

Radiation Therapy for Muscle-invasive Bladder Cancer

Prashant Gabani, MSIV; Nicholas G. Zaorsky, MD

Faculty Advisor: Eric M Horwitz, MD

Fox Chase Cancer Center
Philadelphia, PA

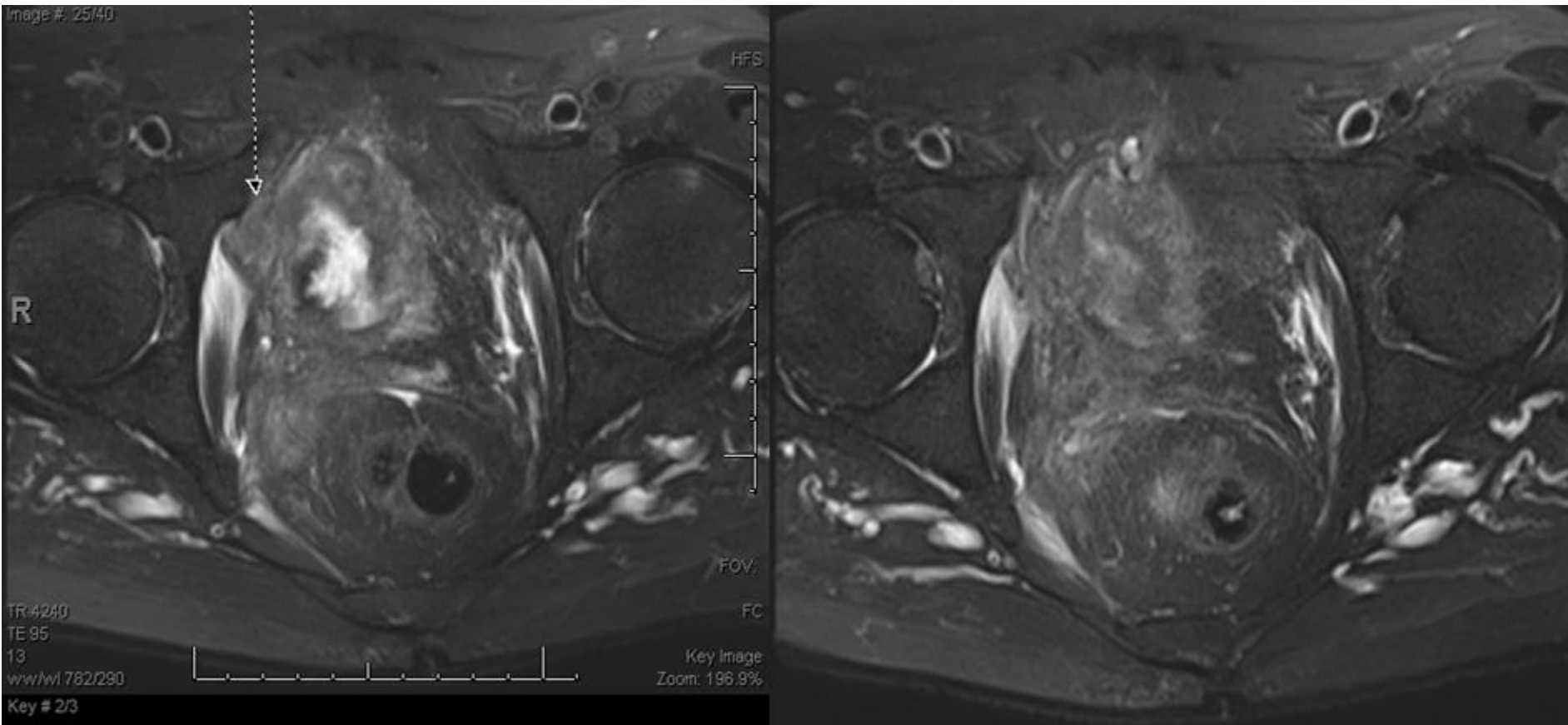
Case: Clinical Presentation

- 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 uretrovesical 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 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a	N0	M0
	T2b	N0	M0
Stage III	T3a	N0	M0
	T3b	N0	M0
	T4a	N0	M0
Stage IV	T4b	N0	M0
	Any T	N1-3	M0
	Any T	Any N	M1

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

Bladder Cancer

- Risk factors- smoking, aromatic amines, nitrites/nitrates, Cytosin 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, and bladder neck
- Presentation: hematuria, irritative voiding, pelvic pain, obstructive uropathy, hydronephrosis
- Lymphatic Drainage: hypogastric, obturator, internal and external iliac, perivesical, sacral, presacral

Montie et al, *J NCCN*, 2009

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

1974-81	1981-86	1986-93	1994-98	1999-2004	2005-
Radiation alone	Radiation + Cisplatin	Neoadjuvant MCV x 2 Radiation + Cisplatin	Radiation (BID) + Cisplatin & 5FU Adjuvant MCV x 3	Radiation (BID) + Cisplatin & Taxol Adjuvant (Cis, Gem, Taxol x 4)	Radiation + Taxol ± Herceptin Radiation (BID + Cis & 5FU vs. QD+ Gem) Adjuvant Gem & Cis
	RTOG 85-12	RTOG 89-03	RTOG 95-06 & 97-06	RTOG 99-06 & 02-33	RTOG 05-24 & 07-12

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

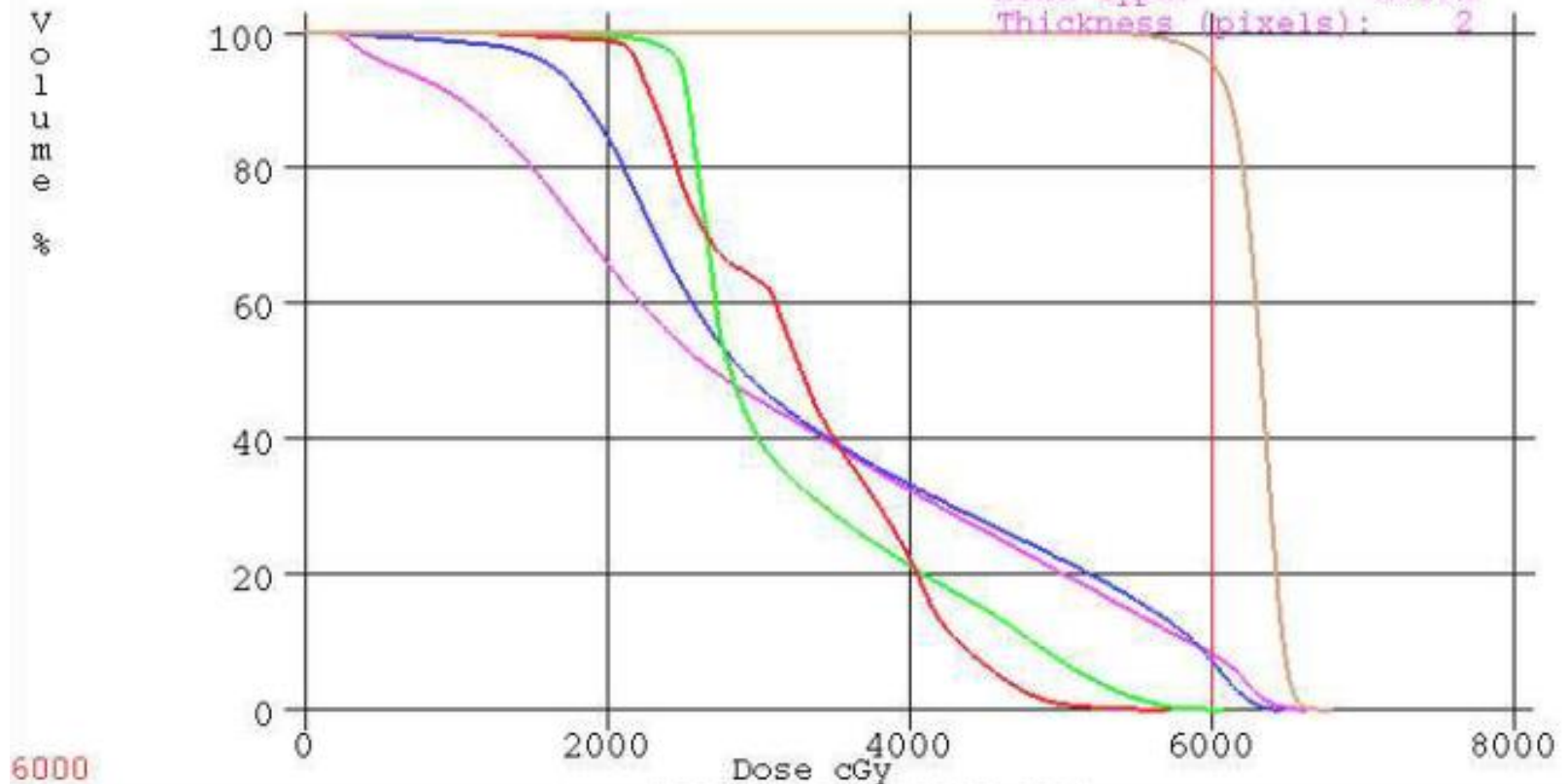
Case treatment

- 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
1.lt femoral hea
1.rt femoral hea
1.rectum
1.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



6000

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 2yrs

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; Rodol 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

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