# Low risk versus high risk BCR: prognosis related to clinical guidance vs imaging

Alastair Lamb

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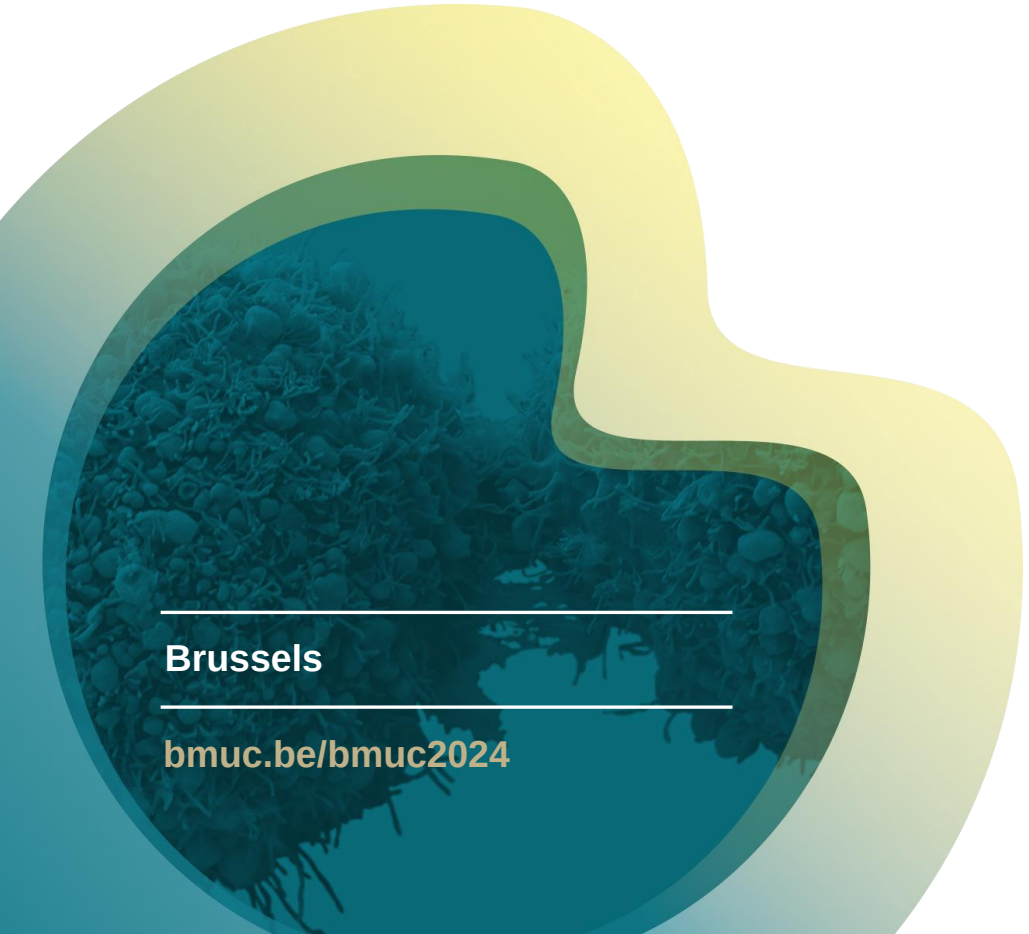
& Honorary Consultant Urologist, Oxford



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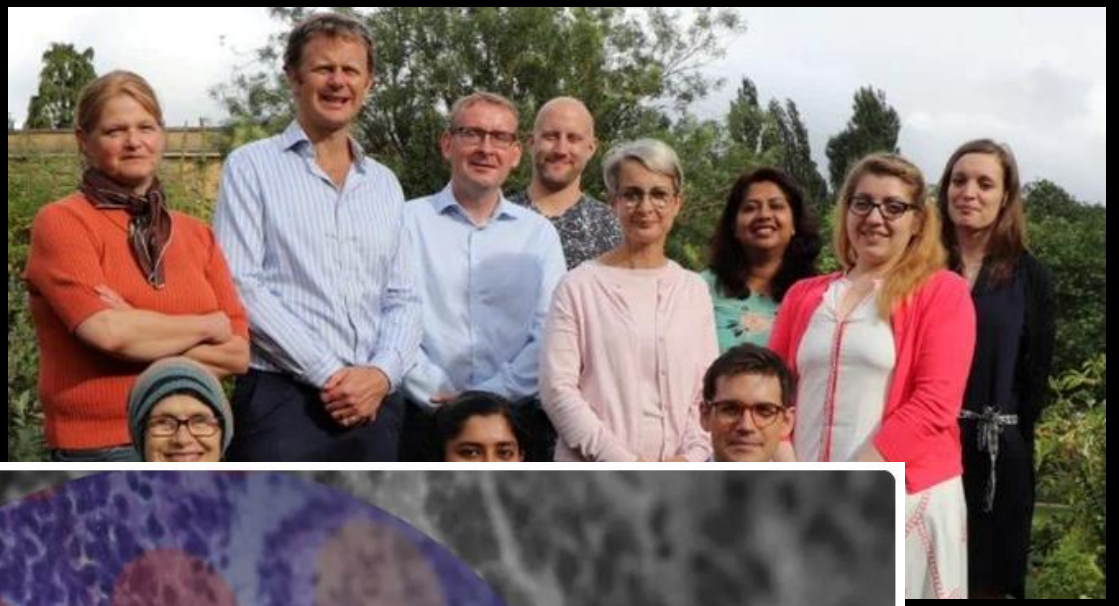

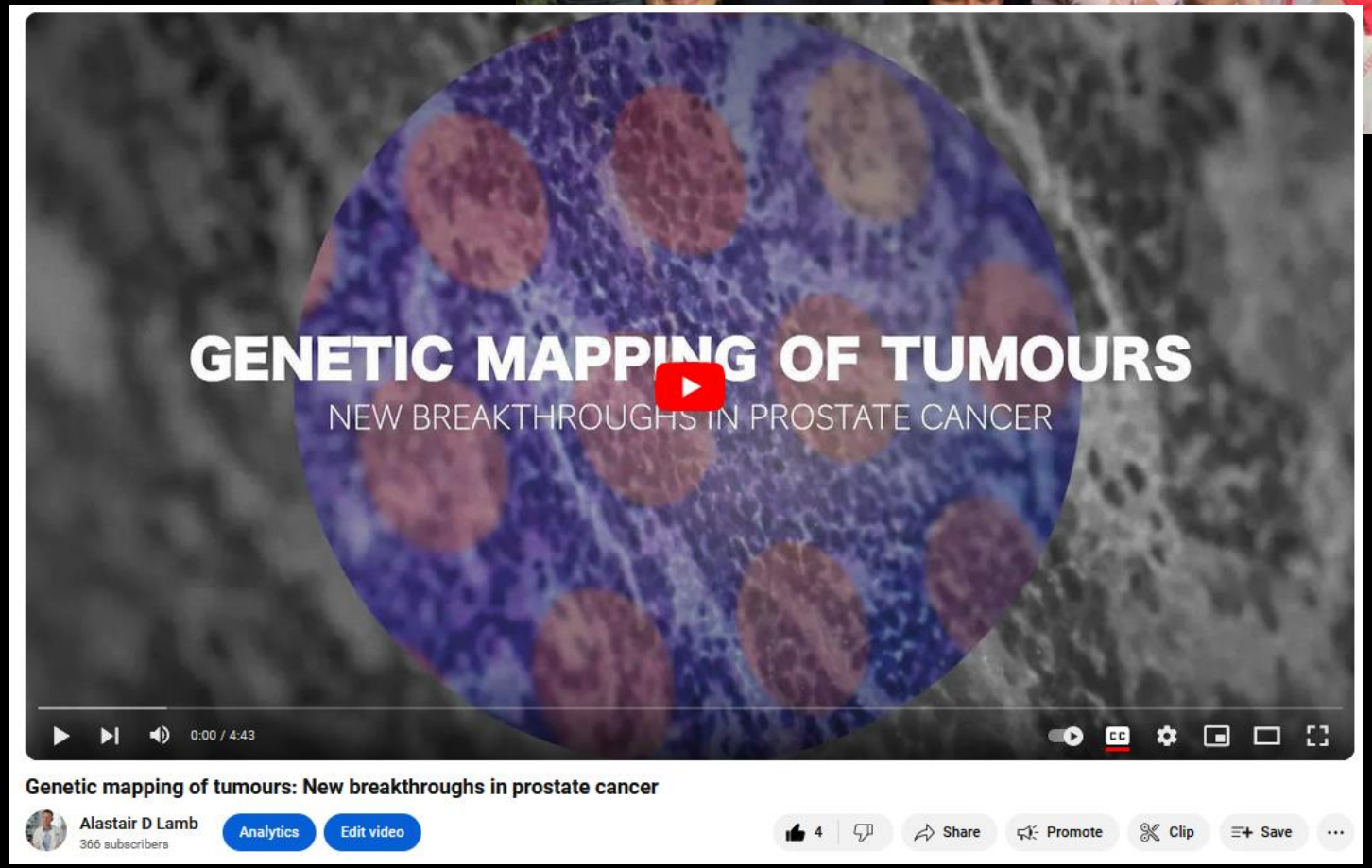
GENETIC MAPPING OF TUMOURS
NEW BREAKTHROUGHS IN PROSTATE CANCER
0:00 / 4:43
Genetic mapping of tumours: New breakthroughs in prostate cancer
Alastair D Lamb
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# Biochemical relapse/recurrence (BCR)

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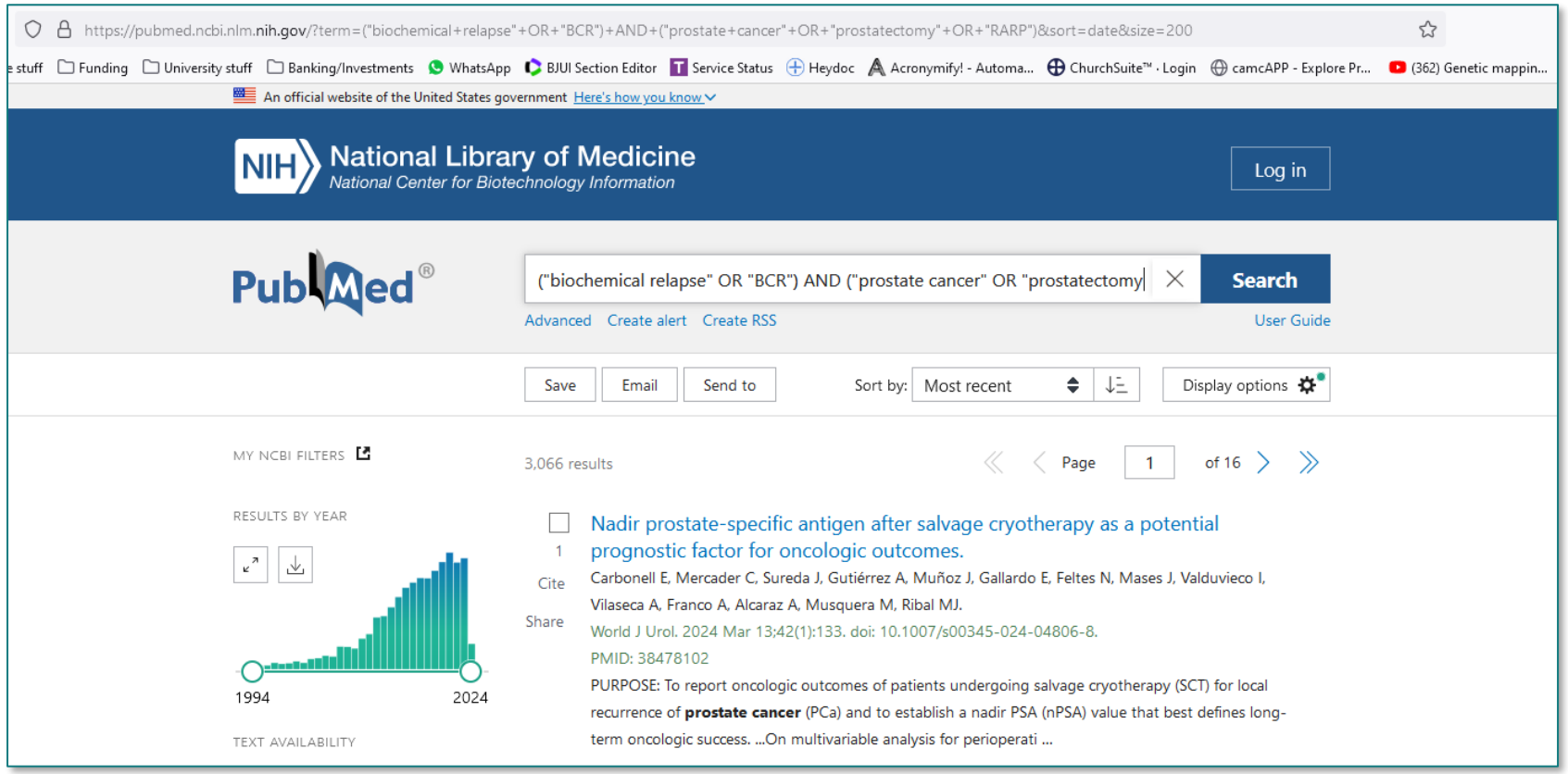
- What is biochemical relapse?
- Counfounders for BCR
- Imaging to investigate BCR
- Risk stratification & Management
- Patient perception
- Non-urological/Non-prostate wallah colleague perceptions
- BCR in research
- Unknowns

…not adjuvant RT!

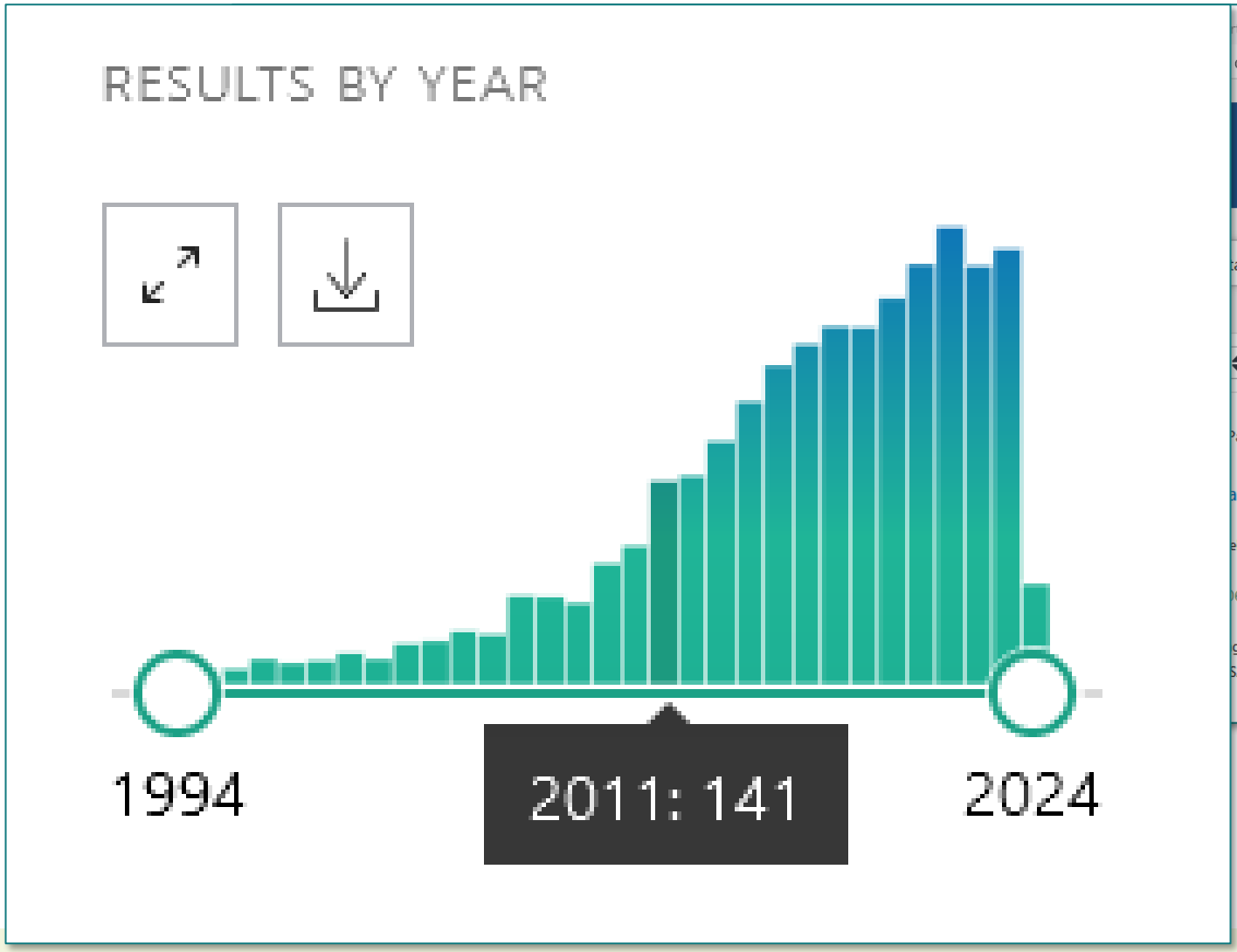
# Publications on BCR

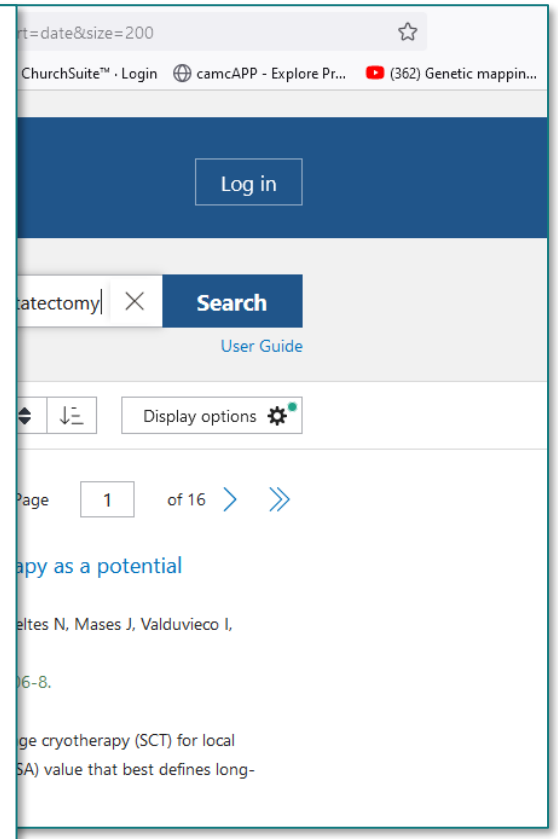




# Publications on BCR





# Definitions of BCR

# Definitions of BCR

>0.2ng/ml

2ng/ml above nadir

NICE Institute for Health and Care Excellence

www.nice.org.uk/guidance/ng131

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American Urological Association

The AUA definition of BCR in the post-prostatectomy setting is a rise in PSA ≥ 0.2 ng/mL and a confirmatory value of > 0.2 ng/mL.[38] Ultra-sensitive PSA assays can provide PSA levels below 0.1 ng/mL; however, these lower levels have not been prospectively evaluated to determine if this earlier detection of a detectable PSA, and subsequent treatment for such patients, results in superior oncologic outcomes compared to treatment when the

SIOG · EAU · EAUN · EUROPA UOMO · ESTRO · European Association of Urology



**RP**

After RP, the threshold that best predicts further metastases is a PSA > 0.4 ng/mL and rising [1001-1003]. However, with access to ultra-sensitive PSA testing, a rising PSA much below this level will be a cause for concern for patients.

**RT**

After primary RT, with or without short-term hormonal manipulation, the RTOG-ASTRO Phoenix Consensus Conference definition of PSA failure (with an accuracy of > 80% for clinical failure) is 'any PSA increase > 2 ng/mL higher than the PSA nadir value, regardless of the serum concentration of the nadir' [1004]. Clinicians should interpret a PSA rise in light of the EAU BCR risk groups (see Section 6.3.3).

**Focal**

After HIFU or cryotherapy no endpoints have been validated against clinical progression or survival; therefore, it is not possible to give a firm recommendation of an acceptable PSA threshold after these alternative local treatments [1005].

## *6.3.4.4 Summary of evidence and guidelines for imaging in patients with biochemical recurrence*

| Summary of evidence | LE |
|---|---|
| After RP there is no specific PSA threshold defining recurrence. | NR |

European Association of Urology · EANM · SIOG International Society of Geriatric Oncology · European Society of Urogenital Radiology · ESTRO European Society for Radiotherapy & Oncology · EUROPA UOMO The Voice of Men with Prostate Cancer in Europe



# Poll


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https://www.opinionstage.com/page/0887a0c8-972b-4790-8788-ac3c321971f1

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# Moul et al & Freedland, PCAN 2023





**Table 1.** Current imaging guidelines for BCR [3–5, 13].

| | EAU/EANM/ESTRO/ESUR/SIOG | | AUA/ASTRO/SUO | | NCCN | | ASCO | |
|---|---|---|---|---|---|---|---|---|
| | Post-RP | Post-EBRT | Post-RP | Post-EBRT | Post-RP | Post-EBRT | Post-RP | Post-EBRT |
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| mpMRI | No recommendations | | No recommendations | | mpMRI preferred over CT for pelvic staging | | Whole-body MRI (mpMRI not specified) | |

*ASCO* American Society of Clinical Oncology, *ASTRO* American Society for Radiation Oncology, *AUA* American Urologic Association, *BCR* biochemical recurrence, *CT* computed tomography, *DCFPyL* 2-(3-{1-carboxy-5-[6-18F-fluoropyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid, *EANM* European Association of Nuclear Medicine, *EAU* European Association of Urology, *ESTRO* European Society for Radiation Oncology, *ESUR EAU* Section of Urological Research, *EBRT* external beam radiation therapy, *mpMRI* multiparametric MRI, *MRI* magnetic resonance imaging, *NCCN* National Comprehensive Cancer Network, *PET* positron emission tomography, *PSA* prostate-specific antigen, *PSMA* prostate-specific membrane antigen, *RP* radical prostatectomy, *SIOG* International Society of Geriatric Oncology, *SUO* Society of Urologic Oncology.

[a]There is no consensus of what threshold PSA value is defined as undetectable.



# Poll

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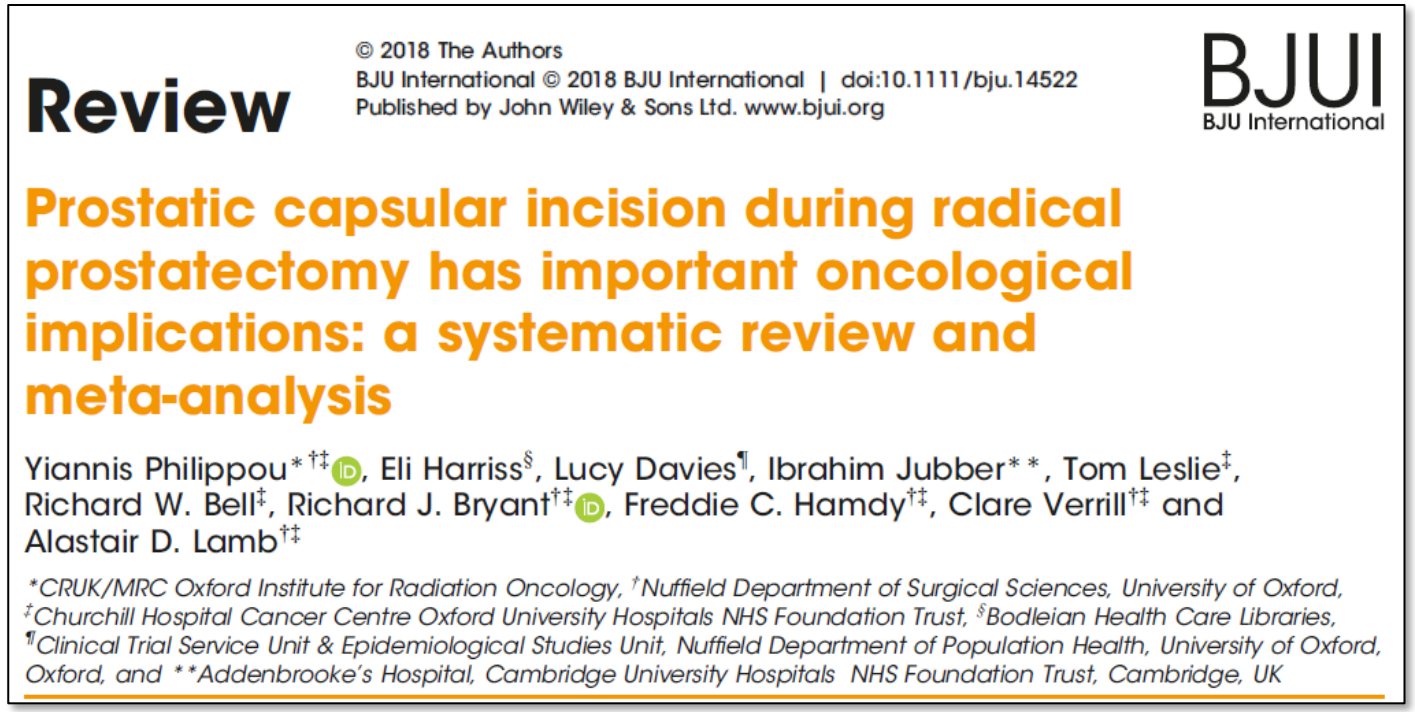
# Counfounders for BCR

# Counfounders for BCR



- Positive ‘benign margins’
- Capsular incisions



Review

 | doi:10.1111/bju.14522
Published by John Wiley & Sons Ltd. www.bjui.org

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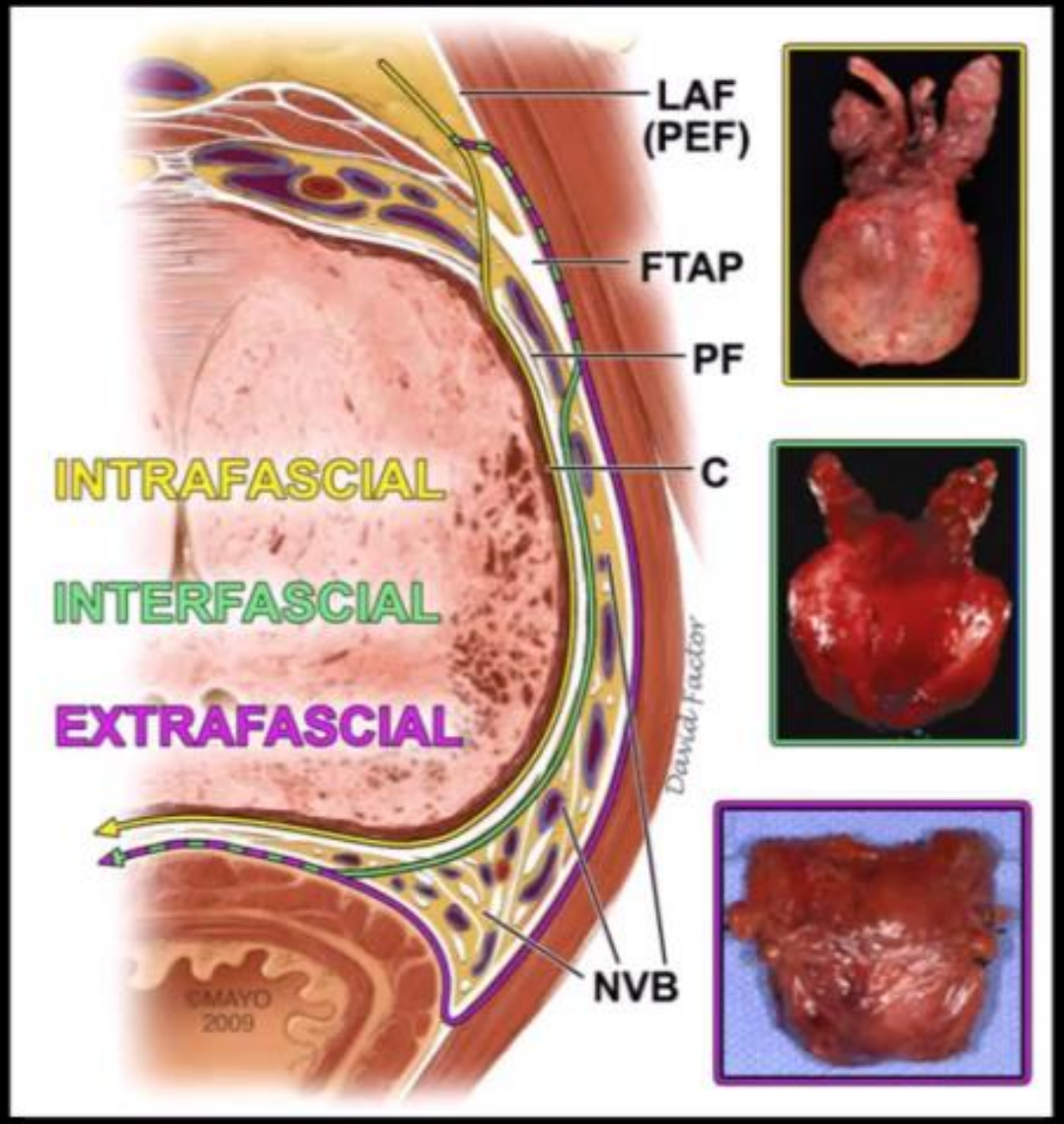
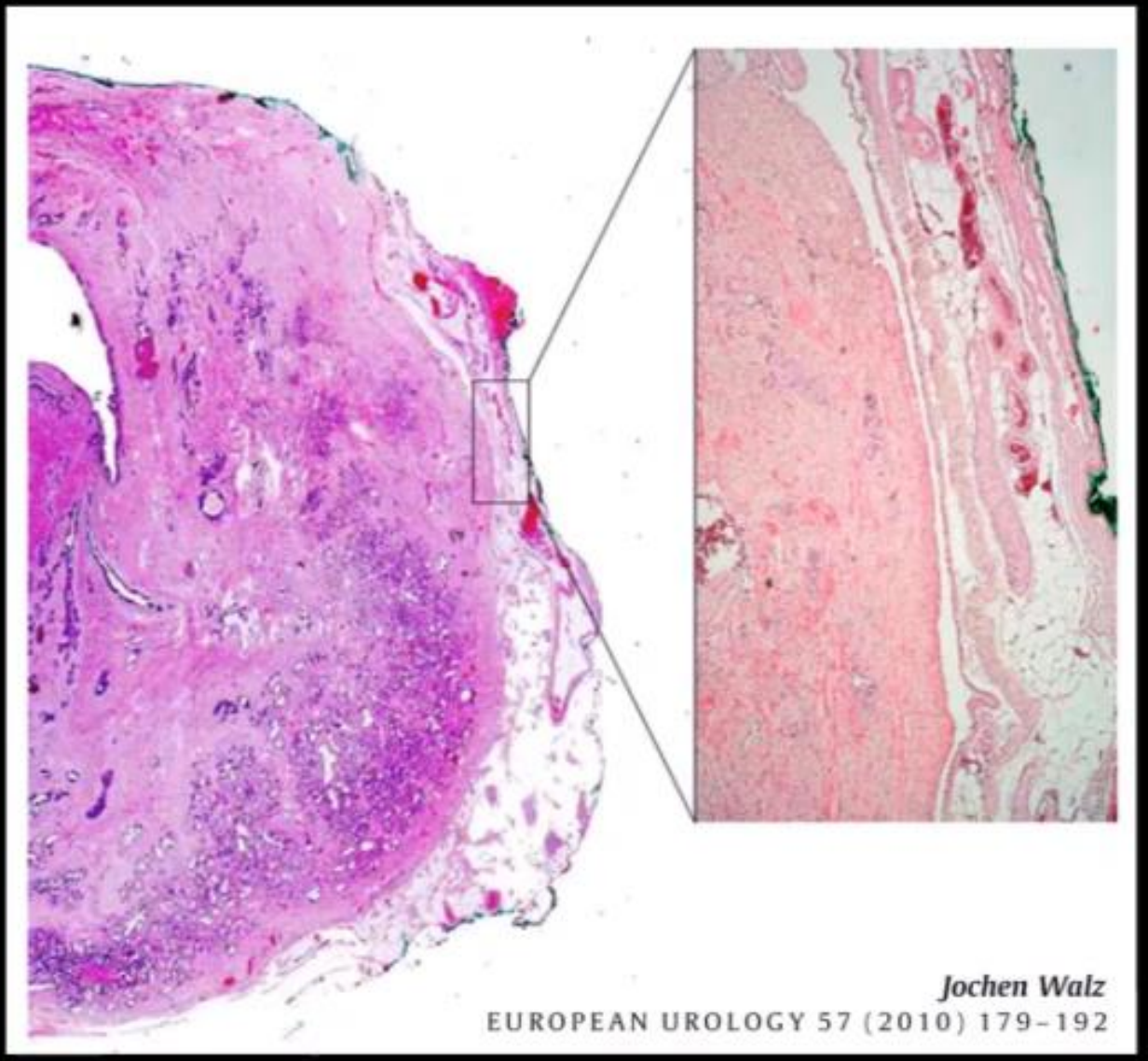
**Prostatic capsular incision during radical prostatectomy has important oncological implications: a systematic review and meta-analysis**

Yiannis Philippou*†‡, Eli Harriss§, Lucy Davies¶, Ibrahim Jubber**, Tom Leslie‡, Richard W. Bell‡, Richard J. Bryant†‡, Freddie C. Hamdy†‡, Clare Verrill†‡ and Alastair D. Lamb†‡

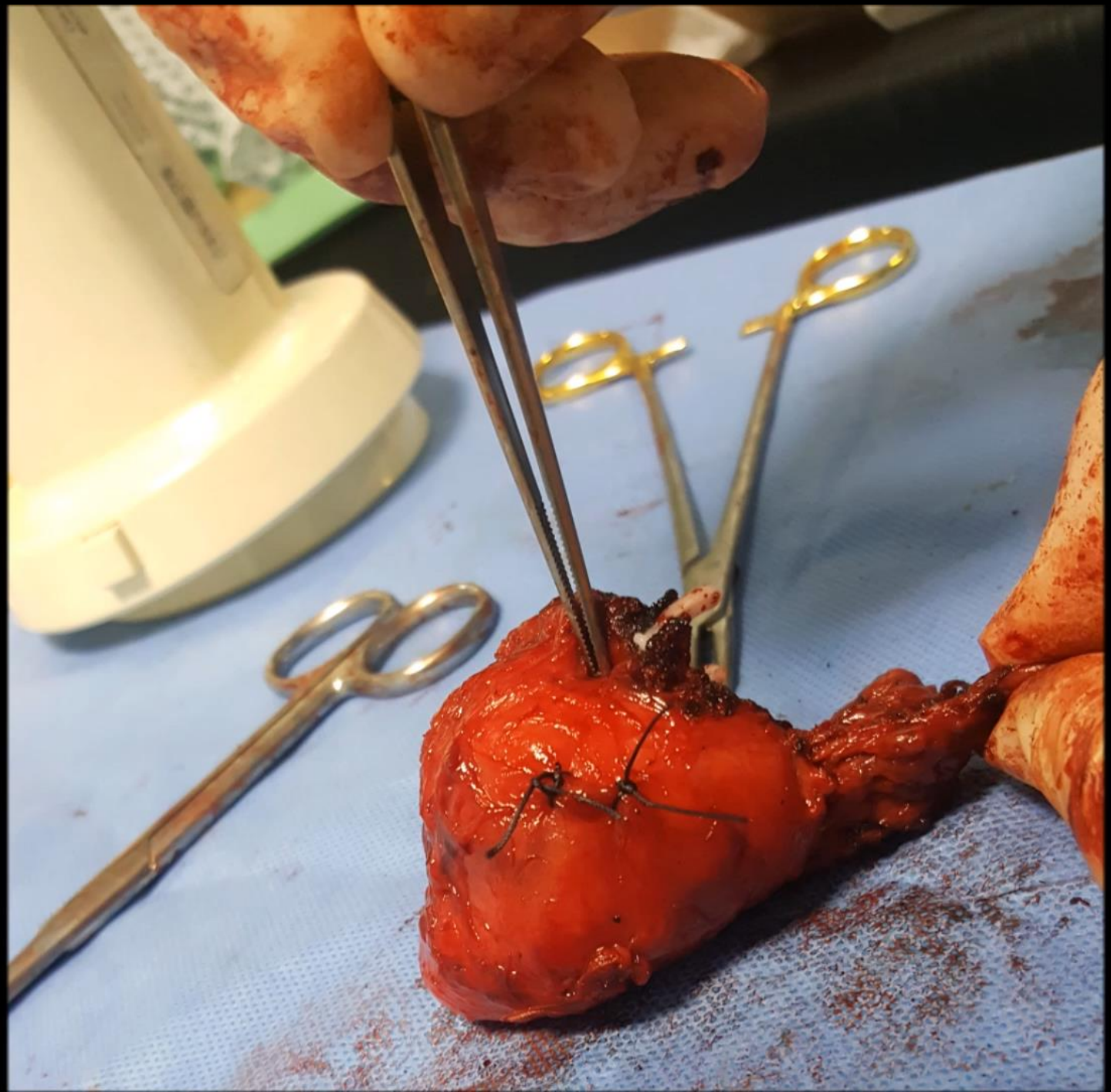
*CRUK/MRC Oxford Institute for Radiation Oncology, †Nuffield Department of Surgical Sciences, University of Oxford, ‡Churchill Hospital Cancer Centre Oxford University Hospitals NHS Foundation Trust, §Bodleian Health Care Libraries, ¶Clinical Trial Service Unit & Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, Oxford, and **Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK



Case 1 - 68yo
Gleason Grade Group 2 'multiple cores' Lt side.
PI-RADS 4 lesion Left peripheral zone.

=>Right interfascial nerve spare (low release)



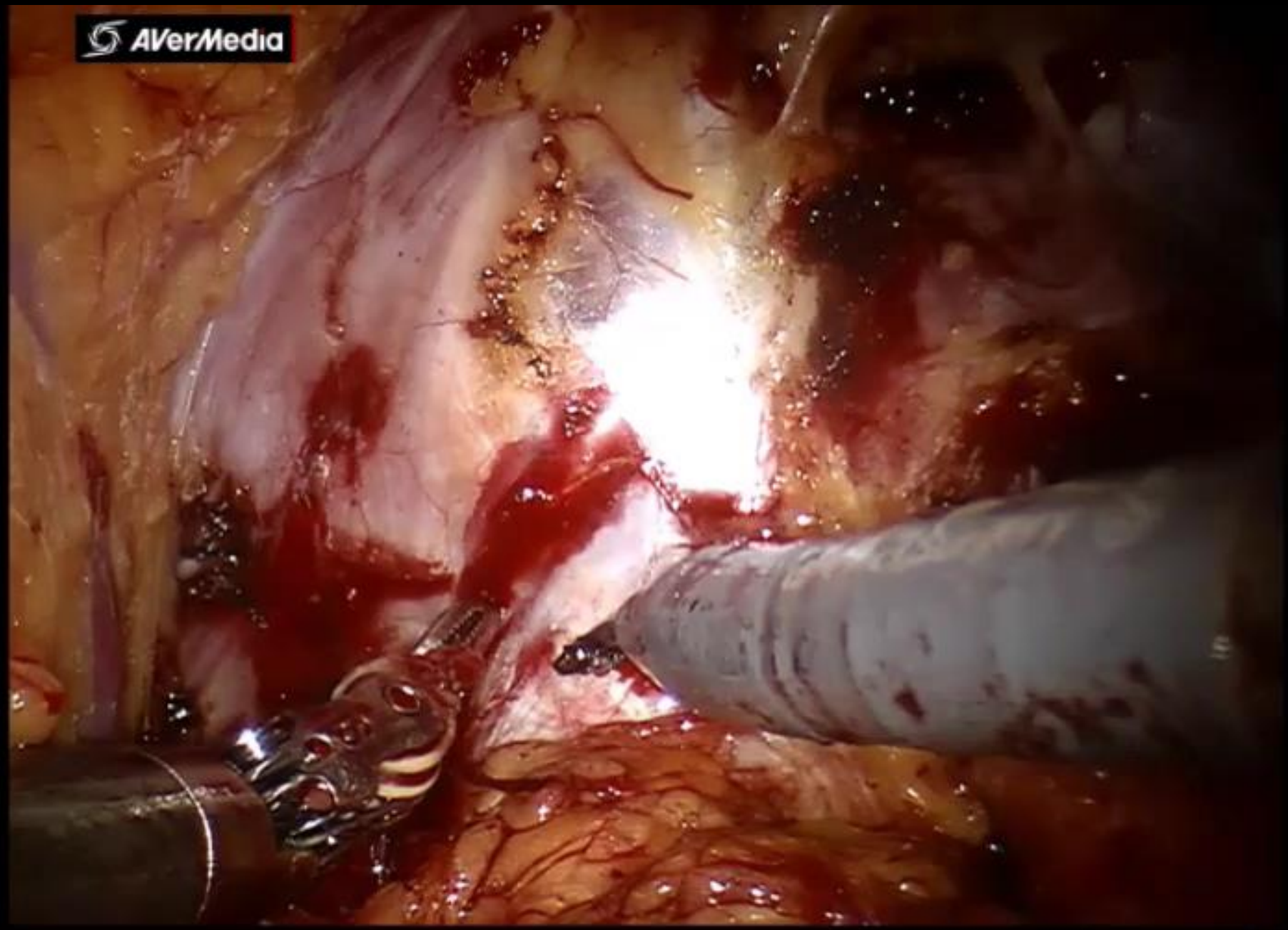
# Counfounders for BCR



- Positive ‘benign margins’
- Capsular incisions
- Residual low grade disease
- Cowpers glands

## Key steps to Anterior Retzius Sparing:

1. Maintenance of urachal attachments
2. Preservation of endopelvic fascia
3. Intrafascial nerve spare
4. Sub-DVC dissection
5. Maximal urethral length preservation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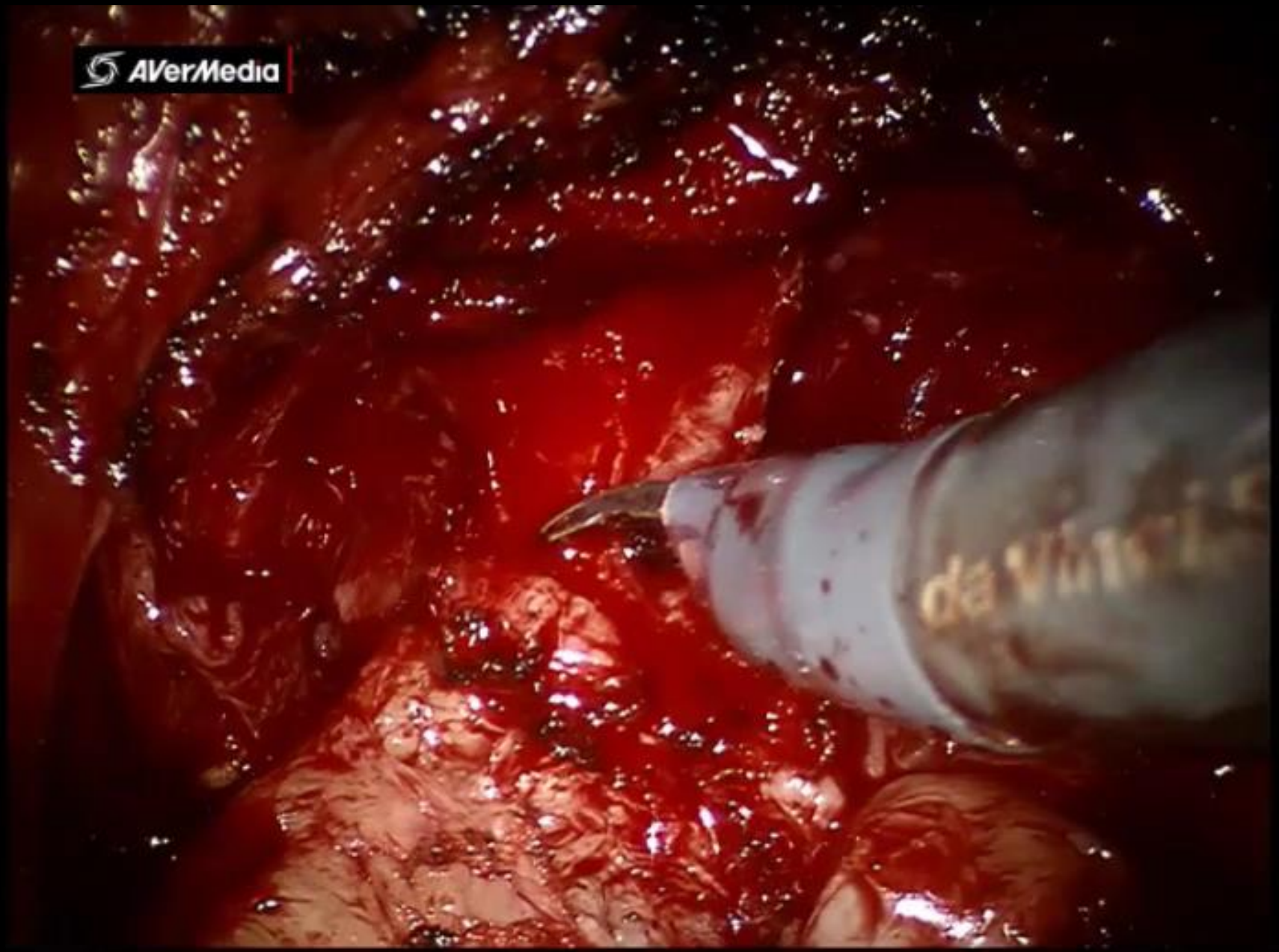
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# Counfounders for BCR



- Positive ‘benign margins’
- Capsular incisions
- Residual low grade disease
- Cowpers glands
- Missed micrometastatic disease

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# Imaging to investigate BCR

Prostate Cancer and Prostatic Diseases

www.nature.com/pcan

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REVIEW ARTICLE OPEN

Clinical Research

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# Application of next-generation imaging in biochemically recurrent prostate cancer

Judd W. Moul[1,8], Neal D. Shore[2,8], Kenneth J. Pienta[3], Johannes Czernin[4], Martin T. King[5] and Stephen J. Freedland[6,7]✉





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[a]There is no consensus of what threshold PSA value is defined as undetectable.

Prostate Cancer and Prostatic Diseases www.nature.com/pcan

REVIEW ARTICLE OPEN

Clinical Research

# Application of next-generation imaging in biochemically recurrent prostate cancer

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## Utility of next-generation imaging for the assessment and clinical management of biochemical recurrence in prostate cancer

**Rationale:** Rising prostate-specific antigen (PSA) after primary definitive therapy for prostate cancer does not completely identify early recurrence or oligometastasis; conventional imaging techniques have limited diagnostic value at PSA <10 ng/ml

### Positron Emission Tomography (PET) Radiotracers

#### Detection rates

46–50% with decreasing PSA levels:

$^{11}$C-Choline (1–3 ng/ml)

$^{18}$F-Fluciclovine (0.5–1 ng/ml)

Prostate-specific membrane antigen (PSMA; 0.2–0.49 ng/ml)

#### Changed treatment

52–64% patients

#### Tissue specificity

$^{11}$C-Choline: pelvic lymph nodes (LN) > local > bone

$^{18}$F-Fluciclovine: bone = local > pelvic LN

$^{68}$Ga-PSMA: bone > local / pelvic LN > extra-pelvic tissue

$^{18}$F-DCFPyl-PSMA: local > pelvic LN > bone > extra-pelvic tissues

#### Patient outcomes

Improved progression-free survival following metastasis-directed therapy

Improved overall survival following external beam radiation therapy

Maintained quality of life

### Whole–body MRI (multi-parametric MRI)

#### Sensitivity for local recurrence

54–100%, post-RP

78–97%, post-EBRT

**Conclusion: Next-generation imaging offers higher sensitivity and selectivity than conventional imaging for detecting early recurrence or micro-metastatic disease in biochemical recurrence at PSA <2.0 ng/ml, with the ability to inform treatment strategies and enhance patient outcomes**

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

https://doi.org/10.1016/j.eururo.2019.01.049

European Association of Urology


Platinum Priority – Review – Prostate Cancer

*Editorial by XXX on pp. x–y of this issue*

# Gallium-68 Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer—Updated Diagnostic Utility, Sensitivity, Specificity, and Distribution of Prostate-specific Membrane Antigen-avid Lesions: A Systematic Review and Meta-analysis

*Marlon Perera* [a,b,c,*], *Nathan Papa* [a], *Matthew Roberts* [b,c], *Michael Williams* [b], *Cristian Udovicich* [d], *Ian Vela* [b,e], *Daniel Christidis* [a], *Damien Bolton* [a,f], *Michael S. Hofman* [g], *Nathan Lawrentschuk* [a,f,h,i], *Declan G. Murphy* [h,i]

[a] *Department of Surgery, Austin Health, The University of Melbourne, Victoria, Australia;* [b] *Department of Urology, Princess Alexandra Hospital, Brisbane, Queensland, Australia;* [c] *Faculty of Medicine, University of Queensland, Brisbane, Queensland, Australia;* [d] *Division of Radiation Oncology, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia;* [e] *Australian Prostate Cancer Research Center QLD, Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Queensland, Australia;* [f] *Olivia Newton-John Cancer and Wellness Centre, Austin Health, Heidelberg, Victoria, Australia;* [g] *Centre for Molecular Imaging, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia;* [h] *Division of Cancer Surgery, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia;* [i] *Sir Peter MacCallum Department of Oncology, University of Melbourne, Parkville, Victoria, Australia*

# $^{68}$Ga-PSMA PET in Advanced Prostate Cancer-–Updated Diagnostic Utility, Sensitivity, Specificity, and Distribution of PSMA-avid Lesions: A Systematic Review and Meta-analysis

*Perera et al. Eur Urol 2019*

## Methods

***Objective:*** **Perform an SR and MA to update predictors of positive $^{68}$Ga-PSMA PET according to prior therapy**

**37 articles, 4,790 patients**

## Outcomes

**Pts with BCR – Mets Detected**

PSA 0-0.19: 33% +ve

PSA 0.20-0.49: 45% +ve

PSA 0.50-0.99: 59% +ve

PSA 1-1.99: 75% +ve

PSA ≥2: 95% +ve

**BCR by Prior Rx – Prostate Bed**

Radical prostatectomy: 22% +ve

Radiotherapy: 52% +ve

## Conclusions

**$^{68}$Ga-PSMA PET improves detection of metastases with BCR, particularly at low PSA**

***Important context for prior therapy***

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Future ONCOLOGY

**SPECIAL REPORT**



# The phytological future of prostate cancer staging: prostate-specific membrane antigen positron emission tomography and the dandelion theory

Niranjan J Sathianathen[1], Nicolas Geurts[1], Rajesh Nair[1], Nathan Lawrentschuk[1,2], Declan G Murphy[1,3] & Alastair D Lamb*[,1,4,5]

**Table 1. $^{68}$Ga-Prostate-specific membrane antigen-positron emission tomography/CT detection rate based on PSA values.**

| PSA (ng/ml) | $^{68}$Ga-PSMA PET/CT detection rate | |
|---|---|---|
| | Perera *et al.* [18] | Eiber *et al.* [20] |
| 0.2–<0.5 | 58% | 57.9% |
| 0.5–<1 | | 72.7% |
| 1–<2 | 76% | 93.0% |
| ≥2 | 95% | 96.8% |

PET: Positron emission tomography; PSA: Prostate specific antigen; PSMA: Prostate-specific membrane antigen.

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology


Platinum Opinion

# "Gotta Catch 'em All", or Do We? *Pokemet* Approach to Metastatic Prostate Cancer

*Declan G. Murphy* [a,b,c,*], *Christopher J. Sweeney* [d], *Bertrand Tombal* [e]

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CANCER, PROSTATE, PSMA-PET

## WHACK-A-MOLE AND PROSTATE CANCER

Oligometastasis: Good News from the ORIOLE Study

To the growing and hopeful list of strategies for attacking prostate cancer, let us add this approach: Whack-a-Mole.

That's how Johns Hopkins radiation oncologist Phuoc Tran, M.D., Ph.D., describes it to his patients. The actual scientific name for this highly sophisticated strategy is stereotactic

https://vitaljake.com/whack-a-mole-and-prostate-cancer/

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# Guidelines on what next after BCR

# AUA guidance re BCR



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Guidelines

## Salvage Therapy for Prostate Cancer: AUA/ASTRO/SUO Guideline Part I: Introduction and Treatment Decision-Making at the Time of Suspected Biochemical Recurrence after Radical Prostatectomy

Todd M. Morgan,[1] Stephen A. Boorjian,[2] Mark K. Buyyounouski,[3] Brian F. Chapin,[4] David Y. T. Chen,[5] Heather H. Cheng,[6] Roger Ch Heather A. Jacene,[8] Sophia C. Kamran,[9] Sennett K. Kim,[10] Erin Ki Amy N. Luckenbaugh,[11] Ben J. Nathanson,[12] Yaw A. Nyame,[13] Edwin M. Posadas,[14] Phuoc T. Tran,[15] and Ronald C. Chen[16]

https://doi.or
www.auajourn

**Table 1.** *High-risk Features in the Setting of BCR to be Considered for Patient Counseling and Management*[a]

- Grade Group 4-5
- Stage pT3b-4
- Surgical margin status[b]
- Node-positive disease
- Short PSA doubling time (PSADT)
- Short interval from primary therapy to PSA recurrence (including persistent detectable PSA after prostatectomy)
- Higher post-prostatectomy PSA
- Genomic classifier risk
- PET imaging findings

[a] The Panel recognizes that the above does not represent an exhaustive list of relevant prognostic variables.
[b] Of note, the presence of positive surgical margins has been associated both with an increased likelihood of BCR as well as a lower risk of disease progression after salvage radiation.

## GUIDELINE STATEMENTS

### Treatment Decision-making at the Time of Suspected BCR after Primary RP

1. Clinicians should inform patients that salvage radiation for a detectable prostate-specific antigen (PSA) after RP is more effective when given at lower levels of PSA. (*Strong Recommendation; Evidence Level: Grade B*)

2. For patients with a detectable PSA after RP in whom salvage RT is being considered, clinicians should provide salvage radiation when the PSA is ≤ 0.5 ng/mL. (*Moderate Recommendation; Evidence Level: Grade B*)

3. For patients with a detectable PSA after RP who are at high risk for clinical progression, clinicians may offer salvage radiation when PSA values are < 0.2 ng/mL. (*Conditional Recommendation; Evidence Level: Grade C*)

4. Clinicians should inform patients that salvage radiation after RP poses inherent risks to urinary control, erectile function, and bowel function. These risks must be considered in the context of the risks posed by recurrent cancer along with patient life expectancy, comorbidities, and preferences to facilitate a shared decision-making (SDM) approach to management. *(Clinical Principle)*

5. Clinicians should use prognostic factors (eg, PSADT, Gleason Grade Group, pathologic stage, surgical margin status, validated post-prostatectomy genomic classifier and/or PET imaging results) to counsel patients with a detectable PSA about their risk of clinical progression. *(Moderate Recommendation; Evidence Level: Grade B)*

6. Clinicians may obtain ultrasensitive PSA following RP in patients who are at high risk of recurrence and in whom salvage RT would be considered. (*Expert Opinion*)

7. For patients who do not meet the AUA definition of BCR after RP (PSA ≥ 0.2 ng/mL) yet have a detectable ultrasensitive PSA, clinicians should confirm a rising trend in PSA before proceeding with therapy. (*Expert Opinion*)

8. In patients with a BCR after local therapy, clinicians may obtain a PSMA-PET in lieu of conventional imaging or after negative conventional imaging for further evaluation of clinical recurrence. (*Conditional Recommendation; Evidence Level: Grade C*)

9. For patients with BCR following RP in whom salvage radiation is being considered, the clinician should perform next generation molecular PET imaging. (*Moderate Recommendation; Evidence Level: Grade C*)

10. In patients with BCR following RP with PET/CT positive pelvic nodal disease, the clinician should incorporate treatment of these positive findings in the radiation plan. (*Moderate Recommendation; Evidence Level: Grade C*)

12. In a patient with a BCR following RP, clinicians should not withhold salvage prostate bed RT in the setting of a negative PET/CT. (*Expert Opinion*)

11. In patients with BCR, clinicians may obtain a pelvic MRI in addition to a PET/CT for evaluation of local recurrence. (*Conditional Recommendation; Evidence Level: Grade C*)

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Vol. 211, 509-517, April 2024
Printed in U.S.A.
www.auajournals.org/jurology

TABLE 1: Strength of Evidence Definitions

| AUA Strength of Evidence Category | GRADE Certainty Rating | Definition |
|---|---|---|
| **A** | High | • Very confident that the true effect lies close to that of the estimate of the effect |
| **B** | Moderate | • Moderately confident in the effect estimate<br>• The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different |
| **C** | Low | • Confidence in the effect estimate is limited<br>• The true effect may be substantially different from the estimate of the effect |
| | Very Low | • Very little confidence in the effect estimate<br>• The true effect is likely to be substantially different from the estimate of effect |

American Urological Association

**APPROVED BY THE AUA BOARD OF DIRECTORS FEBRUARY 2024**

Authors' disclosure of potential conflicts of interest and author/staff contributions appear at the end of the article.



TABLE 2: AUA Nomenclature Linking Statement Type to Level of Certainty, Magnitude of Benefit or Risk/Burden, and Body of Evidence Strength

| Evidence Grade | Evidence Strength A (High Certainty) | Evidence Strength B (Moderate Certainty) | Evidence Strength C (Low Certainty) |
|---|---|---|---|
| Strong Recommendation<br>(Net benefit or harm substantial) | -Benefits > Risks/Burdens (or vice versa)<br>-Net benefit (or net harm) is substantial<br>-Applies to most patients in most circumstances and future research is unlikely to change confidence | -Benefits > Risks/Burdens (or vice versa)<br>-Net benefit (or net harm) is substantial<br>-Applies to most patients in most circumstances but better evidence could change confidence | -Benefits > Risks/Burdens (or vice versa)<br>-Net benefit (or net harm) appears substantial<br>-Applies to most patients in most circumstances but better evidence is likely to change confidence (rarely used to support a Strong Recommendation) |
| Moderate Recommendation<br>(Net benefit or harm moderate) | -Benefits > Risks/Burdens (or vice versa)<br>-Net benefit (or net harm) is moderate<br>-Applies to most patients in most circumstances and future research is unlikely to change confidence | -Benefits > Risks/Burdens (or vice versa)<br>-Net benefit (or net harm) is moderate<br>-Applies to most patients in most circumstances but better evidence could change confidence | -Benefits > Risks/Burdens (or vice versa)<br>-Net benefit (or net harm) appears moderate<br>-Applies to most patients in most circumstances but better evidence is likely to change confidence |
| Conditional Recommendation<br>(Net benefit or harm comparable to other options) | -Benefits = Risks/Burdens<br>-Best action depends on individual patient circumstances<br>-Future Research is unlikely to change confidence | -Benefits = Risks/Burdens<br>-Best action appears to depend on individual patient circumstances<br>-Better evidence could change confidence | -Balance between Benefits & Risks/Burdens unclear<br>-Net benefit (or net harm) comparable to other options<br>-Alternative strategies may be equally reasonable<br>-Better evidence likely to change confidence |
| Clinical Principle | a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature | | |
| Expert Opinion | a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there may or may not be evidence in the medical literature | | |

# Risk stratified approach

Prostate Cancer and Prostatic Diseases www.nature.com/pcan

REVIEW ARTICLE OPEN

Clinical Research

# Biochemical recurrence in patients with prostate cancer after primary definitive therapy: treatment based on risk stratification

Neal D. Shore[1,8], Judd W. Moul[2,8], Kenneth J. Pienta[3], Johannes Czernin[4], Martin T. King[5] and Stephen J. Freedland[6,7]✉



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## Risk-adapted salvage treatment options in patients with biochemical recurrence after primary definitive therapy for prostate cancer

### After Radical Prostatectomy (RP): Prostate-specific antigen (PSA), >0.2 ng/ml[a]

**Salvage EBRT**
- PSA level, <0.7 ng/ml
- PSA doubling time (PSADT), <6 months

**Salvage EBRT + Androgen Deprivation Therapy (ADT)**
- Genomic classifier score, high-risk
- Gleason score, 8–10
- Life expectancy, ≥10 years
- Pre-EBRT PSA level, ≥0.7 ng/ml
- Positive surgical margin

**Salvage ADT (intermittent)**
- PSADT, ≤12 months
- Gleason score, >7
- Life expectancy, >10 years

**Patient with biochemical recurrence (BCR)**

### After External Beam Radiation Therapy (EBRT): PSA increase >0.2 ng/ml above the PSA nadir

**Salvage RP**
- No evidence of distant metastases, including negative MTI
- Life expectancy, > 10 years (few comorbidities)
- Pre-surgical PSA level, <10 ng/ml

**Brachytherapy or High-intensity Focused Ultrasound (HIFU)**
- No evidence of distant metastases, including negative MTI
- International Prostate Symptom Score (IPSS), ≤15
- No grade ≥2 gastrointestinal or genitourinary toxicity
- Prostate volume, ≤45 cc
- PSA level, <10 ng/ml

**Salvage ADT (intermittent)**
- Interval to BCR, ≤18 months
- Gleason score, 8–10
- Life expectancy, ≤10 years

**Fig. 1 Risk-adapted salvage treatment options in patients with biochemical recurrence after primary definitive therapy for prostate cancer.** Clinicopathological and genetic factors recommended by medical societies and expert groups for the consideration of salvage treatments in patients with BCR [8, 9, 16, 48, 94].

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**CONCLUSIONS:** Despite a lack of consensus for BCR treatment among guideline associations and medical societies, risk stratification of patients is essential for personalized treatment approaches, as it allows for an informed selection of therapeutic strategies and estimation of adverse events. In lower-risk disease, observation is recommended while in higher-risk disease, after failed repeat local therapy, ADT and/or clinical trial enrollment may be appropriate. Results from ongoing clinical studies of patients with BCR should provide consensus for management.

*Prostate Cancer and Prostatic Diseases*; https://doi.org/10.1038/s41391-023-00712-z

# Non-urological / non-prostate-wallah perceptions


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EAU19 | BARCELONA
15-19 March 2019

| | | |
|---|---|---|
| G3pT1<br>bladder cancer | = | GG5 T3b<br>prostate cancer |

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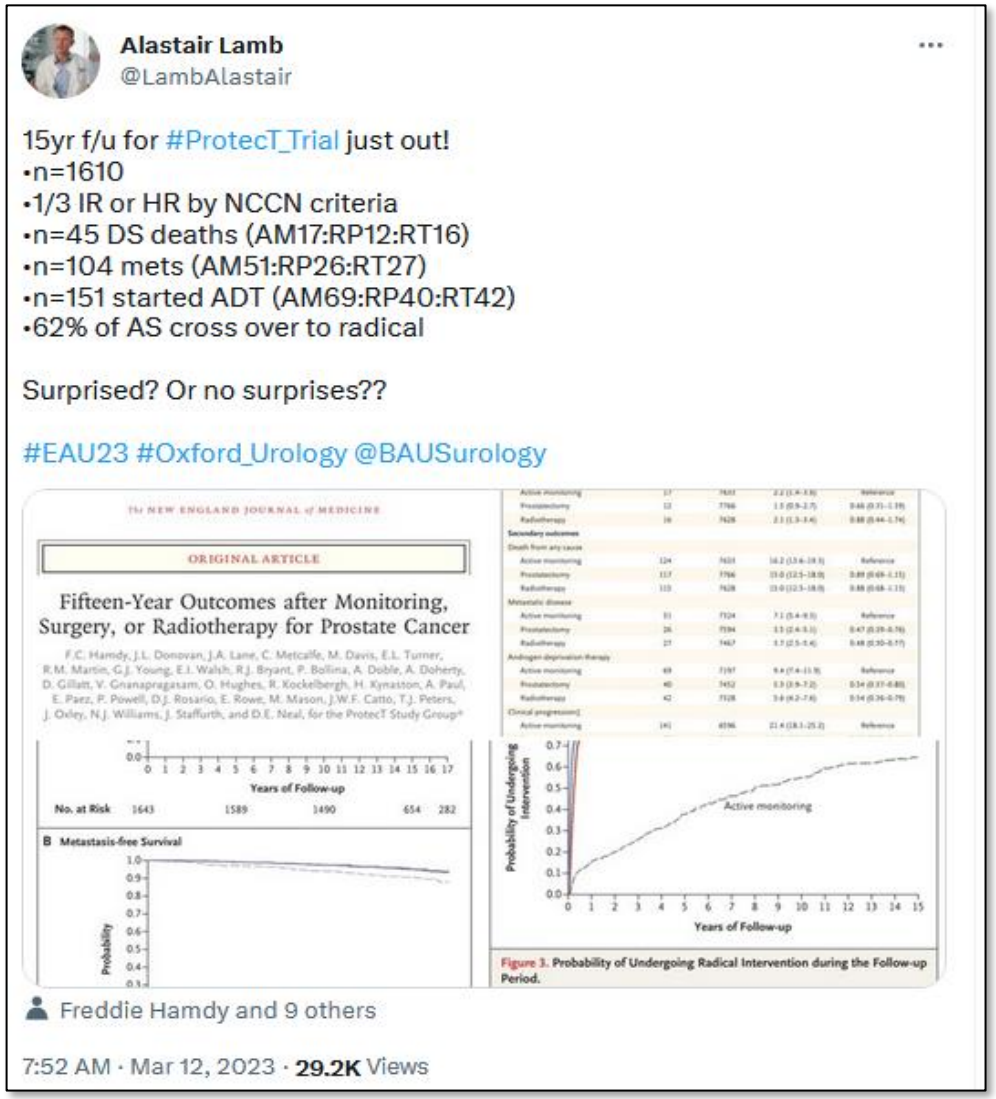
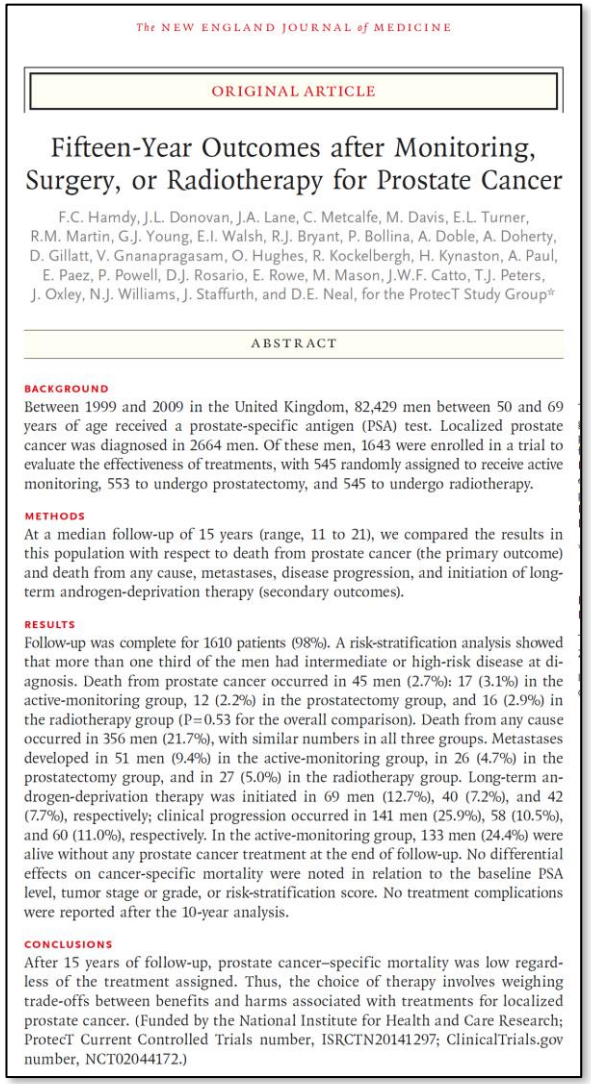
# BCR in efficacy research

# Prostate Cancer trials need OS/DSS

## Most men don't need treating!!

DOI: 10.1056/NEJMoa2214122

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Fifteen-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer

F.C. Hamdy, J.L. Donovan, J.A. Lane, C. Metcalfe, M. Davis, E.L. Turner, R.M. Martin, G.J. Young, E.I. Walsh, R.J. Bryant, P. Bollina, A. Doble, A. Doherty, D. Gillatt, V. Gnanapragasam, O. Hughes, R. Kockelbergh, H. Kynaston, A. Paul, E. Paez, P. Powell, D.J. Rosario, E. Rowe, M. Mason, J.W.F. Catto, T.J. Peters, J. Oxley, N.J. Williams, J. Staffurth, and D.E. Neal, for the ProtecT Study Group*

ABSTRACT

**BACKGROUND**

Between 1999 and 2009 in the United Kingdom, 82,429 men between 50 and 69 years of age received a prostate-specific antigen (PSA) test. Localized prostate cancer was diagnosed in 2664 men. Of these men, 1643 were enrolled in a trial to evaluate the effectiveness of treatments, with 545 randomly assigned to receive active monitoring, 553 to undergo prostatectomy, and 545 to undergo radiotherapy.

**METHODS**

At a median follow-up of 15 years (range, 11 to 21), we compared the results in this population with respect to death from prostate cancer (the primary outcome) and death from any cause, metastases, disease progression, and initiation of long-term androgen-deprivation therapy (secondary outcomes).

**RESULTS**

Follow-up was complete for 1610 patients (98%). A risk-stratification analysis showed that more than one third of the men had intermediate or high-risk disease at diagnosis. Death from prostate cancer occurred in 45 men (2.7%): 17 (3.1%) in the active-monitoring group, 12 (2.2%) in the prostatectomy group, and 16 (2.9%) in the radiotherapy group (P=0.53 for the overall comparison). Death from any cause occurred in 356 men (21.7%), with similar numbers in all three groups. Metastases developed in 51 men (9.4%) in the active-monitoring group, in 26 (4.7%) in the prostatectomy group, and in 27 (5.0%) in the radiotherapy group. Long-term androgen-deprivation therapy was initiated in 69 men (12.7%), 40 (7.2%), and 42 (7.7%), respectively; clinical progression occurred in 141 men (25.9%), 58 (10.5%), and 60 (11.0%), respectively. In the active-monitoring group, 133 men (24.4%) were alive without any prostate cancer treatment at the end of follow-up. No differential effects on cancer-specific mortality were noted in relation to the baseline PSA level, tumor stage or grade, or risk-stratification score. No treatment complications were reported after the 10-year analysis.

**CONCLUSIONS**

After 15 years of follow-up, prostate cancer–specific mortality was low regardless of the treatment assigned. Thus, the choice of therapy involves weighing trade-offs between benefits and harms associated with treatments for localized prostate cancer. (Funded by the National Institute for Health and Care Research; ProtecT Current Controlled Trials number, ISRCTN20141297; ClinicalTrials.gov number, NCT02044172.)

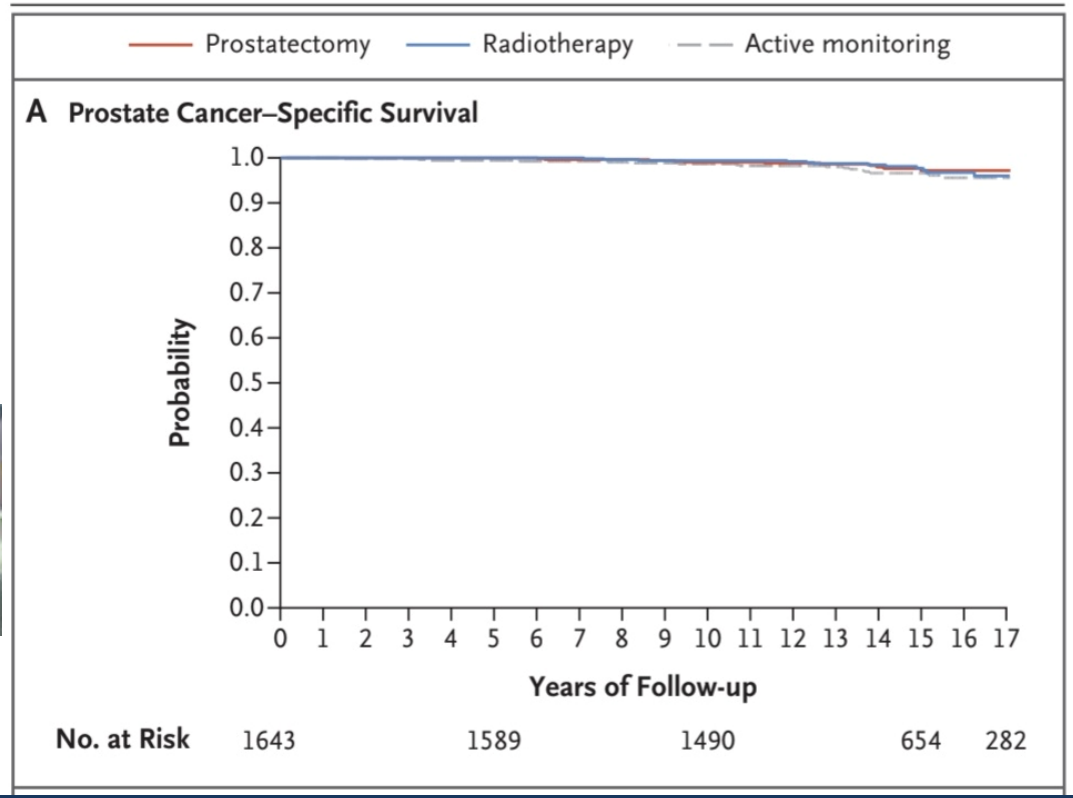
# Prostate Cancer trials need OS/DSS

Most men don't need treating!!

Alastair Lamb
@LambAlastair

15yr f/u for #ProtecT_Trial just out!
•n=1610
•1/3 IR or HR by NCCN criteria
•n=45 DS deaths (AM17:RP12:RT16)
•n=104 mets (AM51:RP26:RT27)
•n=151 started ADT (AM69:RP40:RT42)
•62% of AS cross over to radical

DOI: 10.1056/NEJMoa22141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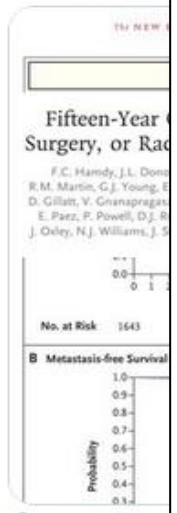
Surprised? Or no surprises??

#EAU23 #O



Freddie Ha

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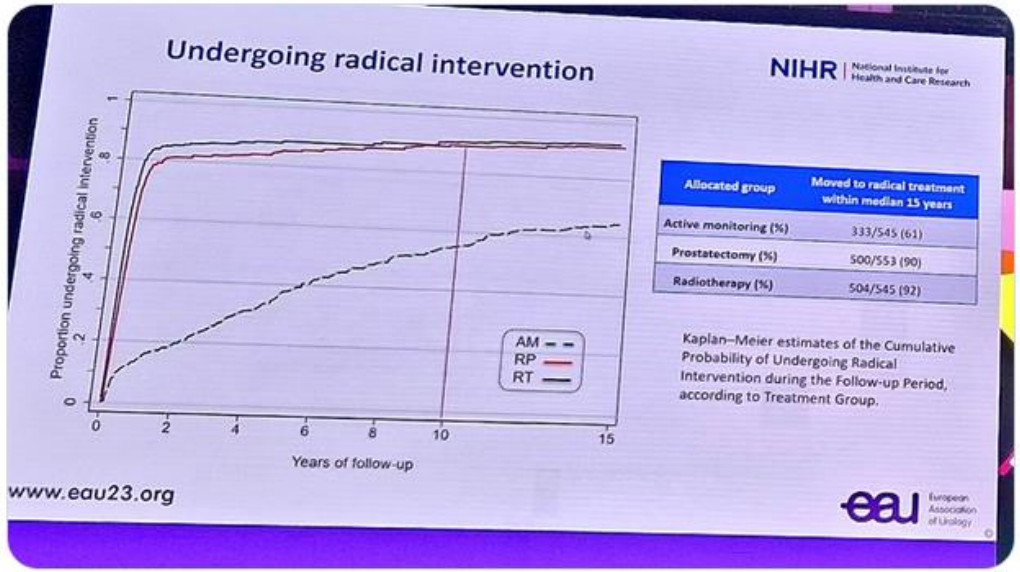
**Alastair Lamb** @LambAlastair · Mar 13

Whatever "progress" would mean in this brave new world??

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# Loose ends

# GG1

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**Risk of Biochemical Recurrence in Patients With Grade Group 1 Prostate Cancer With Extraprostatic Extension Treated With Radical Prostatectomy**

Michael E. Rezaee,[1] Maximilian Pallauf,[1,2] Sean A. Fletcher,[1] Misop Han,[1] Christian P. Pavlovich,[1] Chien-Kuang Cornelia Ding,[1,3] Jonathan I. Epstein,[1,3] Mohamad E. Allaf,[1] Bruce J. Trock,[1,4] and Nirmish Singla[1]

n=2740 with GG1
n= 169 EPE
2005-

Review > J Urol. 2024 Mar;211(3):407-414. doi: 10.1097/JU.0000000000003825. Epub 2023 Dec 18.

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Affiliations + expand

PMID: 38109699 DOI: 10.1097/JU.0000000000003825

## Abstract

**Purpose:** We sought to examine the association of extraprostatic extension (EPE) with biochemical recurrence (BCR) separately in men with Grade Group (GG) 1 and GG2 prostate cancer (PCa) treated with radical prostatectomy.

**Materials and methods:** We reviewed our institutional database of patients who underwent radical prostatectomy for PCa between 2005 and 2022 and identified patients with GG1 and GG2 disease on final pathology. Fine-Gray competing risk models with an interaction between EPE (yes vs no) and GG (GG1 vs GG2) were used to examine the relationship between disease group and BCR-free survival.

**Results:** The cohort consisted of 6309 men, of whom 169/2740 (6.2%) with GG1 disease had EPE while 1013/3569 (28.4%) with GG2 disease had EPE. Median follow-up was 4 years. BCR occurred in 400/6309 (6.3%) patients. For men with GG1, there was no statistically significant difference in BCR-free survival for men with vs without EPE (subdistribution HR = 0.88; 95% CI: 0.37-2.09). However, for GG2 patients BCR-free survival was significantly worse for those with vs without EPE (subdistribution HR = 1.97, 95% CI: 1.54-2.52).

**Conclusions:** Although there is a subset of GG1 PCas capable of invading through the prostatic capsule, patients with GG1 PCa and EPE at prostatectomy experience similar biochemical recurrence and survival outcomes compared to GG1 patients without EPE. However, among men with GG2, EPE connotes a worse prognosis.

**Keywords:** biochemical recurrence; extraprostatic extension; grade group 1; prostate cancer; survival.

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# GG1

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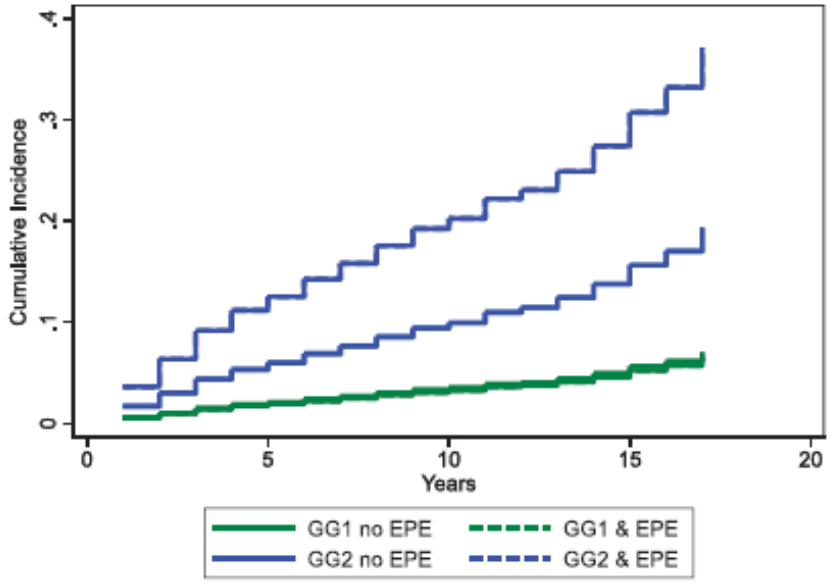
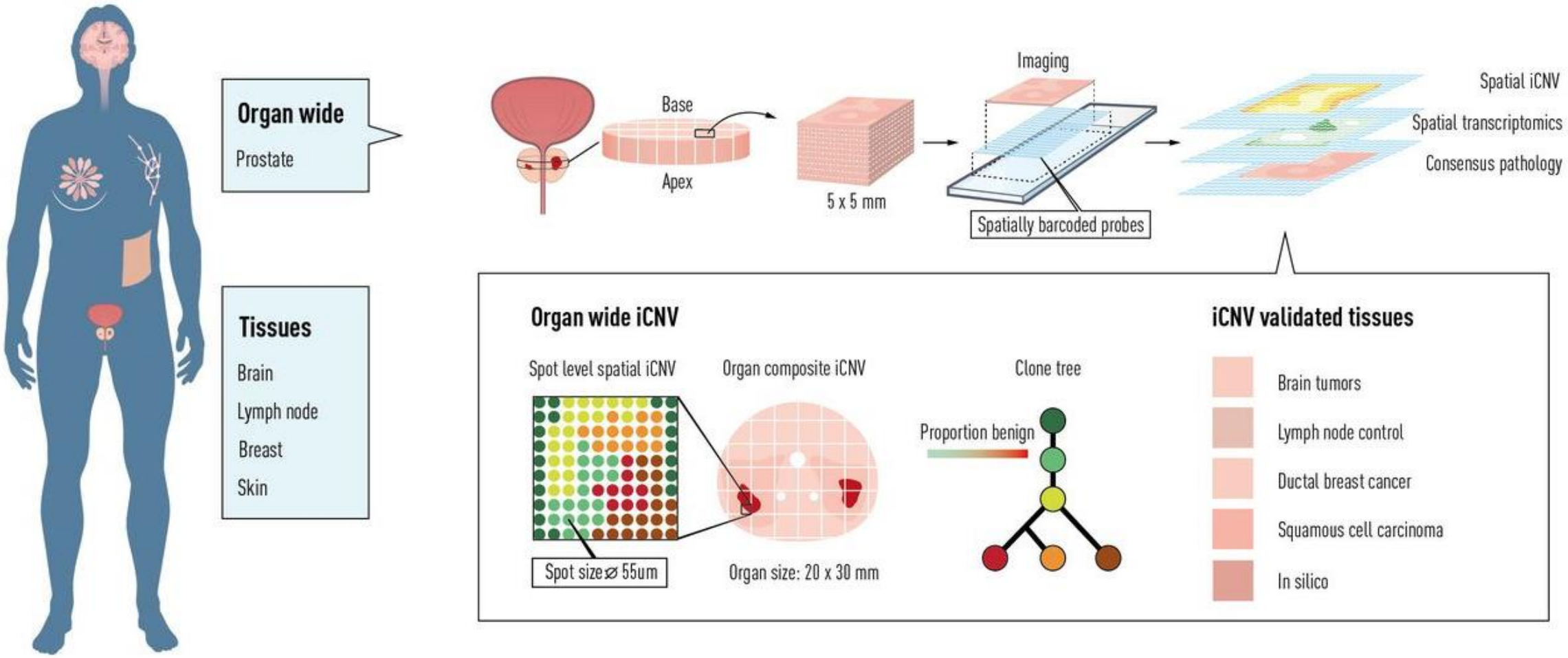



| Num. at Risk | | | | | |
|---|---|---|---|---|---|
| GG1 no EPE | 2571 | 1426 | 833 | 235 | 0 |
| GG1 & EPE | 169 | 88 | 53 | 15 | 0 |
| GG2 no EPE | 2556 | 1102 | 439 | 69 | 0 |
| GG2 & EPE | 1013 | 402 | 166 | 25 | 0 |

Figure 2. Cumulative incidence of biochemical recurrence by extraprostatic extension (EPE) status for Grade Group (GG) 1 and GG2 disease. The GG1 without EPE (solid green) and GG1 with EPE (dash green) lines essentially overlap.

**Keywords:** biochemical recurrence; extraprostatic extension; grade group 1; prostate cancer; survival.

# Prostate Spatial Transcriptomics




Erickson et al & Lamb, Nature, 2022
https://doi.org/10.1038/s41586-022-05023-2

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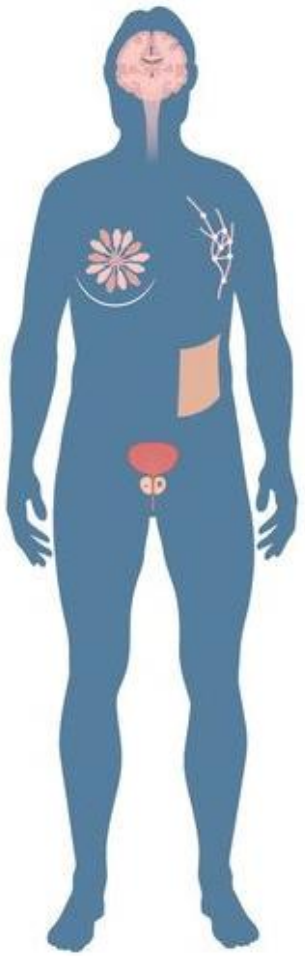


**Organ wide**

Prostate

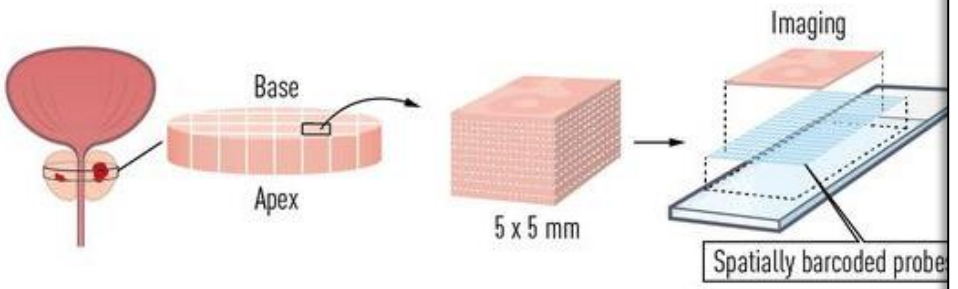
**Tissues**

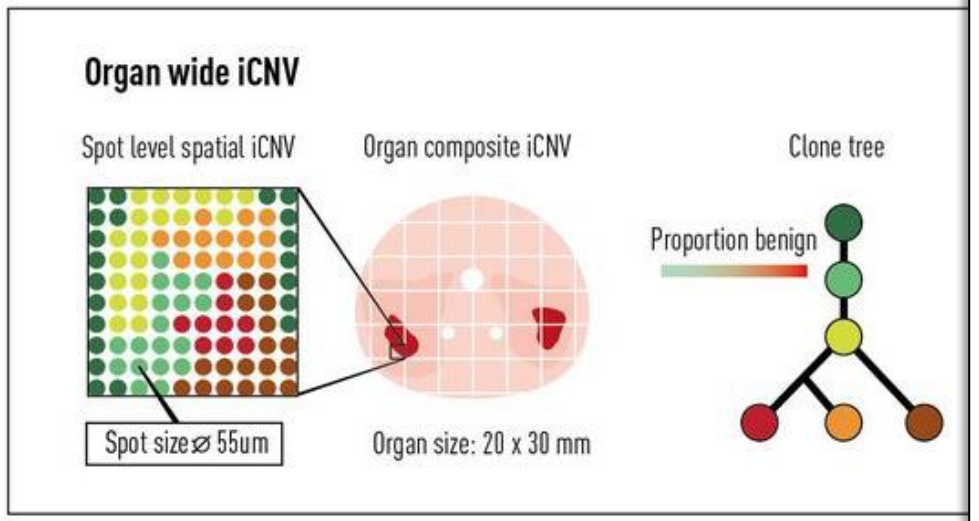
Brain

Lymph node

Breast

Skin




Article

## Spatially resolved clonal copy number alterations in benign and malignant tissue

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Accepted: 23 June 2022
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Check for updates

Andrew Erickson[1,15], Mengxiao He[2,15], Emelie Berglund[2,15], Maja Marklund[2], Reza Mirzazadeh[2], Niklas Schultz[2], Linda Kvastad[2], Alma Andersson[2], Ludvig Bergenstråhle[2], Joseph Bergenstråhle[2], Ludvig Larsson[2], Leire Alonso Galicia[2], Alia Shamikh[4,5], Elisa Basmaci[4,5], Teresita Diaz De Ståhl[4,5], Timothy Rajakumar[3], Dimitrios Doultsinos[1], Kim Thrane[2], Andrew L. Ji[6], Paul A. Khavari[6], Firaz Tarish[2], Anna Tanoglidi[7], Jonas Maaskola[2], Richard Colling[1,8], Tuomas Mirtti[9,10,11], Freddie C. Hamdy[1,12], Dan J. Woodcock[1,12], Thomas Helleday[3,14], Ian G. Mills[1], Alastair D. Lamb[1,12,16] ✉ & Joakim Lundeberg[2,16] ✉

Defining the transition from benign to malignant tissue is fundamental to improving early diagnosis of cancer[1]. Here we use a systematic approach to study spatial genome integrity in situ and describe previously unidentified clonal relationships. We used spatially resolved transcriptomics[2] to infer spatial copy number variations in >120,000 regions across multiple organs, in benign and malignant tissues. We demonstrate that genome-wide copy number variation reveals distinct clonal patterns within tumours and in nearby benign tissue using an organ-wide approach focused on the prostate. Our results suggest a model for how genomic instability arises in histologically benign tissue that may represent early events in cancer evolution. We highlight the power of capturing the molecular and spatial continuums in a tissue context and challenge the rationale for treatment paradigms, including focal therapy.

Mutations can be either inherited or acquired (somatic). Inherited genomic polymorphisms are readily identifiable as these are present in all cells, whereas post-developmental somatic mutations are usually present in only a small fraction of cells[3]. To obtain spatial information about these rarer non-heritable genetic events, studies have commonly used laser-capture microdissection to retrieve histologically defined (or biomarker-defined) tissue regions or even single cells[4,5]. These studies have an inherent bias as only a limited number of spatial regions or single cells per tissue section can be collected and examined. The possibility to perform spatial genome analysis without being confined by histological boundaries would therefore provide an important contribution to delineating the clonal architecture in tumours and co-existing benign tissue.

### Inferred copy number variation predicts clonal hierarchies

Spatially resolved transcriptomics has emerged as a tool for genome-wide analysis of gene expression to explore tissues in an unsupervised manner[6]. In this study, we infer genome-wide copy number variations (CNVs) from spatially resolved mRNA profiles in situ (Fig. 1a). Gene expression has previously been used to infer CNVs in single cells, successfully identifying regions of chromosomal gain and loss[7]. Here we expand into a spatial modality, generating CNV calls in each spatial region represented by barcoded spots. First, using unsupervised clustering methods, we sought corroboration that inferred CNV data (obtained using inferCNV[8]) could mirror DNA-based phylogenies, constructed using simultaneously extracted RNA and DNA from single cells[9] (Extended Data Fig. 1a). Next, we attempted to recapitulate published DNA-based phylogenies in prostate cancer using RNA from the same samples[9–11] (Extended Data Fig. 1b,c) and identified similarity between automated clone calling and published phylogenies. To ensure that inferCNV[8] could robustly capture sufficient and accurate CNV information for individual spots from a multifocal tumour model and enable us to deduce clonal relationships between cells, we designed an in silico system to synthesize a tissue containing multiple clones determined by stochastic copy number mutations in a single artificial chromosome. Using a probabilistic method to generate gene expression from such mutations, we then interrogated the expression data using spatial inferred CNVs (siCNVs), while blind to the underlying 'ground-truth' copy number status, and successfully recapitulated both the copy number status and the clonal groupings (Extended Data Fig. 2a–c).

### Organ-wide clonal landscape in the prostate

Next, we used a cross-section of an entire prostate organ to explore the siCNV landscape of a commonly multifocal malignancy[12]. The

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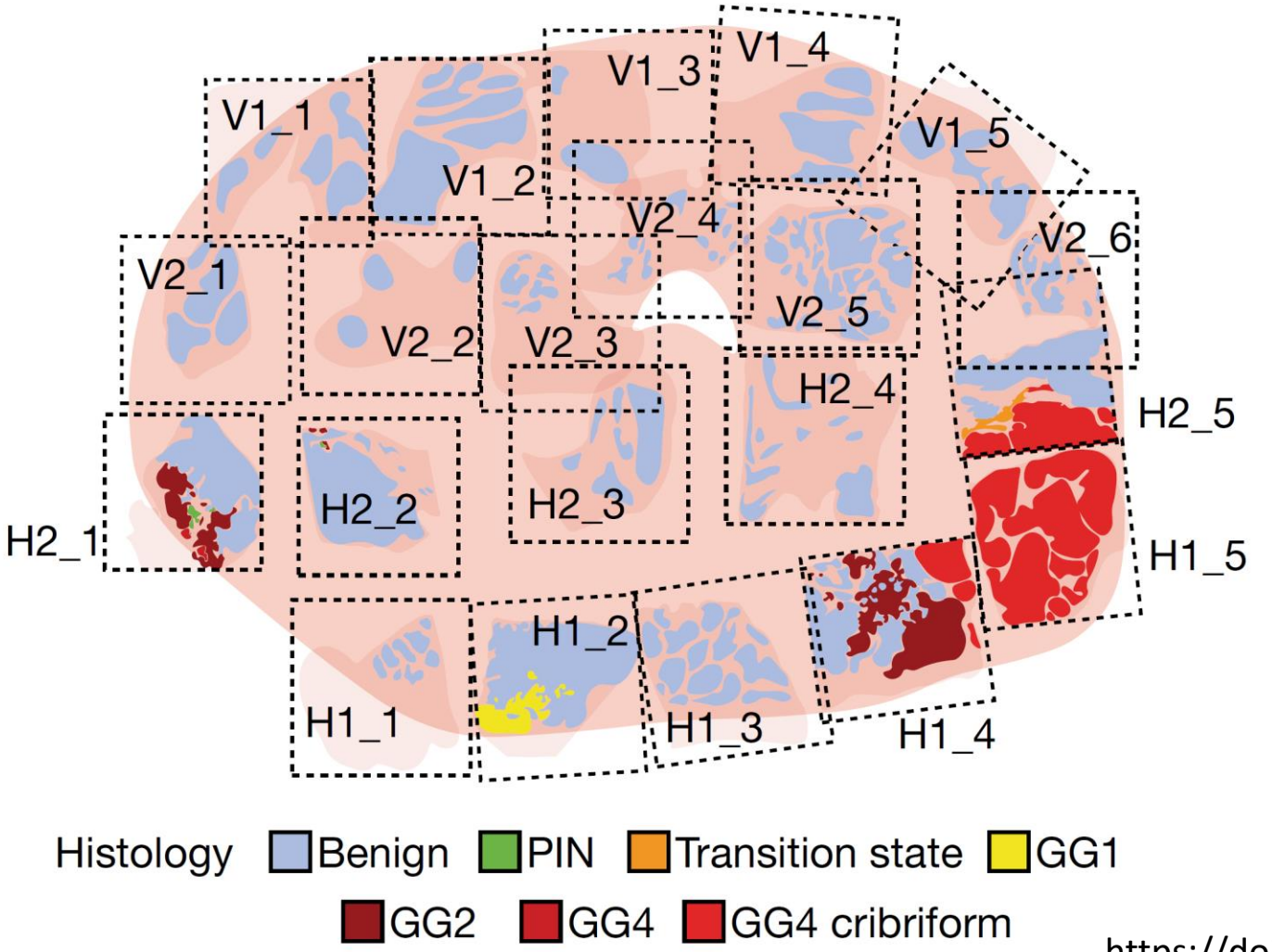
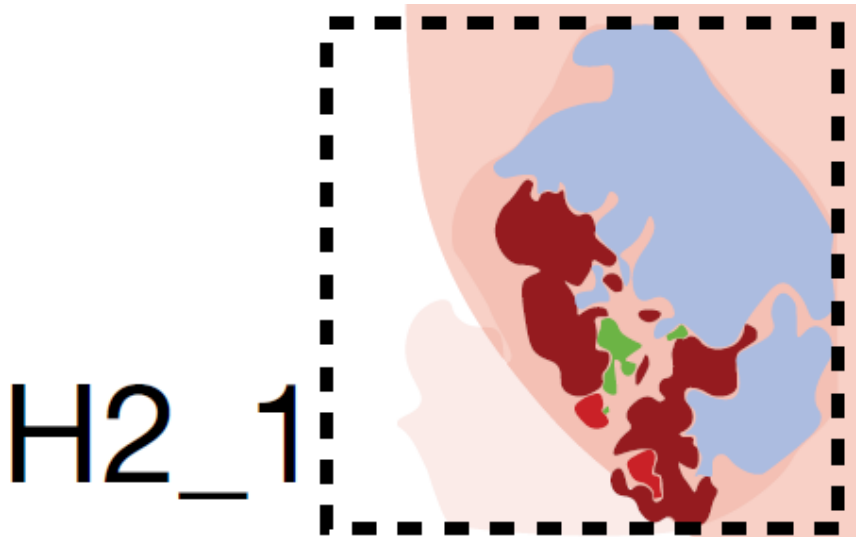
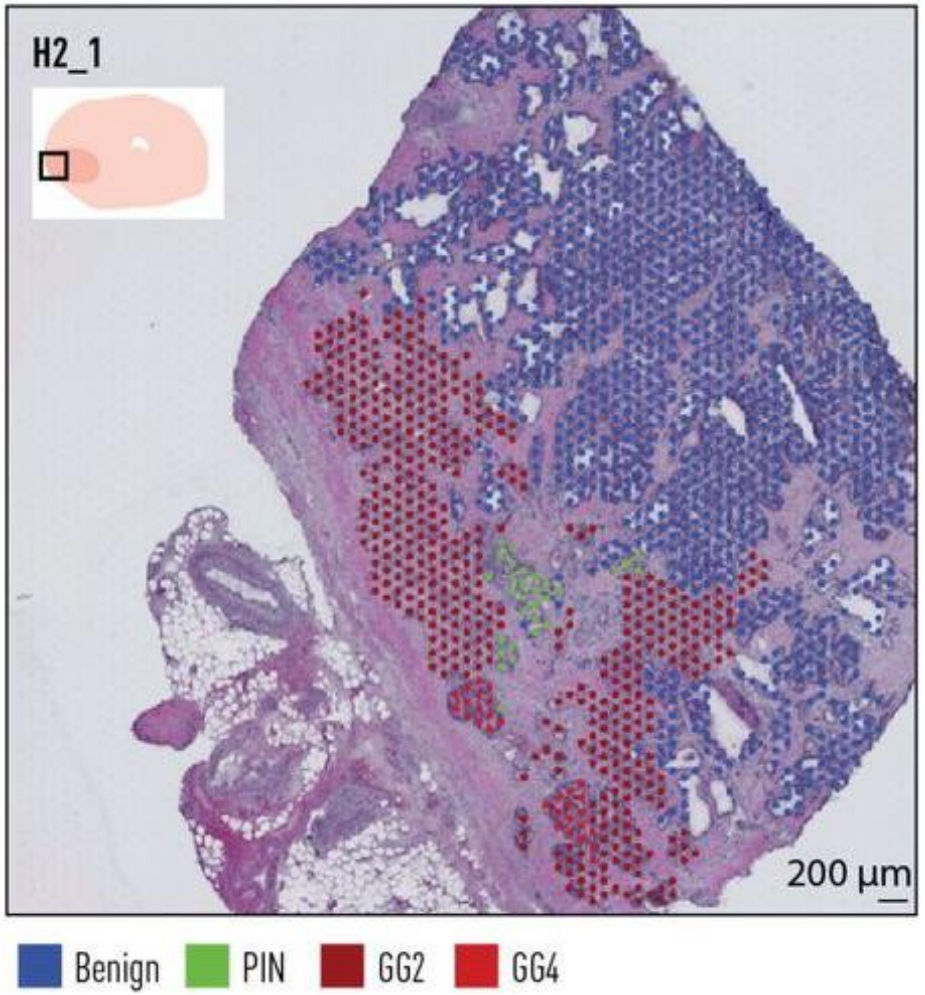
# Organwide histological heterogeneity




Erickson et al, Nature, 2022
https://doi.org/10.1038/s41586-022-05023-2

# Focus on one section with heterogeneity

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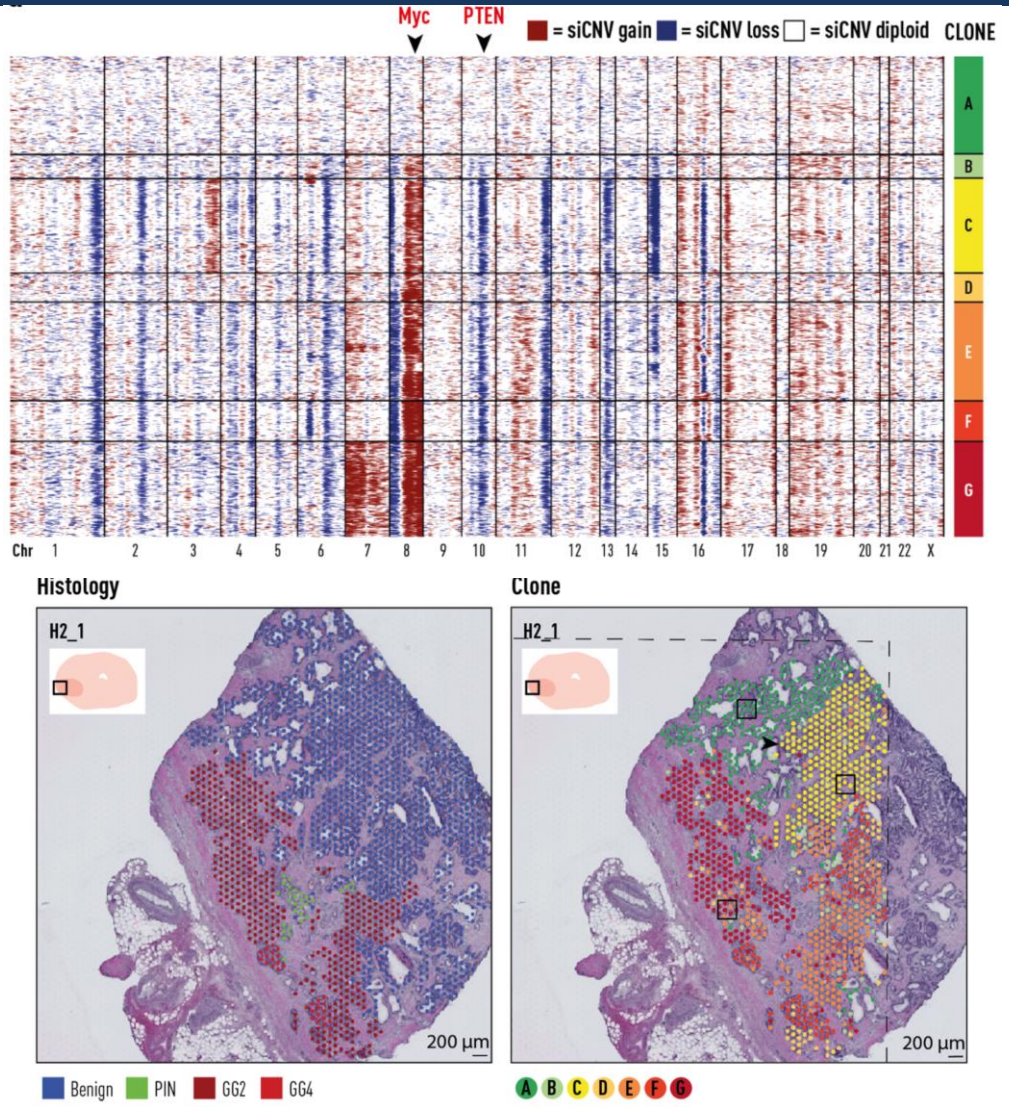
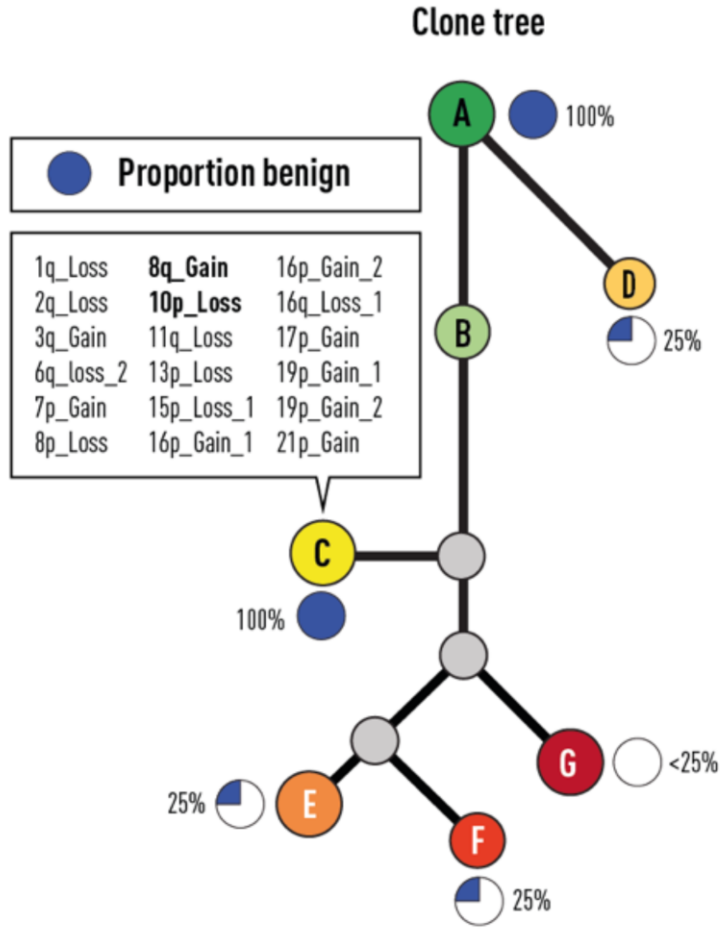
# Clonal lineage of csPCa

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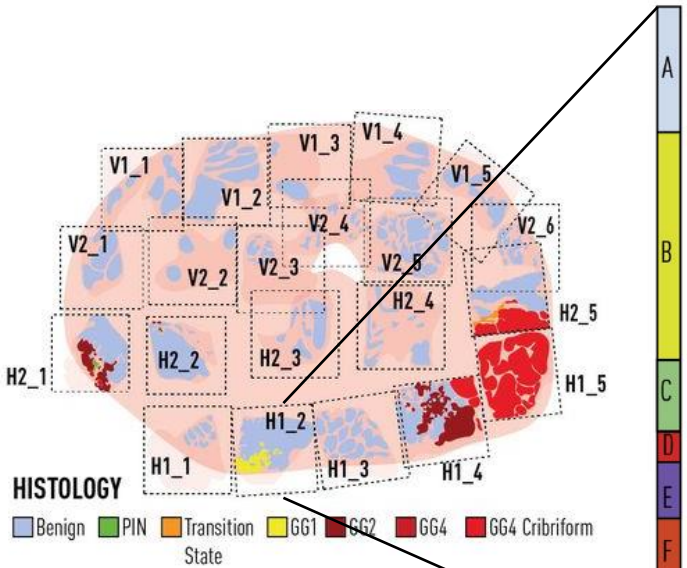
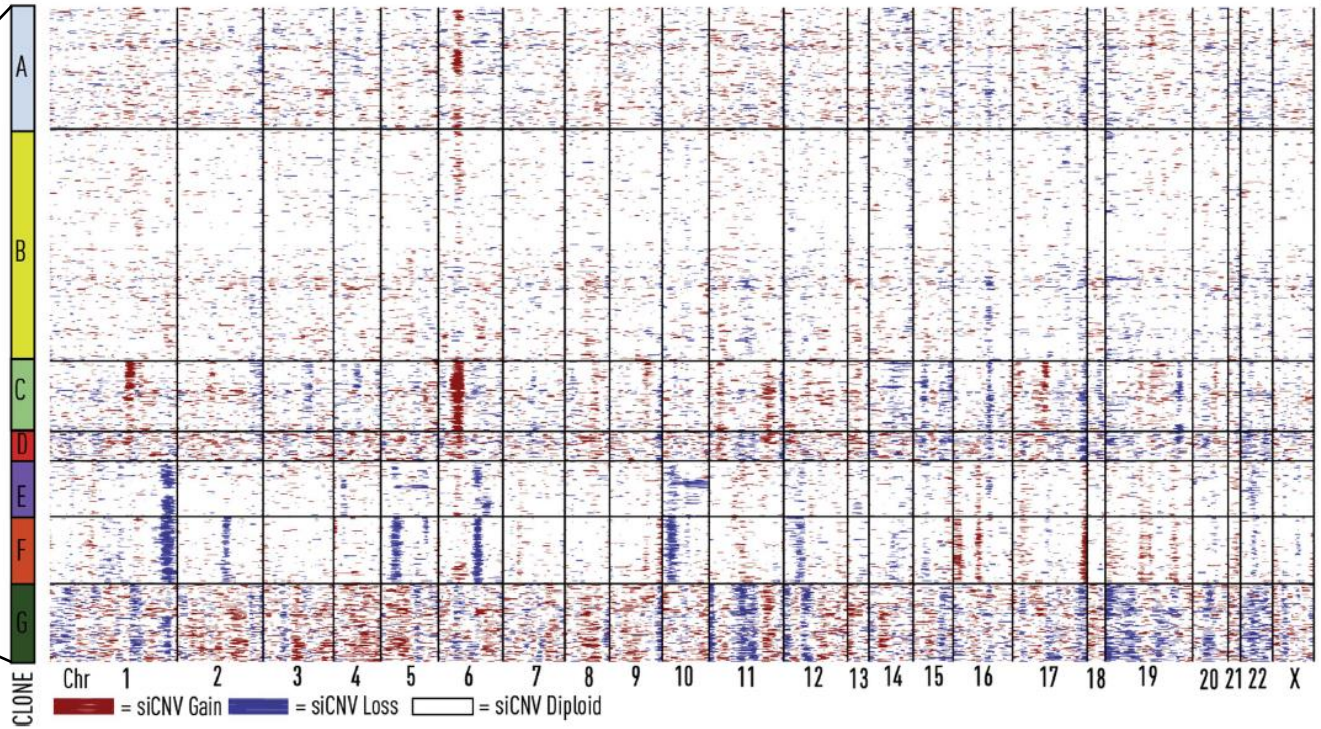
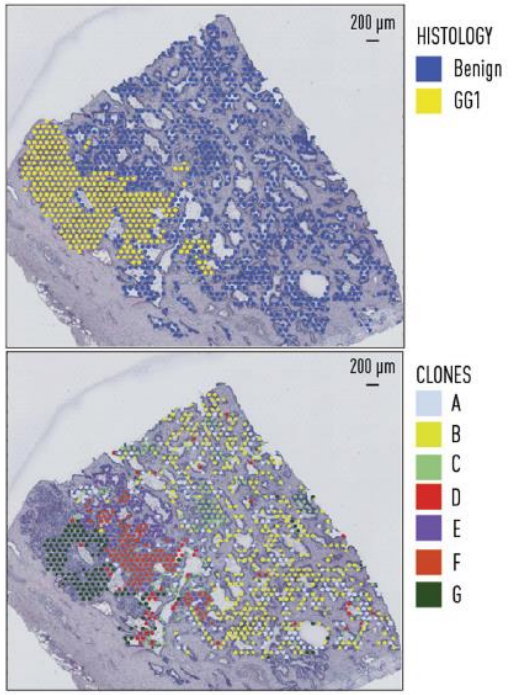
# Low grade PCa lacks key CN events

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