


**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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1




Disclosures

- I have no disclosures.

6/22/20 2

2

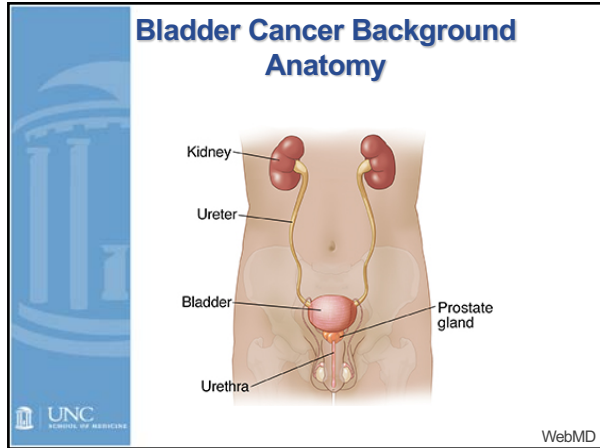


Objectives

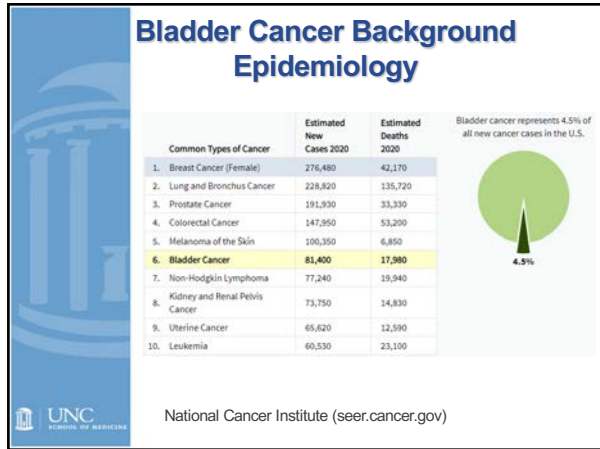
- Describe the role radiation can play in the multidisciplinary management of bladder cancer
- Compare the roles of radiation and surgery in the treatment of muscle invasive bladder cancer
- Recognize the toxicities and quality of life implications of radiation therapy for bladder cancer

6/22/20 3

3



4




5

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

6

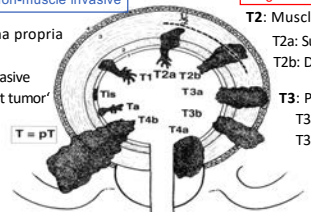
Presentation

- 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



7

Background: Staging



Stage 0-I: Non-muscle invasive

T1: Lamina propria

Ta: Non-invasive

Tis: CIS, 'flat tumor'

T = pT

T4: Beyond perivesical fat

T4a: Prostate, uterus, and/or vagina

T4b: Pelvic/abdominal wall

Stage II-III: Muscle invasive ★

T2: Muscle

T2a: Superficial

T2b: Deep

T3: Perivesical fat

T3a: Microscopic

T3b: Macroscopic

Stage IV

N1: Single node in true pelvis

N2: Multiple nodes in the true pelvis

N3: Common iliac nodes

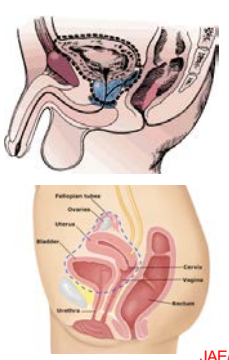
M1: Distant mets

AJCC

8

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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9

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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10

<https://www.coloplast.us/>

11

Are there other treatment options for bladder cancer?

Is there a way for me to keep my bladder?

Yes.

Trimodality therapy.

12

12

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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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13

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Organ preservation

- Organ preservation is a hallmark of modern cancer care, ideally established through randomized controlled trials
- 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**

6/22/20 14

14

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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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15

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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

16

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17

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MIBC bladder-preserving TMT paradigm

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    graph TD
      A[Maximal transurethral resection of bladder tumor (TURBT) U] --> B[Chemoradiation (55-65 Gy) C + XRT]
      B --> C[Cystoscopy for treatment response U]
      C --> D[Partial response]
      C --> E[Complete response]
      D --> F[Salvage cystectomy U]
      E --> G[Surveillance cystoscopies U]
      G --> H[Recurrence]
      H --> F
  
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18

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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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19

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What are the outcomes of TMT?

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20

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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 ↓ RT + C	bidRT+C/5FU ↓ MCV x 3	bidRT+C/5FU or C/Tax qdRT+Gem or 5FU/MMC ↓ G + C x 4

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21

Background: RTOG trial outcomes

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

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

22

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%.

Number at risk	0	1	2	3	4	5	6	7	8	9	10
TURBT complete	332	301	263	221	194	165	143	124	109	97	76
TURBT incomplete	138	120	88	78	63	55	43	40	36	33	29

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Giacalone et al. Eur Urol 2017; 71: 952

23

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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24

24

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%
1990-1993	64	42	67.7%
1994-1997	47	35	74.5%
1998-2001	85	64	75.3%
2002-2005	71	64	90.1%
2006-2009	49	44	89.8%
2010-2013	43	37	86.1%

T2: 47%
 Hydronephrosis: 18%
 Complete TURBT: 60%
 T2: 93%
 Hydronephrosis: 3%
 Complete TURBT: 83%

Giacalone et al. Eur Urol 2017; 71: 952

25

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

26

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27

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How do RC and TMT compare?

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28

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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

6/22/20 Huddart et al. BJU Int 2017; 120:639

29

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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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30

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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: (95%CI)
				TMT	RC	
Seisen 2017 ^a	Claims-based	NCD	2004-2011	1,257	11,586	1.37 (1.16-1.59)
Cahn 2017 ^a	Claims-based	NCD	2004-2013	1,489	22,680	1.58 (1.47-1.69)
Williams 2018 ^b	Claims-based	SEER-Medicare	2002-2011	752	2,448	1.49 (1.31-1.69)
Kulkarni 2017 ^a	Patient-level, retrospective	Institutional	2008-2013	56	56	0.85 (0.43-1.66)
Kim 2017 ^a	Patient-level, retrospective	Institutional	2007-2014	29	50	0.89 (0.39-2.03)
Yashishtha 2017 ^a	Meta-analysis	Heterogeneous studies	1976-2019 ^c	4,050	8,330	0.96 (0.72-1.29)

Abbreviations: OS, overall survival; HR, hazard ratio; TMT, trimodality therapy; RC, radical cystectomy; NCD, National Cancer Data Base; SEER, Surveillance, Epidemiology, and End Results Program
^aComparing TMT (reference) to RC
^bStudy publication years

- Seisen T, Sun M, Liputz SR, et al. Comparative Effectiveness of Trimodal Therapy Versus Radical Cystectomy for Localized Muscle-Invasive Urothelial Carcinoma of the Bladder. *Eur Urol*. 2017;77(4). doi:10.1016/j.eururo.2017.03.039
- 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
- Williams SR, 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
- 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
- Kim YI, 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
- Yashishtha 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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31

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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

NCD 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

32

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33

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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

34

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TMT QoL – UNC-MGH Study

International Journal of Radiation Oncology • Biology • Physics
www.intjradonc.org

Clinical Investigation

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

Kimberley S. Mak, MD, MPH,^{1,2} Angela B. Smith, MD, MS,¹ Alec Eidelman, BS,³ Rebecca Clayman, BS,³ Andrzej Niemierko, PhD,¹ Jed-Sian Cheng, MD, Jonathan Matthews, MPH,¹ Michael R. Drumm, AB,² Matthew E. Nielsen, MD, MS,¹ Adam S. Feldman, MD, MPH,¹ Richard J. Lee, MD, PhD,¹ Anthony L. Zietman, MD,¹ Ronald C. Chen, MD, MPH,¹ William U. Shipley, MD, FACP, FASTRO,¹ Matthew I. Milowsky, MD,¹ and Jason A. Efstathiou, MD, DPhil¹

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35

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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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36

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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, CK), Toronto Health Economics and Technology Assessment Collaborative (MDK, KEBo, KESB), Division of Internal Medicine and Geriatrics (MDK, SMMA), 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

August 2019

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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

41

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A way forward

Factors that may impact treatment choice

<p>Factors that may favor RC</p> <ul style="list-style-type: none"> Poor bladder function IBD or previous RT Diffuse CIS Hydronephrosis 	<p>Favorable prognostic factors for both RC and TMT</p> <ul style="list-style-type: none"> High PS T2 Unifocal tumor
<p>Unfavorable prognostic factors for both RC and TMT</p> <ul style="list-style-type: none"> Poor PS Poor renal function (cis Inelig) T3-4 Multifocal tumor 	<p>Factors that may favor TMT</p> <ul style="list-style-type: none"> High surgical risk Desire to preserve bladder

(caveats: comparative data limited/absent; each case is unique!)

Mouw/JAE/HROP

42

Future directions

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

Primary end point
OS at 5 yr

Secondary end point
• OS at 5 yr
• Clinical response at 5 mths
• DSS
• MFS
• Toxicity at 1& 2 yr
• NMIBC rec
• Cystectomy rate

TTM end points
• MRE 11
• DDR
• Immune markers

*MIBC bladder event-free survival includes: muscle invasive recurrence in the bladder, regional pelvic soft tissue or nodal recurrence, distant metastases, cystectomy, death due to any cause

46

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

Immunotherapy MK3475 200 mg (2-3 Wks) → Maximal TURBT (3-5 Wks) → Radiation Therapy (52 Gy over 4 weeks (5 days/week - 20 fractions)) + Chemotherapy (Gemcitabine 27 mg/m2 Twice Weekly) (12 Weeks) → TURBT

Immunotherapy MK3475 200 mg IV every 3 weeks x 3 doses

47

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

48
