Chemoradiation in Bladder Cancers: Guidelines and Evidence

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Epidemiology

- Fourth most common cancer in men and ninth most common cancer in women worldwide
- Approx. 15000 new case diagnosed each year and 50% of them die from the disease
- In India, more common in males [M:F=4:1]

* *GLOBOCAN* 2008

Staging TNM (AJCC 2010)

TABLE 52-1 AJCC 2010 TNM Bladder Cancer Staging

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

Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N2	Multiple regional lymph node metastases in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N3	Lymph node metastasis to the common iliac region

Distant Metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

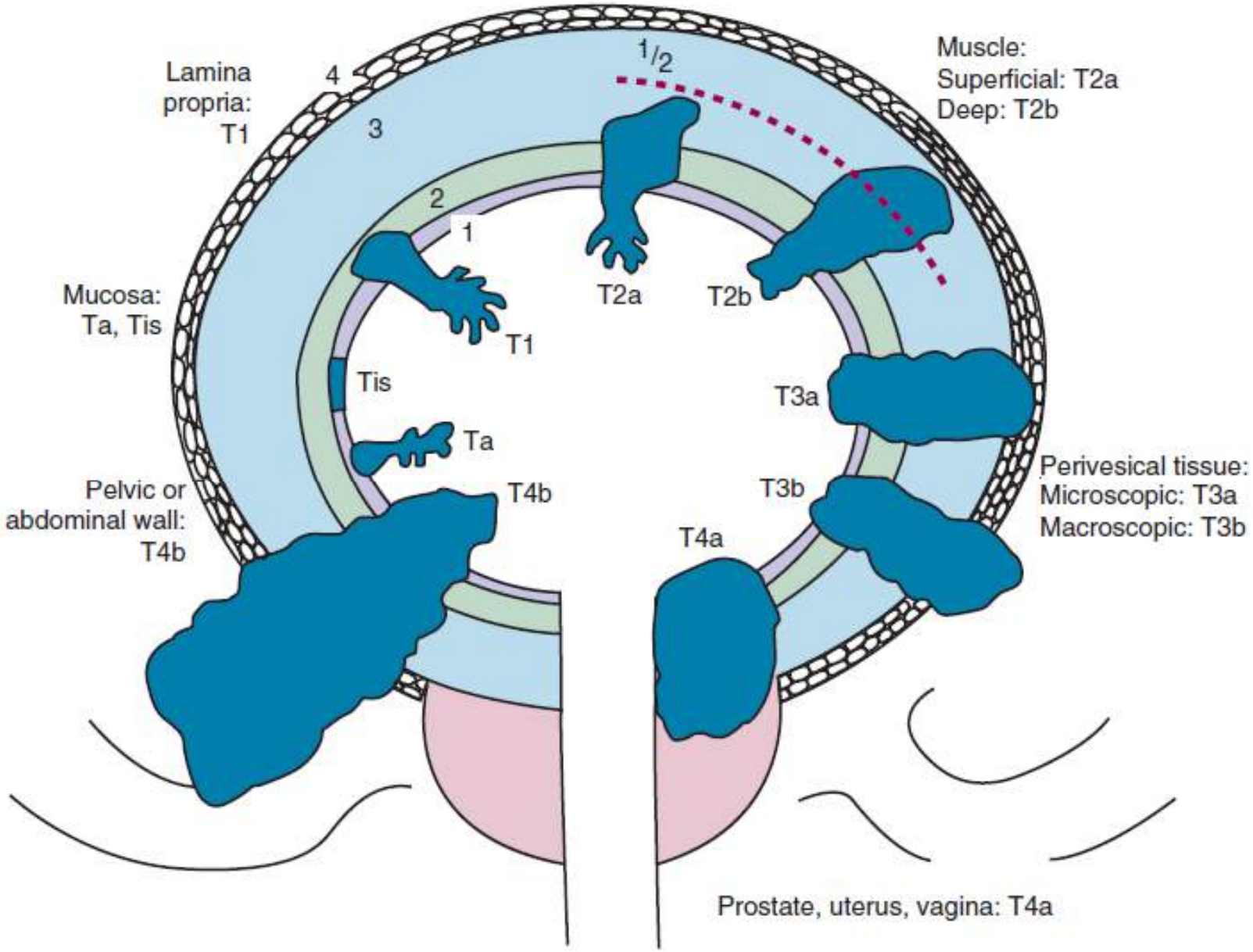
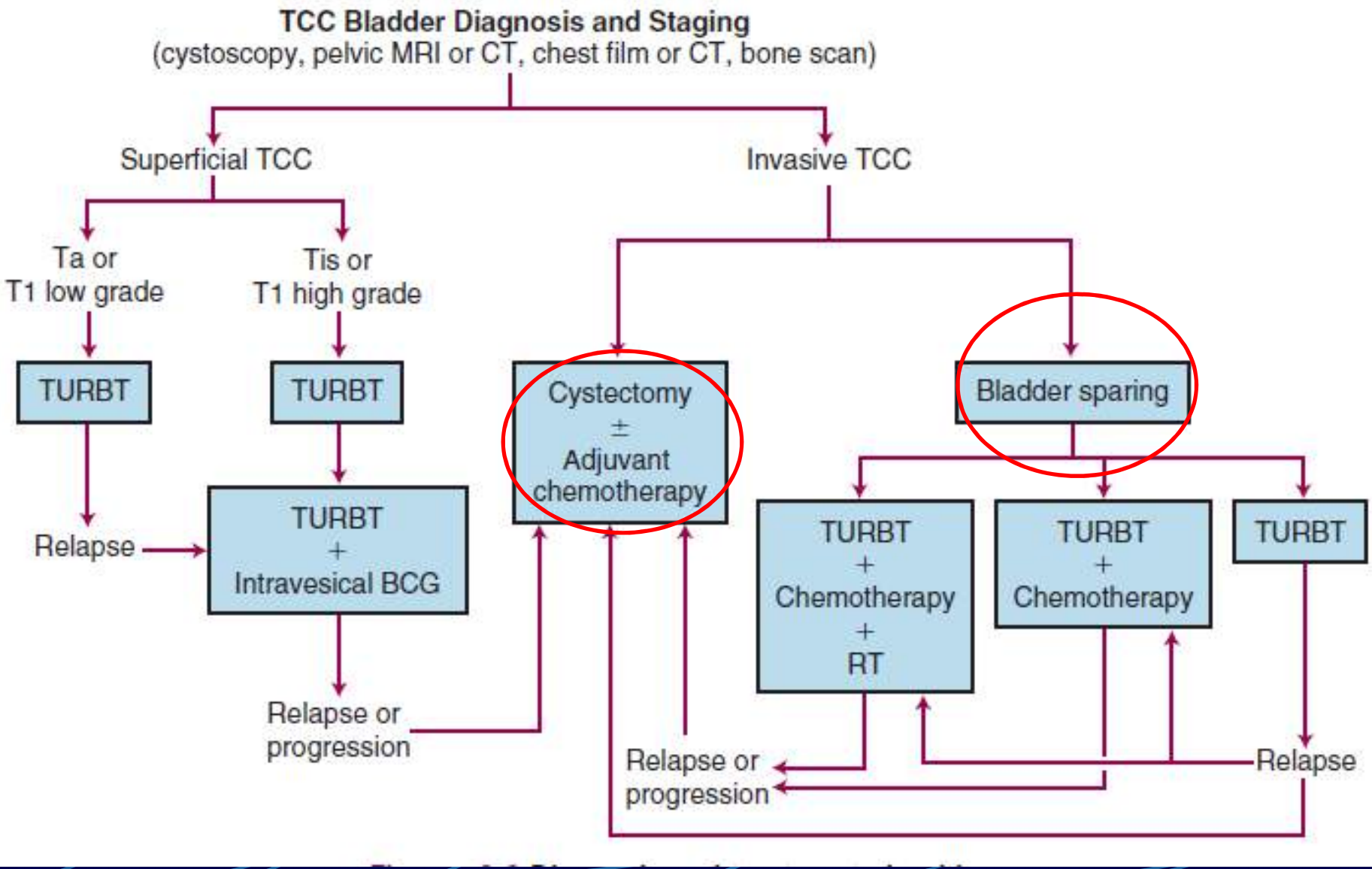


Figure 52-1 Staging of bladder tumors.

Treatment options for Muscle Invasive Bladder Cancer

- Radical Cystectomy +/- PORT
- Pre-operative Radiotherapy f/b Cystectomy
- Bladder Preservation approach:
  - Conservative surgery [Partial cystectomy/TURBT]
  - Radical EBRT +/- Brachytherapy
  - Multimodality Approaches [Combination of surgery, radiotherapy and chemotherapy]

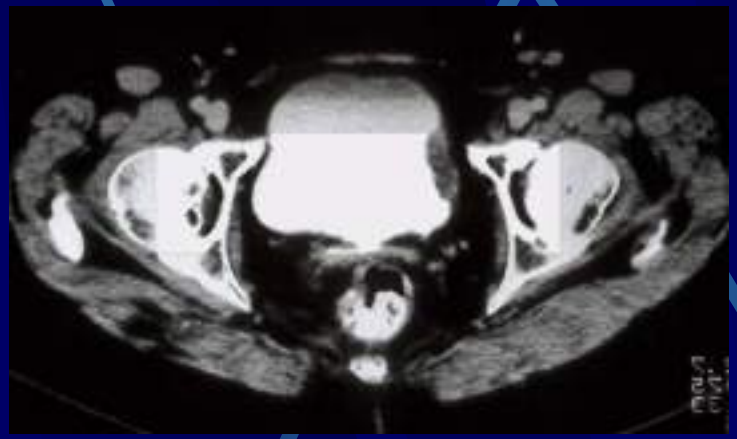
Management Algorithm



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

Outcomes after radical Cystectomy

- University of South California experience
- N=633 [pT2-T4a]
- Actuarial 5 year OS at 5 years :48% and at 10 years : 32%

Stein JP et al. *J Clin Oncol* 2001; 19:666-675.

- MSKCC experience
- N=184 [pT2-T4]
- 5 year OS:36%

Dalbagni G et al. *JUrol* 2001; 165:1111-1116.

Radical EBRT alone

- Radiation dose [55-65 Gy (US); 50-55 Gy @ 2.5-2.75/# (UK)]
- 5 year local control: 31-50%
- Salvage cystectomy rates: 13-24%
- 5 year OS :25-46% [49-71% for T2 tumors and 37-40% for T3b tumors]

Gunderson and Tepper. 3rd edition

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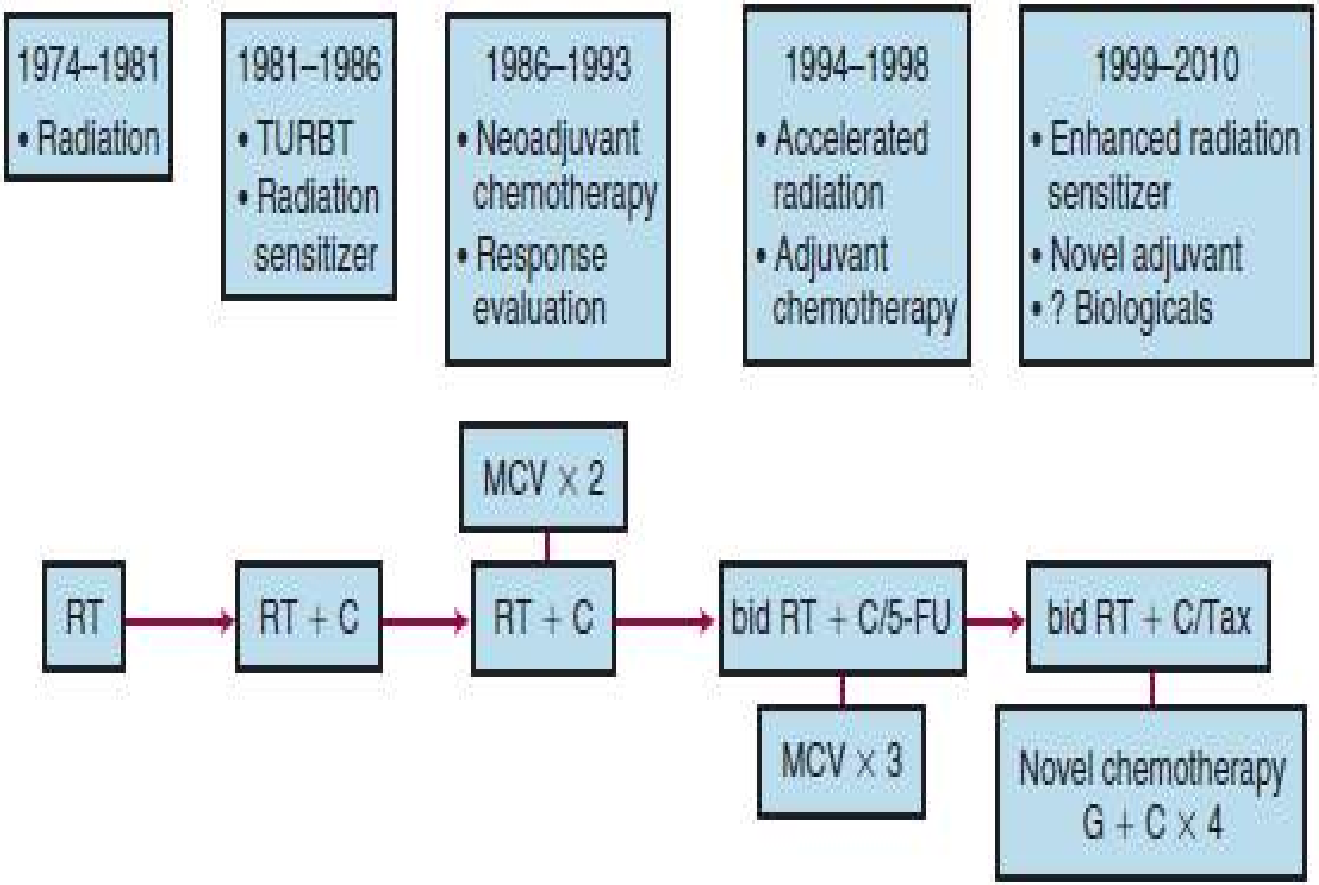
Chemoradiation: Rationale behind

- Synergism: Increased cell killing with concurrent administration of cisplatin/5-Fu
- Control of Occult metastasis: Approximately 50% of patients of muscle invasive bladder cancer harbor occult metastasis
- Bladder preservation: Increased local control may help to preserve functional bladder

Evolution of Multimodality Approach



Combined radiation and chemotherapy for invasive transitional-cell carcinoma of the bladder: a prospective study.

JCO November 1993 vol. 11no. 11 2150-2157

- First prospective study evaluating the role of CTRT for bladder preservation
- N=54 [T2-T4 Operable bladder cancers]
- TUR f/b Concomitant RT with cisplatin+5 Fu
- Partial responders: Cystectomy; Complete responders: Cystectomy or further CTRT [control Cystoscopy done at 4-6 weeks]
- 74% had CR to initial CTRT and OS at 3 years:62%
- Results formed the basis of further studies

Combined-Modality Treatment and Selective Organ Preservation in Invasive Bladder Cancer: Long-Term Results

JOURNAL OF CLINICAL ONCOLOGY

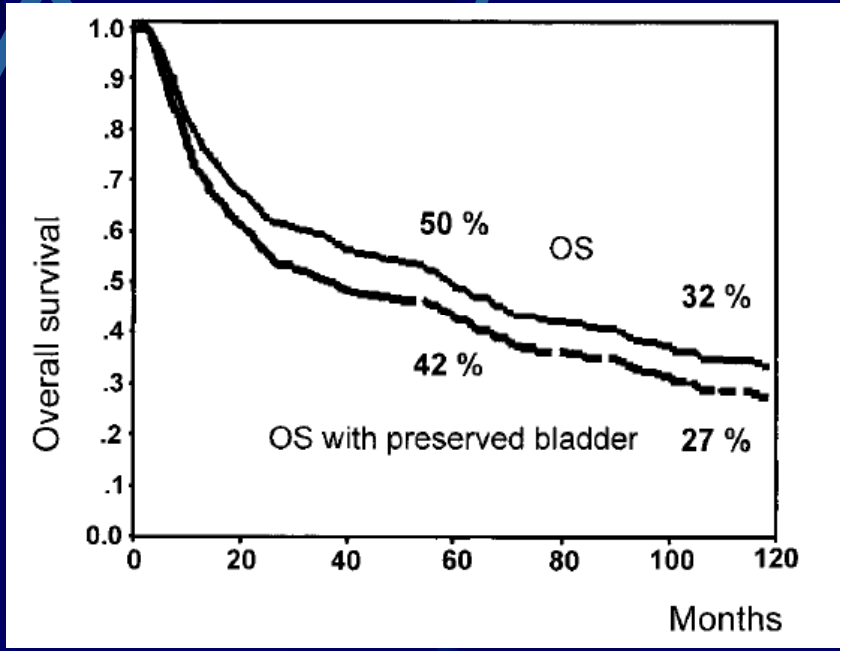
By Claus Rödel, Gerhard G. Grabenbauer, Reinhard Kühn

J Clin Oncol 20:3061-3071.

- N=415 [1982-2000]; T2-T4=326
- Radiotherapy (n=126) and CTRT (N=289)
- Patients underwent TUR f/b RT/CTRT f/b restaging TUR after six weeks
- Persistent/recurrent disease: Salvage Cystectomy
- Median follow up : 5 years

Results

- CR to RT/CTRT: 72%
- 10 years DFS: 42% and > 80% survivors preserved their bladder
- CTRT was more effective than RT alone both in terms of CR [87% vs. 61%] and OS [5 year survival 65% vs. 40%]



Results of CTRT: European Trials

Table 1 Selected European Series of Combined Modality Bladder Preservation Therapy

Series	*N*	Clinical Stage	Induction Treatment	
			Neoadjuvant Treatment	Concurrent Radiochemotherapy
Sauer et al (1990)[4]	67	T1-4	TURBT	50.4 Gy at 1.8 Gy plus Cisplatin
Dunst et al (1994)[6]	79	T1-4	TURBT	50-59 Gy at 1.8 Gy/fx plus Cisplatin
Housset et al (1997)[3]	120	T2-4	TURBT	24 Gy at 3 Gy/fx plus Cisplatin/ 5-FU
Fellin et al (1997)[7]	56	T2-4	TURBT plus 2 cycles of MCV	40 Gy at 1.8 Gy/fx plus Cispaltin
Sauer et al (1998)[8]	333	T1-4	TURBT	50.4-59 Gy at 1.8 Gy plus Carboplatin/Cisplatin
Cervek et al (1998)[9]	105	T2-4	TURBT 2-4 cycles MCV	—
Zapatero et al (2000)[10]	40	T2-4	TURBT plus 3 cycles MCV	—
Arias et al (2000)[11]	50	T2-4	TURBT plus 2 cycles M-VAC	45 Gy at 1.80 Gy/fx plus Cisplatin
Rödel et al (2002)[12]	415	T1-4	TURBT	50.4-59 Gy at 1.8 Gy plus Carboplatin/Cisplatin

Series	Complete Response (%)	Consolidation RCT-Regimen for Complete Reponders (± Adjuvant Chemotherapy)	5-Yr Overall Survival (%)	5-Yr OS with Bladder (%)
Sauer et al (1990)[4]	75	—	66 (3 yr)	n.g.
Dunst et al (1994)[6]	n.g.	—	52	41
Housset et al (1997)[3]	77	20 Gy at 2.5 Gy/fx plus Cisplatin/5-FU	63	—
Fellin et al (1997)[7]	50	24 Gy at 2 Gy/fx plus Cisplatin	55	41
Sauer et al (1998)[8]	71	—	56	41
Cervek et al (1998)[9]	52	50 Gy at 2.0 Gy/fx	58 (4 yr)	45 (4 yr)
Zapatero et al (2000)[10]	70	60 Gy at 2.0 Gy/fx	84 (4 yr)	82.6 (4 yr)
Arias et al (2000)[11]	68	20 Gy at 2.0 Gy/fx	48	—
Rödel et al (2002)[12]	72	—	50	42

Bladder preservation RTOG Trials

Table 1 RTOG Bladder Protocols (1985-2002): Trimodality Therapy with Cystectomy Only for Poorly Responding/Relapsing Patients

Protocol (Ref.)	Induction Treatment	Patients	5-year Survival (%)	Complete Response (%)
85-12[9]	TURBT, CP + XRT	42	52	66[a]
88-02[6]	TURBT, MCV, CP + XRT	91	51	75[a]
89-03[10]	TURBT, ± MCV then CP + XRT	123	49	59
95-06[11]	TURBT, 5-FU plus CP + XRT	34	n.a.	67
97-06[7]	TURBT, CP + BID XRT adj. MCV	52	n.a.	74
99-06[6]	TURBT, TAX plus CP + XRT; adj. CP + GEM	84	n.a.	n.a.
		Total: 426		

TURBT= transurethral resection of bladder tumor; XRT= external beam irradiation; CP= cisplatin; 5-FU= 5-fluorouracil; MCV= methotrexate, cisplatin, vinblastine; TAX= paclitaxel; GEM= gemcitabine; n.a.= not available.

[a]Urine cytology not evaluated as a response criterion.

Cystectomy vs. Bladder preservation

Table 4 Invasive Bladder Cancer — Survival Outcomes in Contemporary Series

Series	Stages	Number	Overall Survival	
			5 yr (%)	10 yr (%)
Cystectomy				
U.S.C.[18] (2001)	P2-P4a	633	48	32
M.S.K.C.C.[19] (2001)	P2-P4a	181	36	27
Selective bladder preservation				
Erlangen[20] (2002)	cT2-T4	326	45	29
M.G.H.[5] (2001)	cT2-T4a	190	54	36
R.T.O.G.[10] (1998)	cT2-T4	123	49	—

Randomized Trials: CTRT vs. RT

JOURNAL OF CLINICAL ONCOLOGY

Improved local control of invasive bladder cancer by concurrent cisplatin and preoperative or definitive radiation. The National Cancer Institute of Canada Clinical Trials Group.

JCO November 1996 vol. 14 no. 11 2901-2907

C M Coppin, M K Gospodarowicz, K James, I F Tannock, B Zee, J Carson, J Pater and L D Sullivan

- Prospective RCT [1st]
- N=99;cT3b-T4
- Treated with either RT or CTRT (with concurrent cisplatin 100mg/m^2)
- Median follow up:6.5 years
- Loco-regional relapse rate better with CTRT (50% vs. 33%)
- No difference in OS or distant metastasis

Radiotherapy with or without Chemotherapy in Muscle-Invasive Bladder Cancer

N Engl J Med 2012;366:1477-88.

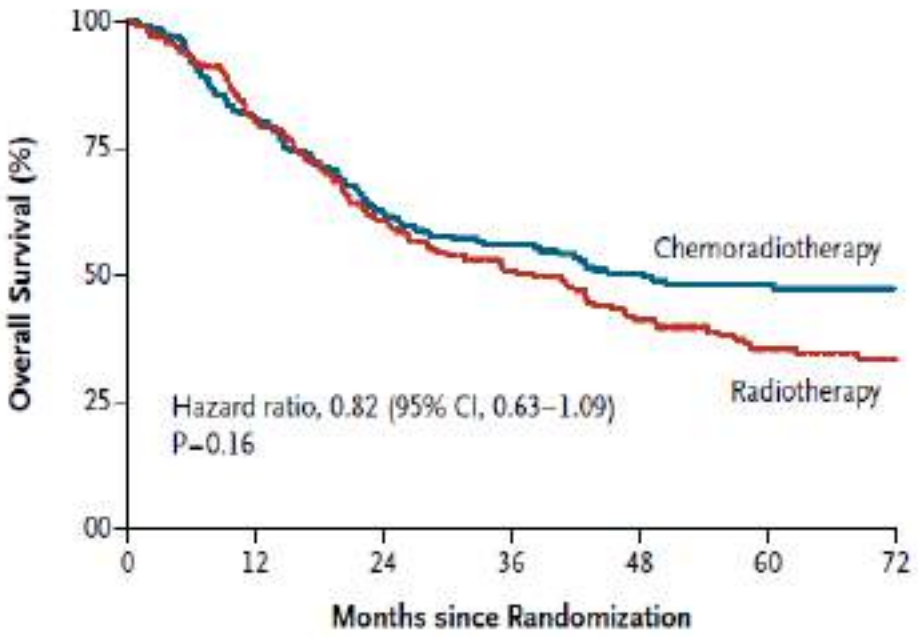
Nicholas D. James, M.B., B.S., Ph.D., Syed A. Hussain, M.B., B.S., M.D.,

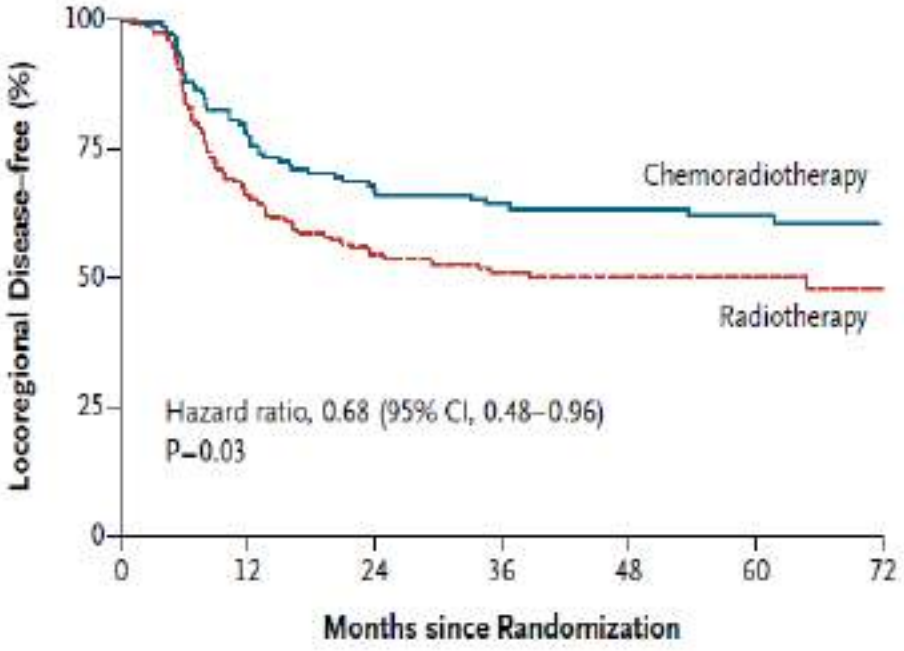
The NEW ENGLAND JOURNAL of MEDICINE

- Multicenter Phase III randomized trial
- N=360
- Muscle invasive bladder cancers randomized to :
  - Whole bladder radiotherapy
  - Modified volume radiotherapy to bladder with concurrent fluorouracil and mitomycin C
- Primary end point: Survival free of loco-regional recurrence
- Secondary end point: Overall survival and toxic effects

Results

- At 2 years, DFS was 67% (CTRT) vs. 54% (RT);P=0.03
- Grade ¾ adverse events were 36% (CTRT) vs. 27.5% (RT);P=0.07





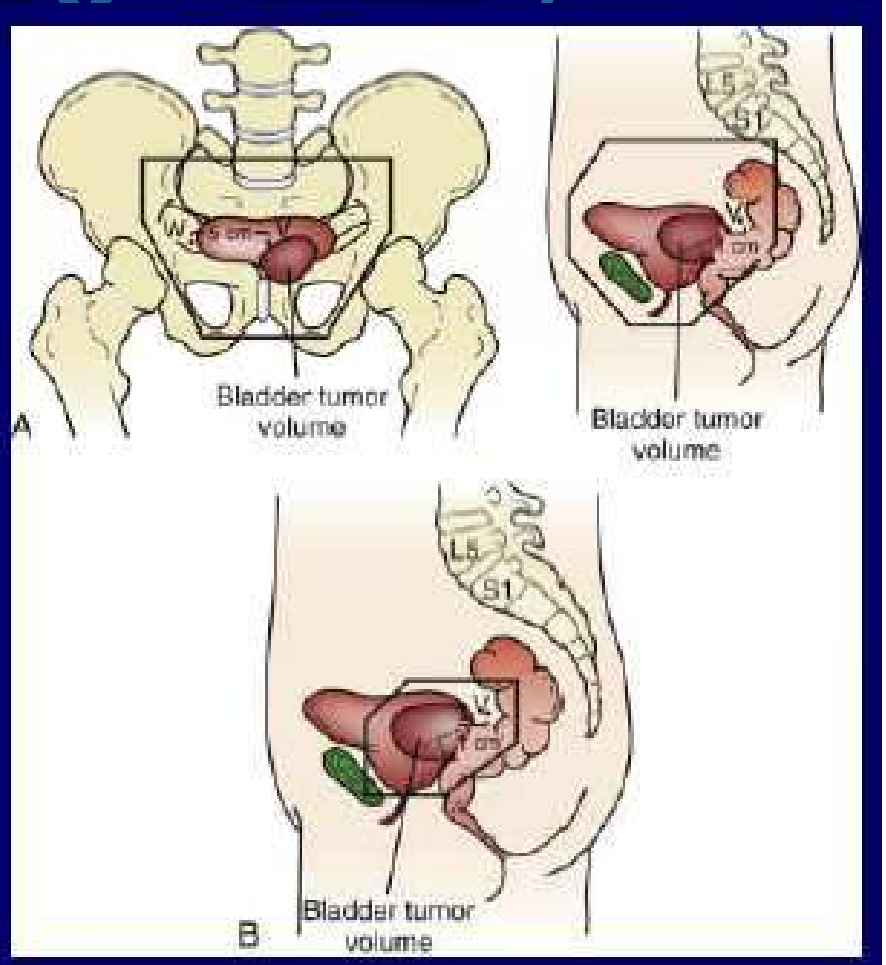
Current Schema of Bladder preservation with concurrent CTRT approach

Radiotherapy treatment techniques

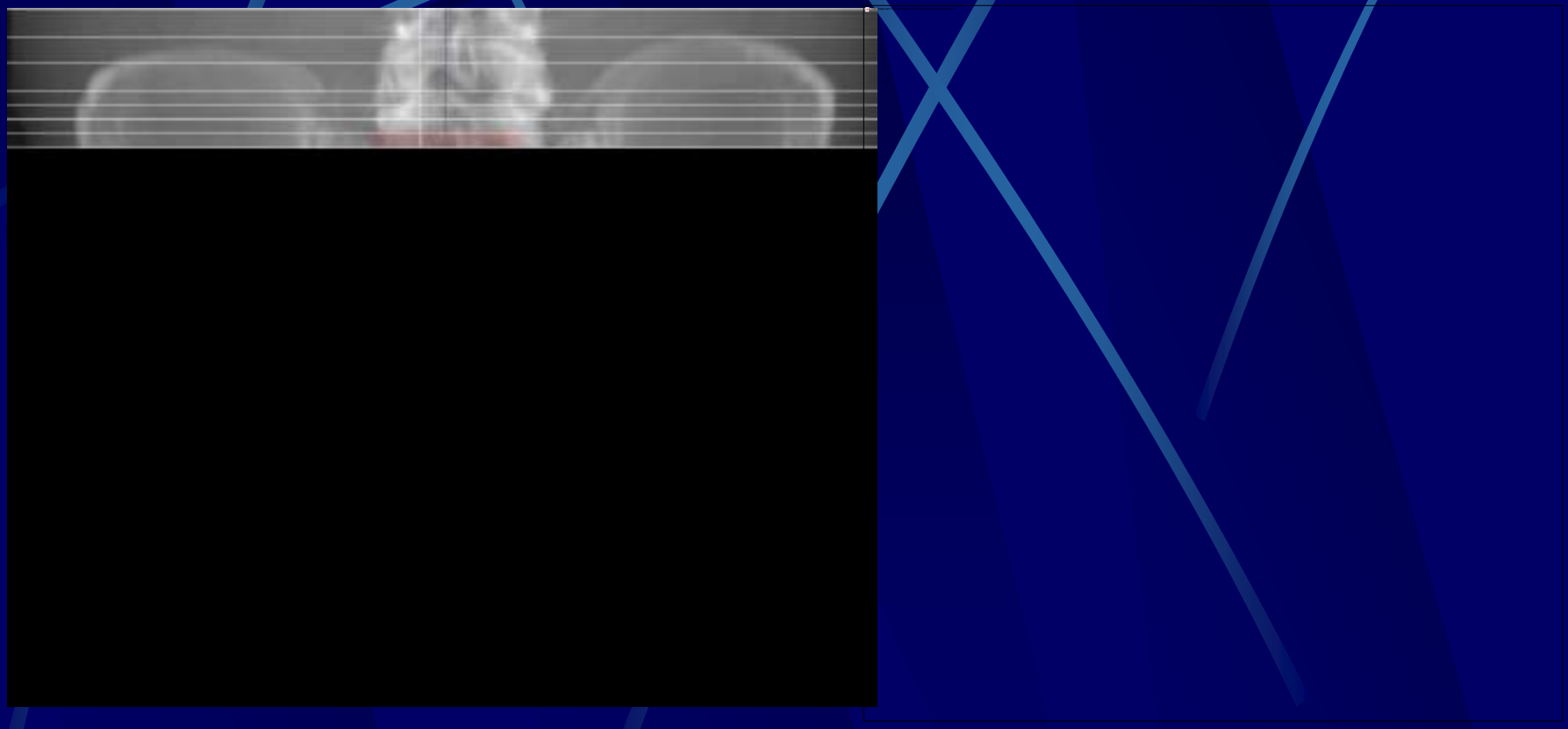
- Simulation:
  - Bladder filling variability to be minimized
  - Supine position with bladder empty [most commonly recommended approach]
- Target Volumes:
  - Initial Phase: Bladder with a margin of 2 cm (Include prostate in males and proximal 2 cm of urethra in females). External and internal iliac group of lymph nodes covered. Care taken to exclude vulva and excess part of bowel (upper border usually not above mid SI Joint)
  - Boost Phase: Controversial [Entire bladder vs. bladder tumor with a 2 cm margin]

Conventional Planning

- Four field planning with differential weight age [70% AP and 30% lateral] for Initial phase
- Two lateral portals for boost phase



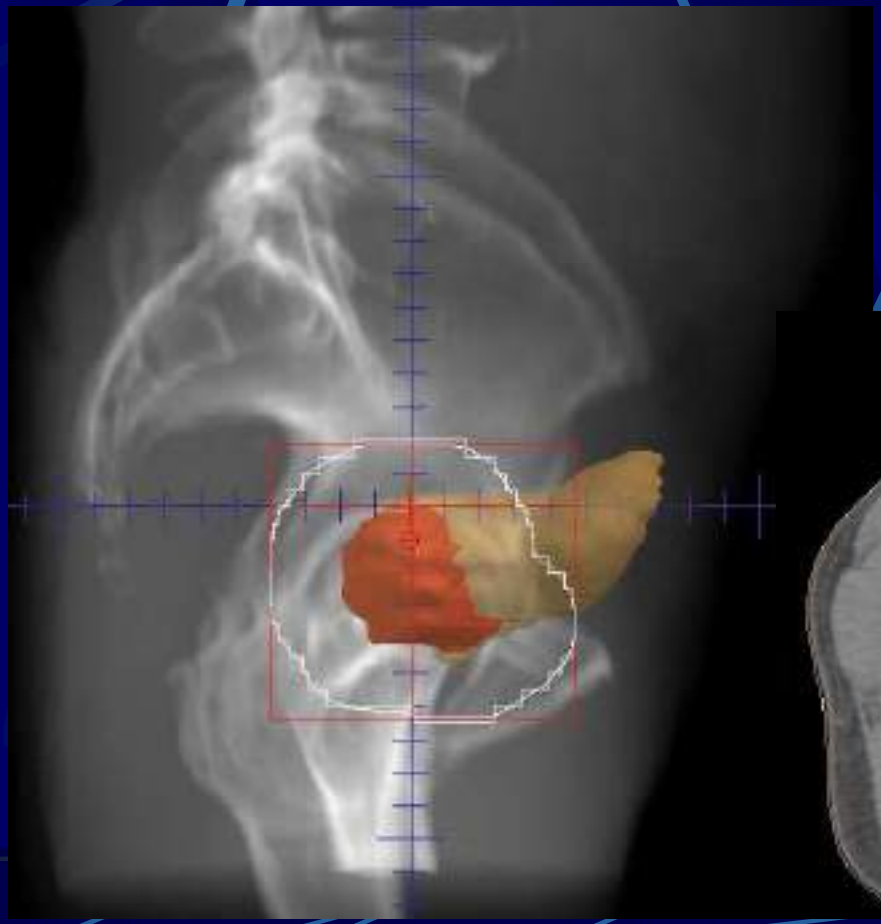
Small Pelvic Fields by 3-D

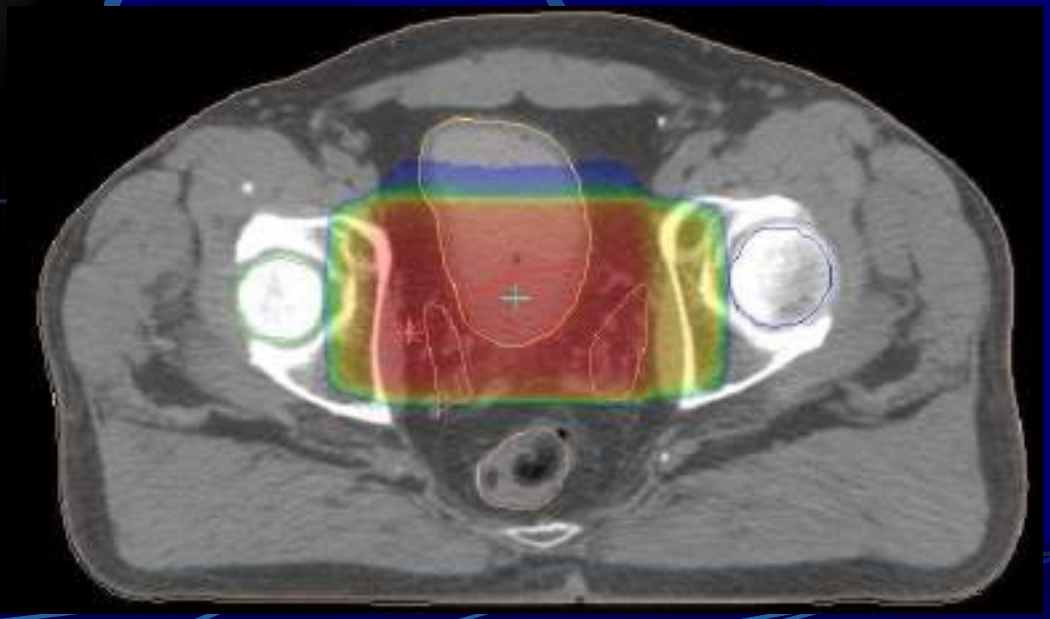


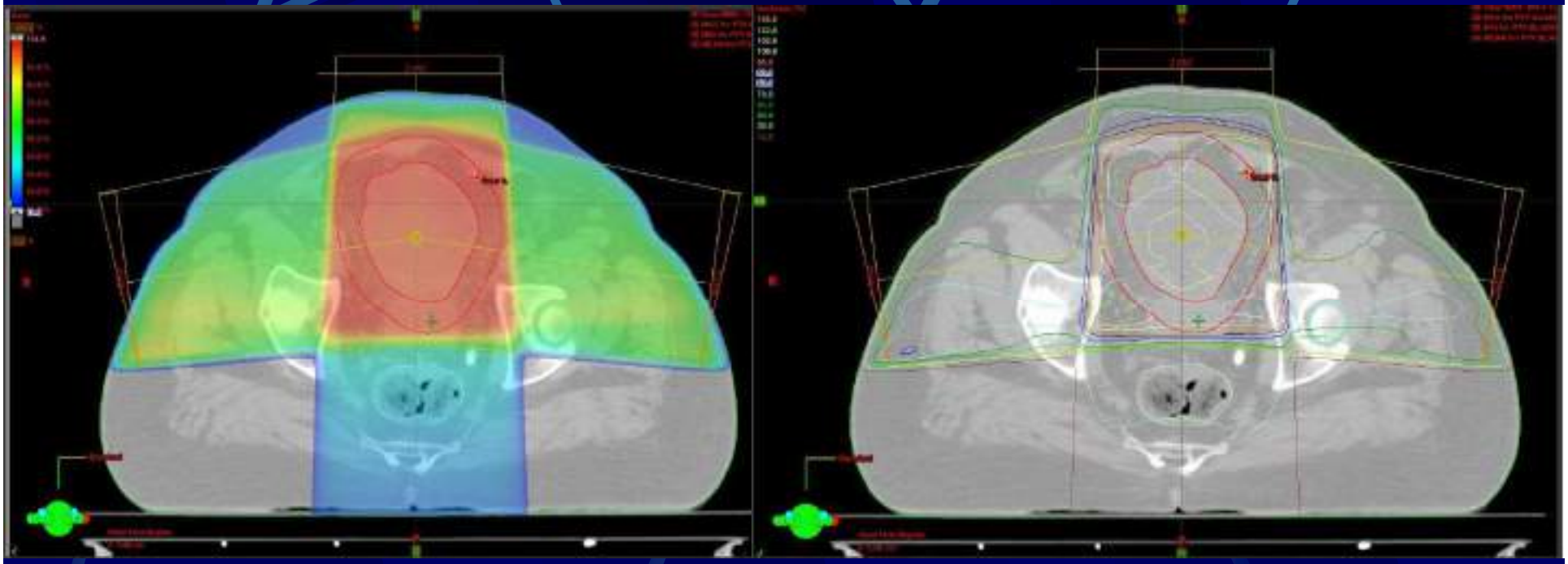
Nodal RT fields (40 to 45Gy) are designed to conserve small bowel for urinary diversions should they be needed

Tumor boost fields by 3-D

- Only partial bladder to high dose (total 65 Gy)
- Incorporate all TURBT and radiographic info
- Simulate and treat with empty bladder







- Radiation dose: 40-45 Gy for the initial phase and 10-20 Gy for the boost phase [Dose response > 62 Gy]
- Dose Fractionation: 1.8- 2 Gy/fraction [Hyper-fractionation has also been tried and practiced at some centers]
- Different practiced fractionation regimens: 64 Gy/32#, 55 Gy/20#,36 Gy/6#

Ideal candidate for CTRT Protocol

- Primary T2 to T3a tumors that are unifocal
- Tumor size less than 5 cm in maximum diameter
- Tumor not associated with extensive CIS
- No presence of ureteral obstruction or tumor-associated hydronephrosis
- Good capacity of the bladder
- Visibly complete TURBT
- Adequate renal function to allow cisplatin to be given concurrently with irradiation

Response Assessment after CTRT

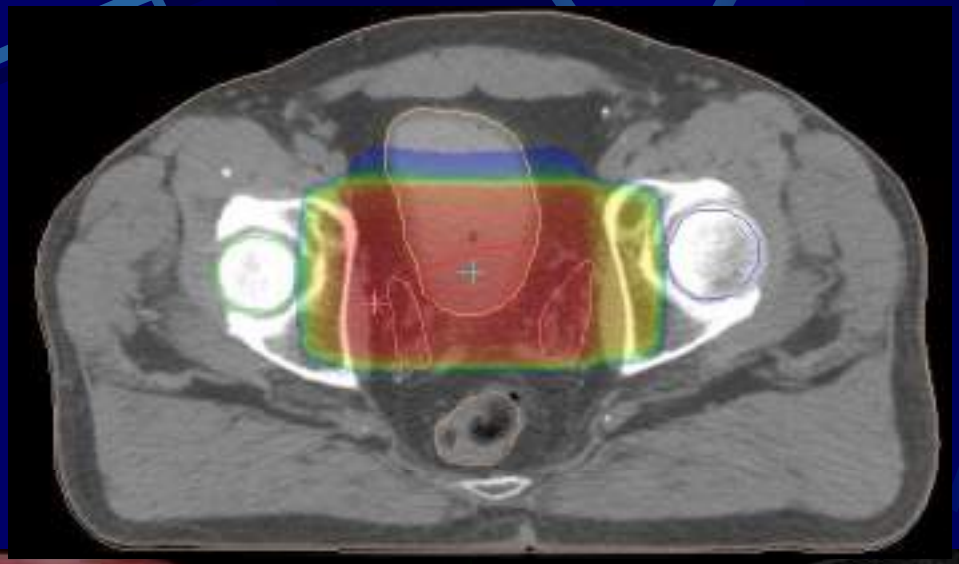
- Assessed after 2-8 weeks after completion of chemoradiation [varies from 70-80% in various series]
- CR higher in patients in whom:
  - macroscopically visible complete TURBT achieved [80-90% vs. 60%]
  - T2/T3a > T3b/T4 [~80% vs. 60%]
  - No Hydronephrosis > Pts with hydronephrosis [~85% vs. 65%]

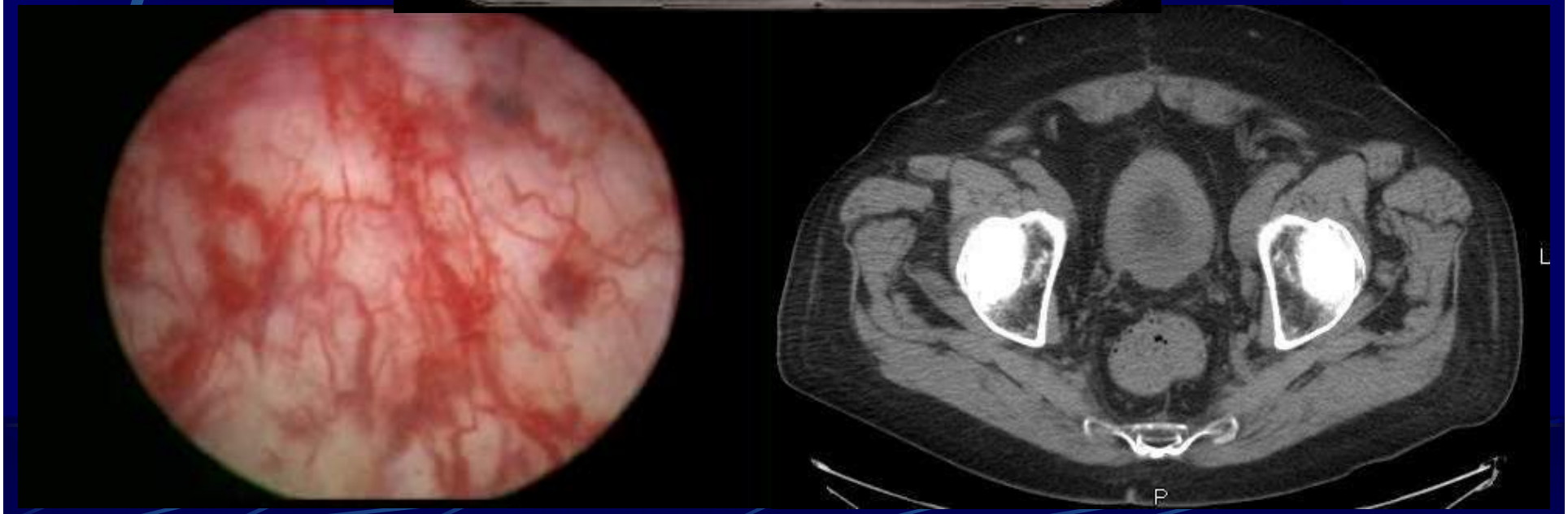
Follow up after CTRT

- All patients opting for bladder preservation approach must be willing for regular follow up
- Optimal time of cystoscopy after completion of RT: Unclear [Usually done at 3 months]
- Cystoscopy and urine cytology every 3 months for first 2 years, then every 6 months until 5 years, and annually thereafter*

*MGH Protocol/NCCN Guidelines

Quality of life after chemo-radiation





THE JOURNAL of UROLOGY
Official Journal of the American Urological Association
Vol. 170, 1772–1776, November 2003

ORGAN CONSERVATION IN INVASIVE BLADDER CANCER BY TRANSURETHRAL RESECTION, CHEMOTHERAPY AND RADIATION: RESULTS OF A URODYNAMIC AND QUALITY OF LIFE STUDY ON LONG-TERM SURVIVORS

ANTHONY L. ZIETMAN,* DIANNE SACCO, URI SKOWRONSKI, PABLO GOMERY,†

- N=221 [T2-4a bladder cancers]
- Treated with tri-modality therapy [1986-2000] at MGH
- 71 alive patients in 2001 included: urodynamic study and a QOL quesstionare
- Median follow up : 6.3 years
- 70% patients participated in the study

Results

- Major morbidity was bowel symptoms: 22%
- Control problems:19%;urgency:15% and flow problems:6%
- Pad use among women:11%
- Majority of men retained sexual function

JOURNAL OF CLINICAL ONCOLOGY

Late Pelvic Toxicity After Bladder-Sparing Therapy in Patients With Invasive Bladder Cancer: RTOG 89-03, 95-06, 97-06, 99-06

VOLUME 27 · NUMBER 25 · SEPTEMBER 1 2009

Jason A. Efstathiou, Kyounghwa Bae, William U. Shipley, Donald S. Kaufman, Michael P. Hagan,

- N=285 [1990-2002]; Patients from four prospective RTOG trials
- 157 patients treated with CTRT and surviving >2 years with intact bladder included in the study
- RTOG late morbidity schema used to grade toxcities

Results

- Median follow up: 5.4 years
- Grade 3+ pelvic toxicity :7% [5.7% GU and 1.9% GI]
- No Grade 4 late toxicity and no treatment related deaths
- Bladder preservation approach: very good late term outcomes with intact bladder

Conclusion

- Concurrent chemo-radiation achieves CR rates of ~70% and preserves bladder with comparable OS to radical Cystectomy.

- QOL studies: Retained native bladder functions well and long-term toxicity of chemoRT to pelvic organs is relatively low

- Long term toxicity of bladder preservation protocols are low

- Patient selection is a key and regular follow up is mandatory

Evidence :CTRT in bladder cancers

Treatment/ Comparison	Evidence	Level of Evidence	Grade of Recommendation
ChemoRT vs RT alone	2 RCTs report significant improvement in bladder tumor eradication	**1b**	**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**
Trimodality therapy vs immediate cystectomy	Comparison of 3 contemporary series of each report similar 5- and 10-yr survival	**3**	**C**