Θεραπευτικές επιλογές για την αντιμετώπιση μυοδιηθητικού καρκίνου κύστεως

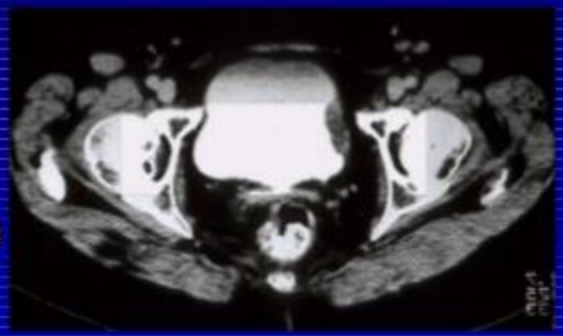
ΣΤΑΘΟΥΡΟΣ Ν. ΓΕΩΡΓΙΟΣ MD , FEBU

ΕΠΙΜΕΛΗΤΗΣ Α ΓΝΑ Γ.ΓΕΝΝΗΜΑΤΑΣ

Muscle-invading TCC bladder

Cystectomy

Cystectomy alternatives



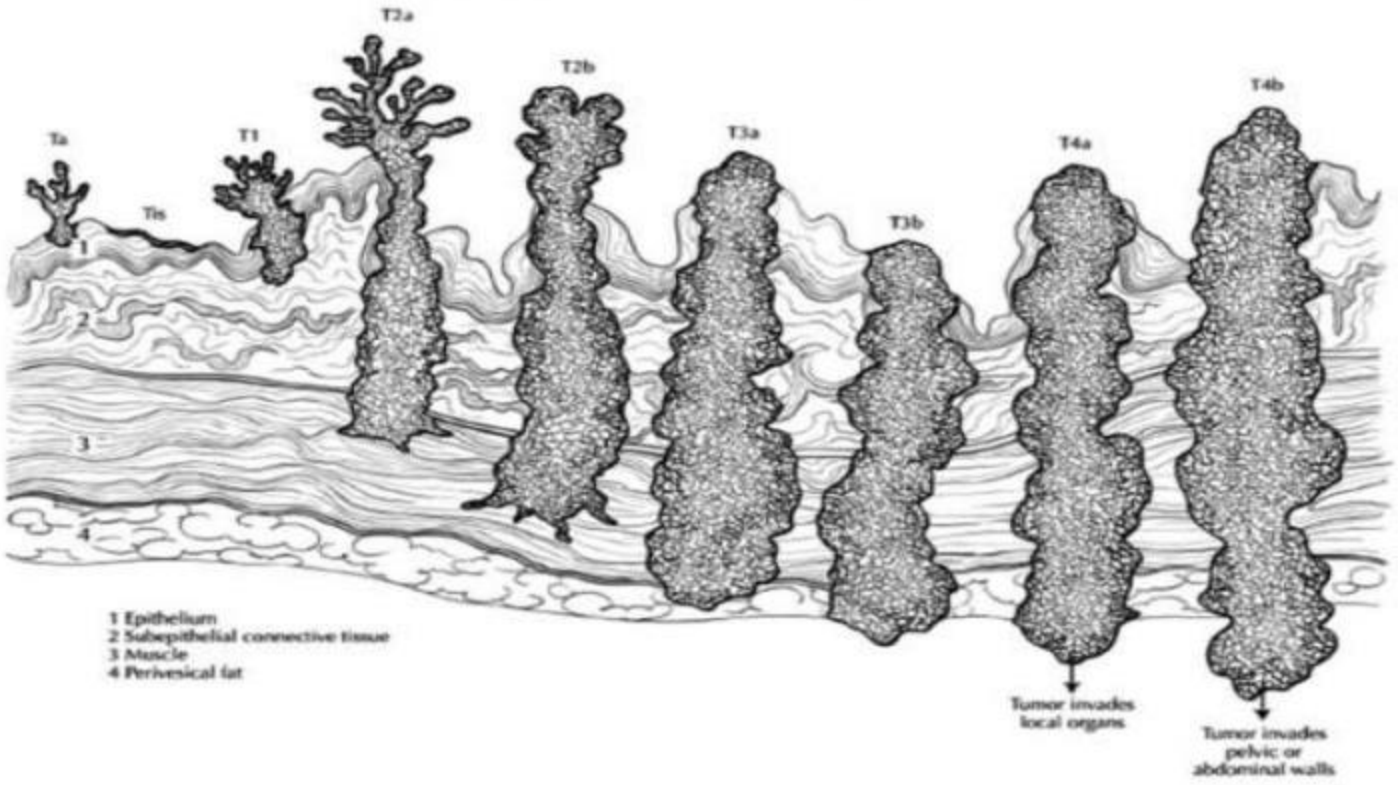
Bladder removal and reconstruction

Bladder conservation

Goals:

- cure patient and optimize survival
- prevention of pelvic failure and distant metastasis
- functional urinary reservoir and high QOL

Extent of Primary Bladder Cancer AJCC - 2010



Radical cystectomy

- Indication:
  - Muscle invasive or locally advanced disease T2-T4a N0-Nx, M0
  - BCG-resistant Cis, T1G3
  - High risk recurrent superficial tumors
  - Extensive papillary tumors not controlled by TUR
- Standard RC:
  - Male: Prostate + bladder + macroscopic visible & resectable tumor extension, adjacent distal ureter + LN
  - Female: Anterior pelvic exenteration include bladder, entire urethra, upper 1/3 vagina , uterus , distal ureters and LN

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 moblize
- Pelvic lymphadenectomy
- Circumferencially incise on cervix
- Close vaginal defect
- Dissection of place bt anterior vaginal wall and posterior surface of bladder
- Divide urethra

Technique to improve QOL

Level of preservation:

- Anterior & membranous urethra + external sphincter
  - For orthotopic neobladder
- Part of prostate and seminal vesicle
  - Fertility , potency and continence
- Autonomic & sensory nerve (NVB)
  - soft tissue adjacent to the tips of the seminal vesicles.
- Uterus & part of vagina ;
  - Improve antomical support for neobladder & autonomic nerves

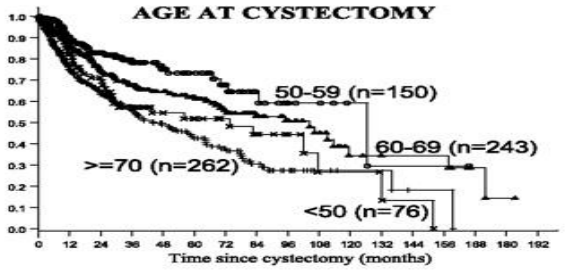
Disadv:

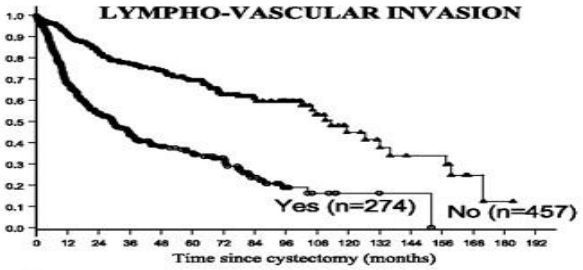
- Residual Ca prostate (30%) → 10% clinically significant
- Increase oncologica risk → need long term data

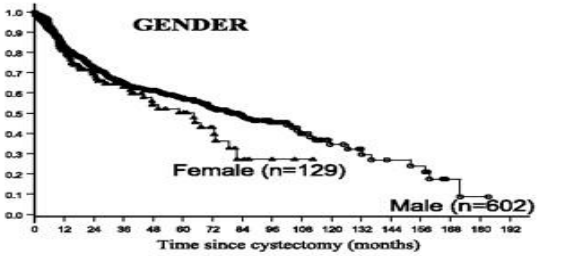
Adv:

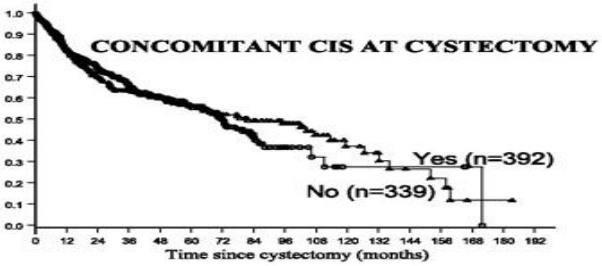
- Improve potency rate after nerve sparing cystectomy (Walsh J Urol 1996)
  - 20y – 29y: 100%, 70y – 79y: 20%
  - Overall 48%, depends on age of patient
  - vs < 30% in non NS cystectomy
- Allow formation of neobladder and more natural voiding

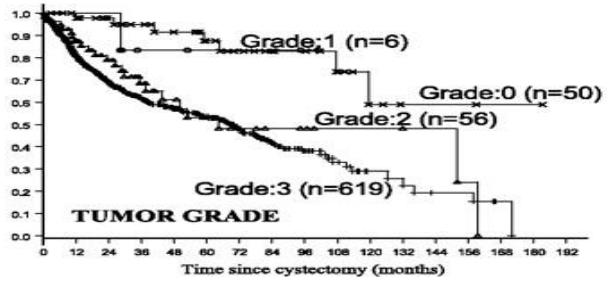
- Complications
  - Re-operation (10%)
  - Bleeding (10%)
  - Sepsis and wound infection (10%)
  - Intestinal obstruction or prolong ileus (10%)
  - Cradio-pulmonary morbidity
  - Rectal injury (4%)
  - Cx of urinary diversion
  - Peri-operative mortality : 3%
  - Early complications (within 3 months of surgery) in **28%** (Stein JP, Skinner DG. Radical cystectomy for invasive bladder cancer: long-term results of a standard procedure. World J Urol 2006)
- Result:
  - Pathological upstaging (40%)
  - LN metastasis : T1 (10%) , T3-4 (33%)
- Survival
  - 10 years recurrence free survival: 60%, overall survival 50% (Stein series)
  - 5 years recurrence free survival (Studer series): overall 70%
    - **90% in pT1/CIS**
    - **74%** in pT2,
    - **52%** in pT3, and
    - **36%** in pT4
  - 5 yr OS: 60%
  - Long term survival in LN +ve: 20% - 30%
- Nomogram to predict survival following RC have been develop but cannot be recommended

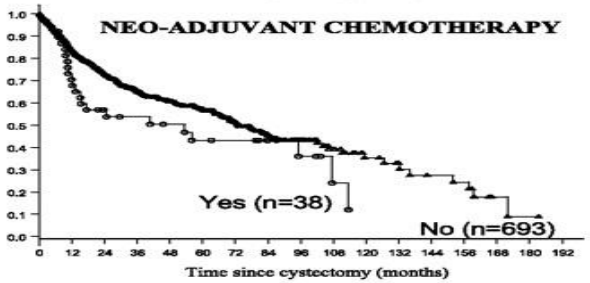

AGE AT CYSTECTOMY
50-59 (n=150)
60-69 (n=243)
>=70 (n=262)
<50 (n=76)
Time since cystectomy (months)

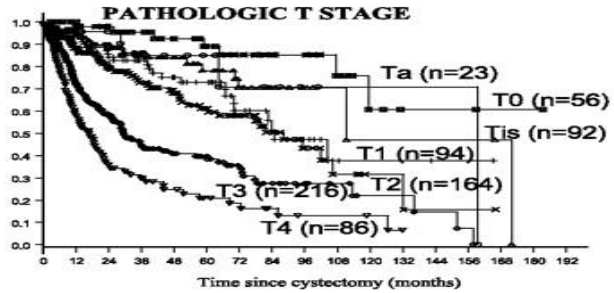

LYMPHO-VASCULAR INVASION
Yes (n=274)
No (n=457)
Time since cystectomy (months)

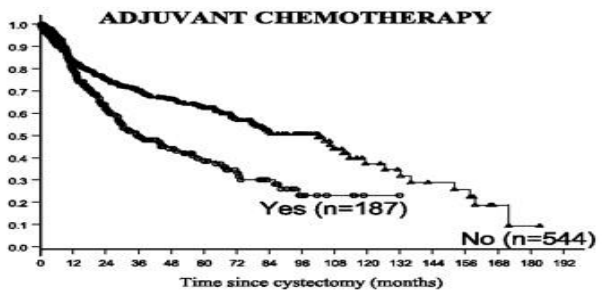

GENDER
Female (n=129)
Male (n=602)
Time since cystectomy (months)

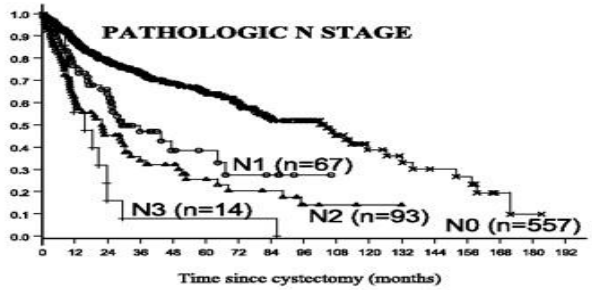

CONCOMITANT CIS AT CYSTECTOMY
Yes (n=392)
No (n=339)
Time since cystectomy (months)

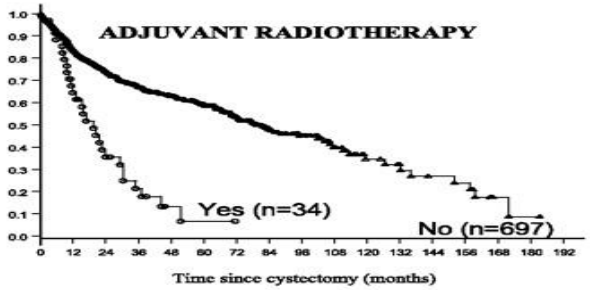

Grade:1 (n=6)
Grade:0 (n=50)
Grade:2 (n=56)
Grade:3 (n=619)
TUMOR GRADE
Time since cystectomy (months)


NEO-ADJUVANT CHEMOTHERAPY
Yes (n=38)
No (n=693)
Time since cystectomy (months)


PATHOLOGIC T STAGE
Ta (n=23)
T0 (n=56)
Tis (n=92)
T1 (n=94)
T2 (n=164)
T3 (n=216)
T4 (n=86)
Time since cystectomy (months)

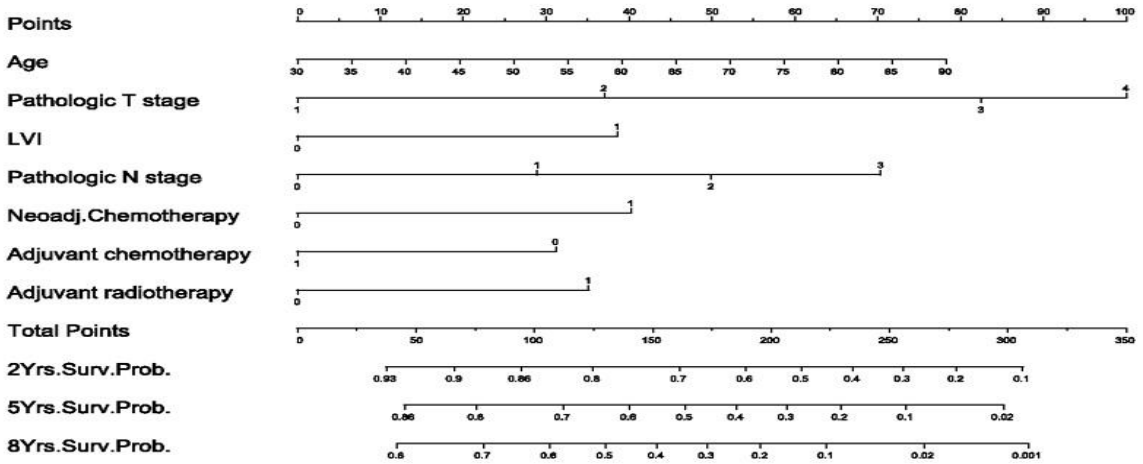

ADJUVANT CHEMOTHERAPY
Yes (n=187)
No (n=544)
Time since cystectomy (months)


PATHOLOGIC N STAGE
N1 (n=67)
N3 (n=14)
N2 (n=93)
N0 (n=557)
Time since cystectomy (months)


ADJUVANT RADIOTHERAPY
Yes (n=34)
No (n=697)
Time since cystectomy (months)

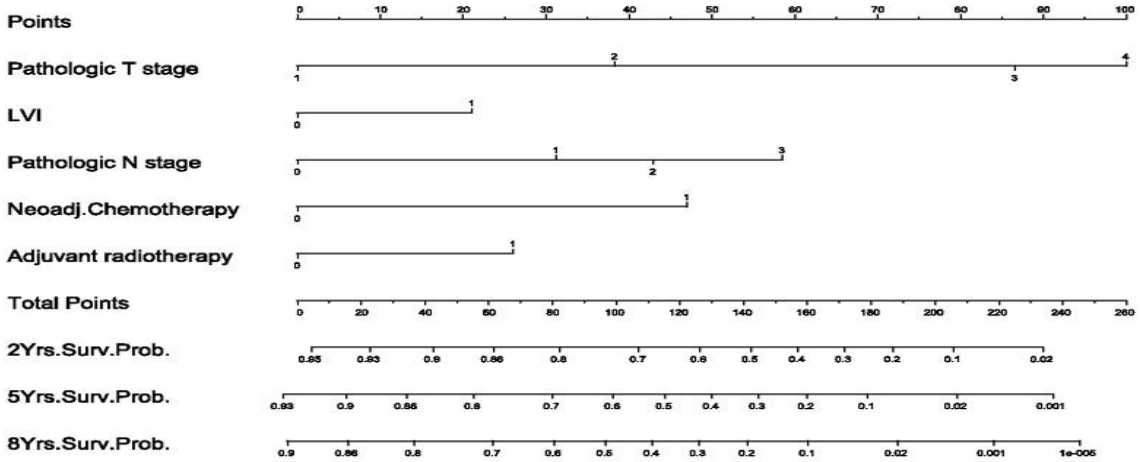
A

ALL-CAUSE SURVIVAL NOMOGRAM



B

BLADDER CANCER-SPECIFIC SURVIVAL NOMOGRAM



T stage :
1 : T_0, T_a, T_{is}, T_1
2 : T_2
3 : T_3
4 : T_4

N stage :
0 : N_0
1 : N_1
2 : N_2
3 : N_3

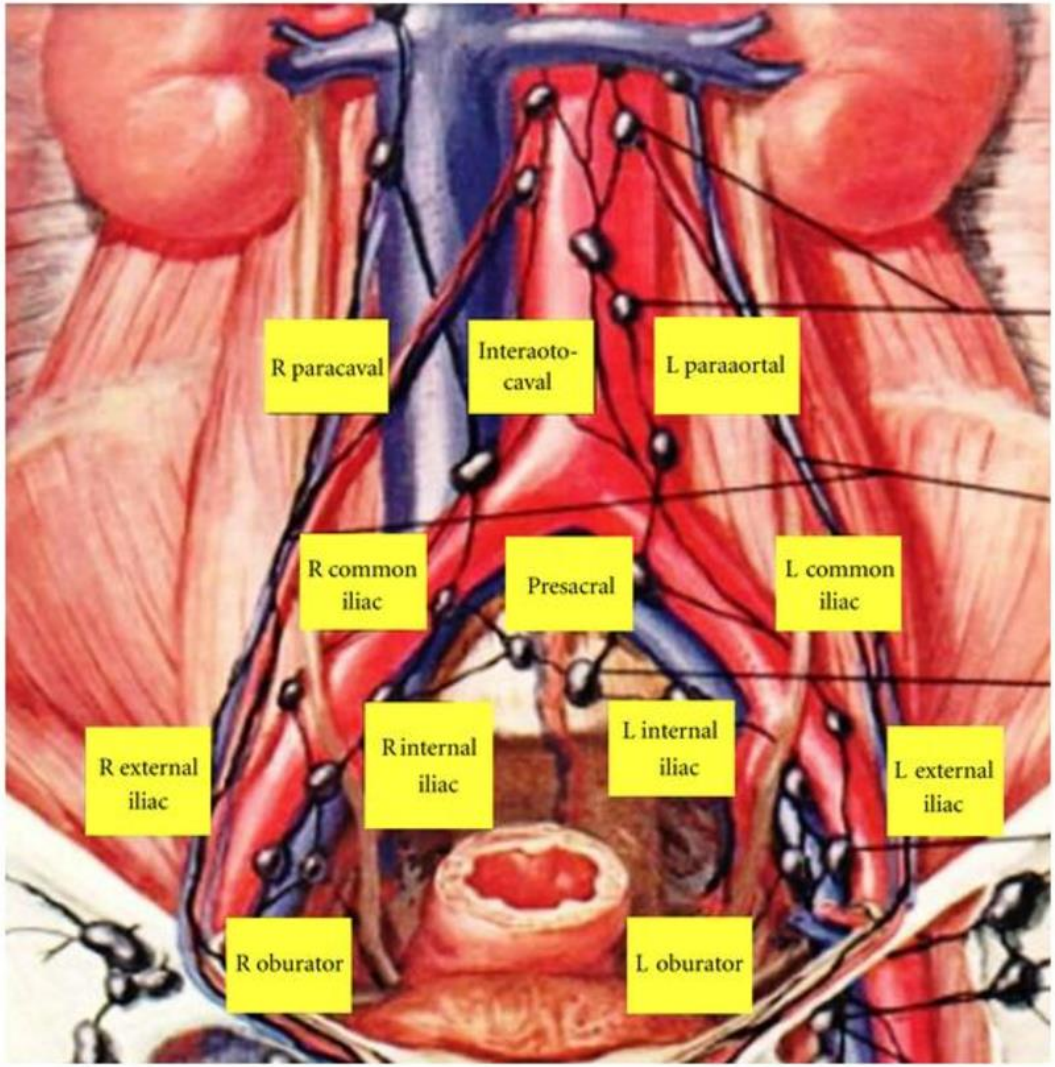
ΛΕΜΦΑΔΕΝΙΚΟΣ ΚΑΘΑΡΙΣΜΟΣ

Correlation of pathological T stage with LN metastases

Study	Poulsen et al. [31]	Viewg et al. [12]	Stein et al. [15]	Madersbacher et al. [17]	Leissner et al. [5]	Vazina et al. [10]	Abdel-Latif et al. [11]	Hautmann et al. [20]	Ghoneim and Abol-Enein [32]
Year	1998	1999	2001	2003	2004	2004	2004	2006	2008
period	1990–1997	1980–1990	1971–1997	1985–2000	1999–2002	1992–2002	1997–1999	1986–2003	1971–2000
Total no. of patients	191	686	1054	507	290	176	418	788	2720
					% of LN metastasis				
pT0, pTis, and pT1	3	10	5	2	2	4	4	1	2
pT2a	18	9	18	17	13	16	7	10	8
T2b	25	23	27	34	22	40	25	41	19
pT3	51	43	45	41	44	50	48	44	39
pT4	44	41	45		50		65		36
Total	26	28	23	24	28	24	26	18	20

Reference : Lymphadenectomy in management of Invasive Bladder Cancer; Ramy F. Youssef and Ganesh V. Raj; International Journal of Surgical Oncology ;Volume 2011

ΛΕΜΦΑΔΕΝΙΚΟΣ ΚΑΘΑΡΙΣΜΟΣ



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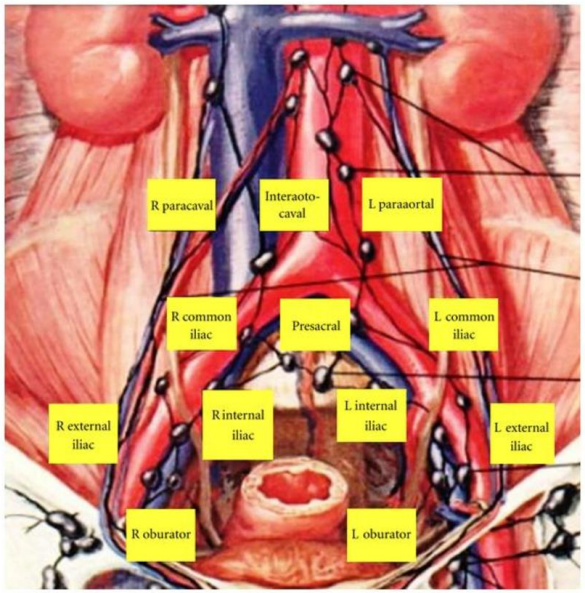

Extended PLND

In the boundaries of:

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

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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 1or 2, pN0	85%	63%
T3	55%	40%
pLN+ 1-5 i.e. density	53%	25%

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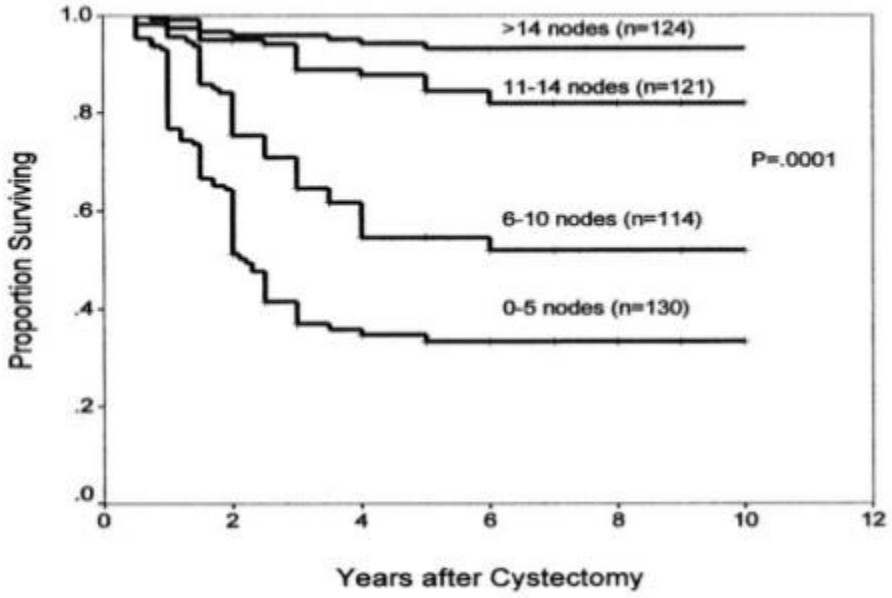
Survival in patients with N0 disease



Herr, Urol 2003

Recommendation

- The Bladder Cancer Collaborative Group recommends 10-14 lymph nodes should be removed at time cystectomy

Herr, J Urol 2004

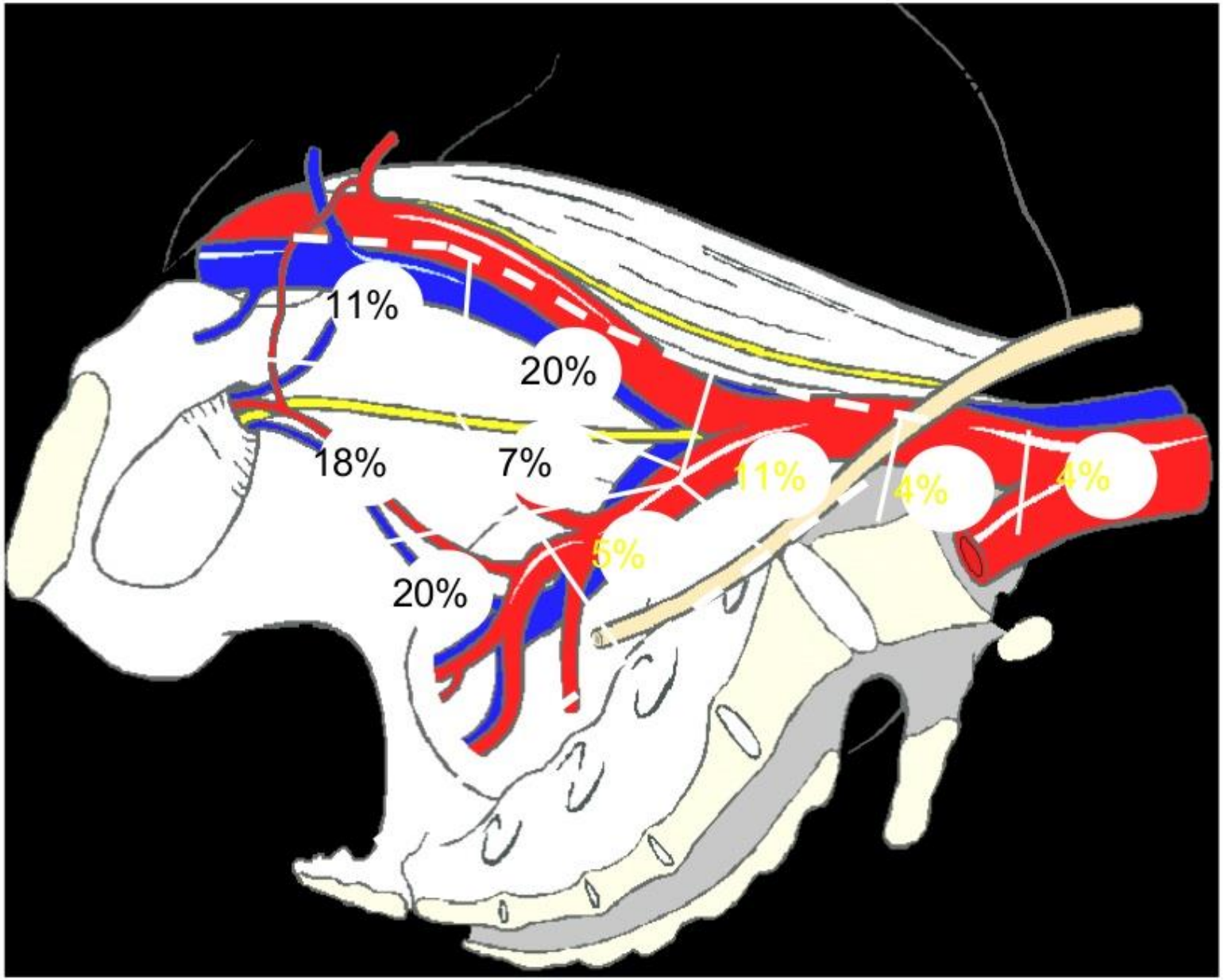
Technical Considerations

- Operation technique
  - Standardized procedure
  - Cystectomy-first or LND-first approach
  - Extra operation time (63 minutes)
- Open versus laparoscopic
  - Technically demanding in laparoscopic procedure
  - No difference in term of lymph node yield and complication rate
  - Increased operation time but blood loss reduced

Finelli, J Urol. 2004. Porpiglia, J Endourol. 2007

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+



B. Roth et al., Eur Urol 57:205-211, 2010

Patients with pT2 and pT3 N0 bladder cancer

Institution	Stage	# of Patients	# with pN+
CC Limited	$pT_2\,pN_{0\text{-}2}$	200	15/200 **(7.5%)**
Bern Extended	$pT_2\,pN_{0\text{-}2}$	150	24/150 **(16%)**
CC Limited	$pT_3\,pN_{0\text{-}2}$	136	29/136 **(21%)**
Bern Extended	$pT_3\,pN_{0\text{-}2}$	172	59/172 **(34%)**

Dhar N., Studer U.E. et al., J. Urol 179: 873-878, 2008

ΛΕΜΦΑΔΕΝΙΚΟΣ ΚΑΘΑΡΙΣΜΟΣ

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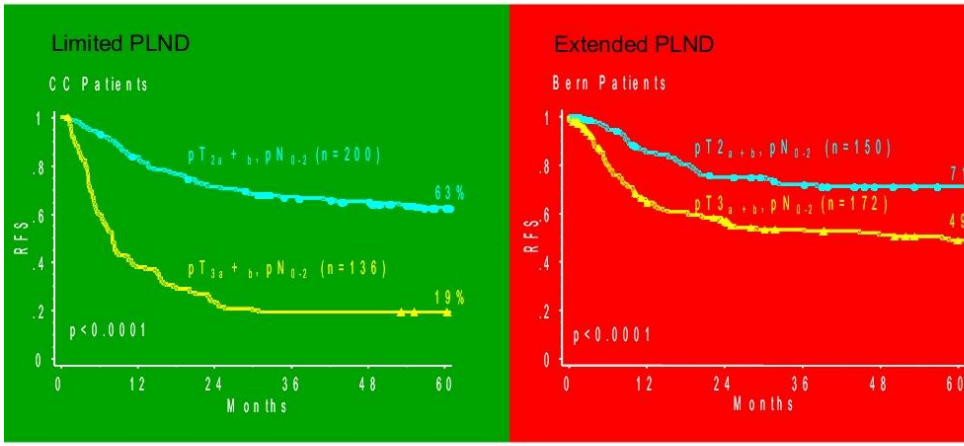
Dhar N., Studer U.E. et al., J. Urol 179: 873-878, 2008

Recurrenc free survival $pT2\,pN_{0-2}$ & $pT3\,pN_{0-2}$ p< 0.001



Dhar N., Studer U.E. et al., J. Urol 179: 873-878, 2008

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

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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 #3 , Consolidating the Data

THE JOURNAL of UROLOGY
Official Journal of the American Urological Association

Neoadjuvant Chemotherapy for Transitional Cell Carcinoma of the Bladder: A Systematic Review and Meta-Analysis

February 2004 Volume 171, Issue 2, Part 1, Pages 561–569

- 2,605 patients
- **6.5%** absolute benefit in 5-year OS
- Chemotherapy can be **administered safely without adverse outcomes resulting in delayed local therapy**
- Further efforts to identify the patients most likely to benefit from neoadjuvant therapy are necessary to optimize its use.

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]

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 cycles[5]

- 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]

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY,
the leading European professional organisation representing medical oncologists.

clinical practice guidelines

Annals of Oncology 25 (Supplement 3): iii40-iii48, 2014
doi:10.1093/annonc/mdu223
Published online 5 August 2014

Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up†

- While there is still insufficient evidence for the routine use of adjuvant chemotherapy in clinical practice, it is likely that high-risk patients, (extravesical and/or lymph node +ve disease)

  that have not received NAC,

  will benefit most from adjuvant chemotherapy.

European Association of Urology

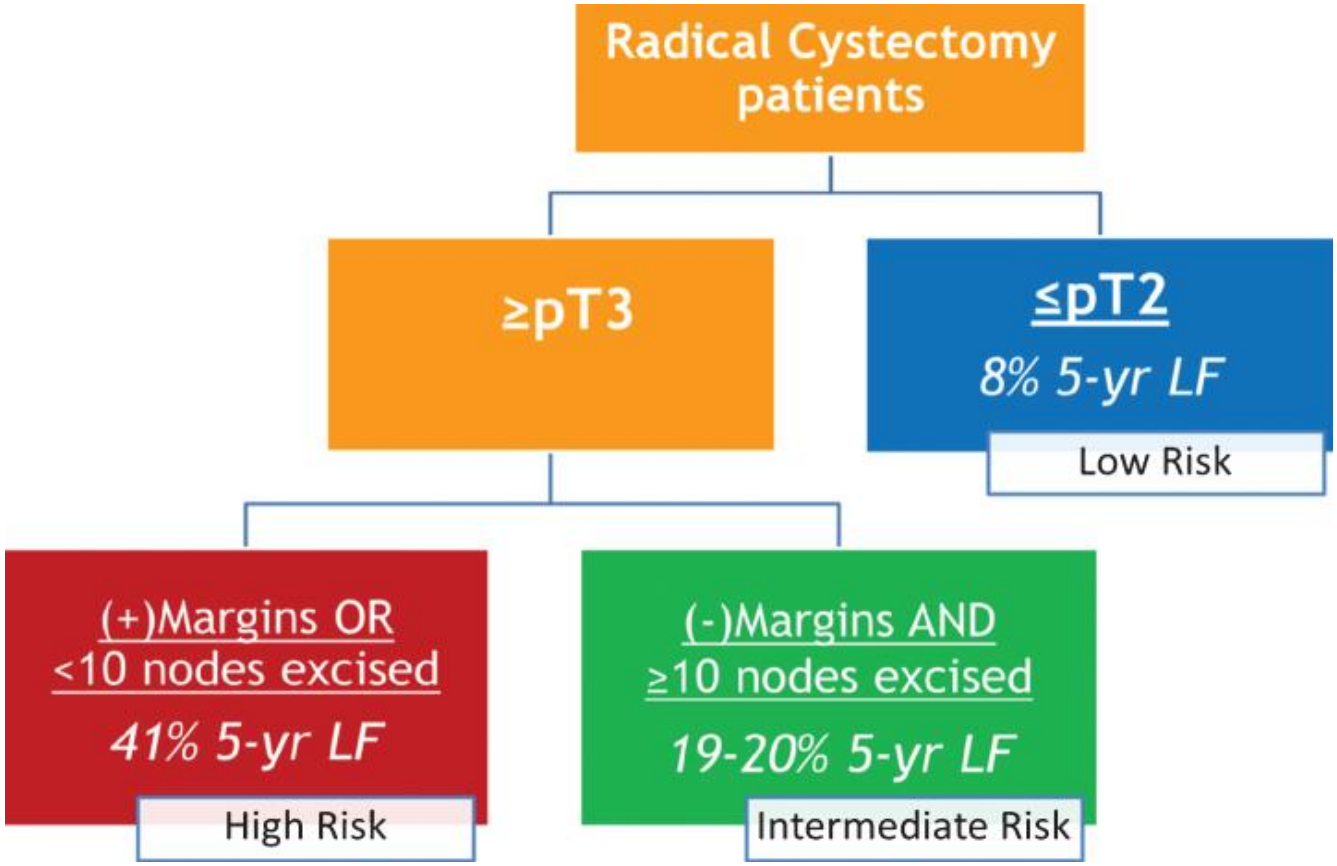
Guidelines on Muscle-invasive and Metastatic Bladder Cancer

6.4 Conclusions and recommendations for neoadjuvant chemotherapy

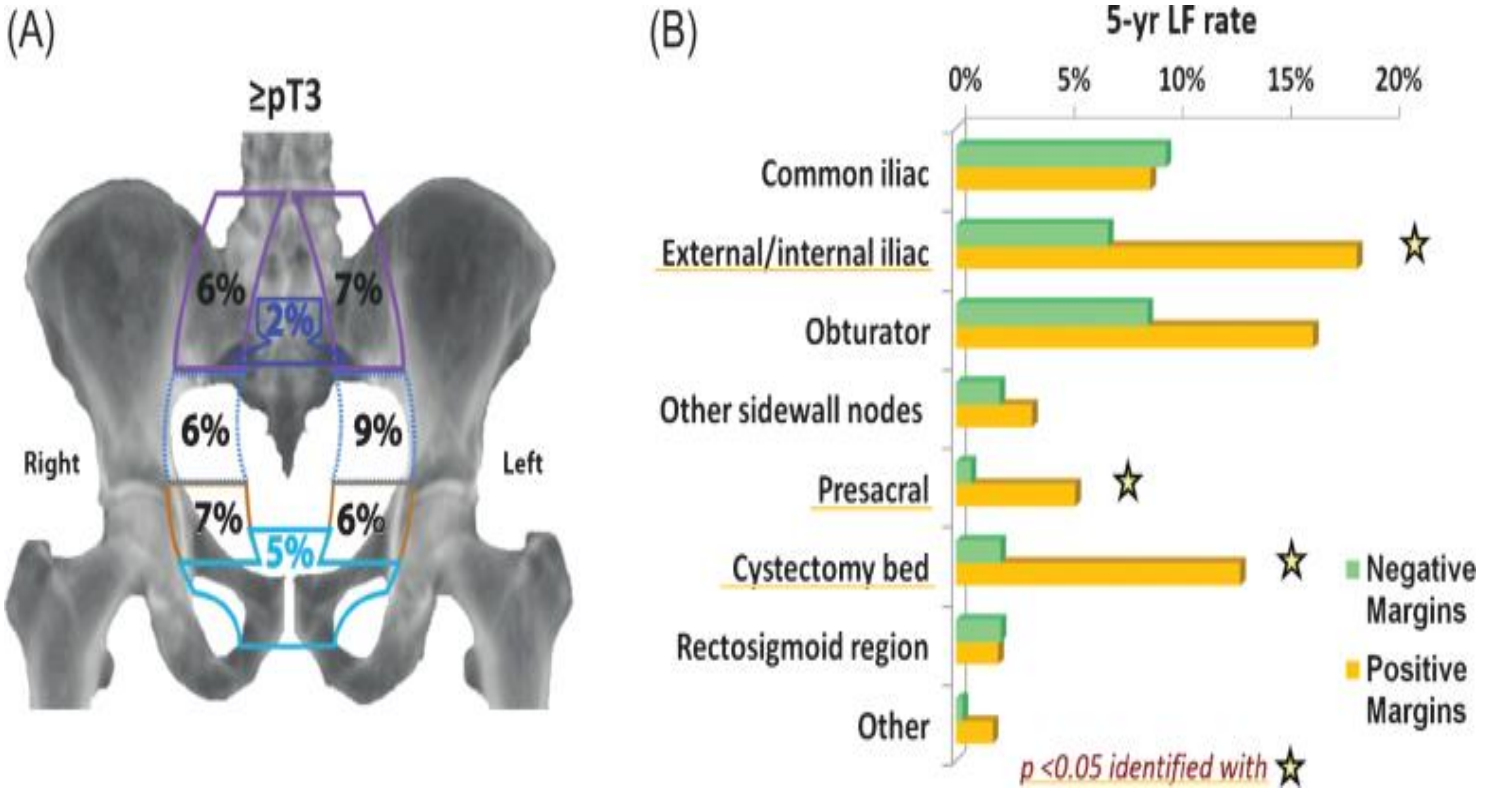
Conclusions	LE
Neoadjuvant cisplatin-containing combination chemotherapy improves overall survival.	1a

Recommendations	GR
Neoadjuvant chemotherapy is recommended for T2-T4a, cN0M0 bladder cancer and should always be cisplatinum-based combination therapy.	A

ADJUVANT RADIATION



ADJUVANT RADIATION



Risk Stratification for Local-Regional Failure After Radical Cystectomy

Brian C. Baumann[1], Jiwei He[2], Wei-Ting Hwang[2], Kai Tucker[1], Seth P. Lerner[3], Cathy M. Tangen[4], Harry W. Herr[5], Thomas J. Guzzo[6], S. Bruce Malkowicz[6], John P. Christodouleas[1]
Departments of [1] Radiation Oncology, [2] Biostatistics , and [6] Urology at the University of Pennsylvania, [3] Department of Urology, Baylor University, [4] Southwest Oncology Group, [5] Department of Urology, Memorial Sloan-Kettering Cancer Center

BACKGROUND & PURPOSE

Patients with muscle-invasive bladder cancer (stage ≥pT3) treated with radical cystectomy + pelvic lymphadenopathy (RC) with or without chemotherapy have an estimated five-year overall survival of approximately 50% (1). While considerable attention has been given to the problem of distant relapse after RC, approximately half of all recurrences occur within the pelvis, either as isolated local-regional failures (LF) or co-synchronous with distant metastases. Several organizations are now considering clinical trials to assess the impact of radiation therapy (RT) after RC. Criteria for the selection and stratification of patients most likely to benefit from adjuvant RT in these trials have not been clearly defined. A LF risk stratification model derived from a single institution has recently been published but not externally validated (2). The purpose of this study was to assess the validity of this LF stratification model within the SWOG 8710 database, a heterogeneous multi-institutional cohort of patients randomized to RC +/- neoadjuvant chemotherapy (1,3).

METHODS

Original risk stratification

The original LF risk stratification model divided patients in the development cohort into three statistically distinct risk groups based on two variables: pathologic stage at cystectomy (≤pT2 or ≥pT3) and the total number of benign or malignant nodes removed at RC (<10 or ≥10). Patients with stage ≤pT2 were found to be at low risk, those with stage ≥pT3 and ≥10 nodes removed were at intermediate risk, and patients with stage ≥pT3 and <10 nodes removed had a high risk of LF (2).

Development cohort

The development cohort included 486 consecutive patients who received RC with or without chemotherapy at the Hospital of the University of Pennsylvania (PENN) between 1990 and 2008. Of these, 44 were excluded because they lacked elements of urothelial carcinoma (37 patients) or had received radiation (7 patients), leaving 442 patients (91%) for analysis. Details of the evaluation, surgery, and pathologic review of these patients have been previously described (2) After surgery, patients were evaluated every 4 months for 2 years, every 6 months until year 5, and then annually with routine chest x-rays and biannual CT or MRI of the abdomen and pelvis.

SWOG cohort

SWOG 8710 was a randomized controlled trial comparing RC alone vs. 3 cycles of neoadjuvant MVAC chemotherapy followed by RC for patients with cT2-T4a transitional cell carcinoma with or without squamous differentiation. 317 patients were accrued between 1987 and 1998. Of these, 53 were excluded because RC was not performed (35 patients) or records were not available for review (18 patients), leaving 264 patients (85%) for analysis. Study patients were operated on by 106 different surgeons at 109 different institutions. The work-up, surgery and pathologic review have been previously described in detail (1,3). The recommended evaluation after surgery was every 3 months for the first year, every 6 months for the second year, and then yearly thereafter with chest x-rays. Abdominal or pelvic imaging was not required per protocol.

Endpoints and Statistical Analyses

The primary endpoint was LF, but overall survival (OS) and isolated distant metastases (DM) were also recorded. In both cohorts, LF was scored as any pelvic failure below the aortic bifurcation detected before or within 3 months of distant failure. Recurrence within the inguinal nodes was classified as DM. Competing risk analysis was used.

RESULTS

SWOG patients differed significantly from PENN patients in mean age, pT stage, number of nodes removed, surgical margin status, and use of neoadjuvant chemotherapy ($p<0.01$ for all comparisons) (Table 1). There was a borderline significant difference with respect to overall survival (OS) (log rank p=0.05) with 5 yr OS estimates of 42% (95% CI: 37-47%) and 49% (95% CI: 43-55%) for the development and SWOG cohorts respectively. There were no significant differences with respect to overall LF or overall isolated DM. The original risk stratification was not fully validated in the SWOG cohort which had less pronounced LF differences in ≥pT3 patients who had ≥10 versus <10 nodes removed. Fine and Gray regression was used to determine whether LF risk stratification in the SWOG cohort could be improved by the addition of one or more patient characteristics within the model. All characteristics that were significantly different between the two cohorts tested (Table 1). Regression analysis of the SWOG data suggested margin status was a more important stratifying variable than number of nodes dissected (Table 2). A revised risk stratification using pT stage, margin status, and number of nodes removed identified 3 subgroups in both SWOG and PENN cohorts with significantly different LF risk: **low-risk** (≤pT2), **intermediate-risk** (≥pT3, negative margins AND ≥10 nodes removed) and **high-risk** (≥pT3 with positive margins OR <10 nodes removed) with 5 year LF rates of 8%, 20% & 41% in the SWOG group and 8%, 19% & 41% in the PENN cohort (Figure 1-2). Gray's test $p<0.01$ and C-index was 0.7 for the risk stratification model for both cohorts. Other alternative stratifications were explored but this one was chosen because it was associated with the highest average Harrell's C index and log likelihood.

Table 1: Differences in Patient Characteristics between the SWOG cohort and the Development Cohort

Characteristic	SWOG Cohort N = 264	Development Cohort N = 264	*P*
Age (years)			
< 65	147 (56%)	192 (43%)	<0.01
≥ 65	117 (44%)	250 (57%)	
Sex			
Male	210 (80%)	348 (79%)	0.87
Female	54 (20%)	94 (21%)	
Histology			
Pure TCC	214(81%)	369 (83%)	0.47
TCC mixed histology	50(19%)	73 (17%)	
Pathologic stage			
≤pT2	183 (69%)	232 (52%)	<0.01
≥pT3	81 (31%)	210 (48%)	
Node status			
Negative	212 (80%)	308 (70%)	<0.01
Positive	52 (20%)	131 (30%)	
Unknown	0 (0%)	3 (<1%)	
Margin status			
Negative	215 (81%)	375 (85%)	<0.01
Positive	23 (9%)	59 (13%)	
Unknown	26 (10%)	8 (2%)	
Nodes removed			
≥ 10 nodes	136 (52%)	336 (76%)	<0.01
< 10 nodes	128 (48%)	101 (23%)	
Unknown	0 (0%)	5 (1%)	
Neoadjuvant chemo			
No	134 (51%)	371 (84%)	<0.01
Yes	130 (49%)	36 (8%)	
Missing	0 (0%)	35 (8%)	
Adjuvant chemo			
No	264 (100%)	310 (70%)	<0.01
Yes	0 (0%)	98 (22%)	
Unknown	0 (0%)	34 (8%)	

Table 2: The association of SWOG characteristics with LF when controlling for the original risk stratification

Characteristic	No. of Patients	5 yr LF rate	Univariate SHR	*P* †	Adjusted SHR	*p* ‡
Age, years						
< 65	147 (56%)	15%	Ref	Ref	Ref	Ref
≥ 65	117 (44%)	17%	1.25	0.48	1.09	0.80
Pathologic stage						
≤pT2	183 (69%)	8%	Ref	Ref	N/A	N/A
≥pT3	81 (31%)	32%	4.66	<0.01		
Node status						
Negative	212 (80%)	13%	Ref	Ref	Ref	Ref
Positive	52 (20%)	27%	2.27	0.02	1.22	0.56
Margin status						
Negative	215 (81%)	10%	Ref	Ref	Ref	Ref
Positive	23 (9%)	NR	1.95	<0.01	3.44	<0.01
Unknown	26 (10%)	31%	1.47	<0.01	3.52	<0.01
Nodes removed						
< 10 nodes	136 (52%)	12%	Ref	Ref	N/A	N/A
≥ 10 nodes	128 (48%)	19%	1.69	0.10		
Neoadjuvant chemo						
No	134 (51%)	17%	Ref	Ref	Ref	Ref
Yes	130 (49%)	14%	0.73	0.32	1.01	0.99

Abbreviations: LF= local-regional failure; SHR = subhazard ratio; Ref = reference variable; N/A = not applicable because variable is included in original risk

† *P* values are univariate *P* values

‡ *P* values are adjusted *P* values

Figure 1: Revised LF Risk Stratification

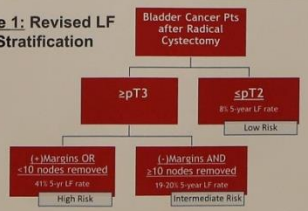
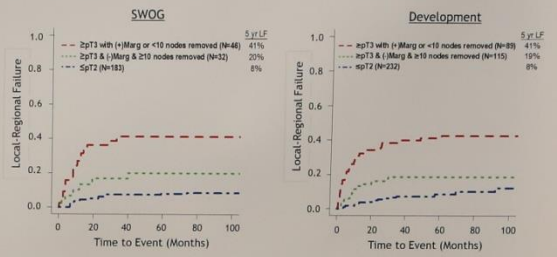
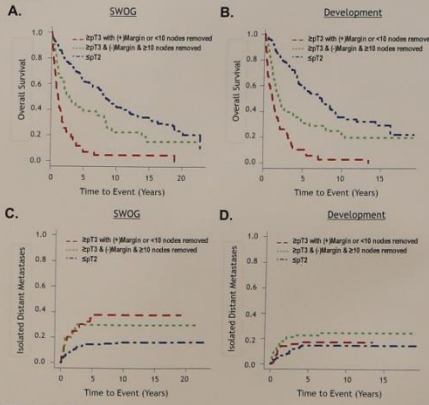


Figure 2: Risk stratification of LF in the SWOG and Development Cohorts



In order to further characterize the behavior of each risk group, we also evaluated the secondary endpoints of overall survival (OS), isolated LF, and isolated distant metastases. Within each cohort, the OS of each risk group was significantly different from the others (log rank p<0.01). The 5-yr OS estimates were 62%, 39%, and 7% for the low, intermediate, and high risk groups in the SWOG cohort (Figure 3A) and 60%, 31%, and 10% for the groups in the development cohort (Figure 3B). In contrast, the three risk groups were not consistently stratified with respect to isolated distant metastases in either the SWOG or the development cohort (Figures 3C-D).

Figure 3: Overall Survival & Isolated Distant Metastases stratified by the LF risk stratification



CONCLUSION

Incorporating margin status with pathologic stage and number of nodes dissected produced a revised risk stratification model that explained LF outcomes in both cohorts with striking similarity. In addition, the revised model identifies subgroups that also have significantly different overall survival, confirming its clinical relevance. Importantly, these subgroups do not have significantly different rates of isolated DM, which suggests that the stratification is not simply a marker of metastatic potential. Because the revised LF risk stratification rubric was developed using both cohorts, external validation in additional datasets is warranted. However, this is the first LF model to show robust stratification in two significantly different RC cohorts and may represent an important step toward developing rigorous clinical trials of adjuvant local-regional therapy.

REFERENCES

1. Grossman HB, Natale RB, Tangen CM, *et al. NEJM* 2003.
2. Baumann BC, Guzzo TJ, He J, *et al. Int J Radiat Oncol Biol Phys* 2013.
3. Herr HW, Faulkner JR, Grossman HB, *et al. JCO* 2004.

Penn Radiation Oncology

Penn Medicine

A Randomized Clinical Trial Comparing Adjuvant Radiation vs Chemo plus Radiation vs Chemo Alone after Radical Cystectomy for Locally Advanced Bladder Cancer

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Presenter: Brian C. Baumann, MD

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January 8, 2016

المعهد القومي للأورام
National Cancer Institute

Penn Medicine

PRESENTED AT: 2016 Genitourinary Cancers Symposium

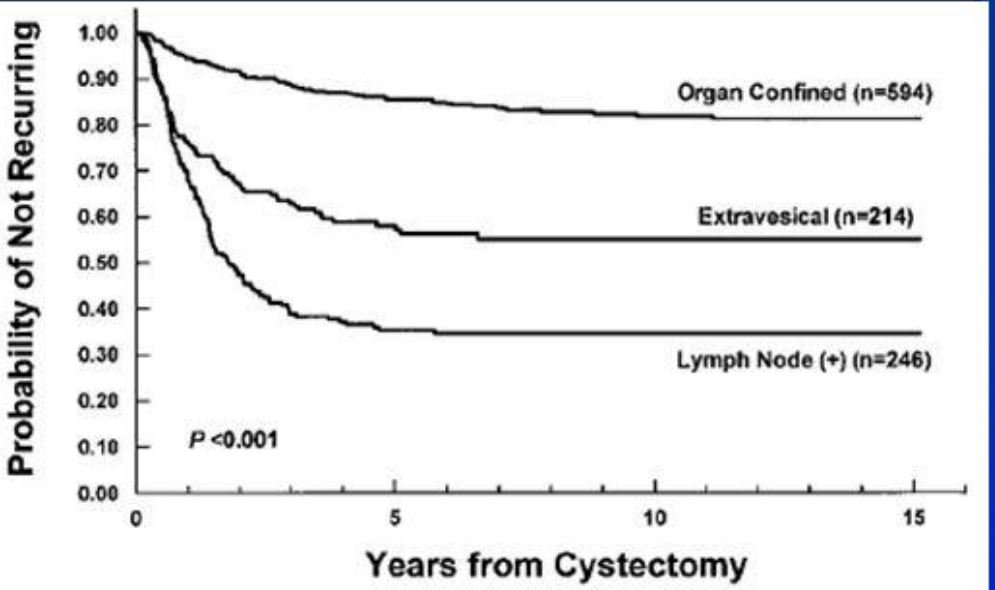
Results of radical cystectomy

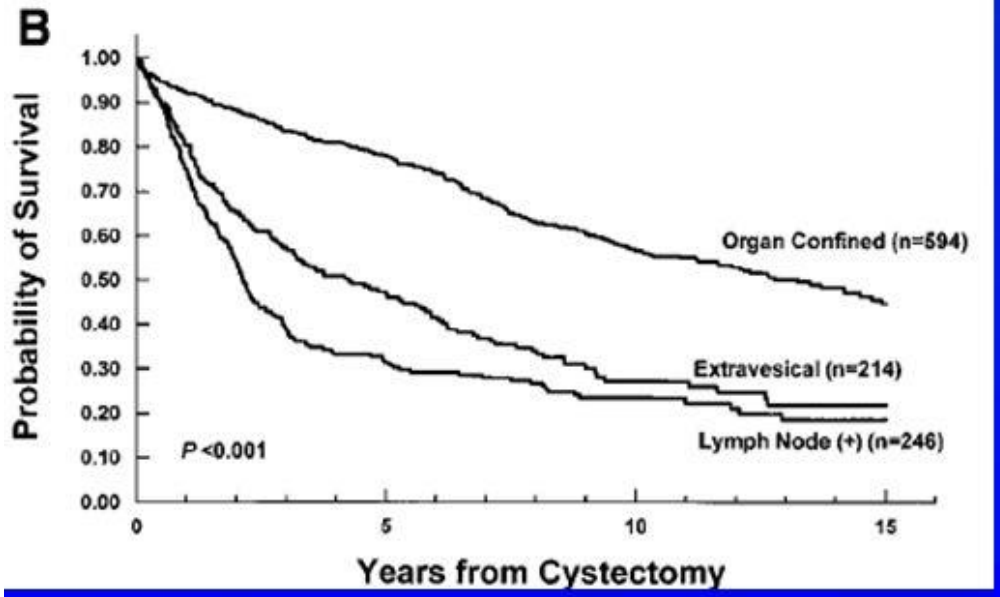
Pathologic Stage[a]	Number of Patients	Probability Overall Survival (%)	
		5 Years	10 Years
T2a N0	94	77	57
T2b N0	98	64	44
T3 N0	135	49	29
T4a N0	79	44	23
Extravesical N0	214	47	27
All node negative pooled	808	69	49
All node positive pooled	246	31	23

SELECTED DATA FROM THE UNIVERSITY OF SOUTHERN CALIFORNIA BLADDER CANCER STUDY OF RADICAL CYSTECTOMY

Radical Cystectomy in the Treatment of Invasive Bladder Cancer: Long-Term Results in 1,054 Patient JCO 2001

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 likley in OC.
- Most series- any recurrence= death.
- Even with LN+ve disease, 30% likelihood of long term survival.

Stein et al. Journal of Clinical Oncology, Vol 19, No 3 (February 1), 2001: pp 666-675

SURVIVAL DATA OF RADICAL CYSTECTOMY AND SELECTIVE BLADDER PRESERVATION

Series	Year	Category	No. Patients	Overall Survival 5-yr	Overall Survival 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%	—

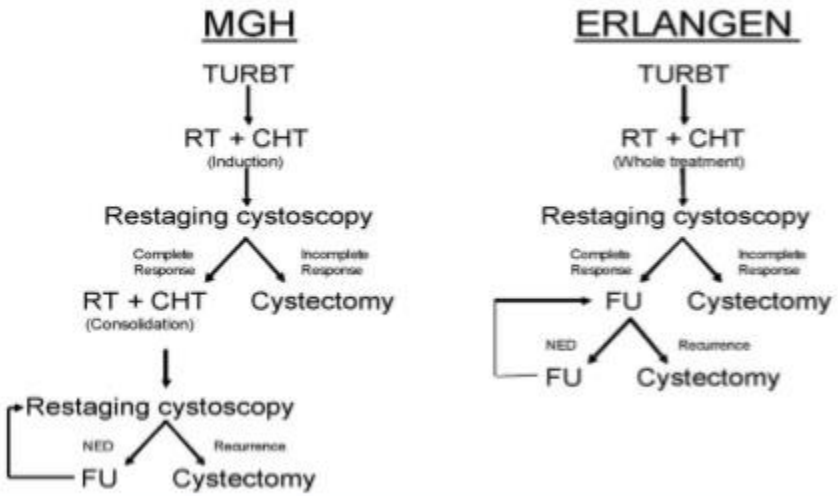
COMPARABLE

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

Trimodality Therapy

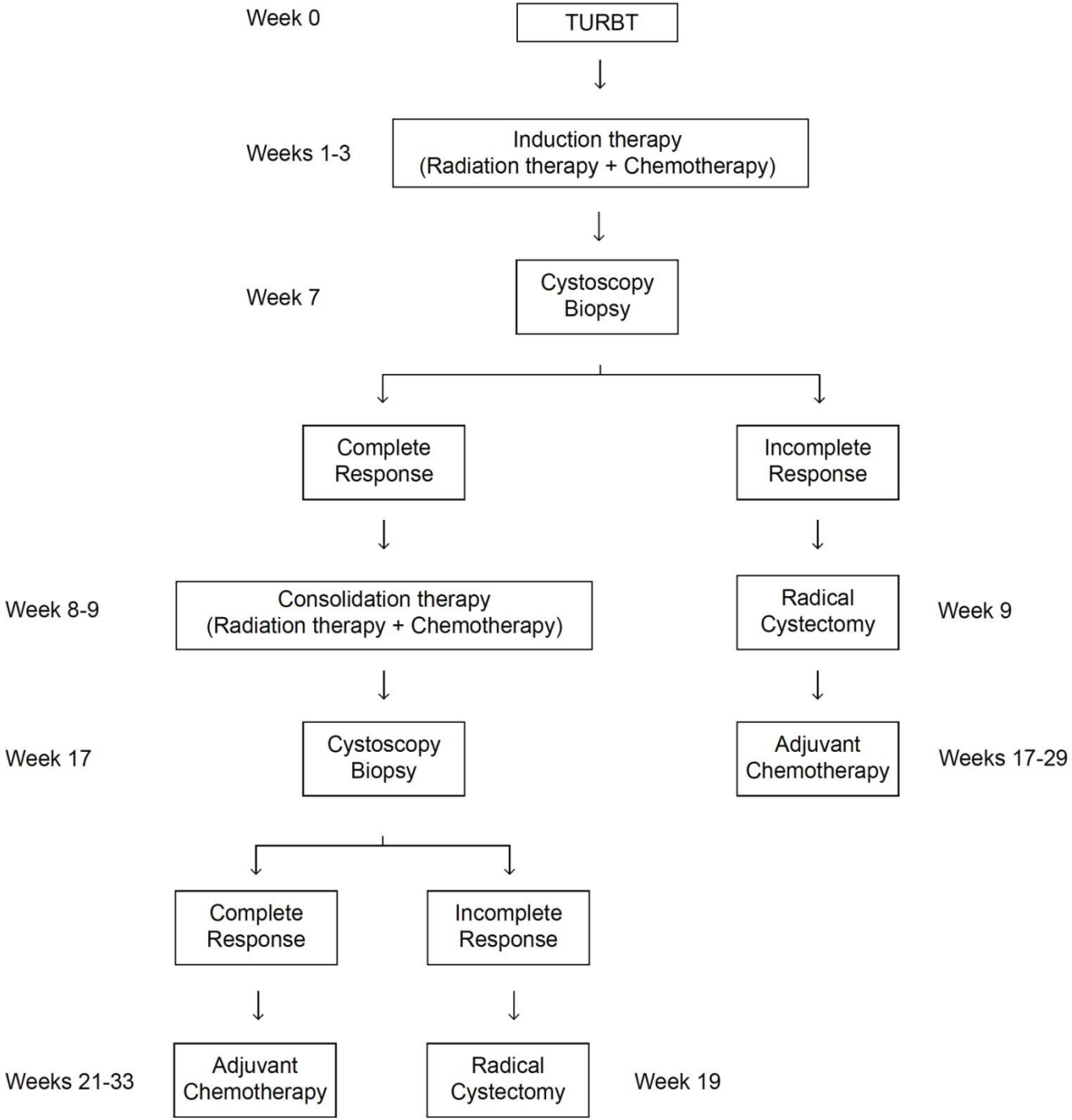
- Combination of Limited Resection, Chemotherapy, and Irradiation in Bladder Preservation
  - Best results till date in bladder preservation when the 3 modalities are combined together
  - Based on both **single institutional data** and large **randomised control trials**

PIONEERING SINGLE INSTITUTION STUDIES OF TRIMODALITY TREATMENT

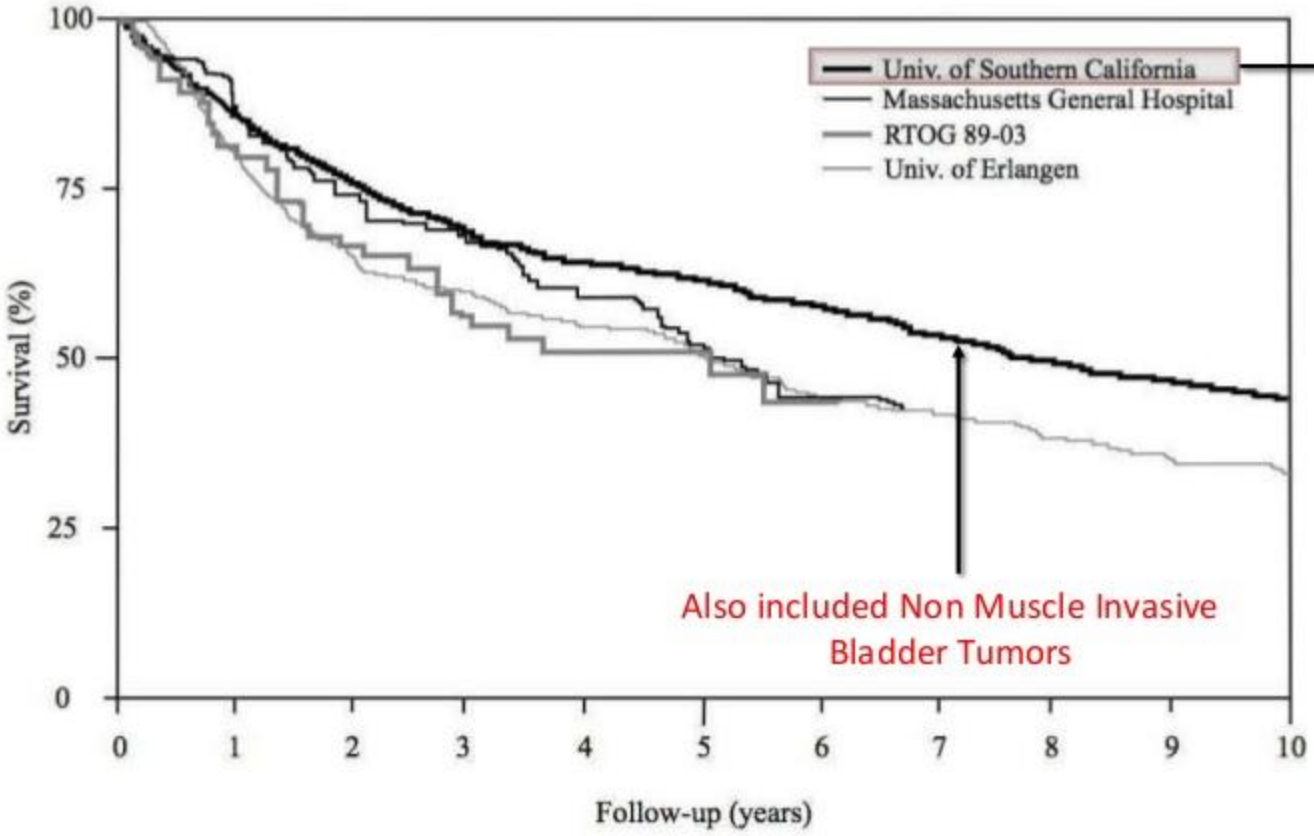


TRI MODALITY TREATMENT

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%


Week 0
TURBT
Weeks 1-3
Induction therapy
(Radiation therapy + Chemotherapy)
Week 7
Cystoscopy
Biopsy
Complete
Response
Incomplete
Response
Week 8-9
Consolidation therapy
(Radiation therapy + Chemotherapy)
Radical
Cystectomy
Week 9
Week 17
Cystoscopy
Biopsy
Adjuvant
Chemotherapy
Weeks 17-29
Complete
Response
Incomplete
Response
Weeks 21-33
Adjuvant
Chemotherapy
Radical
Cystectomy
Week 19

KAPLAN – MEIER GRAPH OF SURVIVAL IN MUSCLE INVASIVE BLADDER CANCER



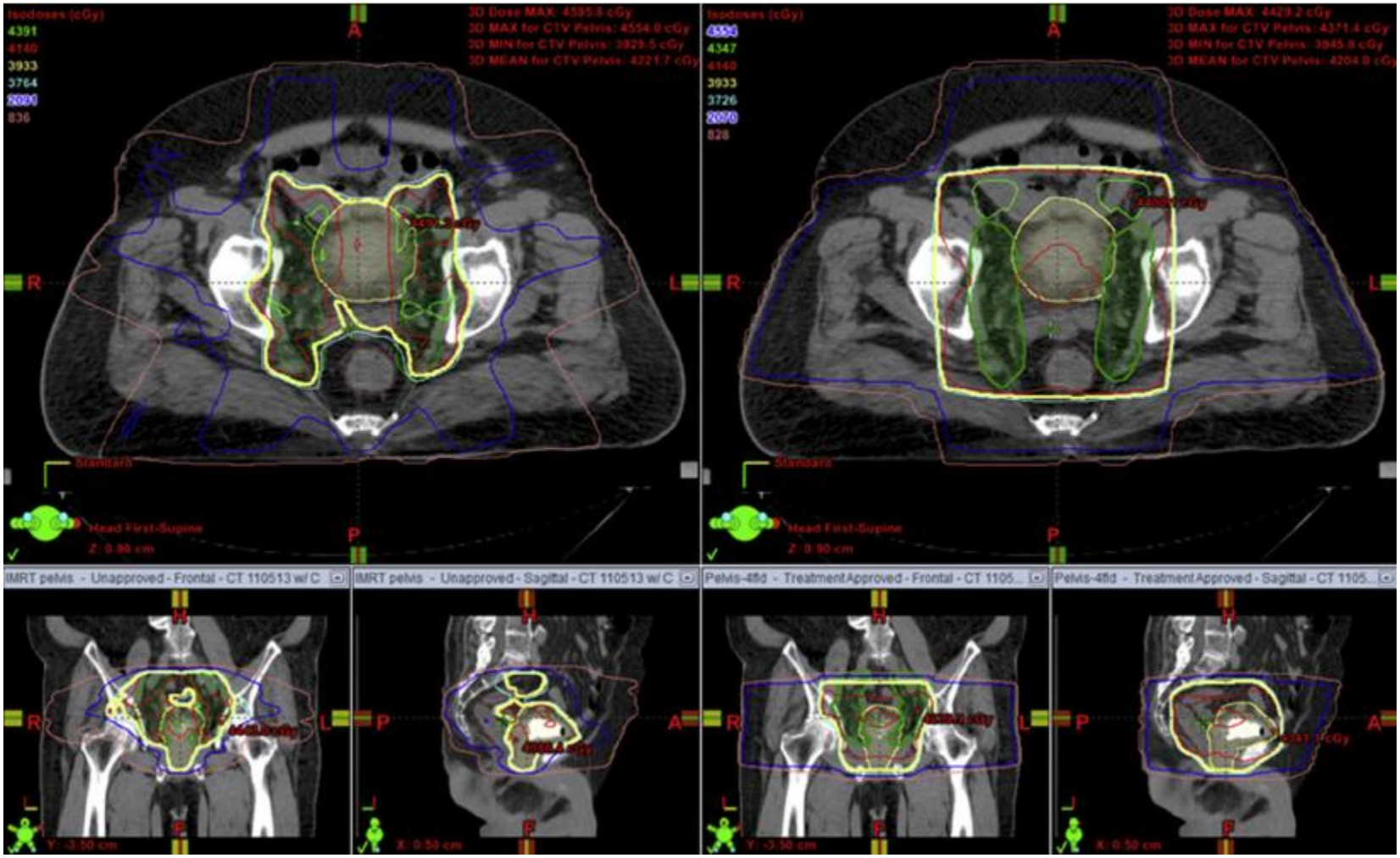
The Benefit of Radiation in Bladder Preservation

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

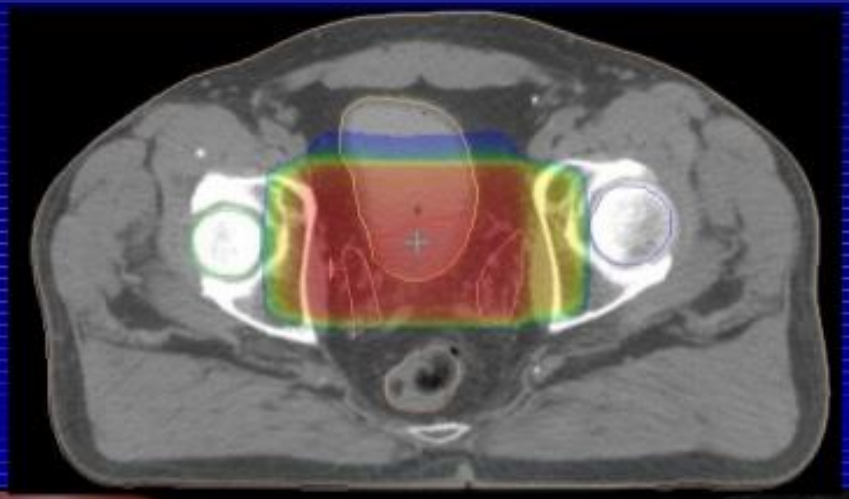
Cystectomy rate is increased by 88-125% without radiation

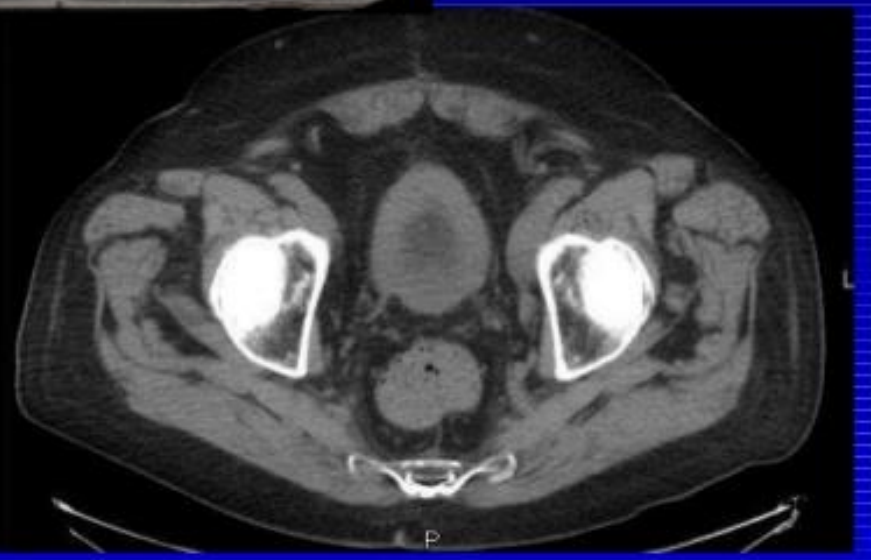
**C. Sternberg, V. Pansadora et al. Cancer 97:1644, 2003*

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


Isodoses (cGy)
4391
4140
3933
3764
2000
836
3D Dose MAX: 4595.5 cGy
3D MAX for CTV Pelvis: 4554.0 cGy
3D MIN for CTV Pelvis: 3929.5 cGy
3D MEAN for CTV Pelvis: 4221.7 cGy
Isodoses (cGy)
4554
4347
4140
3933
3726
2070
828
3D Dose MAX: 4429.2 cGy
3D MAX for CTV Pelvis: 4371.4 cGy
3D MIN for CTV Pelvis: 3945.8 cGy
3D MEAN for CTV Pelvis: 4204.0 cGy
Standard
Head First-Supine
Standard
Head First-Supine
IMRT pelvis - Unapproved - Frontal - CT 110513 w/ C
IMRT pelvis - Unapproved - Sagittal - CT 110513 w/ C
Pelvis-4fld - TreatmentApproved - Frontal - CT 1105...
Pelvis-4fld - TreatmentApproved - Sagittal - CT 1105...

Quality of life after chemo-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 dissatis-fied	mostly dissatisfied	unhappy	terrible
18.5%	51.7%	17.2%	9.1 %	0.8%	2 %	0.7%

Weiss et al 2005

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

Efstathiou et al J Clin Oncol 2009

What is the situation cystectomy is prefer as opposed to RT?

- CIS (RT does not treat CIS)
- Upper tract obstruction
- Inflammatory bowel disease
- Severe irritative LUTS
- Previous RT

But if significant comorbidity or preserve sexual function > RT