Approaches in the Management of Muscle Invasive Bladder Cancer

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ICRO

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Outline

- Introduction
- Evaluation
- Staging
- Management options
- RT techniques
- Recent advances

Introduction

- Majority are diagnosed with superficial bladder cancers
- Up to 15% present with muscle invasive disease
- For whom the risk of progression or metastasis is substantial
- Prognosis and recurrences vary by stage of disease as well as other prognostic features , including lymph node involvement, lymphovascular invasion, tumor stage, presence of variant histology, and molecular sub typing

- RC has historically been the cornerstone of treatment for MIBC
- Optimizing outcomes with NAC and alternative options for bladder preservation strategies have also emerged as treatment

Evaluation

- Full history and physical examination
- Comprehensive blood tests(CBC,LFT,RFT)
- Cystoscopy & TURBT – HPE
- Experienced GU pathologist review
- Imaging of chest –CXR/CT thorax
- Cross sectional CT imaging of abdomen and pelvis with IV contrast if not contraindicated
- MDT discussion

TNM staging 8th edition

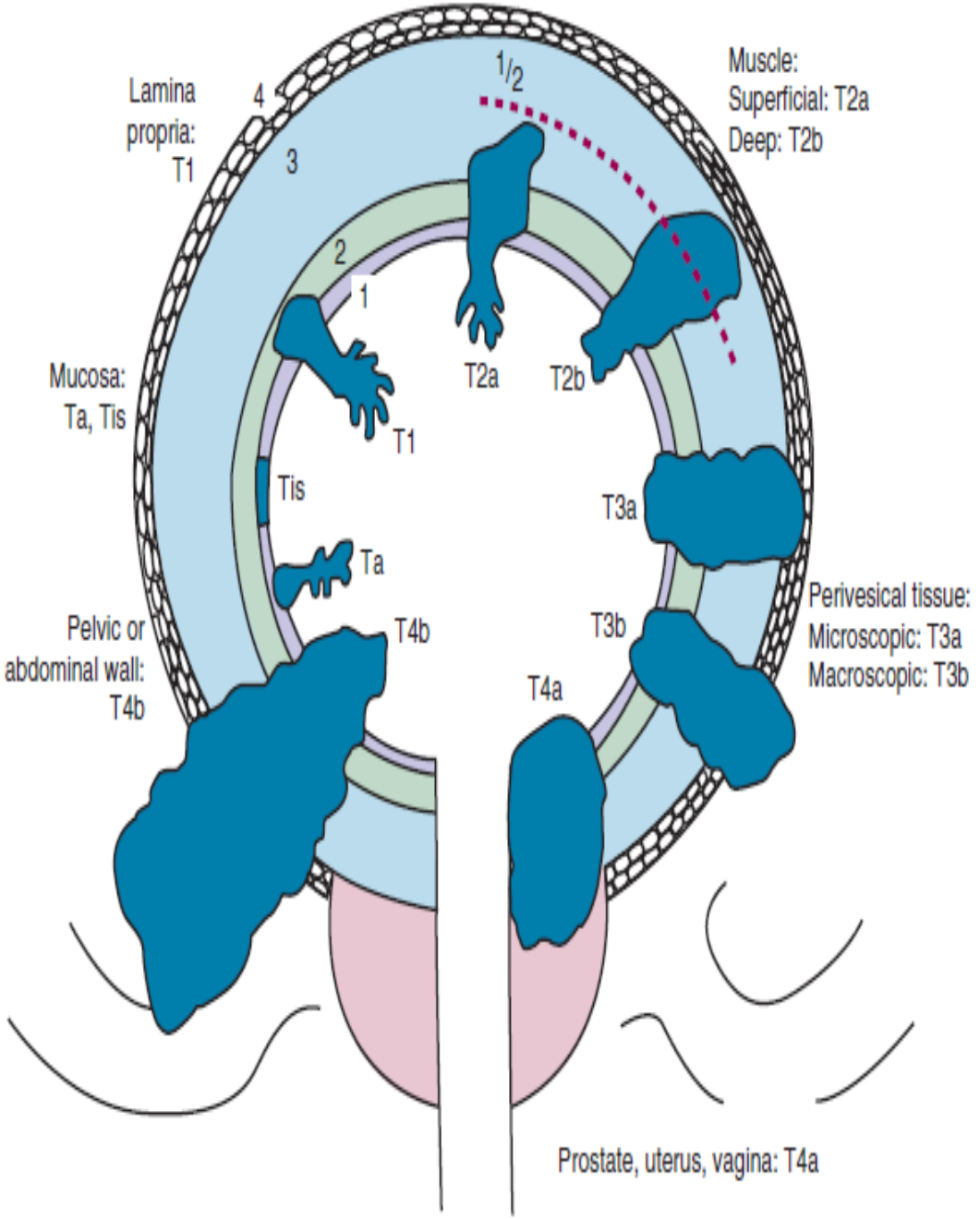


Figure 52-1 Staging of bladder tumors.

AJCC 8th editi

TNM Staging System for Bladder Cancer 8th ed., 2017)

T	**Primary Tumor**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Noninvasive papillary carcinoma
Tis	Urothelial carcinoma in situ: "flat tumor"
T1	Tumor invades lamina propria (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	Extravesical tumor directly invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Extravesical tumor invades prostatic stroma, seminal vesicles, uterus, vagina
T4b	Extravesical tumor invades pelvic wall, abdominal wall

N	**Regional Lymph Nodes**
NX	Lymph nodes cannot be assessed
N0	No lymph node metastasis
N1	Single regional lymph node metastasis in the true pelvis (perivesical, obturator, internal and external iliac, or sacral lymph node)
N2	Multiple regional lymph node metastasis in the true pelvis (perivesical, obturator, internal and external iliac, or sacral lymph node metastasis)
N3	Lymph node metastasis to the common iliac lymph nodes

M	**Distant Metastasis**
M0	No distant metastasis
M1	Distant metastasis
M1a	Distant metastasis limited to lymph nodes beyond the common iliacs
M1b	Non-lymph-node distant metastases

Prognostic Staging

T	N	M	STAGE
Ta	N0	M0	0a
Tis	N0	M0	0is
T1	N0	M0	I
T2a	N0	M0	II
T2b	N0	M0	II
T3a,T3b,T4a	N0	M0	IIIA
T1-T4a	**N1**	M0	**IIIA**
T1-T4a	**N2-3**	M0	**IIIB**
T4b	N0	M0	IVA
ANY T	ANY N	**M1a**	**IVA**
ANY T	ANY N	**M1b**	**IVB**

Grouping

75 – 80% - Superficial bladder cancer – pTa, pTis, pT1

10 – 15% - **Muscle invasive bladder cancer** – pT2, pT3, pT4

5% - Metastatic bladder cancer - M+ (Non regional nodes and distant)

MANAGEMENT OPTIONS

MANAGEMENT OPTION: 1

NACT FOLLOWED BY RADICAL CYSTECTOMY & PLND &URINARY DIVERSION

Criteria

- cT2- T4N+
- Cisplatin eligibility
- Fit for Radical cystectomy (based on patient co morbidity and tumor characteristics)
- Willing for RC after counseling regarding the complications and the implications of treatment on QOL

Evidence

The NEW ENGLAND JOURNAL of MEDICINE

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.

CONCLUSIONS

As compared with radical cystectomy alone, the use of neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin followed by radical cystectomy increases the likelihood of eliminating residual cancer in the cystectomy specimen and is associated with improved survival among patients with locally advanced bladder cancer.

Evidence

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

Conclusion

We conclude that CMV chemotherapy improves outcome as first-line adjunctive treatment for invasive bladder cancer. Two large randomized trials (by the Medical Research Council/European Organisation for Research and Treatment of Cancer and Southwest Oncology Group) have confirmed a statistically significant and clinically relevant survival benefit, and neoadjuvant chemotherapy followed by definitive local therapy should be viewed as state of the art, as compared with cystectomy or radiotherapy alone, for deeply invasive bladder cancer.

Neoadjuvant Chemotherapy in Invasive Bladder Cancer: Update of a Systematic Review and Meta-Analysis of Individual Patient Data

Advanced Bladder Cancer (ABC) Meta-analysis Collaboration

Meta-analysis Group, Medical Research Council Clinical Trials Unit, 222 Euston Road, London NW1 2DA, UK

Accepted 6 April 2005

- Updated results are based on 11 trials, 3005 patients; comprising 98% of all patients from known eligible randomised controlled trials
- 5.5 % absolute improvement in survival at 5 years.
- Significant disease-free survival benefit associated with **platinum-based combination chemotherapy** (HR = 0.78 95% CI 0.71-0.86, p < 0.0001), equivalent to a 9% absolute improvement at 5 years.

MANAGEMENT OPTION 2 :

RADICAL CYSTECTOMY & PLND &URINARY DIVERSION FOLLOWED BY ADJUVANT CHEMOTHERAPY/ADJUVANT RT

Criteria

- Eligible patients who have not received Cisplatin based NAC
- Non organ confined disease(pT3/T4 and /or N+ disease at cystectomy

Evidence

Immediate versus deferred chemotherapy after radical cystectomy in patients with pT3–pT4 or N+ M0 urothelial carcinoma of the bladder (EORTC 30994): an intergroup, open-label, randomised phase 3 trial

Cora N Sternberg, Iwona Skoneczna, J Martijn Kerst, Peter Albers, Sophie D Fossa, Mads Agerbaek, Herlinde Dumez, Maria de Santis, Christine Théodore, Michael G Leahy, John D Chester, Antony Verbaeys, Gedske Daugaard, Lori Wood, J Alfred Witjes, Ronald de Wit, Lionel Geoffrois, Lisa Sengelov, George Thalmann, Danielle Charpentier, Frédéric Rolland, Laurent Mignot, Santhanam Sundar, Paul Symonds, John Graham, Florence Joly, Sandrine Marreaud, Laurence Collette, Richard Sylvester, for the European Organisation for Research and Treatment of Cancer Genito-Urinary Cancers Group, Groupe d'Etude des Tumeurs Urogénitales, National Cancer Research Institute Bladder Cancer Study Group, National Cancer Institute of Canada Clinical Trials Group, and German Association of Urologic Oncology (AUO)

Interpretation Our data did not show a significant improvement in overall survival with immediate versus deferred chemotherapy after radical cystectomy and bilateral lymphadenectomy for patients with muscle-invasive urothelial carcinoma. However, the trial is limited in power, and it is possible that some subgroups of patients might still benefit from immediate chemotherapy. An updated individual patient data meta-analysis and biomarker research are needed to further elucidate the potential for survival benefit in subgroups of patients.

Evidence

Review – Urothelial Cancer

A Systematic Review and Meta-analysis of Adjuvant and Neoadjuvant Chemotherapy for Upper Tract Urothelial Carcinoma

Jeffrey J. Leow[a,b], *William Martin-Doyle*[c], *André P. Fay*[a], *Toni K. Choueiri*[a], *Steven L. Chang*[a,b], *Joaquim Bellmunt*[a,*]

[a] *Bladder Cancer Center, Dana-Farber/Brigham and Women's Cancer Center, Harvard Medical School, Boston, MA, USA;* [b] *Division of Urology and Center for Surgery and Public Health, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA;* [c] *University of Massachusetts Medical School, Worcester, MA, USA*

Conclusions: There appears to be an OS and DFS benefit for cisplatin-based AC in UTUC. This evidence is limited by the retrospective nature of studies and their relatively small sample size. NC appears to be promising, but more trials are needed to confirm its utility. ***Patient summary:*** After a comprehensive search of studies examining the role of chemotherapy for upper tract urothelial cancer, the pooled evidence shows that cisplatin-based adjuvant chemotherapy was beneficial for prolonging survival.

JAMA Surgery | Original Investigation

Adjuvant Sandwich Chemotherapy Plus Radiotherapy vs Adjuvant Chemotherapy Alone for Locally Advanced Bladder Cancer After Radical Cystectomy

A Randomized Phase 2 Trial

Mohamed S. Zaghloul, MD, MSc, MBBCh; John P. Christodouleas, MD, MPH; Andrew Smith, MS; Ahmed Abdallah, MD; Hany William, MD; Hussein M. Khaled, MD; Wei-Ting Hwang, PhD; Brian C. Baumann, MD

CONCLUSIONS AND RELEVANCE Adjuvant chemotherapy plus RT was reasonably well tolerated and was associated with significant improvements in LRFS and marginal improvements in disease-free survival vs chemotherapy alone in LABC. The addition of adjuvant RT should be considered for LABC. This regimen warrants further study in phase 3 trials.

International Consensus Contouring Guidelines for Adjuvant Radiation after Radical Cystectomy for Bladder Cancer

Brian C. Baumann, Walter R. Bosch, Amit Bahl, Alison J. Birtle, Rodney H. Breau, Amarnath Challapalli, Albert J. Chang, Ananya Choudhury, Sia Daneshmand, Ali El-Gayed, Adam Feldman, Steven E. Finkelstein, Thomas J. Guzzo, Serena Hilman, Ashesh Jani, S. Bruce Malkowicz, Constantine A. Mantz, Viraj Master, Anita V. Mitra, Vedang Murthy, Sima P. Porten, Pierre M. Richaud, Paul Sargos, Jason A. Efstathiou, Libni J. Eapen, John P. Christodouleas

Contours adopted for the NRG-GU001 trial

NRG ONCOLOGY

NRG-GU001

(ClinicalTrials.gov NCT #: NCT02316548***)***

RANDOMIZED PHASE II TRIAL OF POSTOPERATIVE ADJUVANT IMRT FOLLOWING CYSTECTOMY FOR pT3/pT4 UROTHELIAL BLADDER CANCER

MANAGEMENT OPTION : 3

BLADDER SPARING THERAPY

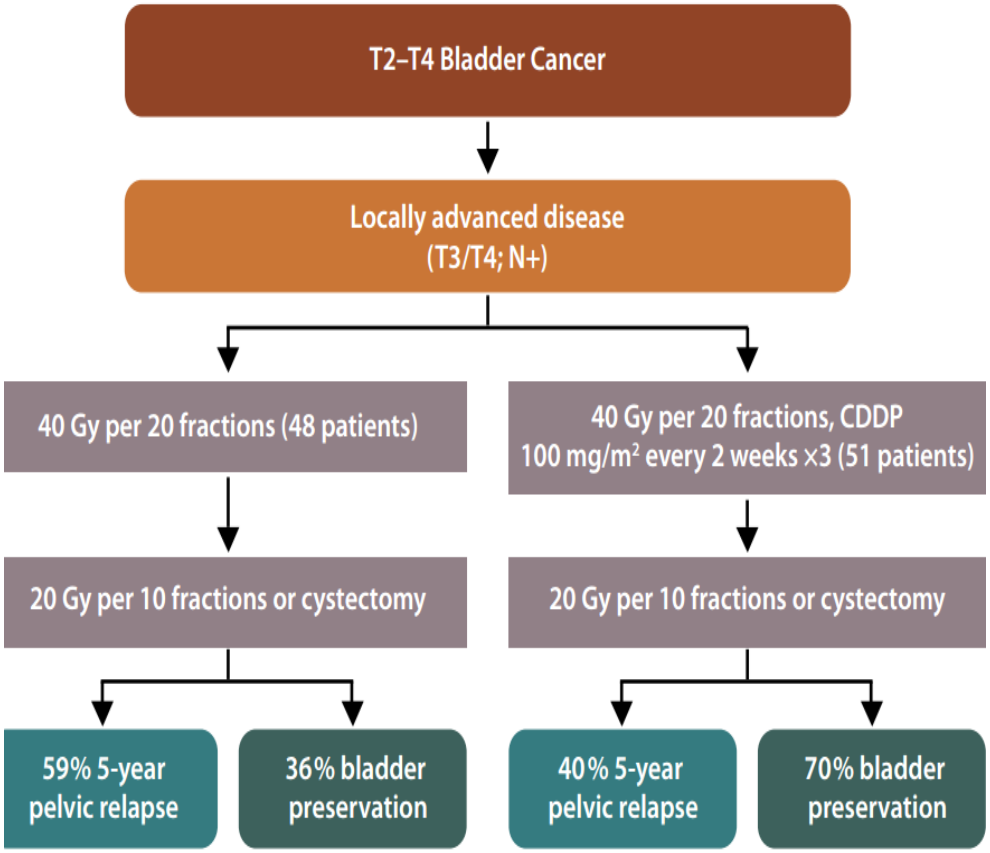
Bladder conservation approach

- **Main concerns about bladder preservation compared with radical cystectomy**
  - Toxicity
  - Field cancerisation effect: 30 – 50% of patients experience local recurrence, either in the are of tumour or in a different part of bladder
  - Close surveillance is critical

Ideal candidates of trimodality treatment

- Solitary T2 or early T3 < 5 cms
- No tumour associated hydronephrosis
- Complete TURBT
- No CIS
- Adequate renal function to allow cisplatin concurrent with RT
- TCC histology
- Willing to be on close surveillance
- Willing for cystectomy in case of progression

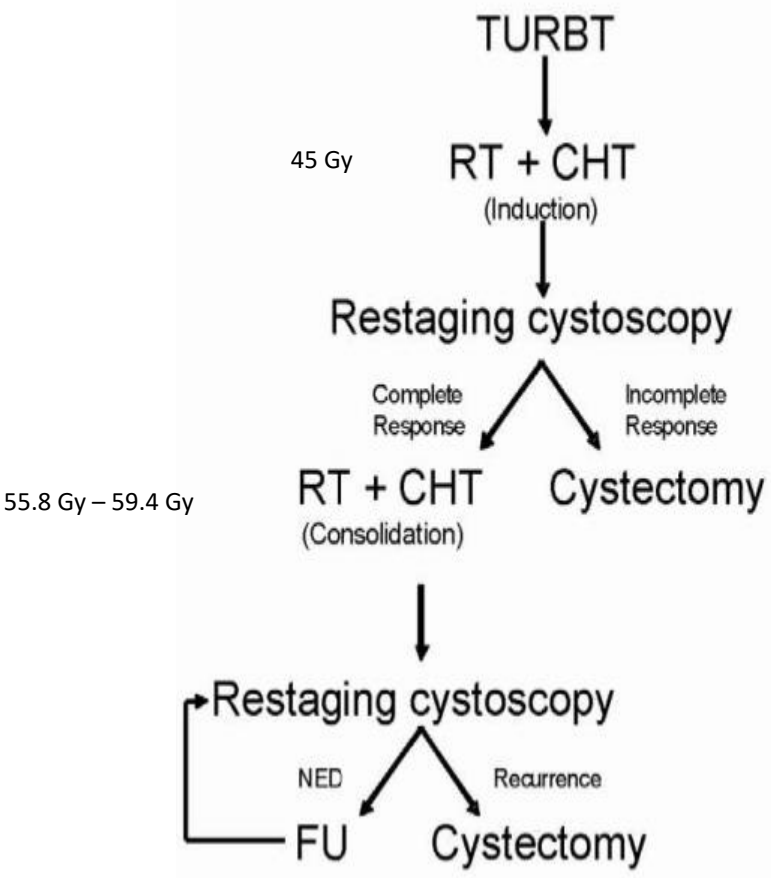
NCIC, Canada trial - RT Vs ChemoRT



- RT Vs ChemoRT
- Significant benefit in adding CDDP along with RT in terms of local regional relapse rates
- Lesser cystectomy rate and pelvic relapse rates
- No difference in OS or distant metastasis.

PIONEERING SINGLE INSTITUTION STUDIES OF TRIMODALITYTREATMENT

MGH



ERLANGEN

Treatment	Overall survival (%)	Complete response (%)
RT alone	40	61
RT+carboplatin	45	66
RT+cisplatin	62	82
RT+cisplatin+5FU	65	87

TRIALS ON BLADDER CONSERVATION

Investigators	Stage	Treatment	No. of Patients	Survival With Intact Bladder
Shipley et al[9]	T2-T4a	TURBT + chemotherapy + radiation therapy	190	45% (10-yr DSS with intact bladder)
Rödel et al[10]	T1-T4	TURBT + chemotherapy + radiation therapy	415	42% (5-yr OS with intact bladder)
Housset et al[11]	T2-T4	TURBT + chemotherapy + radiation therapy	54	Not reported (62% 3-yr DSS)
Sternberg et al[12]	T2-T4	Neoadjuvant M-VAC + TURBT	104	44% (5-yr OS, with intact bladder)
Herr[13]	T2	TURBT alone	99	57% (10-yr with intact bladder; includes only patients selected for bladder sparing)

TURBT = transurethral resection of the bladder tumor
M-VAC = methotrexate, vinblastine, doxorubicin, and cisplatin
DSS = disease-specific survival
OS = overall survival

Bladder Preservation

Success rate of bladder preservation:

- TURBT alone - 20% free of invasive bladder recurrence
- Radiation Therapy alone - 41%
- Chemotherapy alone - 19%

Complete response rate:

- Radiation Therapy alone - 45%
- Chemotherapy alone - 27%
- TURBT + chemotherapy - 51%
- TURBT + chemo irradiation - 70-80%

QUALITY OF LIFE ISSUES

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,†
DONALD S. KAUFMAN, JACK A. CLARK, JAMES A. TALCOTT AND WILLIAM U. SHIPLEY

From the Departments of Radiation Oncology (ALZ, US, WUS), Urology (DS, PG) and Medical Oncology (DSK, JAT), Massachusetts General Hospital, Harvard Medical School, and Department of Health Services (JAC), Boston University School of Public Health, Boston, Massachusetts

221 patients, T2-4Nx-0M0 bladder cancer,

Treated on protocols 1986-2000, median follow up : 6.3 years

Urodynamic study, QOL questionnaire

- 78% have compliant bladders with normal capacity and flow parameters
- 85% have no urgency or occasional urgency
- 25% have occasional to moderate bowel control symptoms
- 50% of men have normal erectile function

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

Jason A. Efstathiou, Kyounghwa Bae, William U. Shipley, Donald S. Kaufman, Michael P. Hagan, Niall M. Heney, and Howard M. Sandler

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%

0% - Grade 4

0% - Grade 5

Table 4. Late Grade 3+ Pelvic Toxicity in RTOG Protocols

RTOG Protocol	Complete Response Rates (%)*	No. of Analyzable Patients	Grade 3+ Toxicity			
			GU		GI	
			No.	%	No.	%
89-03	59	56	4	7	2	4
95-06	67	24	0	0	0	0
97-06	74	24	2	8	1	4
99-06	87	53	3	6	0	0
Total		157	9	5.7	3	1.9

Abbreviations: RTOG, Radiation Therapy Oncology Group; GU, genitourinary.
*Complete response rates are for all eligible patients.

RT TECHNIQUES

TECHNIQUES

- 2D CONVENTIONAL

- CONFORMAL – IMRT, VMAT, TOMOTHERAPY

Simulation and positioning

- Supine position with arms over chest
- Bladder localisation is important

Phase 1 – can be treated with full or optimal bladder filling

Phase 2 – in empty bladder

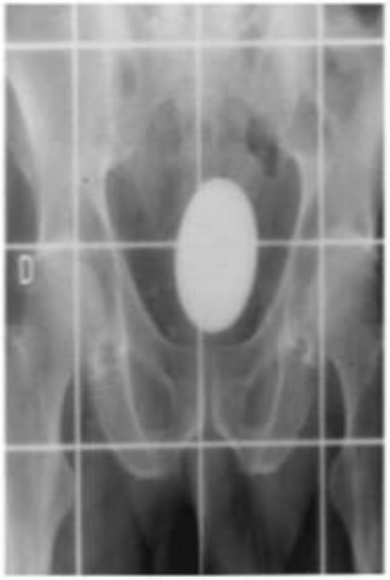
Or,

- Foley catheter inserted shortly after the patient has voided
- Post voiding urine residual is measured
- This volume is replaced by an equal volume of bladder contrast plus an additional 25 mL of contrast and 15 mL of air.

- Phase 1-
  - The whole pelvis , encompassing the pelvic lymph nodes, bladder and proximal urethra
  - Elective irradiation of the pelvic lymph nodes
- Phase 2-
  - Then cone down to boost the bladder alone

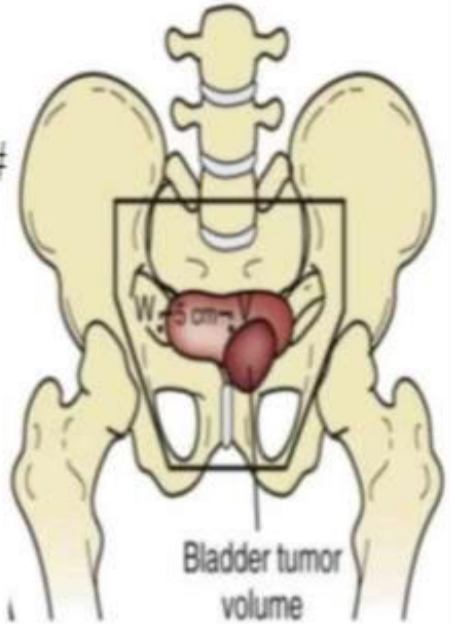
Conventional planning

Phase I:



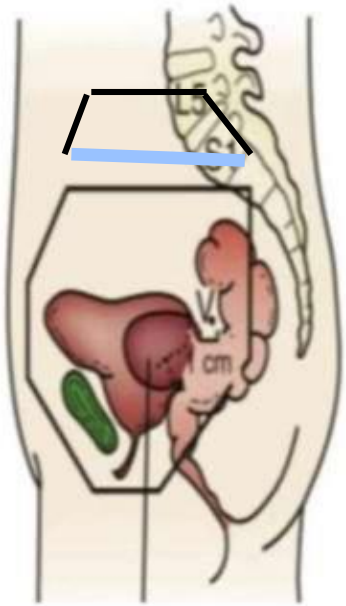
- Superior :at the L5-S1 disc space
- Inferior : below obturator foramen.
- Laterally:1.5-2 cm to the bony pelvis at its widest section

- Dose:40-45 GY @ 1.8-2Gy/#



Lateral fields

- Anterior : anterior to bladder with a margin with 1.5 – 2cm
- Posterior : 2-3 cm posterior to bladder



Phase II

- PORTALS
  - Anterior : bladder with a margin of 1.5-2 cm
  - Lateral – bladder with a margin of 1.5-2cm

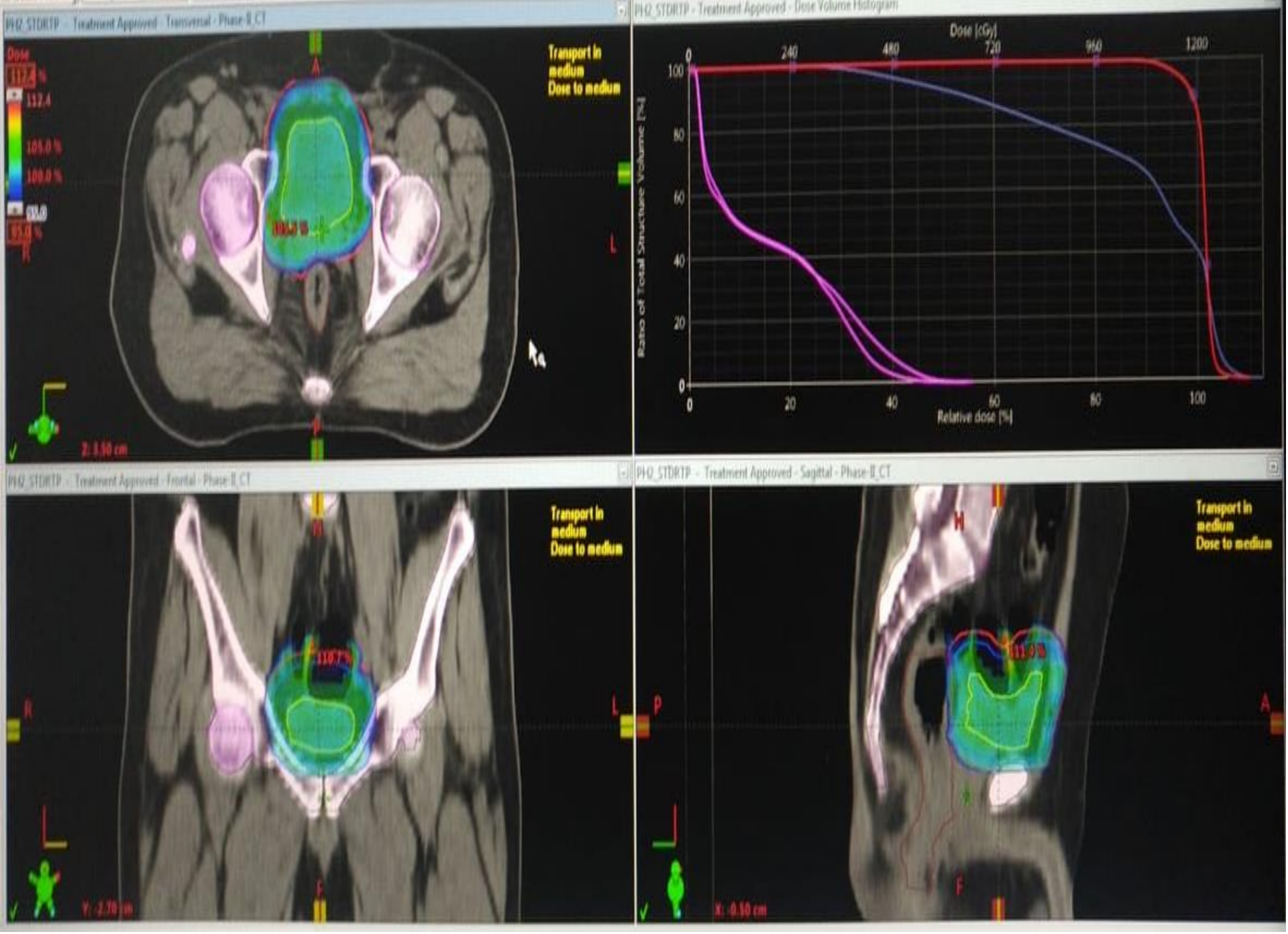
- Fields
  - 2 lateral and one anterior
  - 2 oblique's and one anterior
- Dose : 60-66 Gy to bladder

Conformal Planning and simulation

- Supine position with arms over chest
- Rectum should be empty of flatus and feces
- 3 – 5mm CT cuts
- IV contrast may be used but is not mandatory
- Bladder filling variability to be minimised

Radiation therapy Volumes

- GTV – Should integrate information from staging CT or MRI as well as TURBT
- CTV – GTV + whole bladder + proximal urethra + Prostate and prostatic urethra (Men) +/- Elective nodes
- PTV – CTV + 1.5-2.0 cms margins


PHQ_STDRTP - Treatment Approved - Transversal - Phase II_CT
Transport in medium
Dose to medium
PHQ_STDRTP - Treatment Approved - Dose Volume Histogram
Dose [cGy]
Ratio of Total Structure Volume [%]
Relative dose [%]
PHQ_STDRTP - Treatment Approved - Frontal - Phase II_CT
Transport in medium
Dose to medium
PHQ_STDRTP - Treatment Approved - Sagittal - Phase II_CT
Transport in medium
Dose to medium

Radiation Dose

- Most commonly used schedule – SPLIT SCHEDULE
  - 40 - 45GY in 1.8 – 2Gy per fraction – Phase 1
  - If good response – To go to radical dose of 64 - 66Gy

- Hypofractionation (55Gy in 20 fractions) – Practiced in some centers in UK
- Hyper fractionation (BD RT) – Also tried and used in trials

Recent advances

- Pathology : Biomarkers
- Surgery : Robotic Vs Open Cystectomy
- RT : Adaptive Radiotherapy
- Systemic therapy : Immunotherapy

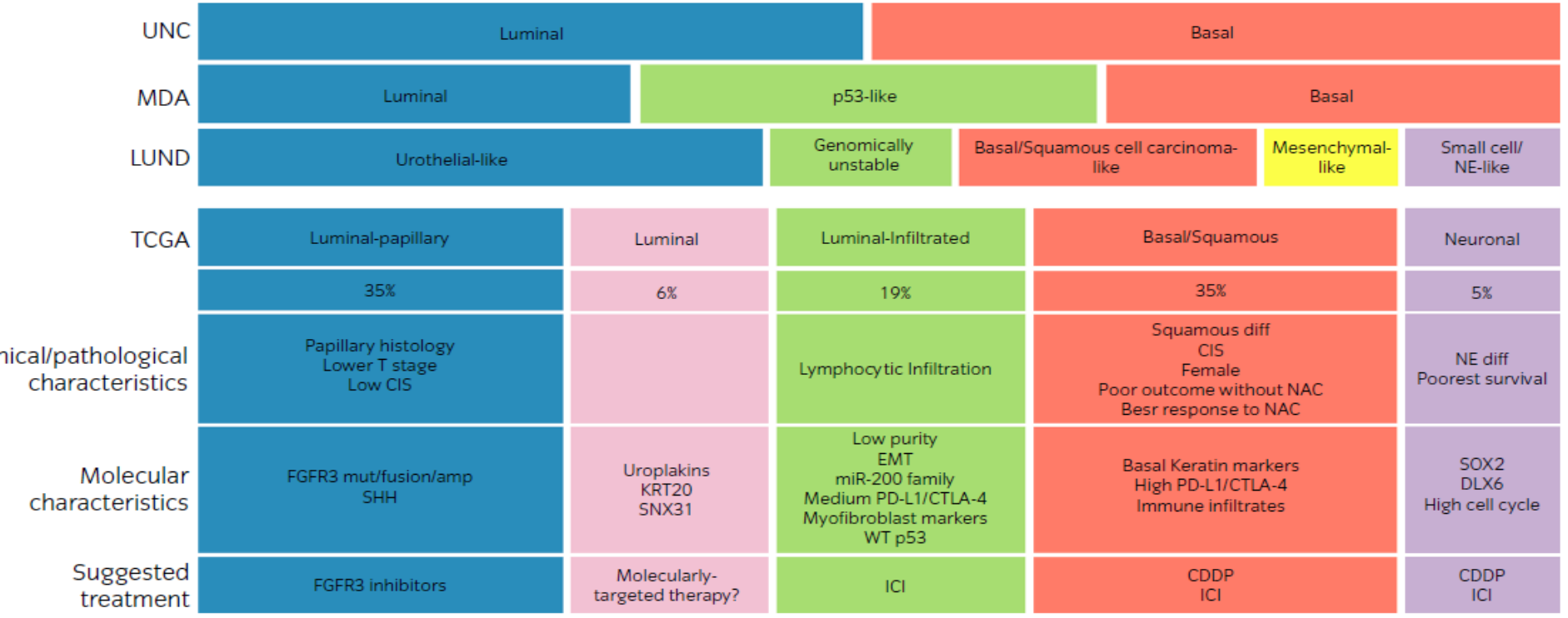
INTERNATIONAL JOURNAL OF UROLOGY
International Journal of Urology (2019) 26, 1044–1053 doi: 10.1111/iju.14082

Review Article

Predictive biomarkers for drug response in bladder cancer

Takahiro Yoshida,[1,†] Max Kates,[1,2] Kazutoshi Fujita,[3] Trinity J Bivalacqua[1,2] and David J McConkey[1,2]

[1]Department of Urology, The James Buchanan Brady Urological Institute, Johns Hopkins School of Medicine, [2]The Johns Hopkins Greenberg Bladder Cancer Institute, Baltimore, Maryland, USA, and [3]Department of Urology, Osaka University Graduate School of Medicine, Suita, Osaka, Japan



Cochrane Library

Cochrane Database of Systematic Reviews

Robotic versus open radical cystectomy for bladder cancer in adults (Review)

Authors' conclusions

Robotic cystectomy and open cystectomy may have similar outcomes with regard to time to recurrence, rates of major complications, quality of life, and positive margin rates (all low-certainty evidence). We are very uncertain whether the robotic approach reduces rates of minor complications (very low-certainty evidence), although it probably reduces the risk of blood transfusions substantially (moderate-certainty evidence) and may reduce hospital stay slightly (low-certainty evidence). We were unable to conduct any of the preplanned subgroup analyses to assess the impact of patient age, pathological stage, body habitus, or surgeon expertise on outcomes. This review did not address issues of cost-effectiveness.

BMJ Open

Protocol for hypofractionated adaptive radiotherapy to the bladder within a multicentre phase II randomised trial: radiotherapy planning and delivery guidance

Shaista Hafeez ,[1,2] Emma Patel,[3] Amanda Webster,[3] Karole Warren-Oseni,[1,2] Vibeke Hansen,[4] Helen McNair,[1,2] Elizabeth Miles,[3] Rebecca Lewis,[5] Emma Hall,[5] Robert Huddart[1,2]

Radiotherapy and Oncology 99 (2011) 55–60

Contents lists available at ScienceDirect

Radiotherapy and Oncology

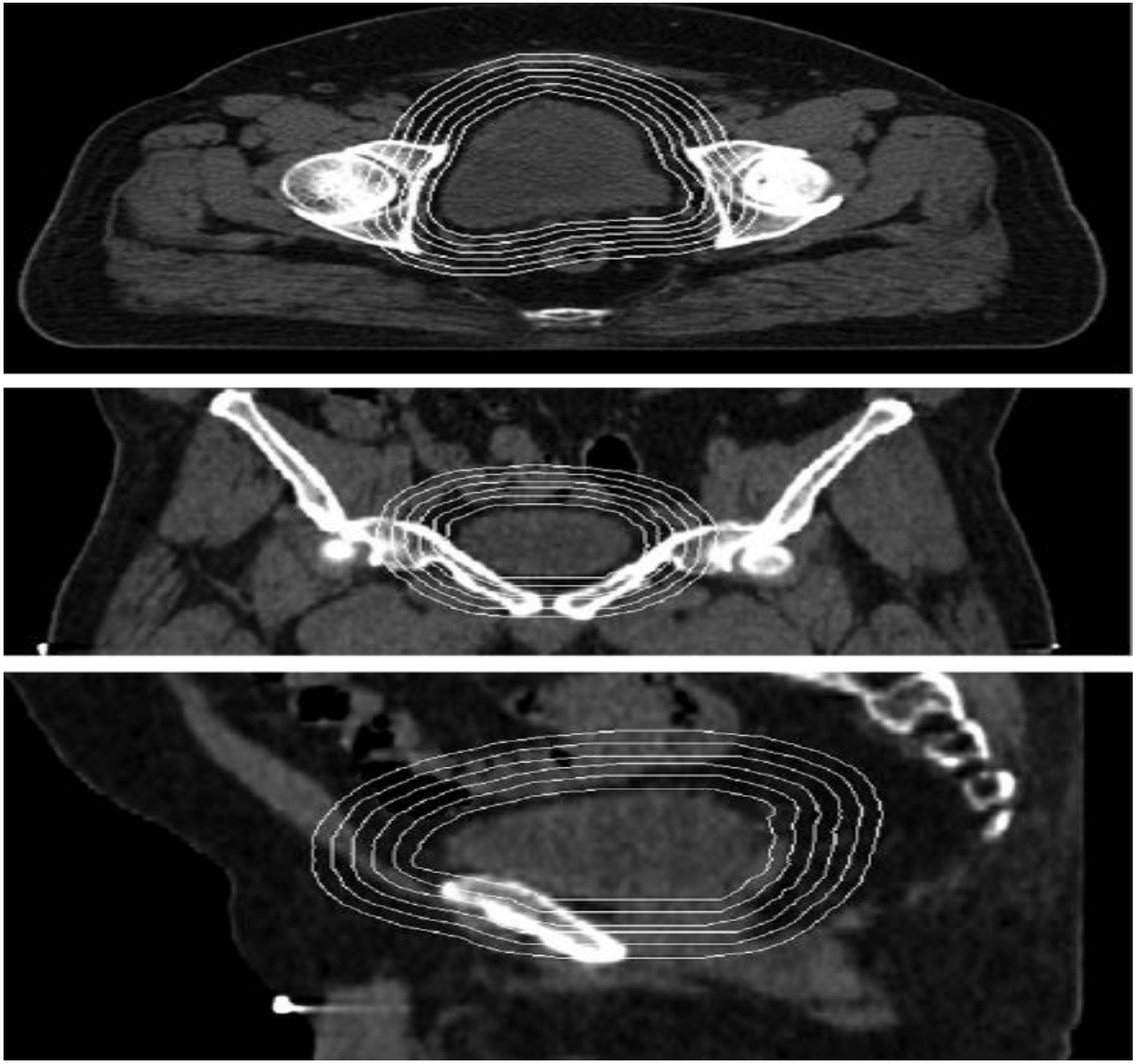
journal homepage: www.thegreenjournal.com

Adaptive radiotherapy

'Plan of the day' adaptive radiotherapy for bladder cancer using helical tomotherapy

Vedang Murthy[a,*], Zubin Master[b], Pranjal Adurkar[b], Indranil Mallick[a], Umesh Mahantshetty[a], Ganesh Bakshi[c], Hemant Tongaonkar[c], Shyamkishore Shrivastava[a]

[a] Department of Radiation Oncology; [b] Department of Medical Physics, Tata Memorial Centre, Mumbai, India; [c] Department of Urology, Tata Memorial Hospital, Mumbai, India



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RAPID COMMUNICATION

Pembrolizumab as Neoadjuvant Therapy Before Radical Cystectomy in Patients With Muscle-Invasive Urothelial Bladder Carcinoma (PURE-01): An Open-Label, Single-Arm, Phase II Study

Andrea Necchi, Andrea Anichini, Daniele Raggi, Alberto Briganti, Simona Massa, Roberta Lucianò, Maurizio Colecchia, Patrizia Giannatempo, Roberta Mortarini, Marco Bianchi, Elena Farè, Francesco Monopoli, Renzo Colombo, Andrea Gallina, Andrea Salonia, Antonella Messina, Siraj M. Ali, Russell Madison, Jeffrey S. Ross, Jon H. Chung, Roberto Salvioni, Luigi Mariani, and Francesco Montorsi

Conclusion

Neoadjuvant pembrolizumab resulted in 42% of patients with pT0 and was safely administered in patients with MIBC. This study indicates that pembrolizumab could be a worthwhile neoadjuvant therapy for the treatment of MIBC when limited to patients with PD-L1–positive or high-TMB tumors.