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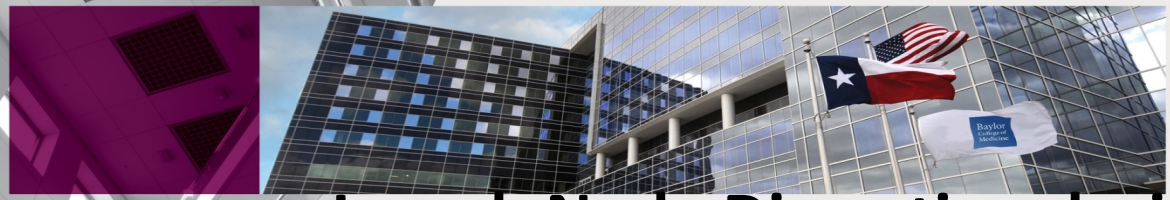

Lymph Node Dissection during Radical Cystectomy – Current State of the Art

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Disclosures

- Clinical trials
  - Endo, FKD, JBL (SWOG), Roche/Genentech (SWOG), Viventia
- Consultant
  - BioCancell, UroGen, Vaxiion
- Advisory Board
  - BioCancell, miR Scientific, QED Therapeutics, UroGen

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Learning Objectives

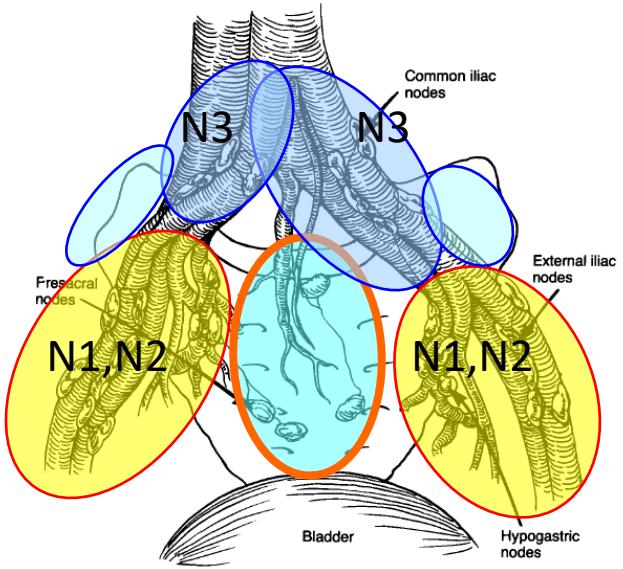
- To describe the anatomy of and stage specific association of lymph node metastasis
- To describe the evidence supporting the anatomic extent of bilateral pelvic lymphadenectomy
- To understand status of current Phase III clinical trials of extended vs. standard PLND

TNM Staging Invasive Cancer (AJCC 8th Edition 2018)

Pelvic Node Staging

- N1 – single node in true pelvis

  includes perivesical
- N2 – multiple nodes in true pelvis
- True pelvis includes external and internal iliac, obturator and pre-sacral nodes
- N3 – lymph node metastasis in common iliac nodes
- *>12 nodes for adequate staging*



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AJCC Revisions

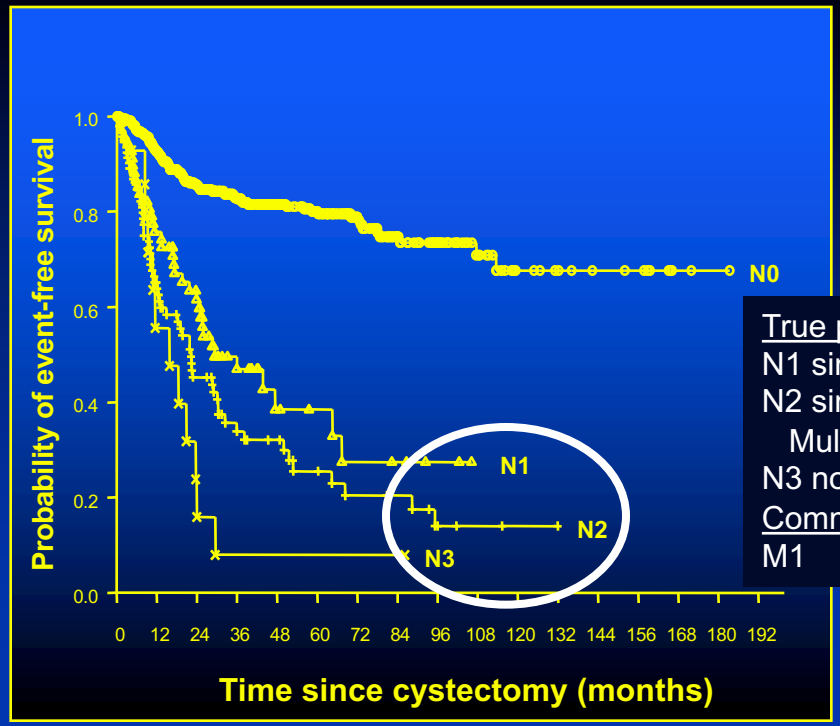
Table 6 – Updates in the American Joint Committee on Cancer staging of urinary bladder cancer

Category	Details
T1	Attempt for subcategorization in TUR recommended
T2	Staging of diverticular cancers has no T2
T4	Prostatic stromal invasion clarified that must be transmural from bladder; subepithelial stromal invasion staged as T2 (urethral)
N1	Perivesical LN added
M1	Divided into nonregional LN only (M1a) and non-LN distant metastases (M1b)
Prognostic stage group III	Divided into IIIA and IIIB based on number of regional LN and involvement of common iliac LNs
Prognostic stage group IV	Divided into IVA and IVB corresponding to the M1a and M1b division

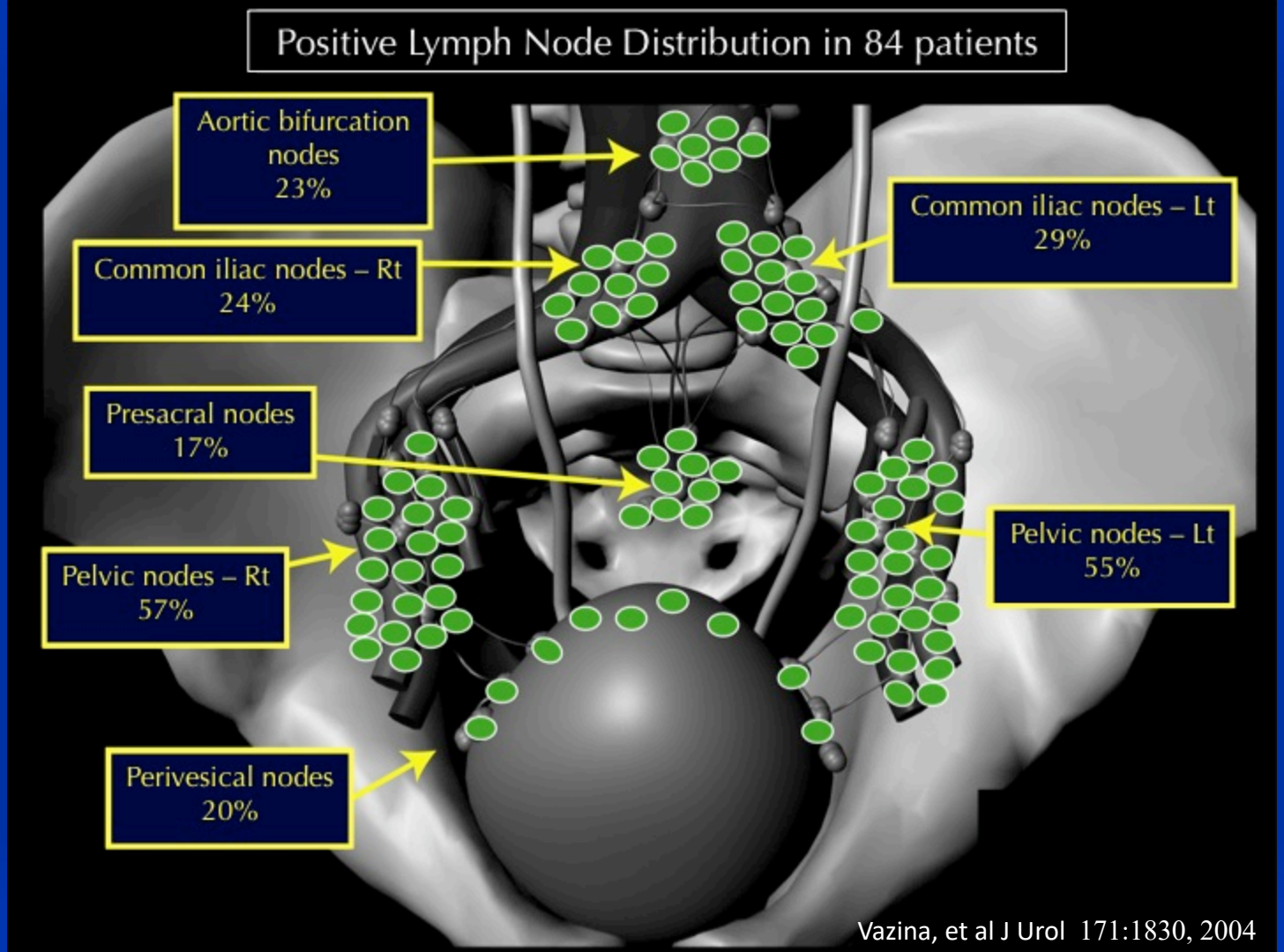
LN = lymph node; TUR = transurethral resection.

Paner, et al Eur Urol 73:560, 2018

Disease-Specific Survival
According to pN Stage at Cystectomy



True pelvis
N1 single node ≤ 2cm
N2 single node >2≤ 5cm;
Mult nodes none >5cm
N3 node > 5cm
Common iliac or above
M1

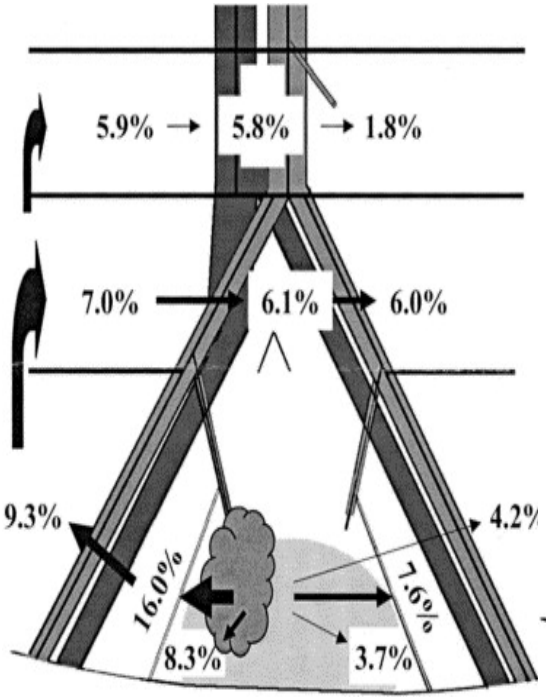


Vazina, et al J Urol 171:1830, 2004

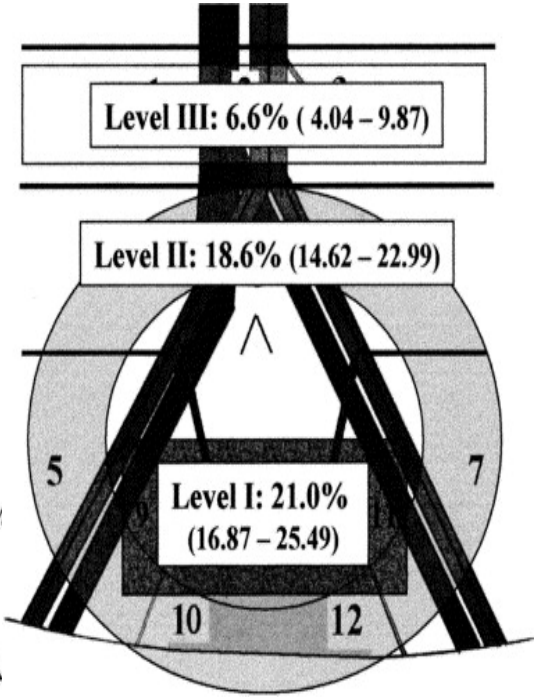
Prospective LN Mapping

- 290 patients
- ePLND in all
- Prospective mapping
- IMA
- 6 centers

Unilateral tumor
Crossover common

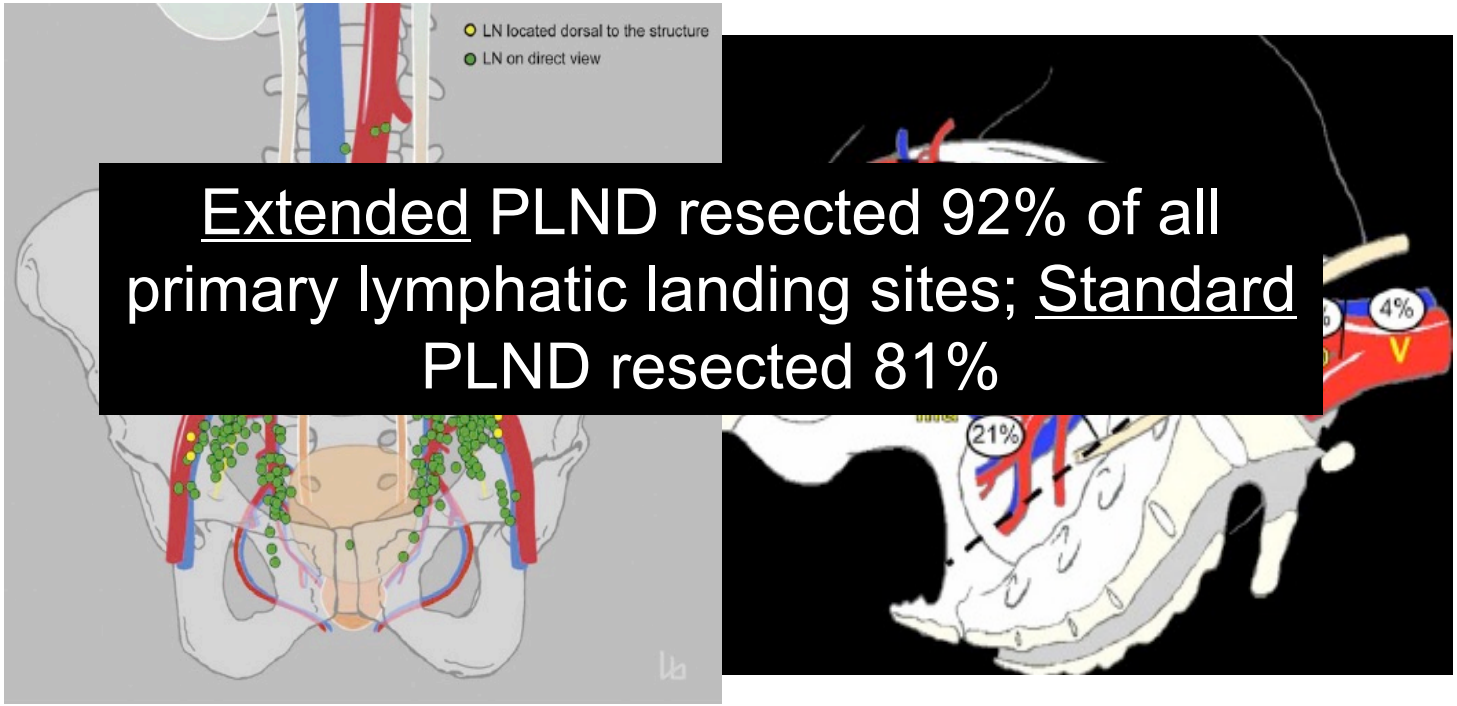


Positive nodes common in extended template



Leissner, et al J Urol 171;139, 2004

Lymph Node Drainage of the Bladder



Extended PLND resected 92% of all primary lymphatic landing sites; Standard PLND resected 81%

Roth, et al Eur Urol 57:205, 2010

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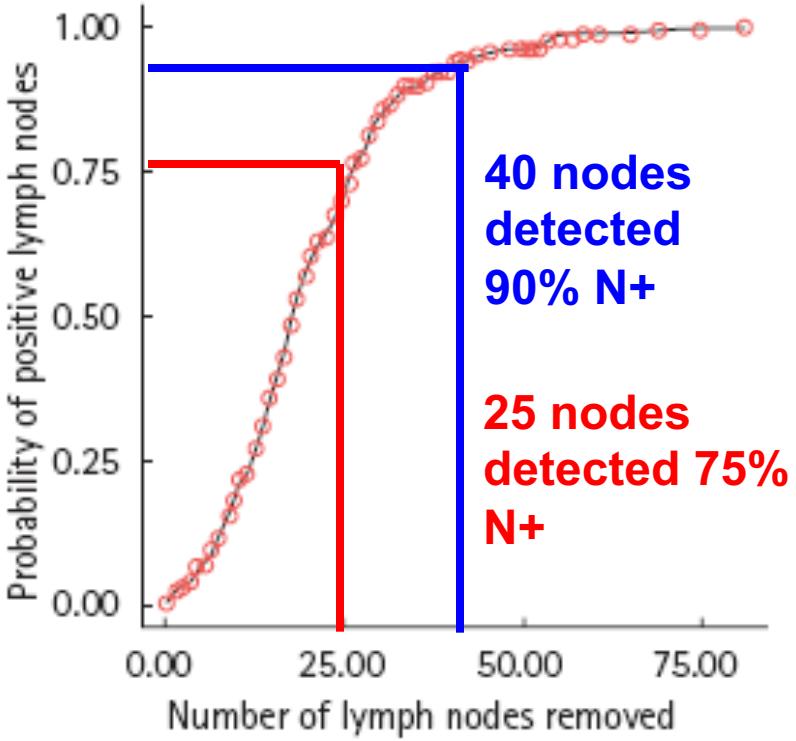
Number of Nodes and Sensitivity for N+

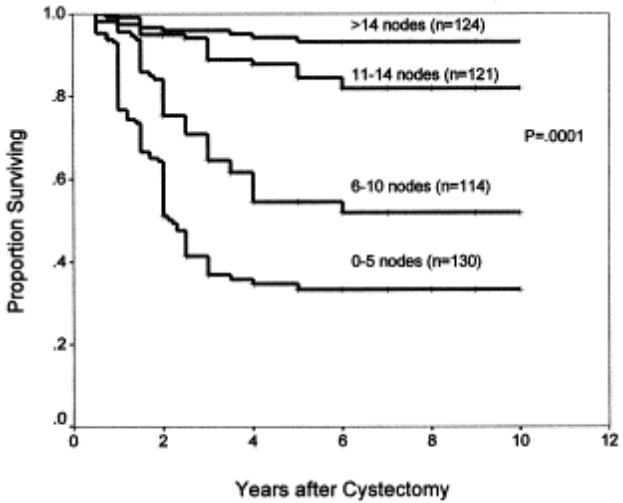


Capitanio, et al BJUI, 2008

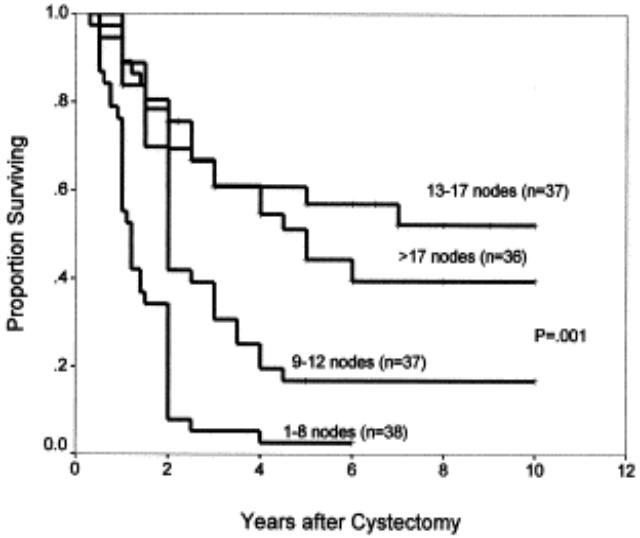
Number of Nodes Affects Outcome

Number of Nodes Sampled Affects Survival in Both Node Negative and Node Positive Patients

Node Negative



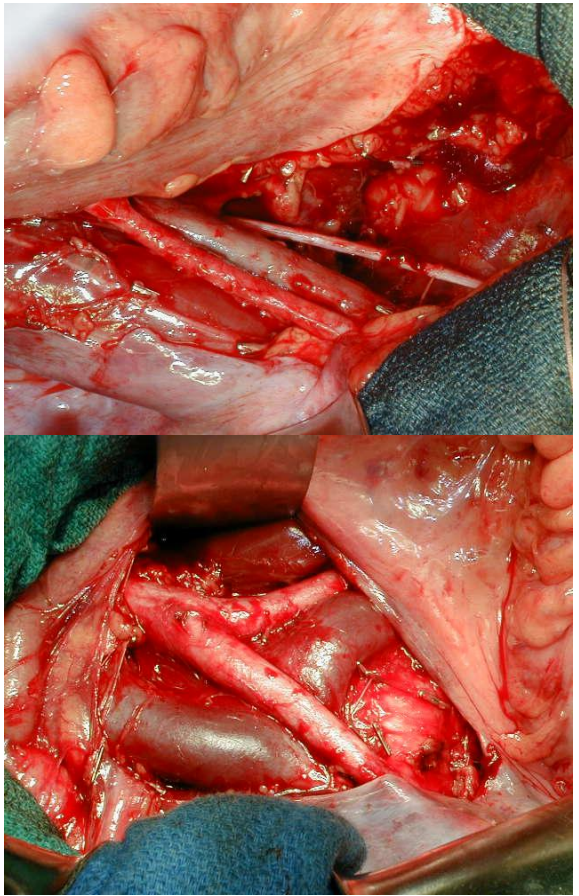
Node Positive



Herr Urology 61:105, 2003

Rationale for Extended PLND

- Standard LND includes external/internal iliac and obturator lymph nodes
  - Identifies ≥95% of N1; skip metastases rare
- Extended LND includes pre-sacral, CI and distal aorta/IVC nodes
  - increases node yield by 34-40%
  - 36-43% of P3,P4N+ have node metastasis above CI bifurcation



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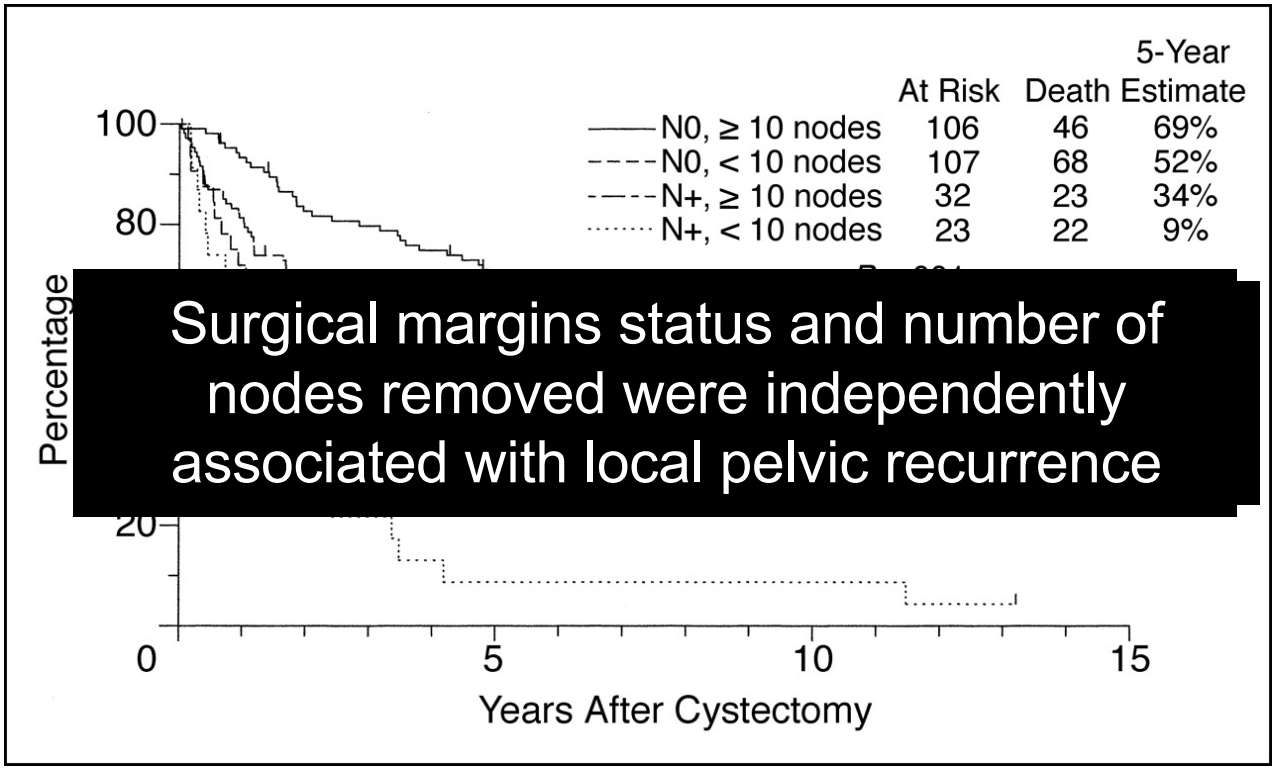
Post-cystectomy survival – Re-analysis of SWOG 8710



Surgical margins status and number of nodes removed were independently associated with local pelvic recurrence

Herr, HW et al, J Clin Oncol; 22:2781 2004

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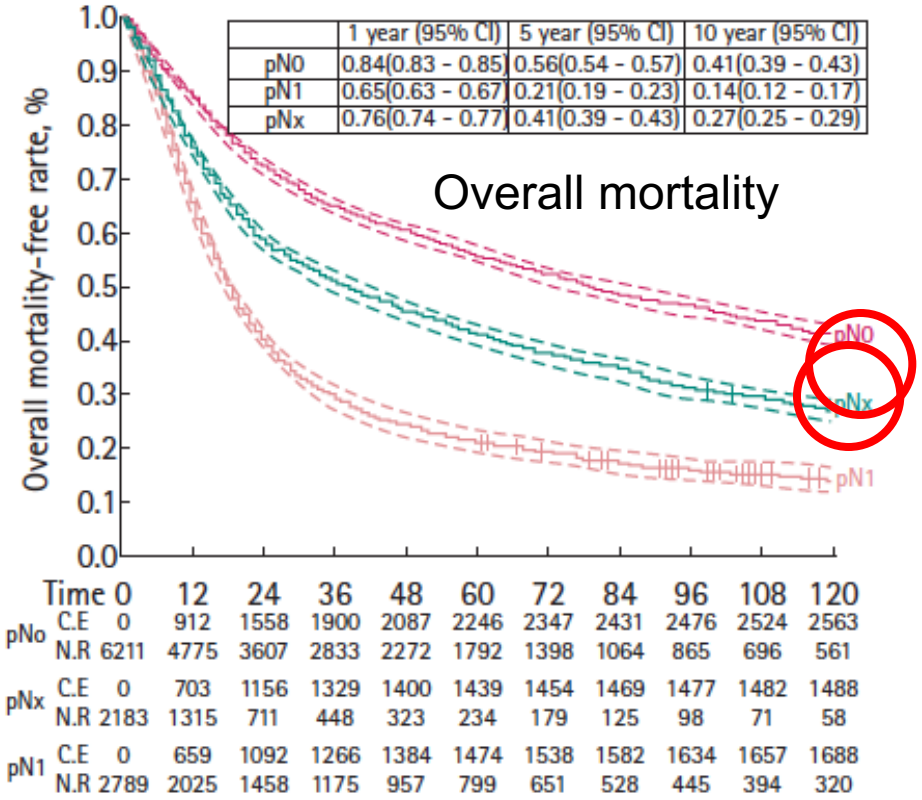
The Cost of Omitting a PLND
SEER 17 1988-2006



Abdollah, et al BJUI 109:1147, 2011

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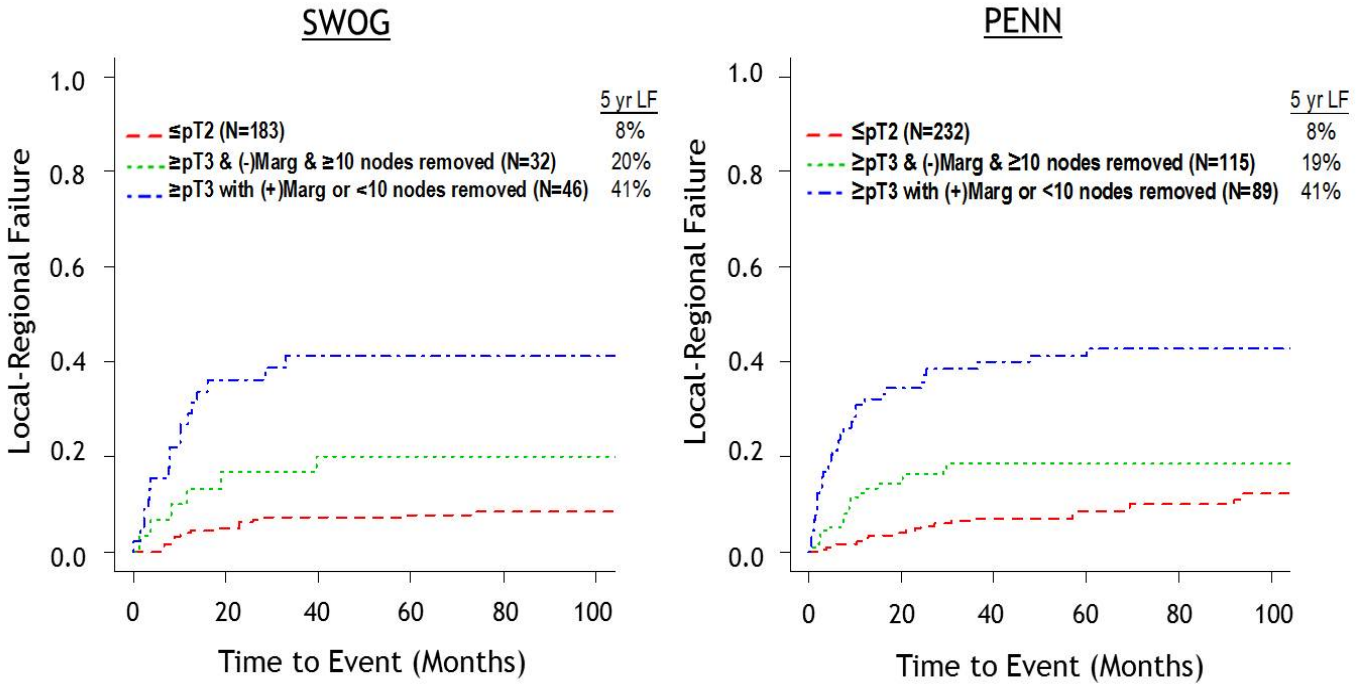
LND and Local Control



Christodouleas JP, et al Cancer 2014

Proximal Node Metastasis Outside the True Pelvis – Curable?

- 316 patients – single surgeon
- Extended pelvic and iliac LND in all
  - At or above the aortic bifurcation
- N+ in 78 patients (25%)
  - 35 (45%) LN metastases common iliac nodes or above

	5-yr Survival	
Site of N+	Ca spec	Overall
Pelvis only	44%	54%
CI or above	27%	37%

NS difference between Pelvis and CI or above

BCM, unpublished

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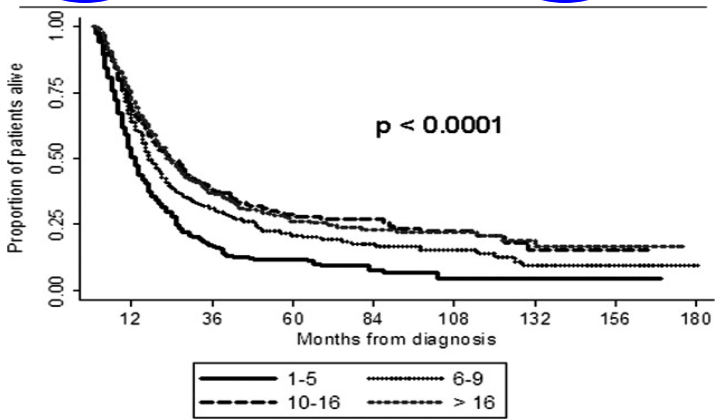
Does a More Extensive LND Improve Survival?

- **SEER – 1988-1996** [1]
  - 1923 patients
  - Improved survival with high number of nodes especially for patients with Stage III and IV
  - **SEER17 (1988-2003)** [2]
  - 1260 pts node pos
  - More LN removed associated with lower mortality

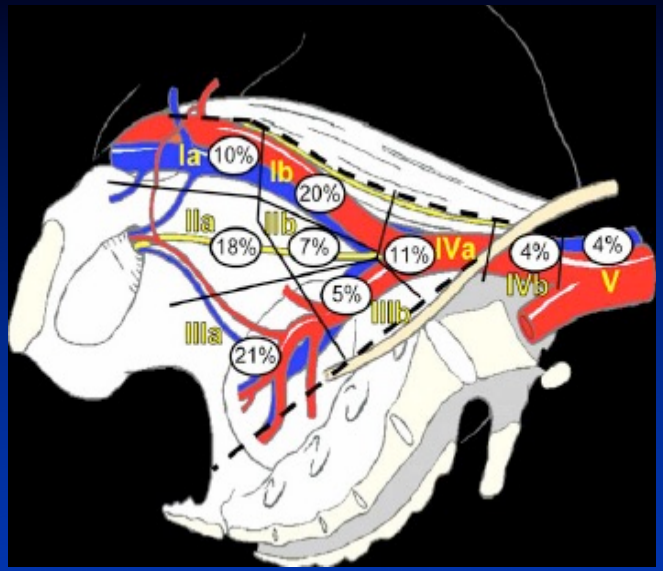
TABLE 4. *Log rank analysis indicating cancer specific survival of patients who were followed a minimum of 2 years according to stage at diagnosis and number of lymph nodes*

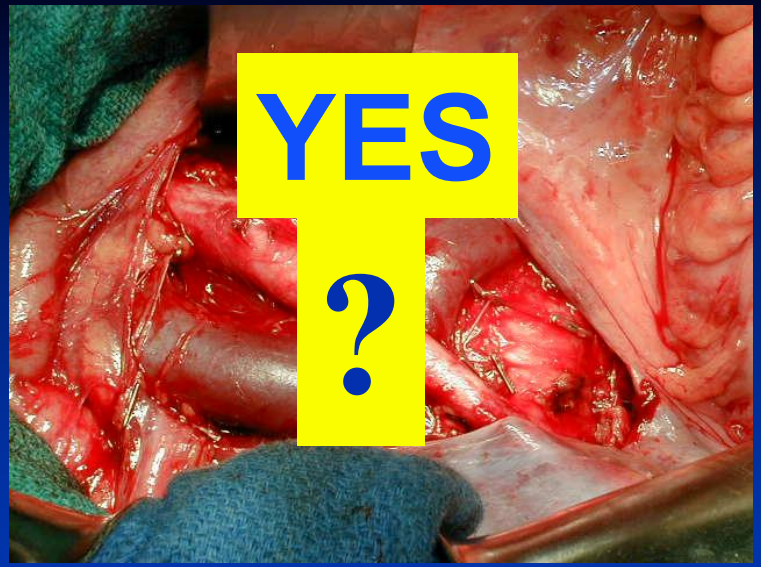
	Stage			
	In Situ/I	II	III	IV
No. lymph nodes (%):				
0	68.6	60.2	42.7	32.6
1–3	85.7	70.6	42.9	29.6
4–6	100	88.2	60.5	35
7–9	100	68.2	46.2	46.2
10–14	100	82.6	81.5	49
15–19	90	75	64.7	39
20 or Greater	100	72.7	60	41.7
No. pts.	138	210	243	395
p Value	0.0147	0.0898	0.0237	0.0046



[1] Konety et al J Urol 169:946, 2003
[2] Wright, et al Cancer 11:2401, 2008

What is the Surgical Standard for Pelvic Lymphadenectomy and Radical Cystectomy?





Roth, et al Eur urol 57:205, 2010

Extent of LND and Survival

- Pancreatic Head Cancer (Surgery 138:618, 2005)
  - Early closure after interim analysis showed increased morbidity and decreased survival with extended LND
- Esophogeal Cancer (Ann Surg 246:992, 2007)
  - Extended transthoracic resection compared with limited transhiatal resection - No survival benefit

Extent of LND and Survival

- Esophogeal Cancer (JAMA Surg 151:32, 2016)
  - Extent of lymphadenectomy did not influence 5-year all-cause or disease-specific survival
- Gastric Cancer (NEJM 359:453, 2008)
  - No difference in RFS and OS
  - Non-significant increase in morbidity w/extended LND

No Level I Evidence Supporting Extended LND

Technical University of Munich

Arbeitsgemeinschaft Urologische Onkologie

Limited versus extended pelvic lymphadenectomy in bladder cancer patients undergoing radical cystectomy: survival results from a prospective, randomized trial (LEA - AUO AB 25/02, NCT01215071)

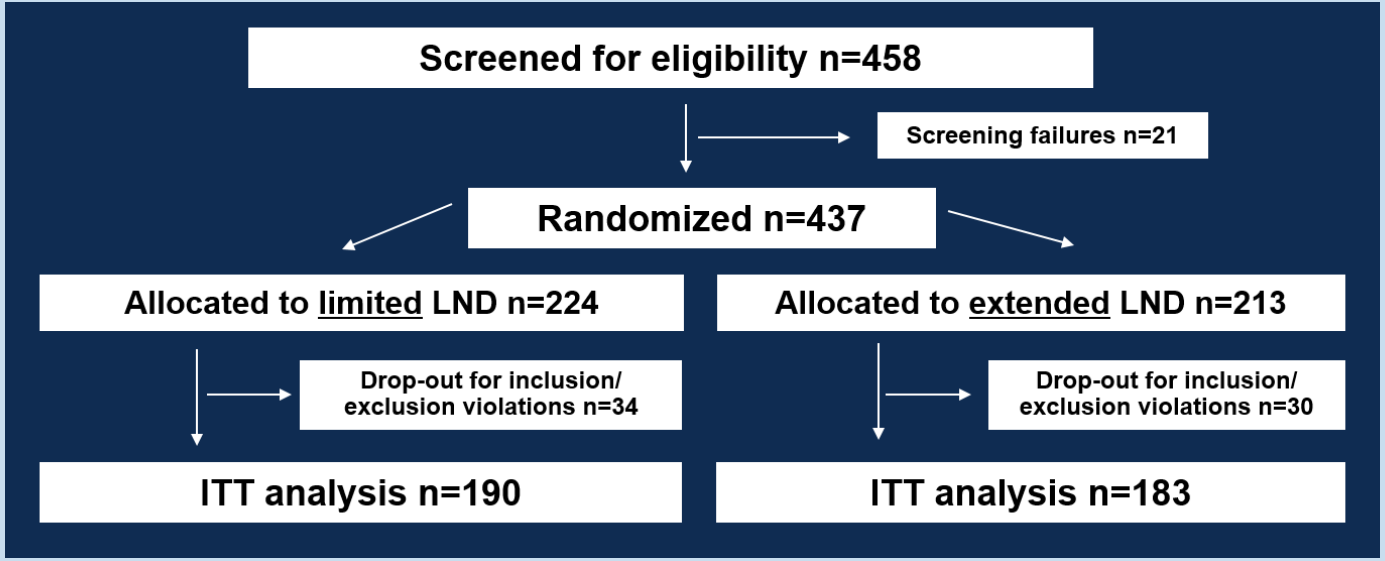
Jürgen E Gschwend, Department of Urology, Technical University of Munich, Germany

MM Heck, J Lehmann, H Rübben, P Albers, A Heidenreich, P de Geeter, JM Wolff, D Frohneberg, T Schnöller, T Kälble, M Stöckle, A Stenzl, M Müller, U-B Liehr, M Truss, S Roth, J Leissner and M Retz

on behalf of the **A**ssociation **of U**rologic **O**ncology **(AUO),** German Cancer Society

PRESENTED AT: ASCO ANNUAL MEETING '16

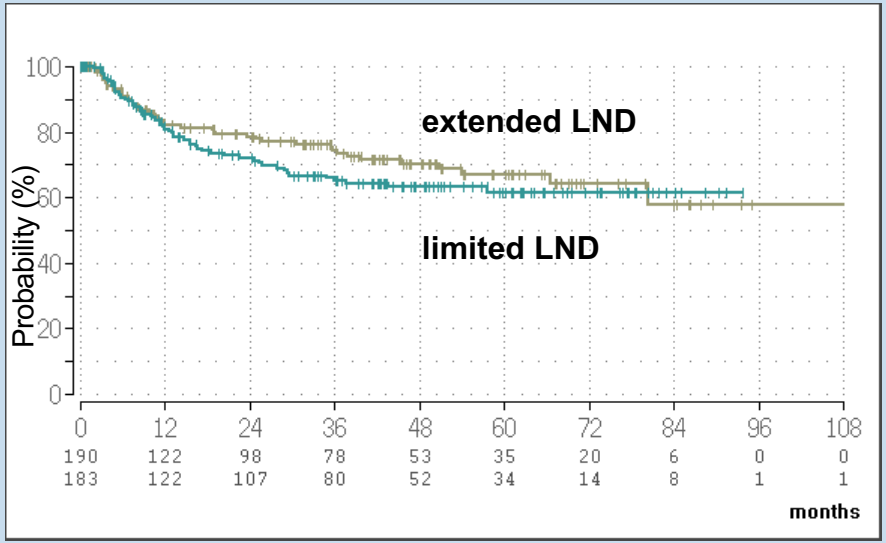
LEA intention to treat (ITT) cohort



Median follow-up was 33.2 months (range 0-108 months)

Gschwend et al. J Clin Oncol, 2016. 34 (suppl; abstr 4503).

Recurrence-free survival ITT



5 yr RFS

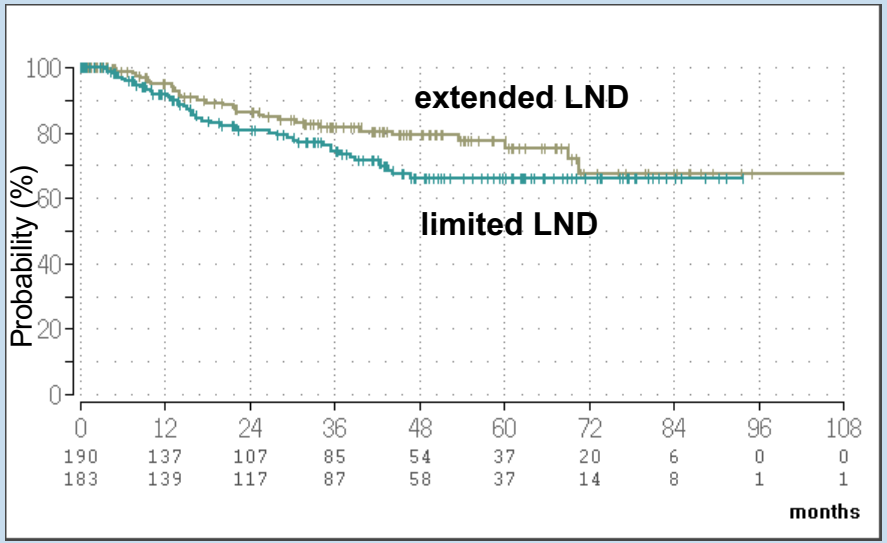
61.5% (limited LND) vs.
67.0% (extended LND)
(absolute difference of 5.5%)

Median RFS not reached

Log-rank p=0.34
HR=0.83 (95% CI 0.56-1.22)

Gschwend et al. J Clin Oncol, 2016. 34 (suppl; abstr 4503).

Cancer-specific survival ITT



5 yr CSS

66.2% (limited LND) vs.
77.6% (extended LND)
(absolute difference of 11.4%)

Median CSS not reached

Log-rank p=0.12
HR=0.70 (95% CI 0.44-1.09)

Gschwend et al. J Clin Oncol, 2016. 34 (suppl; abstr 4503).

LEA Trial Conclusions

- Negative trial for primary endpoint
- Included T1
- Standard LND was limited – no dissection below obturator nerve
- No neoadjuvant chemotherapy
- Post-hoc unplanned analysis
  - T2 possible benefit

Schema – SWOG S-1011

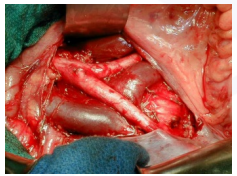
T2-T4a Urothelial ca
Radical Cystectomy
Neoadjuvant Ctx allowed

RANDOMIZE

Standard PLND
External/internal iliac,
obturator nodes

pT3-4N0,
pTanyN+
Adjuvant
Chemotherapy

Extended LND
Standard + CI, pre sacral,
distal IVC and aorta



Powered to detect 10% improvement in
3 yr DFS from 55-65%

Sample Size Based on PFS

- Sample size of 564 patients (282 per arm)
  - Total planned accrual 620 (10% drop out)
- 85% power to detect a 28% reduction in the hazard rate of progression or death (HR 0.72)

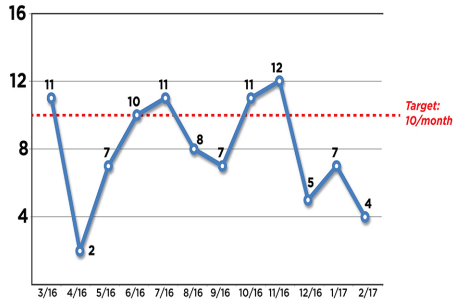
Status: Opened August, 2011

Accural: 659 reg; 620 randomized
Completed February 2017

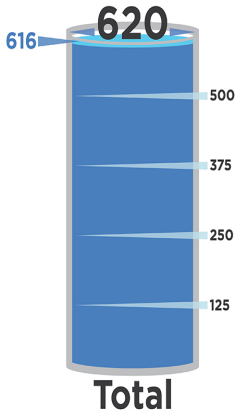
Quality Management – Data Submission

- Intra-operative surgical assessment form, op and path report, intra-operative photos within 14 days of surgery
  - SC review within 7 days of receipt
  - Independent oversight by Surgery Quality Committee - review annually
- Post-op and AE forms within 7 days following discharge

S1011 Randomizations as of February 28, 2017

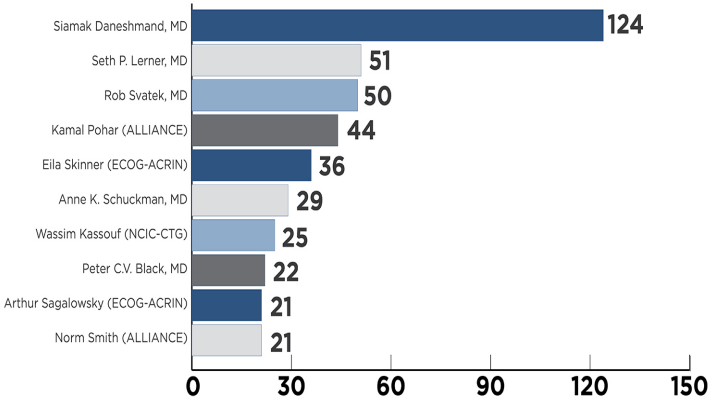


Monthly



Total

Outstanding Accruers as of February 28, 2017



	No Neoadjuvant	Neoadjuvant
Total Randomized Patients	267 (44%)	346 (56%)
RANDOMIZED ARM		
Extended LND (302/49%)	133 (44%)	169 (56%)
Standard LND (311/51%)	134 (43%)	177 (57%)
AGE (years)		
Median	71.9	67.1
SEX		
Males	204 (76%)	281 (81%)
Females	63 (24%)	65 (19%)
CLINICAL STAGE		
cT2 (431/70%)	215 (81%)	216 (62%)
cT3-4a (182/30%)	52 (19%)	130 (38%)
NEOADJUVANT CHEMOTHERAPY		
Cisplatin Based	------	303 (88%)
Carboplatin Based	------	22 (6%)
Other	------	21 (6%)

Comparison LEA and SWOG

	LEA	S-1011
Eligibility	T1-T4a	T2-T4a
Neoadjuvant chemo	Not allowed	Allowed (56%)
Planned randomized	400	564
Registered (n)	438	659
Randomized (n)	433	620
Drop out/ineligible	71 (16.4%)	Assume 10% ineligible
ITT	362	Estimate 576
LND control arm	Limited	Standard
ePLND	IMA	Aorta bifurcation → IMA
Primary endpoint	RFS at 5 years	PFS at 3 years
Effect size	15% (50→ 65%)	10% improvement (55 →65%)
Power	90%	85%
Hazard ratio	0.80 (final result)	0.72

Summary

- AUA Guidelines (2016): Radical cystectomy with bilateral pelvic lymphadenectomy for surgically curable non-metastatic (M0) disease
  - External and internal iliac and obturator nodes
- A thorough PLND contributes significantly to local control
- Extending the proximal limits of PLND increases the number of nodes identified and maximizes sensitivity for detection of node metastases
- Randomized trials of extended vs. standard PLND are required to demonstrate improved progression free and overall survival