The Role of Pelvic Lymph Node Dissection for Prostate Cancer- *focus on the intermediate risk patient*

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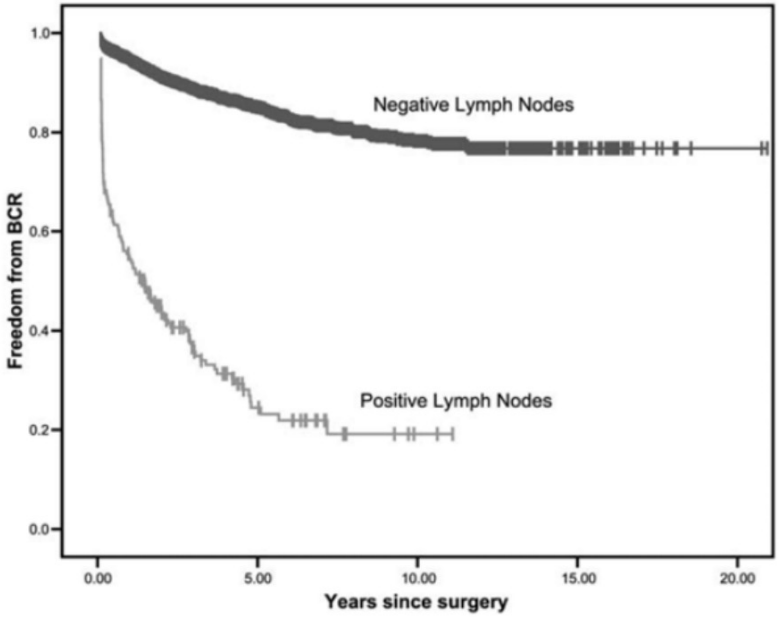
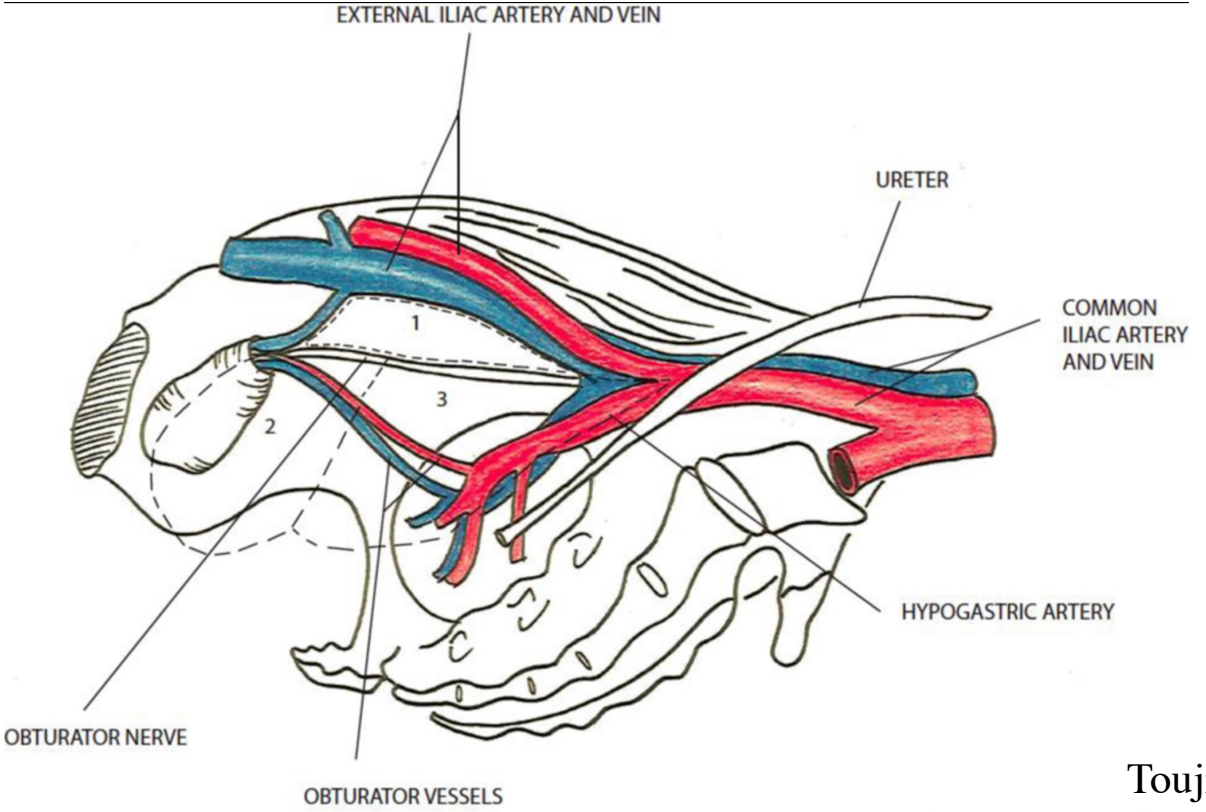
Historical Context

- Lymph node metastases in clinically localized PCa is a poor prognostic factor for BCR and survival (Bader, 2003, JU; Masterson 2006, JU)
- Advent of serum PSA testing has led to stage migration (Allaf, 2004 JU; Masterson 2006, JU)
  - Majority of PCa is being detected earlier, when localized to the prostate
- Historically, nodal metastases were found in up to 25% of patients
- Now, series find 0.3-10% depending on the population (Fossati, 2017, EU)
- The role of PLND remains controversial



Extent of PLND is Controversial



Not uncommon
For prostate cancer to be found outside of these templates

Toujier et al, Eur Urol Oncol 2021

Role of Lymph Node Dissection

- Staging- Does it more accurately stage men with prostate cancer?
- Therapeutic- improvement in BCR, MFS, OS?

Low Risk
Intermediate Risk
High Risk

Question:

In intermediate risk patients, as defined by the NCCN, would you recommend pelvic lymph node dissection when undergoing RP?

Preoperative Staging

- What is intermediate risk
  - NCCN
  - EAU

Table 4.2: EAU risk groups for biochemical recurrence of localised and locally advanc

Definition			
Low-risk	**Intermediate-risk**		**High-risk**
PSA < 10 ng/mL	PSA 10-20 ng/mL	PSA > 20 ng/mL	any PS
and GS < 7 (ISUP grade 1)	or GS 7 (ISUP grade 2/3)	or GS > 7 (ISUP grade 4/5)	any G
and cT1-2a	or cT2b	or cT2c	cT3-4
Localised			**Local**

GS = Gleason score; ISUP = International Society for Urological Pathology; PSA = prostate

Risk Group	Clinical/Pathologic Features See Staging (ST-1)		
Very low[e]	Has all of the following: • cT1c • Grade Group 1 • PSA <10 ng/mL • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core[f] • PSA density <0.15 ng/mL/g		
Low[e]	Has all of the following but does not qualify for very low risk: • cT1–cT2a • Grade Group 1 • PSA <10 ng/mL		
Intermediate[e]	Has all of the following: • No high-risk group features • No very-high-risk group features • Has one or more intermediate risk factors (IRFs): ▸ cT2b–cT2c ▸ Grade Group 2 or 3 ▸ PSA 10–20 ng/mL	Favorable intermediate	Has all of the following: • 1 IRF • Grade Group 1 or 2 • <50% biopsy cores positive (eg, <6 of 12 cores)[f]
		Unfavorable intermediate	Has one or more of the following: • 2 or 3 IRFs • Grade Group 3 • ≥ 50% biopsy cores positive (eg, ≥ 6 of 12 cores)[f]
High	Has no very-high-risk features and has exactly one high-risk feature: • cT3a OR • Grade Group 4 or Grade Group 5 OR • PSA >20 ng/mL		
Very high	Has at least one of the following: • cT3b–cT4 • Primary Gleason pattern 5 • 2 or 3 high-risk features • >4 cores with Grade Group 4 or 5		

PLND: Indications

- NCCN
  - Favorable and Unfavorable Intermediate Risk: if >= 2% MSKCC
  - Extended PLND preferred
- EAU
  - Extended PLND for all patients with risk of nodal metastasis >=5% based on pre-operative risk nomograms (Briganti, Roach, Partin, MSKCC)
  - Extended PLND for all patients following MRI-targeted biopsy using updated nomogram (Gandaglia [Updated Briganti]) risk >=7%
- AUA/ASTRO/SUO
  - Can be considered for any localized PCa
  - Recommended for those with unfavorable intermediate

Nomograms

- Use of nomograms spares about 50-60% of patients PLND and misses few positive LN patients (<5%)
- Head to head the nomograms tend to perform similarly

Therapeutic Benefit

DISEASE PROGRESSION AND SURVIVAL OF PATIENTS WITH POSITIVE LYMPH NODES AFTER RADICAL PROSTATECTOMY. IS THERE A CHANCE OF CURE?

PIA BADER, FIONA C. BURKHARD, REGULA MARKWALDER AND URS E. STUDER

From the Department of Urology and Institute of Pathology, University of Bern, Bern, Switzerland

- 367 patients w/ ePLND at time of RP.
- 92 patients (25%) found to have + LN
- Median 45 month follow-up patients w/ 1 + LN: 40% remained free of BCR

Prognosis of patients with lymph node positive prostate cancer following radical prostatectomy: long-term results

Siamak Daneshmand [1], Marcus L Quek, John P Stein, Gary Lieskovsky, Jie Cai, Jacek Pinski, Eila C Skinner, Donald G Skinner

- 235 patients w/ node positive disease after RP and PLND
- Median follow up 11.4 years
- Patients w/ 1 or 2 +LN w/ clinical recurrence-free survival of 70% and 73%

Bader et al. JU 2003, Daneshmand et al. JU 2004

Therapeutic Benefit

Anatomical extent of lymph node dissection: impact on men with clinically localized prostate cancer

Mohamad E Allaf [1], Ganesh S Palapattu, Bruce J Trock, H Ballentine Carter, Patrick C Walsh

- 2,135 RP w/ ePLND and 1,865 RP w/ sPLND
- ePLND found more LNs
- For patients w/ <15% +LN, 5-year PSA progression-free rate of ePLND was 43% vs 10% (P<0.001)

Anatomical Extent of Pelvic Lymph Node Dissection: Impact on Long-Term Cancer-Specific Outcomes in Men with Positive Lymph Nodes at Time of Radical Prostatectomy

Trinity J. Bivalacqua, **Phillip M. Pierorazio**, **Michael A. Gorin**, **Mohamad E. Allaf**, **H. Ballentine Carter**, and **Patrick C. Walsh**
The James Buchanan Brady Urological Institute, Johns Hopkins Medical Institutions, Baltimore, MD, USA

- Following group to median 10.5 year follow up
- 10-year metastasis free survival of 62.2% vs 22.2% (P=0.35)
- 10-year cancer specific survival of 83.6% vs 52.6% (P=0.199)

Allaf et al. JU 2004, Bivalacqua et al. JU 2013

Limited versus Extended Pelvic Lymph Node Dissection for Prostate Cancer: A Randomized Clinical Trial

Karim A. Touijer [a], Daniel D. Sjoberg [b], Nicole Benfante [a], Vincent P. Laudone [a], Behfar Ehdaie [a], James A. Eastham [a], Peter T. Scardino [a], Andrew Vickers [b]

- 1440 patients randomized to extended vs. limited PLND
- No differences in BCR
- Rate of complications were the same

- Number of nodes removed 12 vs. 14– lower than expected

Toujier et al, Eur Urol Oncol 2021

Stage Migration Bias

- Also known as “Will Rogers Phenomenon”
  - “When the Okies left Oklahoma and moved to California, they raised the average intelligence level in both states.”
- Can occur when
  - New procedure classifies disease differently
  - AND outcomes are stratified by severity of disease (stage-specific survival)

Risks of Surgery

Cacciamani et al. Eur Urol Oncol 2021

Intra-Operative Complications

- 84 studies, 28,428 patients
- 534 (1.8%) had complications:
  - Obturator (6.5%)
  - Internal (2%) and External Iliac (1%)
  - Ureteral (12.4%)

Post-Operative Complications

- 151 studies, 73,629 patients
- ~10,000 (14%) had complications:
  - Lymphocele w/ drainage (33%)
  - DVT (21.8%)
  - Obturator palsy (4.6%)

Risks of Surgery

- Symptomatic lymphoceles requiring drainage 0-8% of patients
- Most treated with percutaneous drainage and observation for 1-2 weeks
- <1% will require additional sclerosing agent
- Surgical technique such as peritoneal flap interposition or “Lahey Stitch” may further reduce risk

Ploussard et al. Eur Urol 2014, Lebeis et al. Urology 2015

Risks of Surgery

- Men undergoing prostatectomy have risk factors for DVT including age, malignancy, and surgery.
- PLND increases risk of VTE risk, higher risk for ePLND
- VTE risk is real, patient education is key, low threshold for noninvasive imaging, high risk patients consider pharmacologic prophylaxis versus surgical risk

Klassen et al. World J Urol 2020

PSMA PET Imaging

Colleague: “I no longer perform PLND because my patients get PSMA PET scan”

Valid or Not?

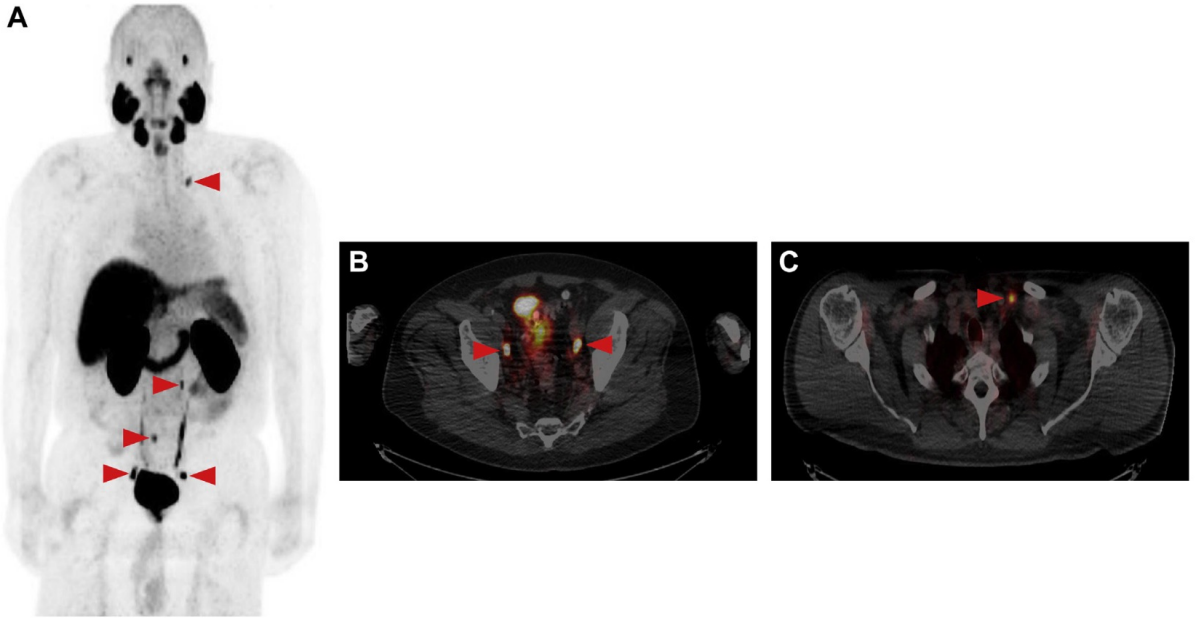
Prostate Specific Membrane Antigen Targeted ^{18}F-DCFPyL Positron Emission Tomography/Computerized Tomography for the Preoperative Staging of High Risk Prostate Cancer: Results of a Prospective, Phase II, Single Center Study

Michael A. Gorin,*,† Steven P. Rowe,† Hiten D. Patel, Igor Vidal, Margarita Mana-ay, Mehrbod S. Javadi, Lilja B. Solnes, Ashley E. Ross, Edward M. Schaeffer, Trinity J. Bivalacqua, Alan W. Partin, Kenneth J. Pienta,† Zsolt Szabo, Angelo M. De Marzo, Martin G. Pomper† and Mohamad E. Allaf

From The James Buchanan Brady Urological Institute (MAG, HDP, MM-a, AER, TJB, AWP, KJP, MEA), Departments of Urology (MAG, HDP, MM-a, AER, TJB, AWP, KJP, MEA) and Pathology (IV, AMDM) and The Russell H. Morgan Department of Radiology and Radiological Science (SPR, MSJ, LBS, ZS, MGP), The Johns Hopkins University School of Medicine, Baltimore, Maryland, and Department of Urology, Northwestern University Feinberg School of Medicine (EMS), Chicago, Illinois

- Enrolled High Risk Prostate Cancer (N=25)
- Negative Conventional Imaging
- 7 Patients had positive LNs on final pathology
- PSMA-PET correctly identified 5 out 7
- PSMA-PET overstaged 2 patients
- Average size of positive LN= 3mm

Patient with N1 M1 Disease



Performance Characteristics

Table 2. *Diagnostic performance of ^{18}F-DCFPyL PET/CT for detecting pelvic lymph node metastases*

Analysis Level	% (95% CI)
Pt:	
Sensitivity	71.4 (29.0–96.3)
Specificity	88.9 (65.3–98.6)
Pos predictive value	71.4 (38.4–90.9)
Neg predictive value	88.9 (71.0–96.3)
Packet:	
Sensitivity	66.7 (29.9–92.5)
Specificity	92.7 (80.1–98.5)
Pos predictive value	66.7 (38.0–86.7)
Neg predictive value	92.7 (83.4–97.0)

Diagnostic Performance and Safety of Positron Emission Tomography with ^{18}F-rhPSMA-7.3 in Patients with Newly Diagnosed Unfavourable Intermediate- to Very-high-risk Prostate Cancer: Results from a Phase 3, Prospective, Multicentre Study (LIGHTHOUSE)

JOHNS HOPKINS MEDICINE

Table 4 – Patient-level PPV and NPV for the detection of pelvic LN metastases

	Reader 1 *N* = 296	Reader 2 *N* = 296	Reader 3 *N* = 296	Majority read *N* = 296
Patient-level PPV for the detection of pelvic LN metastases				
Number of patients with PET-positive finding in pelvic LN (TP + FP)	37	33	23	26
True positive	21 (57%)	19 (58%)	16 (70%)	17 (65%)
False positive	16 (43%)	14 (42%)	7 (30%)	9 (35%)
PPV	57% (21/37)	58% (19/33)	70% (16/23)	65% (17/26)
[95% CI]	[39.5–72.9%]	[39.2–74.5%]	[47.1–86.8%]	[44.3–82.8%]
Patient-level NPV for the detection of pelvic LN metastases				
Number of patients with PET-negative finding in pelvic LN (TN + FN)	284	287	289	287
True negative	231 (81%)	232 (81%)	231 (80%)	230 (80%)
False negative	53 (19%)	55 (19%)	58 (20%)	57 (20%)
NPV	81% (231/284)	81% (232/287)	80% (231/289)	80% (230/287)
[95% CI][a]	[76.3–85.7%]	[75.8–85.2%]	[74.8–84.4%]	[75.0–84.6%]

95% CI = 95% confidence interval; FN = false negative; FP = false positive; LN = lymph node; NPV = negative predictive value; PET = positron emission tomography; PPV = positive predictive value; TN = true negative; TP = true positive.

[a] For the evaluation of NPV, an FN patient was defined as having at least one FN region (right or left pelvis), regardless of any coexisting TN findings.

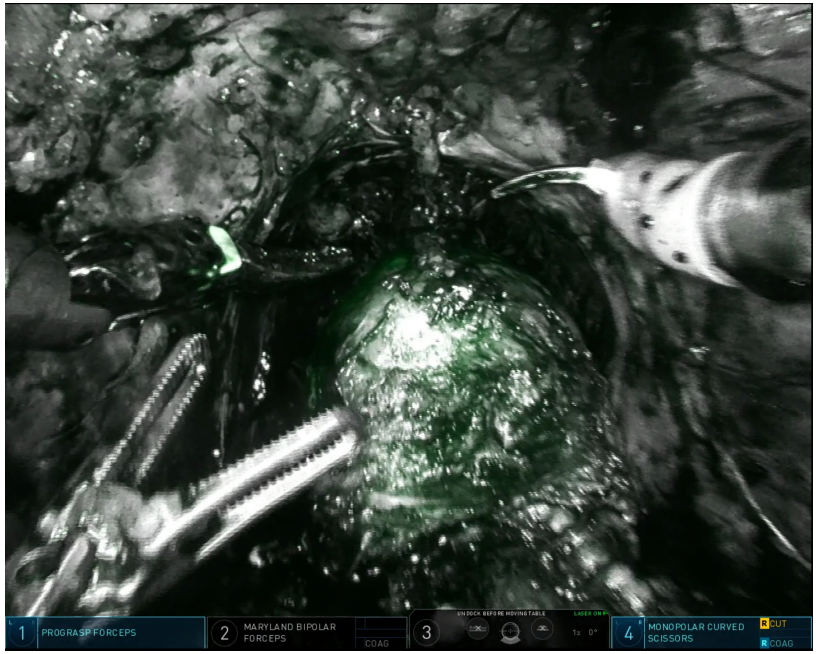
(Surasi at al., Eur Urol 2023)

PSMA Conclusions

- Bladder / Ureteral signal may obscure focal PSMA uptake in lymph nodes
- False negative = 10-20%
- If a positive node is seen, 30% chance another occult node is positive
- Inter-reader variability
- Is false positive nodes due to template used?

Molecularly Directed Surgery?

44 M, EPE on MRI Right, Gleason 4+4
Left Sided Disease
PSMA Fluorescent Agent
Clinical Trial



Conclusions

- Radical Prostatectomy is an oncologic operation
- Accurate disease staging guides treatment and prognosis
- Therapeutic role of PLND suggested but unproven
- Upgrading / upstaging at surgery is not rare
- Surgical risks are real but relatively rare
- Not all surgery is equal- variability in PLND