

Erasmus MC



Who needs a lymphadenectomy in prostate cancer?

17t May 2025

Roderick van den Bergh



12th Belgian Multidisciplinary
Meeting on Urological Cancers

Conflicts of interest

I have the following potential conflict(s) of interest to report

Type of affiliation / financial interest	Name of commercial company
Receipt of grants/research supports:	Astellas, Janssen
Receipt of honoraria or consultation fees:	Astellas, Bayer, Janssen



To be discussed

- Guidelines
- Arguments
- Literature
- Discussion



Avoid repeating



In the lions' den?



Developments PLND and PSMA are connected



Logical argument - Syllogism

- Major premise:
All men are mortal
- Minor premise:
Socrates is a man
- Conclusion/Consequent:
Therefore, Socrates is mortal

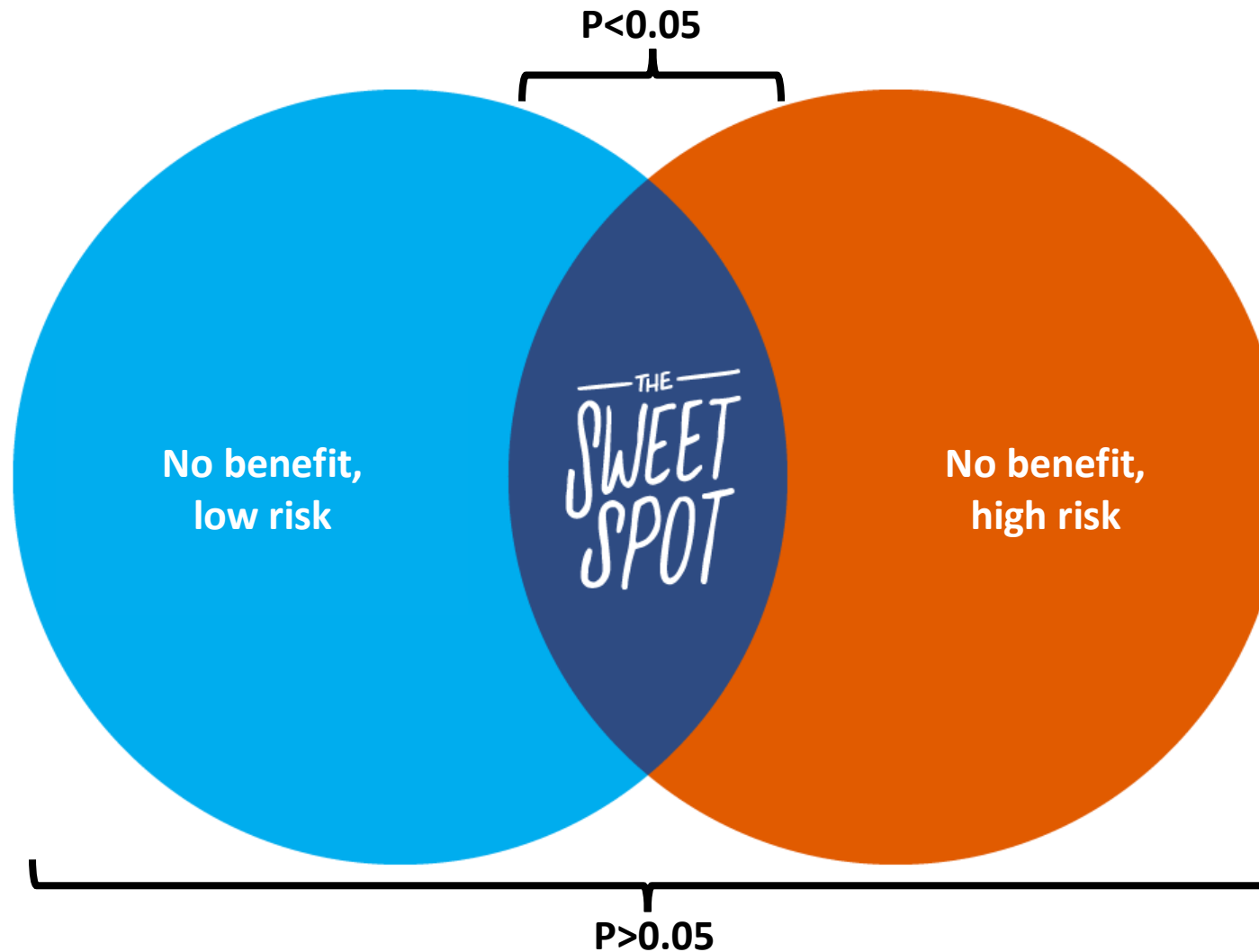


Logical argument – Syllogism – BMUC version

- Removing more cancer has a beneficial impact
- PLND removes more cancer
- Therefore, PLND has a beneficial impact
- **There must per definition be (a few) patients benefitting PLND (?)**



Looking for the PLND sweetspot?



PLND - Overview of guidelines

- *Radical prostatectomy aims at the removal of the entire prostate gland and lymph nodes.*
- *This can be done by an open approach or by keyhole technique (laparoscopic or robotically assisted laparoscopic prostatectomy).*

PLND - overview of guidelines

- *Extended PLND provides more complete staging and may cure some patients with microscopic metastases; therefore, an extended PLND is preferred when PLND is performed.*
- *An extended PLND includes removal of all node-bearing tissue from an area bound by the external iliac vein anteriorly, the pelvic sidewall laterally, the bladder wall medially, the floor of the pelvis posteriorly, Cooper's ligament distally, and the internal iliac artery proximally.*
- *While PLND at the time of RP has not been shown to improve oncologic outcomes, it can provide staging and prognostic information.*



PLND - overview of guidelines

- A PLND can be excluded in patients with low predicated probability of nodal metastases by nomograms, although some patients with lymph node metastases will be missed.
- There is no single evidence-based threshold for performing PLND. Based on the risk of complications with PLND and extra time to perform the procedure, the **published thresholds range from 2% to 7%.**
- A patient who is above the threshold for performing a PLND, but has a **negative PSMA PET scan should still undergo PLND.** In two studies, the sensitivity of PSMA PET for pelvic lymph node involvement among patients undergoing RP and PLND was low (about 40%), and the negative predictive value was about 81%. Thus, basing the decision to perform PLND on a negative PSMA PET scan could result in missing 19% of patients with positive lymph nodes.
- PLND can be performed using an open, laparoscopic, or robotic technique.



PLND - Overview of guidelines



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- Clinicians should inform patients that pelvic lymphadenectomy provides **staging information**, which may guide future management, but **does not have consistently documented improvement in metastasis-free, cancer-specific, or overall survival**. (Moderate Recommendation; Evidence Level: Grade B)
- Clinicians should use **nomograms** to select patients for lymphadenectomy. The potential benefit of identifying lymph node positive disease should be balanced with the risk of complications. (Clinical Principle)
- Clinicians performing pelvic lymphadenectomy should perform an **extended dissection**, which improves staging accuracy compared to a limited dissection. (Moderate Recommendation; Evidence Level: Grade: B)
- Clinicians should complete a radical prostatectomy if suspicious regional nodes are encountered intraoperatively. (Moderate Recommendation; Evidence Level: Grade C)
- Clinicians should risk stratify patients with positive lymph nodes identified at radical prostatectomy based on pathologic variables and postoperative PSA. (Expert Opinion)
- Clinicians may offer patients with positive lymph nodes identified at radical prostatectomy and an **undetectable post-operative PSA adjuvant therapy or observation**. (Conditional Recommendation; Evidence Level: Grade C)



PLND – Overview of guidelines



2023

European
Association
of Urology



12th Belgian Multidisciplinary
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Intermediate risk

Extended pelvic lymph node dissection (ePLND)	
Perform an ePLND based on predicted risk of lymph node invasion (validated nomogram, see Section 6.1.2.3.2.)	Weak
When a lymph node dissection (LND) is deemed necessary based on a nomogram, perform an extended LND template for optimal staging.	Strong

High risk

Extended pelvic lymph node dissection (ePLND)	
Perform an ePLND in high-risk PCa.	Strong
Do not perform a frozen section of nodes during RP to decide whether to proceed with, or abandon, the procedure (see Section 6.2.4.1).	Strong

Advanced

Recommendations	Strength rating
Radical prostatectomy (RP)	
Offer RP to patients with cN0 disease as part of multi-modal therapy.	Weak
Extended pelvic lymph node dissection (ePLND)	
Perform an ePLND.	Strong



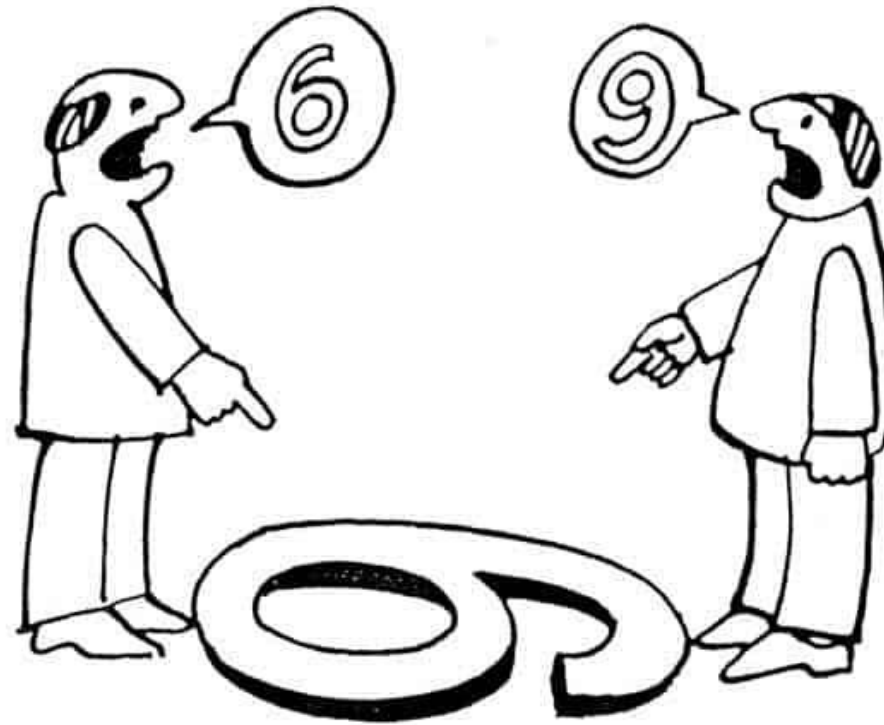
PLND – Overview of guidelines

In patients undergoing a lymph node dissection you should perform an extended PLND.	Strong
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- ePLND provides accurate lymph node staging. Preoperative PSMA-PET/CT is more accurate for staging generally, but can miss smaller lymph nodes



Perspective



EUROPEAN UROLOGY 72 (2017) 84–109

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



Review – Prostate Cancer

The Benefits and Harms of Different Extents of Lymph Node Dissection During Radical Prostatectomy for Prostate Cancer: A Systematic Review

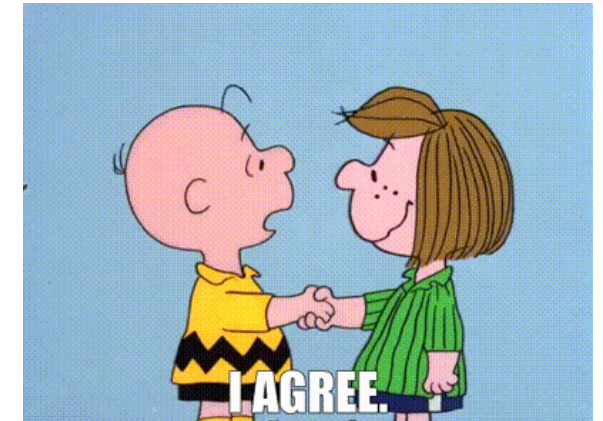
Nicola Fossati^{a,1}, Peter-Paul M. Willemse^{b,1}, Thomas Van den Broeck^c,
Roderick C.N. van den Bergh^d, Cathy Yuhong Yuan^e, Erik Briers^f, Joaquim Bellmunt^{g,h},
Michel Bollaⁱ, Philip Cornford^j, Maria De Santis^k, Ekelechi MacPepple^l, Ann M. Henry^m,
Malcolm D. Masonⁿ, Vsevolod B. Matveev^o, Henk G. van der Poel^p, Theo H. van der Kwast^q,
Olivier Rouvière^r, Ivo G. Schoots^{s,t}, Thomas Wiegel^u, Thomas B. Lam^{v,w}, Nicolas Mottet^x,
Steven Joniau^{c,*}

Quality evidence low

- *RCTs rare...*
- *the overall quality of evidence based on study design and RoB assessment of the studies included was low...*
- *and most studies were judged to have moderate to high RoB...*

Complications / side effects

- *More lymphoceles (up to 1/20)*
- *Trend towards more DVT and overall complication rates*
- *Blood loss similar*
- *90-day mortality rate 0.29% vs 0.13% (one study)*
- *No differences erectile function or incontinence*



Oncological endpoints

- *No good-quality evidence indicating that any form of PLND improves outcomes compared to no PLND.*
- *Of 21 studies, all of which were retrospective in nature, none showed statistically significant differences in favor of PLND when compared to no PLND for BCR, distant metastasis, or survival.*

Effect of Extended Pelvic Lymph Node Dissection on Oncologic Outcomes in Patients with D'Amico Intermediate and High Risk Prostate Cancer Treated with Radical Prostatectomy: A Multi-Institutional Study



Felix Preisser, Roderick C. N. van den Bergh, Giorgio Gandaglia, Piet Ost,* Christian I. Surcel, Prasanna Sooriakumaran, Francesco Montorsi, Markus Graefen, Henk van der Poel, Alexandre de la Taille, Alberto Briganti, Laurent Salomon, Guillaume Ploussard and Derya Tilki,^t on behalf of the EAU-YAUWP

From the Martini-Klinik Prostate Cancer Center, University Hospital Hamburg-Eppendorf (FP, MG, DT) and Departments of Urology, University Hospital Hamburg-Eppendorf (DT), University Hospital Frankfurt (FP), Frankfurt am Main, Germany, Department of Urology, Antonius Hospital (RCNvdB, HvdP), Utrecht, The Netherlands, Unit of Urology, Division of Oncology, URI, IRCCS Ospedale San Raffaele (GG, FM, AB), Milan, Italy, Department of Radiotherapy, Ghent University Hospital (PO), Ghent, Belgium, Centre of Urological Surgery, Dialysis and Renal Transplantation, Fundeni Clinical Institute (CIS), Bucharest, Romania, Department of Uro-oncology, University College London Hospital (PS), London, United Kingdom, and Department of Urology, Henri Mondor Hospital, Assistance-Publique Hôpitaux de Paris (AdIT, LS, GP), Créteil and Department of Urology, La Croix du Sud Hospital and Institut Universitaire du Cancer Toulouse Oncopole, Toulouse (GP), France

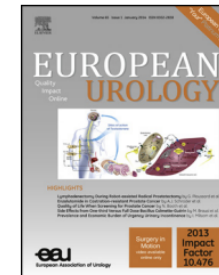


ePLND vs no PLND

- N = 9,742, >5% nomogram LNI
 - 707 no PLND (520 int risk, 187 high risk)
- Propensity score matching
- FU 120 mo
- PLND vs no PLND was not an independent risk factor

	PLND	No PLND	p
BCR free	60.4%	65.6%	0.07
Metastasis free	87.0%	90.0%	0.06
Cancer specific mortality	95.2%	96.4%	0.2

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Platinum Priority – Prostate Cancer

Editorial by Alberto Briganti, Niccolò M. Passoni, Firas Abdollah, Alessandro Nini, Francesco Montorsi and R. Jeffrey Karnes on pp. 26–28 of this issue

Long-term Outcomes of Patients with Lymph Node Metastasis Treated with Radical Prostatectomy Without Adjuvant Androgen-deprivation Therapy

Karim A. Touijer^{a,b,*}, Clarisse R. Mazzola^a, Daniel D. Sjoberg^c, Peter T. Scardino^{a,b}, James A. Eastham^{a,b}

^a Urology Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY, USA; ^b Department of Urology, Weill Medical College of Cornell University, New York, NY, USA; ^c Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

BCR after pN1

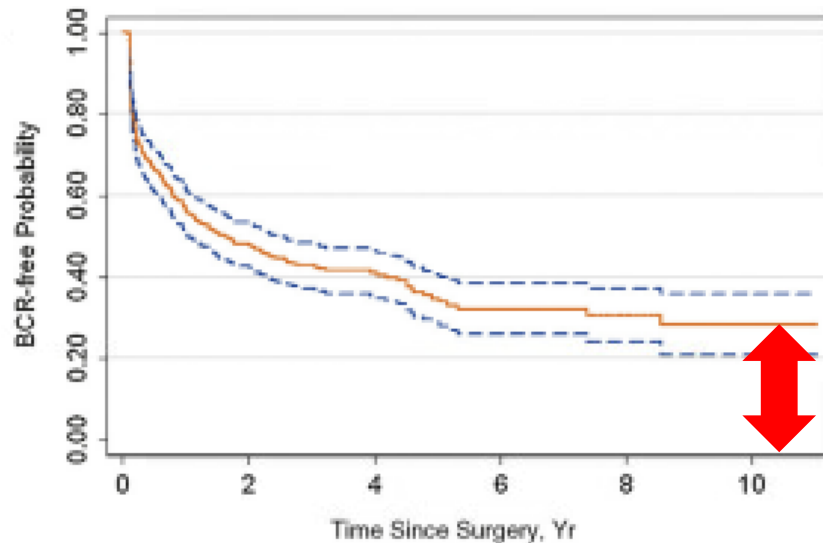


Fig. 5 - Kaplan-Meier curve for probability of freedom from biochemical recurrence (BCR) in patients with node-positive disease.

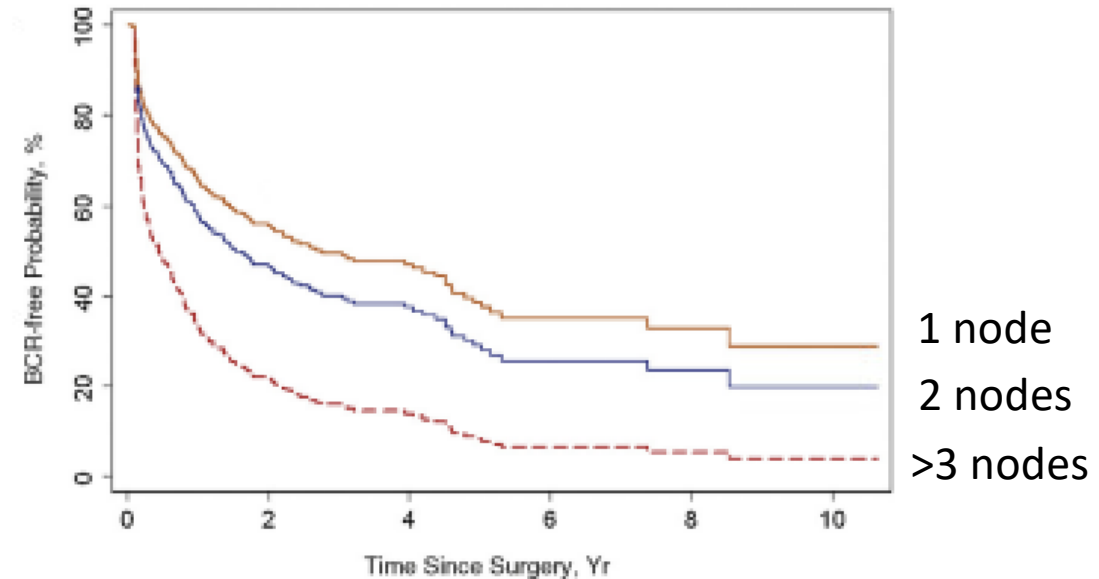


Fig. 6 - Probability of freedom from biochemical recurrence (BCR) by number of positive nodes. Orange line = one positive node; blue line = two positive nodes; red line = three or more positive nodes.

- Would the outcomes of these men have been just as good of with no / later lymph node treatment?

Editorial

Referring to the article published on pp. 253–260 of this issue

Oncological Benefits of Extended Pelvic Lymph Node Dissection: More Fog or Clarity to the Debate?

Matthew J. Roberts^{a,b,c}, Philip Cornford^{d,e}, Derya Tilki^{f,g,h,*}

- RCT: I
- BCR r
- Signif
- ePLND
- Is this
- Dorme

- Small difference in metastasis free survival 85% vs 88%
- Modest difference in node count limited vs extended 12 vs 14 nodes
 - BCR not different, why metastases?
- Confusion on endpoint (distant, regional metastasis), not in protocol.
- Type of imaging not discussed. Increasing use PET. No central review.
 - Differences in use of adjuvant/salvage therapies.
- Impact of pN status on MFS early during follow-up, which is implausible.
- Number of nodes removed may have been tailored by the surgeon.
 - Randomization in blocks of 3 months could lead to bias.

What is a valid endpoint?

- Overall survival
- Disease specific survival
- Metastasis-free survival
- BCR

- Softer endpoints:
 1. Optimize decision-making salvage treatments?
 2. Delay next therapy?



Softer endpoint 1: Optimize salvage therapy

- BCR in:
 - pN0, more likely to be local recurrence
 - pN1, more likely to be lymph node issue
 - pNx, less information on cause
- Avoid / select unnecessary salvage treatments?
- Select salvage therapy recurrence?



We accept avoidance unnecessary treatments

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, Nathan Lawrentschuk, Roslyn J Francis, Colin Tang, Ian Vela, Paul Thomas, Natalie Rutherford, Jarad M Martin, Mark Frydenberg, Ramdave Shakher, Lih-Ming Wong, Kim Taubman, Sze Ting Lee, Edward Hsiao, Paul Roach, Michelle Nottage, Ian Kirkwood, Dickon Hayne, Emma Link, Petra Marusic, Anetta Matera, Alan Herschtal, Amir Iravani, Rodney J Hicks, Scott Williams, Declan G Murphy, for the proPSMA Study Group Collaborators*

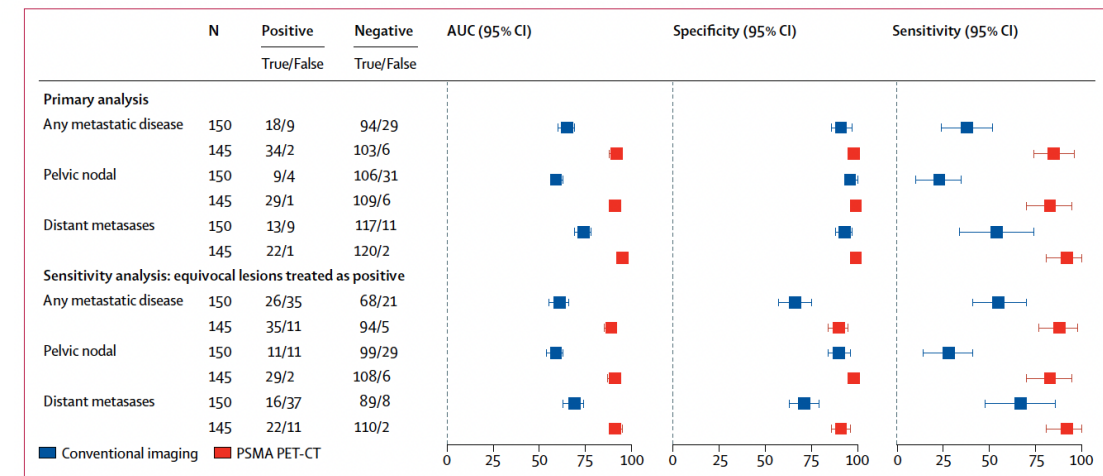


Figure 2: Accuracy, sensitivity, and specificity of conventional imaging compared with PSMA PET-CT
PSMA=prostate-specific membrane antigen. AUC=area under the curve.

Select salvage therapies

Impact of Adjuvant Radiotherapy on Survival of Patients With Node-Positive Prostate Cancer

Firas Abdollah, R. Jeffrey Karnes, Nazareno Suardi, Cesare Cozzarini, Giorgio Gandaglia, Nicola Fossati, Damiano Vizziello, Maxine Sun, Pierre I. Karakiewicz, Mani Menon, Francesco Montorsi, and Alberto Briganti

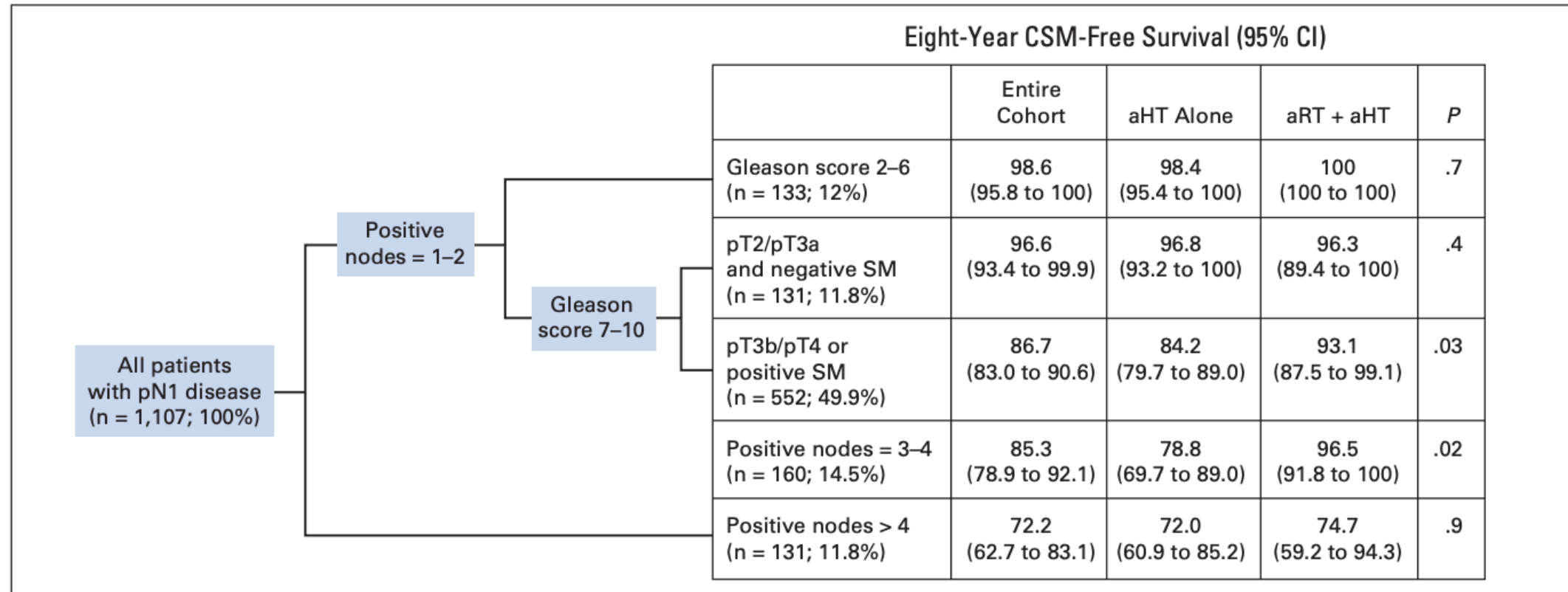


Fig 1. A novel cancer-specific mortality (CSM) risk stratification tree based on data for 1,107 patients with pN1 prostate cancer treated with radical prostatectomy, anatomically extended pelvic lymph node dissection, and adjuvant hormonal therapy (aHT) with or without adjuvant radiotherapy (aRT). SM, surgical margins.

Softer endpoint 2: Delay next therapy



We accept delay of ADT as endpoint

VOLUME 36 · NUMBER 5 · FEBRUARY 10, 2018

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial

Piet Ost, Dries Reynders, Karel Decaestecker, Valérie Fonteyne, Nicolaas Lumen, Aurélie De Bruycker, Bieke Lambert, Louke Delrue, Renée Bultjynck, Tom Claeys, Els Goetghebeur, Geert Villeirs, Kathia De Man, Filip Amey, Ignace Billiet, Steven Joniau, Friedl Vanhaverbeke, and Gert De Meerleer

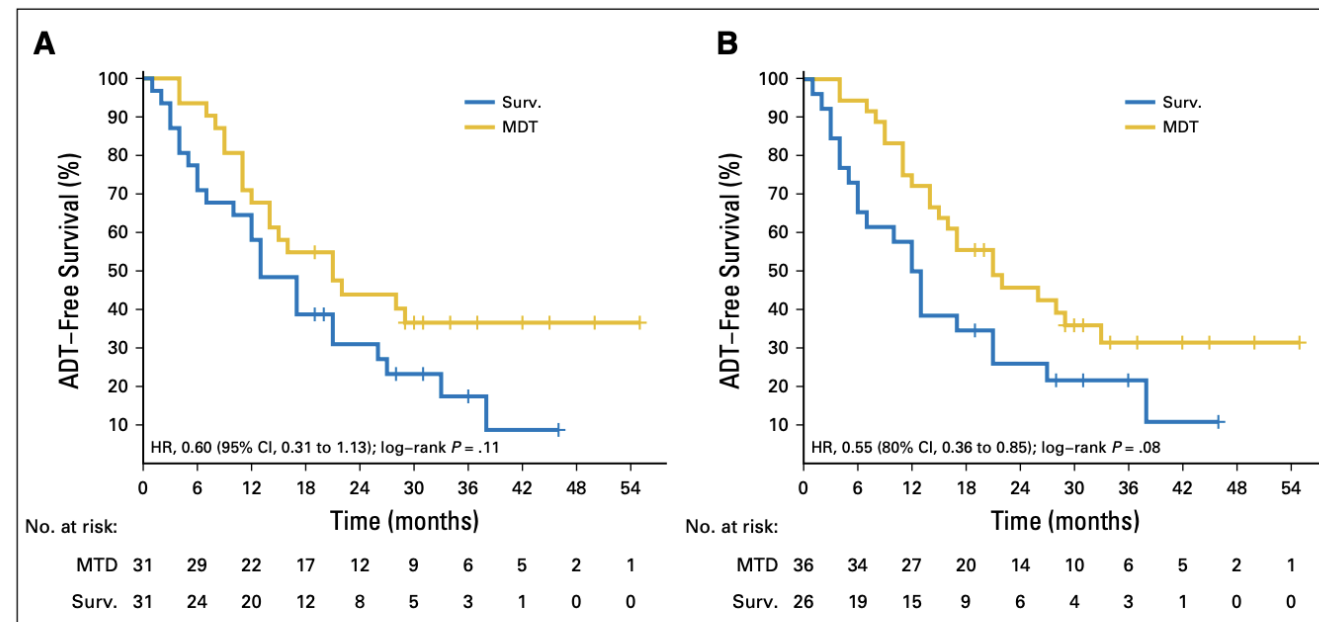
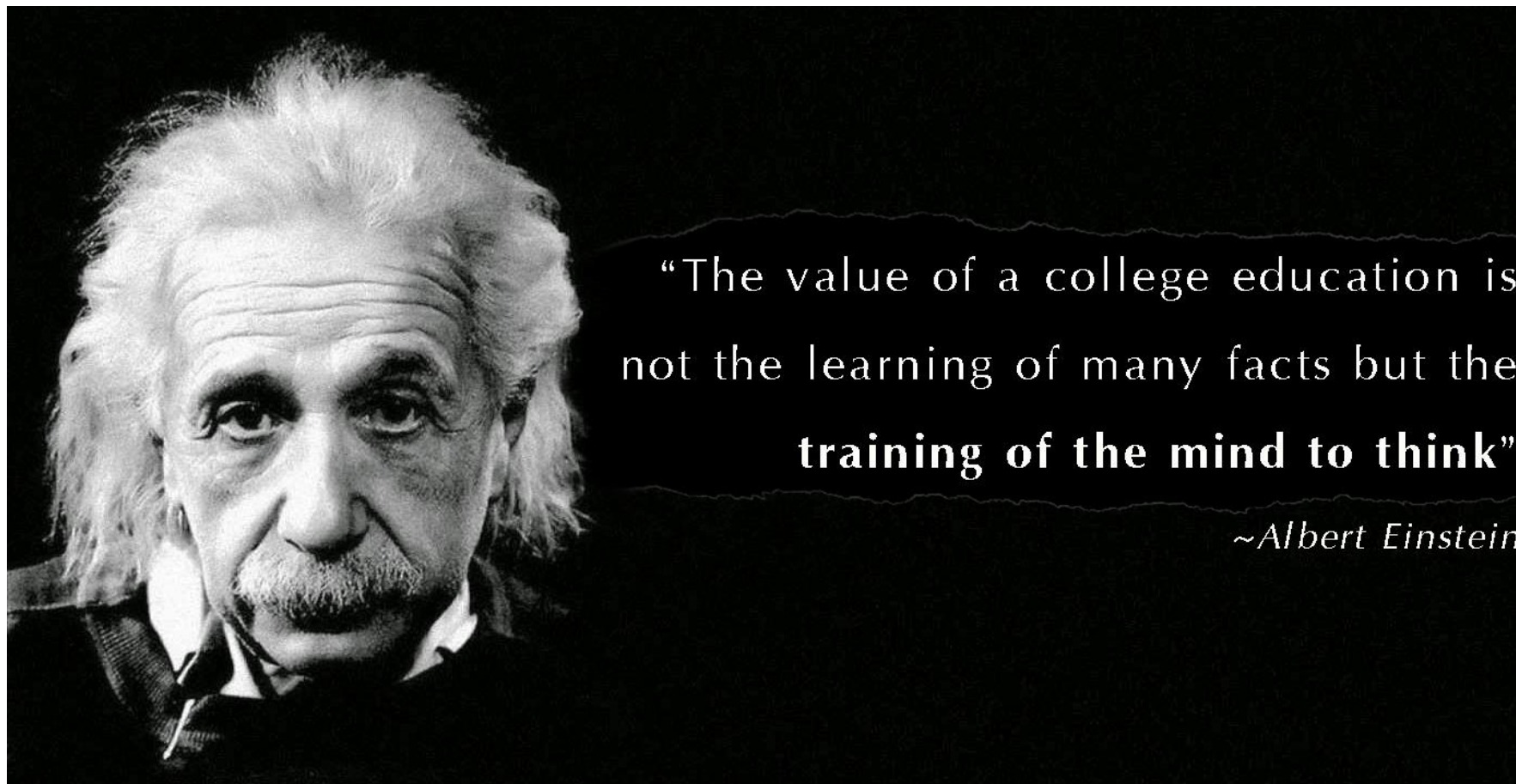
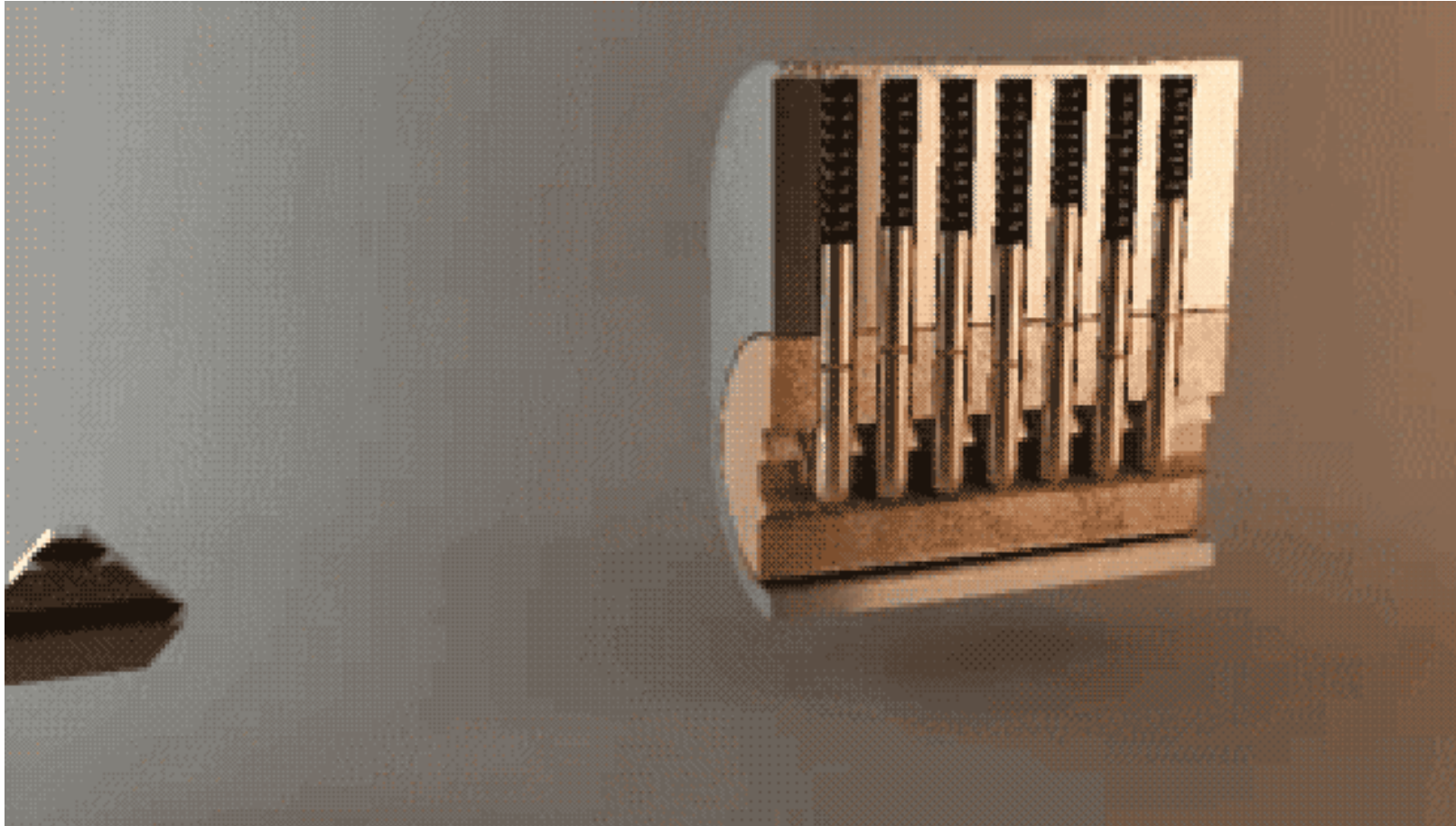


Fig 2. Kaplan-Meier plot comparing androgen deprivation therapy (ADT)-free survival of surveillance versus metastasis-directed therapy (MDT) for (A) the intention-to-treat analysis and (B) the per-protocol analysis. HR, hazard ratio; Surv., surveillance.



Different question: Intervention vs selection?



Do findings PLND change management?

2452109A	9901204S
pT3 R0 ISUP GG 4 pNx vs pT3 R0 ISUP GG 4 pN1 (1 positive node)	PSA rises after surgery: Options: - Direct radiation prostatic fossa? - Direct pelvic radiation +/- ADT? - Wait for PSMA lesions?
4	5



From risk-based to imaging-based approach



Incorporate PSMA in nomogram

EUROPEAN UROLOGY ONCOLOGY 6 (2023) 553–563

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journal homepage: euoncology.europeanurology.com



Editorial by Pierre I. Karakiewicz, Reha-Baris Incesu, Lukas Scheipner, Markus Graefen on pp. 564–565 of this issue

Development and External Validation of a Novel Nomogram to Predict the Probability of Pelvic Lymph-node Metastases in Prostate Cancer Patients Using Magnetic Resonance Imaging and Molecular Imaging with Prostate-specific Membrane Antigen Positron Emission Tomography

André N. Vis^{a,b,†}, Dennie Meijer^{a,b,c,†,*}, Matthew J. Roberts^{d,e,f}, Amila R. Siriwardana^d, Andrew Morton^{d,g}, John W. Yaxley^{d,g,h}, Hemamali Samarasinghe^{g,i}, Louise Emmett^{j,k}, Peter M. van de Ven^l, Martijn W. Heymans^l, Jakko A. Nieuwenhuijzen^{a,b}, Henk G. van der Poel^{a,b}, Maarten L. Donswijk^m, Thierry N. Boellaardⁿ, Ivo G. Schoots^{n,o}, Phillip Stricker^{p,q}, Anne-Maree Haynes^q, Daniela E. Oprea-Lager^c, Geoffrey D. Coughlin^{g,h}, Pim J. van Leeuwen^b

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miN1
OR 10

Table 2 – Multivariable logistic regression analyses predicting pelvic lymph-node metastatic disease in patients with localized prostate cancer in 700 surgically treated patients

	Odds ratio (95% CI)	p value
Natural logarithm (Initial PSA value)	1.22 (1.01–1.46)	0.035
Biopsy GG according to ISUP		
1–2	Reference	
3	1.98 (1.04–3.74)	0.037
4	2.39 (1.26–4.52)	0.007
5	2.44 (1.28–4.66)	0.007
Highest GG derived from		
Systematic biopsies	Reference	
MRI-targeted biopsies	1.94 (1.08–3.51)	0.028
Both	3.88 (2.09–7.19)	<0.001
Percentage of systematic cores with csPca (GG ≥2)	1.02 (1.01–1.02)	0.001
Radiological T stage		
Negative (iT1)/organ-confined disease (iT2)	Reference	
Extracapsular extension (iT3a)	2.01 (1.25–3.24)	0.004
≥Seminal vesicle invasion (iT3b)	5.35 (3.15–9.08)	<0.001
PSMA-PET findings		
miN0	Reference	
miN1	10.06 (5.32–19.0)	<0.001
Model AUC (95% CI)	0.81 (0.78–0.85)	

AUC = area under the receiver operating characteristic curve; CI = confidence interval; csPca = clinically significant prostate cancer; GG = grade group; ISUP = International Society of Urological Pathology; mi = molecular imaging; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; PET = positron emission tomography.
p-values <0.05 in bold.

PSMA Select study

From:
jul-2021

To:
sep-2024

Medisch Centrum ▼

GRAFIEK

TABEL

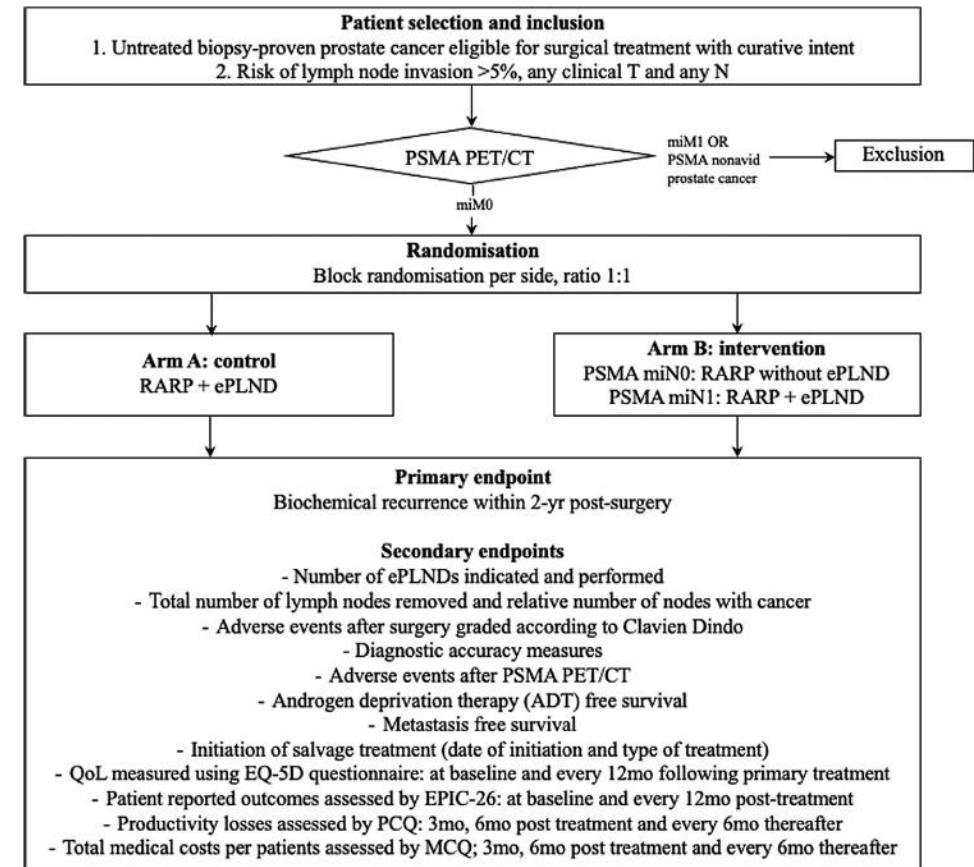
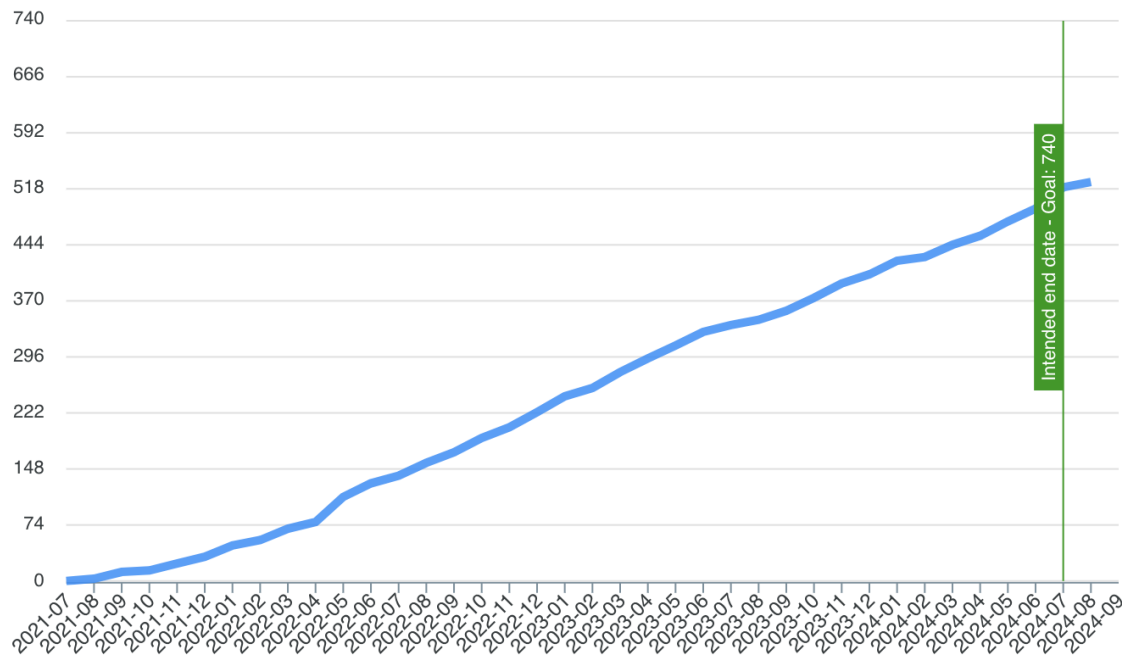


Fig. 1 – Study flowchart. CT = computed tomography; ePLND = extended pelvic lymph node dissection; MCQ = Medical Consumption Questionnaire; PCQ = Productivity Cost Questionnaire; PET = positron emission tomography; PSMA = prostate-specific membrane antigen; QoL = quality of life; RARP = robot-assisted radical prostatectomy.

Alternative approaches?

- No PLND – If PSA rises, do PLND?
- Only do PLND in miN1 disease?
- Prostatectomy and EBRT to pelvis in primary setting?
- miN1 disease – Wait, repeat PSMA after 3 months?
- miN1 or high risk disease – Perform unilateral PLND?
- High risk disease – Sentinel node procedure?
- Use biomarkers to improve risk prediction?
- N1 – intensified systemic therapy?
- N1 – radioligand therapy?

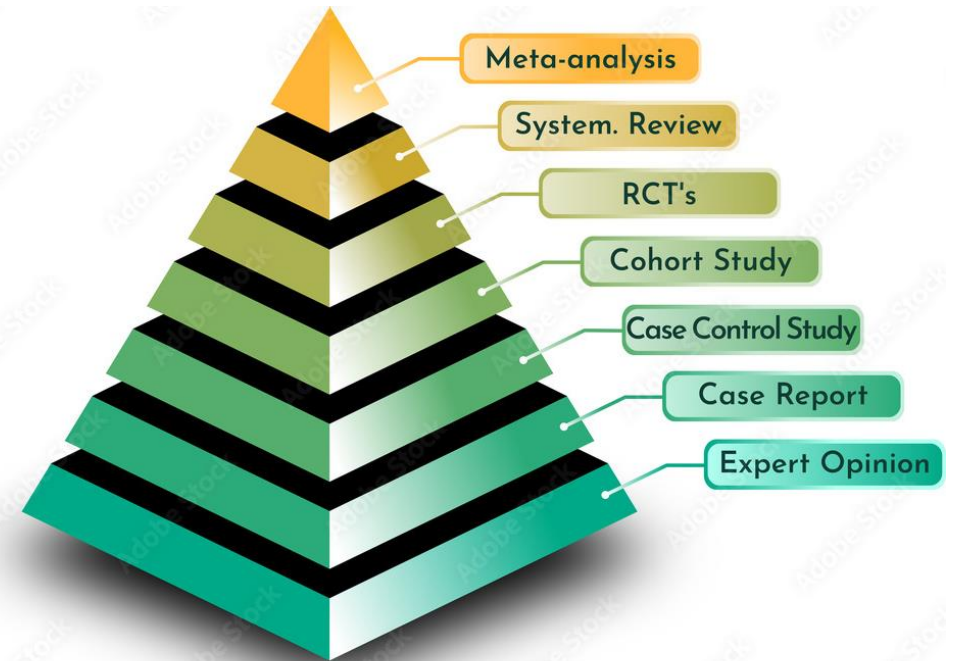


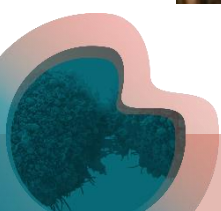
My opinion

- Casemix is changing due to PSMA (RALP cases, miN0, miN1, pN0, pN1)
- A one-size-fits-all approach is rarely the solution
- Many cases don't benefit, more side effects
- Some cases must benefit, but probably few
- Potential benefit: cure, delay of further therapy, specification salvage tx
- If there is a benefit, better to do PLND directly
- Value of PLND in primary setting associated with management BCR
- **Our selection should improve, starting avoiding unnecessary PLNDs**

My perfect case to do PLND

- Young patient
- Low BMI
- Planned for surgery
- High ISUP GG
- PSMA N0 M0 / N1 (1-2 nodes)
- Low PSA
- Non or mixed avidity local tumor
- Nomogram risk of pN1 >50%







Questions?