DANA-FARBER CANCER INSTITUTE

BRIGHAM AND WOMEN'S HOSPITAL

HARVARD MEDICAL SCHOOL

Perioperative and non surgical management of MIBC

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SINGAPORE 2015 ESMO ASIA

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Conflict of Interest Disclosure

- **Advisor**
  - **OncoGenex, Pierre Fabre, Astellas, Genentech, Merck**

- **Non-paid Advisor and/or Research Support**
  - **Sanofi, Novartis, Janssen, ImClone, Genentech, Merck, BMS**

- 236O A randomized phase III study comparing neoadjuvant chemotherapy followed by concurrent chemo-radiotherapy with concurrent chemo-radiotherapy in Asian-Indian (South Asian) population with muscle invasive bladder cancer

  Shankar Jakhar, IN

- 237O Adjuvant chemotherapy in patients with muscle invasive bladder cancer after radical cystectomy: Now or never?

  Mai Ezz El Din, EG

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A randomized phase III study comparing Neoadjuvant chemotherapy followed by concurrent chemo-radiotherapy with concurrent chemo-radiotherapy in Asian-Indian (South Asian) population with muscle invasive bladder cancer

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SINGAPORE 2015 ESMO ASIA 18-21 DECEMBER SINGAPORE

Introduction

- Main treatment of muscle invasive bladder cancer is surgery with

  Neoadjuvant chemotherapy

- Organ-preserving approach is a new trend

Aims

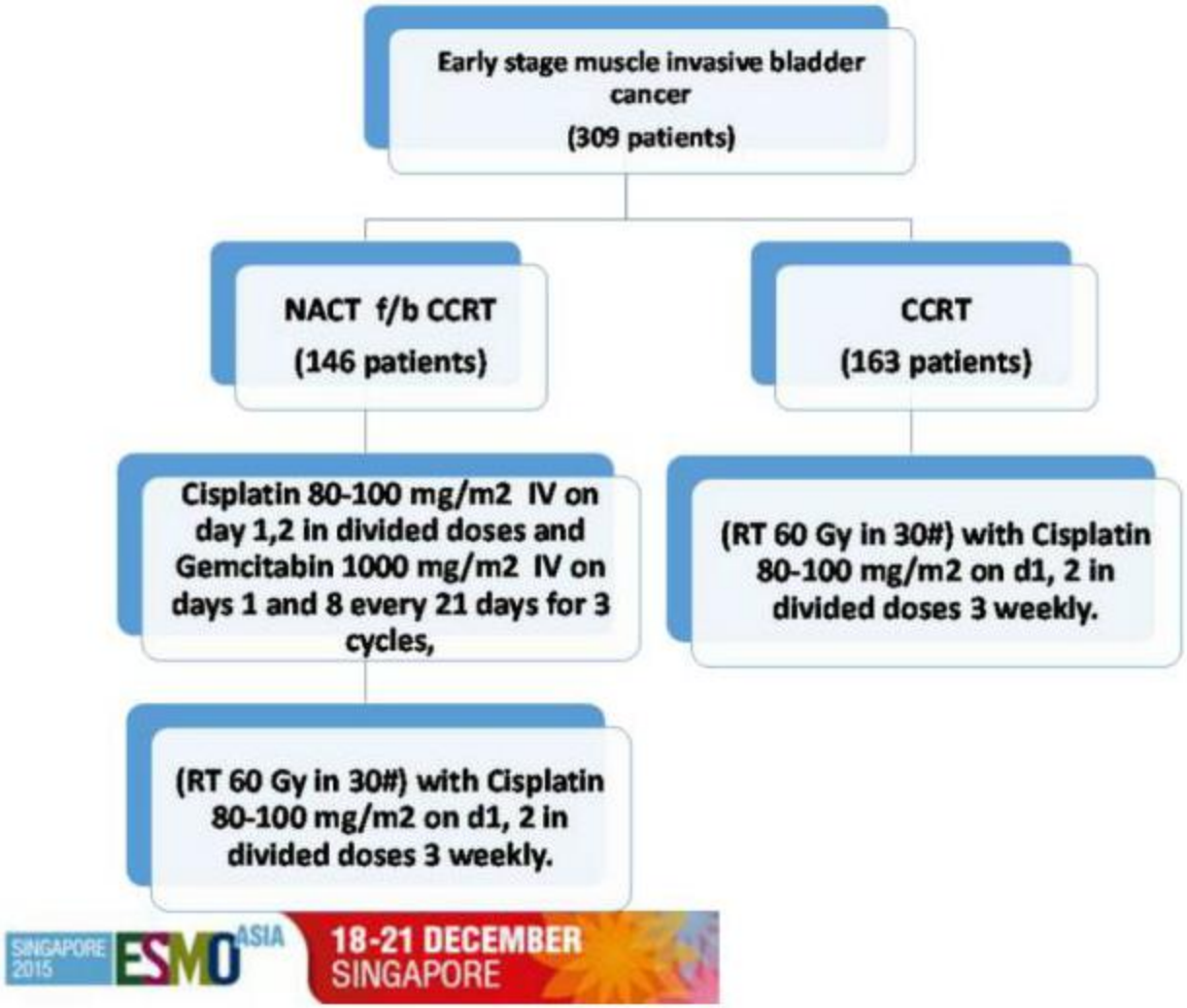
- The aim of this study to identify the additional benefit for bladder preservation, survival and toxicity, in Indian Asian population with muscle invasive early bladder cancer.

of neoadjuvant chemotherapy

Materials & Method

- The histo-pathologically proven transitional cell cancer by TURBT
- Muscle invasive early bladder cancer (cT2-cT4a).
- Patients were randomly enrolled
- All statistical calculations were performed using SPSS version 20.0 software.

Materials & Method



Selection is Key

<u>Tumor presentations with the highest success rates for bladder preservation:</u>

- Solitary T2 or early T3 tumors < 6 cm
- No tumor-associated hydronephrosis
- Tumors allowing a visibly complete TURBT
- Invasive tumors not associated with extensive *carcinoma in situ*
- Adequate renal function to allow cisplatin concurrent with radiation
- TCC histology (→ included)

Modified from Jason Efstathiou

RESULTS

- The 3 year bladder preservation in NACT f/b CCRT arm patients has 62%
- CCRT arm have 54% (8% benefit at 3 years in study arm).
- The median PFS was 26.9 months (95% CI; 23.1-30.5) for NACT f/b CCRT versus 23.1 months (95% CI;19-3-25.6) in the CCRT only arm (p=.59).
- Patients treated with NACT has more grade 2/3 GI and hematological toxicities, but were statistically insignificant.

Endpoint of trial needs to be better defined

- 3 year bladder preservation ?
- With functioning bladder ?
- Median PFS/TTF ?
- Overall survival as mentioned in the aims ?
- Benefit of adding NAC to chemorad ?

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

VOLUME 32 · NUMBER 34 · DECEMBER 1 2014

Long-Term Outcomes in Patients with Muscle-Invasive Bladder Cancer After Bladder-Preserving Combined-Modality Therapy: A Pooled Analysis of RTOG 8802, 8903, 9506, 9706, 9906, and 0233

- Five Phase II studies: RTOG 8802, 9506, 9706, 9906, and 0233
- One Phase III study: 8903

Results: Long-Term Outcomes

- **Median follow-up: 7.8 years among survivors (n=205)**
- **Complete response to TURBT & Chemoradiation: 72.0%**
- **All 468 protocol patients included**

	Failures	5-year Estimate [95% CI]	At risk	10-year Estimate [95% CI]	At risk
Overall Survival	262	57% [52%,61%]	205	36% [31%,42%]	57
Disease-Specific Survival	150	71% [67%,75%]	205	65% [61%,70%]	57

Conclusion

This pooled analysis of multicenter, prospective RTOG bladder-preserving CMT protocols demonstrates long-term DSS comparable to modern immediate cystectomy studies, for patients with similarly staged MIBC. Given the low incidence of late recurrences with long-term follow-up, CMT can be considered as an alternative to radical cystectomy, especially in elderly patients not well suited for surgery.


The Oncologist

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Institution: DANA FARBER CANCER INSTITUTE

Bladder Preservation Therapy for Muscle-Invading Bladder Cancers on Radiation Therapy Oncology Group Trials 8802, 8903, 9506, and 9706: Vascular Endothelial Growth Factor B Overexpression Predicts for Increased Distant Metastasis and Shorter Survival

Tim Lautenschlaeger[a], Asha George[b], Alexander C. Klimowicz[c], Jason A. Efstathiou[d], Chin-Lee Wu[e], Howard Sandler[g], William U. Shipley[f], William J. Tester[e], Michael P. Hagan[i], Anthony M. Magliocco[j] and Arnab Chakravarti[a]

conclusion

- NACT f/b CCRT was well tolerated and better with bladder preservation and PFS survival in Asian Indian population.

Synchronous Chemo-radiotherapy

- Numerous phase I/II studies showing feasibility and safety
- Three phase III studies
  - RT vs RT + Cisplatinum (NCIC)
  - RT vs RT + nicotinamide/carbogen (BCON)
  - RT vs RT + 5FU/MMC (BC2001)

Role of Neoadjuvant Chemotherapy in ChemoRads

No Level 1 (Phase III) data indicating cisplatin-based neoadjuvant chemotherapy given before definitive local treatment by RT or RT and concurrent chemotherapy significantly improves survival.

- RTOG 89-03 trial (n=123) negative (5 year survivals of 49% and 50%)
- Danish Cancer Group trial (n=113) negative (NCT had 5.6% lower survival)
- RT subgroup of MRC trial (n=413) trended insignificant in favor of NCT
- Meta-analysis negative (survival 30.4% vs 28.1%)

Current Recommendations in Cystectomy Candidates "Off-Protocol"

Stage T_3 -T_{4a} with hydronephrosis: Cystectomy

Stage T_{4a} (prostate stromal invasion): Cystectomy

Stage T_2-T_3: TURBT and concurrent cisplatin plus XRT (QD or BID) with prompt cystectomy for failure

Modified from Efstathiou J.

Conclusion

- **The optimal regimen of combined chemoRT**
- **The addition +/- NAC/Adjuvant,**
- **The addition of molecular targeted therapy**
- **The personalized treatment selection based on biomarkers (e.g. DNA repair, apoptosis, proliferation, hypoxia – such as high MRE11, normal Her2, low ERCC1, high XRCC1/APE1)**

→ **continues to be investigated and needs further validation**

Scorecard (abstract #2360)

- Strengths
  - Randomized design
  - The 3 year bladder preservation is consistent with RTOG pooled analysis
  - Can add data to the survival benefit on the role of NAC
- Weaknesses
  - The aims/end-points need to be better described (NAC vs non)
  - No statistical power calculation
  - No clear patient selection (as presented) and Inc/excl
  - Lack of QoL measurement
  - Need to implement translational studies

Adjuvant chemotherapy in patients with muscle invasive bladder cancer after radical cystectomy: now or never?

Ezz El Din M., ElKholy E., Mosalam N

Department of Clinical Oncology and Nuclear Medicine, Ain-Shams University Hospitals, Cairo, Egypt.

Presented by: Mai Ezz El Din, M.D

Clinical Oncology Lecturer

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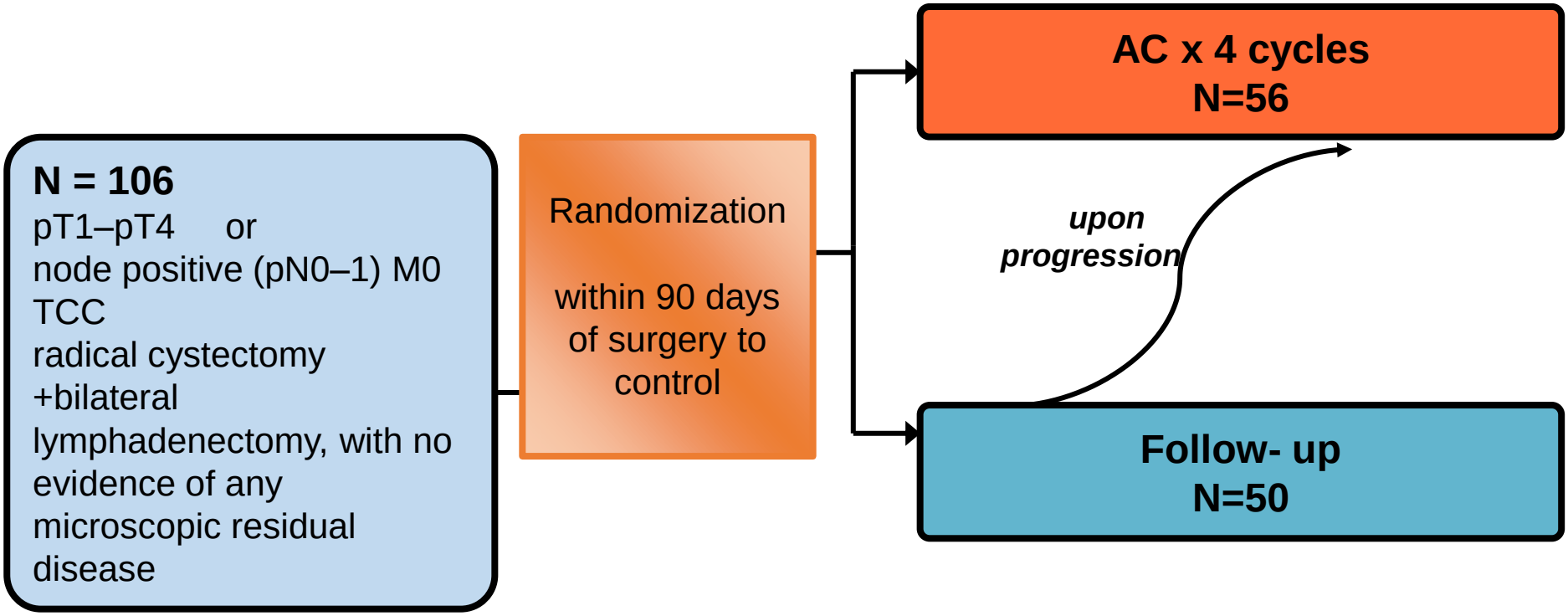
SINGAPORE 2015 ESMO ASIA 18-21 DECEMBER SINGAPORE

Study Design



Primary end point survival
2nd: PFS and toxicity

AC= gemcitabine 1000 mg/m^2 days 1, 8 ,15 +
cisplatin 70 mg/m^2 day 1 / 28 days.

Study summary

- Sample size small with only 106 patients (56 vs 50).
- To detect a …….% improvement in OS. Power ……%, alpha ……0.1, n=……
- T1 = 6 pts (5 control 1 in treatment arm)
- Median follow-up of 38 months.
- MST 42m control group vs 55m in the treatment group
- DFS 28m control group vs 45 m in the treatment group
- Arms generally balanced but: T1, and PS2 included
- LN+ the most important determinant of OS and DFS (N1 ?)

Conclusions by the authors

- Limited in sample size
- incomplete data on the adequacy of LND
- LN + the most important determinant of survival DFS
- OS & DFS failed to show a significant improvement with immediate versus deferred chemotherapy

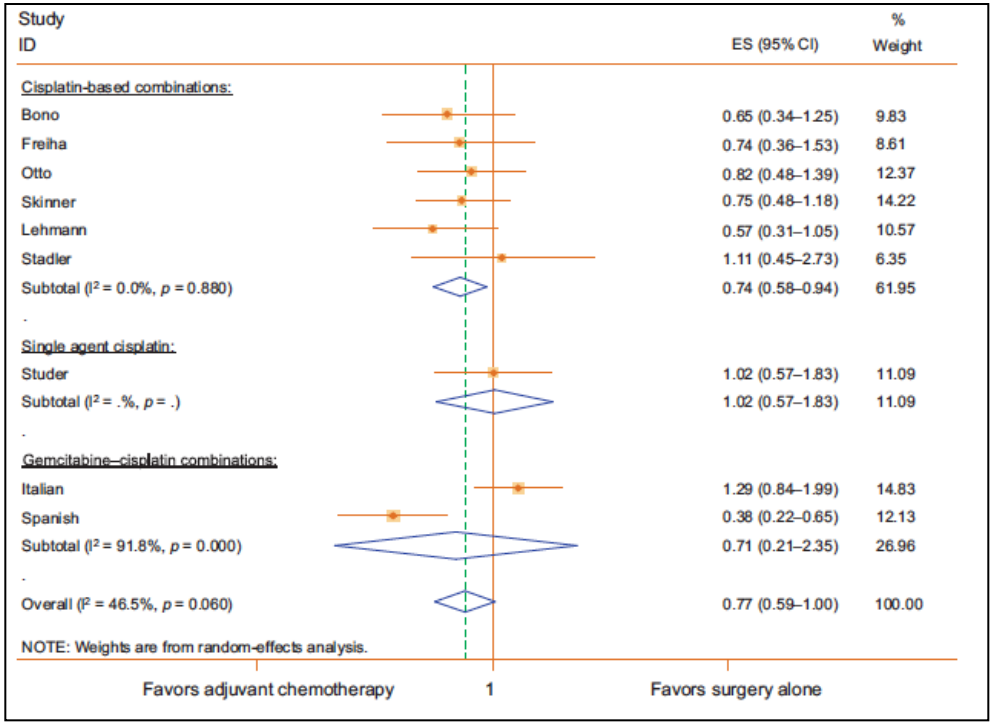
Adjuvant Chemotherapy for Invasive Bladder Cancer: A 2013 Updated Systematic Review and Meta-Analysis of Randomized Trials

Jeffrey J. Leow [a,b,c], William Martin-Doyle [a], Padma S. Rajagopal [a], Chirayu G. Patel [a], Erin M. Anderson [a], Andrew T. Rothman [a], Richard J. Cote [d], Yuksel Urun [e], Steven L. Chang [b,c], Toni K. Choueiri [e], Joaquim Bellmunt [e,f,]*

- 9 randomized controlled trials
- n=945

- OS: pooled HR: 0.77
  (95%CI: 0.59-0.99, p=0.049)

- DFS: pooled HR: 0.66
  (95% CI: 0.45-0.91, p=0.014)
  - Even greater benefit in Node+



Eur Urology 2013

	Events/patients		Statistics		HR (95% CI)
	Adjuvant chemotherapy	Control	(O–E)	Variance	
Single agent cisplatin					
Studer et al, 1994[21]	23/46	22/45	0·2	11·3	1·02 (0·57–1·83)
Subtotal	**23/46 (50%)**	**22/45 (48·9%)**	**0·2**	**11·3**	**1·02 (0·57–1·83)**
Cisplatin combinations					
Bono et al, 1997[22]	43/14	47/23	−3·9	9·1	0·65 (0·34–1·24)
Freiha et al, 1996[8]	27/13	28/17	−2·2	7·4	0·74 (0·36–1·52)
Otto et al, 2003[23]	55/28	53/29	−2·7	13·4	0·82 (0·48–1·40)
Skinner et al, 1991[24]	50/34	52/40	−5·5	19·3	0·75 (0·48–1·17)
Lehmann et al, 2006[25]	26/20	23/20	−5·8	10·4	0·57 (0·31–1·05)
Subtotal	**201/109 (184·4%)**	**203/129 (157·4%)**	**−20·2**	**59·6**	**0·71 (0·55–0·92)**
Heterogeneity χ^2=0·92, df=4; p=0·92					
Gemcitabine plus cisplatin					
Paz-Ares et al, 2010[11]	24/68	45/74	−13	13·3	0·38 (0·22–0·65)
Cognetti et al, 2012[10]	46/102	38/92	5·3	20·9	1·29 (0·84–1·98)
EORTC 30994 trial	66/141	82/143	−9·2	36·4	0·78 (0·56–1·08)
Subtotal	**136/311 (43·7%)**	**165/309 (53·4%)**	**−16·8**	**70·6**	**0·79 (0·62–1·00)**
Heterogeneity χ^2=12·27, df=2; p=0·002					
Total	**360/466 (77·3%)**	**390/483 (80·7%)**	**−36·8**	**141·5**	**0·77 (0·65–0·91)**
Test for heterogeneity χ^2=14·49, df=8; p=0·07					

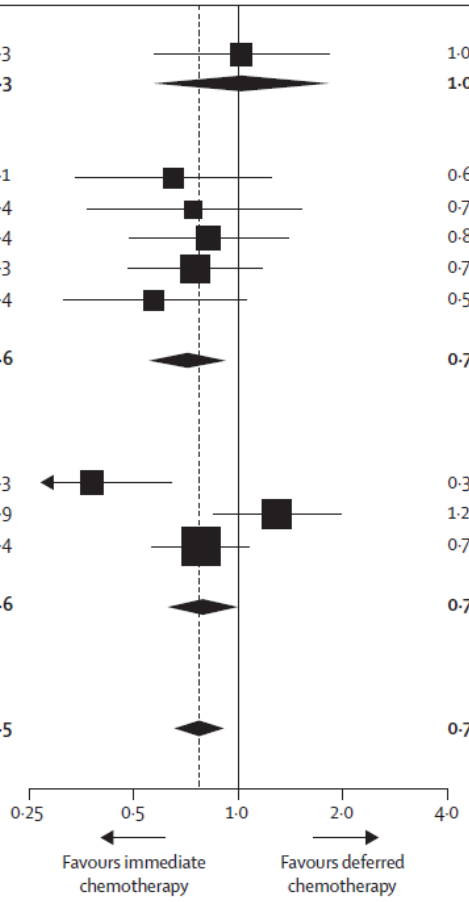


Figure 5: Updated scientific literature-based meta-analysis of studies of adjuvant chemotherapy for advanced urothelial carcinoma
O=observed. E=expected. HR=hazard ratio.

Scorecard (abstract #2370)

Strengths

- Randomized trial
- PFS is quite good with some trend (45 vs 28,75 months)
- Includes pt with history of bilharzial and sq differentiation
- Authors acknowledge the limitations (sample size/No LN path review)

Weaknesses

- Small study and immature study (median follow-up is shorter that the median OS)
- Lack of statistical calculation/end point
- Imbalance in the control arm with 10% of patients being T1
- Only N1 (=one single node) no N2 ?
- Conclusion that OS and DFS failed is wrong due to beta error (small sample size)

Recommendations: Muscle Invasive UC

- Neoadjuvant cisplatin-based chemotherapy followed by RC
  - Gold standard if T2 or greater by clinical staging
- Consider adjuvant cisplatin-based chemotherapy after RC if:
  - >T2
  - Presence of nodal disease
  - Presence of lymphovascular invasion
- Cisplatin ineligible: upfront cystectomy
- Chemoradiation with extensive TURBT ("bladder-sparing")
  - Non-surgical candidate or patient preference to keep bladder
  - Ideal candidate: clinical T2, no hydro or CIS; maximal TURBT possible
  - 25-30% will require salvage cystectomy

RC: radical cystectomy

Topics for discussion in both abstracts

- Role of bladder preservation per se
- Neoadjuvant chemotherapy improves overall survival in Cystectomy – but is it the same for bladder preservation?
- Adjuvant chemotherapy with CCDP chemo is indicated in those not receiving NAC if pathologic Stage III

Congratulations to the presenters for designing and completing these difficult to conduct trials.

Definitive data is missing in this setting of NAC + bladder preservation (chemoRads) and in the adjuvant bladder worldwide

These trials are helping to add evidence to the field and more specifically in the Asian patients

Thank you!