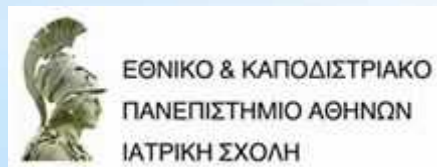




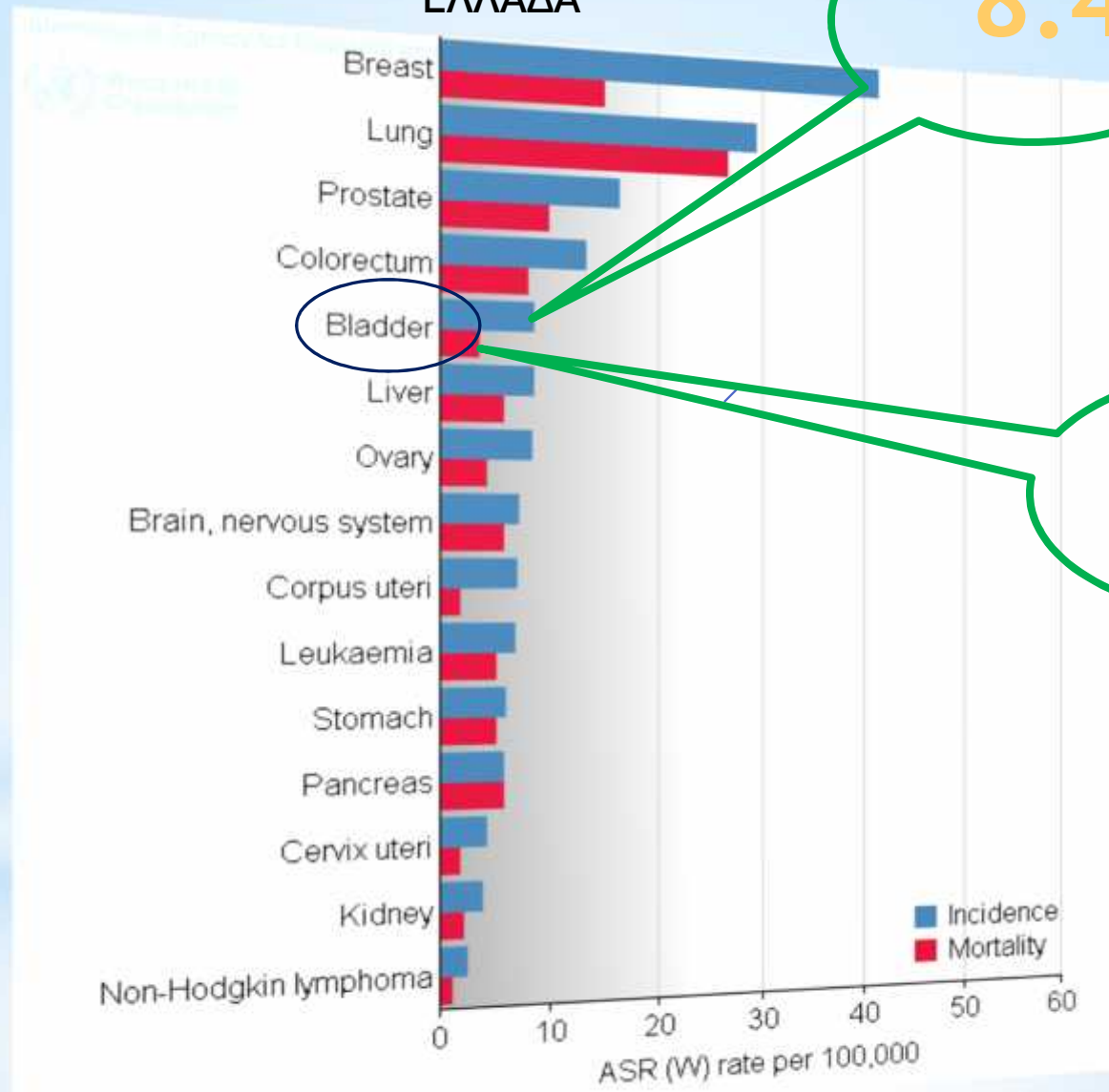
Εκτεταμένη Λεμφαδενεκτομή στον Μυοδιηθητικό Καρκίνο της Ουροδόχου Κύστης. Υπάρχει τεκμηρίωση?

Κωνσταντίνος Γ. Στραβοδήμος
Αναπληρωτής Καθηγητής Ουρολογίας



Επιδημιολογία

ΕΛΛΑΔΑ



3.4

8.4

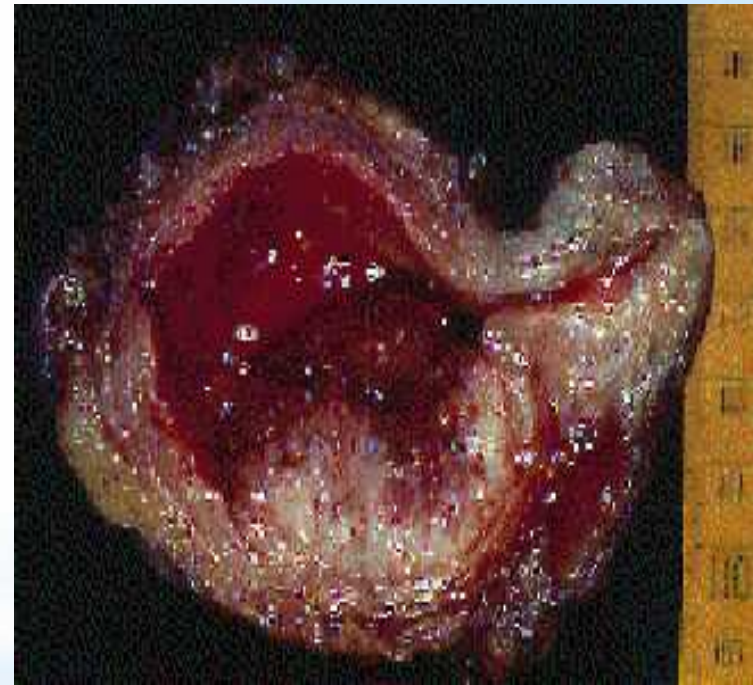
Ποιά τα χαρακτηριστικά του;

Είναι εξ αρχής διηθητικός
τουλάχιστον στο 57% των
ασθενών.

Παλαιότερες σειρές 91% και 84%.

Συχνότερα >50 ετών.

Vaidya A et al. J Urol 2001; 165:47-50



Φυσική ιστορία

Στη 10ετία, OS=16%, CSS=26%.

Low VJ et al. BJU Int 2010; 105:1667-71

Αύξηση θνησιμότητας >12 εβδομάδες.

Gore JL et al. Cancer 2009; 115:988-96

85% πιθανότητα η εντοπισμένη νόσος να προχωρήσει σε εξωκυστική.

Chang SS et al. J Urol 2003; 170:1085-7

Είναι θανατηφόρα νόσος και χρήζει επιθετικής αντιμετώπισης.

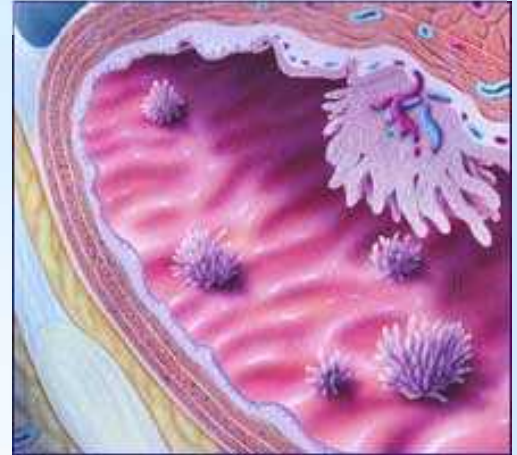
Messing EM et al. J Clin Oncol 2009; 27:2443-9

Γιατί λεμφαδενεκτομή στον καρκίνο?

Η θεωρία της «φυγόκεντρου πορείας»
Κέντρο → λεμφαδένες → μεταστάσεις

Η βιολογία του καρκίνου μάλλον είναι
διαφορετική

Ποιός ο ρόλος της εκτεταμένης λεμφαδενεκτομής
→ σε μια νόσο εντοπισμένη
→ σε μια νόσο επιθετική και μεταστατική



DeVita VT Jr, Rosenberg SA (2010) Two hundred years of cancer research. N Engl J Med 366:2207-2214

Γιατί λεμφαδενεκτομή στον καρκίνο?

Διαγνωστική: ναι

Σταδιοποιητική: ναι

Θεραπευτική: Επιβίωση σχετική με τη νόσο??

Ανατομική κυστεκτομή



Hurle R & Naspro R. Surg Oncol 2010; 19:208-20

Λεμφαδενεκτομή στον καρκίνο της κύστης: δεδομένα

Standard of care → Ριζική κυστεκτομή και πυελική λεμφαδενεκτομή

Turner WH & Studer UE. Semin Surg Oncol 1997

Skinner EC, et al. Urol Oncol 2007

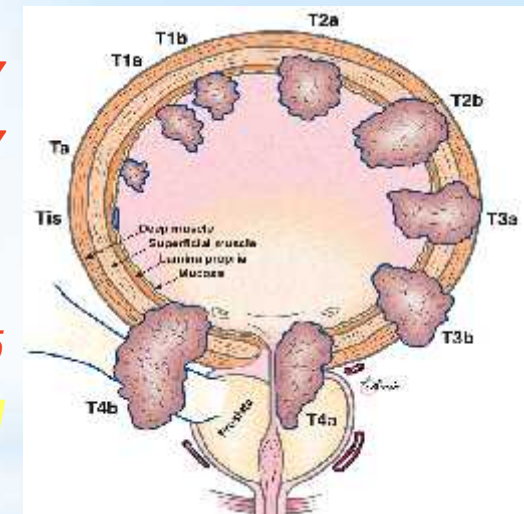
Πάντα

Stein JP, et al. J Clin Oncol 2001; 19:666-75

Yafi FA, et al. BJU Int 2010 Dec 16. [Epub ahead of print]

Αμφοτερόπλευρη.

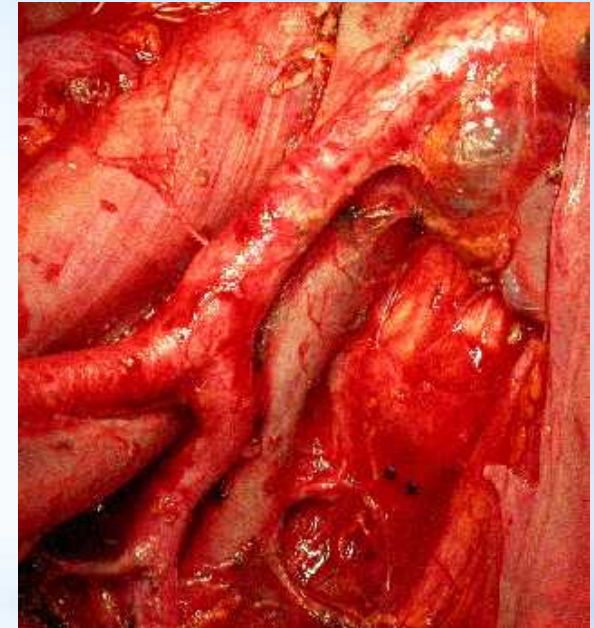
Mills RD, et al. J Urol 2001; 166:19-23



Λεμφαδενεκτομή στον καρκίνο κύστης: Δεδομένα

LN (+) → ο ισχυρότερος
προγνωστικός δείκτης υποτροπής
και κακής επιβίωσης

Μέχρι 80 % των ασθενών με LN+ θα
υποτροπιάσουν και θα πεθάνουν
μετά την κυστεκτομή



*Stein et al J Clin Oncol 2001,
Shariat SF, et al J Urol 2006
Thalmann GN & Stein JP. BJU Int 2008,
Hautmann RE, et al Eur Urol 2012*

Table 3. Estimated 5-Year CSM and OCM Rates in Patients With Urothelial Carcinoma of the Urinary Bladder Treated With Radical Cystectomy, Stratified According to Age and Pathologic T and N Stages

pT and pN Stages	Age at Surgery											
	≤59 Years			60-69 Years			70-79 Years			≥80 Years		
	% Alive	% CSM	% OCM	% Alive	% CSM	% OCM	% Alive	% CSM	% OCM	% Alive	% CSM	% OCM
pT ₁ N ₀ patients	65.7	21.6	12.7	60.9	23.4	15.8	57.1	23.7	19.2	41.2	31.7	27.1
pT ₂ N ₀ patients	62.2	26.3	11.5	57.0	28.6	14.4	53.1	29.3	17.6	36.4	38.9	24.7
pT ₃ N ₀ patients	54.5	35.7	9.8	48.7	38.9	12.4	44.3	40.5	15.2	26.8	52.4	20.8
pT ₄ N ₀ patients	53.0	36.7	10.3	47.1	39.9	13.0	51.8	42.6	15.9	25.1	53.5	21.4
pT _{any} N ₁₋₃ patients	45.6	45.9	8.5	39.2	49.9	10.9	34.5	52.3	13.2	17.2	65.5	17.3

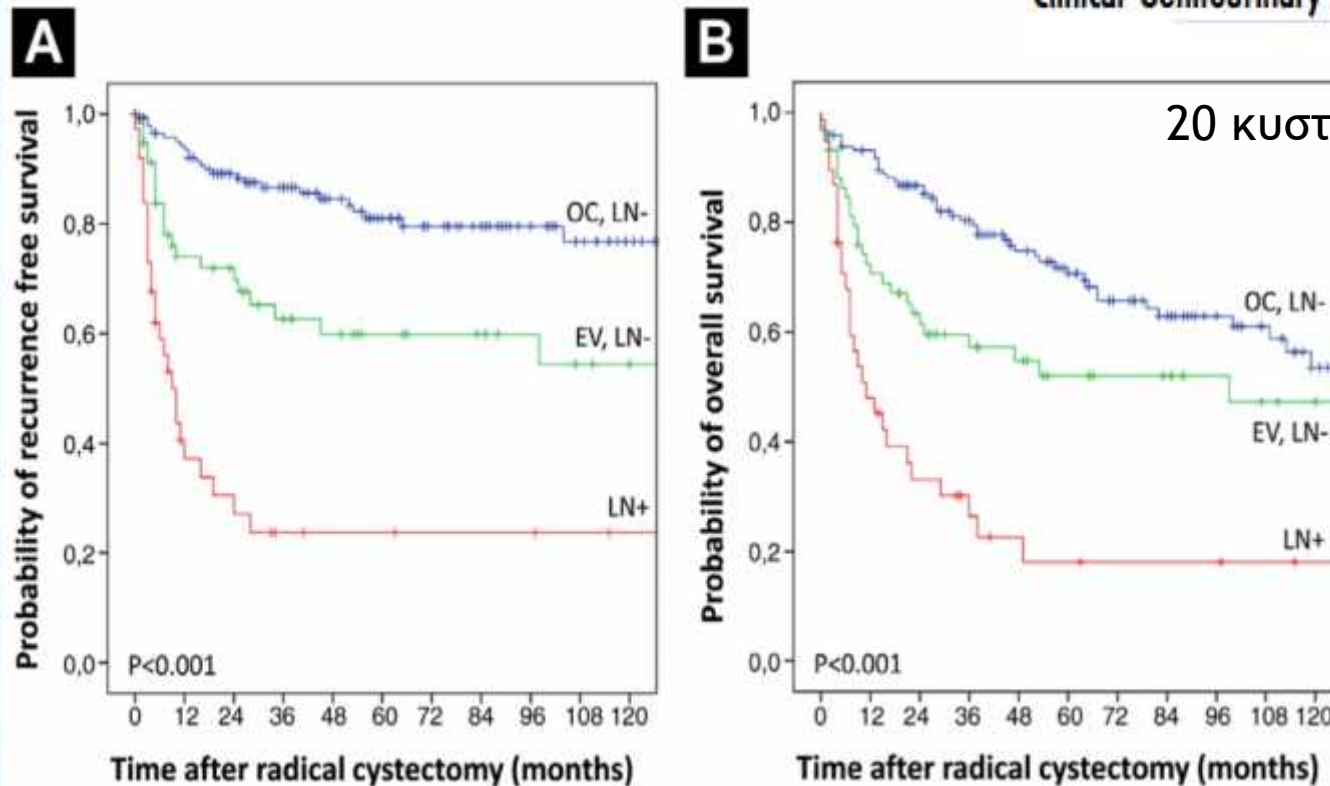
CSM indicates cancer-specific mortality; OCM, other-cause mortality.

Hautmann RE, World J Urol 2006;24:305-14
Lughezzani G, et al. Cancer 2011; 117:103-9

Radical Cystectomy in a Dutch University Hospital: Long-Term Outcomes and Prognostic Factors in a Homogeneous Surgery-Only Series

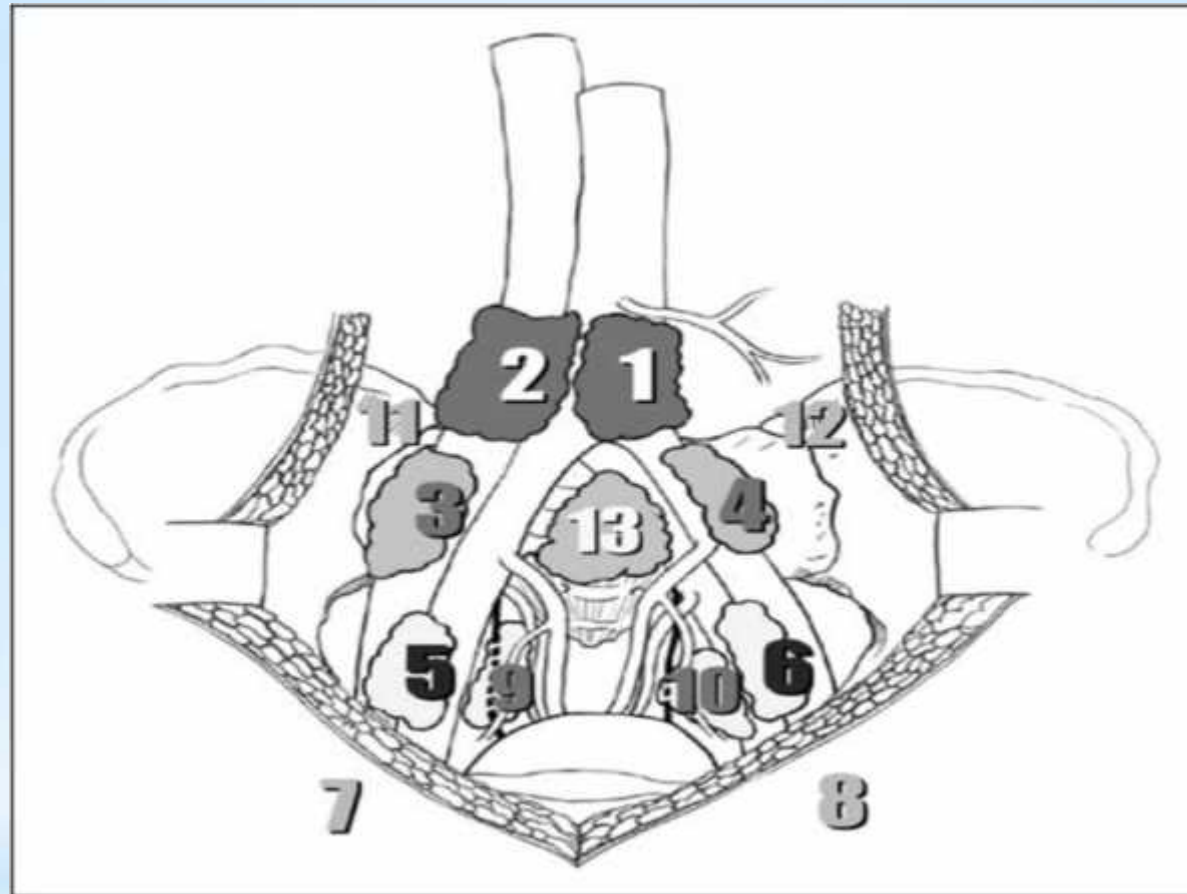
Harman M. Bruins,¹ Tom J.H. Arends,¹ Mijke Pelkman,¹
Christina A. Hulsbergen-van de Kaa,² Antoine G. van der Heijden,¹
J. Alfred Witjes¹

Clinical Genitourinary Cancer Month 2013



5-year	RFS	rates:
OC	→	81.4%
EV	→	61.6%
LN+	→	23.7%

5-year	OS	rates:
OC	→	69.9%
EV	→	55.9%
LN+	→	18.1%



1) (ΑΡ) παραορτικοί, 2) (ΔΕ) παραΚΚΦ, 3) (ΔΕ) κοινοί λαγόνιοι, 4) (ΑΡ) κοινοί λαγόνιοι, 5) (ΔΕ) έξω λαγόνιοι, 6) (ΑΡ) έξω λαγόνιοι, 7) (ΔΕ) λεμφαδένας του Cloquet, 8) (ΑΡ) λεμφαδένας του Cloquet, 9) (ΔΕ) θυροειδικός/υπογάστριος, 10) (ΑΡ) θυροειδικός/υπογάστριος, 11) (ΔΕ) προισχιακός, 12) (ΑΡ) προισχιακός, 13) προϊερός

Ποιά είναι η «καλή» λεμφαδενεκτομή Κριτήριο ο αριθμός?

Τουλάχιστον 9-16 λεμφαδένες

Herr HW, J Urol 2002

Leissner J, J Urol 2004

Capitanio U, BJU Int 2009

Όσο περισσότεροι τόσο καλύτερα (επιβίωση)

Koppie TM, Cancer 2006

Μοντέλα πρόβλεψης μεταστατικών λεμφαδένων σε
σχέση με τον αριθμό αφαιρεθέντων (> η < 20%)

Shariat SF, Eur Urol 2012

Ποιά είναι η «καλή» λεμφαδενεκτομή Κριτήριο ο αριθμός?

Ο αριθμός εξαρτάται από παράγοντες

- Κλινικούς (ηλικία, προεγχ ΧΜΘ)
- Χειρουργικούς (έκταση, εμπειρία, επιμέλεια)
- Παθολογοανατομικούς

Bochner BH, J Urol 2004
Stein JP, J Urol 2007

Δύσκολο να οριστεί συγκεκριμένος αριθμός



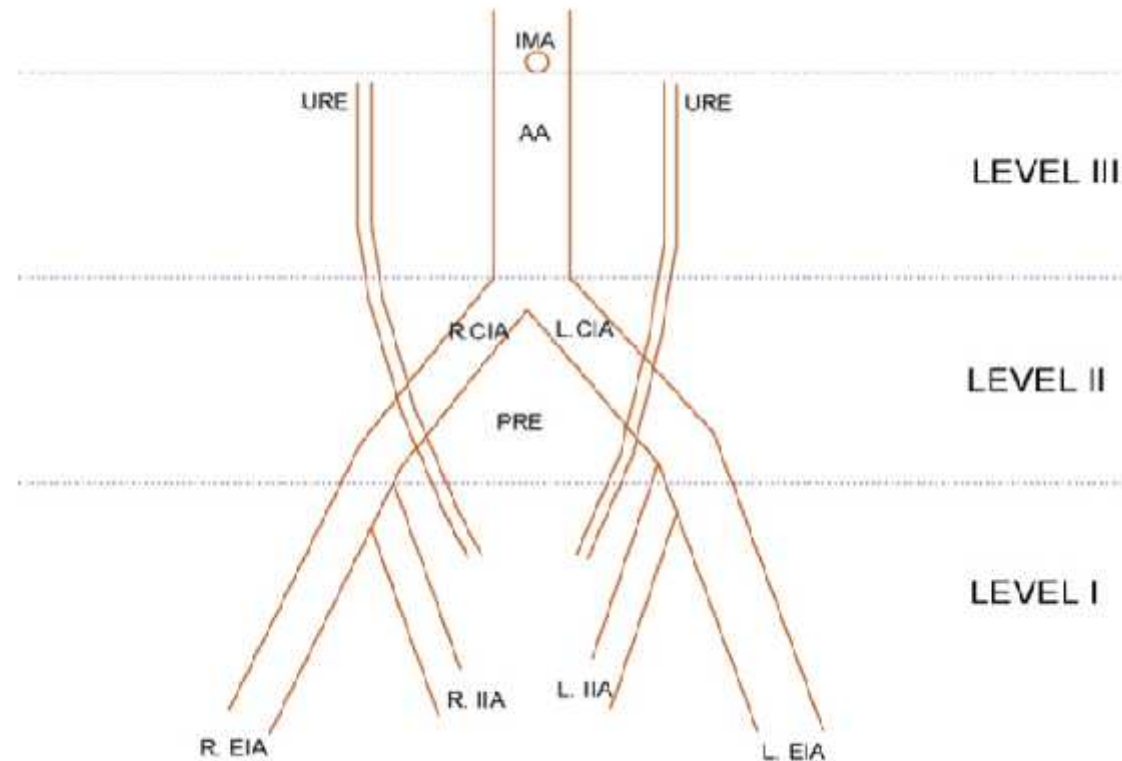
Review – Bladder Cancer

**ICUD-EAU International Consultation on Bladder Cancer 2012:
Radical Cystectomy and Bladder Preservation for Muscle-Invasive
Urothelial Carcinoma of the Bladder**

Υπερεκτεταμένη
(Superextended)

Εκτεταμένη
(Extended)

Κλασική
(Standard)



Έκταση λεμφαδενεκτομής

Table 1 Outcomes of large radical cystectomy/pelvic lymph node dissection series (Original)

Series	^c No. of patients	Type of PLND	% of patients LN+	Median follow-up	5-year RFS LN-	5-year RFS OC	5-year RFS EV	5-year RFS LN+
Stein [42]	1054	Extended	23	10.2 years	78	80	46	39
Steven [27]	336	Extended	19	3.6 years	77	83	34	42
Poulsen [31]	126	Extended	26	n/a	n/a	85	n/a	n/a
Poulsen [31]	68	Standard	n/a	n/a	n/a	64	n/a	n/a
Dhar ^a [40]	322	Standard	26	40 months	68	71	49	35
Dhar ^a [40]	336	Limited	13	25 months	51	63	19	7
Hautmann ^c [43]	788	Standard	18	3 years	74	79	38	21
Madersbacher [44]	507	Standard	24	31 months	65	75	47	33
Herr and Donat ^{b,c} [45]	84	Extended	n/a	10 years	n/a	n/a	n/a	24
Mills [46]	83	Standard	n/a	6 years	n/a	n/a	n/a	29
Abdel-Latif ^d [47]	418	Standard	26	40 months	78 ^e	n/a	n/a	38 ^e

EV, extravesical primary tumor (pT3 or pT4); LN-, no metastatic LNs; LN+, metastatic LNs; OC, organ confined primary tumor (pTa, pT1, pTis, pT2).

^a pT1, pTis, pT4 excluded in this study.

^b all patients had grossly positive LNs at time of cystectomy.

^c all patients treated with surgery only.

^d 30% of patients had squamous cell histology, which conferred significantly improved 3-year survival rates.

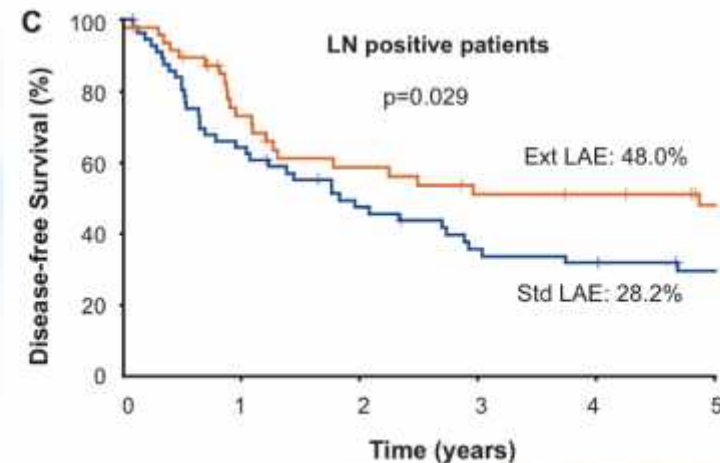
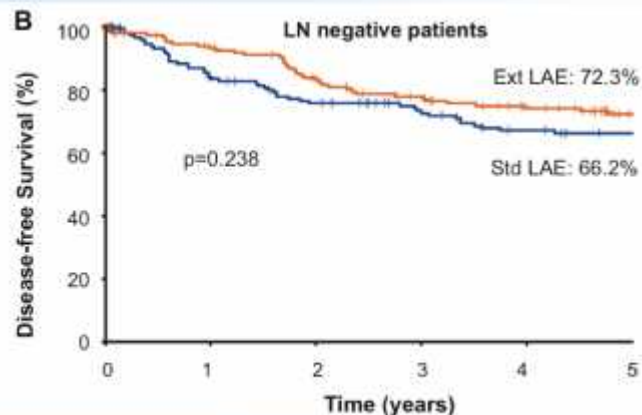
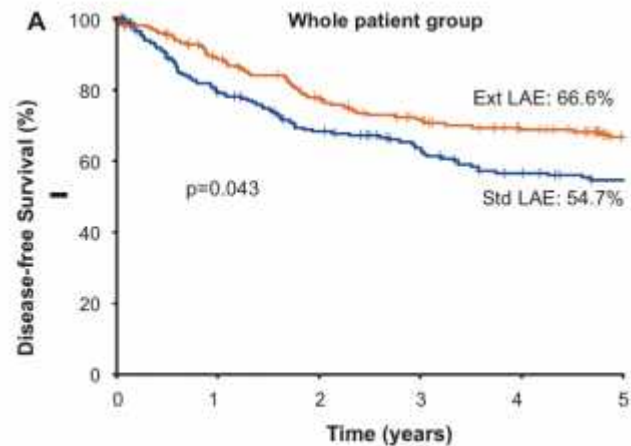
^e 3-year survival rate.

Dorin RP & Skinner EC. Curr Opin Urol 2010; 20:414-20

Bladder Cancer

Does the Extent of Lymphadenectomy in Radical Cystectomy for Bladder Cancer Influence Disease-Free Survival? A Prospective Single-Center Study

Hassan Abol-Enein^{a,1}, Derya Tilki^{a,b,1,*}, Ahmed Mosbah^a, Mahmoud El-Baz^c, Ahmed Shokeir^a, Adel Nabeeh^a, Mohamed A. Ghoneim^a

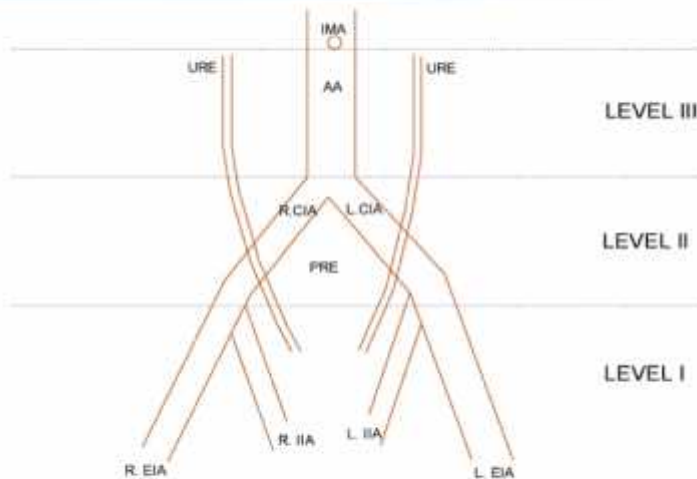


- Προοπτική, ένα κέντρο, 400 ασθενείς
- Εκτεταμένη Vs standard
- 4 χρόνια FU
- Περισσότεροι λεμφαδένες (49 vs 16)
- Καλύτερο 5y DFS για N+ ασθενείς (48.0 vs. 28.2 %)

Table 2 – Multivariate analysis predicting disease-free survival in 400 bladder cancer patients

Variable	Multivariate analysis (stepwise backward elimination)		
	HR	95% CI	<i>p</i> value
Pathologic category			
≤pT2	Referent		
pT3–4	3.6975	1.7854–7.6573	<0.001
Lymph node involvement	2.1718	1.5546–3.0339	<0.001
Extended lymphadenectomy	1.4510	1.060–1.9858	0.02

CI = confidence interval; HR = hazard ratio.
 *Age, gender, grade, and histology were nonsignificant variables.



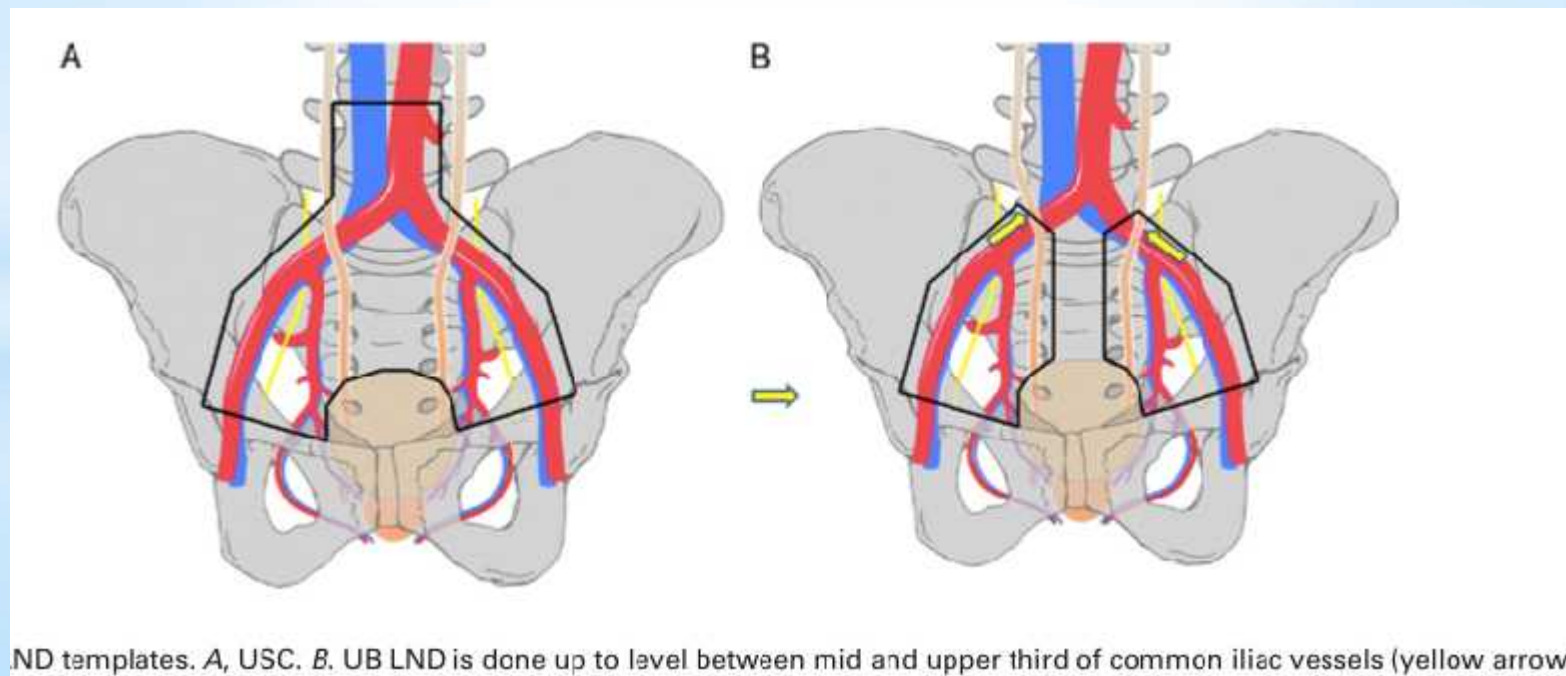
- Ερωτήματα!!!!!!**
- Μή τυχαιοποιημένη
 - 39.3% ασθενείς με πλακώδες καρκίνωμα
 - pT₁ και pT₄
 - Έκταση λεμφαδενεκτομής
Υπερεκτεταμένη

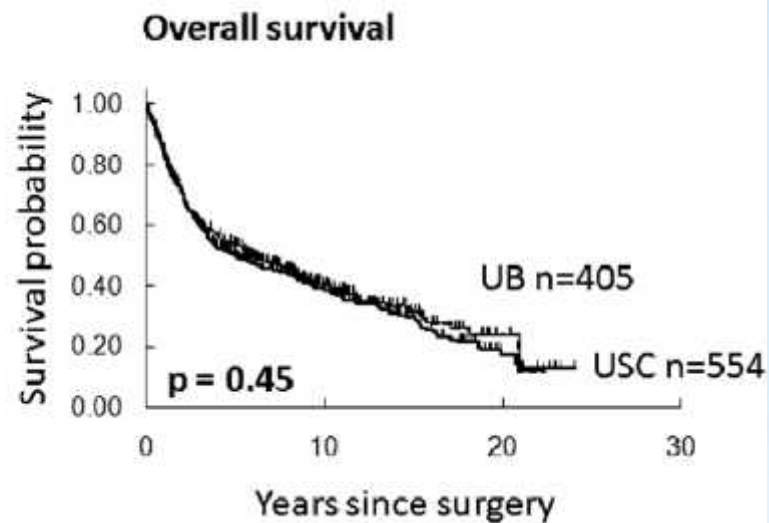
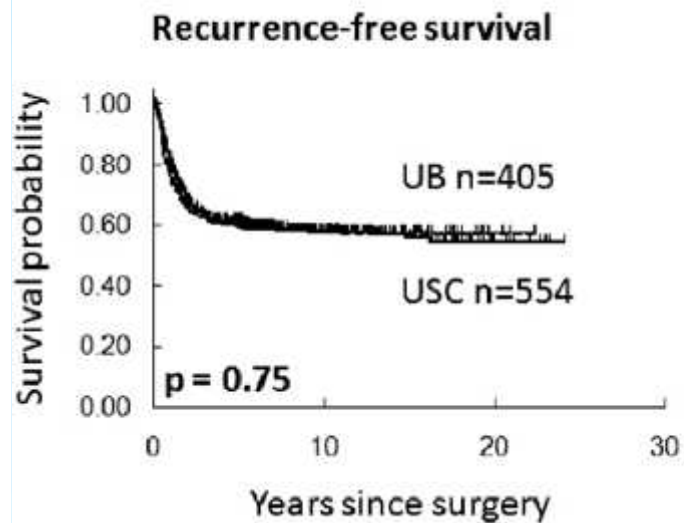
Super Extended Versus Extended Pelvic Lymph Node Dissection in Patients Undergoing Radical Cystectomy for Bladder Cancer: A Comparative Study

J Urol 2011

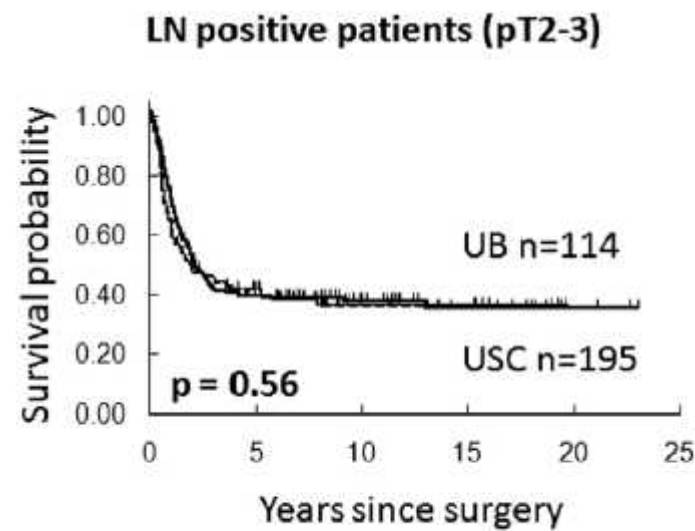
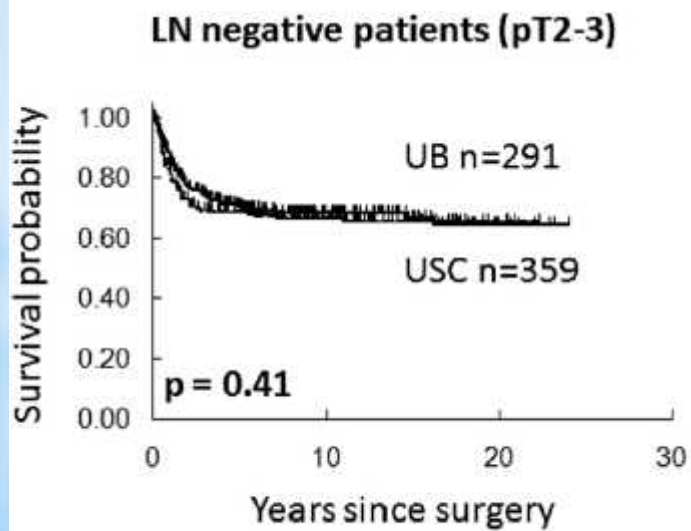
Pascal Zehnder,* Urs E. Studer, Eila C. Skinner, Ryan P. Dorin, Jie Cai, Beat Roth, Gus Miranda, Frédéric Birkhäuser, John Stein,† Fiona C. Burkhard, Sia Daneshmand,‡ George N. Thalmann, Inderbir S. Gill and Donald G. Skinner

959 ασθενείς
pT₂₋₃ κλινικά N₀M₀
Διαφορετική έκταση λεμφαδενεκτομής
10 χρόνια FU





Χωρίς διαφορές
στην επιβίωση



Ανεξάρτητα από
θετικούς ή
αρνητικούς
λεμφαδένες

Figure 4. RFS by LN status

Αριθμός λεμφαδένων

USC → 38 vs UB → 22 (p = 0.0001)

Έκταση λεμφαδενεκτομής

Τρόποι αποστολής στο Παθ Αν (6 vs 13 πακέτα)

Παθολογοανατομική προσέγγιση

Ερωτήματα!!!!

- Αναδρομική μελέτη

- Συμπληρωματική ΧΜΘ

 - Σε LN+ → 62% USC vs 40% UB

 - Σε LN - → 21% USC vs 0% UB

- Διάφοροι χειρουργοί

Τι μπορεί να διαφύγει?

Όλοι οι + λεμφαδένες στα κοινά
λαγόνια συνυπήρχαν με + λεμφαδένες
στην πύελο

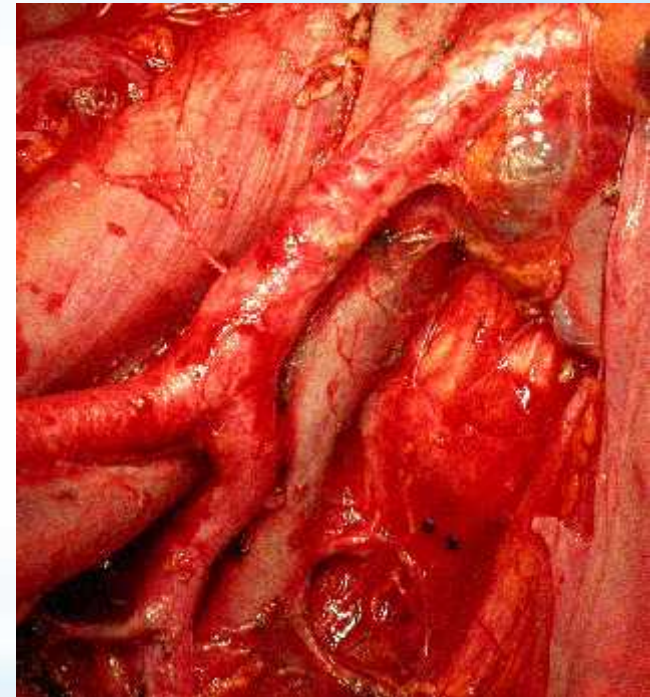
Όταν οι πυελικοί λεμφαδένες είναι
αρνητικοί δεν μπορεί να υπάρχει
μετάσταση σε εξωπυελικούς.

Ghoneim MA & Abol-Enein H, Eur Urol 2004

Χαρτογράφηση με technetium

22/284 (8%) ραδιενεργοί λεμφαδένες
υπήρχαν πάνω από το μέσο των κοινών
λαγονίων αγγείων

Roth B, Eur Urol 2010





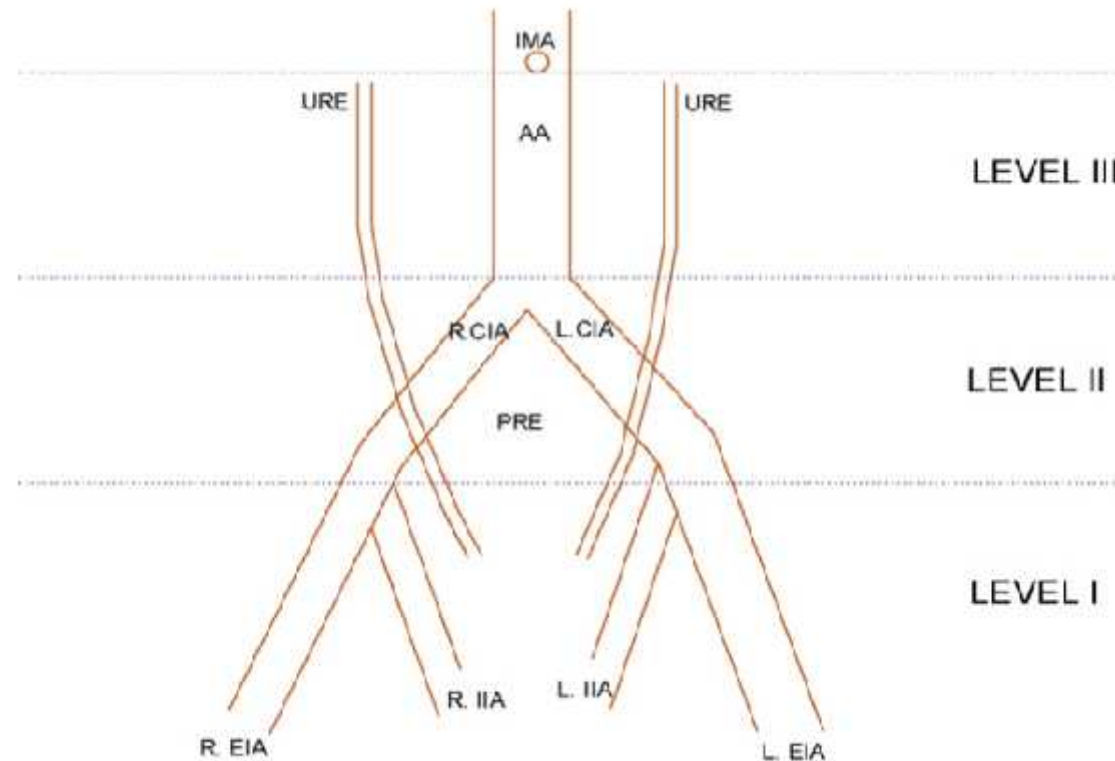
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Υπερεκτεταμένη
(Superextended)

Εκτεταμένη
(Extended)

Κλασσική
(Standard)

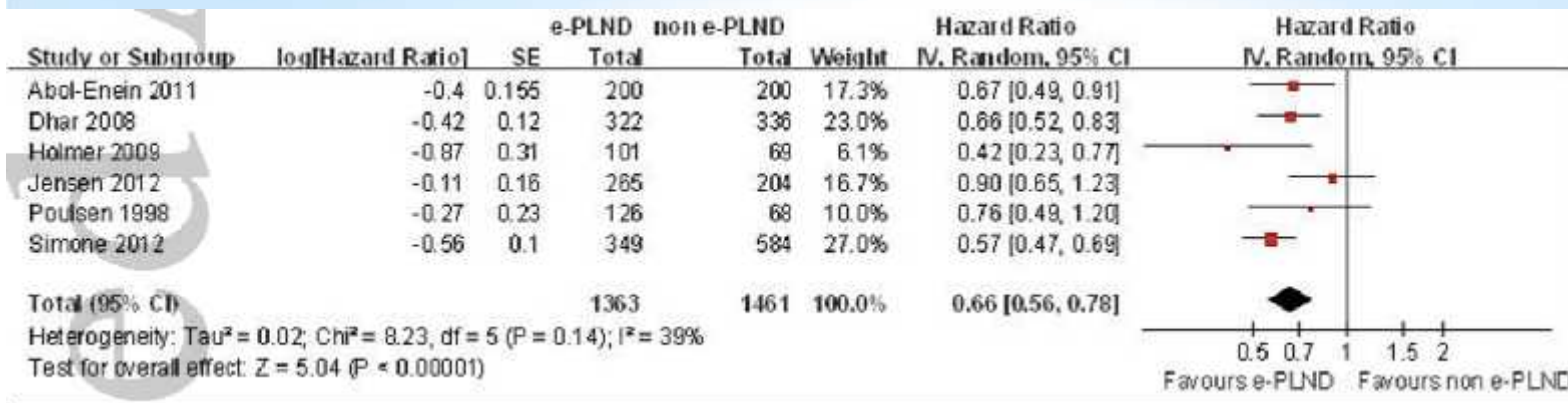


The extent of lymph node dissection and the individual surgeon's expertise are critical, as they significantly affect therapeutic outcome and overall survival after radical cystectomy. Lymphadenectomy at radical cystectomy should remove all lymphatic tissues around the common iliac, external iliac, internal iliac group, and obturator group bilaterally, since as many as one-third of all positive nodes are located around the common iliac artery.

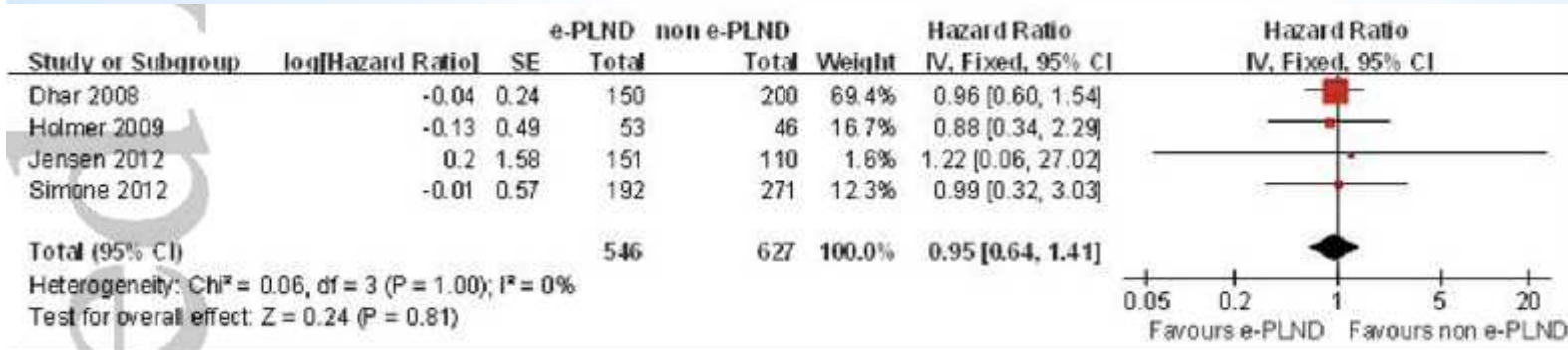
1b A

2b-3 B

Extended vs non-extended pelvic lymph node dissection and their influence on recurrence-free survival in patients undergoing radical cystectomy for bladder cancer: a systematic review and meta-analysis of comparative studies

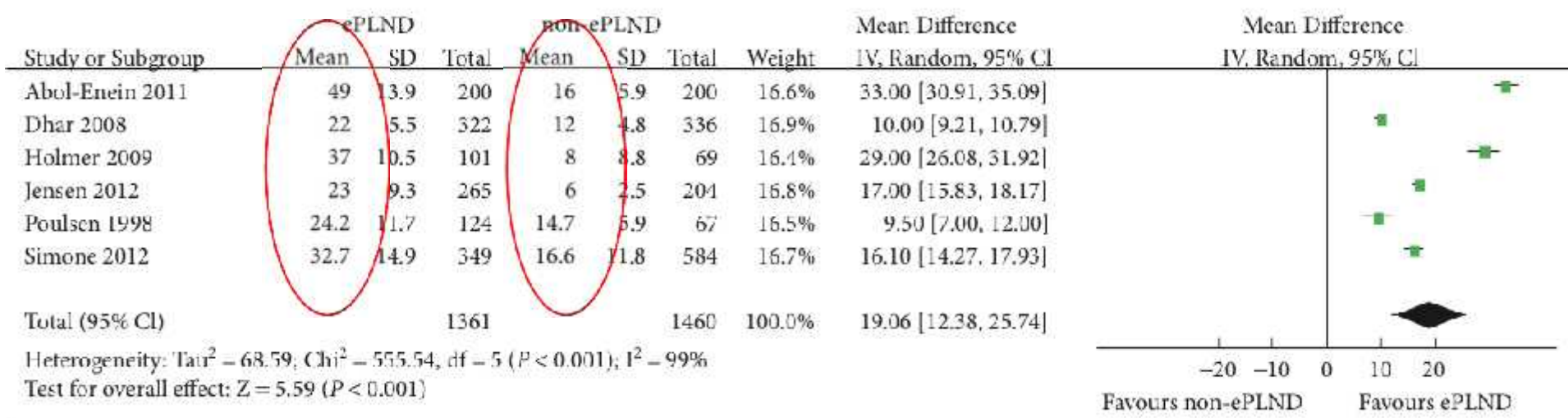


RFS overall



RFS pT2

Extended vs non-extended pelvic lymph node dissection and their influence on recurrence-free survival in patients undergoing radical cystectomy for bladder cancer: a systematic review and meta-analysis of comparative studies



Η εκτεταμένη λεμφαδενεκτομή βελτιώνει το διάστημα ελεύθερο υποτροπής σε ασθενείς → LN+, LN -, pT3-4, pT2??



Review – Bladder Cancer

The Impact of the Extent of Lymphadenectomy on Oncologic Outcomes in Patients Undergoing Radical Cystectomy for Bladder Cancer: A Systematic Review

Harman M. Bruins^{a,*}, Erik Veskimäe^b, Virginia Hernandez^c, Mari Imamura^d, Molly M. Neuberger^e, Philip Dahm^{e,f}, Fiona Stewart^d, Thomas B. Lam^d, James N'Dow^d, Antoine G. van der Heijden^a, Eva Compérat^g, Nigel C. Cowan^h, Maria De Santisⁱ, Georgios Gakis^j, Thierry Lebrét^k, Maria J. Ribal^l, Amir Sherif^m, J. Alfred Witjes^a

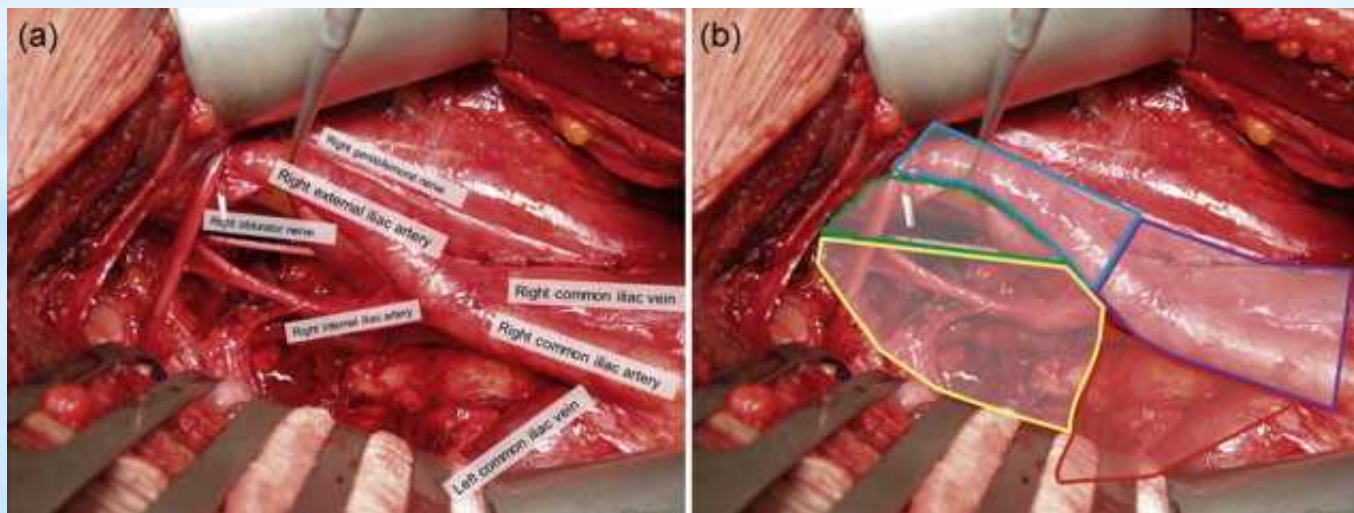
- * Καμιά τυχαιοποιημένη μελέτη
- * Λεμφαδενεκτομή καλύτερη από μη λεμφαδενεκτομή
- * Χωρίς περισσότερες επιπλοκές
- * the findings indicate that E- LND might be superior to lesser degrees of dissection from an oncologic perspective
- * however, further extending the dissection (eg, SE-LND) is not beneficial.

Προοπτική

It is likely that the templates will vary according to patient's risk of LNI

*Shariat SF, Ehdai B, Rink M et al
Clinical nodal staging scores for bladder cancer: a proposal for preoperative risk assessment. Eur Urol 2012*

*Karim Bensalah • Morgan Roupret • Evanguelos Xylinas • Shahrokh Shariat
The survival benefit of lymph node dissection at the time of removal of kidney, prostate and urothelial carcinomas: what is the evidence? World J Urol 2013*





Hot Topic

Systematic review and meta-analysis of comparative studies reporting early outcomes after robot-assisted radical cystectomy versus open radical cystectomy



Kaiwen Li^{a,b,1}, Tianxin Lin^{a,b,1}, Xinxiang Fan^{a,b,1}, Kewei Xu^{a,b}, Liangkuan Bi^{a,b}, Yu Duan^c, Yu Zhou^d, Min Yu^d, Jielin Li^c, Jian Huang^{a,b,*}

Table 1

Characteristics of the included studies.

First author, year of publication	Level of evidence ^a	Country	Study design	No. of patients ^b		Age, RARC/ORC, mean or median	Gender, RARC/ORC, No. of males	Level of PLND	Reconstruction method for urinary diversion	No. of neobladder reconstructions ^c		Match factors	Quality scores ^d
				RARC (364)	ORC (598)					RARC	ORC		
Galich 2006 ²⁸	3	USA	P	13	24	70/70.5	10/18	I	Extracorporeal	5	7	1, 2, 3, 5, 6, 11	*****
Sterrett 2006 ³⁰	3	USA	P	19	33	69.9/65.8	14/24	Unclear	Unclear	NA	NA	1, 2, 3	*****
Pruthi 2007 ²⁹	3	USA	R	20	24	62.3/68.2	20/24	I	Extracorporeal	10	5	2, 5, 6, 11	*****
Wang 2008 ³¹	3	USA	P	33	21	70/66	29/13	II	Extracorporeal	12	5	1, 3, 4, 5, 6, 9, 10, 11	*****
Richards 2010 ⁶	3	USA	R	35	35	65/66	30/25	II	Extracorporeal	3	4	1, 2, 3, 4, 5, 6, 8, 9, 10	*****
Martin 2010 ³²	3	USA	P	19	14	74/68	12/14	Unclear	Unclear	NA	NA	1, 2, 3, 4	*****
Ng 2010 ¹⁶	3	USA	P	83	104	70.9/67.2	65/73	II	Extracorporeal	26	29	2, 3, 4, 5, 6, 7, 11	*****
Nix 2010 ¹⁴	2b	USA	RCT	21	20	67.4/69.3	14/17	II	Extracorporeal	7	6	1, 2, 3, 4, 5, 6	RCT
Sung 2011 ³⁵	3	Korea	R	35	104	62.2/65.9	31/85	II	Extracorporeal	22	19	1, 2, 3, 4, 6, 7, 8, 9, 10	*****
Abaza 2012 ³³	3	USA	P	35	120	67.3/69.8	31/95	II	Unclear	NA	NA	1, 5, 6, 8	*****
Styn 2012 ³⁵	3	USA	P	50	100	66.6/65.6	42/84	I	Extracorporeal	NA	NA	1, 2, 3, 4, 5, 6, 7, 8, 9, 10	*****
Gondo 2012 ³⁴	3	Japan	P	11	15	68.9/69.7	9/13	II	Extracorporeal	4	6	1, 2, 3, 5, 7, 8, 9, 10, 11	*****
Nepple 2012 ³⁶	3	USA	R	36	29	72/67	31/16	I	Extracorporeal	6	11	3, 5, 6, 8, 11	*****

ΡΥΡΚ vs ΑΡΚ

962 ασθενείς

ΡΥΡΚ: μεγαλύτερος χειρουργικός χρόνος ($p < 0.001$)
λιγότερες περιεγχειρητικές επιπλοκές ($p = 0.04$)
μικρότερη απώλεια αίματος ($p < 0.001$)
μικρότερη ανάγκη μετάγγισης ($p < 0.001$)
περισσότεροι λεμφαδένες ($p = 0.009$)
μικρότερη παραμονή στο νοσοκομείο ($p < 0.001$)
Παρόμοια χειρουργικά όρια

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RARC Pasadena Consensus Panel – Review

Editorial by Monish Aron and Inderbir S. Gill on pp. 361–362 of this issue

Systematic Review and Cumulative Analysis of Oncologic and Functional Outcomes After Robot-assisted Radical Cystectomy

case numbers, short follow-up, and potential patient selection bias. The lymph node yield during lymph node dissection was 19 (range: 3–55), with half of the series following an extended template (yield range: 11–55). The lymph node–positive rate was 22%. The performance of lymphadenectomy was correlated with surgeon and institutional volume. Cumulative analyses showed no significant difference in lymph node yield between RARC and ORC. Positive surgical margin (PSM) rates were 5.6% (1–1.5% in pT2 disease and

The RAZOR (randomized open vs robotic cystectomy) trial: study design and trial update

Norm D. Smith, Erik P. Castle¹, Mark L. Gonzalgo², Robert S. Svatek³, Alon Z. Weizer⁴, Jeffrey S. Montgomery⁴, Raj S. Pruthi⁵, Michael E. Woods⁵, Matthew K. Tollefson⁶, Badrinath R. Konety⁷, Ahmad Shabsigh⁸, Tracey Krupski⁹, Daniel A. Barocas¹⁰, Atreya Dash¹¹, Marcus L. Quek¹², Adam S. Kibel¹³ and Dipen J. Parekh¹⁴

PLND and urinary diversion. RAZOR is a multi-institutional, non-inferiority trial evaluating cancer outcomes, surgical complications and HRQL measures of ORC vs RARC with a primary endpoint of 2-year PFS. Full data from the RAZOR trial are not expected until 2016–2017.

EAU Guidelines

Conclusions	LE
For MIBC, radical cystectomy is the curative treatment of choice.	3
A higher case load reduces morbidity and mortality of cystectomy.	3
Radical cystectomy includes removal of regional lymph nodes.	3
There are data to support that extended LND (vs. standard or limited LND) improves survival after radical cystectomy.	3
Radical cystectomy in both sexes must not include removal of the entire urethra in all cases, which may then serve as the outlet for an orthotopic bladder substitution. The terminal ileum and colon are the intestinal segments of choice for urinary diversion.	3
The type of urinary diversion does not affect oncological outcome.	3
Laparoscopic cystectomy and robotic-assisted laparoscopic cystectomy are feasible but still investigational. Current best practice is open radical cystectomy.	3
In patients aged > 80 years with MIBC, cystectomy is an option.	3
Surgical outcome is influenced by comorbidity, age, previous treatment for bladder cancer or other pelvic diseases, surgeon and hospital volumes of cystectomy, and type of urinary diversion.	2
Surgical complications of cystectomy and urinary diversion should be reported using a uniform grading system. Currently, the best-adapted, graded system for cystectomy is the Clavien grading system.	2
No conclusive evidence exists as to the optimal extent of LND.	2a

EAU Guidelines

Recommendations	GR
Do not delay cystectomy for > 3 months because it increases the risk of progression and cancer-specific mortality.	B
Before cystectomy, the patient should be fully informed about the benefits and potential risks of all possible alternatives, and the final decision should be based on a balanced discussion between patient and surgeon.	B
An orthotopic bladder substitute or ileal conduit diversion should be offered to male and female patients lacking any contraindications and who have no tumour in the urethra or at the level of urethral dissection.	B
Preoperative radiotherapy is not recommended in subsequent cystectomy with urinary diversion.	A
Pre-operative bowel preparation is not mandatory. "Fast track" measurements may reduce the time of bowel recovery.	C
Radical cystectomy is recommended in T2-T4a, N0 M0, and high-risk non-MIBC (as outlined above)	A*
Lymph node dissection must be an integral part of cystectomy.	A
The urethra can be preserved if margins are negative. If no bladder substitution is attached, the urethra should be checked regularly.	B
Laparoscopic cystectomy and robot-assisted laparoscopic cystectomy are both management options. However, current data have not sufficiently proven the advantages or disadvantages for oncological and functional outcomes.	C



Ευχαριστώ πολύ

Κ. Γ. Στραβοδήμος