Radical Cystectomy vs Bladder Preservation; past, present, and future

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Outline

- Treatment options for localized muscle-invasive bladder cancer
- Overall culture surrounding treatment paradigms and why
- Evolution of our understanding of treatment outcomes when comparing treatment
- Where we are at currently
- What we still need to investigate

Treatment Options (T2 N0 M0)

CLINICAL STAGING ⁹	ADDITIONAL WORKUP ^b	PRIMARY TREATMENT	SUBSEQUENT TREATMENT
Stage II (cT2, N0)	 Abdominal/pelvic CT or MRI^{b.w} if not previously done Chest imaging (CT chest) Bone scan^b if clinical suspicion or symptoms of bone metastases Estimate glomerular filtration rate (GFR) to assess eligibility for cisplatin^x 	Neoadjuvant cisplatin-based combination chemotherapy ^y followed by radical cystectomy ^c (category 1) or Neoadjuvant cisplatin-based combination chemotherapy ^y followed by partial cystectomy ^c (highly selected patients with solitary lesion in a suitable location; no Tis) or Cystectomy alone for those not eligible to receive cisplatin-based chemotherapy or Bladder preservation with concurrent chemoradiotherapy ^z ,aa,bb (category 1) and maximal TURBT or If patient is not a candidate for cystectomy or definitive chemoradiotherapy: RT ^{aa} or TURBT ^c	See Adjuvant Treatment (BL-6) If Tis, Ta, or T1, consider TURBT +/- intravesical therapy ^P or If persistent T2, consider surgical resection (ie, cystectomy or partial cystectomy in highly selected cases) ⁶ or Treat as metastatic disease (BL-10) Reassess tumor status 2-3 months after treatment completion ^{aa} Tumor + Reassess tumor status 2-3 months after treatment completion ^{aa} No Tumor + Surveillance Reassess tumor status 2-3 months after treatment completion ^{aa} No Tumor + Surveillance Janoths after treatment completion ^{aa} No Tumor + Tumor + Systemic therapydd or radiation therapy (RT) alone (if no prior RT) ^{aa} or TURBT ± intravesical therapy ^P and Best supportive care (Soe NCCN Guidolines for Palliative Care)

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Treatment Options (T3-4a N0-1 M0)

CLINICAL	ADDITIONAL	PRIMARY TREATMENT	SUBSEQUENT TREATMENT
STAGING	WORKUP ^b	Neoadjuvant cisplatin-based combination chemotherapy ^y followed by radical cystectomy ^{c,ee} (category 1) or Cystectomy alone for those not eligible to receive cisplatin-based	See Adjuvant Treatment (BL-6)
Stage IIIA (cT3, N0;	 Abdominal/ pelvic CT or MRI^{b,w} if not previously done Chest imaging 	chemotherapy ee or Biadder preservation with concurrent chemoradiotherapy ^{2,aa,bb} status 2–3	Tumor - If persistent T2, consider TURBT +/- intravesical therapy ^p or If persistent T2, consider surgical resection (ie, cystectomy or partial cystectomy in highly selected cases) ^c or
cT4a, N0; cT1-T4a, N1)	(CT chest) • Bone scan ^b if clinical suspicion or symptoms of bone	If patient is not a candidate for	Treat as metastatic disease (BL-10)
	metastases • Estimate GFR to assess eligibility for cisplatin ^x	status 2-3 status 2-3 months after treatment completion ^{aa}	Tumor - Systemic therapy ^{dd} or TURBT ± intravesical therapy ^p and Best supportive care (See NCCN Guidelines for Palliative Care)

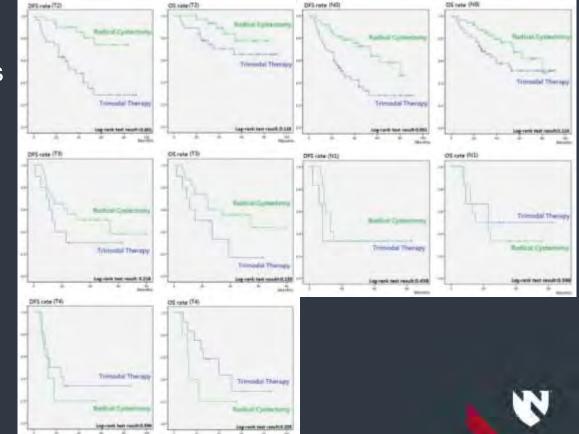
What actually occurs

- A NCDB analysis of patients aged 40-79 with T2-3c N0 UC
 - 2006-2015
 - 2048 pts; 1812 pts underwent RC (88.5%) while only 236 pts (11.5%) underwent BP (PMID: 35058142)
- 2020 VA database analysis of pts treated for T2-4 N0-3 UC
 - 2000-2015
 - 1927 pts; 1775 pts underwent RC (92.2%) while only 152 pts (7.8%) underwent BP (PMID: 34337540)



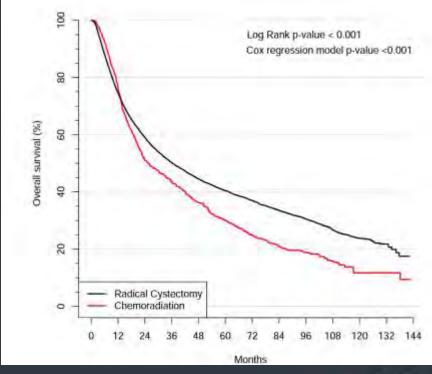
Representative Study:

- Single institutional analysis (Taiwan) comparing BP and RC (Tseng et al, Uro Sci 2021)
 - 119 pts, stratified per tumor stage; 58 BP, 61 RC
 - 3y DFS- 44.1% vs 69.7% (RC wins; p=0.003)
 - On subgroup analysis, only holds true if T2N0
 - 3y OS- 61.7% vs 72.5% (p=0.226)



Representative Study:

- 2019 NCDB Study (PMID: 31401220):
 - 15,854 pts with RC, 2,083 pts with BP
 - Propensity matched
 - T-stage still discordant between groups
 - OS higher with RC (HR:1.18, p<0.001)





- 2014 cost analysis (abstract only) comparing RC to BP using Medicare reimbursement data (Value in Healthcare 2014)
 - Focus on upfront costs
 - BP was \$6,788 less expensive but resulted in 1.2 fewer QALY, reaching a cost of \$5,680 per QALY
- 2022 SEER study on long-term care costs (PMID: 35168881)
 - Cost of treatment at 2 years: \$372,839 (BP) vs. \$191,363 (RC)
 - Cost of treatment at 5 years: \$424,570 (BP) vs. \$253,651 (RC)
 - Difference driven by outpt costs in follow-up (2y: \$318,221 vs \$100,900; 5y: \$367,092 vs. \$146,561)



Issues with past data

• Confounders:

- Most BP pts are those who were not candidates for RC or had overall worse disease (higher comorbidity score, more N+, more T4)
- Outcomes:
 - Most looked at DFS (confounded by local recurrence between groups), and OS (confounded by above), but not Cancer Specific Survival
- Treatments:
 - Most past data were either RT alone or used substandard concurrent chemo (not true of presented studies but true of many others that have fed into overall acceptance)

SPARE trial: direct comparison of RC and BP

- Multicenter trial in UK comparing RC to SBP after neoadj chemo
- T2-3N0; randomized after 3c neoadj chemo (gem/cis q3wk) but before cystoscopy, if < T1 at that time, proceeded to 4th cycle of chemo then RC or BP (If T2+, went to RC)
- Designed to show non-inferiority of SBP; planned 1015 pts with initial feasibility to be shown by 110 pts over first 3 years
- Plagued by poor accrual and non-compliance with protocol (45 pts over 30 months (25 RC, 20 BP) with 6/25 RC pts actually getting BP); so stopped early

2022 NCDB analysis (PMID: 35058142)

- 2006-2015
- T2-3 N0 pts aged 40-79; UCC only
- 1812 pts got RC, 236 got BP
- Propensity matched (no discordance between any variable)
- No difference in OS

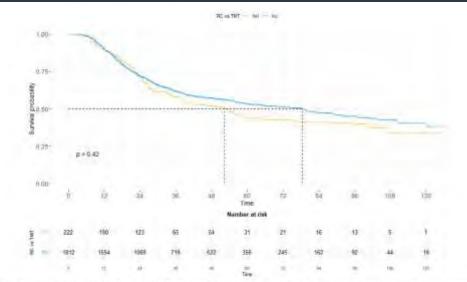
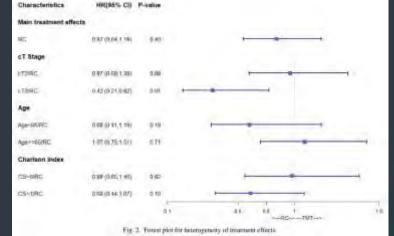


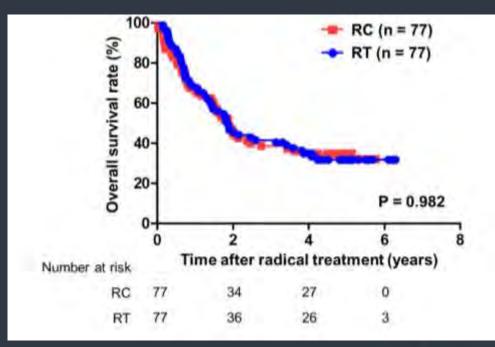
Fig. 1. Association of RC and TMT with OS after sIPW-adjustment. OS = overall survival; RC = radical cystectomy; sIPWs = stabilized inverse probability of treatment weights; TMT = trimodality therapy.





2023 Japanese Cancer Registry (PMID: 36896218)

- 2013-2015
- T2-3 N0-3 pts aged 37-98; UCC only
- 241 pts got RC, 92 got BP
- Propensity matched (77 pts per group, no discordance between any variable)
- No difference in OS



2020 VA database analysis of pts treated for T2-4 N0-3 UC (PMID: 34337540)

- 2013-2015
- T2-4a N0-3 pts aged 52-89; UCC only
- 1472 pts got NAC-RC, 506 pts got RC, 163 pts got BP with preferred chemo, and 165 pts got BP with nonpreferred chemo
 - BP was in those who couldn't get/refused RC
- Worse OS in BP but no difference in CSS

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RC with NAC	505	417	287	214	4	151	111	
RC without NAC	1472	1151	052	661	£ 7	549	408	
TMT (preferred)	763	110	74	.48	10.00	32	20	

Radical cystectomy versus trimodality therapy for muscleinvasive bladder cancer: a multi-institutional propensity score matched and weighted analysis

Alexandre R Zlotta^{*}, Leslie K Ballas, Andrzej Niemierko[†], Katherine Lajkosz[†], Cynthia Kuk, Gus Miranda, Michael Drumm, Andrea Mari, Ethan Thio, Neil E Fleshner, Girish S Kulkarni, Michael A S Jewett, Robert G Bristow, Charles Catton, Alejandro Berlin, Srikala S Sridhar, Anne Schuckman, Adam S Feldman, Matthew Wszolek, Douglas M Dahl, Richard J Lee, Philip J Saylor, M Dror Michaelson, David T Miyamoto, Anthony Zietman, William Shipley, Peter Chung, Siamak Daneshmand, Jason A Efstathiou^{*}

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Closest thing we may ever get to a RCT



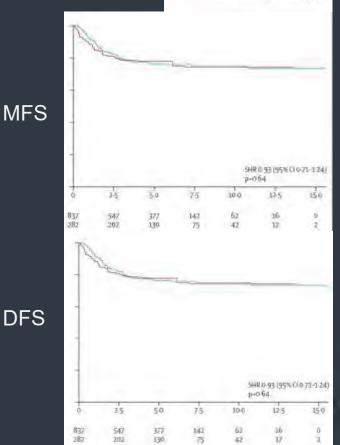
Design:

- Retrospective analysis of 722 pts diagnosed with muscle invasive UCC; 440 RC, 282 BP; <u>ALL eligible for both</u> <u>approaches</u>
- T2-4 N0; all solitary tumors < 7 cm, no bilateral hydroneph, no extensive or multifocal CIS
- Treated across 3 centers; USC, Princess Margaret, MGH
- Primary endpoint MFS; secondary endpoints included OS, CSS, and DFS

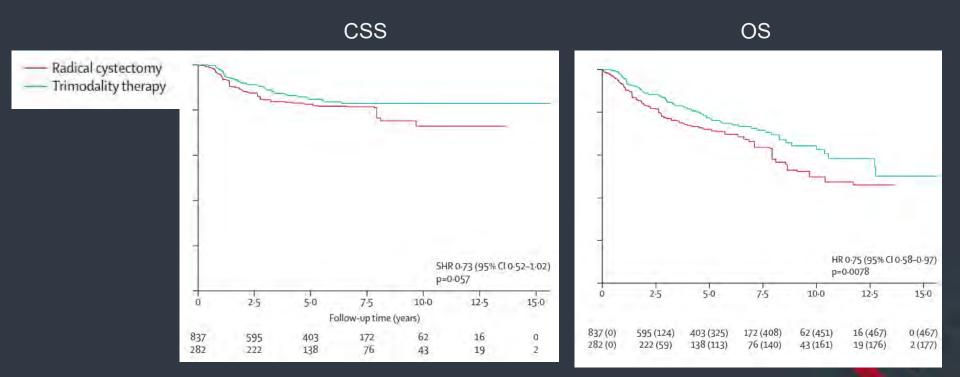


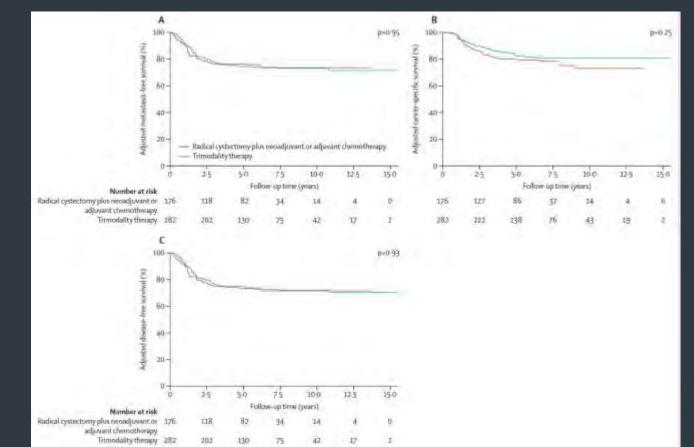
Results: (BP vs RC; using propensity matched data)

- 5y MFS: 74% vs 74%; p=0.64
- 5y CSS: 85% vs 83%; p=0.06
- 5y DFS: 76% vs 76%; p=0.37
- 5y OS: 77% vs 72%; p=0.01



Radical cystectomy Trimodality therapy





Culture Change?-where are we now

- More of a push across both Radiation Oncology and Urology to start to consider BP an a true first-line option in discussions and at scientific meetings
- Unclear how rapidly true referral patterns may change



Future Directions

- Still cannot deny the more extensive follow-up needed with BP...can we make this more efficient or cost effective?
 - cDNA or urine cytology instead of routine imaging and cystoscopies?
- Await NRG GU001 to see if adjuvant RT in high-risk patients after RC may further improve outcomes







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