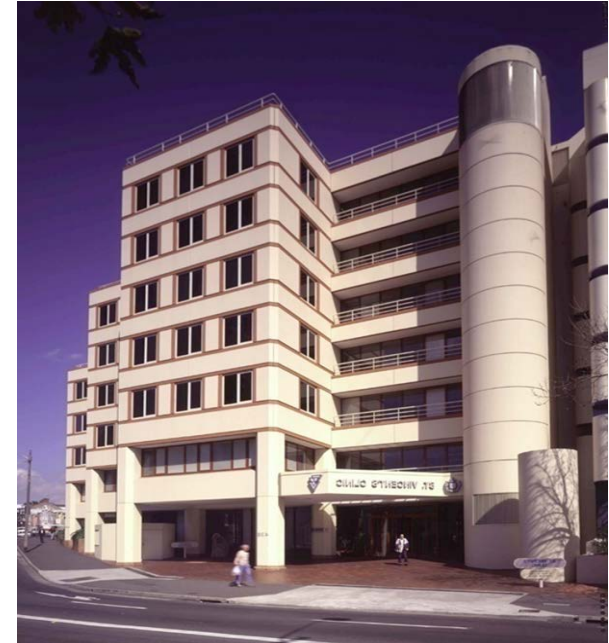


# High Risk PC – What's New

Prof. Phillip D Stricker



High Risk  
PC –  
What's  
Best

- RP + eLND + Adj RT + H
- Brachy + WPRT + H
- Clinical Trial – NeoAdj or Adj



# Factors in Decision

- SURGERY
- Age & Fitness
- Likely SM –ve
- SV ++
- LUTS
- Large Prostate
- Bulky Nodes
- RADIOTHERAPY
- Apex ++
- Complex Pelvis
- Older
- Small Nodes
- Fear of Incontinence

Platinum Priority – Review – Prostate Cancer

*Editorial by Martin Spahn, Alan Dal Pra, Daniel Aebbersold and Bertrand Tombal on pp. 31–32 of this issue*

## **Surgery Versus Radiotherapy for Clinically-localized Prostate Cancer: A Systematic Review and Meta-analysis**

Christopher J.D. Wallis<sup>a,b,c</sup>, Refik Saskin<sup>c,d</sup>, Richard Choo<sup>e</sup>, Sender Herschorn<sup>a,b</sup>, Ronald T. Kodama<sup>a,b</sup>, Raj Satkunasivam<sup>a,b</sup>, Prakesh S. Shah<sup>c,f,g</sup>, Cyril Danjoux<sup>h</sup>, Robert K. Nam<sup>a,b,c,\*</sup>

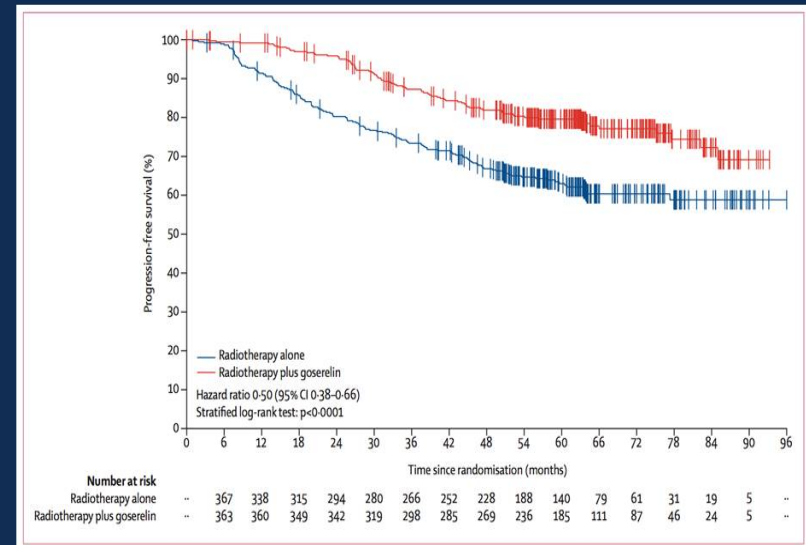
- Meta-analysis
- 19 studies; n = 118.830
- Including < 10y and > 10y follow-up and low-quality studies

## Results

- Risk of overall mortality and PCa-specific mortality higher for RT than surgery (aHR 1.63, p < 0.00001 cq. aHR 2.08, p < 0.00001)

# Salvage Radiotherapy: GETUG-AFU 16

- Rising PSA 0.2-2.0ng/ml
- Post-RP
- No evidence of disease
- Salvage IMRT/3D CFRT
- 66 Gy in 33 fractions
- $\pm$  ADT

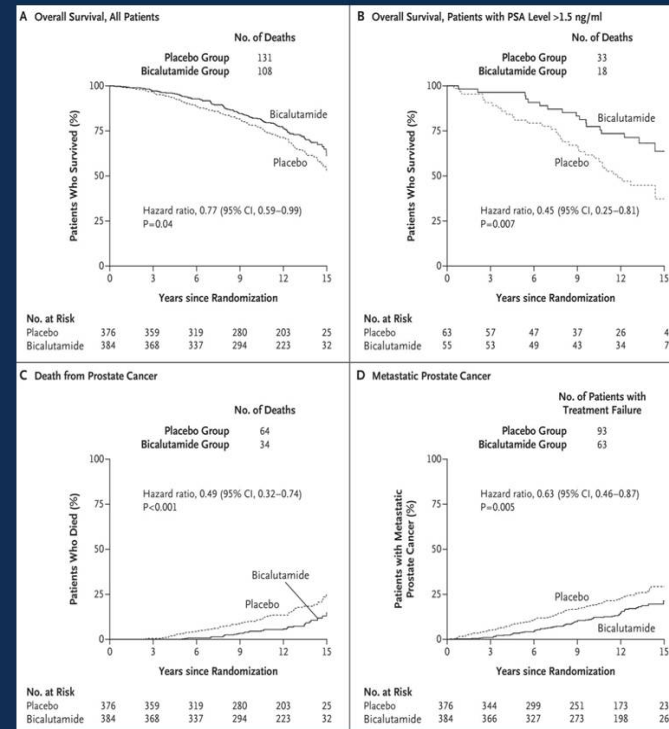


*Lancet Oncol* 2016; 17: 747–56

# Salvage Radiotherapy: RTOG 9601

- Rising PSA 0.2-4.0ng/ml
- Post-RP: T2/T3 N0M0
- Salvage IMRT/3D CFRT
- 66 Gy in 33 fractions
- **760 men**
- $\pm$  Bicalutamide/Placebo

*N Engl J Med* 2017; 376:417-428



PRESENTED AT: **2017 Genitourinary Cancers Symposium | #GU17**

*Slides are the property of the author. Permission required for reuse.*

Presented by:

Presented By James Catto at 2017 Genitourinary Cancers Symposium



**Table 2 – Treatment framework based on pre-RT PSA, grade group, and margin status**

Margin status	ISUP grade group (Gleason score)	Pre-RT PSA (ng/ml)		
		0.1–0.5	0.6–1.0	>1.0
Negative	1 (6)	RT	RT	RT + STADT
	2, 3 (7)	RT	RT + STADT	RT + LTADT
	4, 5 (8–10)	RT <sup>a</sup>	RT + STADT	RT + LTADT
Positive	1 (6)	RT	RT + STADT	RT + LTADT
	2, 3 (7)	RT	RT + STADT	RT + LTADT
	4, 5 (8–10)	RT <sup>a</sup>	RT + LTADT	RT + LTADT

ISUP = International Society of Urologic Pathology; LTADT = long-term androgen deprivation therapy (2 yr); PSA = prostate-specific antigen; RT = radiotherapy; STADT = short-term androgen deprivation therapy (4–6 mo).

<sup>a</sup> Patients with minimal to no comorbidities and a long life expectancy shared decision making, and a discussion of the risks and benefits of hormone therapy is warranted given the potential long-term benefit in these men. Ideally, these men should be enrolled on clinical trials testing the benefit of hormone therapy given that they were poorly represented in RTOG 9601.

### Platinum Priority – Review – Prostate Cancer

Editorial by Chris Parker and Matthew R. Sydes on pp. 166–167 of this issue

## A Systematic Review and Framework for the Use of Hormone Therapy with Salvage Radiation Therapy for Recurrent Prostate Cancer

Daniel E. Spratt<sup>a,†,\*</sup>, Robert T. Dess<sup>a,†</sup>, Zachary S. Zumsteg<sup>b</sup>, Daniel W. Lin<sup>c</sup>, Phuoc T. Tran<sup>d,e,f</sup>, Todd M. Morgan<sup>g</sup>, Emmanuel S. Antonarakis<sup>d</sup>, Paul L. Nguyen<sup>h</sup>, Charles J. Ryan<sup>i</sup>, Howard M. Sandler<sup>b</sup>, Matthew R. Cooperberg<sup>j</sup>, Edwin Posadas<sup>k</sup>, Felix Y. Feng<sup>l</sup>

**February 2018** Volume 73, Issue 2, Pages 156–165

EUROPEAN  
UROLOGY

Review – Prostate Cancer

## **Comparison of Radical Prostatectomy Versus Radiation and Androgen Deprivation Therapy Strategies as Primary Treatment for High-risk Localized Prostate Cancer: A Systematic Review and Meta-analysis**

*Benjamin A. Greenberger<sup>a,\*</sup>, Nicholas G. Zaorsky<sup>b</sup>, Robert B. Den<sup>a</sup>*

<sup>a</sup> Department of Radiation Oncology, Sidney Kimmel Medical College & Cancer Center at Thomas Jefferson University, Philadelphia, PA, USA; <sup>b</sup> Department of Radiation Oncology, Penn State Cancer Institute, Hershey, PA, USA

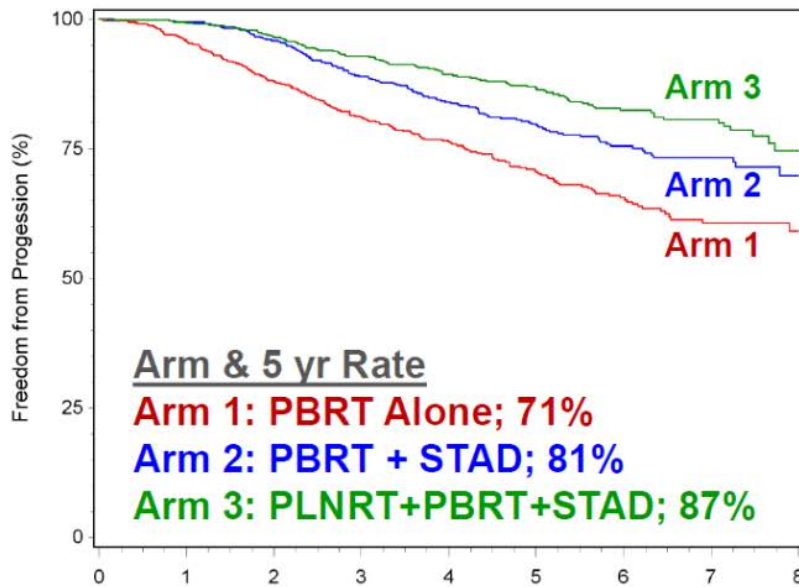
**Conclusions:** Evidence demonstrating definitive superiority of either modality is lacking. Recent studies show improved consideration of ADT, radiation dose, brachytherapy boost, and utilization of postoperative adjuvant radiation. Residual confounding continues to limit the interpretation of observational data.



# Short Term Androgen Deprivation Therapy Without or With Pelvic Lymph Node Treatment Added to Prostate Bed Only Salvage Radiation Therapy: The NRG Oncology/RTOG 0534 SPPORT Trial

A. Pollack<sup>1</sup>, T. G. Karrison<sup>2</sup>, A. G. Balogh<sup>3</sup>, D. Low<sup>4</sup>, D. W. Bruner<sup>5</sup>, J. S. Wefel<sup>6</sup>, L. G. Gomella<sup>7</sup>, E. Vigneault<sup>8</sup>, J. M. Michalski<sup>9</sup>, S. Angyalfi<sup>10</sup>, H. Lukka<sup>11</sup>, S. L. Faria<sup>12</sup>, G. Rodrigues<sup>13</sup>, M. C. Beauchemin<sup>14</sup>, S. A. Seaward<sup>15</sup>, A. M. Allen<sup>16</sup>, D. C. Monitto<sup>17</sup>, W. Seiferheld<sup>2</sup>, and H. M. Sandler<sup>18</sup>

## FFP: All eligible patients (1,792)



**5 yr Rate Comparison**  
 Arm 3 vs Arm 1:  $p < 0.0001$   
 Arm 2 vs Arm 1:  $p < 0.0001$   
 Arm 3 vs Arm 2:  $p = 0.0039$

**HRs and 97.5% CIs**  
 3 vs 1: 0.45 (0.34-0.61)  
 2 vs 1: 0.62 (0.47-0.82)  
 3 vs 2: 0.71 (0.52-0.98)

No. at Risk	0	1	2	3	4	5	6	7	8
PBRT Alone	573	529	480	417	334	243	165	89	37
PBRT+NC-STAD	585	559	532	467	366	275	179	94	39
PLNRT+PBRT+NC-STAD	576	563	540	488	399	315	209	126	52

# Cancer and Leukemia Group B 90203 (Alliance): Radical Prostatectomy With or Without Neoadjuvant Chemohormonal Therapy in Localized, High-Risk Prostate Cancer

James A. Eastham, MD<sup>1</sup>; Glenn Heller, PhD<sup>1</sup>; Susan Halabi, PhD<sup>2</sup>; J. Paul Monk III, MD<sup>3</sup>; Himisha Beltran, MD<sup>4</sup>; Martin Gleave, MD<sup>5</sup>; Christopher P. Evans, MD<sup>6</sup>; Steven K. Clinton, MD, MPH<sup>3</sup>; Russell Z. Szmulewitz, MD<sup>7</sup>; Jonathan Coleman, MD<sup>1</sup>; David W. Hillman, MS<sup>8</sup>; Colleen R. Watt, BS<sup>9</sup>; Saby George, MD<sup>10</sup>; Martin G. Sanda, MD<sup>11</sup>; Olwen M. Hahn, MD<sup>9</sup>; Mary-Ellen Taplin, MD<sup>4</sup>; J. Kellogg Parsons, MD<sup>12</sup>; James L. Mohler, MD<sup>10</sup>; Eric J. Small, MD<sup>13</sup>; and Michael J. Morris, MD<sup>1</sup>

DOI <https://doi.org/10.1200/JCO.20.00315>

Journal of Clinical Oncology®

**CONCLUSION** The primary study end point, 3-year BPF5, was not met. Although some improvement was seen in secondary end points, any potential benefit must be weighed against toxicity. Our data do not support the routine use of neoadjuvant CHT and RP in patients with clinically localized, high-risk PC at this time.

J Clin Oncol 38. © 2020 by American Society of Clinical Oncology

# Radical Prostatectomy, External Beam Radiotherapy, or External Beam Radiotherapy With Brachytherapy Boost and Disease Progression and Mortality in Patients With Gleason Score 9-10 Prostate Cancer

Amar U. Kishan, MD; Ryan R. Cook, MSPH; Jay P. Diezfel, MD; Ashley E. Ross, MD, PhD; Mark M. Pomerantz, MD; Paul L. Nguyen, MD; Talha Shaikh, MD; Phuoc T. Tran, MD, PhD; Kiri A. Sandler, MD; Richard G. Stock, MD; Gregory S. Merrick, MD; D. Jeffrey Demanes, MD; Daniel E. Spratt, MD; Eyad I. Abu-Isa, MD; Trude B. Wedde, MD; Wolfgang Lilleby, MD, PhD; Daniel J. Krauss, MD; Grace K. Shaw, BA; Ridwan Alam, MPH; Chandana A. Reddy, MS; Andrew J. Stephenson, MD; Eric A. Klein, MD; Daniel Y. Song, MD; Jeffrey J. Tosolan, MD; John V. Hegde, MD; Sun Mi Yoo, MD, MPH; Ryan Flans, MPH; Anthony V. D'Amico, MD, PhD; Nicholas G. Nickols, MD, PhD; William J. Aronson, MD; Ahmad Sadeghi, MD; Stephen Greco, MD; Curtiland Deville, MD; Todd McNutt, PhD; Theodore L. DeWeese, MD; Robert E. Retter, MD; Johnathan W. Said, MD; Michael L. Steinberg, MD; Eric M. Horwitz, MD; Patrick A. Kupelian, MD; Christopher R. King, MD, PhD

**CONCLUSIONS AND RELEVANCE** Among patients with Gleason score 9-10 prostate cancer, treatment with EBRT+BT with androgen deprivation therapy was associated with significantly better prostate cancer-specific mortality and longer time to distant metastasis compared with EBRT with androgen deprivation therapy or with RP.



# Evaluation of Cancer Specific Mortality with Surgery versus Radiation as Primary Therapy for Localized High Grade Prostate Cancer in Men Younger Than 60 Years



Hubert Huang, Stefano Muscatelli, Michael Naslund, Shahed N. Badiyan, Adeel Kaiser and Mohummad Minhaj Siddiqui\*

*From the Division of Urology, Department of Surgery (HH, SM, MN, MMS) and Department of Radiation Oncology (SNB, AK), University of Maryland Medical Center, Baltimore, Maryland*

<https://doi.org/10.1016/j.juro.2018.07.049>  
Vol. 201, 120-128, January 2019

**Conclusions:** Our data showed significant survival differences in young men treated initially with surgery vs external beam radiation therapy of high grade prostate cancer. Future prospective randomized trials are needed to confirm the long-term outcomes of these treatment approaches.



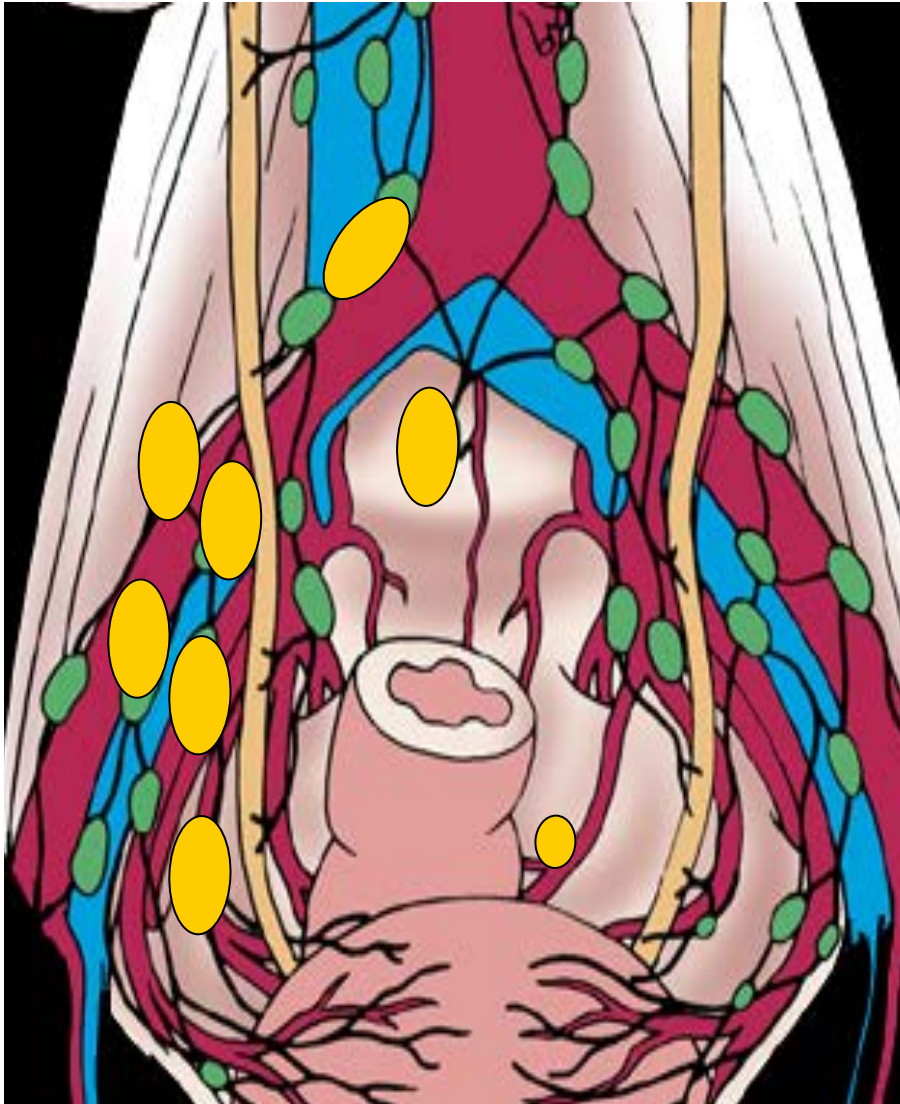
PSMA  
NOW GOLD  
STANDARD  
FOR  
STAGING

- Lancet
- . 2020 Apr 11;395(10231):1208-1216. doi: 10.1016/S0140-6736(20)30314-7. Epub 2020 Mar 22.
- Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study
- Michael S Hofman 1, Nathan Lawrentschuk 2, Roslyn J Francis 3, Colin Tang 4, Ian Vela 5, Paul Thomas 6, Natalie Rutherford 7, Jarad M Martin 8, Mark Frydenberg 9, Ramdave Shakher 10, Lih-Ming Wong 11, Kim Taubman 12, Sze Ting Lee 13, Edward Hsiao 14, Paul Roach 14, Michelle Nottage 15, Ian Kirkwood 16, Dickon Hayne 17, Emma Link 18, Petra Marusic 19, Anetta Matera 20, Alan Herschtal 20, Amir Iravani 21, Rodney J Hicks 21, Scott Williams 22, Declan G Murphy 23, proPSMA Study Group Collaborators

PSMA PET-CT is a suitable replacement for conventional imaging, providing superior accuracy, to the combined findings of CT and bone scanning.



# Where do nodes travel to?



**Variable: no single  
'sentinal' node**

<b>Obturator</b>	<b>30%</b>
<b>External Iliac</b>	<b>30%</b>
<b>Internal iliac</b>	<b>30%</b>
<b>Presacral</b>	<b>7%</b>
<b>Pararectal</b>	<b>4%</b>
<b>Common Iliac</b>	<b>1-2%</b>

13% missed by ePLND

# Arguments for ePLND (in Briganti >8%)

- ‘Direct’ therapeutic benefit:
  - May occasionally cure
    - 1/3 (30%) are BCR-free long term if 1-2 nodes +ve
  - May delay salvage ADT/ RT
- ‘Indirect’ staging benefit:
  - Improve selection of men most likely to derive benefit from early adjuvant RT/ ADT rather than waiting for BCR

# New evidence: Systematic Review of PLND

Fossati et al, Eur Urol, 2017

- 275,000 patients
- Oncological outcomes (29 studies, only one RCT)
  - No survival benefit
  - Conflicting results for biochemical and clinical recurrence
- Non-oncological outcomes (43 studies, three RCTs)
  - ePLND increased adverse outcomes (operating time, blood loss, length of stay, complications)

## Conclusions:

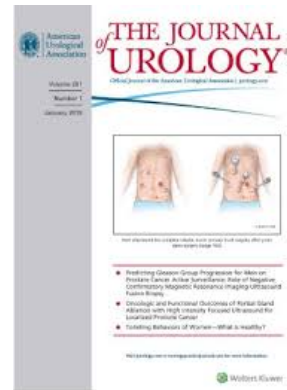
- Although the most accurate staging procedure, no evidence of therapeutic effect
- ePLND has significant morbidity
- Current poor quality evidence; need for robust & adequately powered trials.



# New evidence: Is there a benefit for ePLND?

J Urol, September 2019, Preisser et al:

- Multi-centre study EAU working group
  - Montorsi, Briganti, Walz, Van der Poel, etc
- Methods:
  - n= 10,000 with 10 years follow-up
  - High risk (Briganti nomogram risk >5%)
  - ePLND vs no PLND
- Results:
  - No benefit at 10-years for ePLND



# New data: Our St Vincents cohort data (unpublished)

- Methods
  - 4,200 men underwent RP +/- PLND
  - Median 8 years follow-up
  - 50% Briganti low vs 50% high (>5% risk of pN+)
  - 3.6% pN+
- Results (Multivariate analysis)
  - In low-risk men, no BCR benefit for ePLND vs no PLND
  - In high-risk men, ePLND reduced risk of BCR
    - Compared to no PLND or limited PLND



# Is there a better way?

- Is novel imaging the saviour?
  - PSMA PET
- Is Tc-PSMA guided- PLND the future?
- Should we replace PLND with selective use of:
  - adjuvant nodal RT ?
  - early salvage nodal RT ?
  - salvage LND ?

# PSMA for Node Staging before RP

- Node Staging via CT / MRI is poor

- Sensitivity 44% ; Specificity 85%

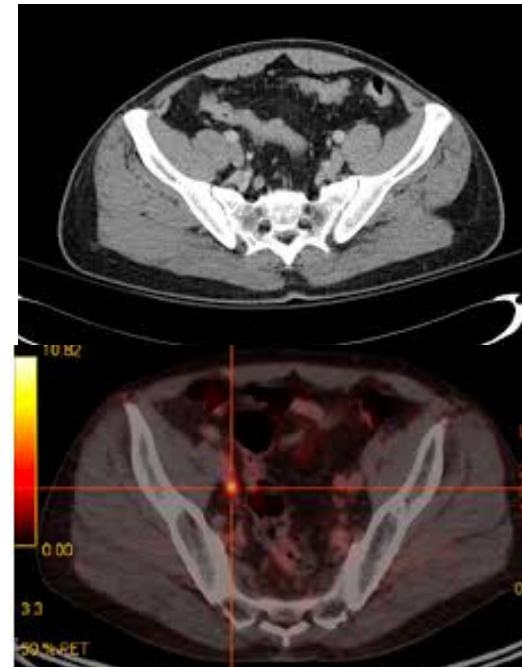
- [Maurer et al, J Urol, 2016]

- PSMA-PET is better, but still imperfect

- Sens 64-66% , Spec 95-98%

- NPV 82% , PPV 88%

- [Van Leeuwen et al, BJUI, 2017] [Maurer et al, J Urol, 2016] , [Hofman et al , Lancet 2020 ]



- NPV 80% means we are 'falsely reassured' by 1/5 'normal' scans
- Small nodal mets are invisible (avg size = 2.7mm)

# Can PSMA improve PLND?

Q: Can pre-op PSMA help identify positive nodes to guide PLND planning/ template

- Especially those outside the standard template eg pre-sacral / common iliac / ext iliac

A: YES

Q: Can intra-PSMA probe find nodes missed by pre-op Ga-PSMA

- A: YES

Q: Can PSMA-PET be used to select men for ePLND?

- A: Maybe (Would reduce unnecessary PLNDs but those most likely to benefit from ePLND (1-2 small node mets) would be missed

# In BCR post-RP, can PSMA guide salvage LND?

## Rationale

### 1) Optimise selection for sLND

- identify those with node only disease, i.e. exclude distant metastases

### 2) Optimise surgical planning

- Precisely localise positive nodes to guide surgery

# Outcomes for salvage LND – SVH evidence

- Siriwardana et al, BJUI 2017
- Multi-institutional series (St V Syd and PA Brisb)
- Cohort:
  - N=35 with BCR post-RP, N+M0 on PSMA, suitable for Sx
- Results:
  - 91% were pN+
  - 23% experienced complications (Clavien 1-2)
  - Less than a third (31%) had success (PSA < 0.05 at 6 wks)
  - Less than a quarter (23%) were free of BCR at 12-months
- A small subset may benefit
  - Slow PSADT
  - Longer time since RP
  - Full bilateral PLND template if no PLND performed at time of RP



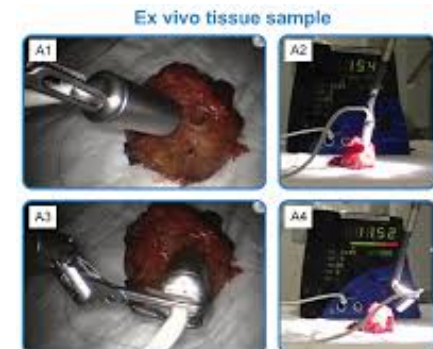
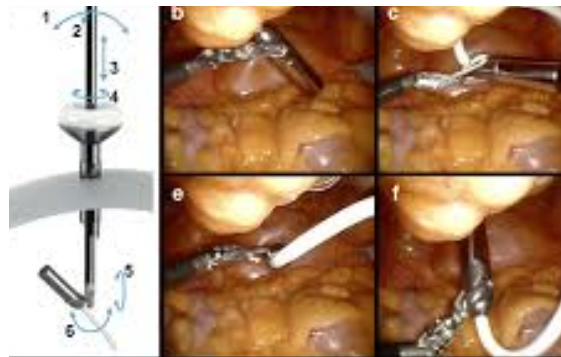
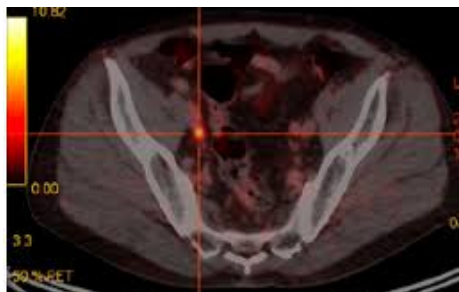


# The 'DETECT' Study

**Aim:** To assess if a PSMA-robotic drop in probe can guide (i) need for PLND and (ii) localisation of suspicious nodes and (iii) PSMs

## Methods:

- Multicentre study (Martini Klinik & NKI Netherlands)
- 60 men with 'High risk' Pca ( > 15% Chance +ve Node )
- Ga68-PSMA then pre-op Injection of PSMA-Tc
- ePLND +/- targeted LND guided by Radio-sensor probe
- Gieger counts: node packages / background / prostate / fossa
- Counts measured on pre-op PSMA (SUV), in vivo and ex vivo
- Primary endpoint: Accuracy of intra-op probe vs final histo

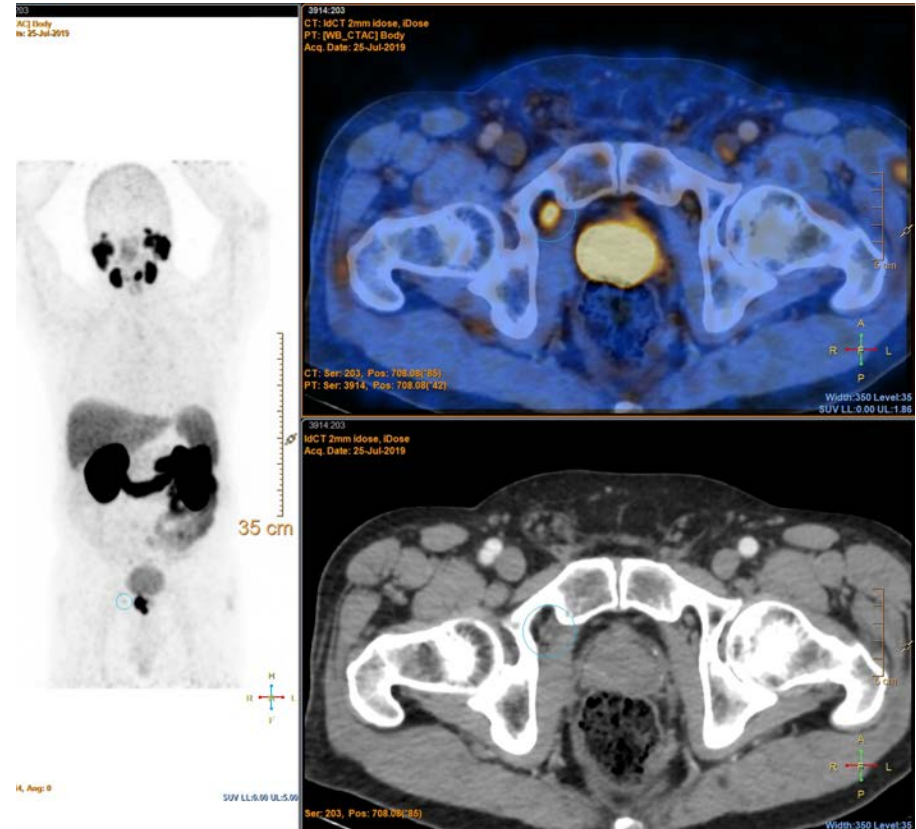


# Setup in theatre



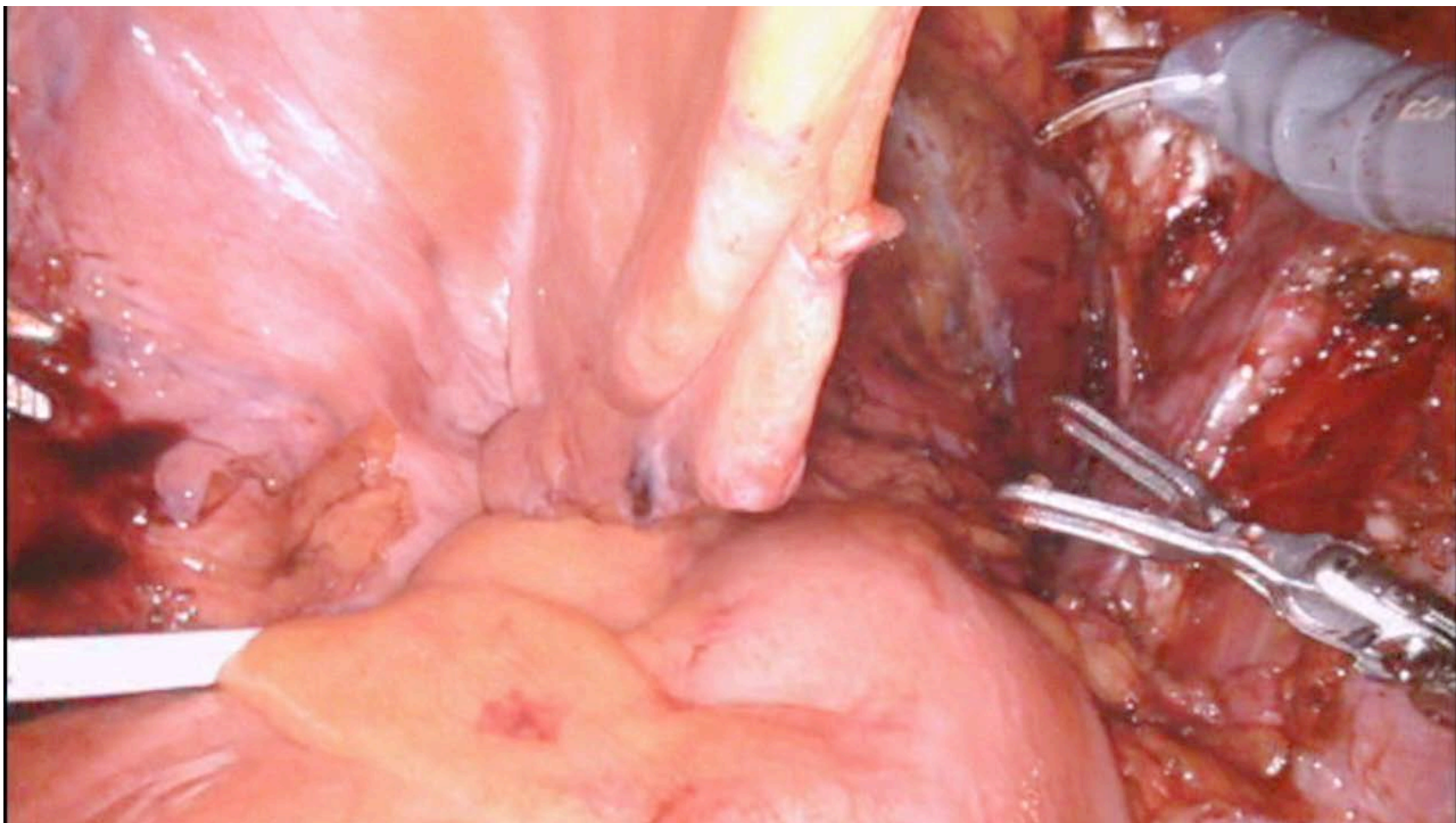
# DETECT trial - cases

- 73M
  - PSA 15
  - Gleason 4+5=9 on Bx
  - PSMA PET shows avidity in the deep right obturator canal
  - Consented to the DETECT trial





# Locating deep obturator lymph nodes



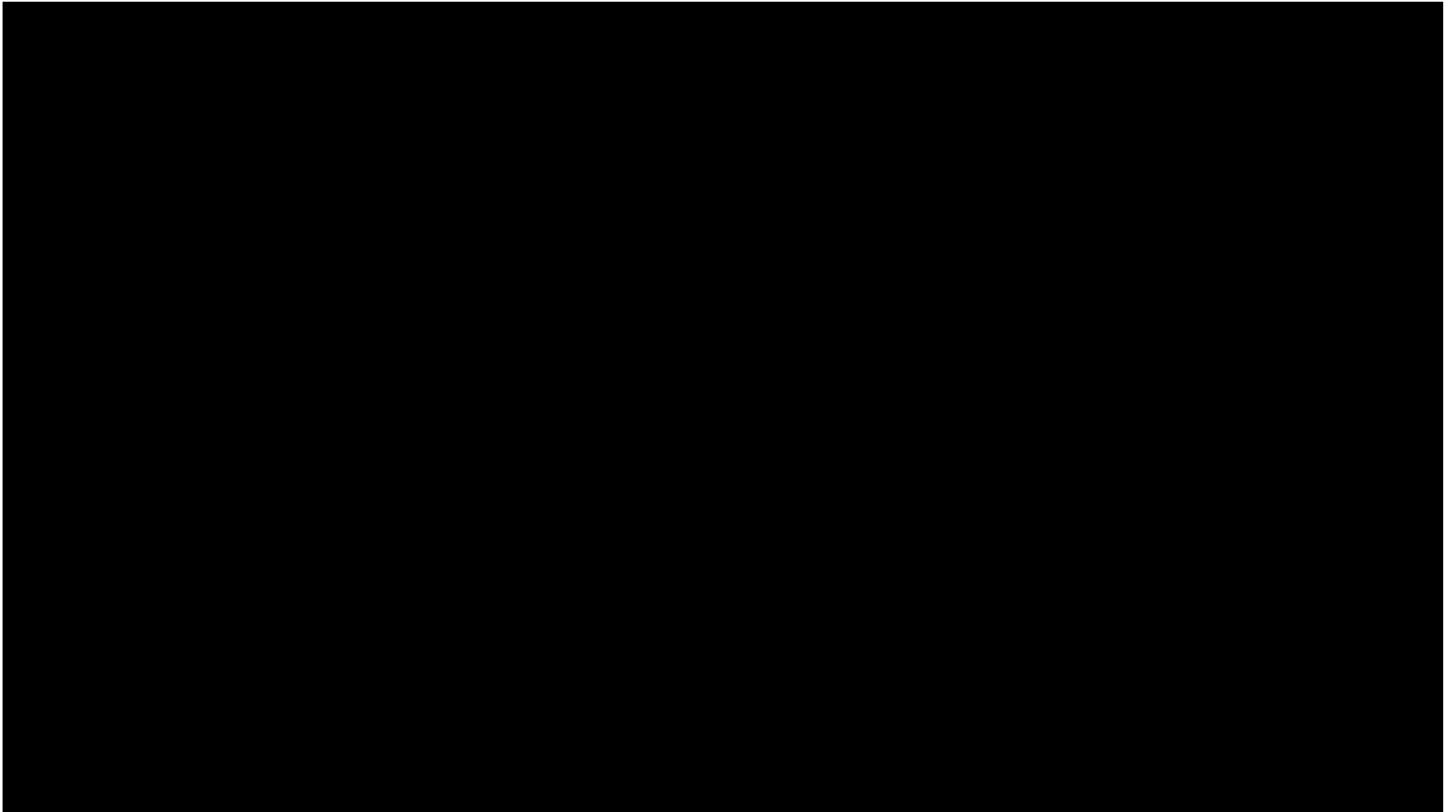
# DETECT trial cases

- 63M
  - PSA 6.7
  - T2a
  - Gleason 4+4=8 on Bx
  - PSMA PET avidity at right mesorectal nodes at level of S5 (SUVmax 6.3)
  - Hookwire and DETECT trial





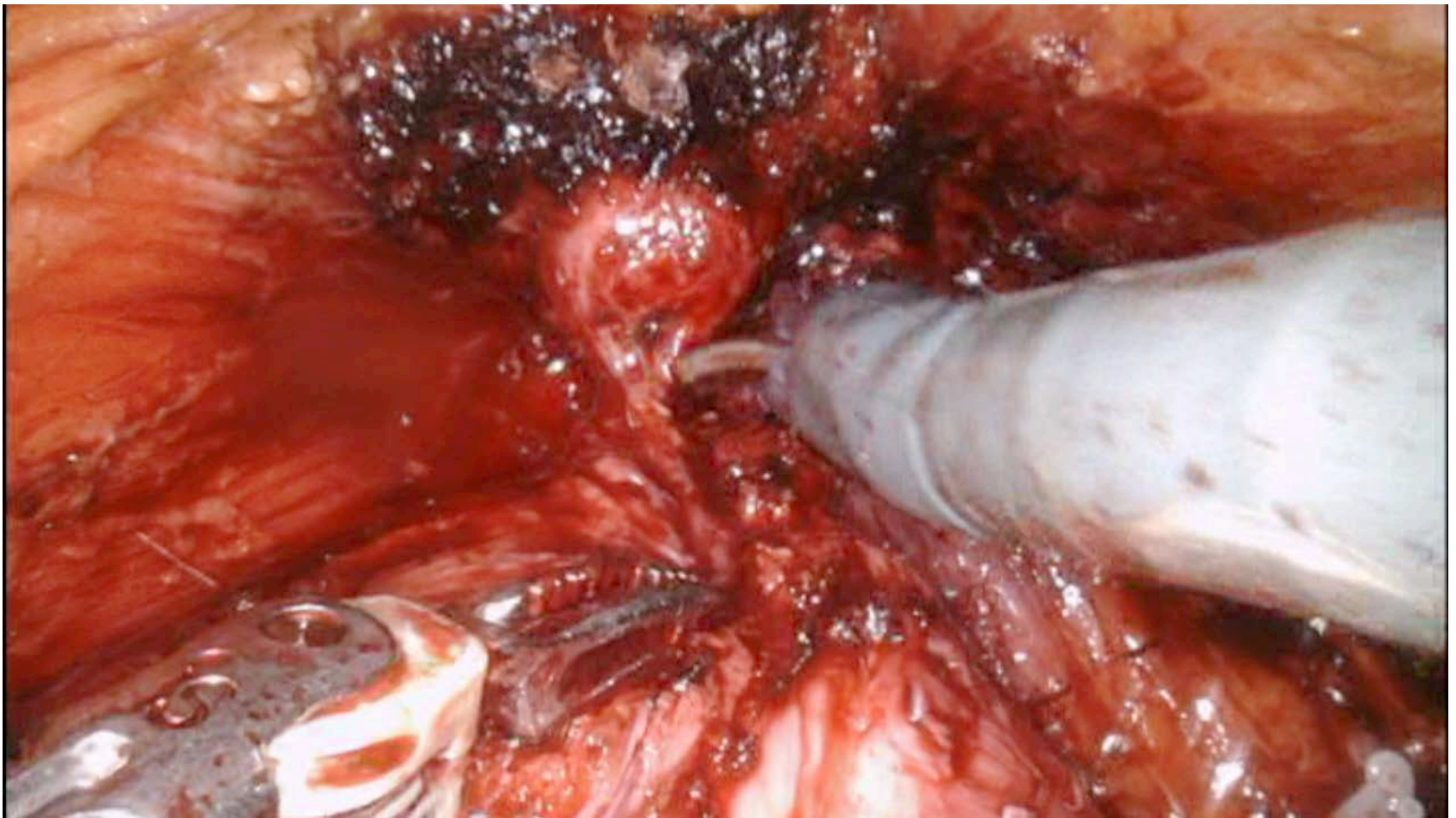
# Mesorectal node resection



# DETECT trial - cases

- 64M
  - PSA 58
  - T2B N0 M0
  - Gleason 4+5=9 on Bx
  - Consented to the DETECT trial

# Prostate bed residual disease



# The potential utility of this technology

- Lymph nodes
  - Can we perform a more accurate lymph node dissection, thus reducing morbidity and increasing cure rates?
- Prostate bed and neurovascular bundles
  - Detection of residual disease – reducing macroscopic cancer load.
    - Effect on overall outcome requires further study