THE INTERNATIONAL CONFERENCE
PROGRESS IN URO-ONCOLOGY 5th Edition

FRIDAY, 26TH SEPTEMBER 2014 Golden Tulip Ana Dome Hotel	
08:00-14:00	**LIVE SURGERY** *Panelists: Andrei Nadu, Israel* *Sandi Potoks, Slovenia* *Mugur Popescu, Romania* Robotic nerve-sparing radical cystectomy with ileal conduit *Surgeons: Ivan Kolombo, Czech Republic* *Vassilios Poulakis, Greece*
09:50-10:40	**STATE OF THE ART** *Chairs: Gabriel Kacso, Romania* *Ottavio de Cobelli, Italy* *Marius Necutolu, Romania* Robotic brachytherapy – video presentation, streaming from The Netherlands *Geert Smits, The Netherlands* Bladder brachytherapy - ready for a change? *Gabriel Kacso, Romania*
10:40-11:00	Coffee break
11:00-11:40	**ASTRAZENECA SYMPOSIUM** *Chairs: Nicolae Grigore, Romania* *Florin Elec, Romania* *Zoltan Mihaly, Romania* High risk prostate cancer: the role of hormone treatment as adjuvant to radical prostatectomy *Cristian Surcel, Romania*
	STATE OF THE ART *Chairs: Delia Victor Matei, Italy* *Ciprian Lucan, Romania* *Gabriel Kacso, Romania* Neoadjuvant chemotherapy for bladder cancer: fighting between evidence 1

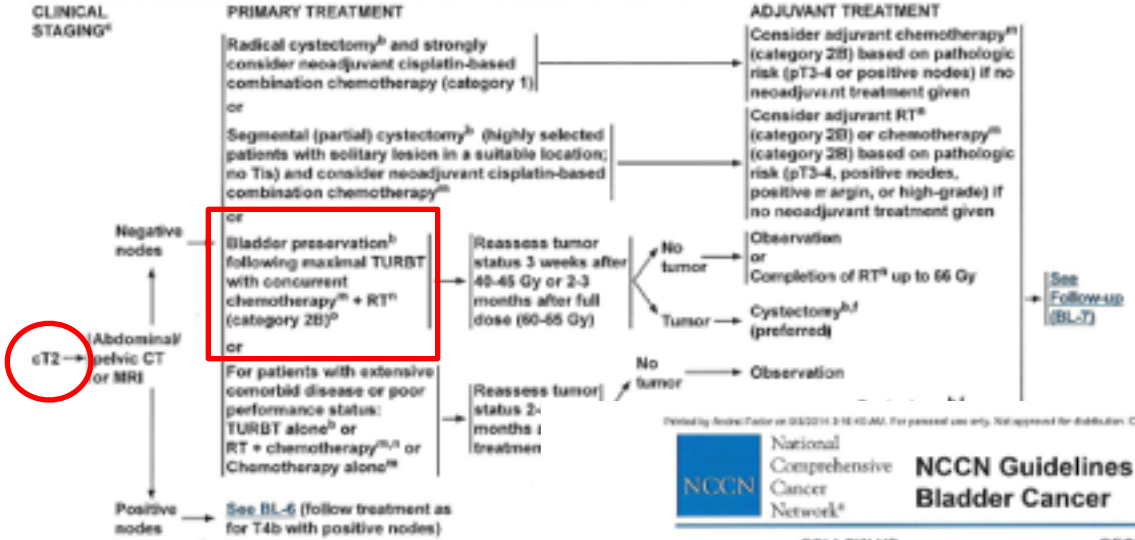
Critical analysis of bladder sparing trimodal therapy in muscle-invasive bladder cancer

***Andrei Fodor**, Italy*

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2014
Bladder Cancer

NCCN Guidelines Index
Bladder Cancer TOC
Discussion



[b] See Principles of Surgical Management (BL-A).
[c] The modifier "c" refers to clinical staging based on bimanual examination under anesthesia and endoscopic surgery (biopsy or transurethral resection) and imaging studies. The modifier "p" refers to pathologic staging based on cystectomy and lymph node dissection.
[f] See Follow-Up After Cystectomy and Bladder Preservation (BL-E).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clin

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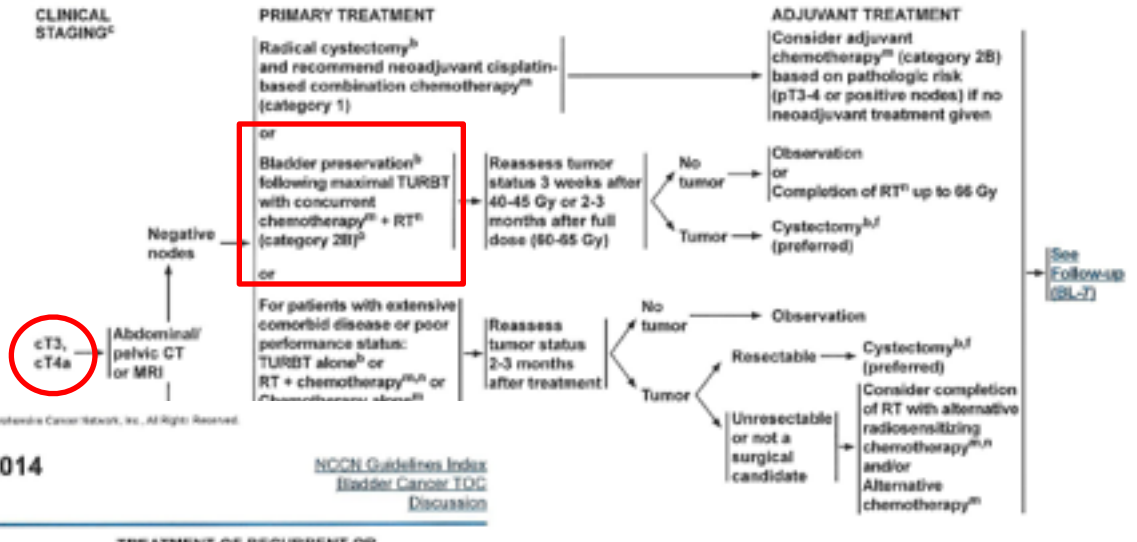

anesthesia and endoscopic surgery (biopsy or transurethral resection) and imaging
lymph node dissection.

about the role of these approaches. Not all institutions have experience with these

al trial. Participation in clinical trials is especially encouraged.

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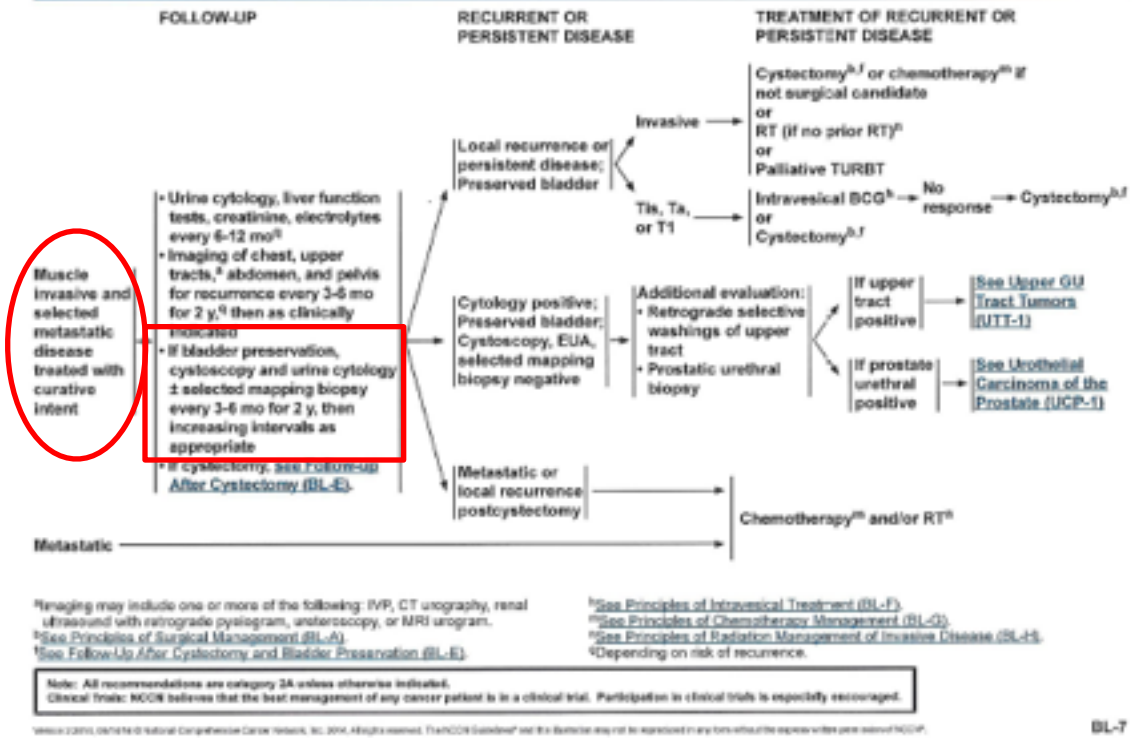


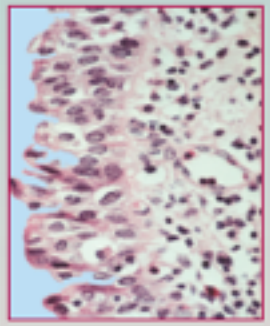
[a] Imaging may include one or more of the following: IVP, CT urography, renal ultrasound with retrograde pyelogram, ureteroscopy, or MRI urogram.
[b] See Principles of Surgical Management (BL-A).
[f] See Follow-Up After Cystectomy and Bladder Preservation (BL-E).
[k] See Principles of Intravesical Treatment (BL-F).
[m] See Principles of Chemotherapy Management (BL-G).
[n] See Principles of Radiation Management of Invasive Disease (BL-H).
[q] Depending on risk of recurrence.

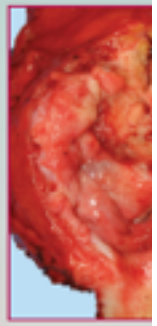
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

BLADDER CANCE

EDITORS

MARK SOLOWAY - SAAD KHOURY





2nd International Consultation on Bladder Cancer - Vien

Second Edition

2012

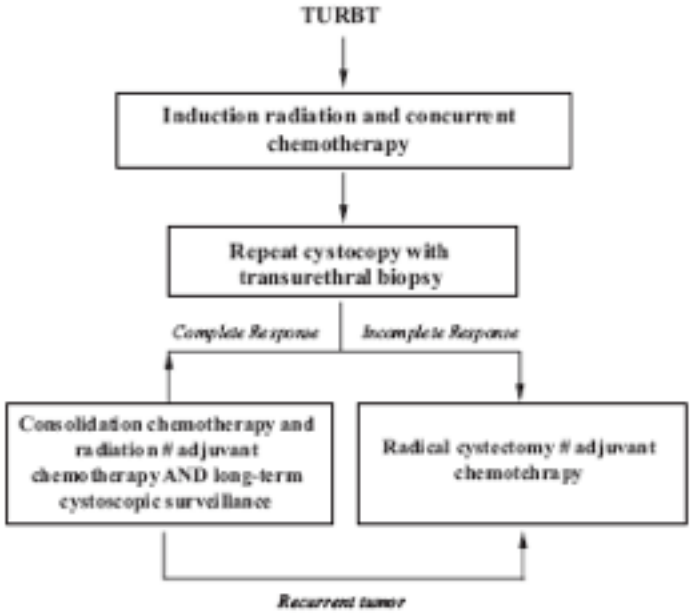


Figure 3. Current Schema for Trimodality Treatment of Muscle-Invasive Bladder Cancer With Selective Bladder Preservation.

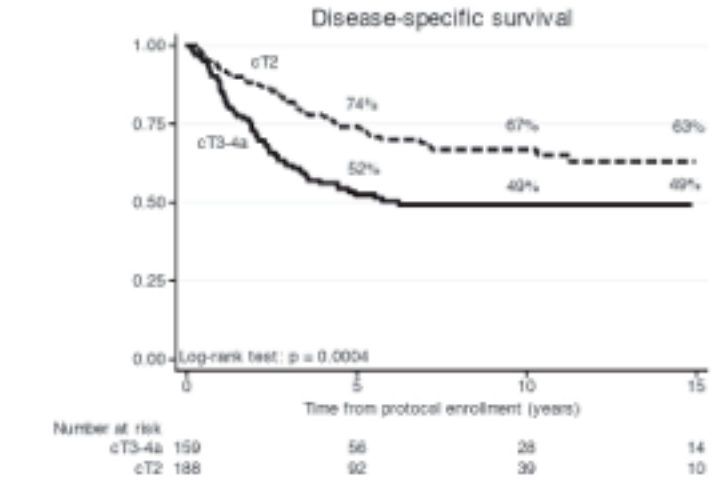


Figure 4. Long-term Disease-specific Survival with Selective Bladder Preservation from the Massachusetts General Hospital Experience (33).

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Trimodal Therapy results

- Adequate local control cannot be achieved with TURBT, chemotherapy or radiotherapy, when used alone

- It is generally recognised that *TURBT alone provides inadequate cancer control* and high rate of bladder cancer recurrence *(Herr HV et al, JCO 2001; Leibovici D et al, Urology 2007; Solsona E et al J Urol 2010)*

- Randomized trial of RT vs chemo-RT in bladder cancer demonstrated an improved control rate with concurrent CDDP *(Coppin CM et al, JCO 1996).* Results confirmed also by BC2001 trial for RT vs RT +concurrent MMC+ 5 FU *(James ND et al, N Engl J Med 2012).* Erlangen study showed a RR of 61% for RT alone and 82% for RT+ CDDP, and a significant improvement in OS *(Rodel C et al, JCO 2002)*→ Level of Evidence 1b

Trimodal Therapy results

Treatment	%CR	OS5	% requiring cystectomy
TURBT+ M-VAC	33-54%	58%	66%
TURBT+ RT+ CT	64-87%	45-62%	29-35%

Cystectomy rate was increased by 88-125% without radiation!- *(Sternberg CN et al, Cancer 2003)*

TABLE 2
Outcomes Reported from Contemporary Treatments on Cooperative Group Trials in Cystectomy Candidates[a]

Protocol	Reference	Treatment	Stage	No. of patients	Five-year survival (%)	Comment
RTOG, 1998	Shipley et al.[4]	TURBT ± MCV then CP + XRT	T2–T4a	123	49	Phase III, 50% of patients received MCV
SWOG, 2001	Hussain et al.[14]	TURBT, CP, 5-FU, + XRT	T2–T4a	25	45	Phase II
SWOG, 2001	Natale et al.[15]	Cystectomy	T2–T4a	303	49	Phase III; 50% of patients received MVAC
Italian trial, 2001	Sternberg and Parmar[16]	Cystectomy	T2–T4a	303	49	Phase III; 50% of patients, received MVAC

RTOG: Radiation Therapy Oncology Group; SWOG: Southwest Oncology Group; TURBT: transurethral resection of bladder tumor; MCV: methotrexate, cisplatin, and vinblastine; CP: cisplatin; XRT: external beam irradiation; 5-FU: 5-fluorouracil; MVAC: methotrexate, vinblastine, doxorubicin, and cisplatin.
[a] Outcomes of all entered patients are included

(Shipley WU et al, Cancer Supplements 2003)

«Old» evidence

Table 1. MGH and RTOG: Series of Combined-Modality Treatment and Selective Bladder Preservation

Series	No. of Patients	Clinical Stage	Induction Treatment		Complete Response pCR (%)	Consolidation CRT-Regimen for Complete Responders (± adjuvant chemotherapy)	5-Year Overall Survival (%)	5-Year OS With Bladder (%)
			Neoadjuvant Treatment	Concurrent Treatment				
MGH 1986-1993[5]	106	T2-4a	TURBT, 2 cycles MCV	39.6 Gy in 1.8 Gy plus cisplatin	66	25.2 Gy in 1.8 Gy plus cisplatin	52	43
RTOG 85-12 1986-1988[6]	42	T2-4a	TURBT	40 Gy in 2 Gy plus cisplatin	66	24 Gy in 2 Gy plus cisplatin	52	42
RTOG 88-02 1988-1990[7]	91	T2-4a	TURBT, 2 cycles MCV	39.6 Gy in 1.8 Gy plus cisplatin	75	25.2 Gy in 1.8 Gy plus cisplatin	62 (4 years)	44 (4 years)
RTOG 89-03 1990-1993[8]	123	T2-4a	TURBT, 2 cycles MCV, *v* no chemotherapy	39.6 Gy in 1.8 Gy plus cisplatin	61 *v* 55	25.2 Gy in 1.8 Gy plus cisplatin	49 *v* 48	36 *v* 40
MGH 1993-1994[9]	18	T2-4a	TURBT	42.5 Gy in 1.25 und 1.5 Gy bid plus FU und cisplatin	78	22.5 Gy in 1.25 and 1.5 Gy bid plus FU and cisplatin, 3 cycles adjuvant MCV	83 (3 years)	78 (3 years)
RTOG 95-06 1995-1997[10]	34	T2-4a	TURBT	24 Gy in 3 Gy bid plus 5-FU and cisplatin	67	20 Gy in 2.5 Gy bid plus FU and cisplatin	83 (3 years)	66 (3 years)
RTOG 97-06 1997-1999[11]	47	T2-4a	TURBT	40.8 Gy in 1.8 und 1.6 Gy bid plus cisplatin	74	24 Gy in 1.5 Gy bid plus cisplatin, 3 cycles adjuvant MCV	61 (3 years)	48 (3 years)

Abbreviations: MGH, Massachussetts General Hospital; RTOG, Radiation Therapy Oncology Group; TURBT, transurethral resection of bladder tumor; MCV, methotrexate, cisplatin, vinblastine; FU, fluorouracil; pCR, pathologic complete response; OS, overall survival.

Rodel C et al, JCO 2006

«Old» evidence

RTOG 85-12: phase II (first trial to use the classic RTOG approach)- *(Tester W et al, IJROBP 1993)*

- ❑ 42 pts T2-T4N0-2
- ❑ WPRT 40 Gy (2 Gy/fr)+ 2c CDDP→ restage after 2 wks: cystoscopy, biopsy, clinical exam under anesthesia, CT: →CR: RT boost 24 Gy (2 Gy/fr)+ 3°c CDDP

  →no CR= cystectomy
- ❑ Results: CR= 67%; OS5= 52%; All pts LC= 42%; Invasive only LC= 50%, LF5= 25%

RTOG 88-02: phase II- *(Tester W et al, JCO 1996)*

- ➢ 91 pts T2-T4N0-2
- ➢ Neoadjuvant MCV (Methotrexate, Cisplatin, Vinblastine)→then RT+ CDDP same as RTOG 85-12
- ➢ Results: CR= 75%; OS5= 62%.

«Old» evidence

RTOG 89-03: phase III- *(Shipley WU et al, JCO 1998)*

- ❑ 123 pts T2-T4aNx- maximal TURBT
- ❑ Randomized: - Neoadjuvant MCV x 2c then WPRT 39.6 Gy (1.8 Gy/fr)+ 2c CDDP ***vs*** WPRT+ CDDP only
- ❑ Restage after 4 wks: cystoscopy, biopsy, clinical exam under anesthesia, cytology

  →CR: RT boost 25.2 Gy (1.8 Gy/fr)+ 3°c CDDP
- ❑ Stopped early (projected 174 pts) due to MCV toxicity (14% died). No significant change in CR, OS, DMFS

RTOG 95-06: phase II- *(Kaufman DS et al, Oncologist 2000)- accelerated hypofractionated RT*

- ➢ 34 pts T2-T4aNx
- ➢ TURBT→WPRT 3 Gy twice daily to 24 Gy+ concurrent 5-FU+ CDDP
- ➢ Restage after 4 wks: → CR: 2.5 Gy twice daily to 20 Gy+ concurrent 5-FU+ CDDP

  → No CR= cystectomy
- ➢ Results: CR= 67%, OS3= 83%, 66% of whom with intact bladder; G3/4= 20%, LR= 45%

«Old» evidence

RTOG 97-06: - *(Hagan MP et al, IJROBP 2003)- accelerated standard fractionation RT*

- 52 pts T2-T4aN0
- TURBT→ within 6 wks twice daily RT: WPRT 21.6 Gy/ 13 fr (1.8 Gy/fr) a.m.+ bladder boost to 40.8 Gy/13 days (1.6 Gy/fr) p.m.+ concurrent CDDP
- Restage at 4 wks: biopsy+ cytology: →CR: twice daily RT in 8 days: WPRT to 45.6 Gy and bladder to 64.8 Gy + CDDP + 3 cycles MCV

  → No CR= cystectomy+ 3 cycles MCV
- Results: CR= 74%; OS3= 61%, with intact bladder 48%; *G3/4 RT+CT= 11%*; only 40% pts received 3c MCV and G3= 41%, G4= 36%; ***total G3 and 4 adj CT = 77%!*** ; LR3= 27%, DM= 29%.

MGH: phase II- III *(Shipley WU et al, Urology 2002)*

- 190 pts T2-T4aNx treated: WPRT 40Gy+ 2c CDDP → restage: CR→ RT boost 24-25 Gy + 3°c CDDP/No CR- Cystectomy
- Additional multidrug chemotherapy neoadjuvant/adjuvant
- Results: OS5= 54%(T2 62%; T3-4a 47%); DSS5= 63% (T2 74%, T3-4a 53%); DSS5 with intact bladder= 46% (T2 57%; T3-4a 35%). Only 35% needed cystectomy, including salvage for recurrence.

ELSEVIER

Selective Bladder Preservation Therapy for Patients with Musc Invasive Bladder Cancer and W Candidates—The Massachusett and Radiation Therapy Oncolog

William U. Shipley,* Anthony L. Zietman,* Donald S. K
Howard M. Sandler‡

The Massachusetts General Hospital and the Radiatio
been leading the charge for organ conservation in bladde
two decades. In a series of six successive studies the gr
is now moving toward a translational future in which nov
with the best current strategies. The North American
selective nature, in that it preselects patients likely to d
and then further selects according to the response to an
and radiation. Only those who are complete responders
point" allows salvage cystectomy to be performed on i
have had full-dose radiation. This preserves the urina
surgeon as well as brings forward the time to a salvage
Semin Radiat Oncol 15:36-41

Table 2 Survival Outcomes by Patient and Tumor Characteristics

		Overall Survival (%)			Disease-Specific Survival (%)		
Patient Group	***n***	**5 yr.**	**10 yr.**	***P* Value**	**5 yr.**	**10 yr.**	***P* Value**
All patients	190	54 ± 7.5*	36 ± 8.3*		63 ± 7.5*	59 ± 8.0*	
Age at entry (yr)							
<75	155	55	40	0.04	65	60	NS
>75	35	51	22		56	56	
Sex							
Female	47	59	40	0.67	60	52	0.50
Male	143	52	34		64	62	
Clinical stage							
T2	90	62	41	0.02	74	66	0.01
T3-T4a	100	47	31		53	52	
Hydronephrosis							
No	163	55	37	0.15	64	61	0.09
Yes	27	48	29		53	49	

*95% confidence interval.

Table 3 Treatment Outcomes by Extent of TURBT*

Outcomes	**All Patients***	**TURBT Visibly Complete**	**TURBT not Visibly Complete**	**Univariate *P* Value**	**Multivariate *P* Value****
All patients	179	109	70		
CR rate	69%	74%	63%	0.15	
Overall survival					
At 5 years	55%	59%	49%		
At 10 years	35%	38%	31%	0.27	0.91
Disease-specific survival (DSS)					
At 5 years	64%	69%	58%		
At 10 years	60%	64%	54%	0.24	0.99
DSS with bladder					
At 5 years	44%	51%	35%		
At 10 years	42%	47%	33%	0.03	0.18
% Undergoing cystectomy					
Total	37%	29%	50%	<0.01	
Immediate (non-CR)	23%	16%	33%		
Salvage	14%	13%	17%		

*Includes only patients with TURBT status known.
**Includes T stage (T2 versus T3-T4a), grade, and gender.

«Old» evidence reproducibility

Erlangen: T2-T4Nx- *(Rodel C et al, JCO 2*

- ❑ 415 pts (89 pts T1 high risk, 326 pts T2-T4), 289 p
- ❑ WPRT to a median dose of 45 Gy (40-59.4 Gy) , b 69.4 Gy)+ concurrent CDDP/CBDCA +/- 5FU
- ❑Results: CR= 72%; LC10 in CR= 64%; DM10= 35% salvage cystectomy for LR→DSS10 = 45%; Toxicity: bladder.

Cluj (IOCN): T2-T4aNx

- ➢49 pts: TURBT → WPRT 40-50 Gy (2Gy/fr)+ 2c CDDP
- ➢→ Restage: →CR: Bladder boost 20 Gy (2 Gy/fr)+ CDDP
  →No CR= cystectomy
- ➢Results: OS3= 54%, with intact bladder 38%; LC with intact bladder= 53%; acute G3&4: 6% GI, 18% GU, late G3&4: GI= 2%, GU=8%

Radioterapie & Oncologie Medicală

Tratamentul conservator al cancerului infiltrativ al vezicii urinare

G.Kacso[1,2], N.Todor[1], Cristina Cebotaru[1], Gabriela Morar[1], A. Fodor[3],T. Guttman[1], Anca Hodorog[1], S.Popescu[1], N. Ghilezan[1,2]

[1] Institutul Oncologic „Prof. I. Chiricuță" Cluj-Napoca, [2] UMF „I. Hațieganu" Cluj-Napoca, [3] Instituto Europeo Di Oncologia Milano, Italia

Cistectomia radicală (CSTR) rămâne în prezent standardul terapeutic în cancerul infiltrativ al vezicii urinare. Date recente confirmă însă posibilitatea conservării vezicale fără a prejudicia pe termen lung supraviețuirea (SV) acestor pacienți. Nu există la ora actuală rezultate publicate ale unor trialuri randomizate comparative cistectomie radicală versus radiochimioterapie curativă (RCTc). *Obiectiv:* analiza retrospectivă intrainstituțională a eficacității și toxicității RCTc ca tratament conservator al cancerelor infiltrative ale vezicii urinare (VU). *Material & metodă:* 49 pacienți cu diagnostic de carcinom tranzițional infiltrativ al VU, T2-4a (TNM 1997), considerați inoperabili radical "per primam"(extindere, comorbidități sau/ și refuz CSTR), < 80 ani, IP <3, funcție renală, cardiacă și hepatică bune, radiochimiotratați curativ în Institutul Oncologic „Prof. I. Chiricuță" (IOIC) între 1991-2001, după o rezecție conservatoare maximală. Reevaluare după 40-50 Gy/fracționare standard (FS) pe pelvis concomitent cu 2 cicluri de Cisplatin (CDDP) 20mg/m² Z1-5 &22-26 : refuz principial categoric al CSTR-continuarea RCTc cu 20Gy/10fr/12zile + /- încă un ciclu de CDDP; în caz contrar- bilanț clinic, imagistic, citologic urinar, [illegible] tic, cu simplu control periodic pentru cei cu remisie completă (RC), cistectomie radicală pentru ceilalți. [illegible] un „follow-up" median de 18 luni (6-141luni), SV3 a fost 54 %, controlul local cu vezica intactă 53 %, iar SV3 cu păstrarea VU 38 %, 14 % necesitând cistectomie (6% pentru răspuns incomplet după RCT și 8% pentru recidivă locală infiltrativă). Toxicitatea G3-4 acută (NCI), respectiv tardivă (SOMA LENT) digestivă și urinară au fost 6% și 18% respectiv 2% și 8%. *Concluzie:* RCTc este eficace, cu toxicitate acută acceptabilă, toxicitate tardivă semnificativă, posibil a fi diminuată prin „plafonarea" dozei totale la 50 Gy pentru T2, 60 Gy pentru T3-4 și protecție digestivă personalizată. [illegible] biopsică după 40-50Gy/FS + 2xCDDP ca radiosensibilizator.

Cuvinte cheie: Carcinom infiltrativ al vezicii urinare, Radiochimioterapie, Tratament conservator.

Radioterapie & Oncologie Medicală, 2004, 1:40-47

QoL after Radiotherapy

MGH study on 221 pts: urodynamics, QoL questionnaire:- *(Zietmann AL et al, J Urol 2003)*
- 78% had compliant bladders with normal capacity and flow parameters
- 85% had no urgency or only occasional urgency
- 25% had occasional to moderate bowel control symptoms
- 50% of men had normal erectile function

Comparative cross-sectional study – *(Henningsohn L et al, Radiother Oncol 2002)*
-Urinary function: 74% of RT pts had little or no urinary symptom distress
-Bowel function: 32% of RT pts and 24% of cystectomy pts presented moderate or much distress (statisticaly not significant) vs 9% in control groups (significant vs both)
-Sexual function: 38% intercourse in the previous month in RT arm vs 13% in cystectomy arm

«New» evidence

EUROPEAN UROLOGY 61 (2012) 705–711

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journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Bladder Cancer

Editorial by Giuseppe Simone and Michele Gallucci on pp. 712–713 of this issue

Long-Term Outcomes of Selective Bladder Preservation by Combined-Modality Therapy for Invasive Bladder Cancer: The MGH Experience

Jason A. Efstathiou [a,], Daphna Y. Spiegel [a], William U. Shipley [a], Niall M. Heney [b], Donald S. Kaufman [c], Andrzej Niemierko [a], John J. Coen [a], Rafi Y. Skowronski [a], Jonathan J. Paly [a], Francis J. McGovern [b], Anthony L. Zietman [a]*

[a] Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA, USA; [b] Department of Urology, Massachusetts General Hospital, Boston, MA, USA; [c] Division of Hematology and Oncology, Massachusetts General Hospital, Boston, MA, USA

348 pts cT2-T4a (1986-2006)
102 pts= 29% underwent radical cystectomies (60 pts for less than CR and 42 pts for recurrent invasive tumors)
Results: CR= 72% (78% for T2)
- DSS5= 64%, DSS10= 59%, DSS15= 57% (T2= 74%, 67%, 63% vs T3-4: 53%, 49%, 49%)
- OS5= 52%, OS10= 35%, OS15=22% (T2= 61%, 43%, 28% vs T3-4= 41%, 27%,16%)
- LR 10 non invasive= 29%, invasive= 16%, pelvic= 11%, distant= 32%
- Salvage cystectomy in 22% of pts with complete TURBT vs 42% with incomplete TURBT
- Bladder preserved in >70% pts
- Multivariate analysis: T stage and CR→ OS and DSS. Neoadjuvant CT- no effect

«New» evidence

RTOG 99-06: phase I-II trial on 80 pts *(Kaufman DS et al, Urology 2009), accelerated hyperfractionated RT*

- TURBT→induction therapy in 13 days with concomitant boost: 1.6 Gy to the pelvis in the morning followed by 1.5 Gy to the bladder for the first five sessions (7.5 Gy), then to the tumor for eight sessions (12 Gy) in the afternoon for a total dose of 20.8 Gy to the pelvis , 28.3 Gy to whole bladder and 40.3 Gy to the tumor).
-Weekly CDDP and paclitaxel were included as radiation sensitizers.
-CR pts- consolidation CRT: 1.5 Gy pelvic RT twice daily to 24 Gy for a total dose of 44.8 Gy to the pelvic lymph nodes and 64.3 Gy to the tumor
-Adjuvant chemotherapy: 4 cycles Gemcitabine+ Cisplatin

CR= 81%, 36/80 pts died, 22 of bladder cancer→ actuarial OS5= 56%, DSS5= 71%
Chemo- RT G3&4 acute toxicity= 26% (25% GI)
Adjuvant CT toxicity: G3= 46%, G4= 26%; 1 fatal hemorrhagic stroke
Late toxicity: G3 bladder 3/53 pts with fup > 2 year

«New» evidence

BC 2001: phase III British Bladder Cancer Clinical Trial Group *(James ND et al, N Engl J Med 2012)*
-360 pts with median f-up of 69.9 mts
-Compared RT alone vs RT+ concurrent MMC+ 5 FU
-Pts were also *randomly asigned to undergo whole bladder or modified –volume RT* (the volume of bladder receiving full-dose RT was reduced) in a partial 2 by 2 factorial design
Results: LDFS 2= 67% in CRT arm vs 54% in RT arm
OS5= 48% in CRT arm vs 35% in the RT arm
Acute G3&4 = 36% vs 27.5%, p= 0.07
Late G3&4 = 8.3% vs 15.7%, p=0.07

RTOG 05-24: phase I-II trial *(Michaelson MD et al, JCO 2014, ASCO abstract*)
68 pts: 21 pts Her2neu ≥2+ received concurrent weekly paclitaxel and weekly trastuzumab vs 47 pts Her2neu< 2+ with paclitaxel only. *Both groups received RT to 64.8 Gy/ 36 fr*
G3 toxicity: 33% arm I vs 30% arm II, mostly marrow supression, diarrhea and hyponatriemia.
Three pts died: colonic perforation, pneumonia, sudden death. RT completion rates: 72 vs 85%, CT completion rates: 52 vs 51%.

«New» evidence

Table 4. Role of Molecular Markers in Predicting Favorable or Unfavorable Outcome in Bladder Cancer Series Treated With Radiotherapy Alone or With Radiotherapy As a Treatment Component

	Favorable			No Effect	Unfavorable		
	TR/LC	DFS/DSS	OS		TR/LC	DFS/DSS	OS
High-AI	X[73], X[60], X[58], X[75]	X[61]	X[61]		X[64]		X[64]
bcl-2 overexpression				X[73], X[59]	X[58], X[71]	X[60]	X[62]
Bax overexpression				X[67]			
p53 overexpression	X[74]	X[74]	X[74]	X[73], X[62], X[76], X[59], X[72], X[69], X[63], X[71], X[57], X[67]	X[66], X[68]	X[60], X[60]	X[60]
Loss of pRb	X[66], X[70], X[71]	X[56]	X[56]	X[66], X[53], X[60], X[57]			
Cyclin D1 overexpression				X[64]			
p21 overexpression			X[59]	X[58], X[72], X[68]		X[60]	X[60]
p16 overexpression				X[57], X[68]			
p27 overexpression				X[58]			
mdm2 overexpression				X[74]			
High-Ki67	X[73], X[75]	X[75]		X[69]	X[65]	X[66], X[67]	
High-MI	X[58]			X[64]			
DNA aneuploidy			X[69]	X[93]	X[91]	X[91]	
GLUT1/CAIX						X[77]	X[77]
EGFR overexpression		X[57]	X[57]				
Her2/neu overexpression					X[57]		
High-XRCC1		X[78]					
High-APE1		X[78]					

Abbreviations: TR, tumor response; LC, local control; DFS, disease-free survival; DSS, disease-specific survival; OS, overall survival; AI, apoptotic index; bcl-2, antiapoptotic protein, prevents activation of proapoptotic caspase proteins; bax, homo-or heterodimers of proapoptotic bax repress the antiapoptotic activity of bcl-2; p53, transcriptional activator of genes with a p53-binding site, associated with cell cycle arrest and apoptosis; Rb, retinoblastoma protein, its phosphorylation state has important implications for cell cycle progession; Cyclin D, pairs with cyclin-dependent kinases CDK 4 and 6 and acts in the G1 phase of the cell cycle; p16, p21 and p27, cyclin-dependent kinase inhibitors, bind to cyclin-CDK-complexes, leading to cell cycle arrest in the G1-phase; mdm2, (mouse double minute 2), induction of mdm2 transcription is induced by p53 and results in p53 degradation; Ki67, marker of proliferation, expressed in the nucleus of proliferating cells; MI, mitotic index; GLUT1/CAIX, glucose transporter-1 protein and carbonic anhydrase IX are both regulated by hypoxia inducible factor-1 (HIF-1), intrinsic cellular markers of hypoxia; EGFR, epidermal growth factor receptor; HER2/neu, human epithelial growth factor receptor-2, belongs to the EGFR family, activation leads to proliferative signals within the cells; XRCC1 and APE1, x-ray repair cross complement group 1 and human AP endonuclease, DNA repair proteins of the base excision repair pathway.

(Rodel C et al, JCO 2006)

RTOG Genitourinary Translational Research Group:
-Her2 expression was significantly associated with reduced tumor response
-EGFR expression intriguingly predicted improved overall and disease free survival
(Chakravarti A et al, IJROBP 2005)

RTOG 05-24 trial was activated, using chemoradiotherapy with paclitaxel and trastuzumab for Her 2–neu overexpressing tumors (≥2+) whereas pts < 2+ will receive radiotherapy with weekly paclitaxel.

«New» evidence

Toxicity: analysis on 157 pts treated with combined modality treatment of 285 pts enrolled on RTOG 8903, 9506, 9706 and 9906 prospective trials- *(Efstathiou et al, JCO 2009)*

Median follow up: 5.4 yrs (2-13.2 yrs)

G1= 22%, G 2= 10%, G3= 7% (*5.7% GU, 1.9%GI*) ; G4&5= 0

G3 GU toxicity persisted in only 1 of 9 pts.

QoL: *(Weiss C et al, JCO 2006)- T1 pts(!) treated with trimodal therapy:*

Table 3. Quality of Life Due to Urinary Symptoms

Delighted	Pleased	Mostly Satisfied	About Equally Satisfied and Dissatisfied	Mostly Dissatisfied	Unhappy	Terrible
16.9%	53.5%	15.5%	12.7%	0%	1.4%	0%

NOTE. Seventy-one of 72 patients alive with their native bladder completed the question: "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?"

Evidence conclusion

Table 8 – Recommendations for radiation-based bladder-preserving strategies

Treatment/comparison	Evidence	Level of evidence	Grade
Chemoradiotherapy vs RT alone	Two RCTs report significant improvement in bladder tumor eradication.	1b	A
Chemoradiotherapy preserves good bladder function	Three QOL studies and RTOG protocols report good tolerance.	2a	B
Complete TURBT with chemoradiotherapy	Three reports (one phase 3, two phase 2) show benefit.	2a	B
Trimodality therapy vs immediate cystectomy	Comparison of three contemporary series of each treatment report similar 5- and 10-yr survival.	3	C

RT = radiation therapy; RCT = randomized controlled trial; QOL = quality of life; RTOG = Radiation Therapy Oncology Group; TURBT = transurethral resection of bladder tumor.

Gakis G et al, Eur Urol 2013

Controversies

1) Comparison with radical cystectomy: no randomized controlled trials!

Cystectomy series OS5 = 62-68% in centers of excellence *(Madersbacher S et al, JCO 2003)* vs 48-60% for trimodal therapy *(Kotwal S et al, IJROBP 2008; Mitin T et al Lancet Oncol 2013).*

In the update of Medical Research Council neoadjuvant trial BA06 30894, which randomised pts to neoadj CT or not followed by cystectomy, RT alone or RT+cystectomy the *OS rate of pts in the cystectomy arm was higher than in the RT arm* *(Griffiths G et al, JCO 2011).* *But* the randomisation was for neoadjuvant CT and there was a *selection bias* in subsequent local therapy choice.

Different inclusion criteria in cystectomy and chemo-RT, *clinical* (TURBT in RT-CT) vs *pathologic* (cystectomy) *staging* also *limit the validity* of any comparison.

2) Range of results: study pooling various protocols *(Efstathiou JA et al, Eur Urol 2012):*

CSS 5= 60-65%; Range 50-82%

OSS 5= 50%; Range 36-74%

Cause: differences in: inclusion period, patient selection, accuracy of staging, duration of follow-up, chemotherapy and radiation regimens, use of neoadjuvant/adjuvant chemotherapy.

Controversies

3) TMT strategy: maximal TURBT→ RT+CT, *but* includes salvage cystectomy for pts without CR or with LR→more an *attempt* at bladder preservation than *definitive* bladder preservation – *(Ploussard G et al, Eur Urol 2014).* Early salvage cystectomy prevents a loss in survival!

4)Split vs Continuous RT: *Induction* therapy consists of radiation to a dose of 40 Gy.

Consolidation is continued to a full dose of approximately 65 Gy after the restaging in *split course* trials *or the restage is deferred until* up to 1-3 months after the end of TMT in continuous course.

A *split course* is of some *radiobiologic concern* since tumor cell proliferation may occur during interruption→ a retrospective analysis *(Wittlinger M et al, Radiother Oncol 2009)* suggests that tumor clonogenic *repopulation* in bladder cancer *accelerates* after a lag period of *5-6 wks* after the start of treatment→ dose increment of 0.36 Gy/day is required to compensate the repopulation!

Controversies

5) Early vs late response evaluation: *(Rodel C et al, JCO 2006)*

-The early-response evaluation selects non –responders as early as possible because the curative potential of cystectomy might decrease if delayed

-The late-response evaluation may theoretically increase the chance of bladder preservation, because some slow-responders may maintain the bladder with late –response evaluation.

What would be the best approach?

6) Radiation therapy fractionation regimens: Which is best?

- RTOG 95-06 used *accelerated hypofractionation* (3 Gy bid first phase, 2.5 Gy bid second phase),
- RTOG 97-06 used *accelerated* radiotherapy, but *normal fractionation* (1.6-1.8 Gy),
- RTOG 85-12, 88-02 and 89-03 used *standard fractionation* (1.8-2 Gy, 1 fr/ day)
- MGH 1993-1994 used *accelerated hypefractionation* (1.25-1.5 Gy bid)

Stuschke M et al, IJROBP 1997, in a meta analysis based on pooled data of two old studies observed a significant improvement in local control and overall survival with hyperfractionated treatment and higher total dose. *Horwich A et al, Radiother Oncol 2005*, in a randomized trial suggested equivalent efficacy for twice daily vs once-daily treatments.

LoE→ we have to await the results of RTOG 07-12 protocol to evaluate twice daily vs once daily regimens.

Controversies

7) What total dose?

Generally 64-65 Gy but a meta- analysis of 15 radiation series with different fractionation schedules and total dose *Pos FJ et al, IJROBP 2006* found evidence for an overall dose-response relationship with an increase in local control by a factor of 1.44 to 1.47 for an increment in dose of 10 Gy→ *indicates that a dose escalation could significantly improve local control.*

8) Inclusion of pelvic lymph-nodes: lymphadenectomy and number of nodes removed have proven to be independent predictors of survival after cystectomy *(Svatek R et al, Curr Urol Rep 2012)*

Generally in *induction phase RT is performed on pelvis* but *Tunio MA et al, IJROBP 2012,* on a randomised trial including 230 pts targeted only the bladder with 2 cm margins without affecting survival! The BC2001 trial *(James ND et al, N Engl J Med 2012)* comparing RT with or without CT (MMC+ 5 FU) targeted the bladder + 1.5 cm (2 cm around visible tumor)- only 5% nodal recurrence!

Controversies

9) Whole- bladder or partial bladder volume? – BC 2001 trial also randomly assigned pts to undergo either whole- bladder or reduced bladder volume RT *(Huddart RA et al, IJROBP 2013)*

-failed to demonstrate any side effect benefit from reducing the volume

-the non- inferiority of locoregional control could not be concluded formally!

10) Concurrent chemotherapy regimens:

Analysis of 17 trials or retrospective studies- Cisplatin is the most active single agent, improves local control, no impact on OS *(Ploussard G et al, Eur Urol 2014; Sternberg C et al, Eur Urol 2013)*. *Different schedules= similar response rate*. *Intensification- no definitive benefit. Intra-arterial- higher toxicity.*

Alternative combinations with *similar results:* MMC+ 5-FU *(Hussain et al, Br J Cancer 2004; James et al N Engl J Med 2012)* (only unfit for platinum –based regimen)?; Gemcitabine weekly *(Choudhury et al, JCO 2011)?* → *What would be the best?* - wait for RTOG 07-12 results…

Controversies

11) New technologies?
Daily CT set-up has been shown to be superior to traditional EPID portals and to decrease treatment related toxicity *(Foroudi F et al, Clin Oncol 2012)*

= conserve the small bowel for future urinary diversions, if necessary!

Proton beam - only preliminary reports *(Hata M et al, IJROBP 2006)*

(Rodel C et al JCO 2006)

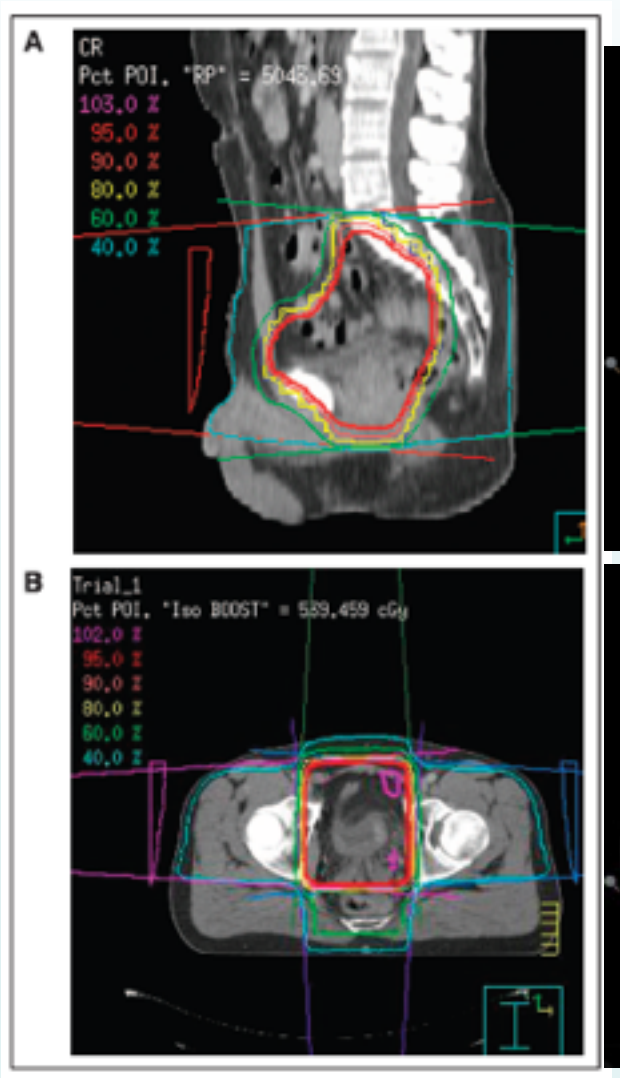
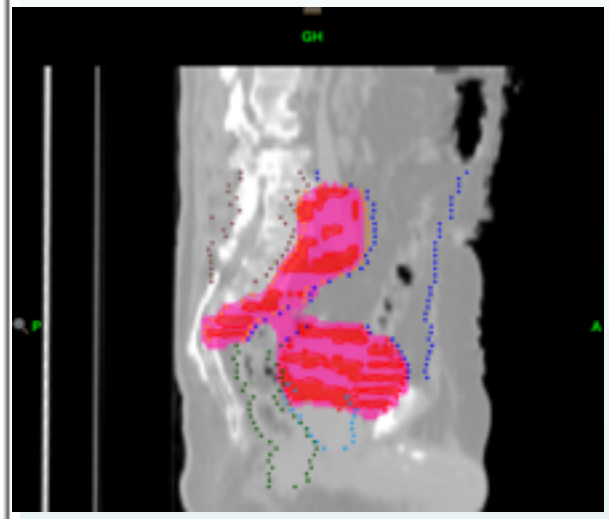
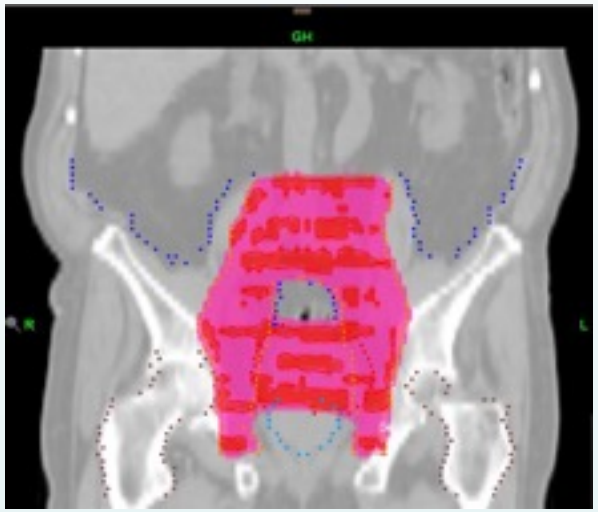
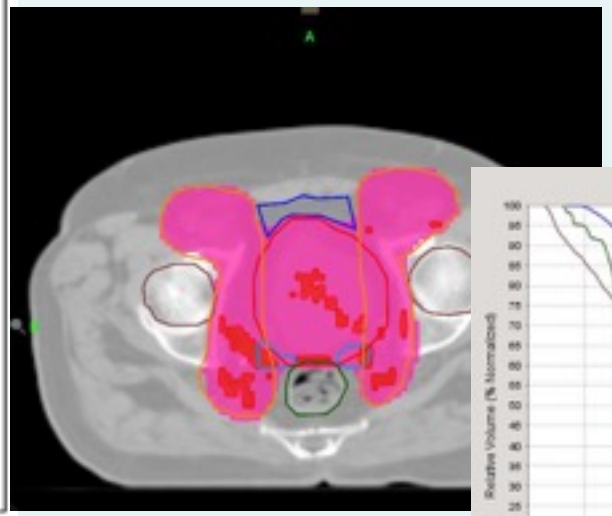


Fig 2. Radiation treatment plans frequently encompass pelvic lymph nodes to a total dose of 45 to 50 Gy (A), then a cone-down is applied to boost the whole bladder or the bladder tumor alone (B). Difference in bladder and tumor position as a result of variation in bladder and rectal filling require an isotropic margin of 2 cm around the gross tumor volume (GTV). Image-guided radiotherapy with day-to-day optimization of treatment volumes may help to eliminate geographical miss and reduce normal tissue toxicity.[41,42]







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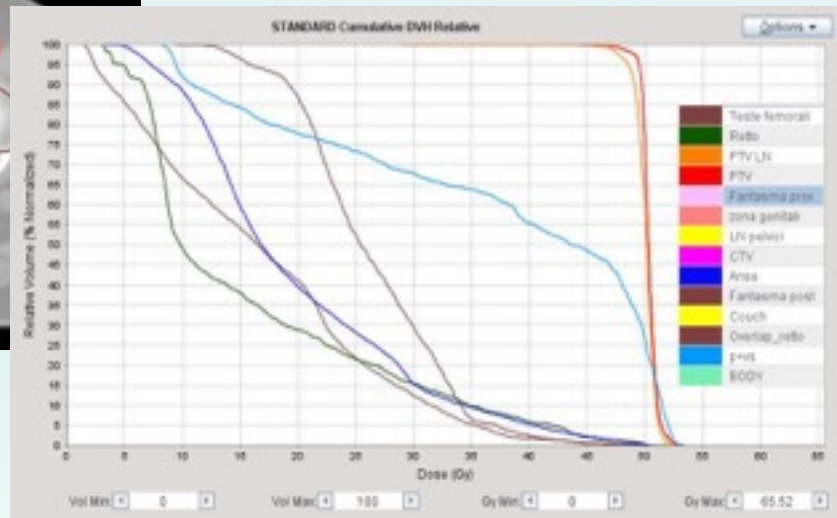

Controversies

12) Role of Neoadjuvant chemotherapy: evident role before cystectomy *(Yafi FA et al, BJU Int 2011; Bekelman JE et al, Value Health 2013, Sternberg C et al, Eur Urol 2013)* with a 5% improvement in OS 5 in a meta-analysis *(Smith ZL et al BJU Int 2013).* But:

a) BA06 30894 suggests a greater impact in LRFS before cystectomy (a significant 26% RR) than *before RT (a non significant 9% RR)-* *(Griffiths G et al, JCO 2011)*

b) limited completion rates because of high toxicity rates (77% G3&4 in RTOG 89-03, stopped early, with no significant difference in CR, DMFS, OS)

MGH did not find neoadjuvant chemotherapy to be a predictor of better survival *(Efstathiou JA et al, Eur Urol 2012)*

Why? Insufficient chemotherapy? Patient selection? Selection of radioresistant clones because of cross-resistence chemotherapy-radiotherapy? Induction of accelerated repopulation? Reduced compliance? Or only inadequately powered studies?

13) Role of Adjuvant chemotherapy:

Lower completion than for neoadjuvant treatment (45-70%) *(Hagan MP et al, IJOBP 2003; Kaufman DS et al, Urology 2009)* with high G3&4 toxicity.

But *no survival outcomes from phase III trials* evaluating adjuvant chemotherapy folowing trimodal therapy *have yet been published* *(Ploussard G et al, Eur Urol 2014).*

Controversies

14) Bladder preservation assessed in different cohorts of inoperable pts: Medically inoperable patients vs surgically unresectable disease - in SWOG 9312 trial pts classified in the two categories→ medical comorbidities *contraindicating general anesthesia or surgery were associated with* poorer OS *(Hussain MH et al, J Urol 2001);* result confirmed by the GETUG 97-015 QoL assessment by *Lagrange JL et al, IJROBP 2011.*

15) Real response rate? *Overall mean response rate 73% (Ploussard G et al, Eur Urol 2014)*. Defined by: absence of visible tumor+ absence of persistent pathologically proven bladder tumor on biopsy+ absence of tumor cells in the urine cytology→ *significantly better (by one third) survival rate than no CR*. *But*:

- *Housset et al, JCO 1993* observed that only 45% of CR pts treated with cystectomy and without TMT completion were pT0 disease!!!

- *Donat SM et al, J Urol 1996-* MSKCC experience: 30% of pts following chemotherapy alone have residual disease after cystectomy that was not detected by preoperative TURBT.

Probably today we perform better, but what is the real response rate?- Downstaging rate between TURBT and cystectomy series ranging from 17-30% and presumed cT2 tumors treated by chemo-RT may persist as pT0/pT1 after TURBT *(Svatek RS et al, BJU Int 2011; Yafi Fa et al, BJU Int 2011; Culp SH et al, J Urol 2014)*

Controversies

16) Predictors of response: identify the subgroup of bladder cancer pts that would not respond with lower CSS 5 = 20-40% *(Efstathiou JA et al, Eur Urol 2012)* :

a)Carcinoma in situ (not in multivariable analysis…),

b)incomplete resection (20% loss in CR)- re-TURBT?,

c)locally advanced disease (T4),

d)uretheral obstruction, hydronephrosis (occur in 10-35% of pts),

e)multiplicity (yes/no?),

f)Pathologic: clinical stage, high tumor grade, lymph node involvement, L-VI

àLimited number of pts meet the criteria!- 10-15% of medically operable pts *(Smith ZL et al, BJU Int 2013)* *but*- limited level of evidence and *trimodal therapy is used as an alternative in non ideal candidates for cystectomy*…

Controversies

17) Follow-up: requires: voided urine cytology, cystoscopy, CT/MR and prompt salvage cystectomy, risk adapted surveillance for distant metastasis and the upper tract.

Some authors suggest systematic tumor-site rebiopsy, bi-manual examination under general anesthesia with additional biopsies if negative cystoscopy but tumor growth underneath the TUR scar- no strong Level of evidence.

How long?

Risk of late metastatic or muscle –invasive bladder failure decrease in time and a flattening of CSS curve beyond the first 5 years after trimodal treatment, similar to cystectomy results, was observed in some trials *(Efstathiou JA et al, Eur Urol 2012)*

Other series report late recurrences beyond the first 5 years *(Herr HW et al, Br j Urol 1997; Zietman AL et al, Urology 2001; Weiss C et al, IJROBP 2008)*

àLifelong cystoscopy follow up recommended!!! *(Ploussard G et al, Eur Urol 2014)*

Costs and quality of life of follow-up?

18) Late toxicity and QoL: many toxicities were physician reported rather than patient reported. *Was late toxicity underestimated?* QoL studies are small with interpretation biases→LoE 2°

Many bladder cancer pts have *significant lower urinary tract symptoms* from *benign prostatic obstruction-* The symptoms worsen after irradiation? *(Ploussard G et al, Eur Urol 2014)*

Conclusions

1) **Trimodal therapy is the primary bladder preservation strategy**

2) **Ideal candidates for bladder preservation should :**

   a) have adequate renal function (allow Cisplatin based chemotherapy)
   b) have adequate bladder capacity and function
   c) be motivated, without history of pelvic radiation, accepting an ileal neobladder upon recurrence
   d) have organ confined tumor (cT2), small tumor size, absence of palpable mass
   e) have undergone a TUR of all visible tumor
   f) have no hydronephrosis
   g) have no extensive CIS
   h) have no multifocal disease
   i) have negative Her2-neu and positive EGFR

San Raffaele Scientific Institute

Thank you!