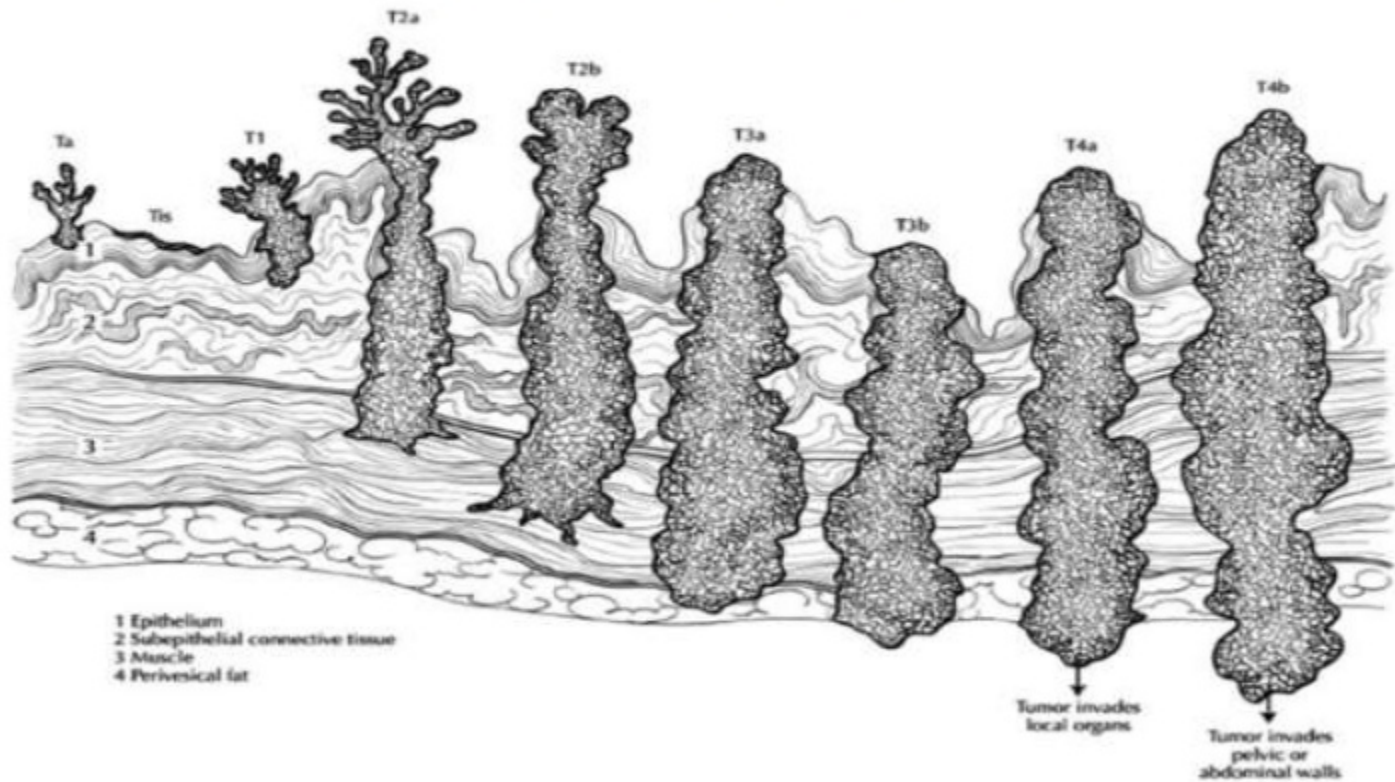
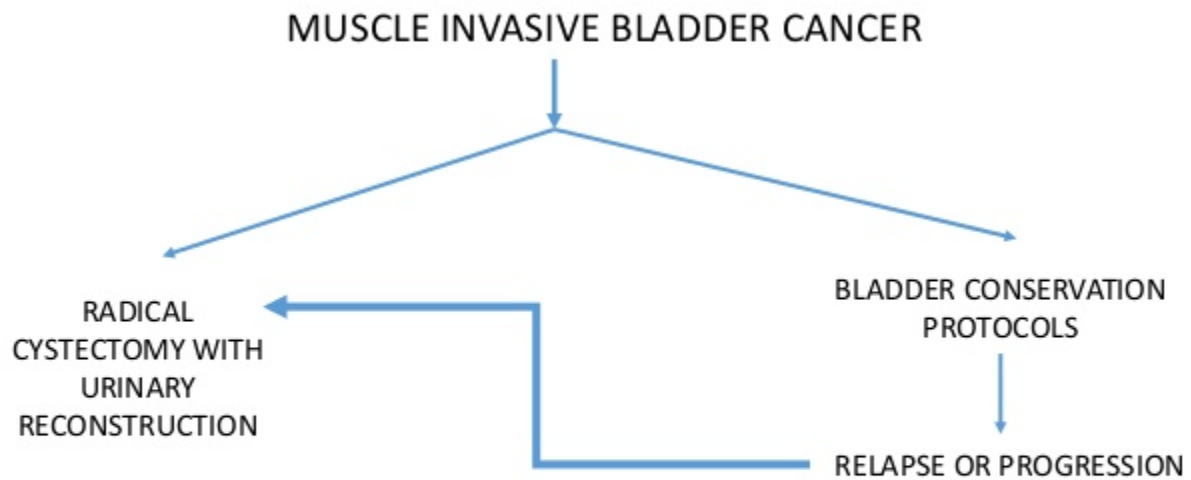


Θεραπευτικές επιλογές για την αντιμετώπιση
μυοδιηθητικού καρκίνου κύστεως

ΣΤΑΘΟΥΡΟΣ Ν. ΓΕΩΡΓΙΟΣ MD , FEBU
ΕΠΙΜΕΛΗΤΗΣ Α ΓΝΑ Γ.ΓΕΝΝΗΜΑΤΑΣ

Extent of Primary Bladder Cancer AJCC - 2010





Indications for radical cystectomy

- Infiltrating muscle-invasive bladder cancer without evidence of metastasis or with low-volume, resectable locoregional metastases (stage T2-T3b)
- Superficial bladder tumors characterized by any of the following:
 - Refractory to cystoscopic resection and intravesical chemotherapy or immunotherapy
 - Extensive disease not amenable to cystoscopic resection
 - Invasive prostatic urethral involvement
- Stage-pT1, grade-3 tumors unresponsive to intravesical BCG vaccine therapy
- CIS refractory to intravesical immunotherapy or chemotherapy
- Palliation for pain, bleeding, or urinary frequency
- Primary adenocarcinoma, SCC, or sarcoma

Modern Radical Cystectomy

- **Radical Cystectomy**

- Removal of bladder with surrounding fat
- Prostate/seminal vesicles (males)
- Uterus/fallopian tubes/ovaries/cervix (females)
- ± Urethrectomy

- **Pelvic Lymphadenectomy**

- More is better

- **Urinary Diversion**

- Ileal conduit
- Continent cutaneous reservoir
- Orthotopic neobladder

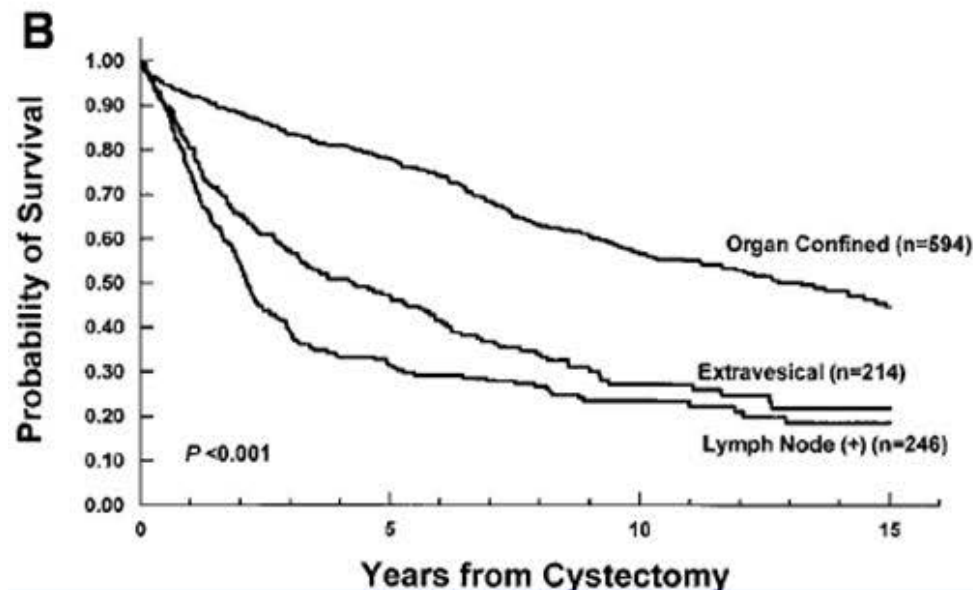
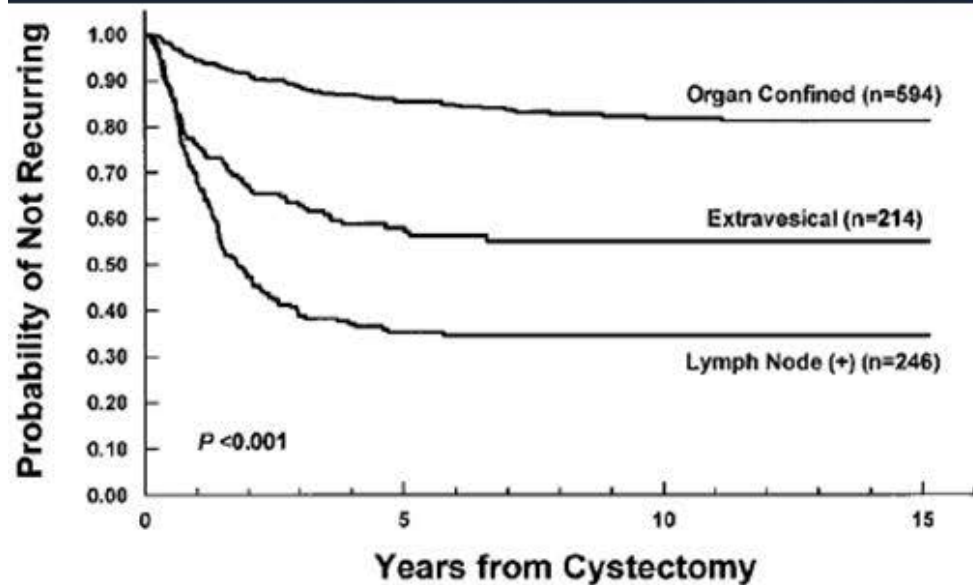
Goals of Treatment

- Cure patient
- Optimize survival
- Prevention of Pelvic failure and Distant metastasis
- Functional Urinary reservoir and High Quality Of Life (QoL)

Rationale For Radical Cystectomy

- lowest local recurrences.
- good long-term survival rates.
- provides accurate pathologic staging for determining the need for adjuvant therapy
- morbidity and mortality of radical cystectomy has substantially improved over the past decades.

The Outcomes of Radical Cystectomy



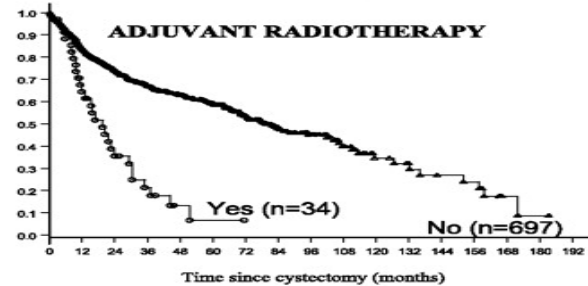
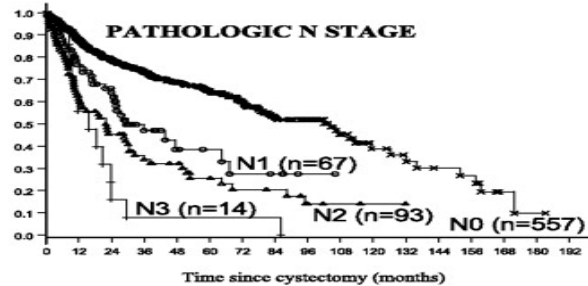
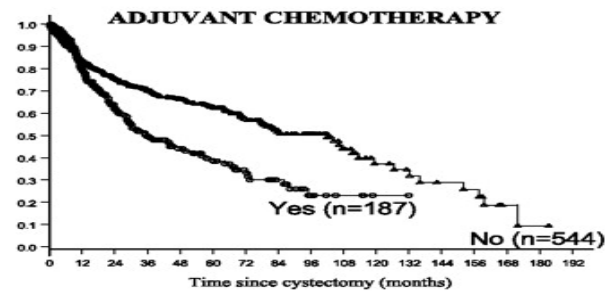
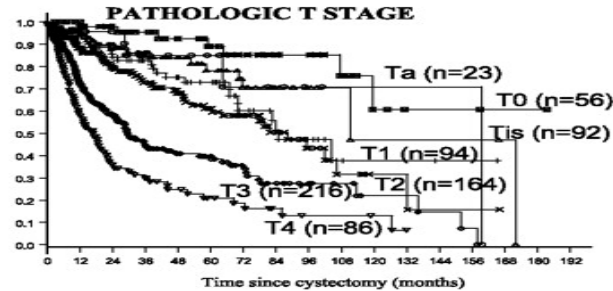
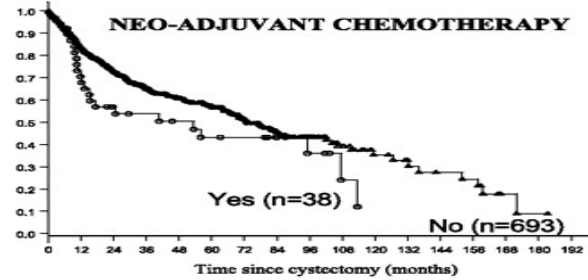
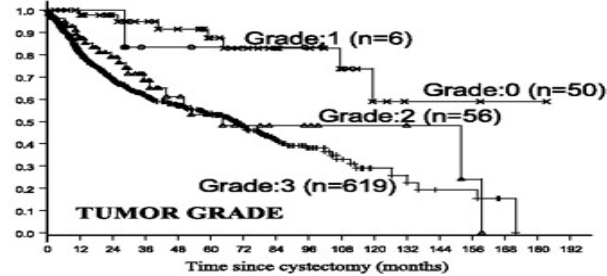
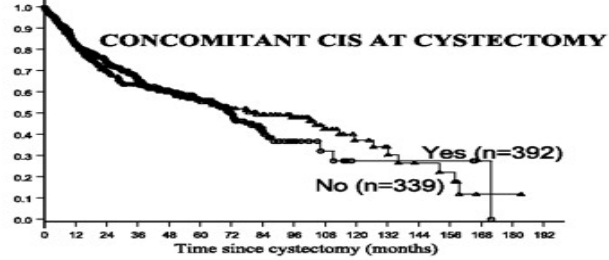
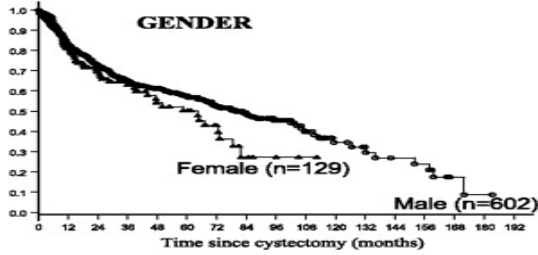
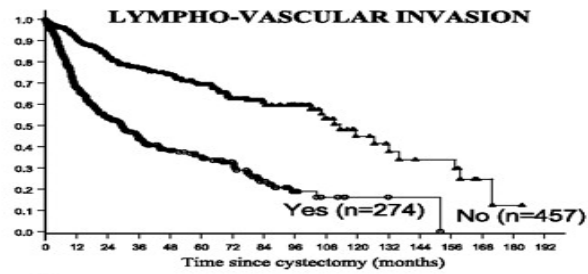
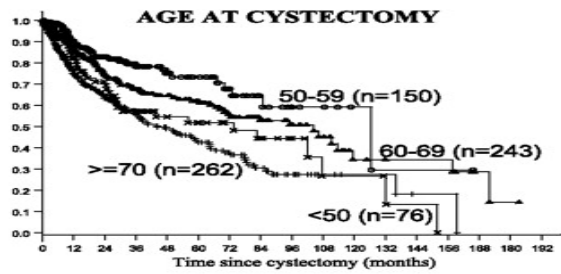
- Outcomes of RC are very good.
- Recurrences occur:
- Median 12 months
- 86% of recurrences occur in first 3 years.
- Local only recurrence more likely in OC.
- Most series- any recurrence = death.
- Even with LN+ve disease, 30% likelihood of long term survival



Optimum Timing for cystectomy

Within 3 months of TURBT. Delay of treatment beyond 90 days of primary diagnosis causes

- significant increase in extravesical disease (81 vs. 52%), .
- Also affect the options of urinary diversion
 - Hautmann RE, et al. Does the option of the ileal neobladder stimulate patient and physician decision toward earlier cystectomy?. J Urol 1998;159(6):1845-50.
- decrease in overall survival, recurrence-free survival, cause-specific survival
 - Chang SS, et al. Delaying radical cystectomy for muscle invasive bladder cancer results in worse pathological stage. J Urol 2003;170(4 Pt 1):1085-7



NEO ADJUVANT CHEMO

Evidence #1 , The Spark

THE LANCET

Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis*

[Volume 361, No. 9373, p1927–1934, 7 June 2003](#)

[Advanced Bladder Cancer \(ABC\) Meta-analysis Collaboration](#)

- A meta-analysis of ten randomized trials of NAC,
- 2,688 patients,
- significant relative reduction in the risk of death (**13%**) and improved 5-year survival from 45% to 50% ($P = .016$).

NEO ADJUVANT CHEMO

Evidence #2, Eliminating the Concerns



The NEW ENGLAND
JOURNAL of MEDICINE

HOME

ARTICLES & MULTIMEDIA ▾

ISSUES ▾

SPECIALTIES & TOPICS ▾

FOR AUTHORS ▾

CME ▶

ORIGINAL ARTICLE

Neoadjuvant Chemotherapy plus Cystectomy Compared with Cystectomy Alone for Locally Advanced Bladder Cancer

H. Barton Grossman, M.D., Ronald B. Natale, M.D., Catherine M. Tangen, Dr.P.H., V.O. Speights, D.O., Nicholas J. Vogelzang, M.D., Donald L. Trump, M.D., Ralph W. deVere White, M.D., Michael F. Sarosdy, M.D., David P. Wood, Jr., M.D., Derek Raghavan, M.D., Ph.D., and E. David Crawford, M.D.

N Engl J Med 2003; 349:859-866 | [August 28, 2003](#) | DOI: 10.1056/NEJMoa022148

- Cited **999** times since 2003
- Result: median survival with surgery alone was **46** months, **77** months with combination therapy

NEO ADJUVANT CHEMO

Evidence #4, The Long Term Effect

VOLUME 29 · NUMBER 16 · JUNE 1 2011

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

International Phase III Trial Assessing Neoadjuvant Cisplatin, Methotrexate, and Vinblastine Chemotherapy for Muscle-Invasive Bladder Cancer: Long-Term Results of the BA06 30894 Trial

International Collaboration of Trialists on behalf of the Medical Research Council Advanced Bladder Cancer Working Party (now the National Cancer Research Institute Bladder Cancer Clinical Studies Group), the European Organisation for Research and Treatment of Cancer Genito-Urinary Tract Cancer Group, the Australian Bladder Cancer Study Group, the National Cancer Institute of Canada Clinical Trials Group, Finnbladder, Norwegian Bladder Cancer Study Group, and Club Urologico Espanol de Tratamiento Oncologico Group

- A controlled trial by the (MRC) and the (EORTC) randomly assigned **976** patients with **T3** or **T4a** or **high-grade T2** BC to undergo either definitive treatment immediately or preceded by NAC.

NEO ADJUVANT CHEMO

The Long Term Effect

- Definitive treatment included **cystectomy** (428 pt), **RTx** (403 pt), or **RTx + cystectomy** (66 pt).
- At a median **follow-up of 8 years**, OS was significantly greater in the arm of NAC.
- The survival benefit was **6%** absolute increase in the likelihood of being alive at **3 years** (56% vs. 50%), **5 years** (49% vs. 43%), and **10 years** (36% vs. 30%). [[Level of evidence: 1A](#)]



NCCN Guidelines Version 2.2014 Bladder Cancer

[NCCN Guidelines Index](#)
[Bladder Cancer TOC](#)
[Discussion](#)

PRINCIPLES OF CHEMOTHERAPY MANAGEMENT

Perioperative chemotherapy (neoadjuvant or adjuvant)

- Regimens
 - › DDMVAC (dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin) with growth factor support for 3 or 4 cycles^{1,2}
 - › Gemcitabine and cisplatin for 4 cycles^{3,4}
 - › CMV (cisplatin, methotrexate, and vinblastine) for 3 cycles⁵
- Randomized trials and meta-analyses show a survival benefit for cisplatin-based neoadjuvant chemotherapy in patients with muscle-invasive bladder cancer.^{1,6,7}
- Meta-analysis suggests a survival benefit to adjuvant therapy for pathologic T3, T4 or N+ disease at cystectomy.⁷
- Neoadjuvant chemotherapy is preferred over adjuvant-based chemotherapy on a higher level of evidence data.
- DDMVAC is preferred over standard MVAC based on category 1 evidence showing DDMVAC to be better tolerated and more effective than conventional MVAC in advanced disease.^{2,8} Based on these data, the traditional dose and schedule for MVAC is no longer recommended.
- Perioperative gemcitabine and cisplatin is a reasonable alternative to DDMVAC based on category 1 evidence showing equivalence to conventional MVAC in the setting of advanced disease.^{4,9}

Guidelines on Muscle-invasive and Metastatic Bladder Cancer

6.4 Conclusions and recommendations for neoadjuvant chemotherapy

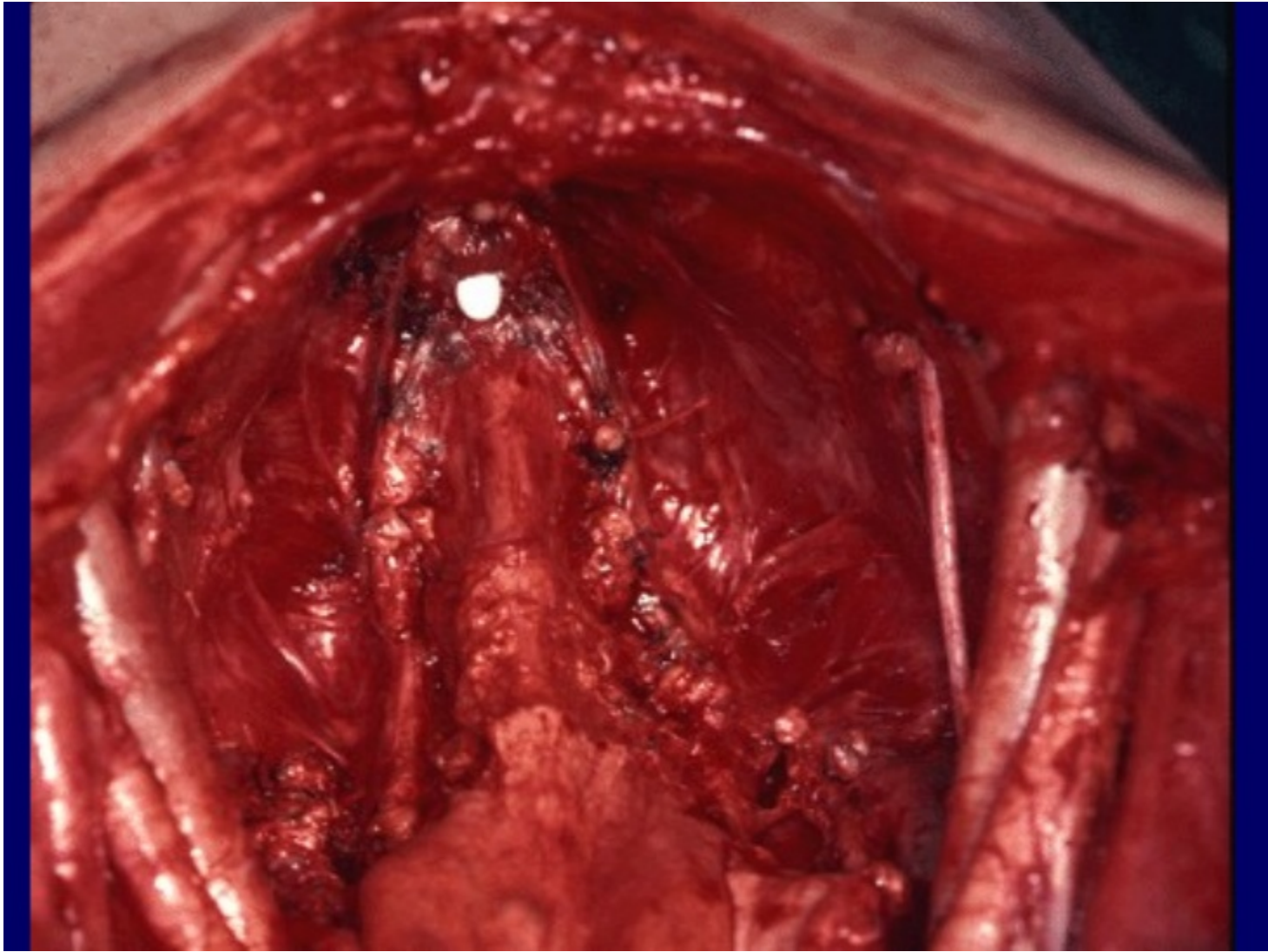
Conclusions	LE
Neoadjuvant cisplatin-containing combination chemotherapy improves overall survival.	1a
Recommendations	GR
Neoadjuvant chemotherapy is recommended for T2-T4a, cN0M0 bladder cancer and should always be cisplatin-based combination therapy.	A

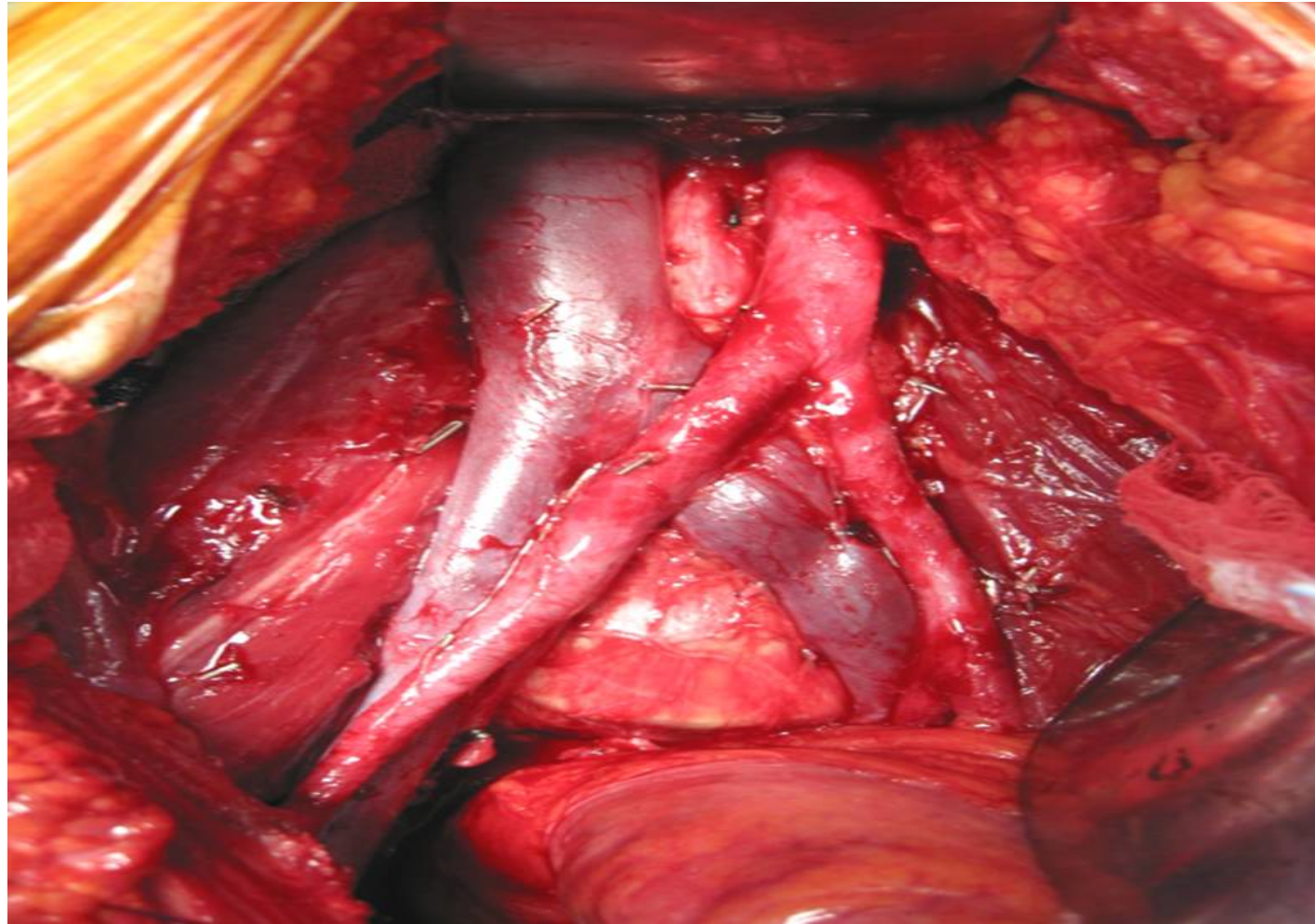
How to perform radical cystectomy in male?

- Fr 18 Foley
- Midline incision
- Develop space of Retzius
- Mobilize bladder from pelvic side wall
- Divide the urachus remnant
- Divide vas
- Divide posterior peritoneum to expose ureters
- Mobilize ureter proximally to preserve the periureteral blood supply
- Pelvic lymphadenectomy
- Divide endopelvic fascia
- Divide lateral vascular bladder pedicles
- Establish plane between rectum and posterior bladder wall
- Ligate dorsal vein
- Dissect neurovascular bundles off prostate bilaterally
- Incise urethra
- Divide posterior bladder pedicle

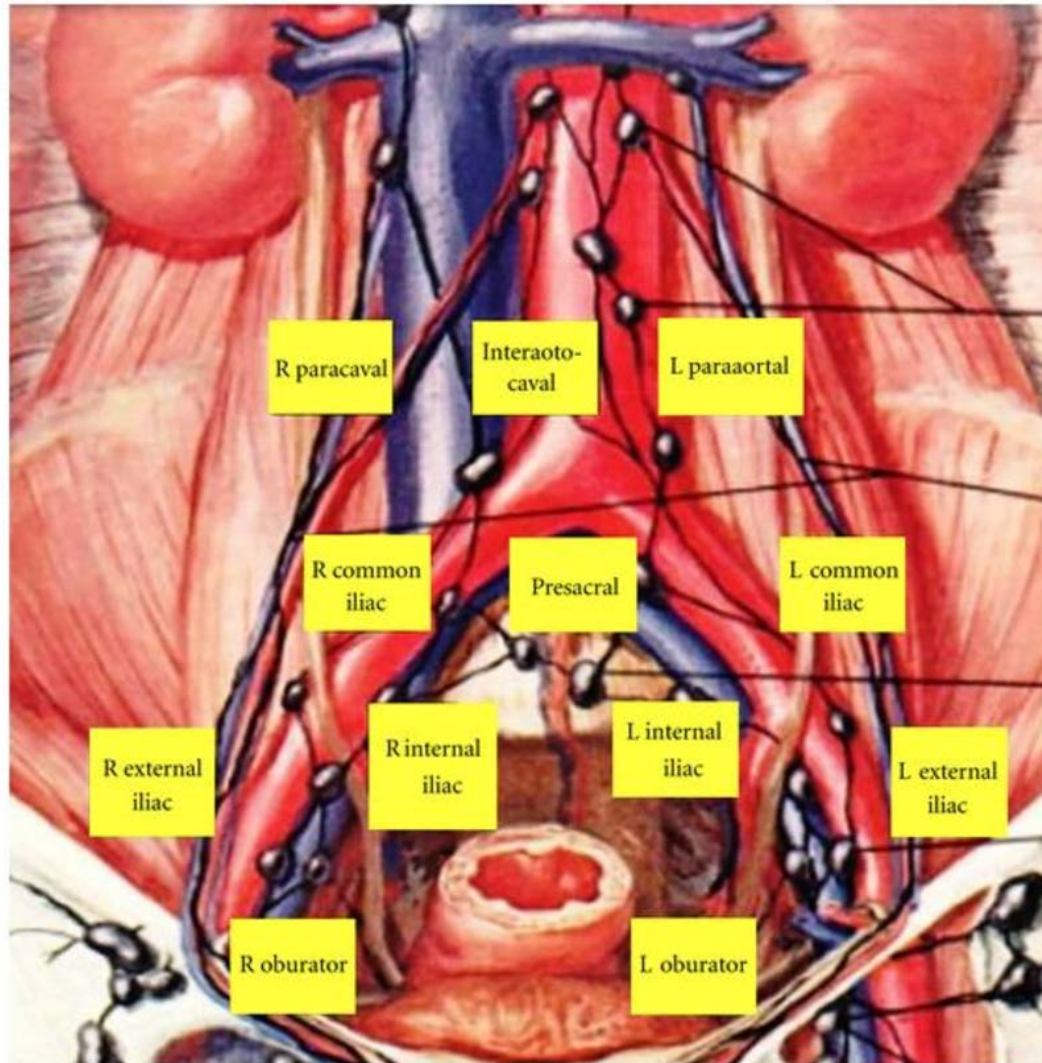
How to perform radical cystectomy in female (anterior pelvic exenteration)?

- Mobilization of bladder from pelvic side wall
- Divide urachus
- Ligate infundibulopelvic ligaments (ovarian artery) and round ligaments (vas)
- Incise broad ligament to expose ureters and mobilize
- Pelvic lymphadenectomy
- Circumferentially incise on cervix
- Close vaginal defect
- Dissection of plane between anterior vaginal wall and posterior surface of bladder
- Divide urethra

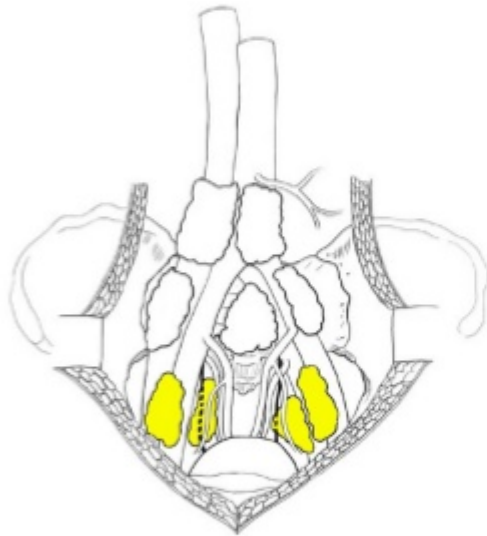




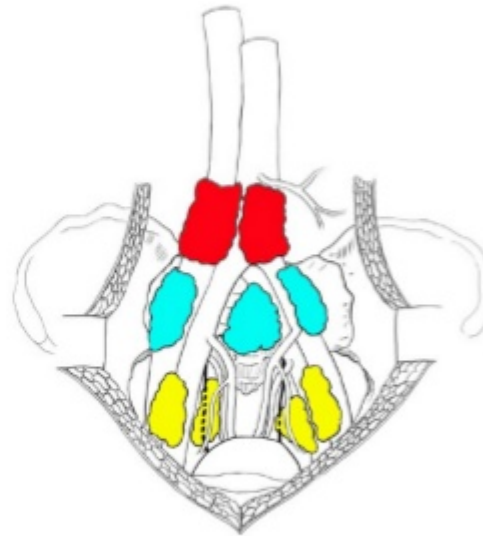
ΛΕΜΦΑΔΕΝΙΚΟΣ ΚΑΘΑΡΙΣΜΟΣ



Pelvic Lymphadenectomy

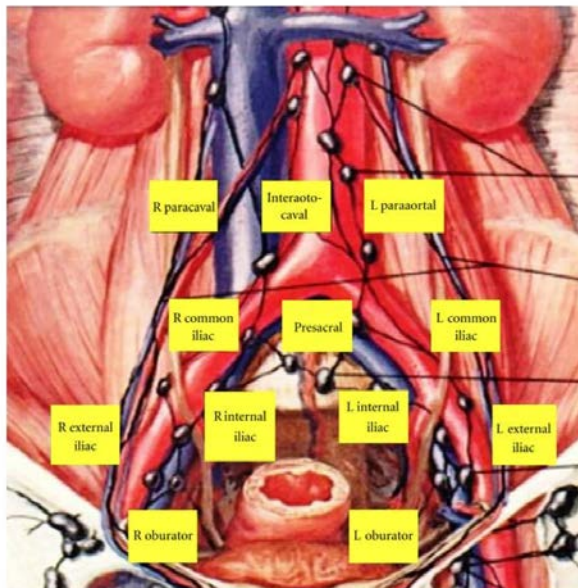


Standard LND



**Extended
LND**

ΛΕΜΦΑΔΕΝΙΚΟΣ ΚΑΘΑΡΙΣΜΟΣ



Extended PLND

In the boundaries of:

- Aortic bifurcation and common iliac vessel
- Genitofemoral nerve
- Circumflex iliac vein and node of Cloquet
- Hypogastric vessels

Including:

- obturator, internal, external, common iliac and presacral nodes as well as nodes at the aortic bifurcation May also Extend to IMA
- Rationale of extended lymphadenectomy
 - Early lymph node metastasis can occur in pT1 (5%) and pT2 (18-27%) diseases
 - Long term survival is possible in patients with lymph node metastasis
 - 20-30% of metastatic lymph nodes outside the field of "standard" LND

J Stein, D Skinner, 2006 BUJI

Key Concepts of LN Metastasis

- Number of lymph nodes removed
- Number of lymph node metastasis
- Lymph node density

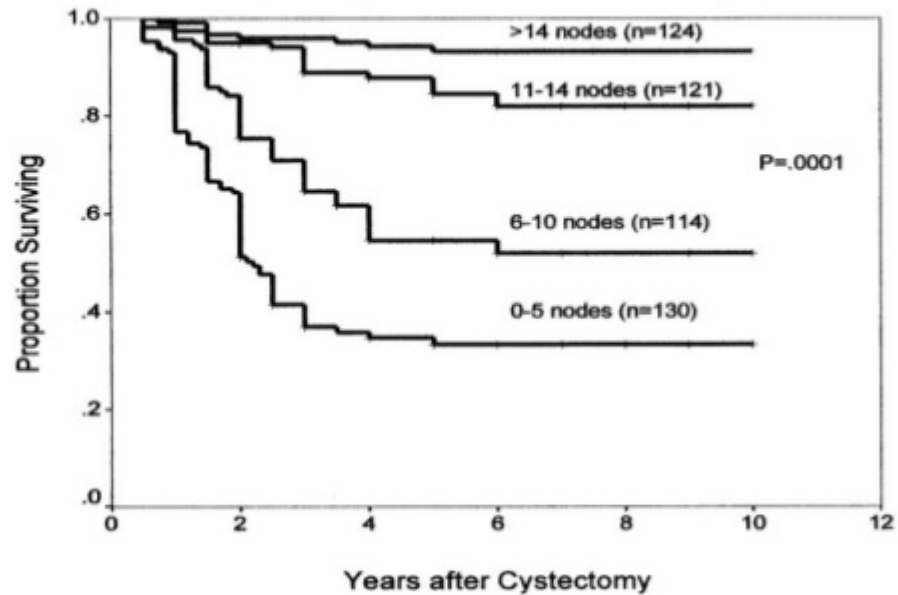
Benefit of Extended LND

- Patients with TxN+ disease
 - Leissner *et al.* evaluated 79 patients with < 5 positive lymph nodes, and demonstrated improved survival when >16 lymph nodes were removed, although a multivariate analysis was not reported. [Leissner, BJU Int 2000]
 - Herr *et al.* reviewed a lymph node-positive cystectomy series of 162 patients and observed that the removal of >13 total lymph nodes was not a significant predictor of survival on multivariate analysis (P = 0.56). [Herr, J Urol 2003]
 - Stein *et al.* described the largest lymph node-positive series with 244 patients and observed no recurrence-free survival advantage with the removal of ≥15 lymph nodes (P = 0.21). [Stein, J Urol 2003]
- However:
 - Based on the 1260 patients from SEER database, removal of >10 lymph nodes was associated with increased overall survival (hazard ratio, 0.52; 95% confidence interval , 0.43 - 0.64). [Wright, Cancer 2009]

Leissner, BJUI 2000;85;817-823

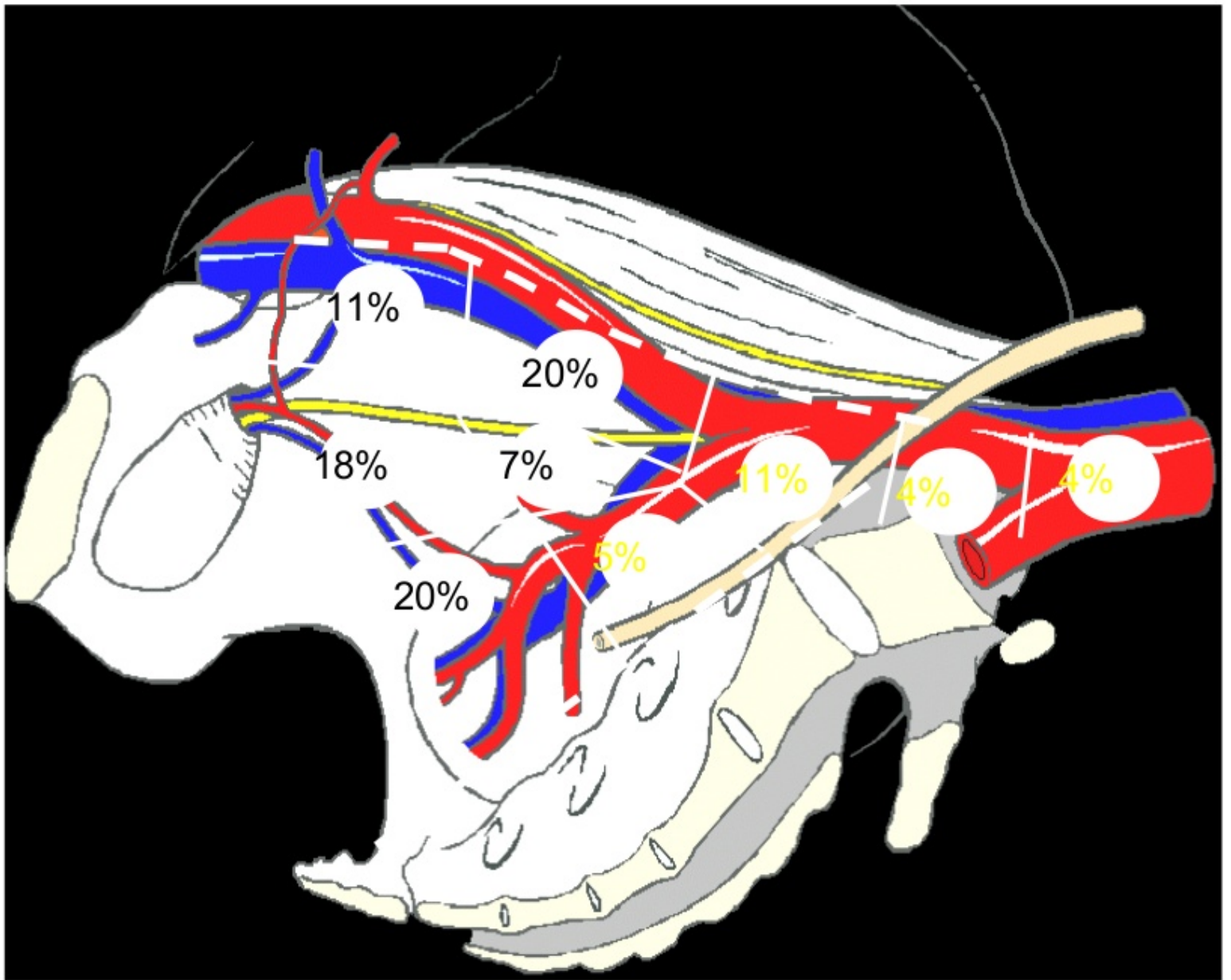
5yRFS	≥ 16	≤ 15
Tis or 1 or 2, pN0	85%	63%
T3	55%	40%
pLN+ 1-5 i.e. density	53%	25%

Survival in patients with N0 disease



Why need extended LN?

- 90% of bladder draining LN distal and caudal to where ureter cross common iliac arteries [Studer EU2010]
- Limited LND likely understage LN status [Studer JU2008]
 - Cleveland clinic vs University of Bern
 - 1) overall pLN +ve rate lower
 - 2) more recurrence despite same pT2 / pT3 / pLN+

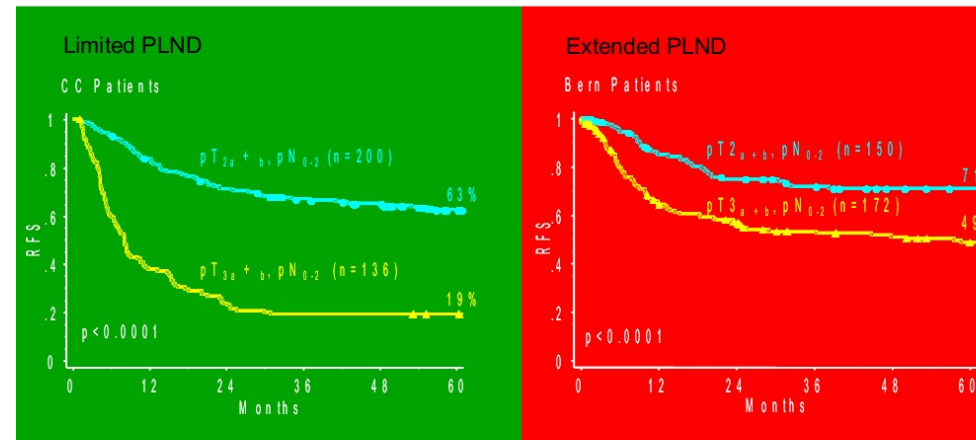


ΛΕΜΦΑΔΕΝΙΚΟΣ ΚΑΘΑΡΙΣΜΟΣ

Patients with pT2 and pT3 N0 bladder cancer

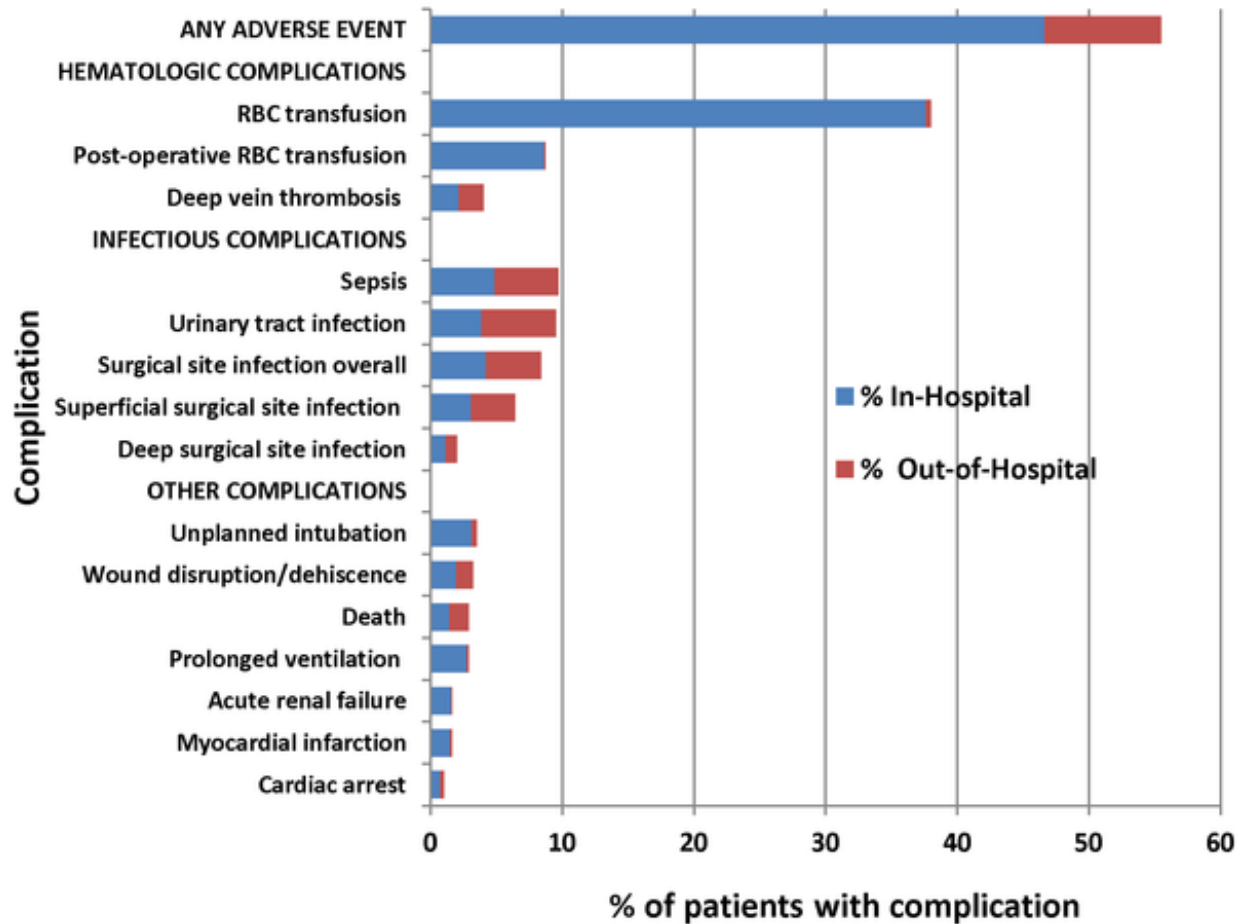
Institution	Stage	# of Patients	# with pN+
CC Limited	pT ₂ pN ₀₋₂	200	15/200 (7.5%)
Bern Extended	pT ₂ pN ₀₋₂	150	24/150 (16%)
CC Limited	pT ₃ pN ₀₋₂	136	29/136 (21%)
Bern Extended	pT ₃ pN ₀₋₂	172	59/172 (34%)

Recurrence free survival pT2 pN₀₋₂ & pT3 pN₀₋₂ p < 0.001





% of Patients with Complications after Cystectomy In-Hospital vs. Out-of-Hospital



Complications of cystectomy

Mortality 1 – 2% in major centers

Morbidity

How to prevent

**Cardiovascular
(stroke, MI)**

preop work – up, monitor blood pressure

Pulmonary embolism

low molecular heparin started on the eve of surgery, stockings,

mobilisation, bipolar

coagulation

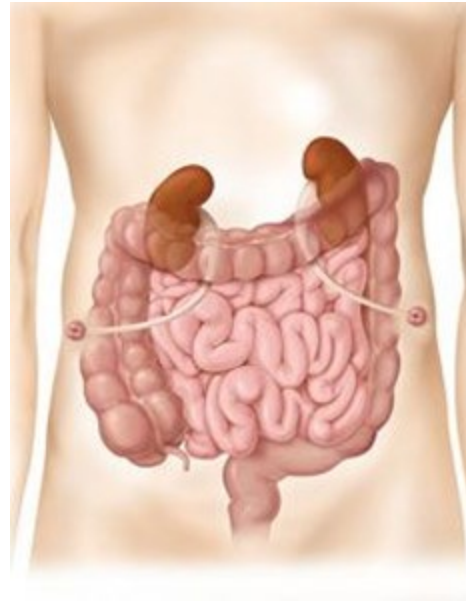
Ileus

Prostigmine, Metoclopramide

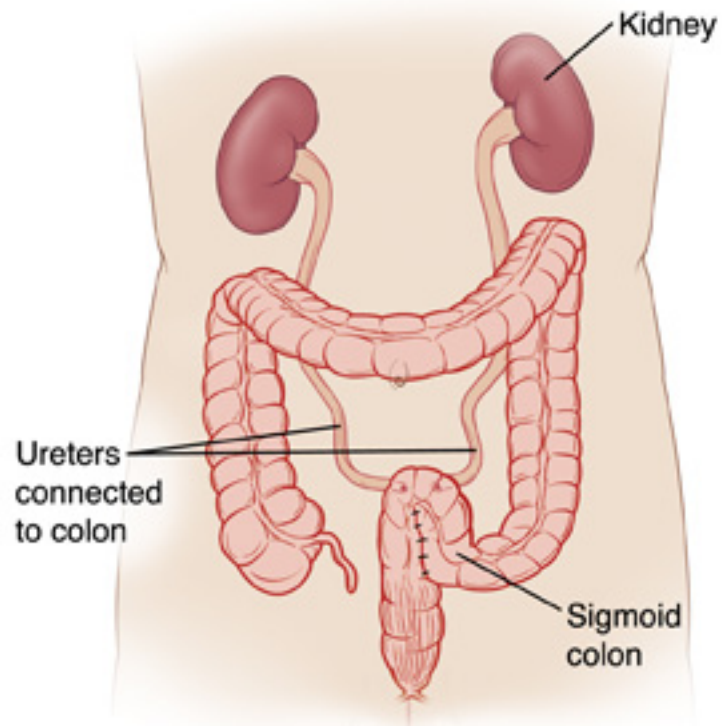
Urinary Diversion

- Use of **intestinal segment** to bypass/ reconstruct/ replace the normal urinary tract
- **Goals:**
 - Storage of urine without absorption
 - Maintain low pressure even at high volumes to allow unobstructed flow of urine from kidneys
 - Prevent reflux of urine back to the kidneys
 - Socially-acceptable continence
 - Empties completely
- “**Ideal**” diversion has yet to be discovered

Ureterostomy

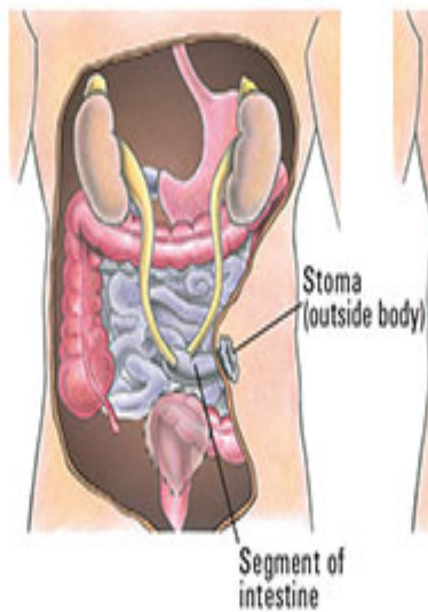


Ureterosigmoidostomy

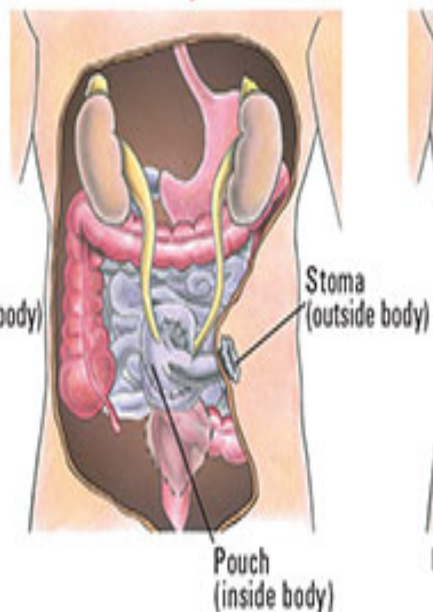


UROSTOMY (BLADDER REMOVAL AND RECONSTRUCTION)

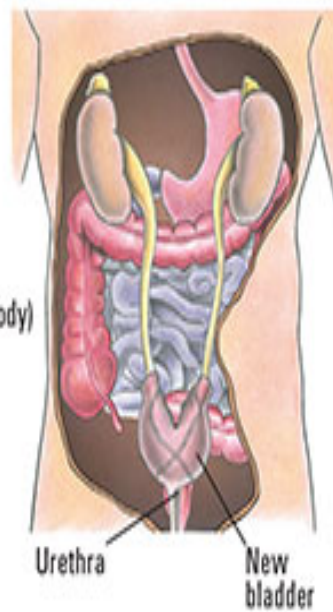
Ileal conduit



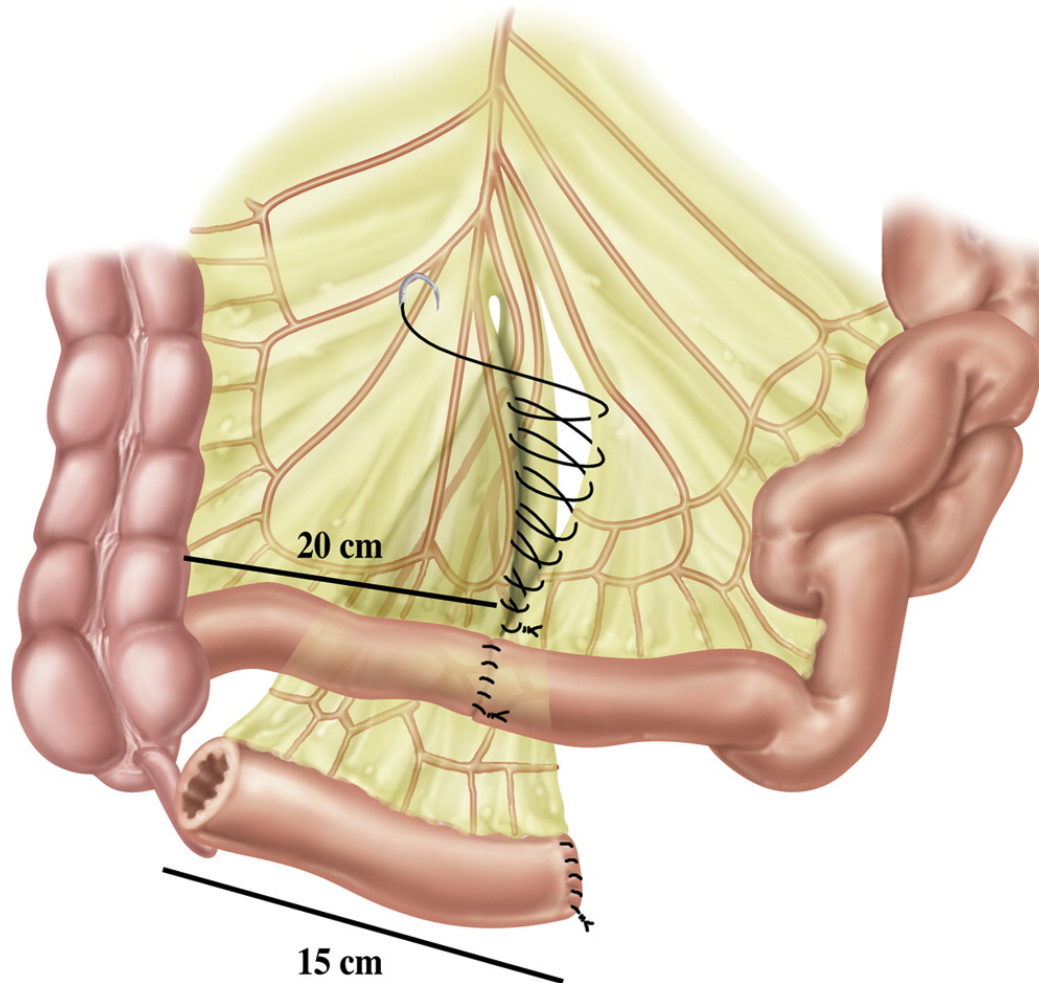
Continent cutaneous pouch (Indiana pouch)



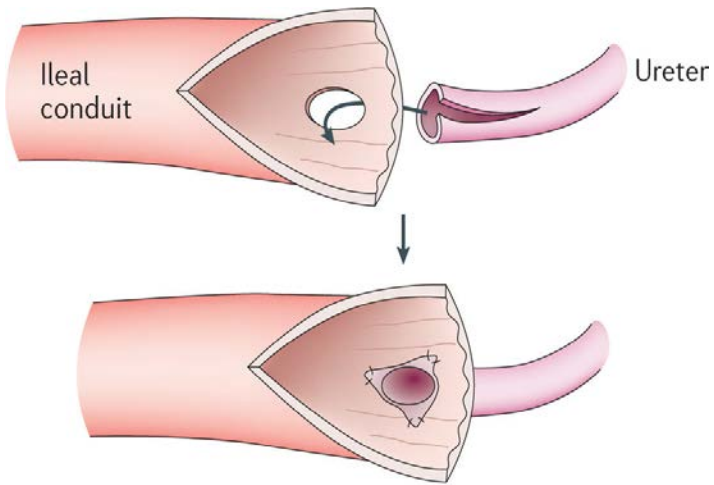
Orthotopic bladder (neobladder)



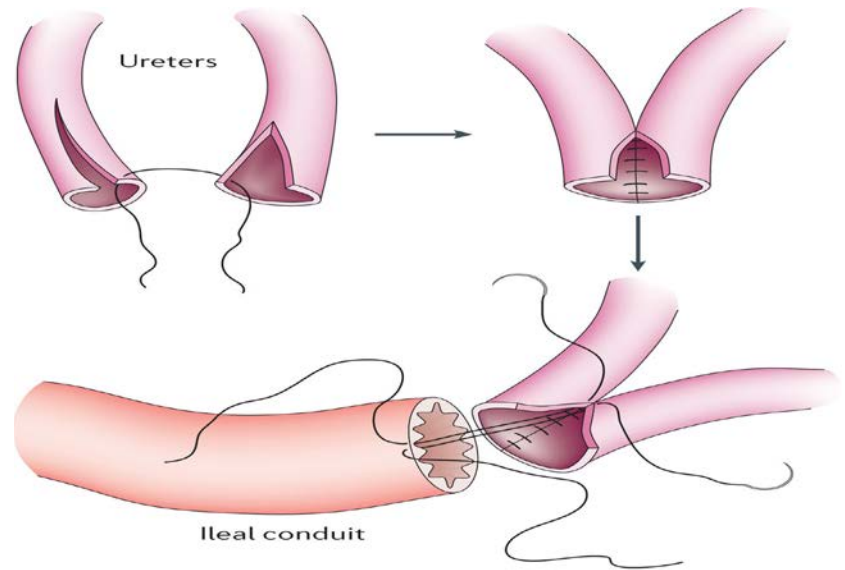
Ileal Conduit



Ileal Conduit



Nature Reviews | Urology



Nature Reviews | Urology

How to perform ileal conduit ?

- 15cm segment with major arch, 15cm from ileocecal valve
- Ileostomy
- Closure of mesenteric window
- Flush conduit with copious saline
- Ureteroileal anastomosis
 - Bricker
 - Wallace – lowest complication like stricture and leakage, not recommended extensive CIS (difficult mx in recurrence + bil obstruction)
 - Absorbable suture, spatulation, water-tight mucosa to mucosa apposition over stent (bilateral separate stent)
- Abdominal stoma (everting, tension free, ant abd fascia not too tight)
- Complications
 - Fewer than the other 2 urinary diversion method
 - Early: pyelonephritis, uertero-ileal leakage, stenosis
 - Late: stoma complications (24%), upper tract changes (30%), urolithiasis
 - Higher chance or urethral recurrence than neobladder (

orthotopic neobladder

Orthotopic Neobladder

WHAT IS AN ORTHOTOPIC NEOBLADDER?

"Orthotopic" means "in the same place" and "neobladder" means new bladder.

So an orthotopic neobladder is a substitute or "new" bladder that is placed in the same location as the "old" bladder.

HOW IS THE ORTHOTOPIC NEOBLADDER CONSTRUCTED?

The neobladder is made from loops of the intestine.

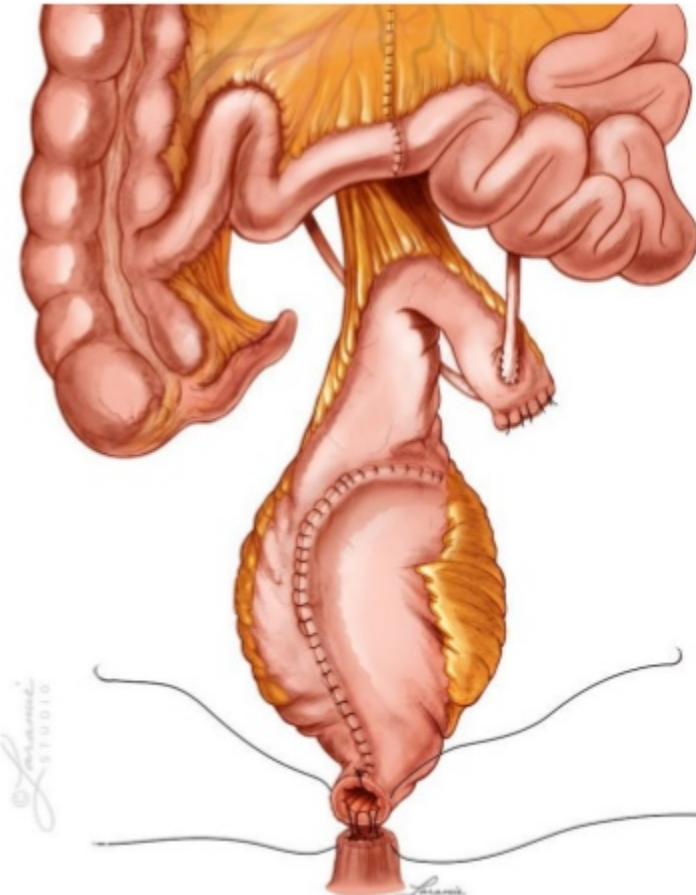
First, the surgeon removes a section of intestine.

He then reconnects the bowel so there are no changes in bowel function.

The piece of intestine that was removed is cut open to create a "flat piece" instead of a hollow tube.

The flat piece of intestine is sewn together to form a pouch. The ureters (kidney tubes) are connected to one end of this pouch, the other end of the pouch is connected to the urethra. Urine will drain from the kidneys through the ureters and into the new "bladder."

The new bladder will store the urine and the individual will void through normal channels.



orthotopic neobladder

Laplace law: $p = T/r$

— 40 cm —



● R=1 cm volume=125cc

— 20 cm —



● R=2 cm volume=250cc

— 10 cm —

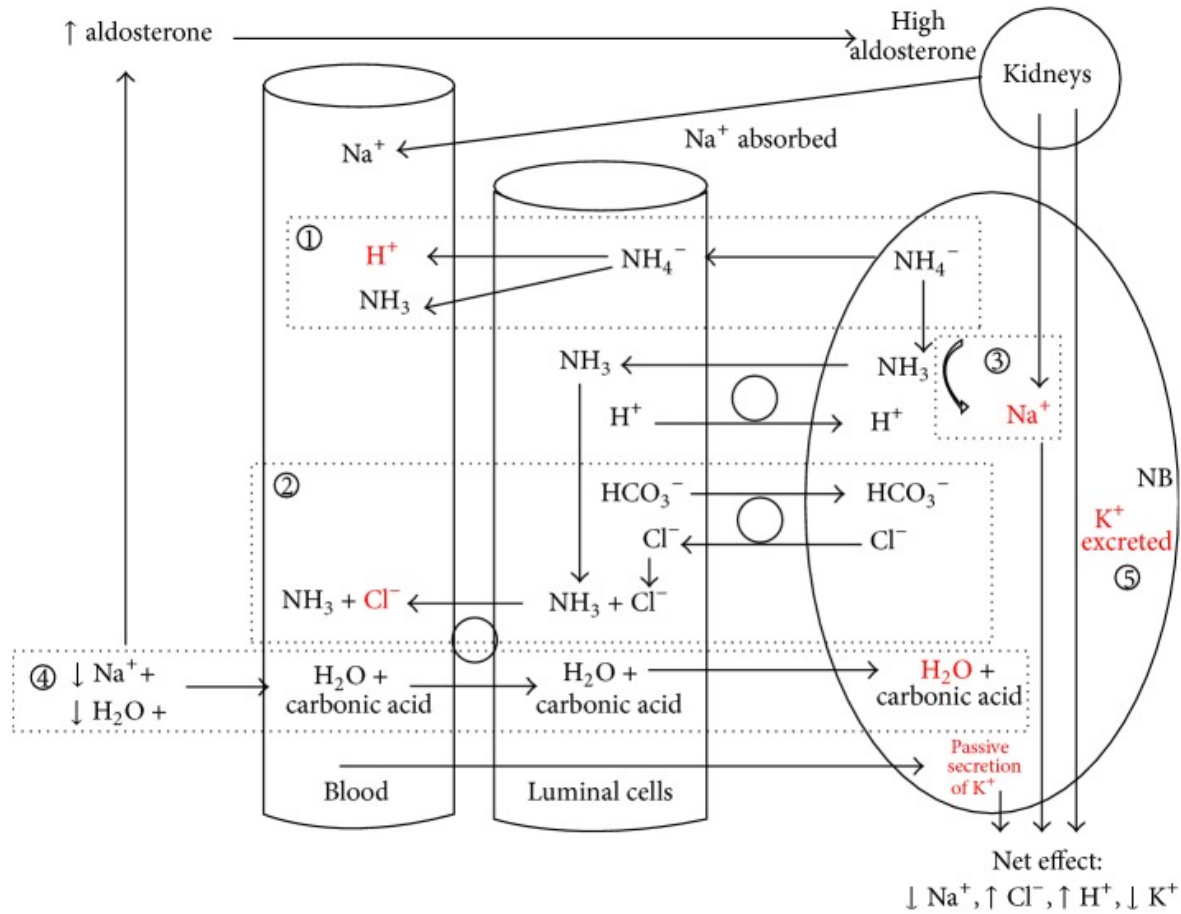


● R=4 cm volume=500cc

Orthotopic Urinary diversion

- Assessment: self cath ability, renal function 60ml/min, life expectancy (<75), no liver failure
- Relative contraindication specific to orthotopic bladder :
 - Pre-operative RT
 - Complex urethral stricture
 - Severe urethral sphincter related incontinence
- Contraindication:
 - Severe neurological & psychiatric illness
 - Limited life expectancy
 - Impaired LRFT
 - +ve urethral margin or other surgical margin
- Overall risk of urethral recurrence 10%
- Terminal ileum most often used for bladder substitution
- Long term complications:
 - urinary retention
 - diurnal/nocturnal incontinence
 - ureterointestinal stenosis
 - metabolic disorders (hyperCl metabolic acidosis)
 - Vit B12 deficiency

orthotopic neobladder



Complications

Early

- Hydronephrosis
- Urinary leakage
- Fluid collections
 - Hematoma
 - Urinoma
 - Abscess
 - Lymphocele
- Fistula
- Adynamic ileus/bowel obstruction
- Infection
 - Pyelonephritis
 - Ureteritis
 - Sepsis
 - Wound infection
- Urinary obstruction (not frequently seen)

Late

- Urolithiasis
- Ureteral stenosis/stricture
- Recurrent UTIs/Pyelonephritis
- Parastomal herniation
- Tumour recurrence
- Not directly related to urinary diversion procedure

Orthotopic Neobladder

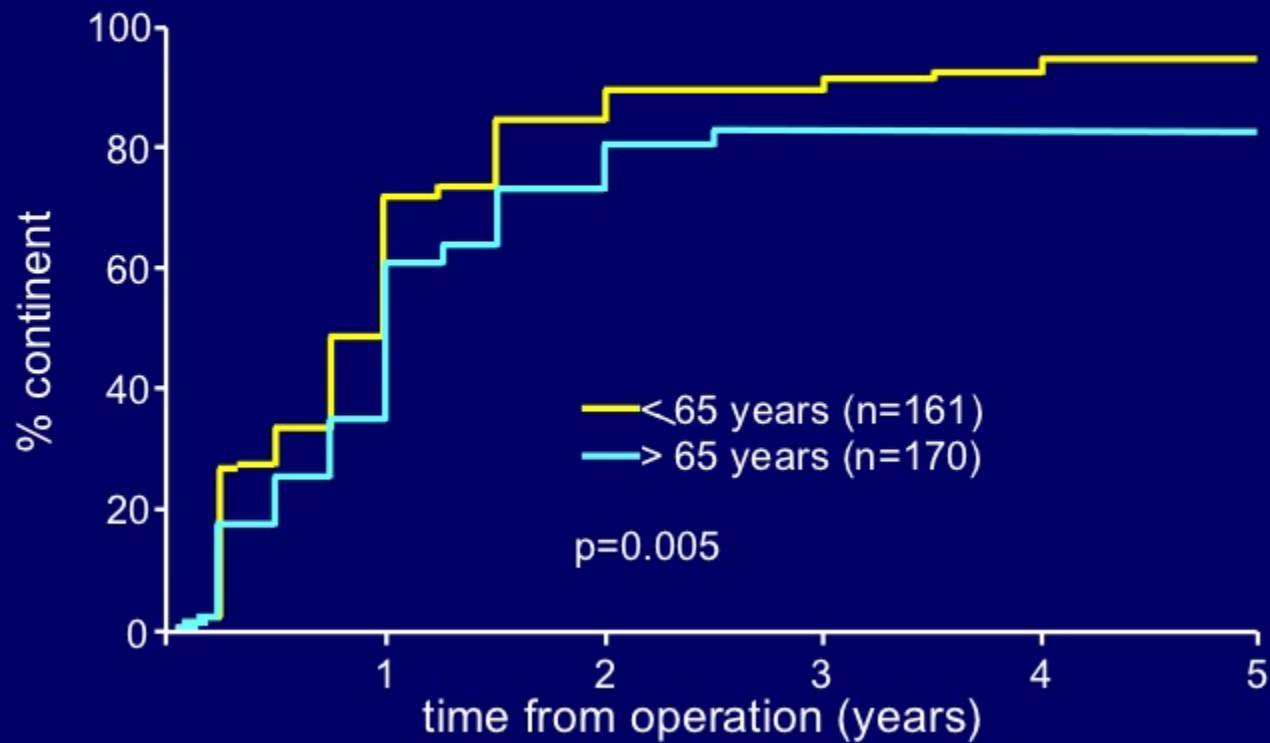
ADVANTAGES

- No external bag
- Urinate through urethra
- May not need catheterization

DISADVANTAGES

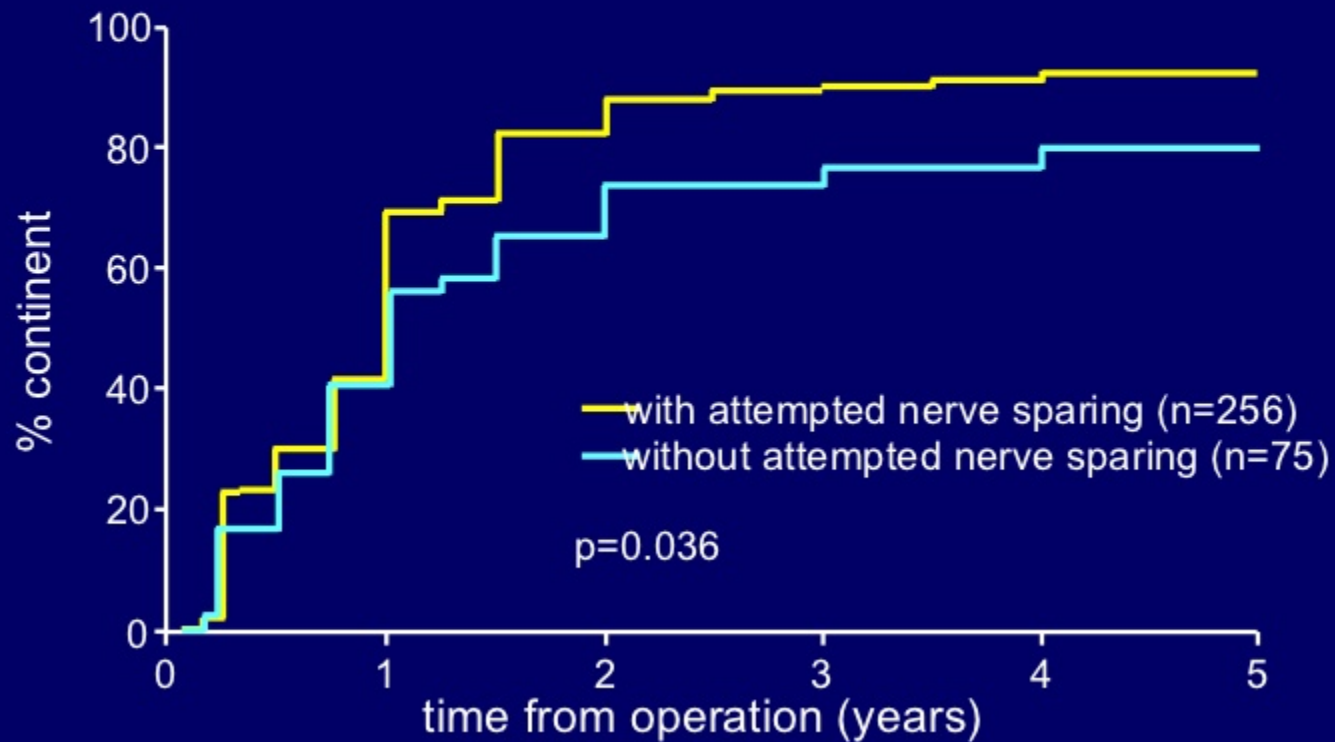
- Incontinence (10-30%)
- Retention (5-20%)
- Risk of stones, UTI's
- Need to “train” neobladder

Nighttime continence according to age at the time of operation



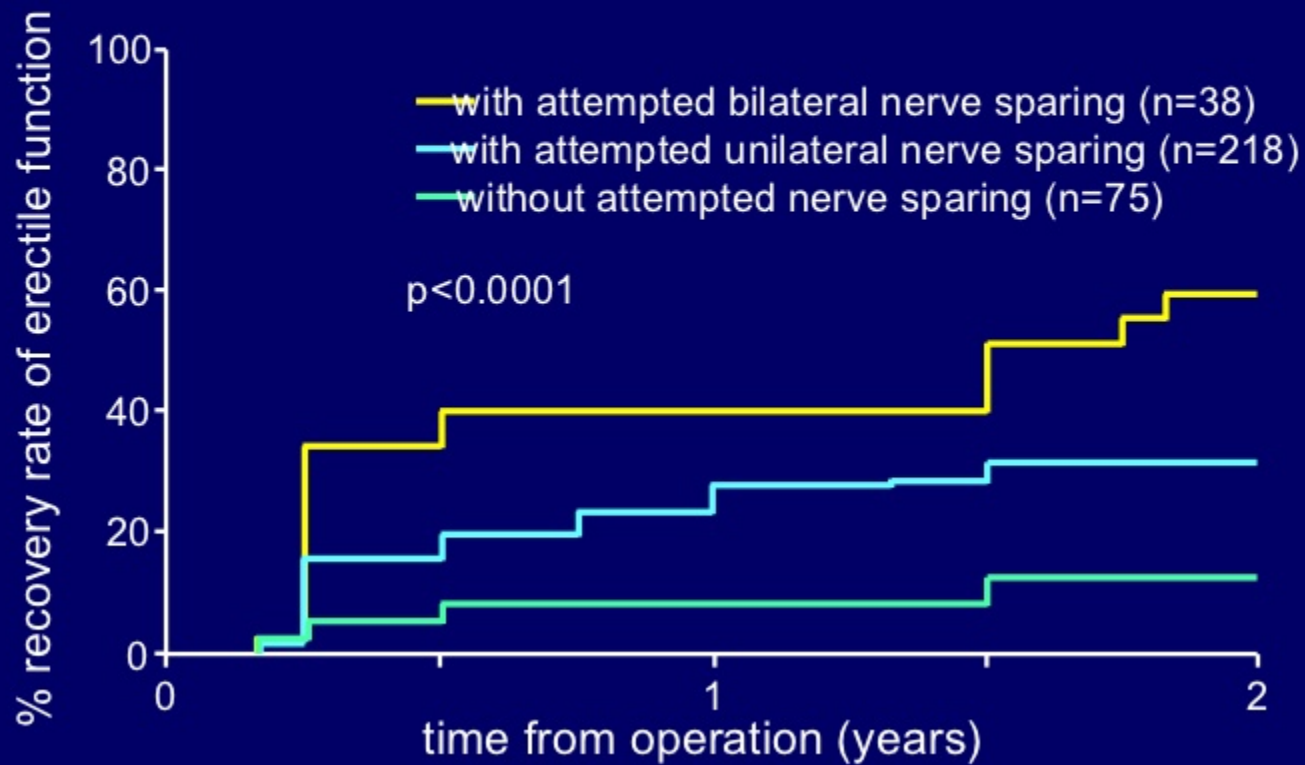
Kessler et al., J Urol, 172, 1323, 2004

Nighttime continence according to attempted neurovascular bundle preservation



Kessler et al., J Urol, 172, 1323, 2004

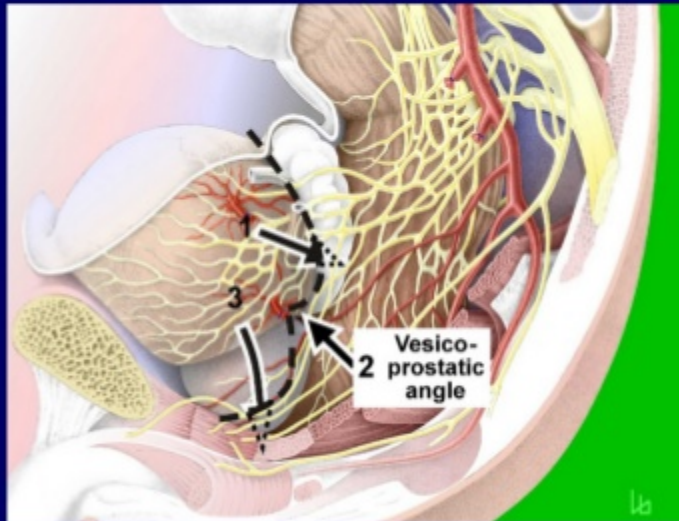
Reported recovery of erectile function (no versus reduced or normal erections) according to attempted sparing of one, both or neither neurovascular bundles



Kessler et al., J Urol, 172, 1323, 2004

Individualized Seminal Vesicle Sparing Cystoprostatectomy Combined With Ileal Orthotopic Bladder Substitution Achieves Good Functional Results

N = 31 100% continent 74% potent preoperatively
17(55%) Unilateral SVS RC 14(45%) Bilateral SVS RC



Median Follow up 18 months (range 3 – 63)

Daytime continence	27/29 (93%)
Nighttime continence	19/29 (66%)
Remained potent	5/19 (79%)
Pelvic recurrence	1 (3%)
Distant recurrence	4 (13%)

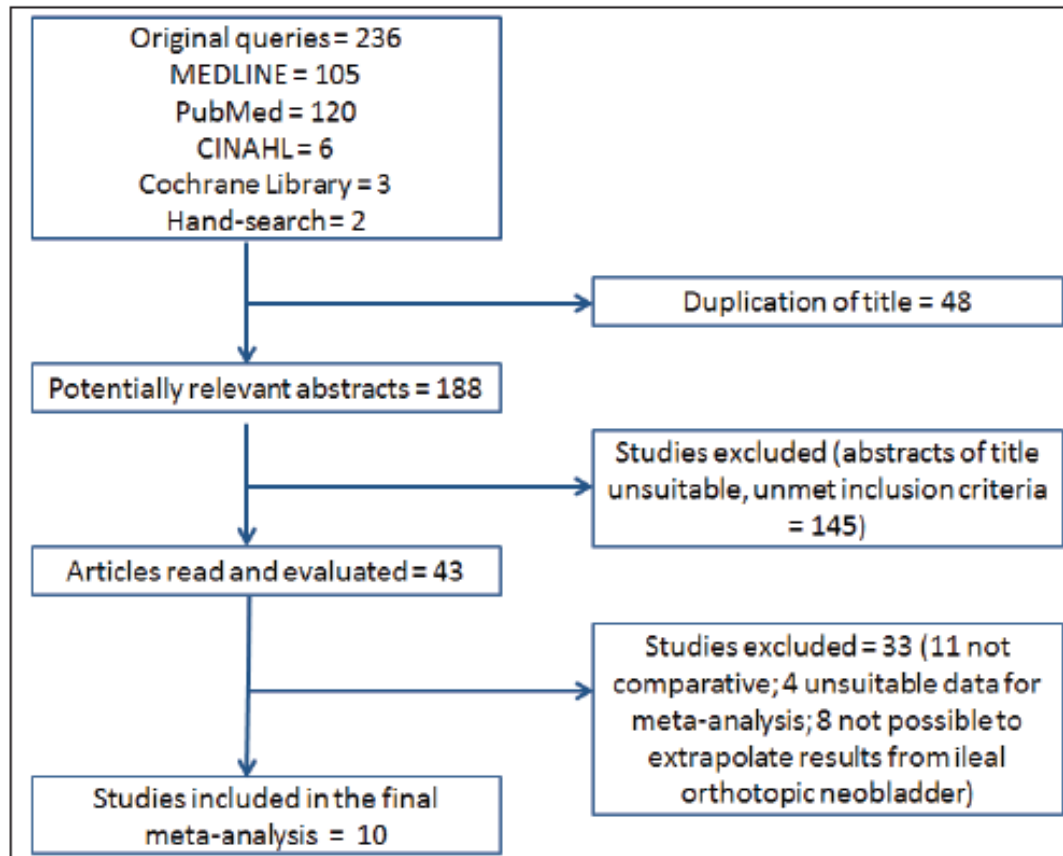
The preliminary results on continence and oncological outcomes are at least as good as those of conventional RC.

Ong CH et al., J Urol 183, 1337–1342, 2010

Is Health-Related Quality of Life after Radical Cystectomy Using Validated Questionnaires Really Better in Patients with Ileal Orthotopic Neobladder Compared to Ileal Conduit: A Meta-Analysis of Retrospective Comparative Studies

Maria A. Cerruto^a Carolina D’Elia^a Salvatore Siracusano^a Antonio B. Porcaro^a
Giovanni Cacciamani^a Davide De Marchi^a Mauro Niero^b Cristina Lonardi^b
Massimo Iafrate^c Pierfrancesco Bassi^d Emanuele Belgrano^e Ciro Imbimbo^f
Marco Racioppi^d Renato Talamini^g Stefano Ciciliato^e Laura Toffoli^e
Michele Rizzo^e Francesco Visalli^e Paolo Verze^f Walter Artibani^a

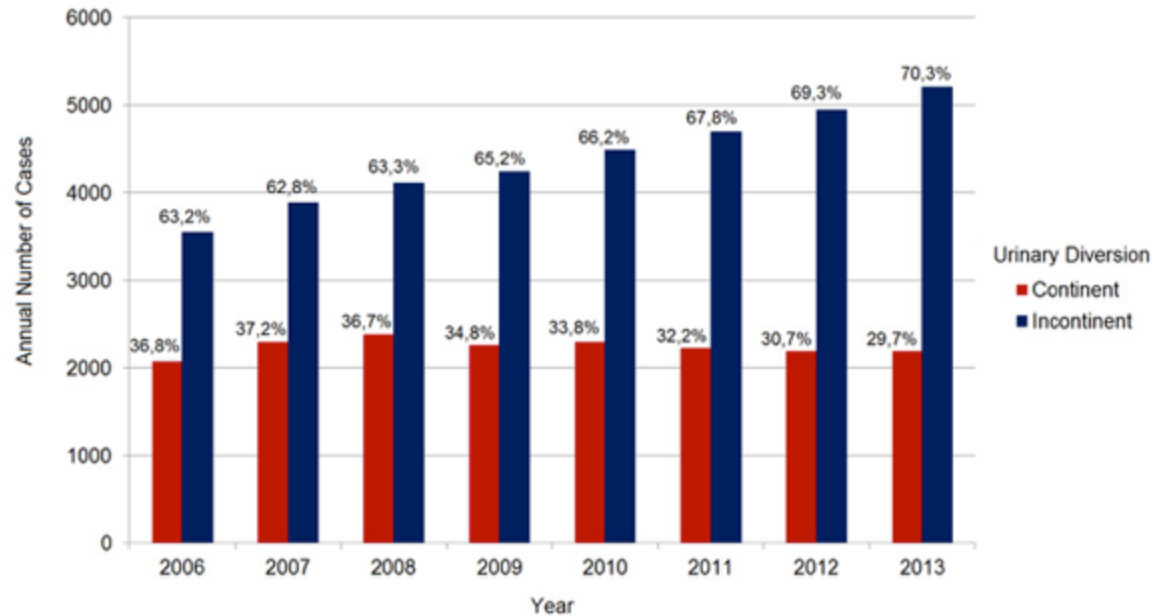
^aUrology Department, University of Verona, Verona; ^bTESIS Department, University of Verona, Verona; ^cUrology Department, University of Padua, Padua; ^dUrology Department, Catholic University Policlinico Gemelli, Rome; ^eUrology Department, Trieste University, Trieste; ^fUrology Department, University of Naples, Naples; ^gUnit of Epidemiology and Biostatistics, IRCCS-CRO, Aviano, Italy



Instrument	Generic	Cancer-specific	Bladder cancer-specific	Brief description
EORTC QLQ C30		×		30 items questionnaire with 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptoms scale (fatigue, pain, and nausea/vomiting) and a global health and quality of life scale
EORTC QLQ BLM 30			×	30 items questionnaire for patients with muscle invasive bladder cancer with additional items concerning urostomy problems, body image, use of catheters
FACT-G (Functional Assessment of Cancer Therapy–General)	×	×		27 item questionnaire evaluating 4 domains (physical social/family, emotional and functional well being)
FACT-BL (Bladder)			×	27+12 item questionnaire specific for patients with bladder cancer
FACT-VCI (Vanderbilt Cystectomy Index)			×	27+12 item questionnaire specific for patients with bladder cancer who underwent cystectomy and various urinary diversions
SF 36	×			36 item survey evaluating 2 major domains: physical health (physical functioning, role-physical, bodily pain and general health) and mental health (vitality, social functioning, role emotional and mental health)

First author	Year	Country	Journal	HR-QoL questionnaires	Patients No. (IC/IONB)	Female (%)	pT2 (%)	Age (years)	Follow-up (months)	Conclusion
McGuire (14)	2000	US	Ann Surg Oncol	SF-36	76(38/38)	0	-	IC = 70 (median at surgery; range 48-83); IONB= 64 (median at surgery; range 37-78)	IC = 42 (median; range 4-90); IONB = 48 (median; range 9-103)	Patients with IC had significantly decreased mental quality of life (p = 0.01) than population-based norm
Hobish (15)	2000	Austria	World J Urol	EORTC QO-L-C30	102(33/69)	26,47	-	IC = 65.1 (mean at surgery); IONB = 60.7 (mean at surgery)	IC = 55.5 (mean); IONB = 28.3 (mean)	QoL is preserved to a higher degree after IONB than after IC diversion
Dutta (16)	2002	US	J Urol	SF-36; FACT-G	72 (23/49)	19	74	Population = 67.1 (mean age at survey +/- 9.7 SD)	Population = 32.28 (mean +/- 17.76 SD)	Patients with IONB had marginal QoL advantage (p = 0.06)
Protogerou (17)	2004	Greece	BJU Int	EORTC QO-L-C30	108 (58/50)	16,67	-	IC = 65 (mean at surgery; range 54-72); IONB = 61 (mean at surgery; range 48-67)	IC = 28 (mean; range 14-72); IONB = 26 (mean; range 16-70)	No significant differences in the QoL
Kikuchi (18)	2006	Japan	Jpn J Clin Oncol	FACT-BL	35 (20/15)	20,4	73,5	Population = 69.6 (mean at survey +/- 9.3 SD)	Population = 83 (mean +/- 50.2 SD; range 20-202)	No significant differences in FACT-G mean scores. Significant less trouble controlling urine in IC patients (p = 0.018). Significant worse QoL score regarding body image in IC group (p = 0.036)
Autorino (19)	2008	Italy	EJSO	SF-36	79 (44/35)	0	74,68	IC = 65.9 (mean at surgery +/- 5.9 SD); IONB = 63.5 (mean at surgery +/- 7.2 SD)	IC = 35.5 (mean +/- 14.4 SD); IONB = 28.3 (mean +/- 18.8 SD)	No significant difference between IC and IONB groups. Patients with IONB aged 65 or older had significantly lower scores for role-physical functioning and role emotional functioning than those younger (p < 0.05).
Philip (20)	2009	UK	Ann R Coll Surg Eng	SF-36	52 (24/28)	23,08	-	IC = 73.5 (median at surgery; range 32-85); IONB = 65.5 (median at surgery; range 50-79)	IC = 12 (median; range 3-75); IONB = 15 (median; range 3-39)	IONB patients had not significant higher mean scores when compared to IC in all HR-QoL scales, except marginally lower scores in vitality, social functioning and bodily pain. IONB patients had significantly better physical functioning (p = 0.037) than IC patients.
Erber (21)	2012	Germany	ISRN Urology	EORTC QO-L-C30; EORTC QOL-BLM30	58 (24/34)	20,3	42,53	IC = 70 (mean at surgery; range 64-75); IONB = 62 (mean at surgery; range 56-66)	IC = 33.2 (mean +/- 32.77 SD); IONB = 50.6(mean +/- 44.98 SD)	Patients with ileal IONB had significantly better GHS and QoL (p = 0.02), better physical functioning (p = 0.02), but also a higher rate of diarrhoea (p = 0.004).
Gacci (22)	2013	Italy	Health and Quality of Life Outcomes	EORTC QOL-C30; EORTC QOL-BLM30; FACT-BL	25 (16/9)	100	68	Population = 67.3 (mean at surgery +/- 8.7 SD) and 73.1 (mean at survey +/-8.7); IC = 74.4 (mean at survey +/- 8.8 SD); IONB = 71.8 (mean at survey +/- 7 SD)	Population = 60.1 (mean; range 36-122)	Only female patients evaluated. No significant difference between IC and IONB subgroups.
Metcalfe (23)	2013	Canada	Can J Urol	FACT-VCI	84 (53/31)	14,28	75	IC = 68 (mean at surgery); IONB = 62 (mean at surgery)	Population = 67.20 (median; range 25.2-111.6)	Type of UD was not associated with QoL after RC.

Ileal Conduit vs orthotopic neobladder



Robotic cystectomy



Comparing Open Radical Cystectomy and Robot-assisted Laparoscopic Radical Cystectomy: A Randomized Clinical Trial

Bernard H. Bochner^{a,*}, Guido Dalbagni^a, Daniel D. Sjoberg^b, Jonathan Silberstein^{a,c}, Gal E. Keren Paz^a, S. Machele Donat^a, Jonathan A. Coleman^a, Sheila Mathew^a, Andrew Vickers^b, Geoffrey C. Schnorr^b, Michael A. Feuerstein^a, Bruce Rapkin^{d,e}, Raul O. Parra^a, Harry W. Herr^a, and Vincent P. Laudone^a

^aUrology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA

^bDepartment of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA

^cDepartment of Urology, Tulane University School of Medicine, New Orleans, LA, USA

^dDepartment of Psychiatry and Behavioral Services, Memorial Sloan Kettering Cancer Center, New York, NY, USA

^eDepartment of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY, USA

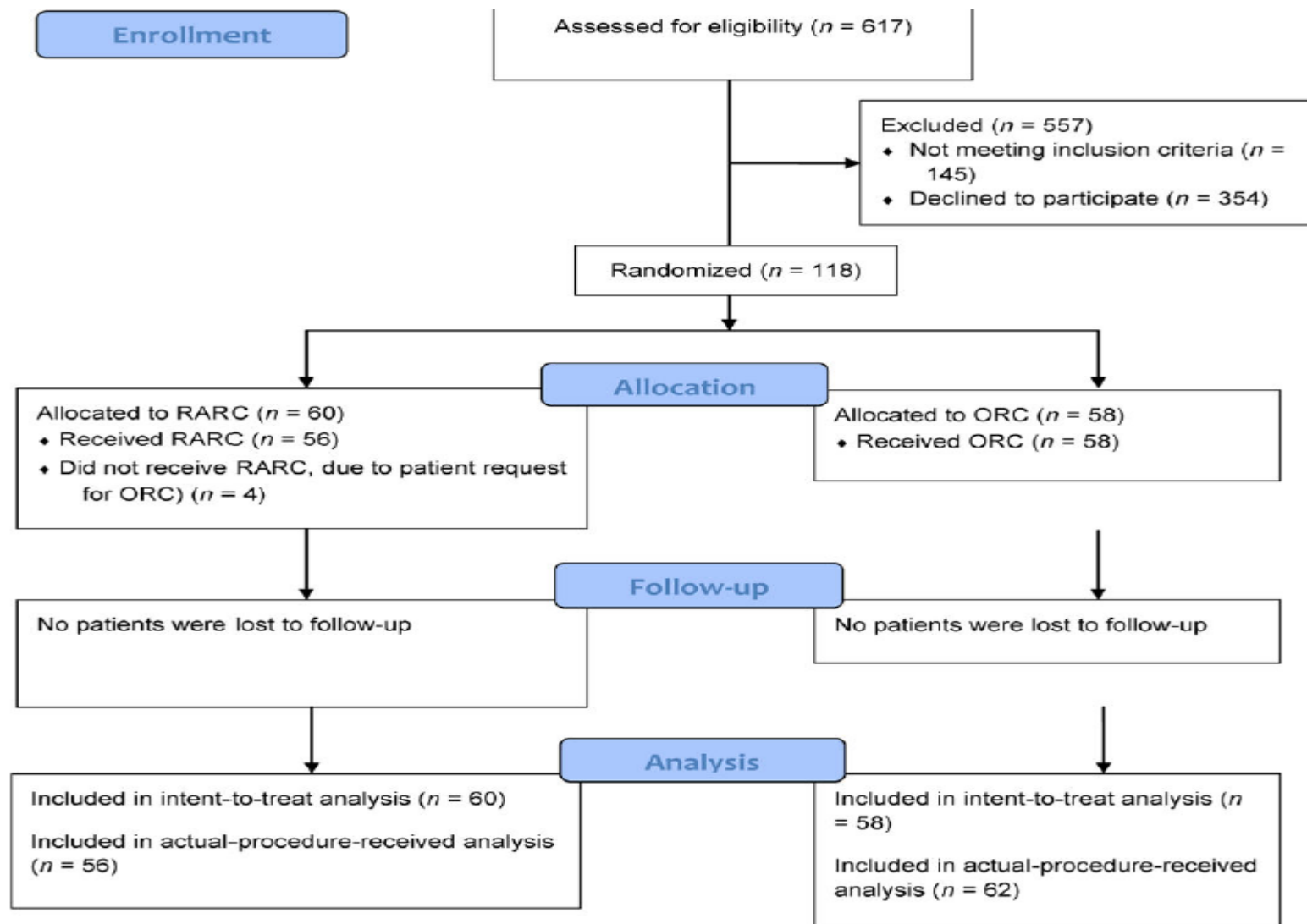


Fig. 1. Randomization and follow-up of study patients

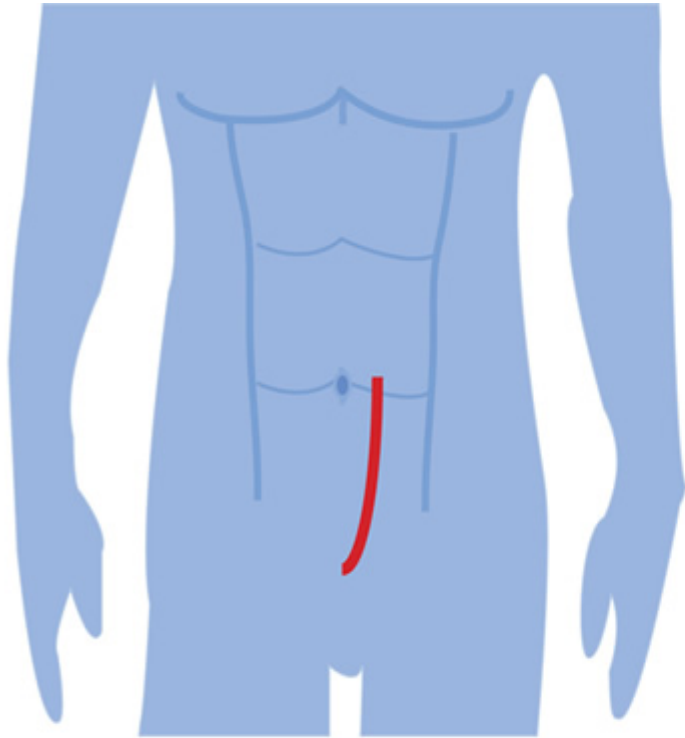
ORC = open radical cystectomy; RARC = robot-assisted laparoscopic radical cystectomy.

Participant characteristics

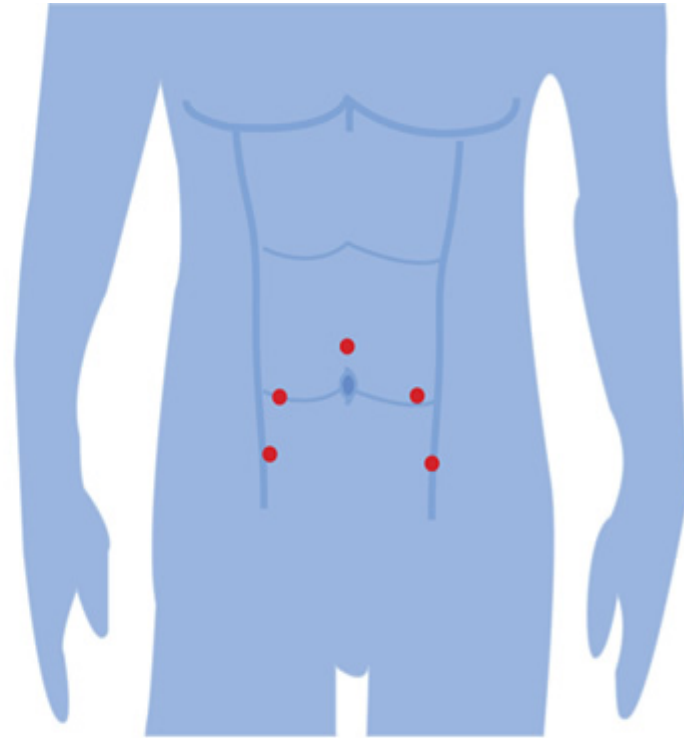
	Robotic (<i>n</i> = 60)	Open (<i>n</i> = 58)
Baseline		
Age, yr, median (IQR)	66 (60–71)	65 (58–69)
Male sex, <i>n</i> (%)	51 (85)	42 (72)
Body mass index, kg/m ² , median (IQR)	27.9 (24.7–31.0)	29.0 (26.3–33.7)
ASA score, <i>n</i> (%)		
2	17 (28)	12 (21)
3	42 (70)	43 (74)
4	1 (1.7)	3 (5.2)
Prior bacillus Calmette-Guérin therapy, <i>n</i> (%)	30 (50)	18 (31)
Clinical stage, <i>n</i> (%) *		
Tis	8 (14)	2 (3.5)
Ta	1 (1.7)	3 (5.3)
T1	21 (36)	19 (33)
T2	24 (41)	28 (49)
T3	4 (6.8)	5 (8.8)
T4	1 (1.7)	0 (0)
Neoadjuvant chemotherapy, <i>n</i> (%)	19 (32)	26 (45)
Intraoperative		
Urinary diversion type, <i>n</i> (%)		
Ileal conduit	27 (45)	23 (40)
Neobladder	33 (55)	32 (55)
Continent cutaneous	0 (0)	3 (5.2)
Level of lymph node dissection, <i>n</i> (%)		
External iliac	0 (0)	4 (6.9)
Common iliac	13 (22)	26 (45)
Aortic bifurcation	33 (55)	20 (34)
Inferior mesenteric artery	14 (23)	8 (14)
Received assigned surgery	56 (93.3)	58 (100)
Pathology from final cystectomy specimen		
Histology, <i>n</i> (%)		
Adenocarcinoma	0 (0)	1 (1.7)
Squamous cell carcinoma	1 (1.7)	1 (1.7)
Small cell carcinoma	1 (1.7)	1 (1.7)
Small cell plus transitional cell carcinoma	1 (1.7)	0 (0)
Transitional cell carcinoma	57 (95)	55 (95)
Pathologic stage, <i>n</i> (%)		

Outcomes after radical cystectomy

	Robotic	Open	Difference, %	95% CI for difference, %	<i>p</i> value
By randomization arm/intention-to-treat	<i>n</i> = 60	<i>n</i> = 58			
Grade 2–5 complication, <i>n</i> (%)	37 (62)	38 (66)	–3.9	–21 to 13	0.7
Grade 3–5 complication, <i>n</i> (%)	13 (22)	12 (21)	1.0	–14 to 16	0.9
Total number of grade 2–5 complications, mean (SD)	1.4 (1.80)	1.5 (1.66)	–0.2	–0.8 to 0.5	0.6
Total number of grade 3–5 complications, mean (SD)	0.3 (0.58)	0.3 (0.76)	0.0	–0.3 to 0.2	0.7
Any intraoperative complications, <i>n</i> (%)	3 (5.0)	3 (5.2)	–0.2	–8 to 8	>0.9
Operative room time, min, mean (SD)	456 (82)	329 (77)	127	98 to 156	<0.001
Estimated blood loss, ml, mean (SD)	516 (427)	676 (338)	–159	–300 to –19	0.027
Hospital length of stay, d, mean (SD)	8 (3)	8 (5)	0	–2 to 1	0.5
Positive surgical margin, <i>n</i> (%)	2 (3.3)	3 (5.2)	–1.8	–9 to 5	0.6
Subgroup of patients \geq T3, <i>n/n</i> (%)	2/17 (12)	3/19 (16)	–4.0	–26 to 18	0.7
Lymph node–positive patients, <i>n</i> (%)	10 (17)	9 (16)	1.1	–12 to 14	0.9
By type of surgery received	<i>n</i> = 56	<i>n</i> = 62			
Grade 2–5 complication, <i>n</i> (%)	35 (63)	40 (65)	–2.0	–19 to 15	0.8
Grade 3–5 complication, <i>n</i> (%)	12 (21)	13 (21)	0.5	–14 to 15	>0.9
Total number of grade 2–5 complications, mean (SD)	1.4 (1.85)	1.5 (1.63)	–0.1	–0.7 to 0.6	0.9
Total number of grade 3–5 complications, mean (SD)	0.3 (0.59)	0.3 (0.74)	0.0	–0.3 to 0.2	0.8
Any intraoperative complications, <i>n</i> (%)	3 (5.4)	3 (4.8)	0.5	–7 to 8	0.9
Operating room time, min, mean (SD)	464 (79)	330 (75)	134	106 to 162	<0.001
Estimated blood loss, ml, mean (SD)	500 (437)	681 (328)	–181	–321 to –41	0.012
Hospital length of stay, d, mean (SD)	8 (4)	8 (5)	0	–2 to 1	0.9
Positive surgical margin, <i>n</i> (%)	2 (3.6)	3 (4.8)	–1.3	–8 to 6	0.7
Subgroup of patients \geq T3, <i>n/n</i> (%)	2/16 (13)	3/20 (15)	–2.5	–25 to 20	0.8
Lymph node yield, mean (SD)					
Extended dissection	31.9 (12)	30.0 (12)	2.0	–3.8 to 7.8	0.5
Standard dissection	19.5 (10)	18.9 (10)	0.6	–6.2 to 7.5	0.5
Lymph node–positive patients, <i>n</i> (%)	10 (18)	9 (15)	3.3	–10 to 17	0.6



Open Prostatectomy Incision



da Vinci Prostatectomy Incisions

SURVIVAL DATA OF RADICAL CYSTECTOMY AND SELECTIVE BLADDER PRESERVATION

Series	Year	Category	No. Patients	Overall Survival	
				5-yr	10-yr
Cystectomy					
USC ¹³⁶	2001	pT2-pT4a	633	48%	32%
MSKCC ¹³⁷	2001	pT2-pT4a	181	36%	27%
SWOG/ECOG/CALGB [†] ²¹⁶	2002	cT2-cT4a	317	49%	34%
Selective Bladder Preservation					
University of Erlangen ^{*123,234}	2002	cT2-cT4a	326	45%	29%
MGH ^{*233}	2009	cT2-cT4a	348	52%	35%
RTOG ^{*209}	1998	cT2-cT4a	123	49%	

C
O
M
P
A
R
A
B
L
E

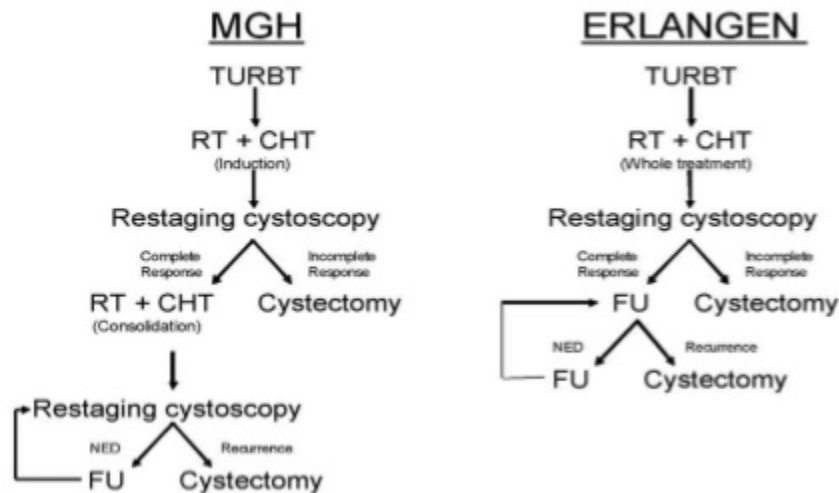
**No trials have till date directly compared
Cystectomy and Bladder-preservation**

Trimodality Therapy

- Combination of Limited Resection, Chemotherapy, and Irradiation in Bladder Preservation
- Best results till date in bladder preservation when the 3 modalities are combined together
- Based on both **single institutional data** and large **randomised control trials**

41

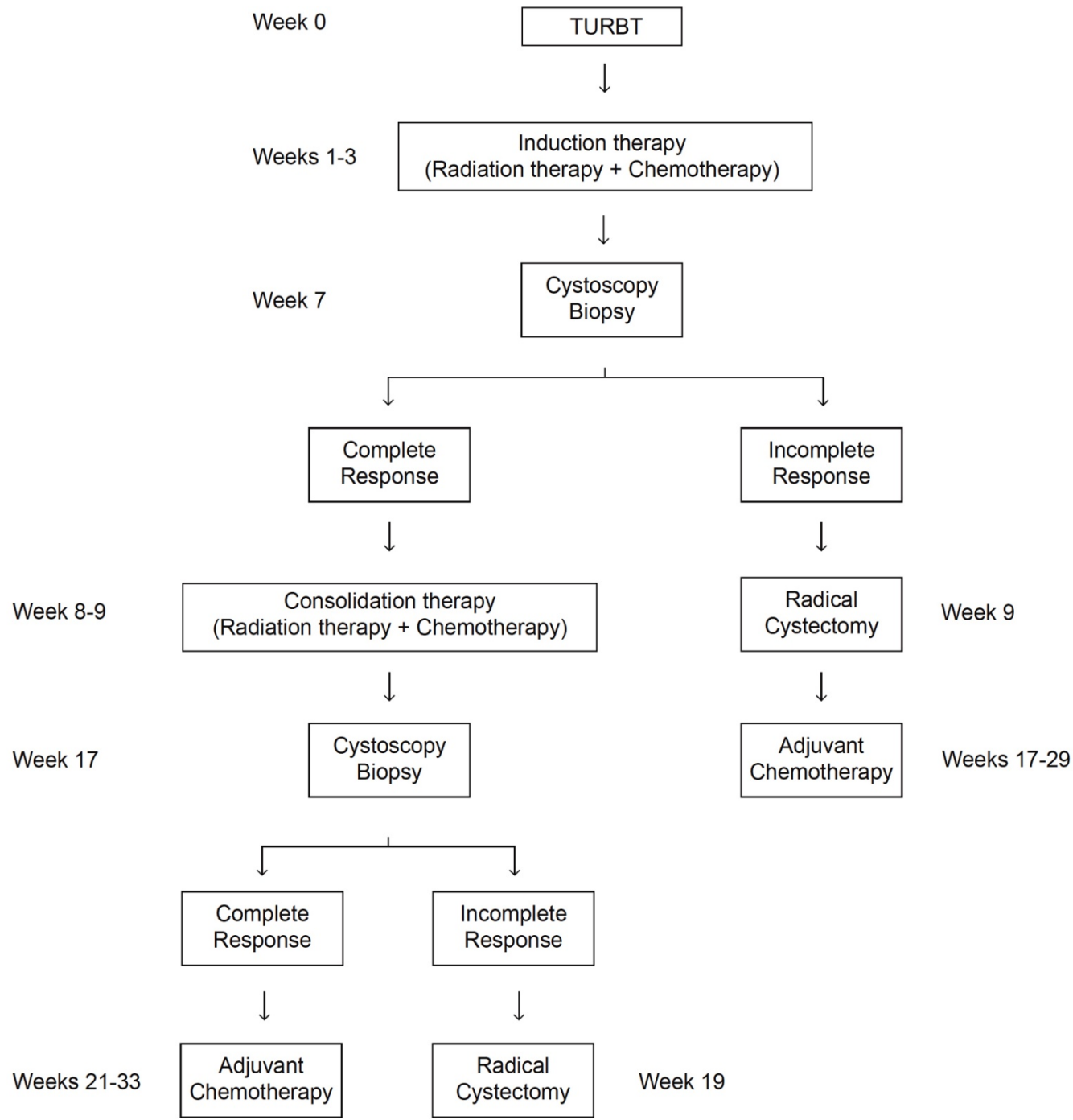
PIONEERING SINGLE INSTITUTION STUDIES OF TRIMODALITY TREATMENT



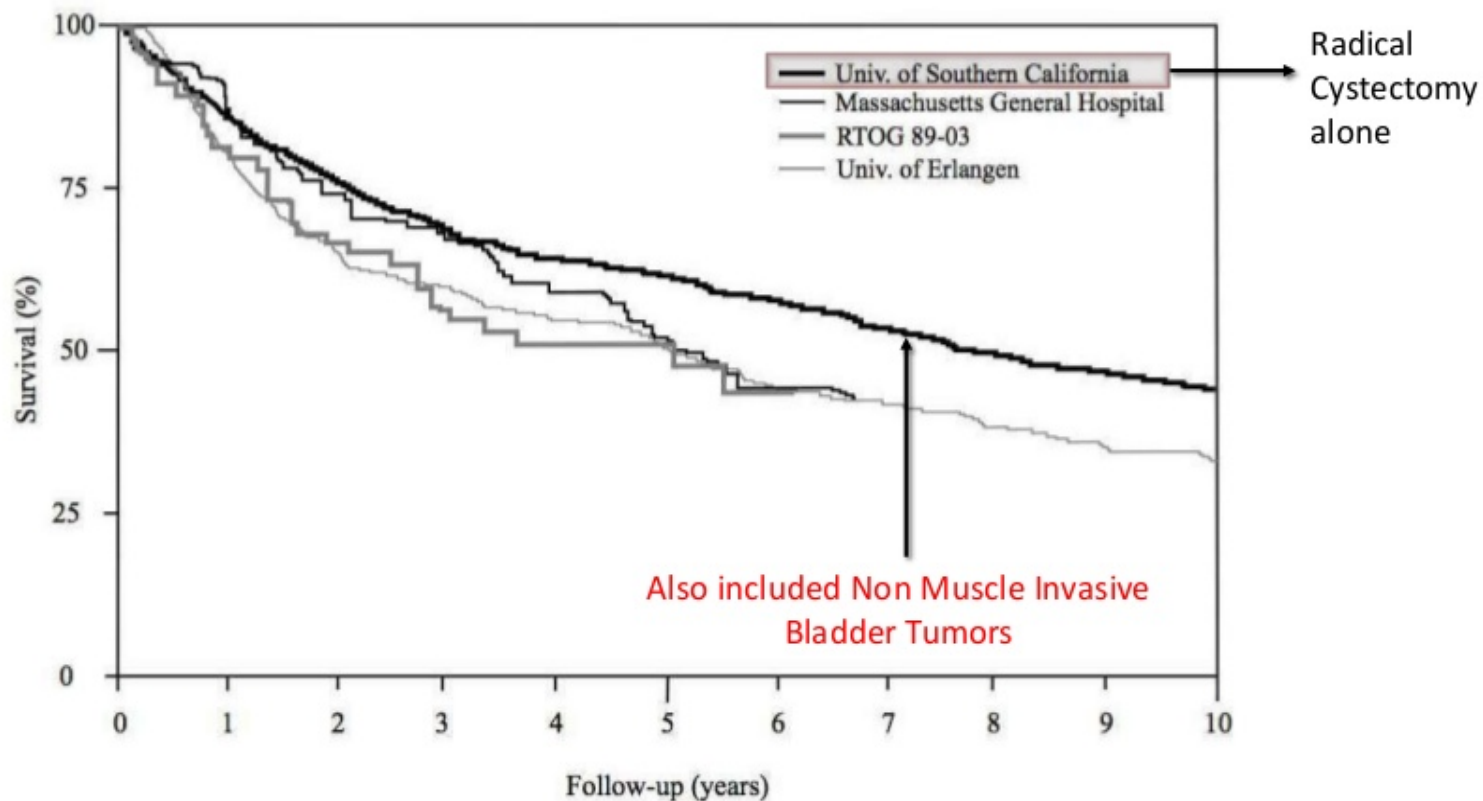
42

TRI MODALITY TREATMENT

Trial	Induction RT	Induction chemo	Planned break	Consolidative RT	Consolidative chemo	Total RT dose	pCR	Survival
RTOG 99-06	40.3/26	cisplatin/taxol	3 weeks	24/16	cis/taxol, cis/gem x4	64.3/42	81%	5y: 56%
RTOG 97-06	40.8/24	cisplatin	3 weeks	24/16	cisplatin	64.8/40	74%	3y: 61%
RTOG 95-06	24/8	cisplatin/5-FU	3-4 weeks	20/8	cisplatin/5-FU	44/16	67%	3y: 86%
RTOG 89-03	39.6/22	±MCV x2 alone, then cisplatin	4 weeks	25.2/14	cispaltin	64.8/36	61%	5y: 48%
RTOG 88-02	39.6/22	MCV x2 alone, then cisplatin	2 weeks	25.2/14	cispaltin	64.8/36	80%	4y: 62%
RTOG 85-12	40/20	cisplatin	2 weeks	24/12	cisplatin	64/32	74%	3y: 59%
Harvard; 1993	39.6/22	MCV x2 alone, then cisplatin	2 weeks?	25.2/14	cispaltin	64.8/36	77%	5y: 48%
Paris; 1993	24/8	cisplatin/5-FU	6 weeks	20/8	cisplatin/5-FU	44/16	67%	3y: 64%



KAPLAN – MEIER GRAPH OF SURVIVAL IN MUSCLE INVASIVE BLADDER CANCER



The Benefit of Radiation in Bladder Preservation

<u>Treatment</u>	<u>%CR</u>	<u>5 year survival</u>	<u>% requiring cystectomy</u>
TURBT + M-VAC* (TWO-MODALITY)	33-54%	58%	66%
TURBT + XRT+chemo (TRI-MODALITY)	64-87%	45%-62%	29-35%

Cystectomy rate is increased
by 88-125% without radiation

QoL due to urinary symptoms after TURBT and chemoRT

If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?

delighted	pleased	mostly satisfied	mixed – about equally satisfied and dissatisfied	mostly dissatisfied	unhappy	terrible
18.5%	51.7%	17.2%	9.1 %	0.8%	2 %	0.7%

Late Pelvic Toxicity: RTOG Results

**157 patients with bladder preservation who survived
2 to 13 years (median follow-up 5.2 years)**

- 22% Grade 1
- 10% Grade 2
- 7% Grade 3 (5.7% GU, 1.9% GI)
- 0% Grade 4
- 0% Grade 5

Treatment/ Comparison	Evidence	Level of Evidence	Grade of Recommendation
RT alone vs 40Gy+Cystectomy	3 of 4 RCTs report similar survival	1b	A
ChemoRT vs RT alone	2 RCTs report significant improvement in bladder tumor eradication	1b	A
Neoadjuvant CT with RT or ChemoRT	3 RCTs and 1 meta-analysis report no benefit	1a	A
ChemoRT preserves good bladder function	3 QOL studies and RTOG protocols report good tolerance	2a	B
Complete TURBT with ChemoRT	3 reports (1 phase III, 2 phase II) show benefit	2a	B
Predictive Biomarkers of outcome after RT	MRE 11 expression predicts improved CSS (1 study)	2b	B
Trimodality therapy vs immediate cystectomy	Comparison of 3 contemporary series of each report similar 5- and 10-yr survival	3	C

"It is important to preface this discussion with the reality of the disease: high-grade invasive bladder cancer is a lethal disease and any short cuts/mistakes in the treatment can be lethal to the patient"

Richard Hautmann