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Österreich
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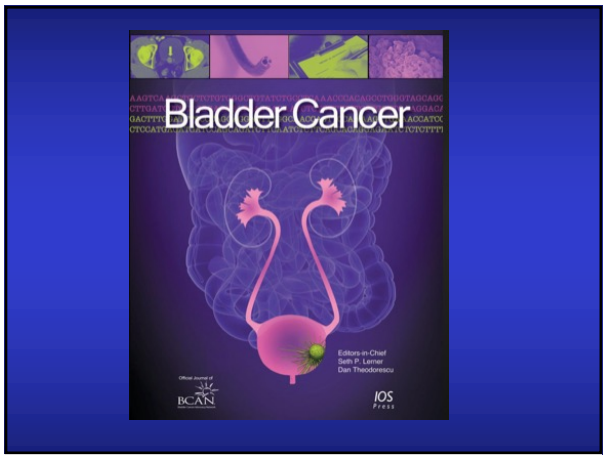
Bladder Cancer
Editors-in-Chief
Seth P. Lerner
Dan Theodorescu
BCAN
IOS Press

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UNIVERSITY of TORONTO

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Princess Margaret Hospital
University Health Network

Trimodal Therapy in Muscle Invasive Bladder Cancer Management

based on AUA Update series 2020

Maria C Mir, Elvira Polo-Alonso, Georgi Guruli, Cynthia Kuk, Peter Chung and Alexandre R Zlotta

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UHN

Toronto UHN Multidisciplinary BC Clinic

Referral-based clinic started in 2008- > 900 new patients

- Uro-Oncs: Zlotta, Fleshner, Kulkarni, **(Jewett)**
- Rad Onc: **Chung, Berlin, Raman,** (Bristow), (Warde), (Milosevic), (Catton)
- Med Oncs: Sridhar, Jiang, Fallah-Rad
- Clinic coordinators: Cynthia Kuk/(Annette Erlich)/Steph Wong
- **PAs:** D Kot/ J Misurka
- Pathologists: Van der Kwast, Sweet, **(Evans)**
- Nurses: Monica Zarrello, Audrey Bunce, Nedy Crossland
- **And thanks to our uro-oncology fellows over the years!!**

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Fellows around the World

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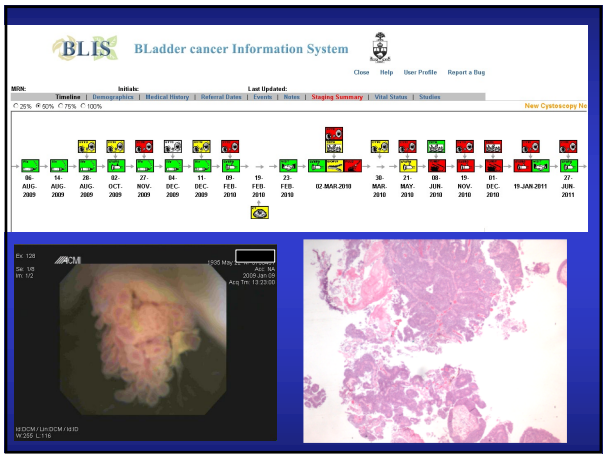
BLIS BLadder cancer Information System



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JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Propensity Score Analysis of Radical Cystectomy Versus Bladder-Sparing Trimodal Therapy in the Setting of a Multidisciplinary Bladder Cancer Clinic

Girish S. Kulkarni, Thomas Hermanns, Yanliang Wei, Bimal Bhindi, Raj Satkunasivam, Paul Athanasopoulos, Peter J. Bostrom, Cynthia Kuk, Kathy Li, Arnoud J. Templeton, Srikala S. Sridhar, Theodorus H. van der Kwast, Peter Chung, Robert G. Bristow, Michael Milosevic, Padraig Warde, Neil E. Fleshner, Michael A.S. Jewett, Shaheena Bashir, and Alexandre R. Zlotta

JCO 2017

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Trimodal Therapy (TMT)

- The TMT concept in MIBC includes a combination of complete TURBT followed by RT with radio-sensitizing chemotherapy
- Most robust bladder sparing approach

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Patient Selection for Bladder Preservation

Clinical Features for Ideal TMT Candidates
cT2- cT3
No hydronephrosis or minimal unilateral hydronephrosis
No multifocal CIS
Unifocal tumor < 7 cm
Complete TURBT
Good bladder function and capacity

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Radiotherapy Regimens and follow-up protocols

End of TMT	3mo	6mo	9mo	12mo
Yr 1	Cysto + CT A/P/C, BS	Cysto + CT A/P/C	Cysto	Cysto + CT A/P/C
Yr 2	Cysto	Cysto + CT A/P/C	Cysto	Cysto + CT A/P/C
Yr 3		Cysto		Cysto + CT A/P + CXR
Yr 4		Cysto		Cysto + CT A/P + CXR
Yr 5		Cysto		Cysto + CT A/P + CXR

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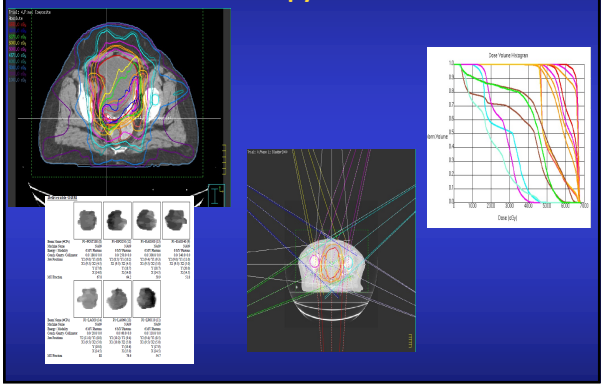
Intensity Modulated RT (IMRT)- delivery of radiation therapy to the bladder



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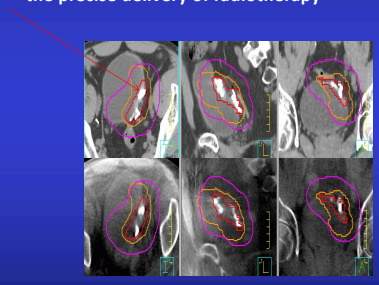
RT technique – lipiodol for tumor delineation

Lipiodol injected during cystoscopy to help the precise delivery of radiotherapy



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Drug	n	Inclusion Criteria	Combination	Primary Endpoint	Secondary Endpoint	Expected Accrual
Pembrolizumab						
NCT02662062	30	cT2-4a TCC, Nx or N0	Pembrolizumab + Cisplatin + RT	% pts w/ grade 3 and 4	Efficacy of adding pembrolizumab to SOC TMT; % pts w/ M+; % pts w/ SC	2024
NCT02621151	54	cT2-T4a TCC N0 M0 TCC	Pembrolizumab + Gemcitabine + RT	Bladder-intact DFS at 2y	Safety, CR rates, OS, MFS	2026
Durvalumab						
NCT 03702179 (IMMUNOPRESERVE)	32	cT2-T4a TCC	Durva + Treme + RT	% pts w/ path response	% pts w/ bladder preserved at 24mo; % SC; DFS, OS, ,AE	2022
NCT02891161	42	cT3-4N0-2 M0; cTxN1-2M0; cT2N1-2 M0	Durvalumab + RT + Adjuvant durvalumab	DLT; PFS; Disease control rate	CR rates; OS; PDL-1 expression	2019
Nivolumab						
NCT03421652 (NUTRA)	34	cT2-4b N0-1	Nivolumab + RT	PFS	AE; Response rate, MFS, OS	2020
NCT03171025 (NEXT)	28	cT2-T4a N0 or N+ M0; T1 w/ N+	Adjuvant Nivolumab after TMT	2y-Failure Free Sx (locaregional recurrence and distand)	Failure Free Survival at 2y	2024
NCT03529890 (RACE IT)	33	cT2-T4 N0	Nivo + RT- RC	Rate pts w/completed at least 2 cycles	Acute toxicity preop; immunorelated toxicities	2022
Avelumab						
NCT03617913	27	cT2-4a N0M0 TCC	Avelumab + 5FU/MMC/Cisplatin + RT	CR	Adverse events; EORTC-QLQ-30/BLM 30; PFS,	2025

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Tri-modality vs. Radical Cystectomy

- A recent meta-analysis found no differences in 5- and 10-year OS, CSS and progression-free survival rates between TMT and RC.
- This meta-analysis included patients until 2016 with more recent treatment techniques.

Vashistha V, Wang H, Mazzone A, Liss MA, Svatek RS, Schleicher M, et al. Radical Cystectomy Compared to Combined Modality Treatment for Muscle-Invasive Bladder Cancer: A Systematic Review and Meta-Analysis. Int J Radiat Oncol Biol Phys. 2017;97(5):1002–20.

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PLOS ONE

RESEARCH ARTICLE

Systematic review and meta-analysis on trimodal therapy versus radical cystectomy for muscle-invasive bladder cancer: Does the current quality of evidence justify definitive conclusions?

Marian S. Wettstein[1,2], Jasjit K. Rooprai[1], Clinsy Pazhepurackel[3], Christopher J. D. Wallis[1], Zachary Klaassen[1], Elizabeth M. Uleryk[2], Thomas Hermanns[2], Neil E. Fleshner[1], Alexandre R. Zlotta[1,4], Girish S. Kulkarni[1]*

1 Division of Urology, Department of Surgery, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, Ontario, Canada, 2 Department of Urology, University Hospital of Zurich, University of Zurich, Zurich, Switzerland, 3 E.M. Uleryk Consulting, Mississauga, Ontario, Canada, 4 Division of Urology, Department of Surgery, Mount Sinai Hospital, Sinai Health System, University of Toronto, Toronto, Ontario, Canada

Check for updates

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Population-based studies				
Bekelman, 2013 United States	417	1426	1. Multivariable regression analysis	1.28 (0.98–1.68)
			2. Propensity score-adjusted regression analysis	1.32 (0.97–1.77)
			3. Inverse probability weighting-adjusted regression analysis	1.34 (1.02–1.77)
			4. Instrumental variable analysis	0.94 (0.55–1.18)
Cahn, 2017 United States	1489	22680	1. Multivariable regression analysis	
	1489[1]	1489[1]	2. Hard and propensity score matching followed by unadjusted regression analysis	
Fischer-Valuck, 2018 United States	958	1231	1. Multivariable regression analysis	
	650	650	2. Propensity score matching followed by Kaplan-Meier analysis	
Ritch, 2018 United States	1686	1686	Propensity score matching followed by adjusted regression analysis	
Seisen, 2017 United States	1257	11586	Inverse probability weighting-adjusted regression analysis	
Smith, 2014 United States	3724	9704	Multivariable regression analysis	
Williams, 2018 United States	687	687	Propensity score matching followed by unadjusted regression analysis (DSS: accounting for competing risks)	1.55 (1.32–1.83)

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Multi-institutional matched comparison of radical cystectomy to trimodality therapy for muscle invasive bladder cancer: a propensity analysis

Alexandre R Zlotta, Andrzej Niemierko, Katherine Lajkosz, Leslie K Ballas, Cynthia Kuk, Gus Miranda, Michael Drumm, Andrea Mari, Neil E Fleshner, Girish S Kulkarni, Peter Chung, Rob Bristow, Alie Berlin, Srinivas Raman, Mike Milosevic, Padraig Warde, Charles Catton, Mike Jewett, Srikala S Sridhar, Adam S Feldman, Matthew Wszolek, Richard Lee, Anthony Zietman, William Shipley, Siamak Daneshmand and Jason A. Efstathiou

UHN/ Mass General Hospital (Harvard University-Boston)/Univer of South California, LA

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Introduction

- Prior RCTs comparing bladder preservation to radical cystectomy (RC) closed early due to lack of accrual (SPARE trial/Catto et al 2021/ University of San Antonio)
- Given that no future RCTs are foreseen, and in the absence of level 1 data, we compared outcomes of trimodality therapy (TMT, maximal transurethral resection of bladder tumor followed by concurrent chemoradiation) to RC in matched cohorts from multiple institutions in order to guide management.

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Material and Methods

- Retrospective analysis
- 703 patients with MIBC clinical stage T2-T3/4aN0M0 MIBC (urothelial), 421 RC and 282 TMT who would have been eligible for both TMT or RC, treated at the Massachusetts General Hospital, Boston; PMCC, Toronto; and University of Southern California, Los Angeles between 2005-2017.
- In order to compare homogenous cohorts, all patients included in this analysis had

1. Solitary tumors <7 cm
2. No or unilateral hydronephrosis
3. No multifocal carcinoma in situ.

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Material and Methods

- Treatment propensity scores estimated using logistic regression
- Patients matched 1:1 with replacement Caliper matching: = 0.25 x SD of logit of PS
- Covariates :age, sex, clinical T stage, hydronephrosis, (neo)adjuvant chemotherapy, BMI, smoking history and ECOG status.
- OS estimated with adjusted Cox models; CSS, distant failure-free, pelvic nodal failure-free and metastasis-free survival (combined distant and pelvic nodal failure) estimated with adjusted competing risk models.
- Primary endpoint of interest: metastasis-free survival.
- Analysis performed as intent-to-treat.

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Actuarial methods of analysis for matched and imputed datasets

- Multivariable competing risks regression on imputed datasets (Rubin's rule for pulling results from individual datasets):
  - Time to distant failure
  - Time to regional failure
  - Time to regional/distant failure
  - Cancer-specific survival
- Multivariable Cox regression (Rubin's rule for pulling results from individual datasets):
  - Overall survival

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Stats

- Analyses performed independently and blindly in Toronto and Boston
- Same results observed independently!!!
- Stats merged then as full consistency between statisticians!

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Baseline characteristics before matching

Factor	RadC	TMT	p-value
N	421	282	
Age, median (IQR)	71.0 (63.6, 76.7)	71.6 (64.0, 78.9)	0.16
Sex			0.32
Female	88 (20.9%)	68 (24.1%)	
Male	333 (79.1%)	214 (75.9%)	
CIS			0.15
No	313 (74.3%)	223 (79.1%)	
Yes	108 (25.7%)	59 (20.9%)	
cTstage			0.078
T2	362 (86.0%)	255 (90.4%)	
T3	59 (14.0%)	27 (9.6%)	
BMI			0.026
Non-obese	323 (76.7%)	193 (68.4%)	
Obese	98 (23.3%)	86 (30.5%)	
	0 (0.0%)	3 (1.1%)	

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Baseline characteristics before matching

Factor	RadC	TMT	p-value
N	421	282	
Hydronephrosis			<0.001
No	325 (77.2%)	255 (90.4%)	
Yes	96 (22.8%)	27 (9.6%)	
Peri-treatment chemo			<0.001
No	253 (60.1%)	123 (43.6%)	
Yes	168 (39.9%)	159 (56.4%)	
Smoking history			0.57
Never smoked	111 (26.4%)	69 (24.5%)	
Current or Former	310 (73.6%)	213 (75.5%)	
ECOG			0.63
0	182 (43.2%)	218 (77.3%)	
1 or 2	59 (14.0%)	64 (22.7%)	
	180 (42.8%)	0 (0.0%)	

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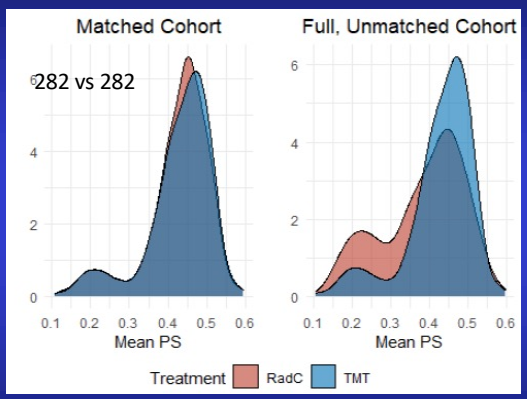

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RESULTS

- Met-free (76 vs 78%, p=0.93), CCS (83 vs 84%, p=0.45), distant failure-free (80 vs 78%, p=0.91), and pelvic nodal failure-free (96 vs 92%, p=0.1) survival not different between RC and TMT at 5 years
- OS favored TMT (67 vs 75%, p=0.02)
- Salvage cystectomy performed in 38 patients (13%) treated by TMT
- Final pT stage in the RC patients: pT0 14%, pT1 7%, pT2 29%, pT3/4 42% and N+ 24%.
- Peri RC mortality:2.1%
- Median nodes removed : 40
- NMIBC recurrence occurred in 57/278 (20.5%) TMT patients.

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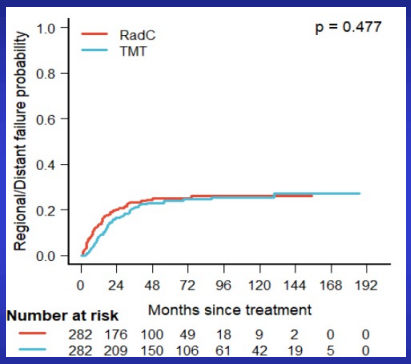
Metastatic-free survival



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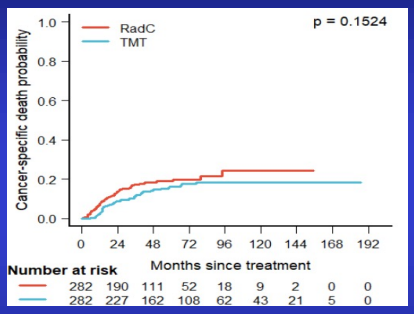
Cancer Specific Survival



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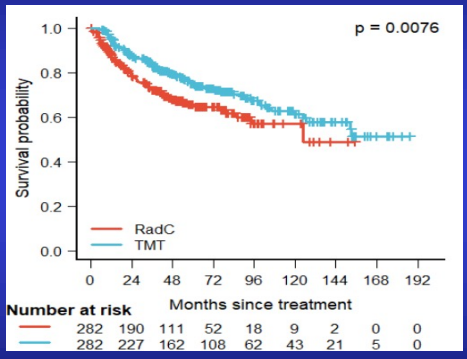
OS



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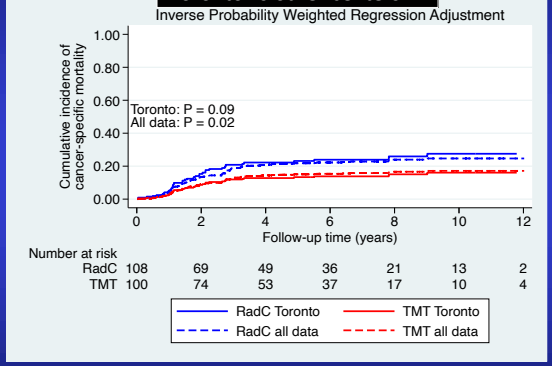
Toronto vs other centers



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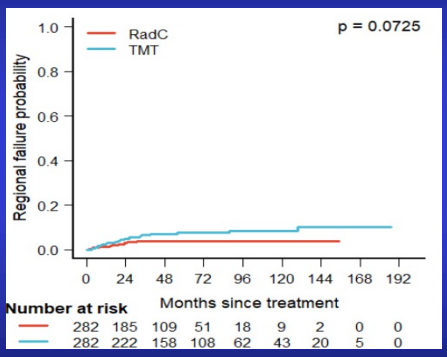
Regional failure



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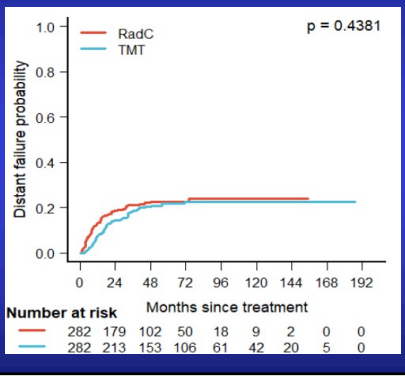
Distant metastatic failure



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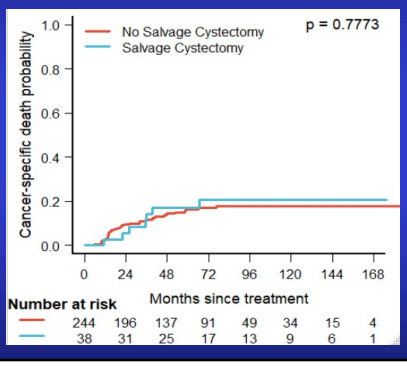
TMT: CSS in patients requiring salvage RC vs those who didn't



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Conclusions

- This large multi-institutional contemporary study provides the best evidence to date, in the absence of RCT, supporting TMT for select patients with MIBC
- Oncologic outcomes seem to be equivalent between TMT and RC
- TMT should be offered as an effective alternative for these patients
- Limitations: select MIBC pts only, rigorous follow-up, centers performing post RT RC, 13% of RC post TMT, 25% NMIBC recurrence after TMT, the best PS matched cohorts cannot replace RCTs (still possibility of confounders)

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EUROPEAN UROLOGY 73 (2018) 543–557

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Review – Bladder Cancer
Editorial by Bernard H. Bochner on pp. 558–559 of this issue

The Role of Surgery in Metastatic Bladder Cancer: A Systematic Review

Mohammad Abufaraj[a,b], Guido Dalbagni[c], Siamak Daneshmand[d], Simon Horenblas[e], Ashish M. Kamat[f], Ryu Kanzaki[g], Alexandre R. Zlotta[h], Shahrokh F. Shariat[a,i,j,k,]*

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Role of Surgery after Immune Checkpoint Inhibitors

??????????????????????????

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Conclusion

- improved survival in patients with low volume disease after measurable response to CHT in the lung, pelvic, and retroperitoneal LN metastases.
- Evidence shows that surgical resection is technically feasible with acceptable morbidity and can achieve long-term cancer control in well- selected patients.
- Anecdotal reports of resection of pulmonary metastasis as part of multimodal approach suggest possible improved survival in well-selected patients.

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Personal take

- PET might be useful but underestimates the extent of microscopic involvement
- When nodes are negative, patients do well but one has to ask whether surgery was not a staging procedure
- When nodes are positive on final path after chemotherapy, patients in our experience do uniformly poorly, unfortunately
- Similar experience at MD Anderson (Ashish Kamat) and Ottawa
- RPLND unfortunately does not seem to help much unless pCR
- With the JAVELIN 100 data, we have now IO maintenance therefore even less enthusiastic about RPLND

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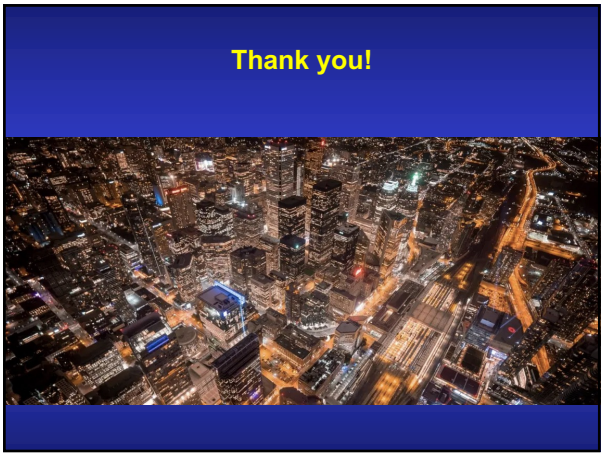

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