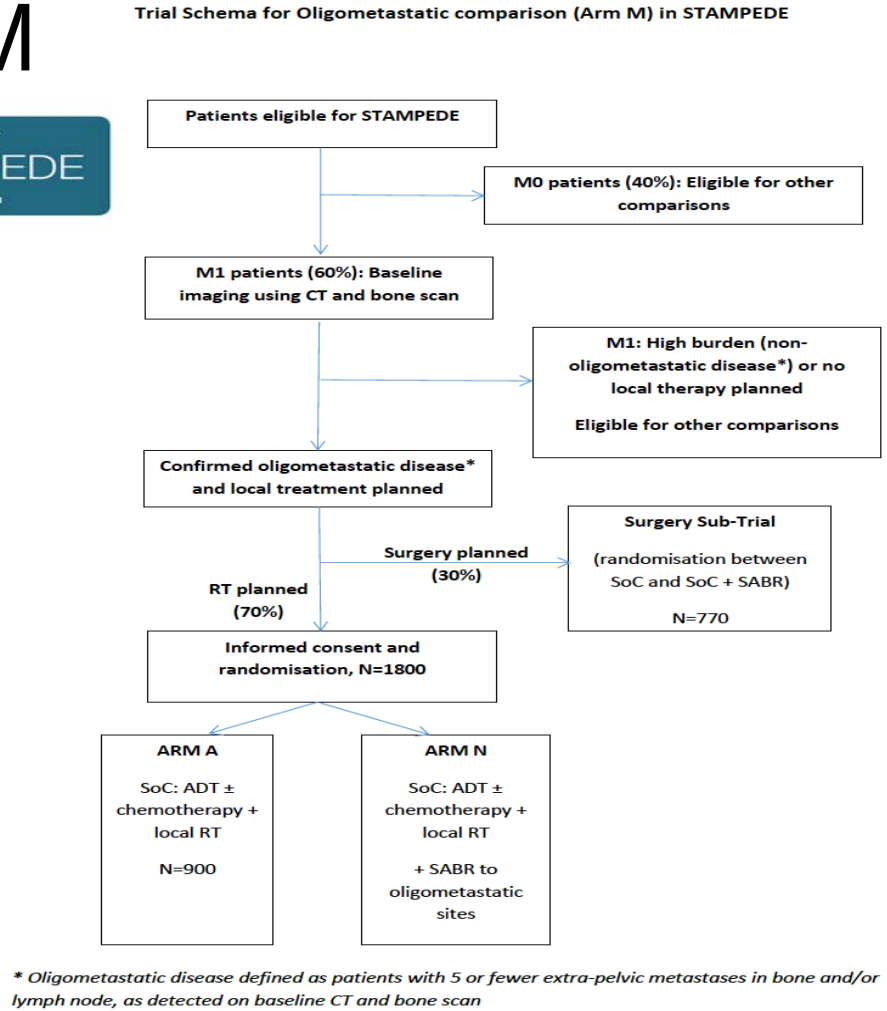
If someone criticizes what you do, then it means that you are doing a good job...

However, what to do with synchronous metastatic sites?

Future trials will need to answer to:

- ✓ Surgery vs radiotherapy
- ✓ Dfferent doses and volumes of RT
- ✓ Efficacy of ablative therapies
- ✓ Use of modern imaging
- ✓ Germline changing systemic therapies
- ✓ More information on tumor biology

Trial M



- ✓ Newly diagnosed oligo-metastatic prostate cancer
- ✓ Based on conventional imaging (Imaging sub-study)
- ✓ 5 or fewer extra-pelvic nodal/skeletal metastases
- ✓ All get standard care systemic therapy
- ✓ Choice of radiotherapy or surgery to the primary lesion
- ✓ SABR versus no SABR to the oligometastases

nmCRPC: new standards of care in 2022

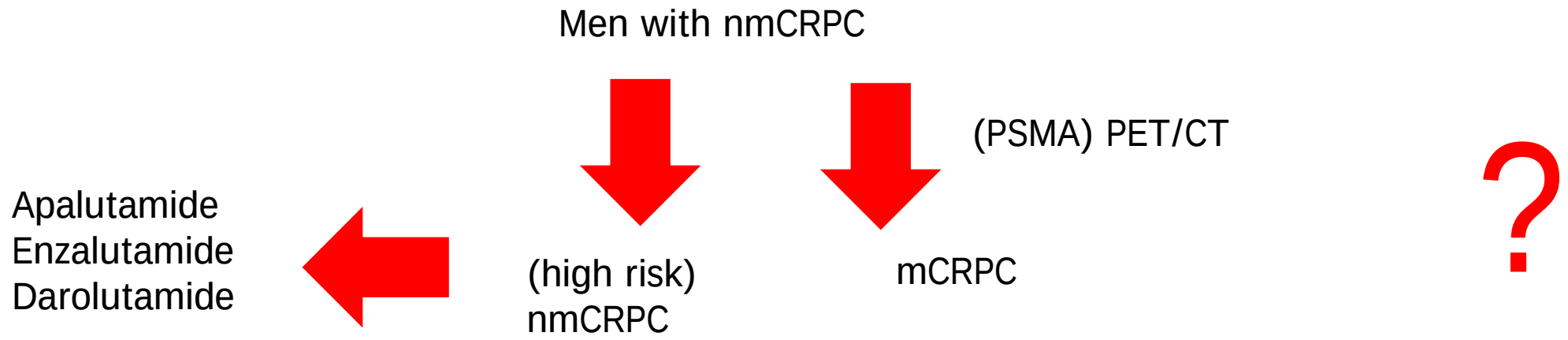
nmCRPC and
PSADT<=10 months

Apalutamide
Darolutamide
Enzalutamide

^ All at conventional imaging only !

What to do with a positive test?

Recommendations	Strength rating
Offer a prostate-specific membrane antigen positron-emission tomography (PSMA PET) scan to men with a persistent prostate-specific antigen > 0.2 ng/mL if the results will influence subsequent treatment decisions.	Weak



- ✓ Perform metastasis directed therapy in case of positive imaging in case of oligo-M+
- ✓ Treat the primary in case of negative imaging (low risk nmCRPC)
- ✓ Use information of imaging for disease prediction

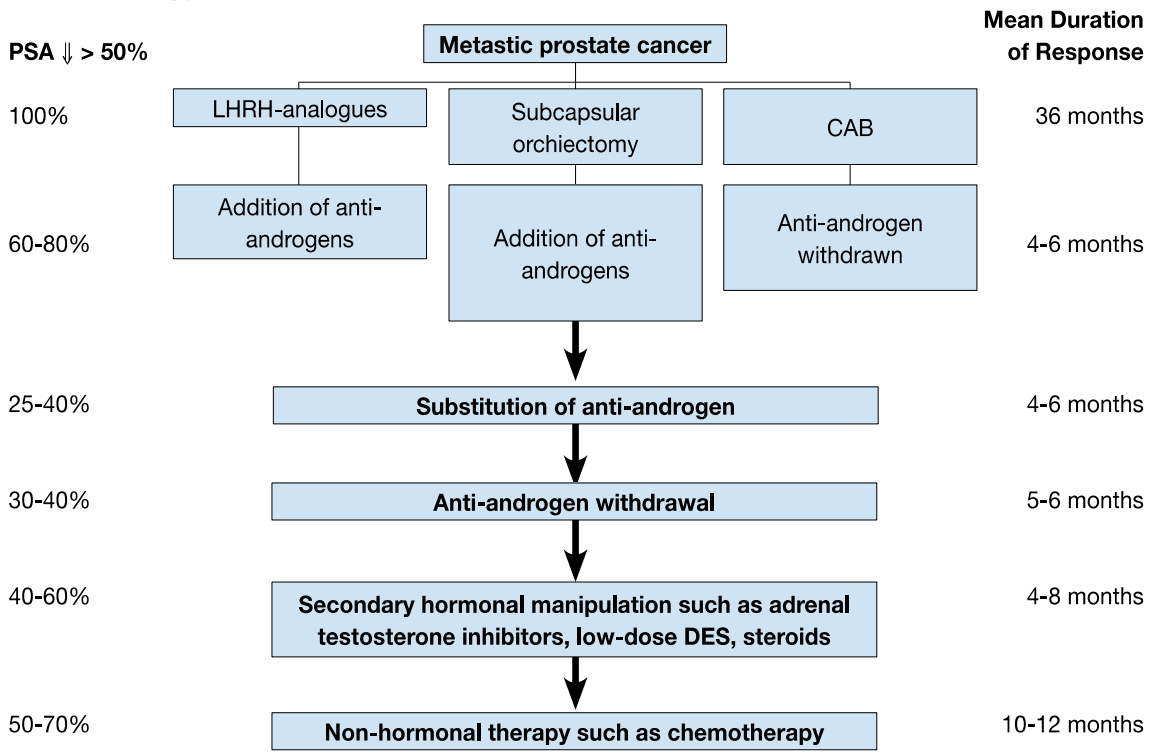
Consensus statements on the role of PSMA PET/CT in patients with prostate cancer

- ✓ Assess expert opinion regarding the use of PSMA-based imaging and therapy to develop interim guidance
- ✓ Twenty-one PCa expert panel members from various disciplines received thematic topics and relevant

Number	Round one (original phrasing)	Round two (rephrased)	Round one Median*	Round one consensus achieved	Round two Median*	Round two consensus achieved
4	PSMA PET/CT should be performed in nmCRPC patients	PSMA PET/CT should be performed in the majority of nmCRPC patients	5.5	Yes	5	Yes
5	PSMA PET/CT should be performed in any mCRPC patient to evaluate disease progression	PSMA PET/CT should be performed in the majority of mCRPC patients to evaluate disease progression	3	No	3	Yes

Fanti et al, Eur Urol Oncol, 2022

CRPC: 2012



Abiraterone and cabazitaxel recommended in men progressing after docetaxel

EAU guidelines on prostate cancer, 2012

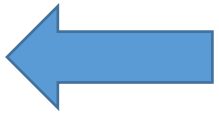
mCRPC: new standards of care in 2022

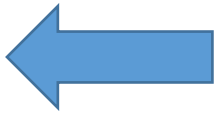
- Abiraterone
- Cabazitaxel
- Docetaxel
- Enzalutamide
- Olaparib
- Radium 223
- Sipuleucel-T
- Lu-PSMA-617

^ All at conventional imaging only !

CRPC

Recommendations	Strength rating
Base the choice of treatment on the performance status (PS), symptoms, co-morbidities, location and extent of disease, genomic profile, patient preference, and on previous treatment for hormone-sensitive metastatic PCa (mHSPC) (alphabetical order: abiraterone, cabazitaxel, docetaxel, enzalutamide, olaparib, radium-223, sipuleucel-T).	Strong
Offer patients with mCRPC who are candidates for cytotoxic therapy and are chemotherapy naive docetaxel with 75 mg/m^2 every 3 weeks.	Strong
Offer patients with mCRPC and progression following docetaxel chemotherapy further life-prolonging treatment options, which include abiraterone, cabazitaxel, enzalutamide, radium-223 and olaparib in case of DNA homologous recombination repair (HRR) alterations.	Strong
Base further treatment decisions of mCRPC on PS, previous treatments, symptoms, co-morbidities, genomic profile, extent of disease and patient preference.	Strong
Offer abiraterone or enzalutamide to patients previously treated with one or two lines of chemotherapy.	Strong
Avoid sequencing of androgen receptor targeted agents.	Weak
Offer chemotherapy to patients previously treated with abiraterone or enzalutamide.	Strong
Offer cabazitaxel to patients previously treated with docetaxel.	Strong
Offer cabazitaxel to patients previously treated with docetaxel and progressing within 12 months of treatment with abiraterone or enzalutamide.	Strong
Novel agents	
Offer poly(ADP-ribose) polymerase (PARP) inhibitors to pre-treated mCRPC patients with relevant DNA repair gene mutations.	Strong
Offer ^{177}Lu-PSMA-617 to pre-treated mCRPC patients with one or more metastatic lesions, highly expressing PSMA (exceeding the uptake in the liver) on the diagnostic radiolabelled PSMA PET/CT scan.	Strong





EAU guidelines on prostate cancer, 2022

CONCLUSIONS

- ✓ Significant steps forward have been made in different aspects of prostate cancer including diagnosis, staging and treatment

- ✓ Imaging has led to a real revolution in the diagnostic and staging processes but some important clinically meaningful questions are still unanswered

- ✓ The available treatment options for metastatic disease are multiple and based on high level of evidence. However, important questions on treatment sequencing and identification of the ideal candidate for each tretment need still to be addressed