Approaches in the Management of Muscle Invasive Bladder Cancer

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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 subtyping

- 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
Figure 52-1 Staging of bladder tumors.
AJCC 8th edition

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

N

M1b
# Prognostic Staging

<table>
<thead>
<tr>
<th>T</th>
<th>N</th>
<th>M</th>
<th>STAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ta</td>
<td>N0</td>
<td>M0</td>
<td>0a</td>
</tr>
<tr>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
<td>0is</td>
</tr>
<tr>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>I</td>
</tr>
<tr>
<td>T2a</td>
<td>N0</td>
<td>M0</td>
<td>II</td>
</tr>
<tr>
<td>T2b</td>
<td>N0</td>
<td>M0</td>
<td>II</td>
</tr>
<tr>
<td>T3a, T3b, T4a</td>
<td>N0</td>
<td>M0</td>
<td>IIIA</td>
</tr>
<tr>
<td>T1-T4a</td>
<td>N1</td>
<td>M0</td>
<td>IIIA</td>
</tr>
<tr>
<td>T1-T4a</td>
<td>N2-3</td>
<td>M0</td>
<td>IIIB</td>
</tr>
<tr>
<td>T4b</td>
<td>N0</td>
<td>M0</td>
<td>IVA</td>
</tr>
<tr>
<td>ANY T</td>
<td>ANY N</td>
<td>M1a</td>
<td>IVA</td>
</tr>
<tr>
<td>ANY T</td>
<td>ANY N</td>
<td>M1b</td>
<td>IVB</td>
</tr>
</tbody>
</table>
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

NeoadjuvantChemotherapy 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

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.
• 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


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\textsuperscript{a,b}, William Martin-Doyle\textsuperscript{c}, André P. Fay\textsuperscript{a}, Toni K. Choueiri\textsuperscript{a}, Steven L. Chang\textsuperscript{a,b}, Joaquim Bellmunt\textsuperscript{a,*}

\textsuperscript{a}Bladder Cancer Center, Dana-Farber/Brigham and Women’s Cancer Center, Harvard Medical School, Boston, MA, USA; \textsuperscript{b}Division of Urology and Center for Surgery and Public Health, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA; \textsuperscript{c}University of Massachusetts Medical School, Worcester, MA, USA

\textbf{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. \textbf{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.
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

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 area 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 TRIMODALITY TREATMENT

**MGH**

- TURBT
- **RT + CHT** (Induction)
  - Restaging cystoscopy
    - Complete Response
    - Incomplete Response
  - **RT + CHT** (Consolidation)
    - Cystectomy
    - Restaging cystoscopy
      - NED
      - Recurrence
    - FU
      - Cystectomy

**ERLANGEN**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Overall survival (%)</th>
<th>Complete response (%)</th>
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<tbody>
<tr>
<td>RT alone</td>
<td>40</td>
<td>61</td>
</tr>
<tr>
<td>RT + carboplatin</td>
<td>45</td>
<td>66</td>
</tr>
<tr>
<td>RT + cisplatin</td>
<td>62</td>
<td>82</td>
</tr>
<tr>
<td>RT + cisplatin + 5FU</td>
<td>65</td>
<td>87</td>
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# TRIALS ON BLADDER CONSERVATION

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

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
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
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

<table>
<thead>
<tr>
<th>RTOG Protocol</th>
<th>Complete Response Rates (%)</th>
<th>No. of Analyzable Patients</th>
<th>GU No.</th>
<th>GU %</th>
<th>GI No.</th>
<th>GI %</th>
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<td>89-03</td>
<td>59</td>
<td>56</td>
<td>4</td>
<td>7</td>
<td>2</td>
<td>4</td>
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<td>95-06</td>
<td>67</td>
<td>24</td>
<td>0</td>
<td>0</td>
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<tr>
<td>97-06</td>
<td>74</td>
<td>24</td>
<td>2</td>
<td>8</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>99-06</td>
<td>97</td>
<td>53</td>
<td>3</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>157</td>
<td>9</td>
<td>5.7</td>
<td>3</td>
<td>1.9</td>
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</tbody>
</table>

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 @ 1.8-2 Gy/

**Lateral fields**

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

- 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
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
**Predictive biomarkers for drug response in bladder cancer**

Takahiro Yoshida,† Max Kates, Kazutoshi Fujita, Trinity J Bivalacqua and David J McConkey

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

<table>
<thead>
<tr>
<th>UNC</th>
<th>Luminal</th>
<th>Basal</th>
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<tr>
<td>MDA</td>
<td>Luminal</td>
<td>p53-like</td>
</tr>
<tr>
<td>LUND</td>
<td>Urothelial-like</td>
<td>Genomically unstable</td>
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<th>TCGA</th>
<th>Luminal-papillary</th>
<th>Luminal-Infiltrated</th>
<th>Basal/Squamous</th>
<th>Neuronal</th>
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<tr>
<td></td>
<td>35%</td>
<td>6%</td>
<td>10%</td>
<td>35%</td>
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<tr>
<td>Clinical/pathological characteristics</td>
<td>Papillary histology</td>
<td>Lower T stage</td>
<td>Low CIS</td>
<td>Lymphocytic Infiltration</td>
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<td>Molecular characteristics</td>
<td>FGFR3 mut/fusion/amp</td>
<td>Uroplakins KRT20, SNX31</td>
<td>Low purity EMT miR-200 family Medium PD-L1/CTLA-4 Myofibroblast markers WT p53</td>
<td>Basal Keratin markers High PD-L1/CTLA-4 Immune infiltrates</td>
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<tr>
<td>Suggested treatment</td>
<td>FGFR3 inhibitors</td>
<td>Molecularly-targeted therapy?</td>
<td>ICI</td>
<td>CDDP</td>
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</table>
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.
Protocol for hypofractionated adaptive radiotherapy to the bladder within a multicentre phase II randomised trial: radiotherapy planning and delivery guidance

Shaista Hafeez, Emma Patel, Amanda Webster, Karole Warren-Oseni, Vibeke Hansen, Helen McNair, Elizabeth Miles, Rebecca Lewis, Emma Hall, Robert Huddart

Radiotherapy and Oncology 99 (2011) 55-60

Adaptive radiotherapy

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

Vedang Murthy, Zubin Master, Pranjal Adurkar, Indranil Mallick, Umesh Mahantshetty, Ganesh Bakshi, Hemant Tongaonkar, Shyamkishore Shrivastava

aDepartment of Radiation Oncology; bDepartment of Medical Physics, Tata Memorial Centre, Mumbai, India; cDepartment of Urology, Tata Memorial Hospital, Mumbai, India
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.