Radiation Oncology in North Carolina: Bladder Cancer Updates for 2020

The multidisciplinary management of bladder cancer: a radiation oncologist's perspective

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Disclosures

- I have no disclosures.

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Objectives

- Describe the role radiation can play in the multidisciplinary management of bladder cancer
- Compare the roles of radiation and surgery in the treatment of muscle invasive bladder cancer
- Recognize the toxicities and quality of life implications of radiation therapy for bladder cancer

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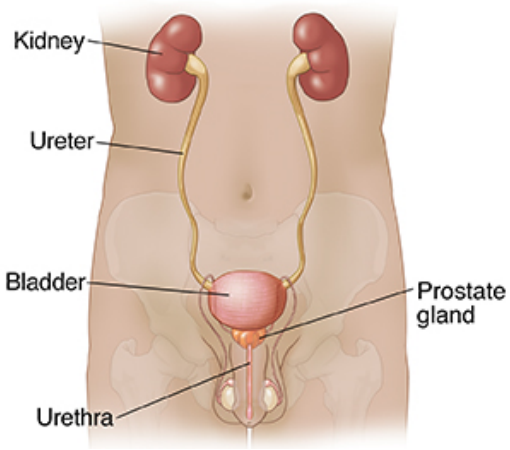
Bladder Cancer Background Anatomy



WebMD

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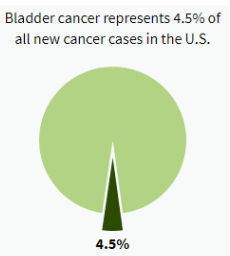
Bladder Cancer Background Epidemiology

	Common Types of Cancer	Estimated New Cases 2020	Estimated Deaths 2020
1.	Breast Cancer (Female)	276,480	42,170
2.	Lung and Bronchus Cancer	228,820	135,720
3.	Prostate Cancer	191,930	33,330
4.	Colorectal Cancer	147,950	53,200
5.	Melanoma of the Skin	100,350	6,850
6.	**Bladder Cancer**	**81,400**	**17,980**
7.	Non-Hodgkin Lymphoma	77,240	19,940
8.	Kidney and Renal Pelvis Cancer	73,750	14,830
9.	Uterine Cancer	65,620	12,590
10.	Leukemia	60,530	23,100



National Cancer Institute (seer.cancer.gov)

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Bladder Cancer Background Epidemiology

- Smoking
- Chemical exposure
  - » Chemical dye industry (azo dyes: naphthylamine, benzidine)
  - » Rubber and plastics industry
  - » Cyclophosphamide (Cytoxan) exposure
- Chronic irritation
  - » Bladder stones
  - » Chronic indwelling foley catheter
  - » Schistosomiasis
- Prior pelvic irradiation

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Presentation

- Presentation
  - » Blood in urine
    - Gross or microscopic
    - 75% of cases
  - » Irritation w/voiding
    - 25-30%
  - » Pelvic pain
  - » Obstructive symptoms
- Tumors often multifocal in nature
- On initial diagnosis
  - » 70-75% non-muscle invasive (superficial)
  - » 20-25% muscle-invasive
  - » ~5% metastatic

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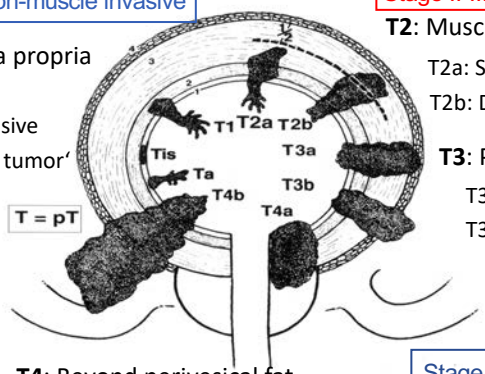
Background: Staging

Stage 0-I: Non-muscle invasive

T1: Lamina propria

Ta: Non-invasive

Tis: CIS, 'flat tumor'



Stage II-III: Muscle invasive

T2: Muscle

T2a: Superficial

T2b: Deep

T3: Perivesical fat

T3a: Microscopic

T3b: Macroscopic

T4: Beyond perivesical fat

T4a: Prostate, uterus, and/or vagina

T4b: Pelvic/abdominal wall

Stage IV

N1: Single node in true pelvis

N2: Multiple nodes in the true pelvis

N3: Common iliac nodes

M1: Distant mets

AJCC

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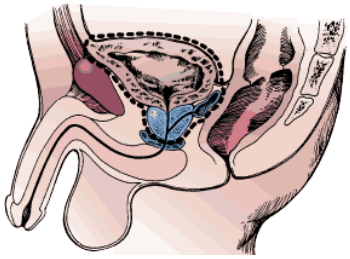
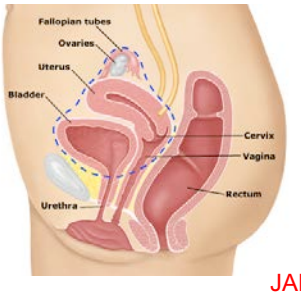
Treatment: Radical Cystectomy

- Removal of bladder and pelvic lymph nodes, plus:
- Men:
  - Prostate
  - Seminal vesicles
  - Proximal vas deferens
  - Proximal urethra
- Females:
  - Uterus
  - Fallopian tubes
  - Ovaries
  - Anterior vaginal wall
  - Fascia
  - Proximal urethra
- 5% increase in 10-yr OS with neoadjuvant chemotherapy





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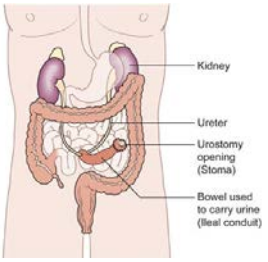
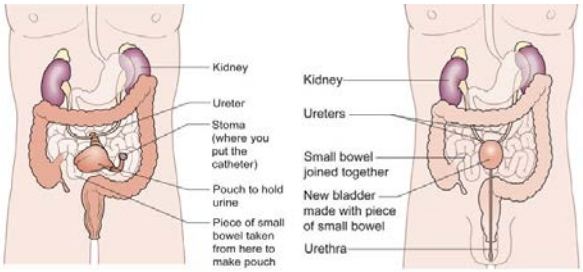
Urinary diversion post-cystectomy

- Incontinent Diversion
  - Ileal conduit urostomy



- Continent Diversion
  - Gut-derived stomal reservoir requiring intermittent catheterization
  - Gut-derived orthotopic neobladder attached to distal urethra



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https://www.coloplast.us/

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Are there other treatment options for bladder cancer?

Is there a way for me to keep my bladder?

Yes.

Trimodality therapy.

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"In God we trust. All others must have data."

Bernard Fisher, MD, FACS – Surgeon and Cancer Pioneer

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Organ preservation

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- Breast cancer: mastectomy -> breast conservation therapy
- Larynx cancer: laryngectomy -> larynx preservation
- Sarcomas: amputation -> limb-sparing

- General principles
  - » Multidisciplinary and interdependency
  - » Maximal cytoreduction: Surgery
  - » Microscopic/regional/distant disease: Systemic therapy, radiation
  - » **Goals: maintain function/preserve quality of life without compromising disease control**

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Goal: to maintain function/preserve quality of life without compromising disease control

- Is there a role for organ preservation in bladder cancer?
- What is the role of radiation?
- What is the impact on disease control?
- What is the impact on quality of life?

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Background: Radiation Strategy

- Radiation works by damaging DNA in a manner that prevents effective cellular division
- **Fractionation** – delivering radiation over many doses
  - Allows normal tissue to repair DNA damage (free radical-induced double strand breaks)
  - Tumor cells struggle with DNA damage repair due to failure of cell cycle checkpoints
  - Thus, presenting a therapeutic window that favors lethal tumor cell damage over normal cellular impairment
  - Systemic therapy ("radiosensitizer") can enhance this process
- "Conventional fractionation"
  - » Small doses of radiation daily over many weeks
  - » 1.8 – 2 Gy per daily treatment ("fraction") over 4 - 8 weeks to doses of 45 - 80 Gy
- "Moderate Hypofractionation"
  - » Larger doses over fewer weeks
  - » 2 – 4 Gy per fraction over 3-4 weeks to 35 – 50 Gy
- "Ultra hypofractionation" (stereotactic body radiation therapy, radiosurgery)
  - » Even larger doses over days
  - » >5 Gy over 1-2 weeks

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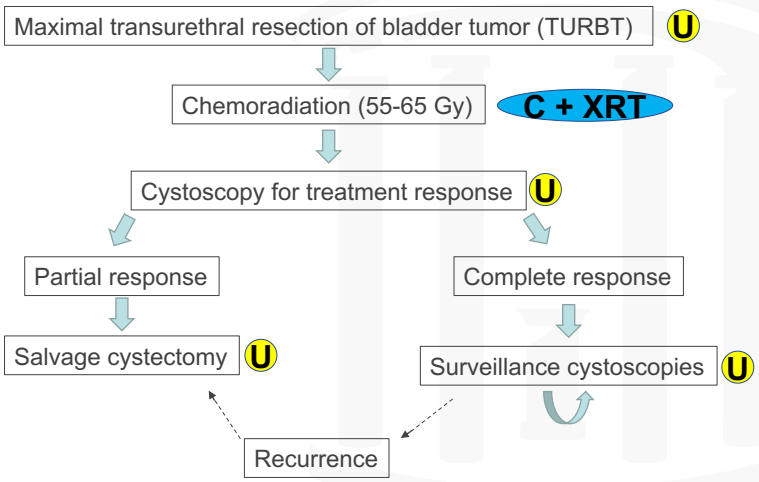
MIBC bladder-preserving TMT paradigm



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"TMT starts and end with the urologist" - William Shipley

- This includes three primary urologic interventions:
- 1) a maximal TURBT, which is associated with improvement in disease-specific survival and overall survival
- 2) if subsequent chemoradiation is unsuccessful in producing a complete response in the short term, or they relapse in the long-term, the urologist can salvage with immediate or delayed cystectomy, respectively
- 3) lifelong cystoscopic surveillance, which permits early detection and initiation of salvage therapy as needed

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What are the outcomes of TMT?

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Background: history of TMT for MIBC

- TMT for MIBC has been systematically investigated for over three decades via consecutive institutional and cooperative group protocols and domestic and international trials.
- Long-term results of TMT are comparatively excellent in appropriately selected patients

1986-93	1994-98	1999-2018
Neoadjuvant chemo	Accelerated radiation	Enhanced Radiation sensitization
Response evaluation	Adjuvant chemotherapy	Adjuvant chemotherapy
MCVx2	bidRT+C/5FU	bidRT+C/5FU or C/Tax qdRT+Gem or 5FU/MMC
RT + C	MCV x 3	G + C x 4

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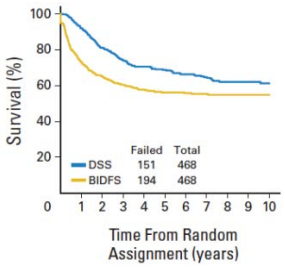
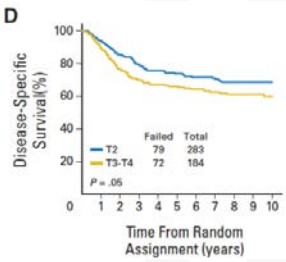
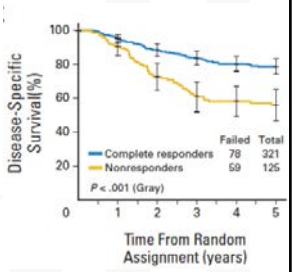
Background: RTOG trial outcomes

- Most recent published update of completed RTOG MIBC trials: 8802, 8903, 9506, 9706, 9906, 0233.







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Mak et al. J Clin Oncol 2014; 32: 3801

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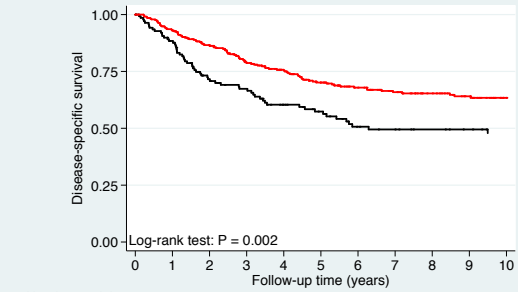
TMT relies on MDC Success: Surgery

- TURBT and Salvage Cystectomy are key to the success of TMT
  - » The risk of salvage cystectomy at 5 yr was 29%.



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Giacalone et al. Eur Urol 2017; 71: 952

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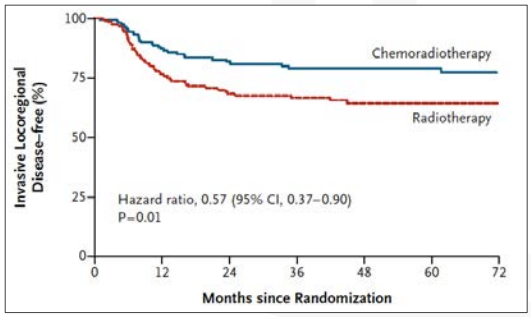
TMT relies on MDC Success: Systemic therapy

- BC2001. James et al. NEJM 2012.
- Randomized trial (RCT): 2x2 design. 458 patients
  - » RT +/- concurrent chemo (5FU+MMC)
  - » Whole bladder vs reduced high dose volume
- Concurrent chemo improves DFS in MIBC TMT



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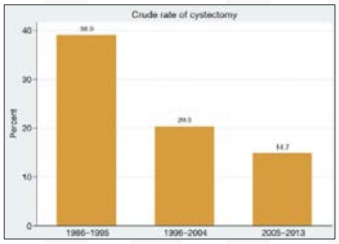
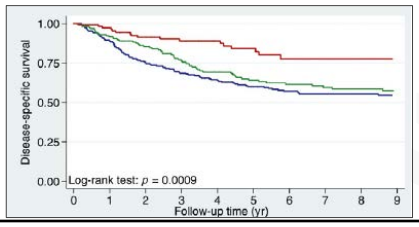
Background: Improved outcomes in modern era

- Improved patient selection and improved techniques (urologic, radiation oncology, and medical oncology) have led to improvements in tumor response and survival outcomes

Years Treated	Total No. Patients	No. with CR	% CR	
1986-1989	116	71	64.5%	T2: 47% Hydronephrosis: 18% Complete TURBT: 60%
1990-1993	64	42	67.7%	
1994-1997	47	35	74.5%	
1998-2001	85	64	75.3%	
2002-2005	71	64	90.1%	T2: 93% Hydronephrosis: 3% Complete TURBT: 83%
2006-2009	49	44	89.8%	
2010-2013	43	37	86.1%	





Giacalone et al. Eur Urol 2017; 71: 952

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Background: "Appropriately-selected patients"

- Optimal TMT outcomes:
  - » Patient factors
    - Age, comorbidities
    - Underlying bladder function
  - » Tumor factors
    - T stage (T2 vs T3/4)
    - Presence/extent of CIS (carcinoma in situ)
    - Hydronephrosis
    - Extent of TURBT

Covariates	Comparison	Overall survival			Disease-specific survival			Bladder-intact disease-specific survival		
		HR	*p* value	95% CI	HR	*p* value	95% CI	HR	*p* value	95% CI
Age at diagnosis	Continuous	1.03	<0.001	1.01–1.04	–	–	–	–	–	–
Clinical T stage	T2 vs T3/T4a	0.57	<0.001	0.44–0.75	0.51	<0.001	0.36–0.73	–	–	–
Response to chemoradiation	Complete vs incomplete	0.61	0.001	0.46–0.81	0.49	<0.001	0.34–0.71	0.16	<0.001	0.12–0.21
Hydronephrosis	Presence vs absence	1.51	0.02	1.06–2.15	–	–	–	1.89	<0.001	1.33–2.63
Tumor-associated CIS	Presence vs absence	1.56	0.002	1.17–2.08	1.50	0.03	1.03–2.17	–	–	–
TURBT	Complete vs incomplete	–	–	–	–	–	–	0.72	0.02	0.55–0.96

CI = confidence interval; CIS = carcinoma in situ; HR = hazard ratio; TURBT = transurethral resection of bladder tumor.

Giacalone et al. Eur Urol 2017; 71: 952

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How do RC and TMT compare?

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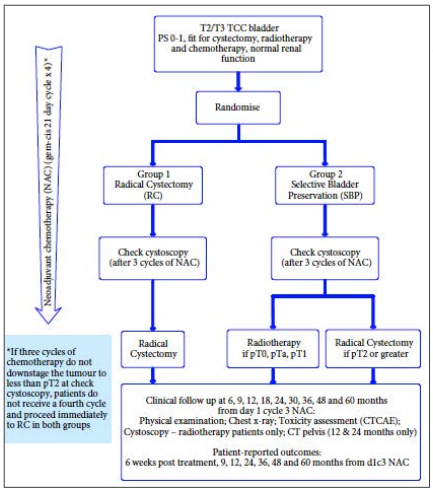
SPARE trial (UK)



- Closed early due to poor accrual
- 45 patients enrolled in 30 months (25 RC; 20 TMT)
- Significant non-compliance (6/25 RC patients received TMT)
- 73% long-term bladder preservation rate in TMT
- No difference in OS
- Improvement in Quality of Life (QoL) at 12 months in TMT patients. Underpowered

Huddart et al. BJU Int 2017; 120:639

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What to do when the RCT fails us?

- We must turn to alternative, lower levels of evidence (often retrospective)
- Claims-based studies
  - Leverage large numbers to detect even modest differences
  - Exposure misclassification
    - E.g. incorrectly identifying the technique/dose of radiotherapy; or cycles/type/timing of chemotherapy
  - Outcome misclassification
    - E.g. incorrectly assuming that billing codes accurately capture clinical toxicities
- Patient-level studies
  - Granular data that can be missing from claims based studies
    - E.g. baseline comorbidities and details of treatment
    - E.g. toxicity measured directly by physicians or patients
  - Fewer subjects
  - Lack external validity or generalizability
    - E.g. TMT at MGH
- Meta-analysis
  - Increase sample size
  - But only as good as the studies used ("garbage in equals garbage out"). Heterogeneity.
- Unable to adequately control for known much less unknown confounders
  - Were those who pursued TMT appropriate RC candidates? Or RC cisplatin candidates?
- These methods have been attempted to compare RC and TMT…

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Representative recent studies comparing the efficacy (in overall survival) of trimodality therapy versus radical cystectomy.

Study	Study type	Data source	Years	Sample size		OS HR[a] (95%CI)
				TMT	RC	
Seisen 2017[1]	Claims-based	NCDB	2004-2011	1,257	11,586	1.37 (1.16-1.59)
Cahn 2017[2]	Claims-based	NCDB	2004-2013	1,489	22,680	1.58 (1.47-1.69)
Williams 2018[3]	Claims-based	SEER-Medicare	2002-2011	752	2,448	1.49 (1.31-1.69)
Kulkarni 2017[4]	Patient-level, retrospective	Institutional	2008-2013	56	56	0.85 (0.43-1.66)
Kim 2017[5]	Patient-level, retrospective	Institutional	2007-2014	29	50	0.89 (0.39-2.03)
Vashistha 2017[6]	Meta-analysis	Heterogeneous studies	1976-2015[b]	4,050	8,330	0.96 (0.72-1.29)

Abbreviations: OS, overall survival; HR, hazard ratio; TMT, trimodality therapy; RC, radical cystectomy; NCDB, National Cancer Data Base; SEER, Surveillance, Epidemiology, and End Results Program
[a]Comparing TMT (reference) to RC
[b]Study publication years

1. Seisen T, Sun M, Lipsitz SR, et al. Comparative Effectiveness of Trimodal Therapy Versus Radical Cystectomy for Localized Muscle-invasive Urothelial Carcinoma of the Bladder. *Eur Urol*. 2017;72(4). doi:10.1016/j.eururo.2017.03.038
2. Cahn DB, Handorf EA, Ghiraldi EM, et al. Contemporary use trends and survival outcomes in patients undergoing radical cystectomy or bladder-preservation therapy for muscle-invasive bladder cancer. *Cancer*. 2017;123(22):4337-4345. doi:10.1002/cncr.30900
3. Williams SB, Shan Y, Jazzar U, et al. Comparing Survival Outcomes and Costs Associated With Radical Cystectomy and Trimodal Therapy for Older Adults With Muscle-Invasive Bladder Cancer. *JAMA Surg*. 2018;77555:1-9. doi:10.1001/jamasurg.2018.1680
4. Kulkarni GS, Hermanns T, Wei Y, et al. Propensity Score Analysis of Radical Cystectomy Versus Bladder-Sparing Trimodal Therapy in the Setting of a Multidisciplinary Bladder Cancer Clinic. *J Clin Oncol*. 2017;35(20):JCO2016692327. doi:10.1200/JCO.2016.69.2327
5. Kim YJ, Byun SJ, Ahn H, et al. Comparison of outcomes between trimodal therapy and radical cystectomy in muscle-invasive bladder cancer: a propensity score matching analysis. *Oncotarget*. 2017;8(40):68996-69004. doi:10.18632/oncotarget.16576
6. Vashistha V, Wang H, Mazzone A, et al. Radical Cystectomy Compared to Combined Modality Treatment for Muscle-Invasive Bladder Cancer: A Systematic Review and Meta-Analysis of over 12,000 patients. *Int J Radiat Oncol*. 2016;97(5):1002-1020. doi:10.1016/j.ijrobp.2016.11.056

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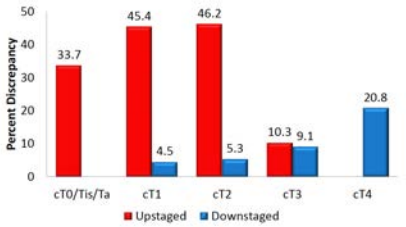
Summary: What to do when the RCT fails us?

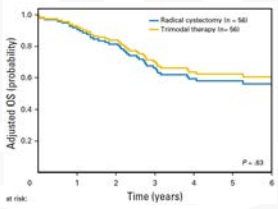
- Many retrospective studies have tried to compare RC and TMT
- Limitations
  - TMT patients of older and/or lower performance status
  - Challenges with clinical staging (clinical staging w imaging a TURBT may underestimate true stage)
  - Actual treatment regimen often unclear

NCDB study of MIBC patients treated with upfront cystectomy



Gray et al. IJROBP 2014; 88: 1049

Propensity-matched study of MIBC patients receiving RC or TMT in multi-disciplinary setting at single Canadian institution:



Kulkarni et al. J Clin Oncol 2017; 35:2299

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TMT QoL

- An area ripe for investigation
- Data limited

- MGH Quality of Life Study
- 221 patients treated on TMT protocols 1986-2000 w median follow up of 6.3 years. Receive urodynamics studies and QoL questionnaires.

- 78% have compliant bladder w normal capacity and flow parameters
- 85% have no urgency or occasional urgency
- 50% of men with normal erectile function

JAE/HROP; Zietman et al J Urol 2003

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TMT QoL – UNC-MGH Study

International Journal of Radiation Oncology biology • physics
www.redjournal.org

Clinical Investigation

Quality of Life in Long-term Survivors of Muscle-Invasive Bladder Cancer

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TMT QoL – UNC MGH Study

- 206 TMT and RC patients (all fit for RC) surveyed using 6 validated QoL instruments
- TMT associated with
  - Modestly higher general QoL (by 7-10 points)
  - Similar urinary scores
  - Modestly higher bowel function (by 3-7 points)
  - Markedly better sexual QoL (by 9-32 points)
  - Better informed decision-making (by 14 points)
  - Less concerns about appearance (by 14 points)
  - Less interference from cancer or cancer treatment (less life interference from cancer or cancer treatment (by 9 points)
- Hypothesis generating. Potential for real QoL benefit with TMT

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TMT QoL

Comparative Effectiveness of Bladder-preserving Tri-modality Therapy Versus Radical Cystectomy for Muscle-invasive Bladder Cancer

Trevor J. Royce,[1] Adam S. Feldman,[2] Matthew Mossanen,[2] Joanna C. Yang,[3] William U. Shipley,[4] Pari V. Pandharipande,[5,6] Jason A. Efstathiou[4]

Abstract

We modeled the lifetime outcomes after tri-modality therapy versus radical cystectomy in patients with muscle-invasive bladder cancer and compared the 2 strategies' effectiveness using the endpoint of quality-adjusted life years. We found that the use of tri-modality therapy resulted in greater quality of life than radical cystectomy.

Introduction: There are limited randomized data comparing radical cystectomy (RC) with bladder-sparing tri-modality therapy (TMT) in the treatment of muscle-invasive bladder cancer (MIBC). Both strategies are thought to have similar survival outcomes with different morbidity profiles. We compare the effectiveness of TMT and RC using decision-analytic modeling and the endpoint of quality-adjusted life years (QALYs). **Patients and Methods:** Using a Markov model, we simulated the lifetime outcomes after TMT versus RC ± neoadjuvant chemotherapy for 67-year-old patients with clinical stage T2-T4aN0M0 MIBC. Model probabilities and utilities were extracted from the literature. The incremental effectiveness was reported in QALYs and sensitivity analyses were performed. **Results:** For all patients with MIBC, although the model showed identical survival, TMT was the most effective strategy with an incremental gain of 0.59 QALYs over RC (7.83 vs. 7.24 QALYs, respectively). When limiting the model to favorable, contemporary cohorts in both the TMT and RC strategies, TMT remained more effective with an incremental gain of 1.61 QALYs (9.37 vs. 7.76 QALYs, respectively). One-way sensitivity analyses demonstrated the model was sensitive to the quality of life parameters (ie, the utilities) for RC and TMT. When testing the 95% confidence interval of the RC utility parameter the model demonstrated an incremental gain with TMT from −0.54 to 4.23 QALYs. Probabilistic sensitivity analysis demonstrated that TMT was more effective than RC for 63% of model iterations. **Conclusions:** This modeling study found that treatment of MIBC with organ-sparing TMT in appropriately-selected patients may result in a gain of QALYs relative to RC.

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Keywords: Comparative effectiveness, Cystectomy, Radiation, Urothelial cell carcinoma

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TMT QoL

Table 2 Markov Cohort Base Case Analysis

Strategy	EV (LYs)	Incremental Value[a]	EV (QALYs)	Incremental Value[a]
TMT, all patients	8.89	–	7.83	–
RC, all patients	8.89	0.00	7.24	0.59
RC, favorable cohort	9.34	−0.45	7.76	0.07
TMT, favorable cohort	10.52	–	9.37	–
RC, all patients	8.89	1.63	7.24	2.13
RC, favorable cohort	9.34	1.18	7.76	1.61

Abbreviations: EV = Expected value; LY = life years; QALY = quality-adjusted life years; RC = radical cystectomy; TMT = tri-modality therapy.
[a]Incremental value of TMT strategy relative to RC strategy.

- Hypothesis generating.
- Potential for real QoL benefit with TMT.

Royce Clinical Genitourinary Cancer 2018

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"The best bladder you will ever have is the one you are born with"

-Anthony Zietman

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Future directions

The Bladder Utility Symptom Scale: A Novel Patient Reported Outcome Instrument for Bladder Cancer

Nathan Perlis,* Murray D. Krahn, Kirstin E. Boehme, Shabbir M. H. Alibhai, Munir Jamal, Antonio Finelli, Srikala S. Sridhar, Peter Chung, Rushi Gandhi, Jennifer Jones, George Tomlinson, Karen E. Bremner and Girish Kulkarni

From the Division of Urology, Department of Surgery (NP, AF, RG, GK), Toronto Health Economics and Technology Assessment Collaborative (MDK, KEBo, KEBr), Division of Internal Medicine and Geriatrics (MDK, SMHA), and Departments of Medical Oncology (SSS) and Radiation Oncology (PC), University of Toronto and University Health Network, University Health Network and Toronto General Research Institute (GT), and Princess Margaret Cancer Centre, Toronto and Division of Urology, Trillium Health Partners (MJ), Mississauga, Ontario, Canada

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A way forward

- Reframe the discussion: NAC+RC and TMT are complimentary tools in the treatment of bladder cancer
- Long-term results of TMT are comparatively excellent in *appropriately selected patients*
- This illustrates this well…

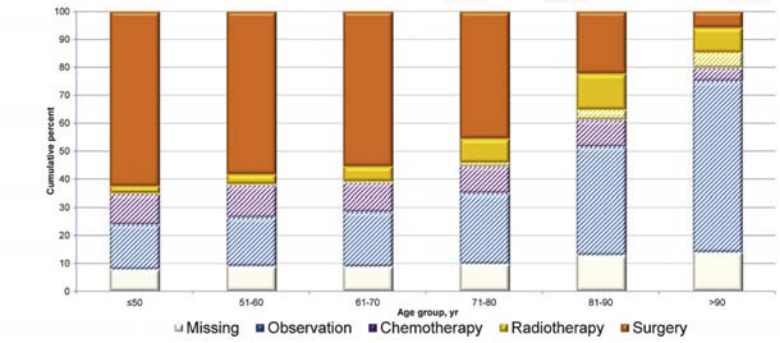

Fig. 1 – Distribution of primary therapies received by patients with muscle-invasive bladder cancer by age group. Aggressive therapies are shown in solid colors, nonaggressive therapies are shown in striped colors.

Use of Potentially Curative Therapies for Muscle-invasive Bladder Cancer in the United States: Results from the National Cancer Data Base
Gray et al. *European Urology* 63 (2013) 823 - 829

Mouw/JAE/HROP

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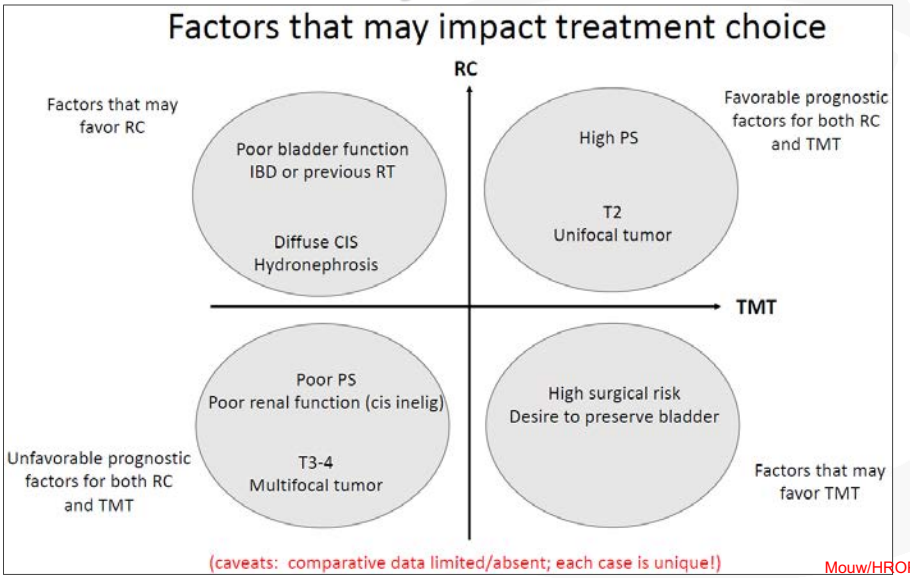
A way forward



Mouw/HROP

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TMT

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2019
Bladder Cancer

NCCN Guidelines Index
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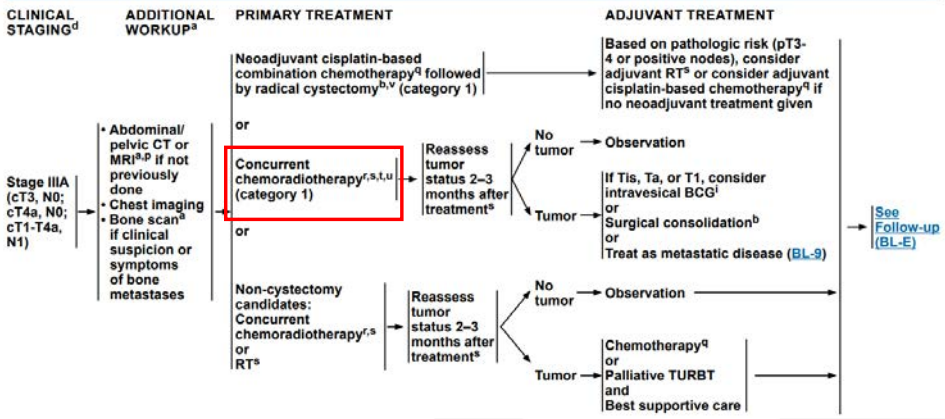

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Future directions

- Adjuvant radiation following RC?
  - » Local recurrences following RC are common in a subset of MIBC patients (LRR ~10-40%)
    - pT3/T4
    - Positive margins
    - pN1-2 disease
  - » Only randomized data is from Egypt (Zaghloul et al. IJROBP 2002)
    - Accrued 1981-1984
    - RC +/- adjuvant RT
    - Improved DFS with RT (5 yr DFS ~45% vs 25%)
    - Caveats: 80% squamous, one RT arm had TID radiation
  - » NRG GU001 closed due to poor accrual

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Future directions

- Currently, no routine role for RT in management of recurrent NMIBC
- RT or chemoRT for non-cystectomy candidates?

ChemoRT for NMIBC:

RTOG 0926 A Phase II Protocol For Patients With Stage T1 Bladder Cancer To Evaluate Selective Bladder Preserving Treatment By Radiation Therapy Concurrent With Radiosensitizing Chemotherapy Following A Thorough Transurethral Surgical Re-Staging		
Institutional TURBT for re-staging →	**Full-dose Radiation* and Concurrent Chemotherapy** →**	**Cystoscopic Surveillance 8-10 weeks after treatment; if negative, q 3 months for the 1st year, q 4 months for year 2, q 6 months for years 3, 4, and 5*** and then annually**
Stage T1 (high grade)	*Total dose of 61.2 Gy in 34 daily fractions **Cisplatin 3 days/week during Weeks 1, 3, and 5 OR Mitomycin day 1 and 5-fluorouracil Weeks 1 and 4	***For T1 and Tcis tumor recurrence after RTOG 0926 treatment, recommend early salvage cystectomy. For Ta tumor recurrence, recommend either appropriate conservative treatment or cystectomy.

(Fully accrued; awaiting report)

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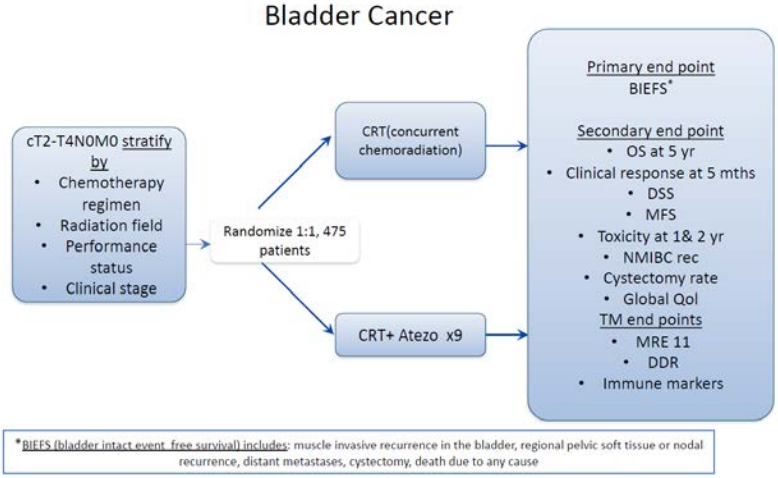
Future directions

SWOG/NRG Intergroup Trial (1806): Phase III Trial of Concurrent Chemoradiation With or Without Atezolizumab for Localized Muscle Invasive Bladder Cancer



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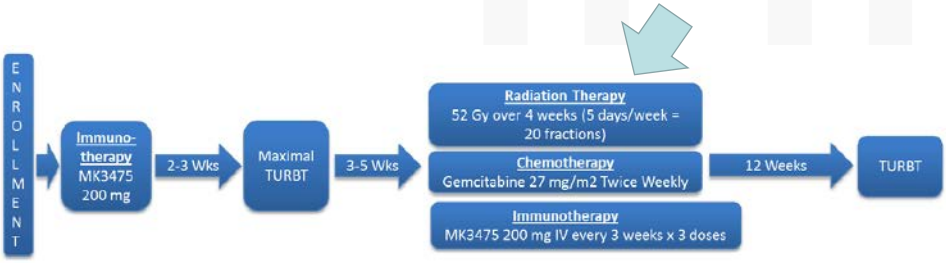
Future directions

- NYU PCC S15-00220. A Phase II Trial of MK3475 (pembrolizumab) in Combination with Gemcitabine and Concurrent Hypofractionated Radiation Therapy as Bladder Sparing Treatment for Muscle-Invasive Urothelial Cancer of the Bladder



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Emerging paradigms

- Multiple large genomic studies over past ~5 years have transformed understanding of MIBC biology
- Targeted agents beyond immunotherapy
  - » FDA approved erdafitinib (FGFR3 inhibitor) in April 2019…first targeted agent approved in bladder cancer
  - » MIBC has many frequently mutated cancer genes -> opportunity for other targeted agents?
- Using genomic biomarkers to guide therapy
  - » 3 on-going Phase II trials investigating chemo only (ie, no surgery or RT) for MIBC patients with tumor DNA damage repair (DDR) gene alterations who achieve complete clinical response to neoadjuvant cisplatin based chemo

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References

- "Bladder Cancer Background Epidemiology," National Cancer Institute (seer.cancer.gov), https://seer.cancer.gov/statfacts/html/urinb.html
- "Bladder Cancer Stages," https://www.cancer.org/cancer/bladder-cancer/detection-diagnosis-staging/staging.html
- Bladder catheters, https://www.coloplast.us/
- El-Achkar, A., et al. "Bladder Preservation Therapy: Review of Literature and Future Directions of Trimodal Therapy." Curr. Urol. Rep. . 2018 Nov 3;19(12):108. doi: 10.1007/s11934-018-0859-z.
- Giacalone et al. "Long-term Outcomes After Bladder-preserving Tri-modality Therapy for Patients With Muscle-invasive Bladder Cancer: An Updated Analysis of the Massachusetts General Hospital Experience," Eur Urol. 2017 Jun;71(6):952-960. doi: 10.1016/j.eururo.2016.12.020. Epub 2017 Jan 9.
- Gray et al. "Use of Potentially Curative Therapies for Muscle-invasive Bladder Cancer in the United States: Results from the National Cancer Data Base." *European Urology* 63 (2013) 823 – 829
- Gray et al. IJROBP 2014; 88: 1049
- Huddart et al. "Clinical and Patient-Reported Outcomes of SPARE - A Randomised Feasibility Study of Selective Bladder Preservation Versus Radical Cystectomy," BJU Int. 2017 Nov;120(5):639-650. doi: 10.1111/bju.13900. Epub 2017 May 29.
- Kulkarni et al. "Propensity Score Analysis of Radical Cystectomy Versus Bladder-Sparing Trimodal Therapy in the Setting of a Multidisciplinary Bladder Cancer Clinic," J Clin Oncol. 2017 Jul 10;35(20):2299-2305. doi: 10.1200/JCO.2016.69.2327. Epub 2017 Apr 14.
- Mak, RH, et al. "Long-term Outcomes in Patients With Muscle-Invasive Bladder Cancer After Selective Bladder-Preserving Combined-Modality Therapy: A Pooled Analysis of Radiation Therapy Oncology Group Protocols 8802, 8903, 9506, 9706, 9906, and 0233," Mak et al. J Clin Oncol 2014; 32: 3801. doi: 10.1200/JCO.2014.57.5548. Epub 2014 Nov 3.
- Mak KS. "Quality of Life Considerations for Patients with Muscle Invasive Bladder Cancer," https://bcan.org/assets/KMAK-081216.pptx.pdf
- Msaouel, P, et al. "Updated Recommendations on the Diagnosis, Management, and Clinical Trial Eligibility Criteria for Patients With Renal Medullary Carcinoma," Clinical Genitourinary Cancer, Vol. 17, No. 1, 23–31, 2018. DOI:https://doi.org/10.1016/j.clgc.2018.09.005
- "NCCN Guidelines Version 4.2019 Bladder Cancer," https://www.nccn.org/about/news/ebulletin/ebulletindetail.aspx?ebulletinid=3667
- "Neoadjuvant Chemotherapy in Invasive Bladder Cancer: A Systematic Review and Meta-Analysis." Lancet . 2003 Jun 7;361(9373):1927-34. doi: 10.1016/s0140-6736(03)13580-5.
- NYU PCC S15–00220: A Phase II Trial of MK3475 (pembrolizumab) in Combination with Gemcitabine and Concurrent Hypofractionated Radiation Therapy as Bladder Sparing Treatment for Muscle-Invasive Urothelial Cancer of the Bladder
- Perlis, N., et al. "The Bladder Utility Symptom Scale: A Novel Patient Reported Outcome Instrument for Bladder Cancer," J Urol. 2018 Aug;200(2):283-291. doi: 10.1016/j.juro.2018.03.006. Epub 2018 Mar 9.
- Royce TJ, et al. "Comparative Effectiveness of Bladder-preserving Tri-modality Therapy Versus Radical Cystectomy for Muscle-invasive Bladder Cancer," *Clinical Genitourinary Cancer* October 03, 2018. DOI:https://doi.org/10.1016/j.clgc.2018.09.023
- "SWOG/NRG Intergroup Trial (1806): Phase III Trial of Concurrent Chemoradiation with or without Atezolizumab for Localized Muscle Invasive Bladder Cancer," https://uthealth.org/research-study/chemoradiotherapy-or-without-atezolizumab-treating-patients-localized-muscle-invasive
- Zietman AL, et al. "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," J Urol. 2003 Nov;170(5):1772-6. doi: 10.1097/01.ju.0000093721.23249.c3.

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  - Research team
  - Genetics
  - Pharmacy
  - Dieticians
  - Fertility team
  - Navigators
  - Coordinators

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