Radiation Therapy for Muscle-invasive Bladder Cancer

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Case: Clinical Presentation

- **85-year-old male with a 2 year history of hematuria, no other symptoms (no weight loss; no fatigue)**

- **PMH**
  - Prostate cancer (s/p LDR-BT in 1990), hypertension, hypercholesterolemia, diabetes mellitus

- **Family History**
  - Father and brother with prostate cancer
  - Mother with leukemia
  - Brother with lymphoma

- **Social History**
  - Distant smoking history, stopped 35 years ago
Exam / Diagnostic Workup

• Cystoscopy and TURBT
  – Cystoscopy revealed a mass extending on the right lateral wall of the bladder, to the right ureter
  – Pathology: high grade muscle invasive urothelial carcinoma with invasion into the muscularis propria and presence of lymphovascular invasion: urothelial cell cancer

• MRI Pelvis
  – Diffuse nodular thickening of the bladder wall consistent with bladder carcinoma
  – Tumor extends from the right side of the bladder wall into the right obturator internus muscle and along the right mesial rectal fascia
  – Marked dilatation of the right ureter to the right urethrovesical junction due to obstruction by the bladder tumor leading to right sided hydronephrosis

• CT pelvis
  – Suspicion of right pelvic side wall encroachment from extravesical extension, and likely an enlarging perirectal lymph node, posterior to the right seminal vesicle. The right ureteral obstruction is due to a large right sided bladder mass.
Imaging: T1W MRI, post-Gd
TNM Staging AJCC 7th Edition

- **T stage:**
  - Ta: non invasive papillary
  - Tis: CIS
  - T1: invades subepithelial connective tissue
  - T2a: invades superficial muscularis propria (inner half)
  - T2b: invades deep muscularis propria (outer half)
  - T3a: microscopic invasion of perivesical tissue
  - T3b: macroscopic invasion of perivesical tissue
  - T4a: invades prostatic stroma, uterus, vagina
  - T4b: invades pelvic or abdominal wall

- **N stage:**
  - N1: single LN in true pelvis
  - N2: multiple LNs in true pelvis
  - N3: mets to common iliac LN

- **M stage:**
  - M1: distant mets

### Stage Classification

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- **Clinical case:** Urothelial carcinoma of the bladder, Stage III T3bN1M0
Bladder Cancer

• Risk factors- smoking, aromatic amines, nitrites/nitrates, Cytoxan exposure, aniline dyes, *Schistosoma haematobium* infection, chronic indwelling catheter (e.g. in patients with spinal cord injury)
• Transitional Cell Carcinoma
  – 93% of the cases in the United States
• Squamous Cell Carcinoma
  – 5% of the cases in the United States
• Most common sites of the tumor are trigone, lateral and posterior walls, an bladder neck
• Presentation: hematuria, irritative voiding, pelvic pain, obstructive uropathy, hydronephrosis
• Lymphatic Drainage: hypogastric, obturator, internal and external iliac, perivesical, sacral, presacral

West et al, *Urology*, 1999
Work-up: Muscle Invasive Bladder

- History and Physical
- Labs: CBC, CMP including alkaline phosphatase
- Chest imaging
- Imaging of the upper tract collecting system
  - Intravenous pyelogram (IVP), CT urography, renal ultrasound with retrograde pyelogram, ureteroscopy, or MRI urogram
- Abdominal/pelvic CT or MRI
- Exam under anesthesia with cystoscopy
- TURBT
- Bone scan if alkaline phosphatase is elevated or symptoms
Management of Muscle Invasive Disease

• Treatment options:
  – Radical cystectomy (+ neoadjuvant chemo)
  – Partial cystectomy for small tumors in dome with no Tis (+/- neoadjuvant chemo)
  – Bladder preservation therapy
    • ChemoRT
    • Radical RT (if poor surgery/chemo candidate)

• No randomized trials comparing surgery to bladder preservation therapy
  – Surgery is still considered standard of care in the US
Contraindications to Bladder Preservation?

- Hydronephrosis (in this case, the patient had a ureteral stent placed)
- Multifocal CIS
- Incomplete TURBT
- Non-TCC histology
- Poor bladder capacity/function
- Inability to tolerate chemotherapy
Role of Radiotherapy

• In patients with pT3a to pT4a tumors, adjuvant RT has shown to improve 5 year DFS (25% → 49%) and LC (50% → 93%) compared to cystectomy alone (Zaghloul et al.)
  – In a retrospective series, adjuvant RT demonstrated improved cancer specific survival for patients with pT2-pT4a disease (Cozzarini et al.)
• RT alone is inferior to RT combined with chemotherapy in patients undergoing bladder preservation
  – RT with concurrent mitomycin C and 5-FU improved 2 year locoregional disease-free survival from 54% (RT alone) to 67%, and 5-year OS from 35% to 48% (James et al.)
  – RTOG 89-03 compared concurrent cisplatin and RT with vs. without 2 cycles of induction methotrexate, cisplatin, and vinblastine (MCV) (Shipley et al.)
    • No difference in complete clinical response or 5 year OS (49%) was observed
Role of Radiosensitizers

- RT with concurrent cisplatin-based chemotherapy as radiosensitizer is the most common and well-studied chemoradiation method to treat muscle-invasive bladder cancer
- RTOG 8903: patients with clinical stage T2-T4a were treated with concurrent cisplatin, with or without induction MCV chemotherapy (Shipley et al.)
  - 5 year OS was approximately 49% in both arms
- RTOG 9506: patients were treated with twice daily RT and concurrent cisplatin and 5-FU (Kaufman et al.)
  - 3 year OS was 83%
- RTOG 9706: patients were treated with twice daily RT and concurrent cisplatin as well as adjuvant chemotherapy with MCV (Hagan et al.)
  - 3 year OS was 61%
- RTOG 9906: patients were treated with twice-daily RT plus cisplatin and paclitaxel, followed by adjuvant cisplatin and gemcitabine (Kaufman et al.)
  - 5 year OS was 56%
- Currently cisplatin, cisplatin and 5-FU, 5-FU and mitomycin C, and cisplatin and paclitaxel are reasonable bladder-preserving chemo-RT options
# Evolution of Combined Modality Treatment & Bladder Preservation

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<td>Radiation + Cisplatin</td>
<td>Neoadjuvant MCV x 2</td>
<td>Radiation (BID) + Cisplatin &amp; 5FU</td>
<td>Radiation (BID) + Cisplatin &amp; Taxol</td>
<td>Radiation + Taxol ± Herceptin</td>
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<td>Adjuvant (Cis, Gem, Taxol x 4)</td>
<td>Radiation (BID + Cis &amp;5FU vs. QD+ Gem)</td>
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<td>RTOG 99-06 &amp; 02-33</td>
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Radiation Planning

• CT Simulation- supine with immobilization and bladder empty
  – Need CT scan with contrast and consider consulting bladder map from TURBT for planning

• Field design
  – Whole pelvis AP/PA borders: S2-S3, lower pole of obturator foramen, widest bony pelvis margin + 1.5-2 cm
    • Block medial border of femoral heads
  – Whole pelvis lateral borders: 2 cm beyond CTV, same inferior and superior borders as for AP/PA field
    • Block rectum and small bowel
  – Alternative: IMRT to bladder alone

• Treat with empty bladder
Target Volumes

- GTV: macroscopic tumor visible on CT/MRI/cystoscopy
- CTV: GTV + whole bladder +/- lymph nodes (case- and institution-dependent), proximal urethra, prostate + prostatic urethra in men
  - Lymph nodes: obturator, external, and internal iliacs (these were not treated in the current case)
- PTV: CTV + 1.5-2 cm
- Boost volume PTV = GTV + 2 cm

Reference: RTOG 0712, RTOG 0524

Per RTOG 0721
Case treatment

• The patient was treated to 60 Gy in 30 fractions using IMRT.
• CT on rails was used for daily target localization.
• The patient declined chemotherapy.
Dose Volume Histogram

1. PTV BLADDER
2. Lt femoral head
3. Rt femoral head
4. Rectum
5. Small bowel

Total Volume: 156.53 cc
Inclusion: 100%
Minimum Dose: 187.0 cGy
Maximum Dose: 6626.0 cGy
Mean Dose: 3112.0 cGy
Cursor Volume: 8.25%
Plan ID: TUES
Line Type: Solid
Thickness (pixels): 2

Volume %

Dose (cGy)

6000

ASSOCIATION OF RESIDENTS IN RADIATION ONCOLOGY
Dose Constraints

- Femoral heads:
  - max 45 Gy

- Rectum:
  - V55 < 10%
  - V30 < 50%

- Bowel:
  - 300 cc < 45 Gy

Reference: RTOG 0712, RTOG 0524
Surveillance and Follow-up

- Routine cystoscopy, urine cytology, selective biopsies q3-6 months x 2 yrs
- Labs: LFTs, Cr, electrolytes q6-12 months
- CXR q6-12 months
- Imaging: upper tracts, abdomen, pelvis q3-6 months x 2 yrs
Outcomes

- **Cystectomy alone:**
  - 5 yr OS: T2 60-80%; T3-4 20-40%

- **Bladder preservation with CRT:**
  - 70% have CR after induction CRT
  - 5 yr OS: T2 60%; T3-4 45%

- **Intact bladder after bladder preservation:**
  - At 5 yrs: 45%

Shipley WU et al., Urology 2002; Rodel C et al., J Clin Oncol 2002
Teaching Points

• Radical cystectomy remains the standard of care in muscle-invasive bladder cancer
• Bladder preservation treatment is an acceptable alternative
  – Combined chemoRT superior to RT or TURBT alone for locoregional control (not OS)
  – Neoadjuvant chemo not shown to improve outcomes
• There is no evidence to support the use of adjuvant RT after cystectomy, except in the presence of residual disease
• Salvage cystectomy for incomplete response or invasive recurrence
References


