

# The Future of APC Management

## *In Locally Advanced Prostate Cancer*

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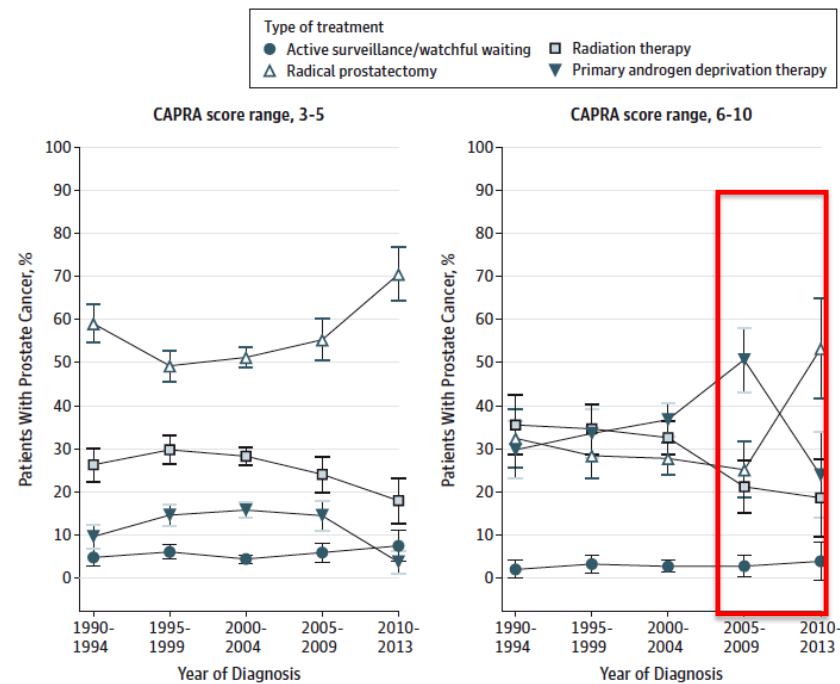
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# Thank you!

.....Absence of evidence is not evidence of absence...



Cooperberg et al, Jama, 314:80-82, 2015

# The Future of APC Management

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1. Intensification of tailored multi-modal approaches
2. Image-guided surgery
3. Novel tools to improve local control
4. Centralization of care

# Neoadjuvant Therapies in PCa... Back to the Future?

## Androgen Deprivation Therapies

Authors	Years	Neoadjuvant	Duration (months before RP)	Patients	Follow-up (months)	OS
Aus et al.	1991-1994	Triptorelin 3.75 mg + cyproterone acetate 50 mg	3	126	82	/, p= 0.5
Schulman et al.	1991-1995	Goserelin acetate 3.6mg + flutamide 250mg	3	402	48	95 vs. 93%, p= 0.64
Klotz et al.	1993-1994	Cyproterone acetate 300mg	3	213	72	93.9 vs. 88.4%, p= 0.38
Soloway et al.	1992-1994	Leuprolide 7.5mg + flutamide 250mg	3	282	60	/
Yee et al.	1992-1996	Goserelin acetate 3.6mg + flutamide 250mg	3	148	96	/

*Bandini et al. Expert Rev Clin Pharmacol 2018;11:425-38*

**2019 EAU Guidelines on PCa:** *Do not offer neoadjuvant androgen deprivation therapy before surgery*

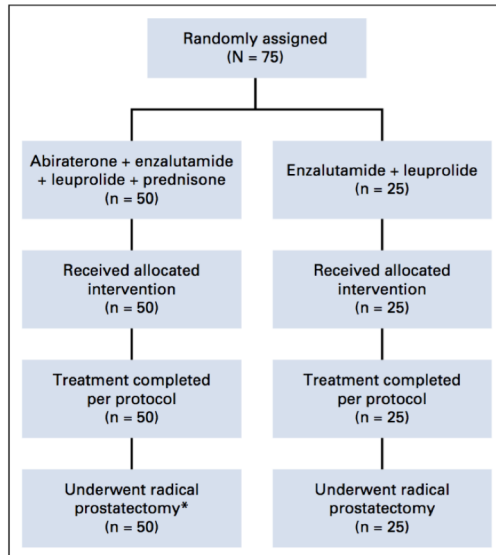
# Novel Neoadjuvant Therapies in PCa... Available Data

Study	Study design	Patient characteristics	Treatment arms	N. Of men	Outcomes
Efstathou et al 2019	RCT, Phase II	Gleason score 8–10 on biopsy or Gleason score 7 $\geq$ T2b PSA>10ng/ml	Abiraterone + LHRHa vs. LHRHa alone	65	Neoadjuvant AA reduced PSA levels. No impact on the
McKay et al. 2019	RCT, Phase II	Gleason score of 4 + 3 = 7 or greater, PSA>20 ng/mL, or T3 disease by mpMRI	Enzalutamide and leuprolide with or without AA	75	The neoadjuvant AA reduced PSA levels or minimal residual disease in ELAP-treated patients. In ELAP-treated patients, PSA levels, positive margins, and lymph nodes were similar
Taplin et al.	RCT, Phase II	Localized high-risk PCa		58	The levels of intraprostatic androgens from 12-week prostate biopsies were significantly lower with LHRHa plus AA compared with LHRHa alone. Prostatectomy pathologic staging demonstrated a low incidence of complete responses and minimal residual disease, with residual T3- or lymph node-positive disease in the majority
Thalgott et al. 2014	Phase II	High-risk PCa	Buserelin, bicalutamide and 3 cycles of docetaxel	30	Post- vs. pretreatment MRI indicated a median tumor volume reduction of 46.4% (-31.3-82.8; p < 0.001). A pathological downstaging was observed in 48.3%
Zhao et al 2015		Locally advanced	6 weekly doses of docetaxel	28	At a median follow-up of 130 months, 10 patients (36%) remained alive and disease free clinically and biochemically with no additional therapy, whereas 18 patients (64%) had BCR

Phase 2 trials, limited number of patients  
Pathological/imaging endpoints still needs to be correlated with clinical outcomes

# Neoadjuvant Therapies in PCa... Back to the Future?

- ✓ Phase II randomized trial (2:1): neoadjuvant **enzalutamide and leuprolide** (EL) with or without **abiraterone and prednisone** (ELAP) before RP in 75 men with locally advanced prostate cancer
- ✓ The pathologic complete response or minimal residual disease rate was **30%** (n= 15 of 50) in ELAP-treated patients and **16%** (n= 4 of 25) in EL-treated patients (P=0.26)
- ✓ Tumor **ERG positivity** and **PTEN loss** were associated with more extensive residual tumors at RP. Tumors with dual ERG positivity and PTEN loss had the highest RTV compared with tumors with no or a single alteration



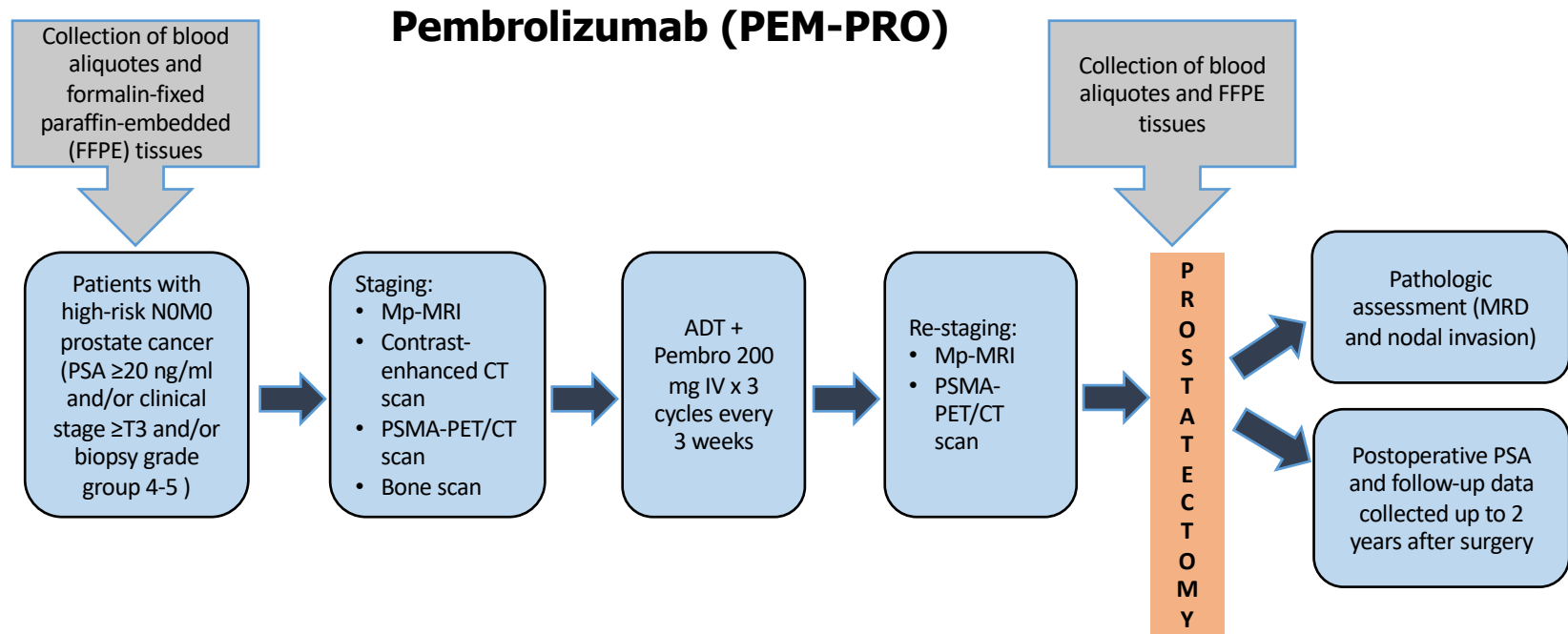
Variable	ELAP, No. (%)	EL, No. (%)
No. of patients	50	25
ypT stage		
T0	5 (10)	2 (8)
T2	20 (40)	9 (36)
T3a	16 (32)	7 (28)
T3b	9 (18)	7 (28)
Pathology N stage		
N0	45 (90)	22 (88)
N1	5 (10)	3 (12)
Positive surgical margins		
No	41 (82)	22 (88)
Yes	9 (18)	3 (12)
Extracapsular extension		
No	27 (54)	12 (48)
Yes	23 (46)	13 (52)
Positive seminal vesicle invasion		
No	41 (82)	18 (72)
Yes	9 (18)	7 (28)
Pathologic response		
pCR	5 (10)	2 (8)
MRD ( $\leq 5$ mm)*	10 (20)	2 (8)
pCR or MRD	15 (30)	4 (16)
Downstaging	3 (6)	1 (4)
Stable staging	10 (20)	5 (20)
Upstaging	21 (42)	15 (60)
Unevaluable†	1 (2)	—
Median total tumor volume, mL (range)	0.6 (0-10.4)	0.8 (0-10.1)
Median cellularity, % (range)	5 (0-60)	7 (0-50)
Median RCB, cm <sup>3</sup> (range)	0.03 (0-4.0)	0.05 (0-5.0)

McKay et al. *J Clin Oncol* 2019;37:923-31

## Ongoing Trials :Novel Molecules in the Neoadjuvant Setting

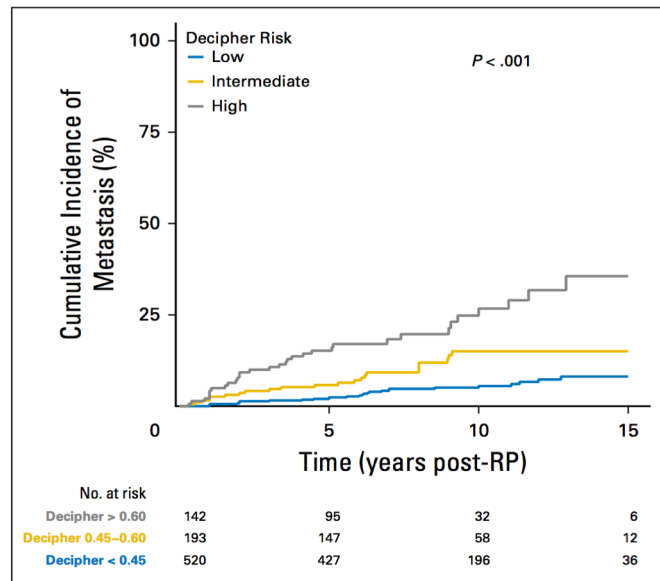
Study ID	Study	Drug	Phase
NCT01547299	Study of Enzalutamide (Formerly MDV3100) as a Neoadjuvant Therapy for Patients Undergoing Prostatectomy for Localized Prostate Cancer	Enzalutamide	II
NCT02789878	Neoadjuvant Androgen Deprivation Therapy Plus Abiraterone With or Without Apalutamide for High- Risk Prostate Cancer	Goserelin, Prednisone, Abiraterone, Apalutamide	II
NCT02643667	A Study of Ibrutinib as Neoadjuvant Therapy in Localized Prostate Cancer	Ibrutinib	I/II
NCT02849990	A Phase II Neoadjuvant Study of Apalutamide, Abiraterone Acetate, Prednisone, Degarelix and Indomethacin in Men With Localized Prostate Cancer Pre-prostatectomy	Abiraterone Acetate, Apalutamide, Degarelix, Indomethacin, Prednisone	II
NCT03258320	Cabazitaxel, Docetaxel, Mitoxantrone or Satraplatin (CDMS) Plus Surgery for Prostate Cancer Patients Without Metastasis	Cabazitaxel, Docetaxel, Mitoxantrone or Satraplatin	I
NCT02903368	Neoadjuvant And Adjuvant Abiraterone Acetate + Apalutamide Prostate Cancer Undergoing Prostatectomy	Apalutamide, Leuprolide, Prednisone, Abiraterone Acetate	II
NCT01804712	Rituximab Neoadjuvant Therapy in Patients With Prostate Cancer Scheduled to Undergo Radical Prostatectomy	Rituximab	I
NCT01990196	Neoadjuvant Phase 2 Study Comparing the Effects of AR Inhibition With/Without SRC or MEK Inhibition in Prostate Cancer	Degarelix, enzalutamide, trametinib, dasatinib	II
NCT03080116	Neoadjuvant Degarelix +/- Apalutamide (ARN- 509) Followed by Radical Prostatectomy for Intermediate and High-risk Prostate Cancer: a Randomized, Placebo-controlled Trial	ARN-509, Degarelix	II
NCT01832259	A Study of VEGF Tyrosine Kinase Inhibitor (Pazopanib) in Men With High-Risk Prostate Cancer Followed by Radical Prostatectomy and Pelvic Lymph Node Dissection	Pazopanib	II
NCT02324998	Studying the Effects of Olaparib ( $\pm$ Degarelix) Given to Men With Intermediate/High Risk Prostate Cancer Before Radical Prostatectomy (CaNCaP03)	Olaparib +Degarelix	I
NCT03767244	A Randomized, Double-blind, Placebo-controlled, Phase 3 Study of Apalutamide in Subjects With High-risk, Localized or Locally Advanced Prostate Cancer Who Are Candidates for Radical Prostatectomy	Apalutamide + ADT	iii
NCT00430183	Surgery With or Without Docetaxel and Leuprolide or Goserelin in Treating Patients With High-Risk Localized Prostate Cancer	Docetaxel + ADT	III

# Neoadjuvant Therapies: Ongoing Trial at OSR



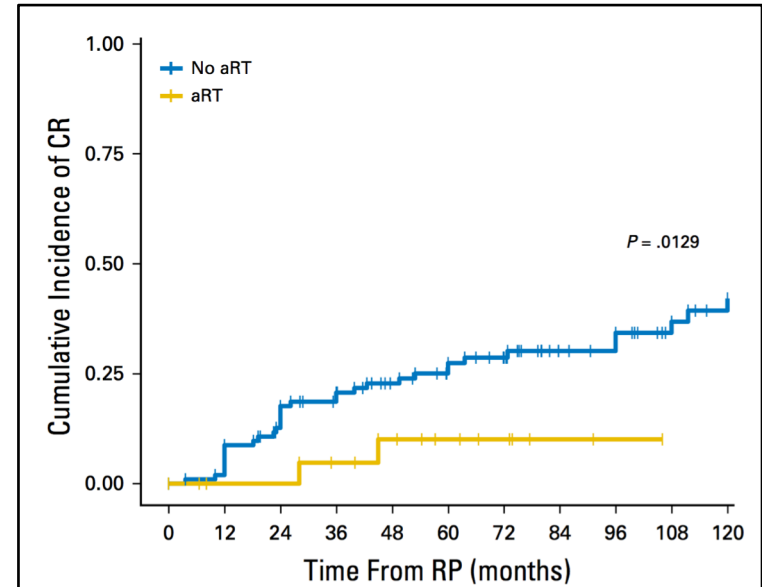
- ✓ **PD-L1 expression** will be evaluated on the hotspot region of the tumor slide
- ✓ Genomic profiling will be performed with a hybrid capture-based next-generation sequencing assay
- ✓ In matched pre-pembrolizumab and post-pembrolizumab samples, we will investigate the expressions of genes—*CCL2*, *CCL7*, *CCL8*, *IL10*, *VEGFA*, and *VEGFC*—that belong to the signature of innate resistance to anti-PD-1 therapy

# Adjuvant Therapies: Decipher to Select Ideal Candidates for RT



- ✓ Decipher is an independent predictor of metastases after adjusting for other variables (c-index: 81%)
- ✓ Decipher can assist physicians in the decision making after RP

*Spratt et al. J Clin Oncol 2017;35:1991-98*



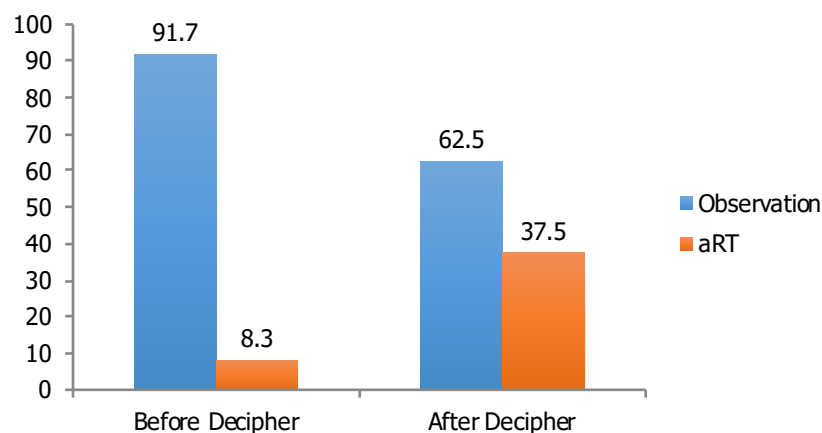
- ✓ Predictors of CR: T3b/T4; Gleason score 8-10; LNI and **Decipher score >0.6**
- ✓ aRT was associated with decreased CR rate in patients with  $\geq 2$  risk factors

*Dalela et al. J Clin Oncol 2017;35:1982-90*

# Genomic-driven Adjuvant Therapies: Prospective Trials

## PRO-IMPACT

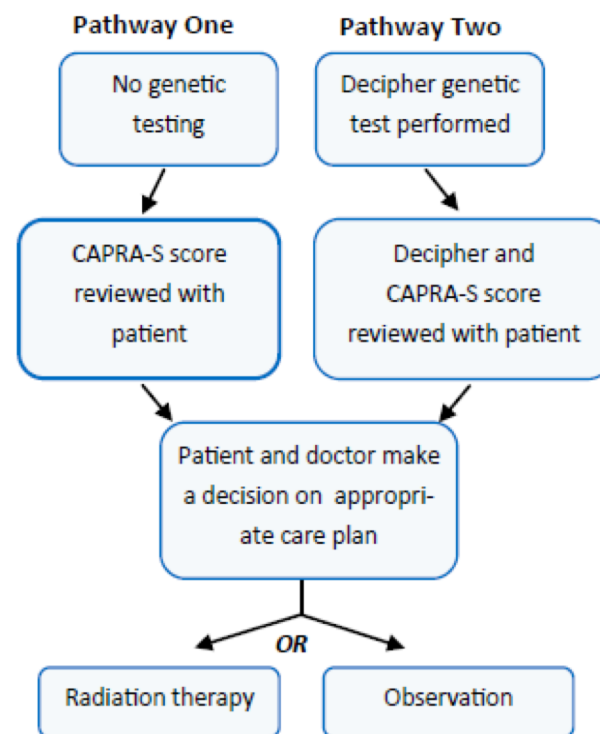
### Change in Treatment Plan



- ✓ Prospective decision impact study
- ✓ Evaluation of the clinical utility of Decipher for the administration of postoperative therapies

*Gore et al. Cancer 2017;123:2850-9*  
*Clinicaltrial.gov: NCT02080689*

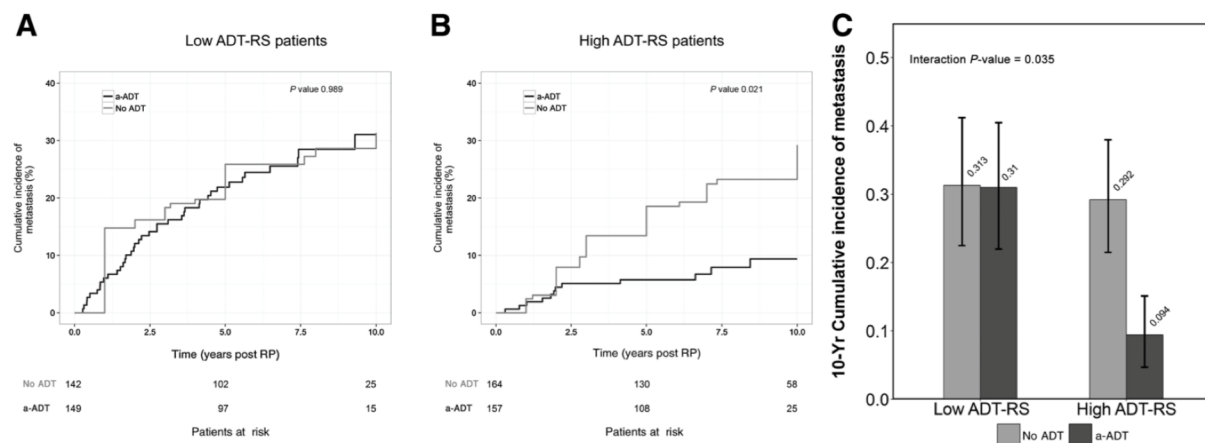
## G-MINOR (Ongoing)



*Morgan et al. J Clin Oncol 2018;TPS154*  
*Clinicaltrial.gov: NCT02783950*

# Adjuvant Therapies: Genomic Signatures to Select Candidates for ADT

- ✓ An ADT Response Signature (ADT-RS) was identified from neuroendocrine and AR signaling–related genes
- ✓ Hypothesis: a score created from gene expression patterns of may serve as an early marker of androgen resistance
- ✓ Patients with Low ADT-RS scores had similar 10-year metastasis in the a-ADT and no-ADT groups
- ✓ Among High ADT-RS patients, 10-year metastasis rates were significantly lower for a-ADT versus no-ADT patients (9.4% vs. 29.2%,  $P=0.02$ )



Karnes et al. Clin Cancer Res 2018;24:3908-16

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# PSMA PET/CT Will Not Replace an Anatomically Defined ePLDN

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- ✓ Assessment of the sensitivity, specificity, and positive and negative predictive values of preoperative PSMA PET/CT to identify LNI in 208 consecutive men who received PLND at RP
- ✓ Of the 143 men with no suspicious nodes at PSMA imaging, 34 had LNI for 80.8% negative predictive value (Specificity: 93.5%; PPV:67.7%)
- ✓ For the 172 histologically identified LNI the sensitivity per node was 24.4%

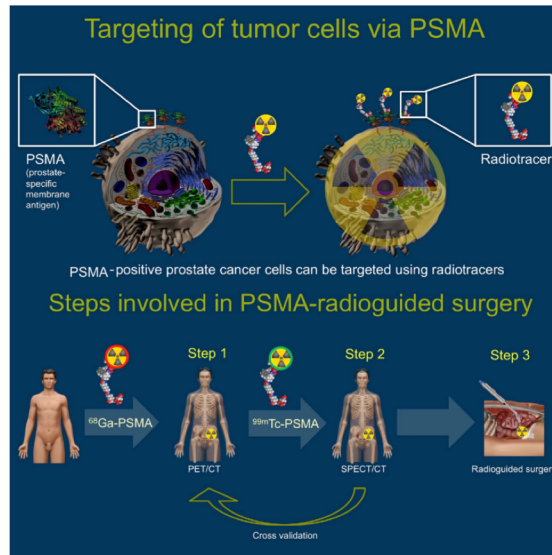
	Per patient	Per node
Sensitivity	38.2%	24.4%
Specificity	93.5%	99.5%

*Yaxley et al. J Urol 2019;201:815-20*

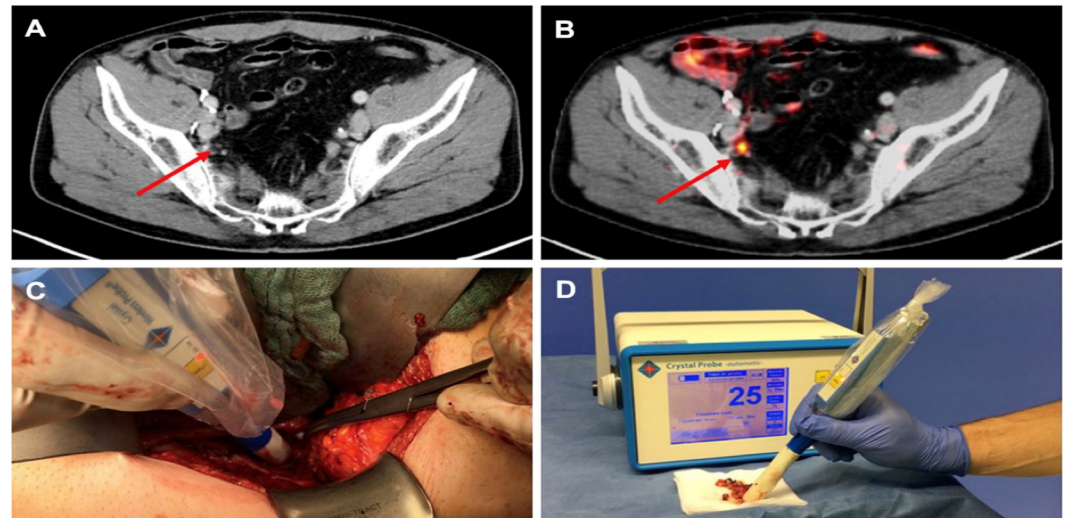
Diameter of nodal mets	Detection rate at PSMA	Prevalence at ePLND
<2	0%	20%
2-5	60%	40%
>5	86%	40%

*Van Leeuwen et al. BJU Int 2017;119:209-15*  
*Briganti et al. Unpublished data*

# Potential Role of Radio-guided Surgery in Prostate Cancer



*Maurer et al. Eur Urol 2019;75:659-66*



*Rauscher, Maurer et al. World J Urol 2018;36:603-8*

- ✓ Compared to  $^{68}\text{Ga}$ -PSMA PET, PSMA-RGS was able to detect **additional suspicious lesions** in 7/60 patients (11.7%) with BCR
- ✓ In 14 of our 60 patients (23.3%) histology showed additional metastatic specimens in comparison to  $^{68}\text{Ga}$ -PSMA PET or PSMA-RGS... still some micrometastatic false negatives...

# Radio-guided Surgery in Prostate Cancer: Ongoing Trial at OSR

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## STUDY PROCEDURES: initial EPLND

	Week before surgery	Day before surgery	Additional Procedures during RP
<b>68Ga-PSMA PET/MRI</b>	<b>X</b>		
<b>Administration of 99mTc-PSMA-I&amp;S</b>		<b>X</b>	
<b>99mTc-PSMA-I&amp;S SPECT/CT imaging</b>		<b>X</b>	
<b>PSMA RGS</b>			<b>X</b>

*Funded by Italian Health Ministry and the Intuitive Surgery Clinical Grant*

# The Future of APC Management

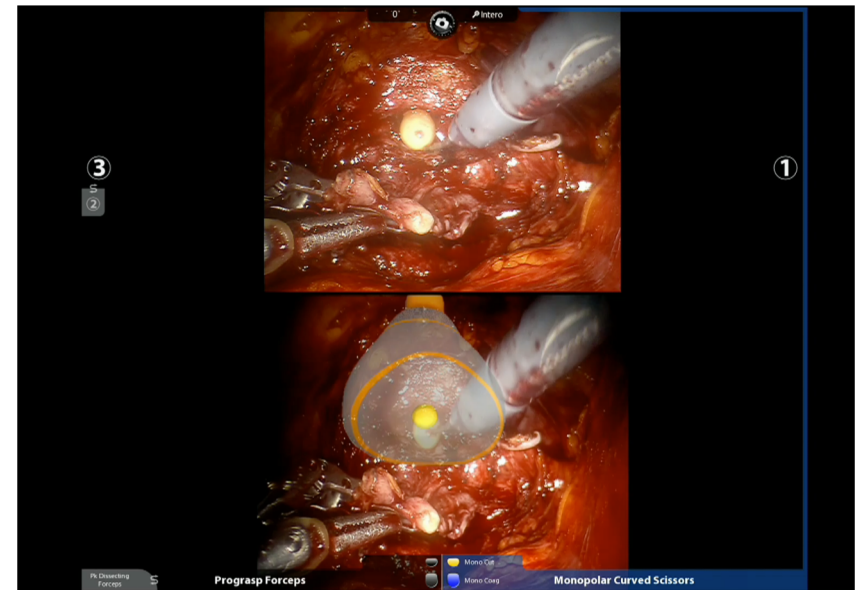
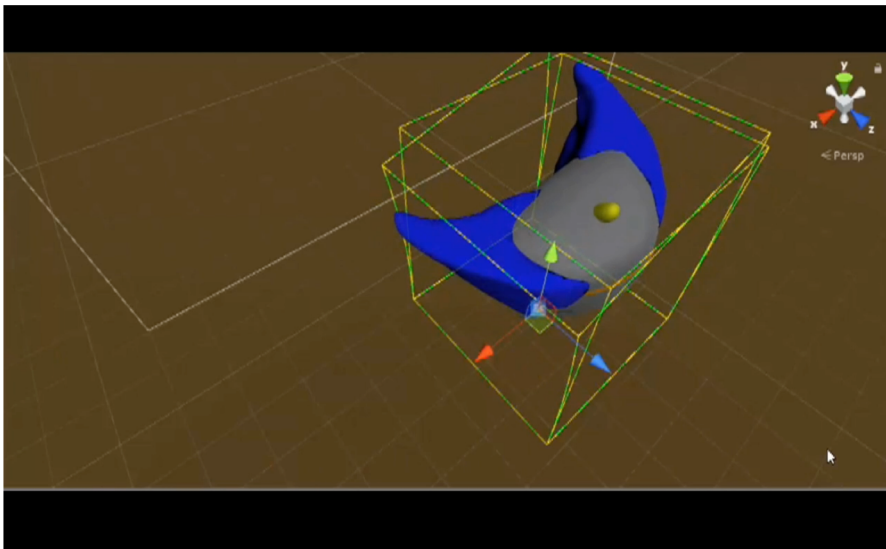
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# Three-dimensional Elastic Augmented-reality RARP using Hyperaccuracy Three-dimensional Reconstruction Technology

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- ✓ Novel system to identify capsular involvement (CI) in nerve-sparing RARP
- ✓ 20 vs. 20 patients underwent 3D-AR RARP vs. 2D cognitive reconstruction
- ✓ All patients had mpMRI visible lesions



*Porpiglia et al. Eur Urol 2019; in press*

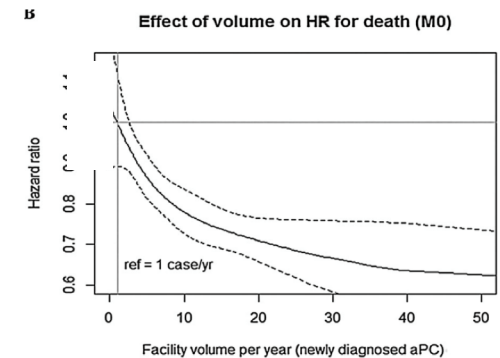
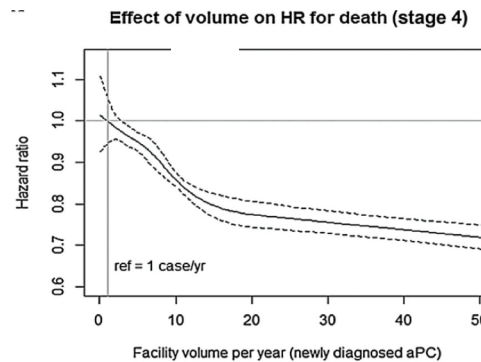
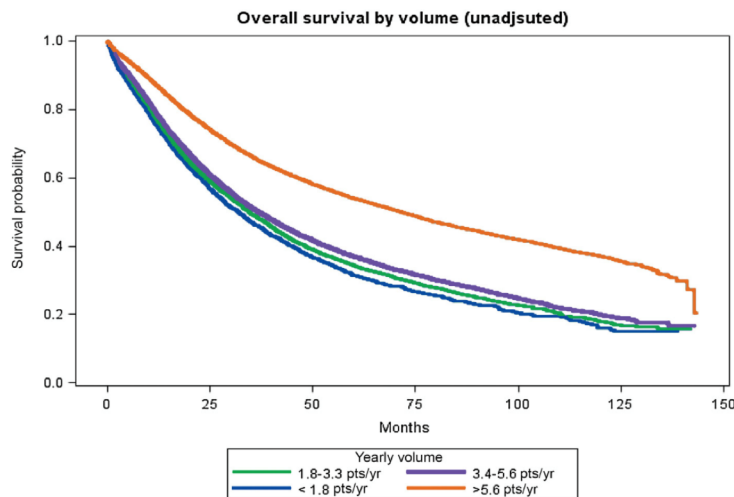
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# Impact of Dedicated (High-volume) Centers on Survival

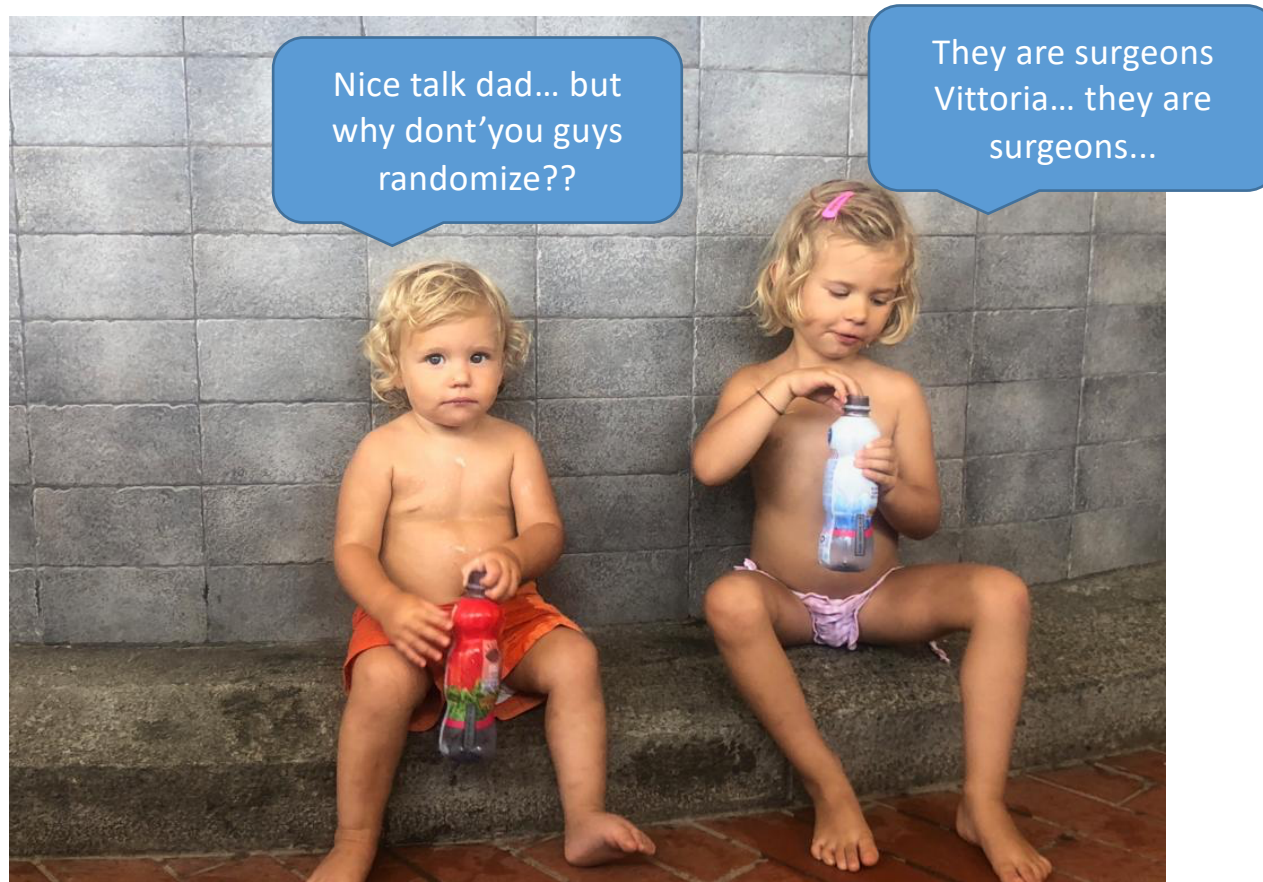
- ✓ The National Cancer Database (NCDB) was queried from 2004 to 2013 for aPC, defined as T4, N+, or M+ disease, identifying 64,815 patients
- ✓ OS improved as facility volume increased (top quartile vs bottom quartile, hazard ratio 0.82, 95% CI:0.77–0.88,  $p < 0.001$ ) and was consistent across patient cohorts
- ✓ Spline models demonstrate a continuous decrease in hazard of death as volume increases



Joshi et al. Eur Urol Oncol 2019; in press

# The Future of APC Management: bright if...

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# The Future of APC Management: SPCG-15

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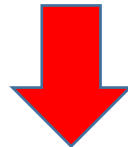
Patients with high risk Pca randomized to



RP + ePLND +/- adjuvant RT  
(with 2 years of bicalutamide)



EBRT +/- HDR-BT + 6 months  
of peri-operative MAB + 18  
months of bicalutamide/ADT



CSS

(currently ongoing: 400/1200 men)