



# Bladder Cancer

Clinical Case Conference

# Clinical Case

- 89 yo M with gross hematuria
- Labs:
  - Chem: BUN/Cr increased **22/1.27**
  - CBC: H/H 13/36, WBCs wnl
  - UA: **>50 RBCs**, otherwise wnl
  - UCx: No growth
- Cystoscopy at OSH showed bladder tumor

# Work-up

- 3/27/12: CT urogram → 2.6x1.4 cm soft tissue mass with irregular borders at the right ureterovesical junction; moderate hydroureter and hydronephrosis (R>L); no distant mets
- 3/27/12: CT chest negative for mets
- 4/2/12: Cystoscopy with biopsy by Dr. Parsons → high-grade invasive urothelial carcinoma
- 4/26/12: TURBT → large tumor involving the bladder trigone with bilateral ureteral orifice involvement. Pathology showed high grade TCC (papillary urothelial carcinoma) with invasion of muscularis propria
- 4/26/12: bilateral ureteral stents placed

# Clinical Case

- **PAST MEDICAL HISTORY:**
  - Hypertension
  - Cholecystitis
  - TB, treated 35 years ago
- **PAST SURGICAL HISTORY:**
  - Open cholecystectomy, 1998
- **MEDICATIONS:**
  - Tamsulosin
  - Nifedipine
  - Atenolol

# Clinical Case

- SOCIAL HISTORY:
  - Immigrated to U.S. from Korea in 1976 and worked in shipyards and later, as a janitor.
  - He is married and has two adult children.
  - Patient has **never smoked**. Occ beer.
- FAMILY HISTORY: No known cancer.

# Clinical Case – CT urogram



# Epidemiology

**TABLE 64.1** 2008 UROLOGICAL CANCER INCIDENCE AND MORTALITY  
WORLDWIDE

<i>Cancer Site</i>	<i>Cases</i>	<i>All Cases (%)</i>	<i>Deaths</i>	<i>All Deaths (%)</i>
Prostate	899,102	7.1	258,133	3.4
Bladder	382,660	3.0	150,282	2.0
Kidney	273,518	2.2	116,368	1.5
Testis	52,323	0.4	9,874	0.1
All cancers	12,662,554		7,564,802	

Data from GLOBOCAN <http://globocan.iarc.fr>.

US:

- Median age at dx → 70yo
- 75% are male
- Whites 2x more than blacks or hispanics

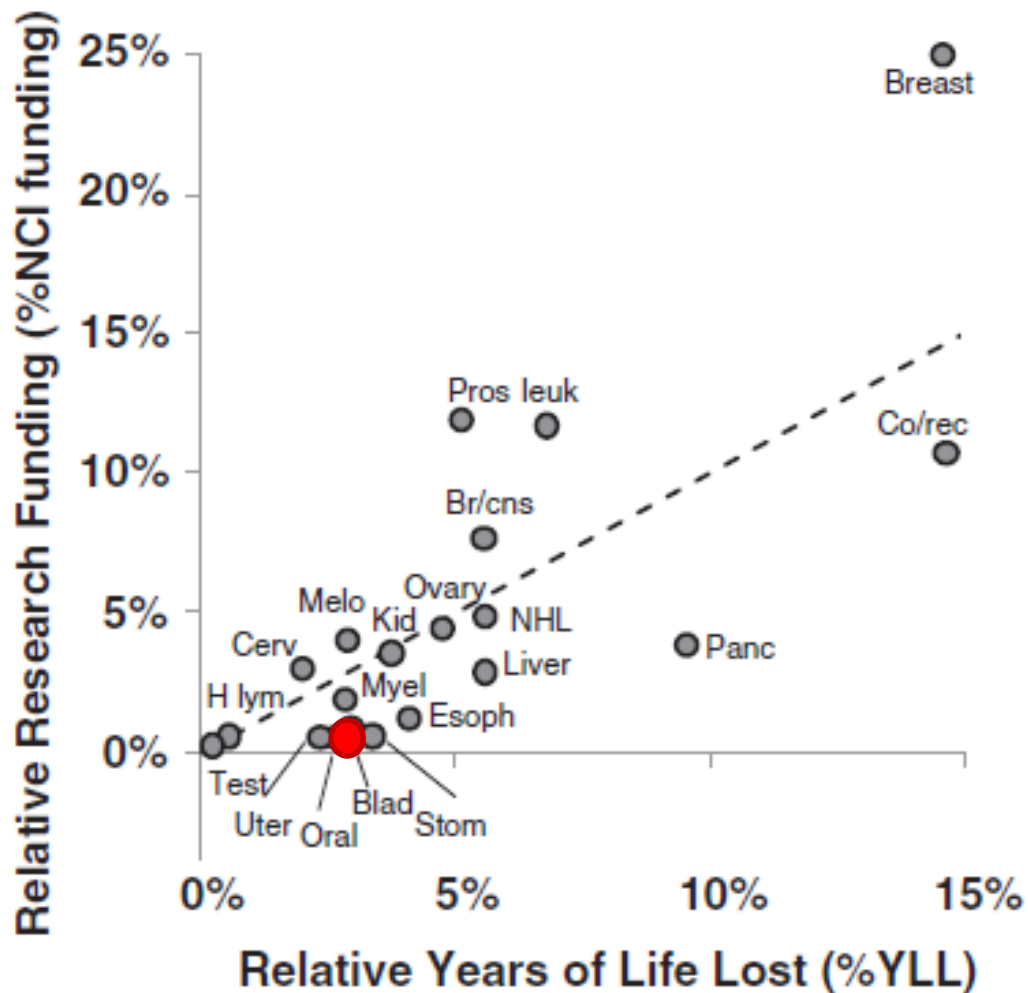
# Epidemiology

- Risk factors
  - **Tobacco smoking (esp cigarette)**
  - Aromatic amines (dyes, paints, solvents, leather dust, inks, rubber, and textiles)
  - Prior radiation therapy
  - Prior chemotherapy (Cytosin)
  - Chronic trauma (long-term indwelling catheters)
  - *Schistosoma haematobium* infection (bilharzia) in Africa, particularly in Egypt



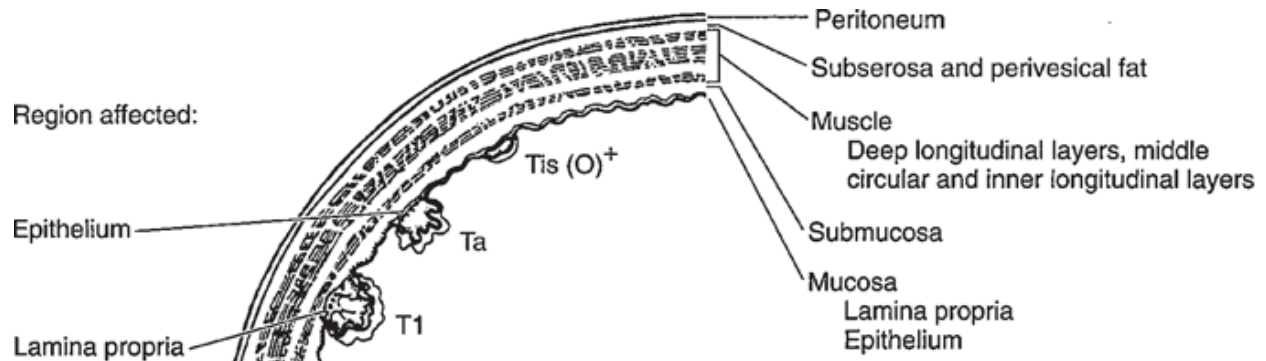
# Economics

- Bladder cancer is **underfunded**

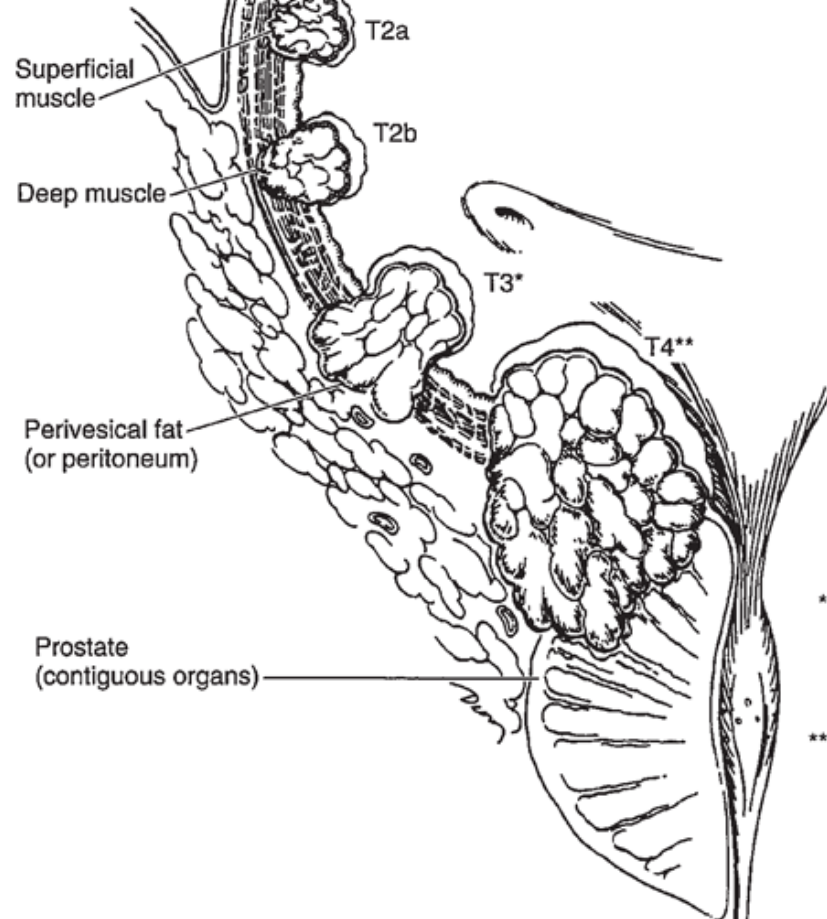


- - - funding if resources shared equitably

(Lung cancer funding is so bad it is off the chart.)



**Muscle Invasive**



- \* T3a—microscopic invasion of perivesical tissue
- T3b—macroscopic invasion of perivesical tissue (extravesical mass)
- \*\* T4a—invasion of prostate, uterus, vagina
- T4b—invasion of pelvic wall, abdominal wall

# Lymph node involvement

Overall ~20%

• pT1 5%

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• pT2-T3a 30% Muscle Invasive

• pT3b 64%

• pT4 50%

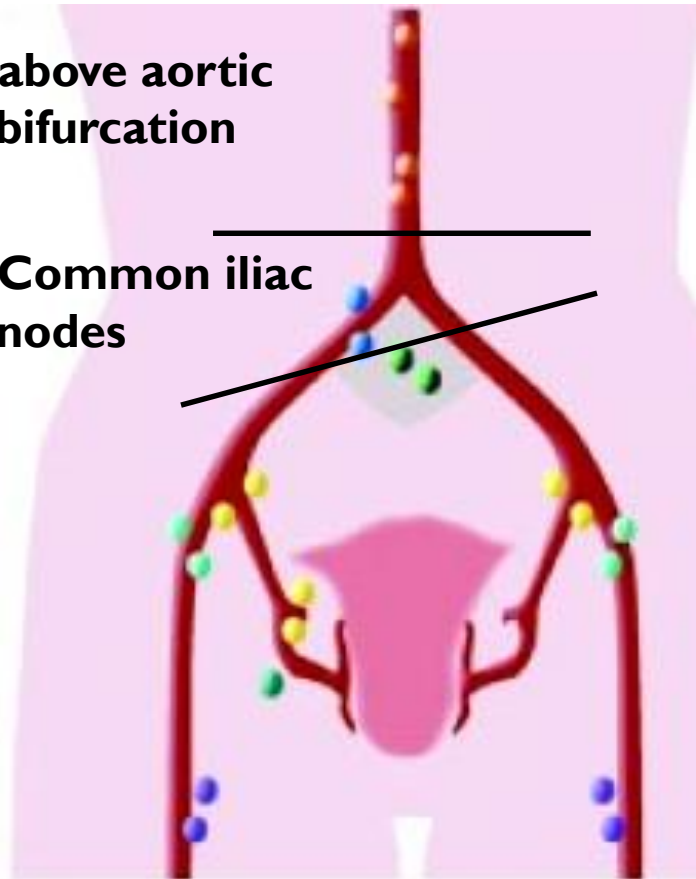
Skinner DG, et al. "High dose, short course preoperative radiation therapy and immediate single stage radical cystectomy with pelvic node dissection in the management of bladder cancer." J Urol 1982.

# N staging

**N1-N2** = Regional lymph nodes = true pelvis  
perivesical → hypogastric, obturator, external iliac, presacral

**M1** = above aortic bifurcation

**N3** = Common iliac nodes



- |                |                  |
|----------------|------------------|
| ● Aortic       | ● External iliac |
| ● Common Iliac | ● Ob durator     |
| ● Pre-sacral   | ● Internal iliac |
| ● Inguinal     | ● Hypogastric    |

# Staging – AJCC 2010 (7<sup>th</sup>)

## TNM staging system for bladder cancer

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Noninvasive papillary carcinoma
Tis	Carcinoma in situ: "flat tumor"
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades muscularis propria
pT2a	Tumor invades superficial muscularis propria (inner half)
pT2b	Tumor invades deep muscularis propria (outer half)
T3	Tumor invades perivesical tissue
pT3a	Microscopically
pT3b	Macroscopically (extravesical mass)
T4	Tumor invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumor invades prostatic stroma, uterus, vagina
T4b	Tumor invades pelvic wall, abdominal wall

# Staging – AJCC 2010 (7<sup>th</sup>)

Regional lymph nodes (N)*			
NX	Lymph nodes cannot be assessed		
N0	No lymph node metastasis		
N1	Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)		
N2	Multiple regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node metastasis)		
N3	Lymph node metastasis to the <b>common iliac lymph nodes</b>		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Anatomic stage/prognostic groups			
Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a	N0	M0
	T2b	N0	M0
Stage III	T3a	N0	M0
	T3b	N0	M0
	T4a	N0	M0
Stage IV	T4b	N0	M0
	Any T	<b>N1-3</b>	M0
	Any T	Any N	M1

Note: cTNM is the clinical classification, pTNM is the pathologic classification.

\* Regional lymph nodes include both primary and secondary drainage regions. All other nodes above the aortic bifurcation are considered distant lymph nodes.

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer New York, Inc.

# Clinical Presentation

- Painless hematuria (75%)
- UTI
- Irritative/obstructive voiding symptoms

# Workup

- 1) H&P, CBC, UA, Ucx +/- urine cytology
  - UA: RBCs, no casts
  - Urine cytology: 34% sensitive, 98% specific
- 2) Cystoscopy w/ biopsy
- 3) Upper urinary tract imaging
  - CT urography > U/S & IV pyelography
  - MRI if patient can't receive contrast



# Workup

- 4) CT/MRI abd/pelvis before TURBT
- 5) Metastatic workup (muscle invasive):
  - Chest imaging
  - Bone scan if sxs or elevated alk-phos
- PET:
  - FDG not used because conc in urine
  - $^{11}\text{C}$  choline – data is poor, difficult to use
  - $^{11}\text{C}$  acetate,  $^{11}\text{C}$  methionine under investigation

# Histology

- Urothelial carcinoma
  - Transitional cell (TCC) ... >90% in US/Europe
- Non-urothelial carcinoma
  - SCC ... 5%
  - Adenocarcinoma ... 1-2%

## Malignancy Grading of Bladder Carcinoma: Old and New Systems\*

### Modified Bergkvist 1987

### WHO 1973

### WHO/ISUP 1998 Consensus WHO, 2004

Papilloma grade 0

Papilloma

Papilloma

Papilloma with atypia grade 1

TCC grade 1

Papillary urothelial neoplasm of low malignant potential

Urothelial carcinoma grade 2A

TCC grade 1

Urothelial carcinoma, low-grade

Urothelial carcinoma grade 2B

TCC grade 2

Urothelial carcinoma, low-grade or high-grade

Urothelial carcinoma grade 3

TCC grade 3

Urothelial carcinoma, high-grade

\*From Droller MJ: Bladder Cancer, Current Diagnosis and Treatment. Totowa, NJ, 2001. With kind permission of Springer Science + Business Media, LLC.

# Natural History

- Non-muscle invasive (NMIBC)
  - 75-80% of patients
  - Most die of other causes
  - 10-20% progress to muscle invasive
- Muscle invasive
  - Leads to metastasis and death
  - 50% survival at 5yrs regardless of tx
- Metastatic
  - <10% of patients (often previously treated localized disease)
  - Lung, bone, liver most common
  - Median survival 12-18 mon

# Non-muscle invasive: Risk stratify

## EORTC Risk Tables for Predicting Recurrence and Progression in Individual Patients with Stage Ta T1 Bladder Cancer

The screenshot shows a web-based calculator interface titled "EORTC Risk Tables for Stage Ta T1 Bladder Cancer". It features several input sections: "Prior Recurrence Rate" with radio buttons for "Primary", "Recurent <= 1 per year", and "Recurent > 1 per year"; "T Category" with radio buttons for "Ta" and "T1"; "Number of Tumors" with radio buttons for "1", "2 to 7", and "8 or more"; "Tumor Diameter" with radio buttons for "< 3cm", "3-7cm", and "> 7cm"; "Grade (WHO 1973)" with radio buttons for "G1", "G2", and "G3"; and "Concomitant CIS" with radio buttons for "No" and "Yes". A "Calculate Probabilities" button is located at the bottom left. Below the input fields, there are tabs for "1 Year", "2 Years", "3 Years", "4 Years", and "5 Years". The output section displays "Probability of Recurrence" and "Probability of Progression". At the bottom, there is a reference citation: "Reference: Sylvester RJ, van der Meijden APM, Oosterlinck W, Witjes JA, Bouffouix C, Denis L, Newling DWW, and Kurth KH. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: A combined analysis of 2596 patients from seven EORTC trials. European Urology 49: 466 - 477, 2006." and "Programmed by Richard Sylvester, EORTC Data Center, 61 avenue Muelart, 1200 Brussels, Belgium. Version 1.0, January 2006."

The provided software implements the EORTC Scoring System and Risk Tables for Stage Ta T1 Bladder Cancer as published in the paper:

Sylvester RJ, van der Meijden APM, Oosterlinck W, Witjes JA, Bouffouix C, Denis L, Newling DWW, and Kurth KH. Predicting Recurrence and Progression in Individual Patients with Stage Ta T1 Bladder Cancer Using EORTC Risk Tables: A Combined Analysis of 2596 Patients from Seven EORTC Trials. *European Urology* 49: 466 - 477, 2006.

They allow the user to estimate the probability of recurrence and progression in patients with stage Ta T1 bladder cancer based on six different factors:

- Number of tumors
- Tumor size
- Prior recurrence rate
- T category
- Concomitant carcinoma in situ
- Grade

[Download the calculator](#)

(Versions are available for Windows, iPhone/iPad and Android phones/tablets)

# Non-muscle invasive: **Management**

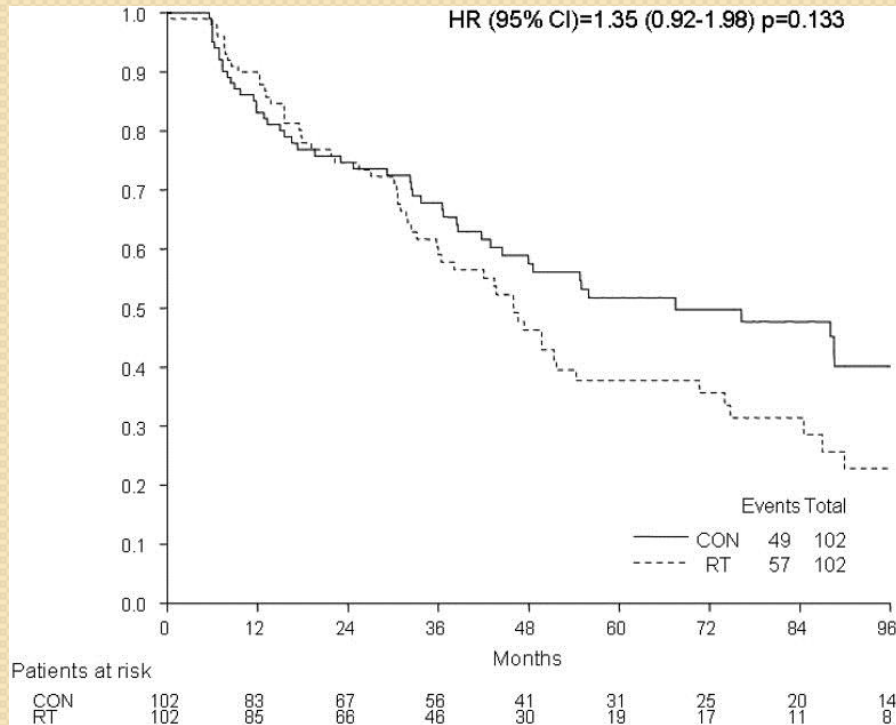
- Risk stratify (EORTC risk calculator)
- TURBT + single dose of mitomycin C and/or additional intravesical chemotherapy.
  - Intravesical Mitomycin C x1 w/in 1 hr
  - **High risk or CIS:** Intravesical BCG weekly then maintenance
- Surveillance
  - Flex cystoscopy and urine cytology
  - Frequency based on risk

# Non-muscle invasive: **XRT?**

- Multi-center randomized trial in UK
- 210 patients with pT1G3 NXM0 transitional cell
- Group 1 – unifocal disease and no Tis
  - Arm 1: TURBT + observation
  - Arm 2: TURBT + 60Gy/30 fractions (3- or 4-field) to bladder only.
- Group 2 – multifocal disease and/or Tis
  - Arm 1: TURBT + BCG or MMC
  - Arm 2: TURBT + 60Gy/30 fractions (3- or 4-field) to bladder only.

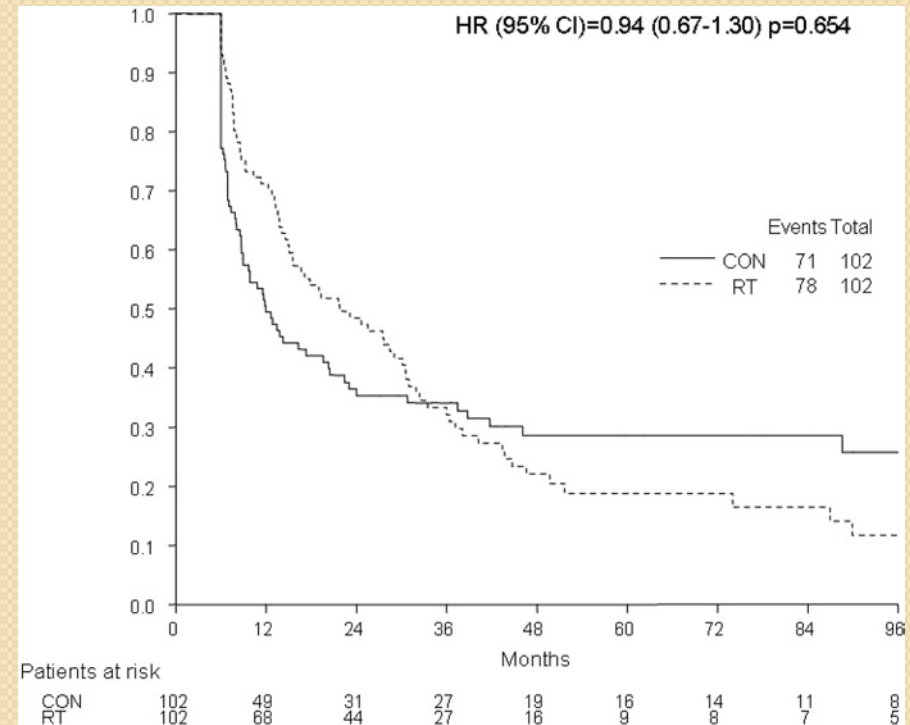
## Progression-free survival

5-year PFS: 52% in control vs.  
41% with adjuvant RT (NS)



## Recurrence-free survival

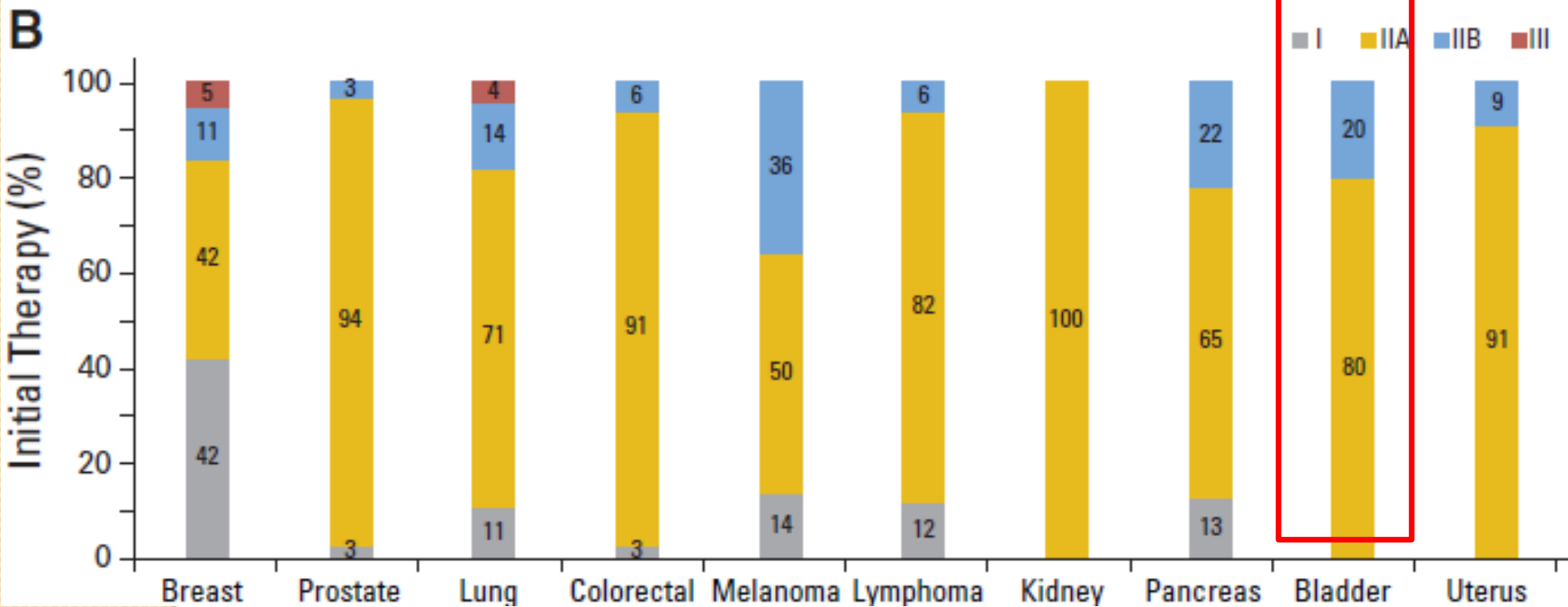
5-year RFS: 29% in control vs.  
31% with adjuvant RT (NS)



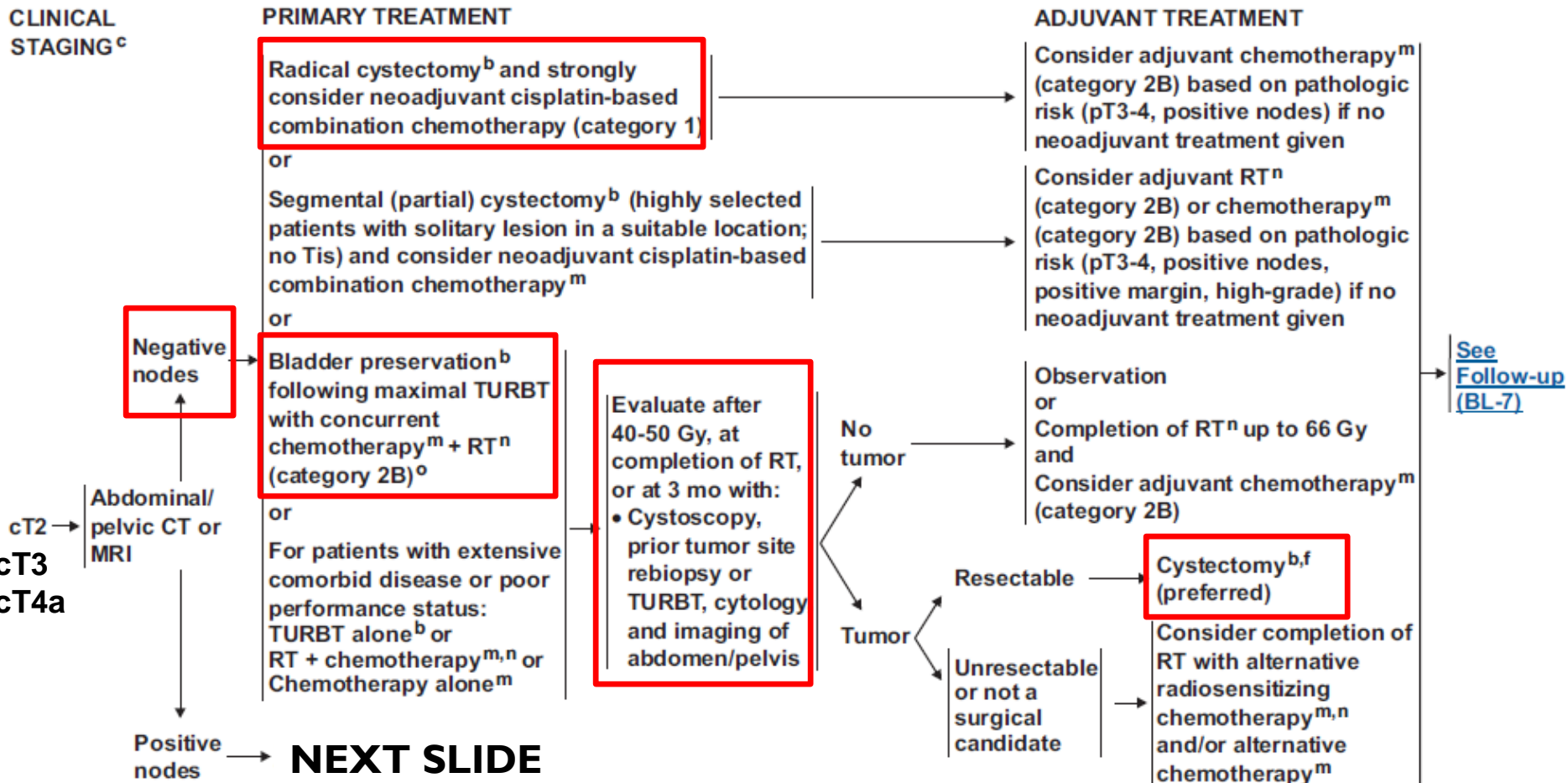
# Non-muscle invasive: No XRT

# Levels of evidence in NCCN Guidelines

➤ Category I recommendations are **the least numerous** in NCCN guidelines.







<sup>c</sup>The modifier "c" refers to clinical staging based on bimanual examination under anesthesia and endoscopic surgery (biopsy or transurethral resection)

# XRT vs. Surgery: SPARE trial

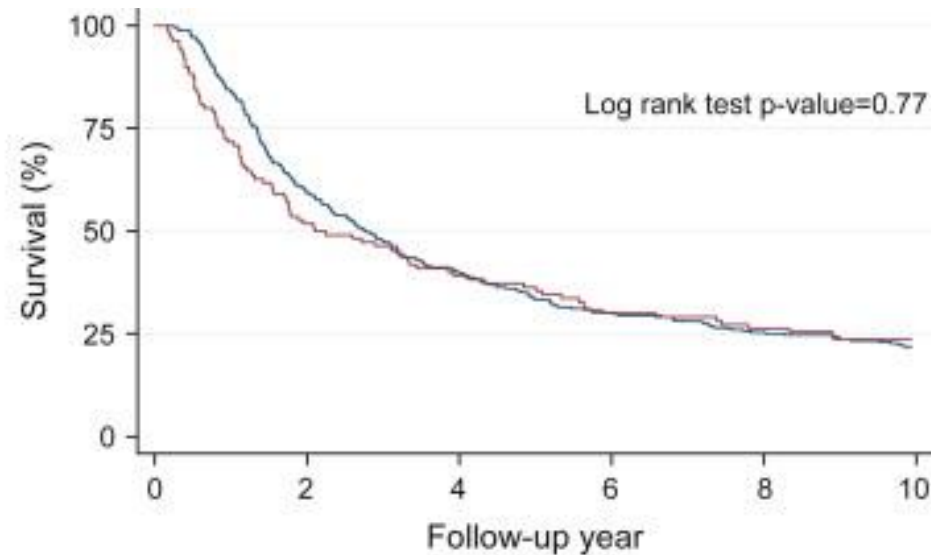
- UK SPARE Trial
- Randomized feasibility trial
- T2/T3 transitional cell carcinoma
- Opened 2007
- **CLOSED** 2009 due to poor accrual
  - (After 30 mon, only 45 patients)

# XRT vs. Surgery

- 10-year **retrospective review**, nonrandomized
- 458 patients undergoing RT or cystectomy in Yorkshire, UK
- Radiotherapy: cystectomy = 3:1
- Overall 10-year survival: 22% RT vs 24% cystectomy (NS)

Table 3. Univariable analysis Cox regression model results.

Factor	Category	HR	95% CI	p value
Treatment 0–2 y	RT	1.0		
	Surgery	1.35	0.99,1.86	0.06
Treatment 2–10 y	RT	1.0		
	Surgery	0.74	0.51,1.09	0.13



Number at risk

RT	347	206	139	105	88	70
Surgery	110	57	43	33	29	24

— RT — Surgery

# Selection Criteria

## Surgery/Cystectomy

In the US, surgery is viewed as “**standard of care**” though no evidence it is superior to RT.

*Surgery often preferred:*

- Multifocal
- Presence of Tis (esp extensive)
- Hydroureter/hydronephrosis
- Subtotal resection

## Radiation/Bladder Preservation

*“Optimal” candidate:*

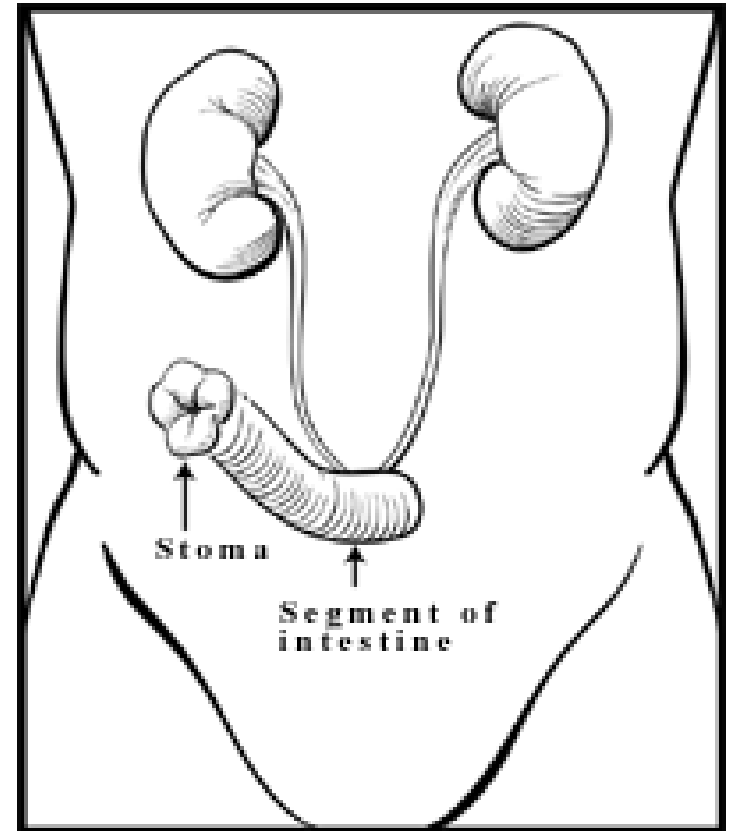
- Unifocal
- <5 cm
- **No** hydronephrosis/hydroureter
- Good bladder function
- Visibly complete TURBT

*Radiation also preferable for:*

- Older, obese, diabetic (anesthesia risk)
- Unable to function s/p cystectomy (elderly)

# Radical Cystectomy → Ileal conduit

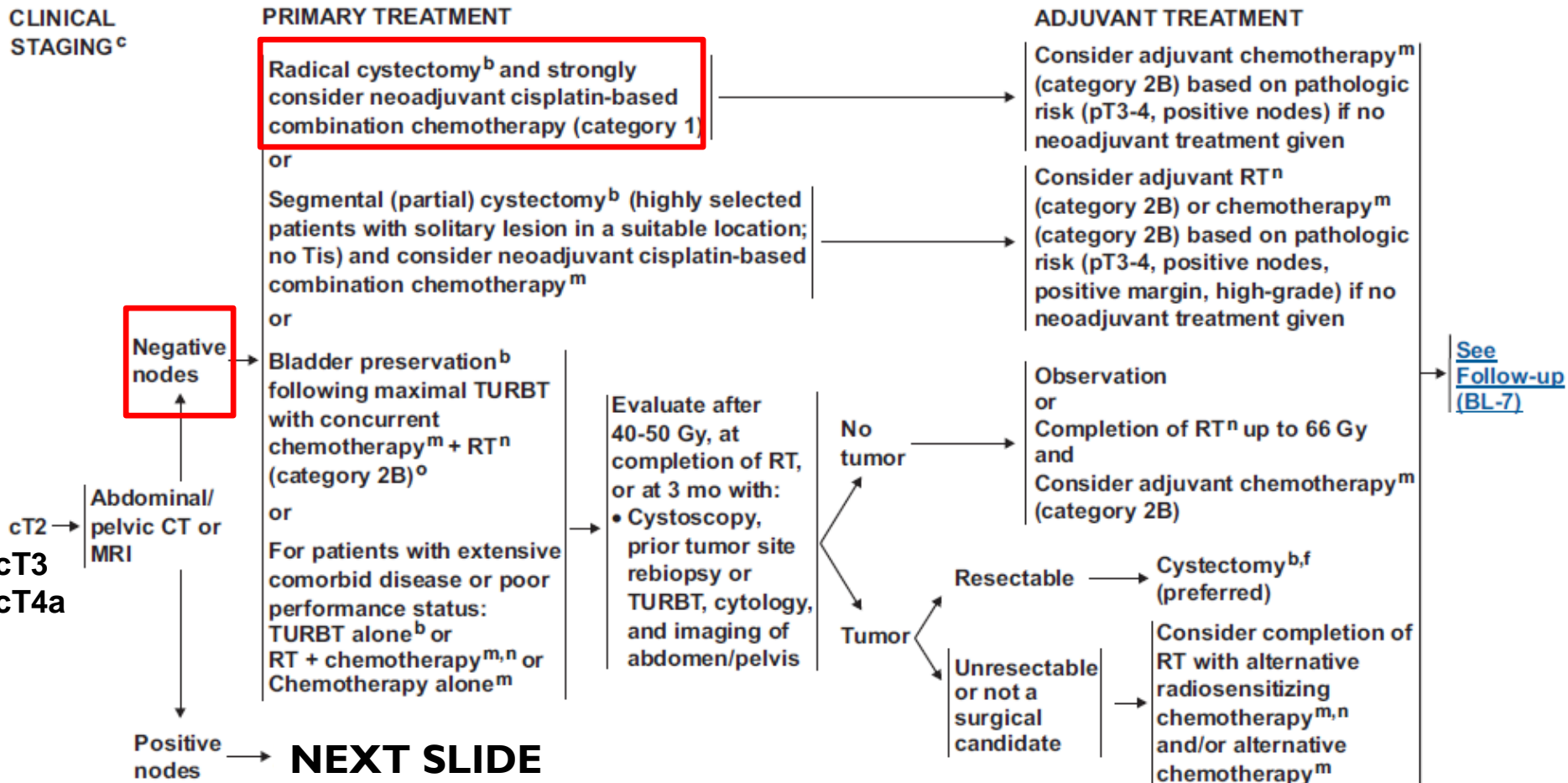
- Bladder, pelvic lymph nodes, perivesical fat, urethra
- Women: anterior wall of vagina, ovaries and uterus
- Men: prostate and SV are also taken
- **Like a long ureter to a stoma**



Ileal conduit urinary diversion

# Cystectomy → Orthotopic Neobladder

- By 2002, 50-90% of patients were getting neobladder
- Must act like a detrusor muscle
- Ileal > colon because it is distensible → less reflux, urgency, incontinence
- Mucosa adapts... absorption → protection/coating
- Disadvantages:
  - Nocturnal incontinence
  - Can take weeks to months to mature
  - Urethral recurrence?
- Relative contra-indications:
  - **Renal disease from long-standing obstruction**
  - Liver disease, IBD
  - Prior chemo-RT
  - **Elderly**



<sup>c</sup>The modifier "c" refers to clinical staging based on bimanual examination under anesthesia and endoscopic surgery (biopsy or transurethral resection)

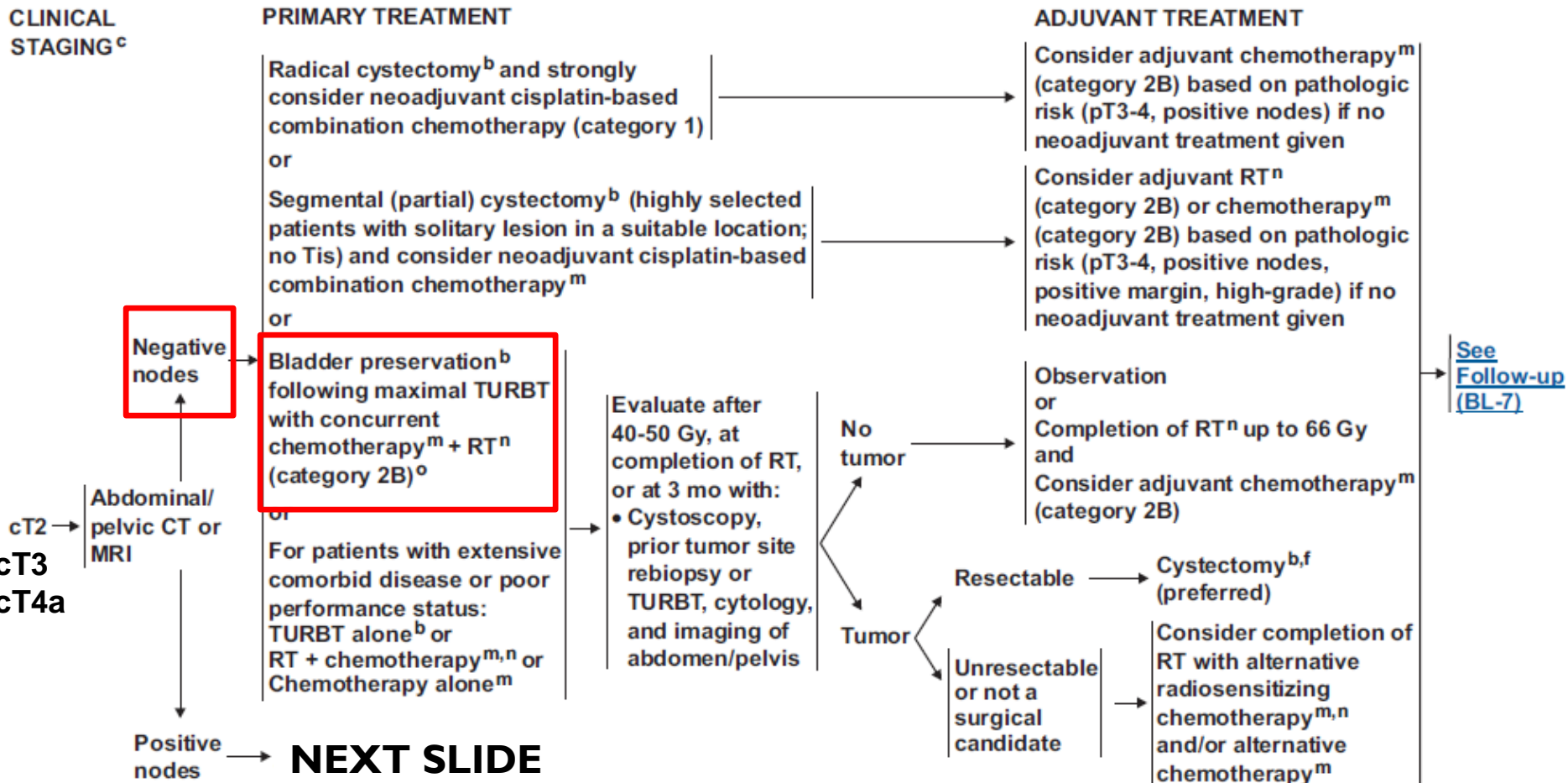
# Neoadjuvant Chemotherapy

- Neoadjuvant CMV chemo for muscle-invasive bladder cancer: long-term results of BA06 30894 trial
- Randomized phase III trial:
  - 976 patients (20 countries, led by UK)
  - T2-T4a
  - Arm 1: CMV + (XRT or Cystectomy)
  - Arm 2: No chemotherapy + (XRT or Cystectomy)
- **16% reduction in risk of death** with chemo
- Median survival 37 → 44 months with chemo



# Neoadjuvant Chemotherapy

- Meta-analyses (incl 2 large RCTs) show **5% OS benefit at 5 yrs with cisplatin-containing regimens** for patients with muscle-invasive bladder cancer
- BUT neoadjuvant chemo still **not** standard of care.



See Follow-up (BL-7)

<sup>c</sup>The modifier "c" refers to clinical staging based on bimanual examination under anesthesia and endoscopic surgery (biopsy or transurethral resection)

# Cystectomy vs. RT → salvage cystectomy

- Retrospective
- 552 patients (1970-2005)
- Christie Hospital in Manchester, UK

	# of Patients	Median Age	OS at 5yrs
Radical cystectomy	313	62.5 yo	45.5%
RT --> salvage cystectomy	239	65.5 yo	42%

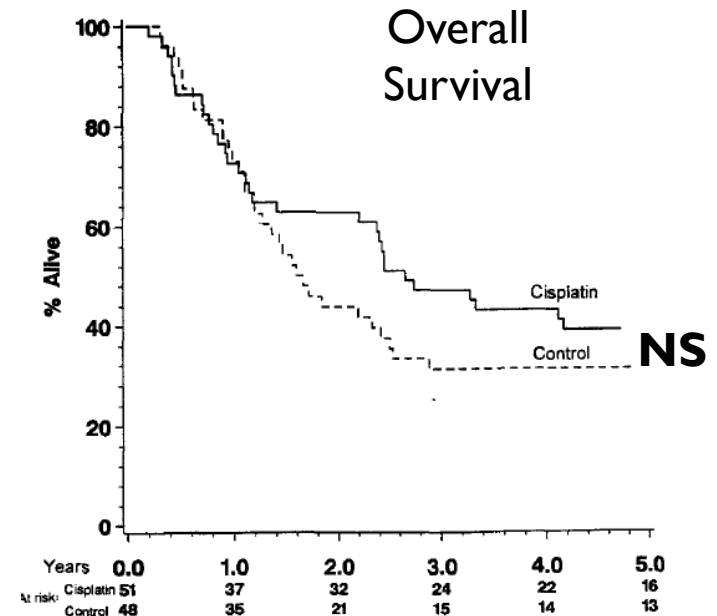
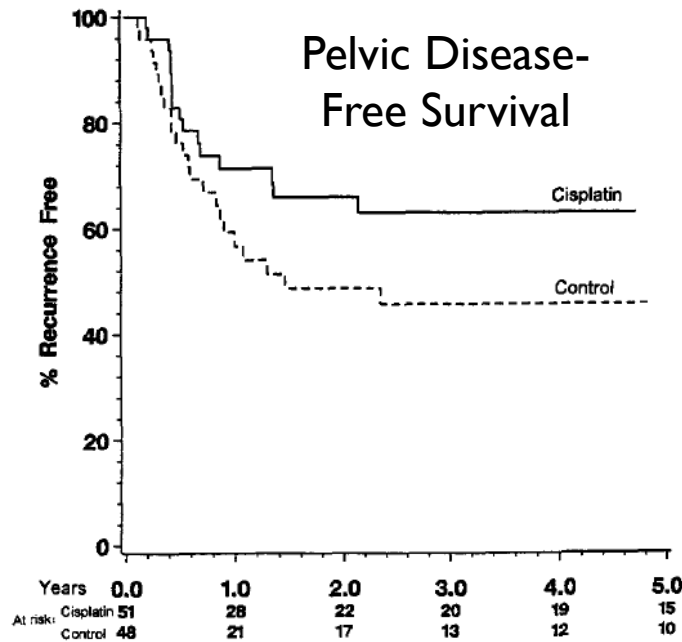
- 2/3 retained their bladder
- *Conclusion:* primary RT with salvage cystectomy does not compromise survival

# ChemoRT: NCIC randomized trial

- National Cancer Institute of Canada Clinical Trials Group
- **Prospective randomized** trial (1985-1989)
  - 99 patients with T2-T4b
  - Randomized to:
    - RT alone (40 Gy in 20 fx) or
    - IV cisplatin (3 cycles) with concurrent RT
  - Interim cystoscopy
  - Definitive therapy: RT (addtl 20 Gy in 10 fx) or cystectomy

# ChemoRT: NCIC randomized trial

- Results:
  - Pelvic failure (5-yr): Chemo-RT (40%) vs. RT (59%) (SS)
  - No difference in 3-yr OS



But then ... 1992 study in JCO MVAC >> cisplatin for metastatic bladder

# Bladder Preservation – RTOG 8802

- Neoadjuvant combined modality program with selective organ preservation for invasive bladder cancer: Results of RTOG 8802
- Phase II trial
- 91 patients
- MCV x 2 cycles + concurrent RT (39.6 Gy/22) and cisplatin.
- Follow up cystoscopy (4 weeks) and complete urologic evaluation:
  - Complete response: consolidation cisplatin-RT (25.2/14)
  - Persistent tumor: Cystectomy
- pCR 80% → 60% of these kept bladder
- Similar survival between chemoXRT and surgery

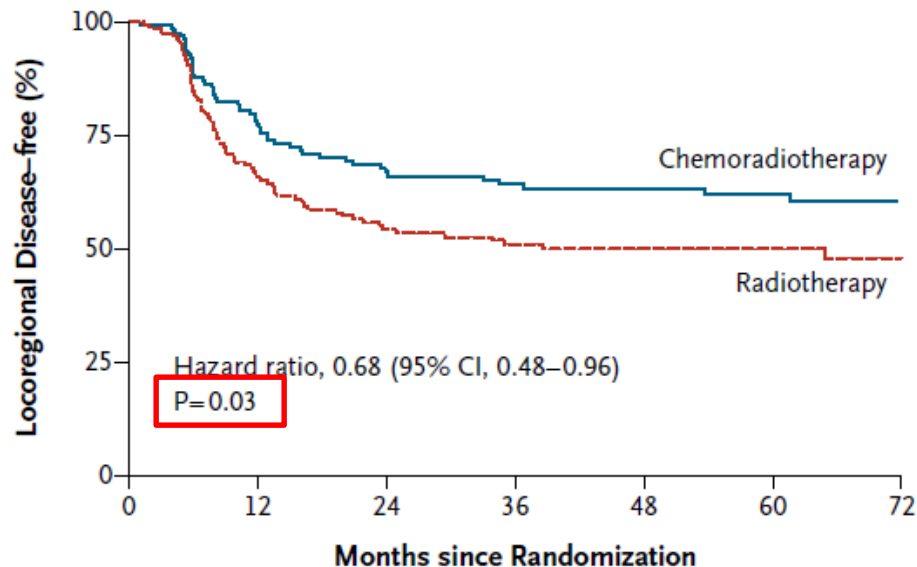
# Bladder Preservation – RTOG 8903

- 123 patients T2-4aNx s/p maximal TURBT
- **Phase III, randomized**
  - neoadjuvant MCV × 2c concurrent cisplatin × 2c + WP  
1.8/39.6 Gy vs.
  - same but no MCV
- Both restaged 4 weeks later with cystoscopy, biopsy, EUA, cytology.
- If CR, then 1.8/25.2 Gy boost (total dose 64.8 Gy) + cisplatin × 1c.
- **Stopped early due to MCV toxicity (14% died).**
- *Results: no significant change in CR, OS, or DMFS.*

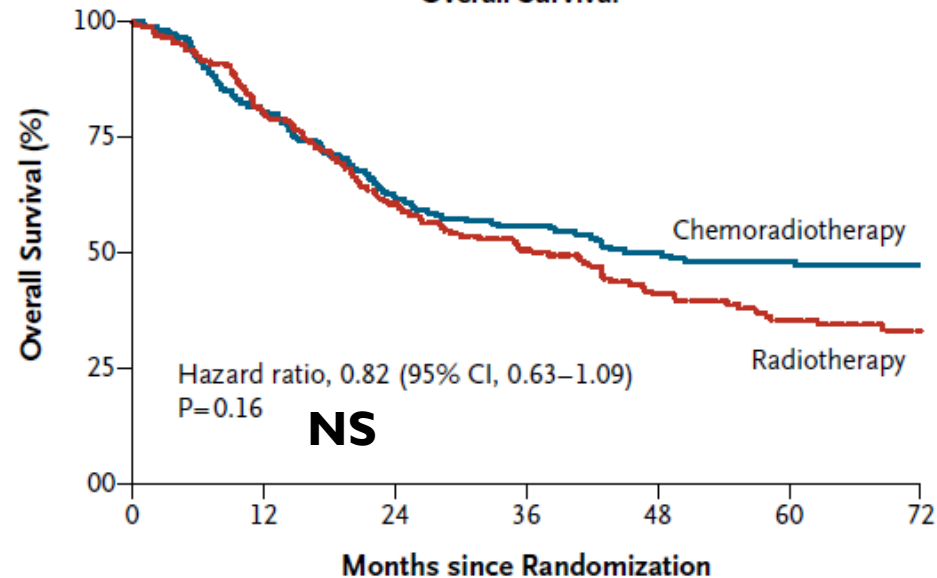
# ChemoRT

- Multicenter, phase III, randomized
- 360 patients with MIBC (T2-T4a, N0)
- RT +/- synchronous 5FU + MMC
  - 55Gy/20 or 64Gy/32

**A** Locoregional Disease-free Survival



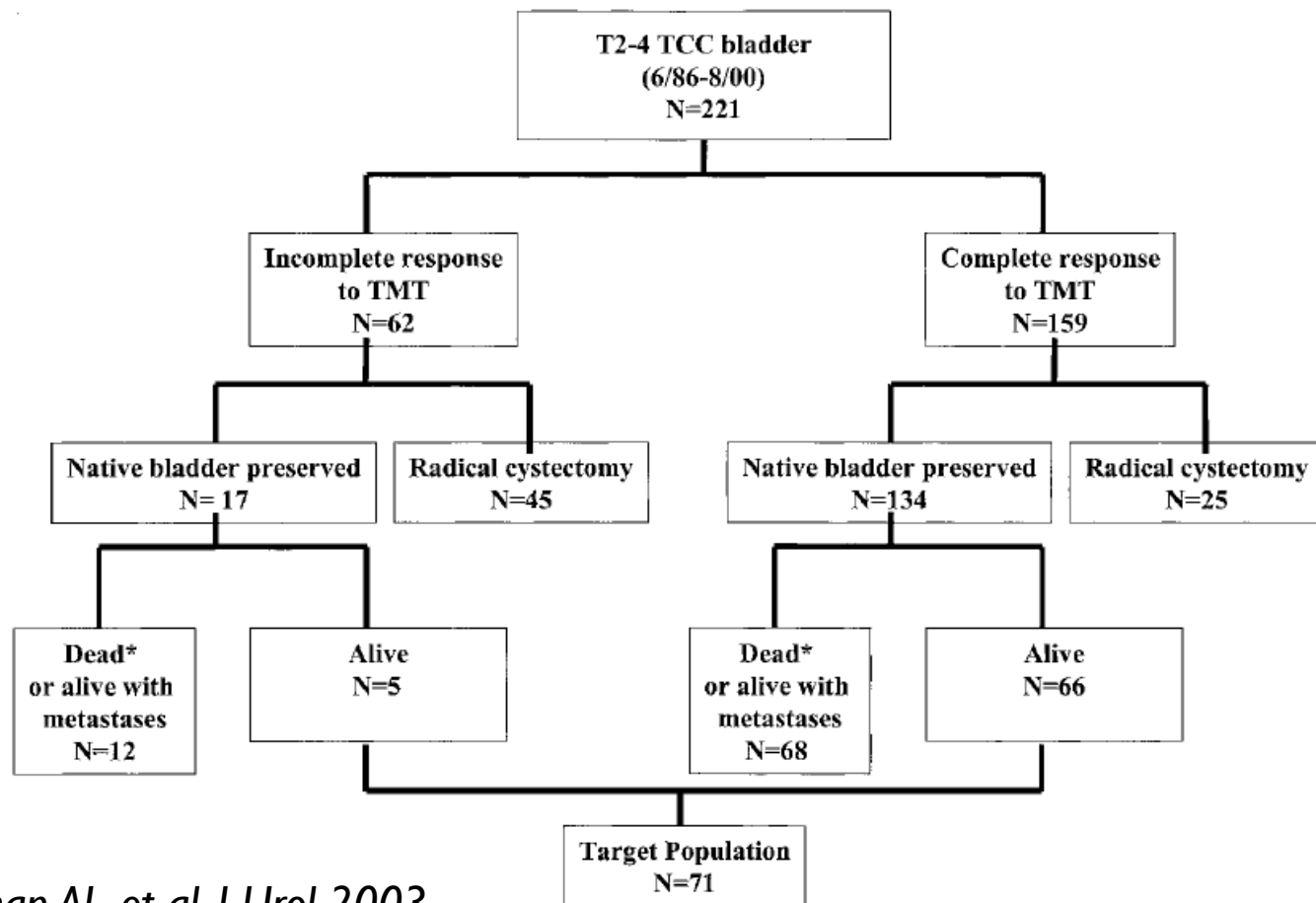
Overall Survival





# QOL after Bladder Preservation

- Long-term survivors from 1986-2000 RTOG protocols

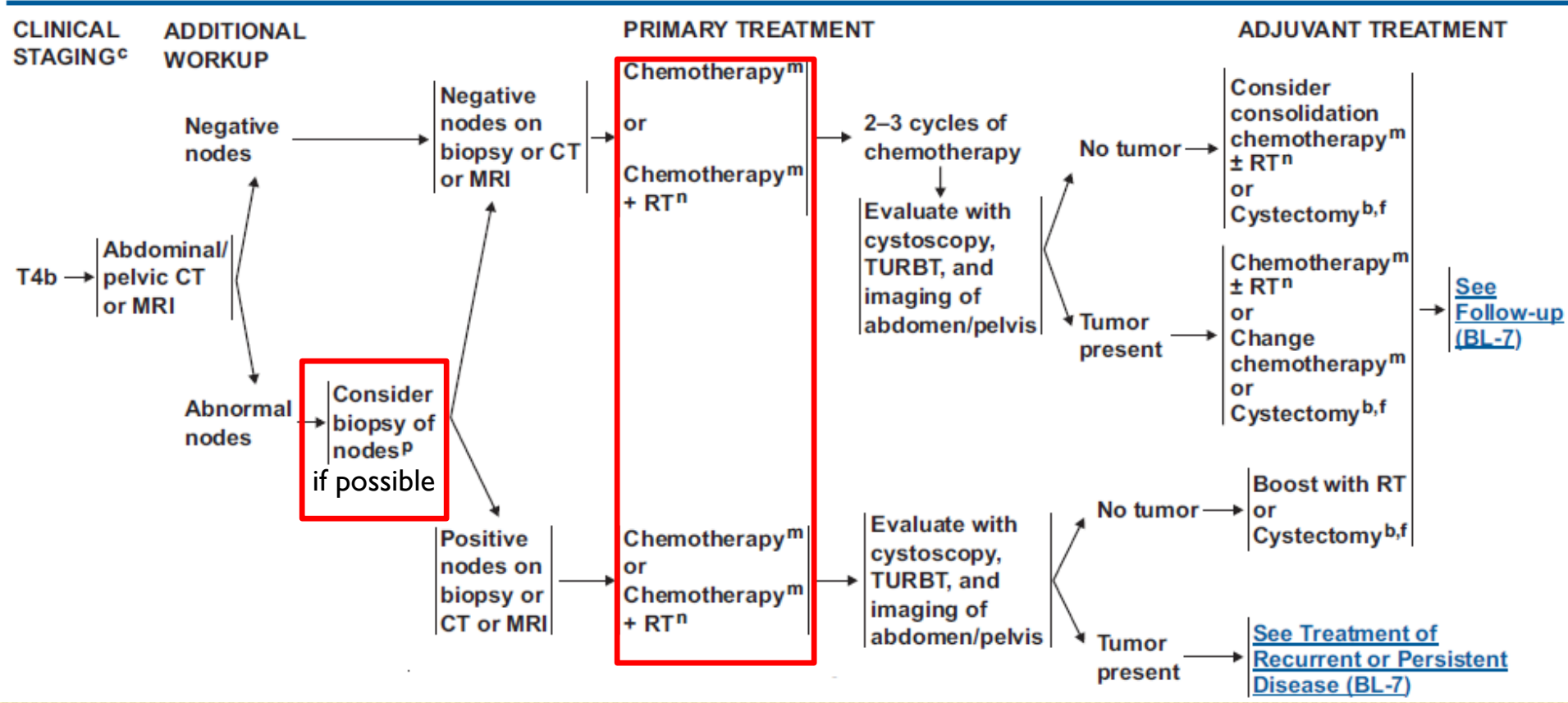


# QOL after Bladder Preservation

- Urodynamics and clinical evaluation:
  - 24 of 32 (75%) had normally functioning bladders
- Symptoms causing distress in the past week:

Symptom	No. Moderate or Greater Distress in Last Wk (%) <sup>†</sup>		
	All	Male	Female
<b>Urinary:</b>			
Difficult flow	3 (6)	3 (8)	0 (0)
Painful or burning	0 (0)	0 (0)	0 (0)
Urgency	0 (0)	0 (0)	0 (0)
Frequency	4 (9)	4 (11)	0 (0)
Leaking	1 (2)	0 (0)	1 (8)
Nocturia	12 (25)	9 (25)	3 (25)
Worry about not reaching bathroom	0 (0)	0 (0)	0 (0)
Embarrassment	2 (4)	2 (6)	0 (0)
<b>Bowel:</b>			
Diarrhea	4 (9)	3 (9)	1 (8)
Tenderness	0 (0)	0 (0)	0 (0)
Bleeding	1 (2)	0 (0)	1 (8)
Abdominal cramping	0 (0)	0 (0)	0 (0)
Mucus passed from rectum	0 (0)	0 (0)	0 (0)
Tenesmus	0 (0)	0 (0)	0 (0)
Urgency	7 (14)	6 (14)	1 (8)

# NCCN Guidelines Version 1.2013 Bladder Cancer



# Palliative RT for Bladder Cancer

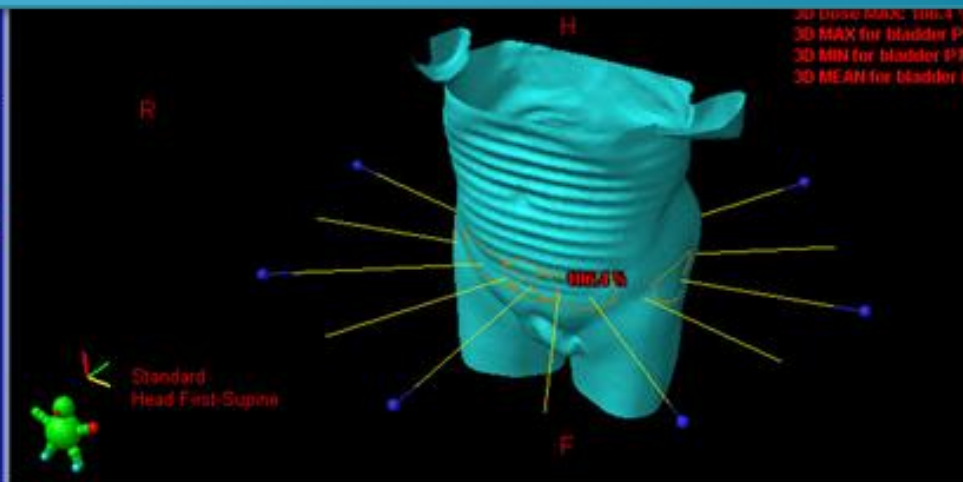
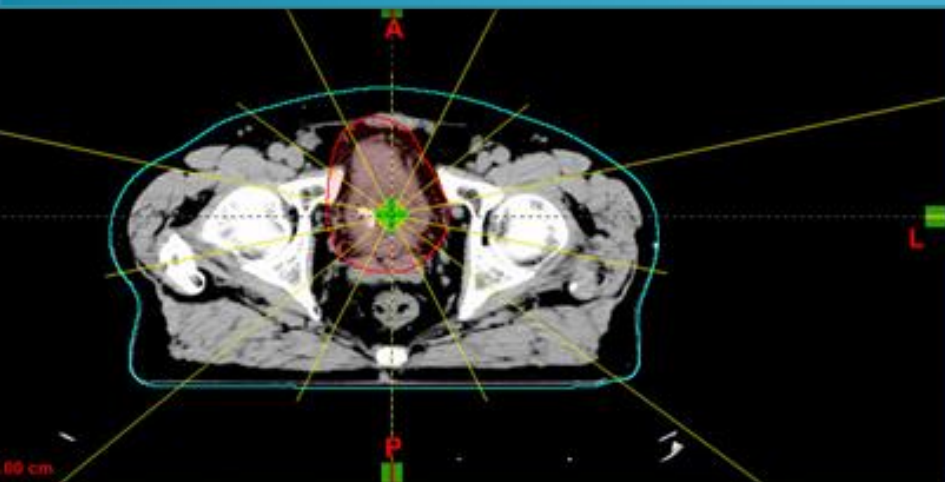
- Multicenter, randomized, prospective trial
- 500 patients recruited, 3 mon data available on 272
- 35 Gy in 10 fractions vs. **21 Gy in 3 fractions**
- Results:
  - Bladder sx improvement 71% vs. 64% (NS)
  - No difference in toxicity

# Radiation Technique

- Sim and treat with an empty bladder
- BOOST: Sim and treat full bladder
- Empty rectum
- Dose constraints:
  - Bladder 65Gy to whole bladder but up to 80Gy if 1/3 of bladder spared (QUANTEC V65<50%)
  - Rectum V50<50%
  - Femoral Heads V50<5%

# Clinical Case – RT Plan

- 50Gy/25 to whole bladder
- Tumor boost to 64 Gy (200cGyx7)
  - Partial bladder
- Daily CBCT for IGRT
- No nodal coverage



Planning Approved - Frontal - CTempty 05242012

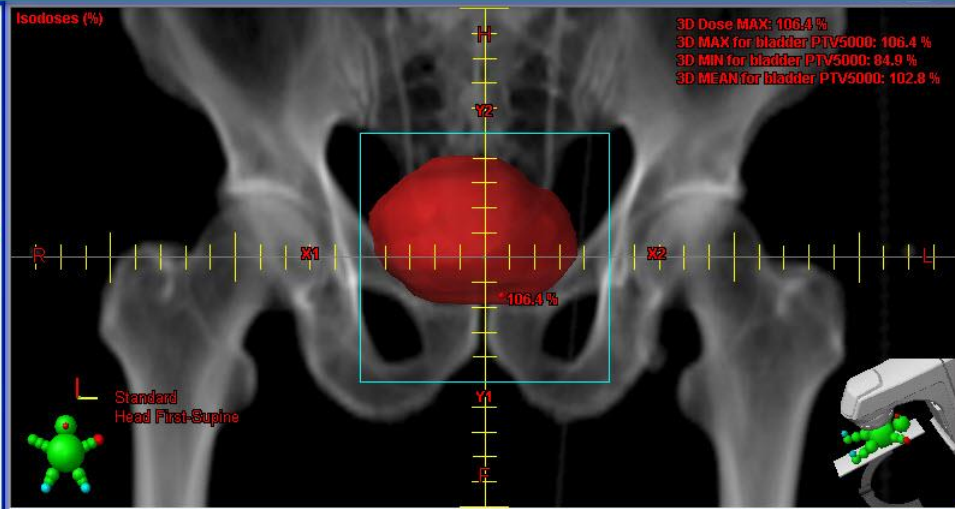
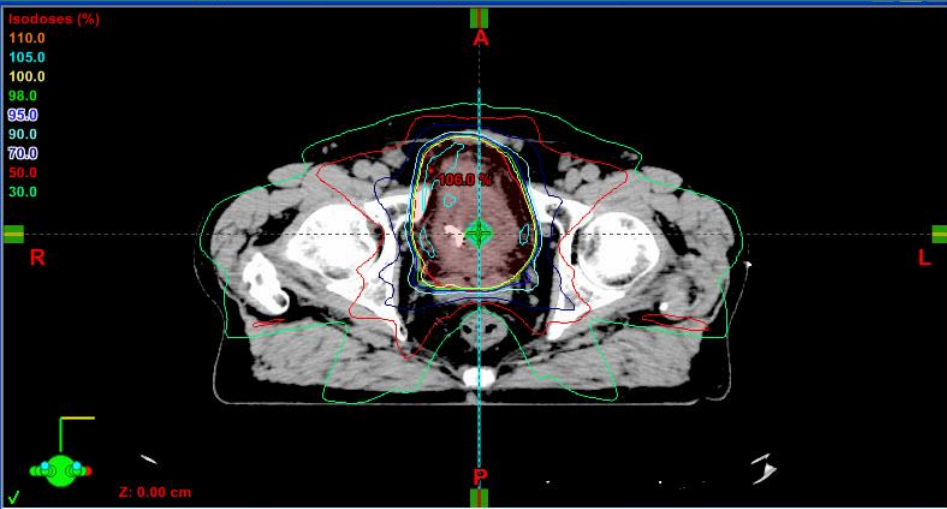
1 PTV5000 - Planning Approved - Sagittal - CTempty 05242012



Contouring Field Setup Plan Evaluation

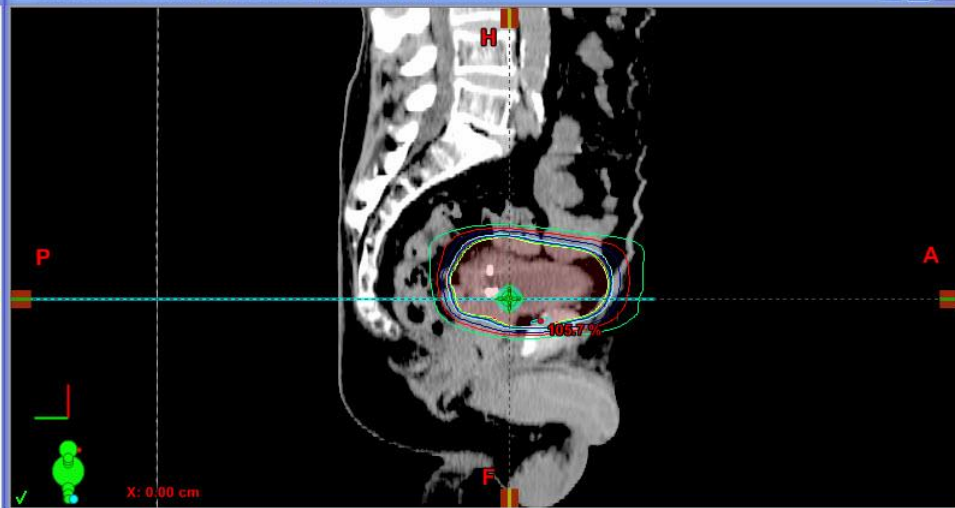
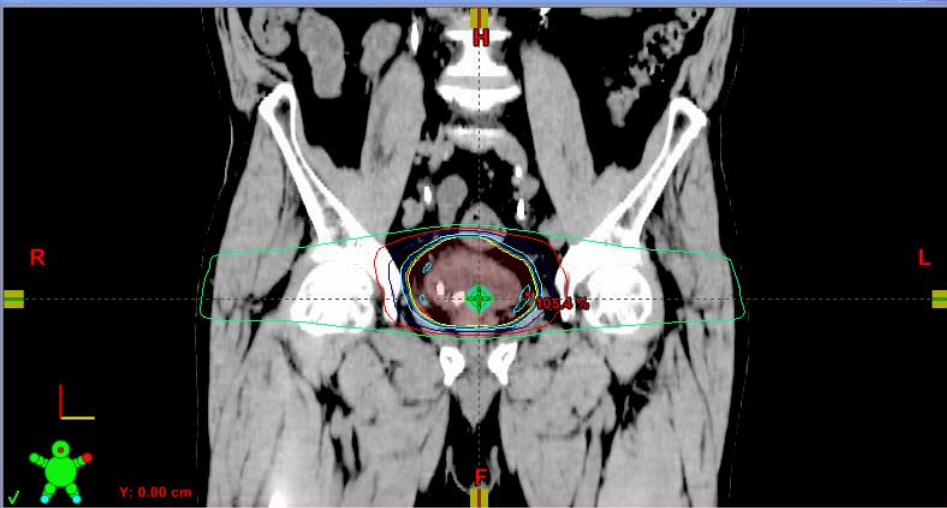
Description  Field Alignments  Plan Objectives  Optimization Objectives | Dose Statistics | Calculation Models | Plan Sum

ID	Technique	Machine/Energy	MLC	Field Weight	Scale	Gantry Rtn [deg]	Coll Rtn [deg]	Couch Rtn [deg]	Wedge	Field X [cm]	X1 [cm]	X2 [cm]	Field Y [cm]	Y1 [cm]	Y2 [cm]	X [cm]	Y [cm]	Z [cm]	SSD [cm]
53	STATIC-I	2304158 - 15X	Dose Dynamic	1.000	Varian IEC	153.0	270.0	0.0	None	8.5	+5.5	+3.0	9.0	+4.0	+5.0	0.0	0.0	0.0	87.4
02	STATIC-I	2304158 - 15X	Dose Dynamic	1.000	Varian IEC	153.0	270.0	0.0	None	8.5	+5.5	+3.0	11.2	+5.8	+4.5	0.0	0.0	0.0	87.4



1 PTV5000 - Planning Approved - Frontal - CTempty 05242012

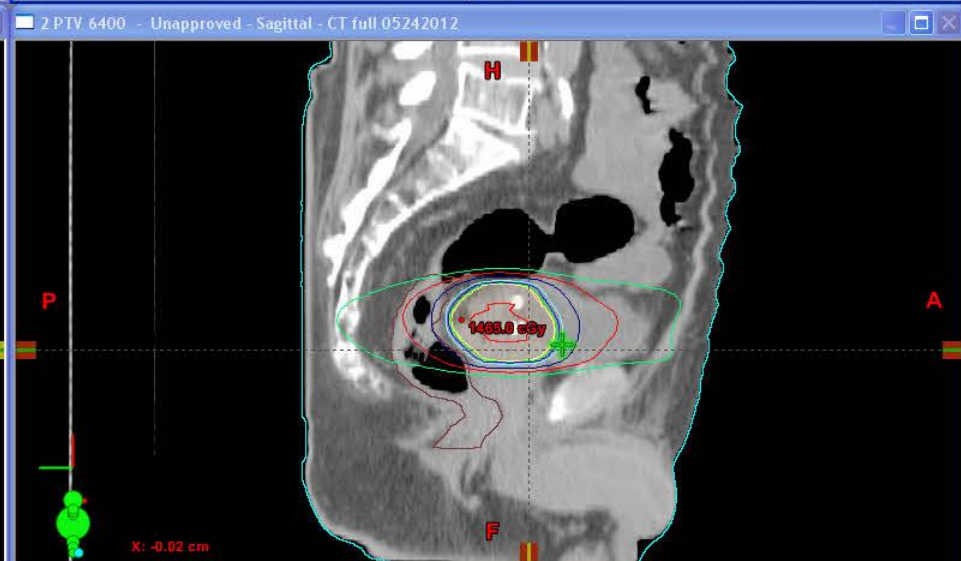
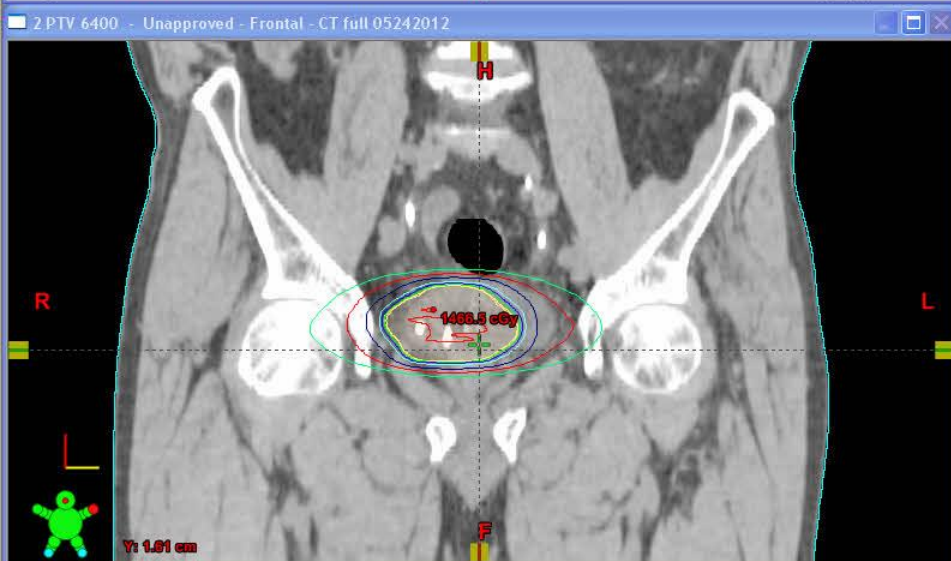
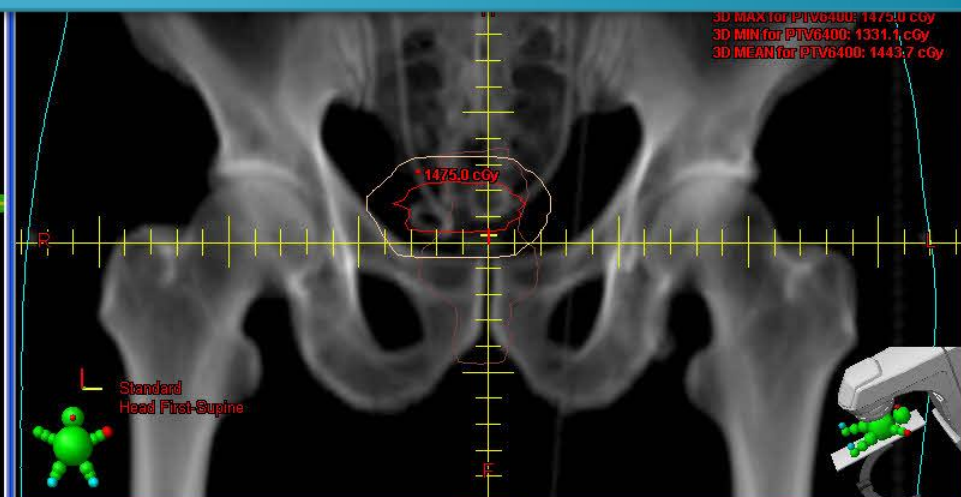
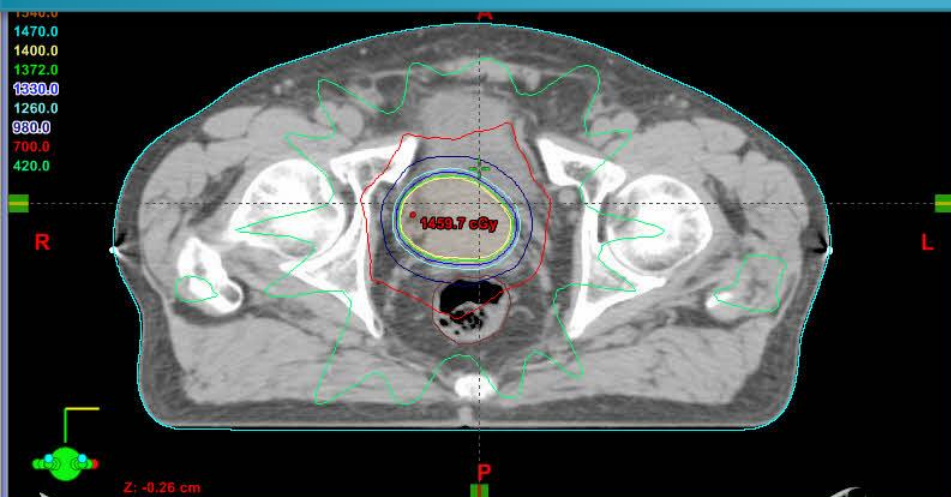
1 PTV5000 - Planning Approved - Sagittal - CTempty 05242012



Selection Registration Contouring Field Setup **Plan Evaluation**

Fields	Dose Prescription	<input type="checkbox"/> Field Alignments	<input type="checkbox"/> Plan Objectives	<input type="checkbox"/> Optimization Objectives	Dose Statistics	Calculation Models	Plan Sum	Plan Normalization Mode		Plan Normalization Value [%]
Fractionation Id	Dose / Fraction [cGy]	Number of Fractions		Total Dose [cGy]	Primary Reference Point	Total Dose at Primary [cGy]	Relative Dose at Primary [%]	Prescribed Percentage [%]	100.0% covers 95.00% of Target Volume	
F1	200.0	25		5000.0	1 PTV5000	5000.0	100.0	100.0	98.1	





Selection Registration Contouring Field Setup **Plan Evaluation**

Fields Dose Prescription  Field Alignments  Plan Objectives  Optimization Objectives Dose Statistics Calculation Models Plan Sum

Fractionation Id	Dose / Fraction [cGy]	Number of Fractions	Total Dose [cGy]	Primary Reference Point	Total Dose at Primary [cGy]	Relative Dose at Primary [%]	Prescribed Percentage [%]	Plan Normalization Mode	Plan Normalization Value [%]
F1	200.0	7	1400.0	1 PTV5000	1400.0	100.0	100.0	100.00% covers 95.00% of Target Volume	101.2

# Clinical Case – Outcome

## MOORES UCSD CANCER CENTER

- 3/x/12           onset of gross hematuria
- 3/17/12          cysto in LA-->BT
- 3/27/12          CTU/chest-->bilat hydro, R>L, BT, old TB
- 4/2/12           cysto-->high-grade UC
- 4/28/12          **TURBT**-->muscle invasive high-grade UC  
bilat stents placed
- 6/4/12           **C1D1 MMC 10mg/M2 + 5-FU 500mg/M2/day x 96 hours**
- 7/2/12           C2D1 5-FU only
- 7/18/12          **finish XRT 6400cGy to bladder**
- 9/21/12          cysto-->visual CR, stents out
- 
- 11/26/12         “He is fully functional and in good spirits!”  
– Patient’s Medical Oncologist

# Questions?

- Thank you!