THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Are We Moving Away from Cystectomy for Bladder Cancer? The Art and Science of Selection

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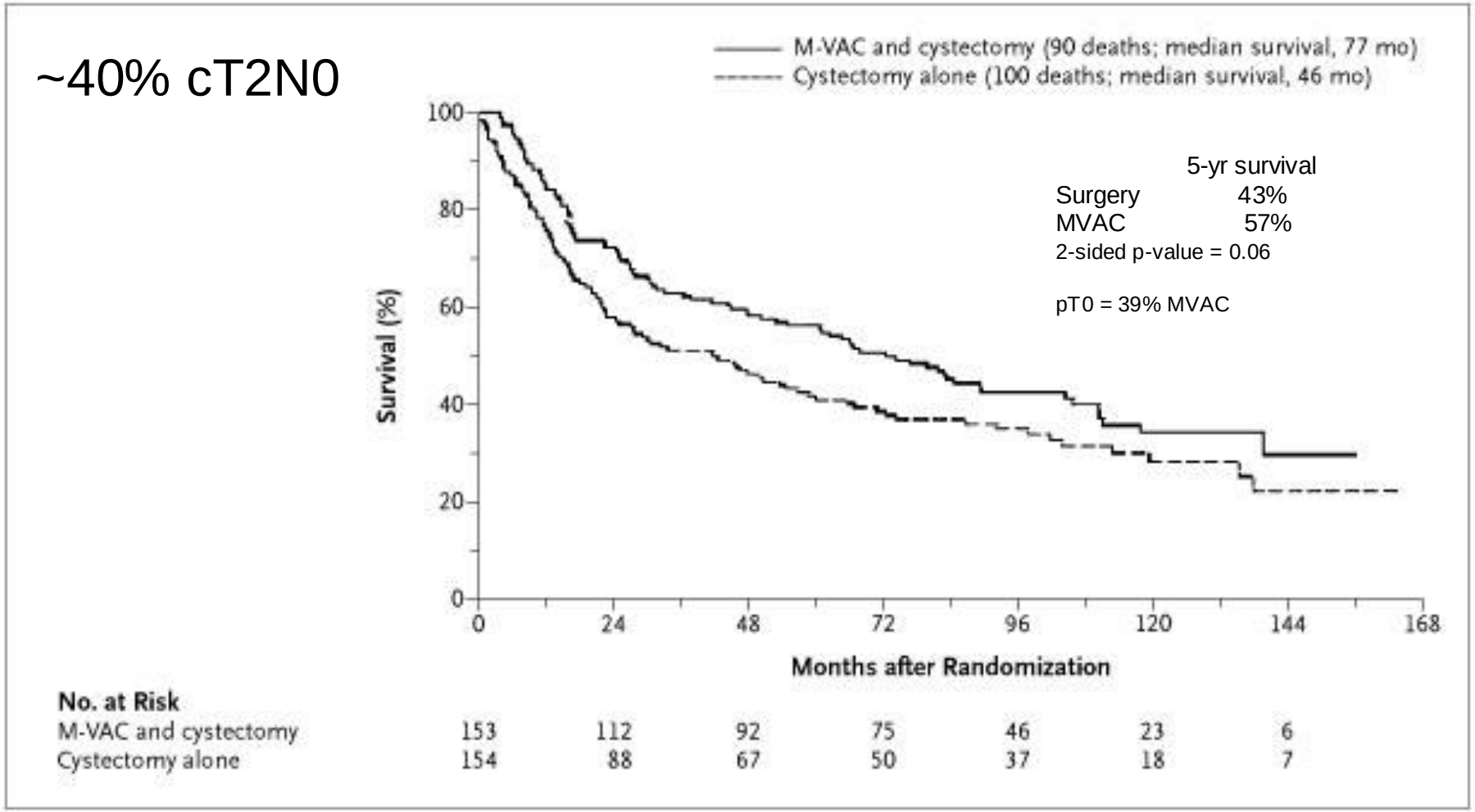
Neoadjuvant Chemotherapy:
Cisplatin remains the standard!

Muscle Invasive: cT2-4aN0 Disease

- Neoadjuvant chemotherapy now standard
  - Cisplatin (not carboplatin!)
  - MVAC historical standard
  - DDMVAC acceptable – improved toxicity and shorter time to surgery
  - GC + durvalumab improved OS compared to GC
  - Ifosfamide with doxorubicin and gemcitabine
- Adverse prognostic factors
  - Lymphovascular invasion (LVI)
  - Positive EUA
  - Tumor at ureteral orifice/hydronephrosis
  - HG upper tract
  - Extension to local but resectable organs

SWOG Intergroup Trial

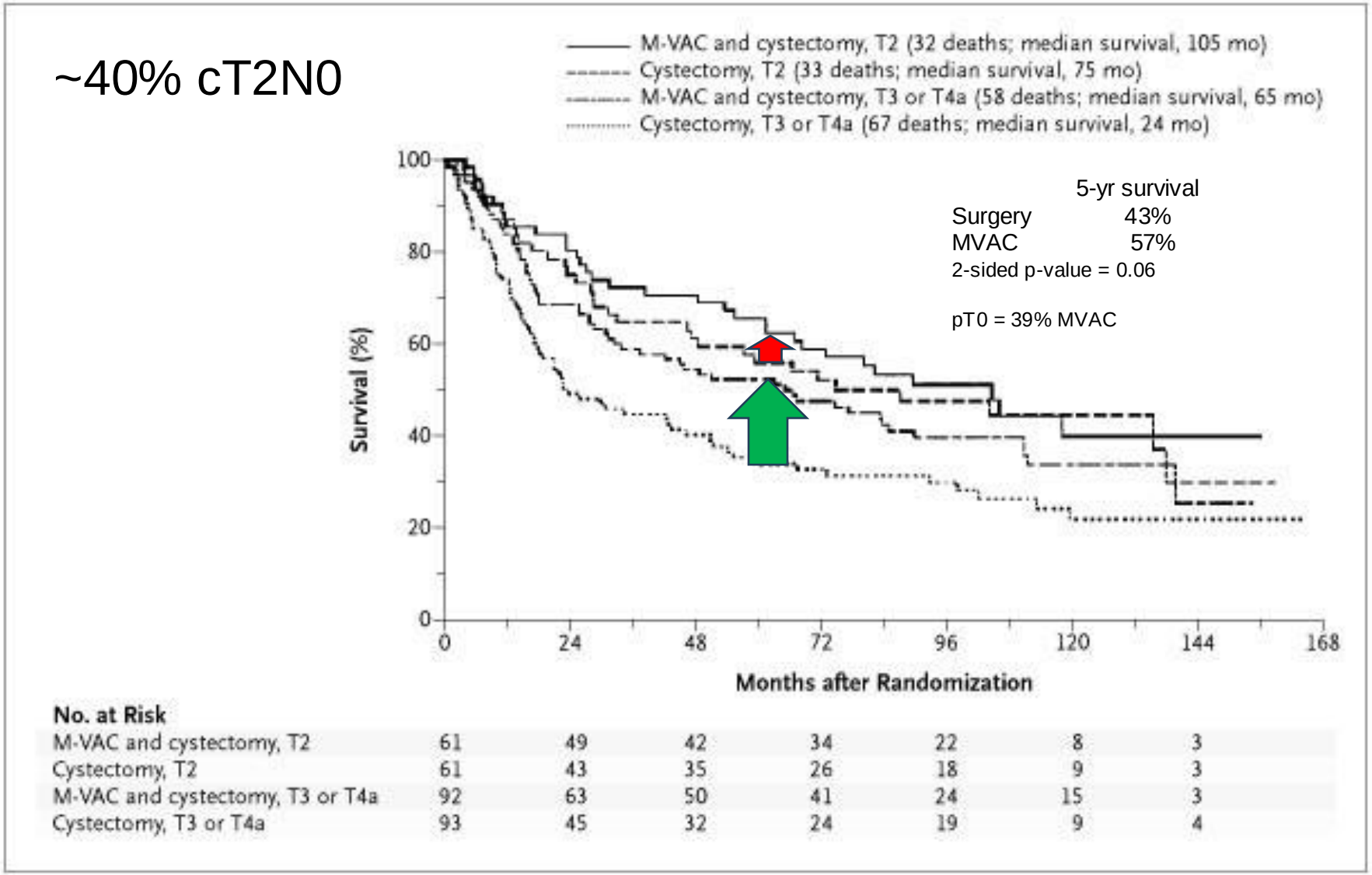
~40% cT2N0



Grossman et al. NEJM 349;9: 859-866, 2003

SWOG Intergroup Trial: Greatest benefit in >= T3 disease

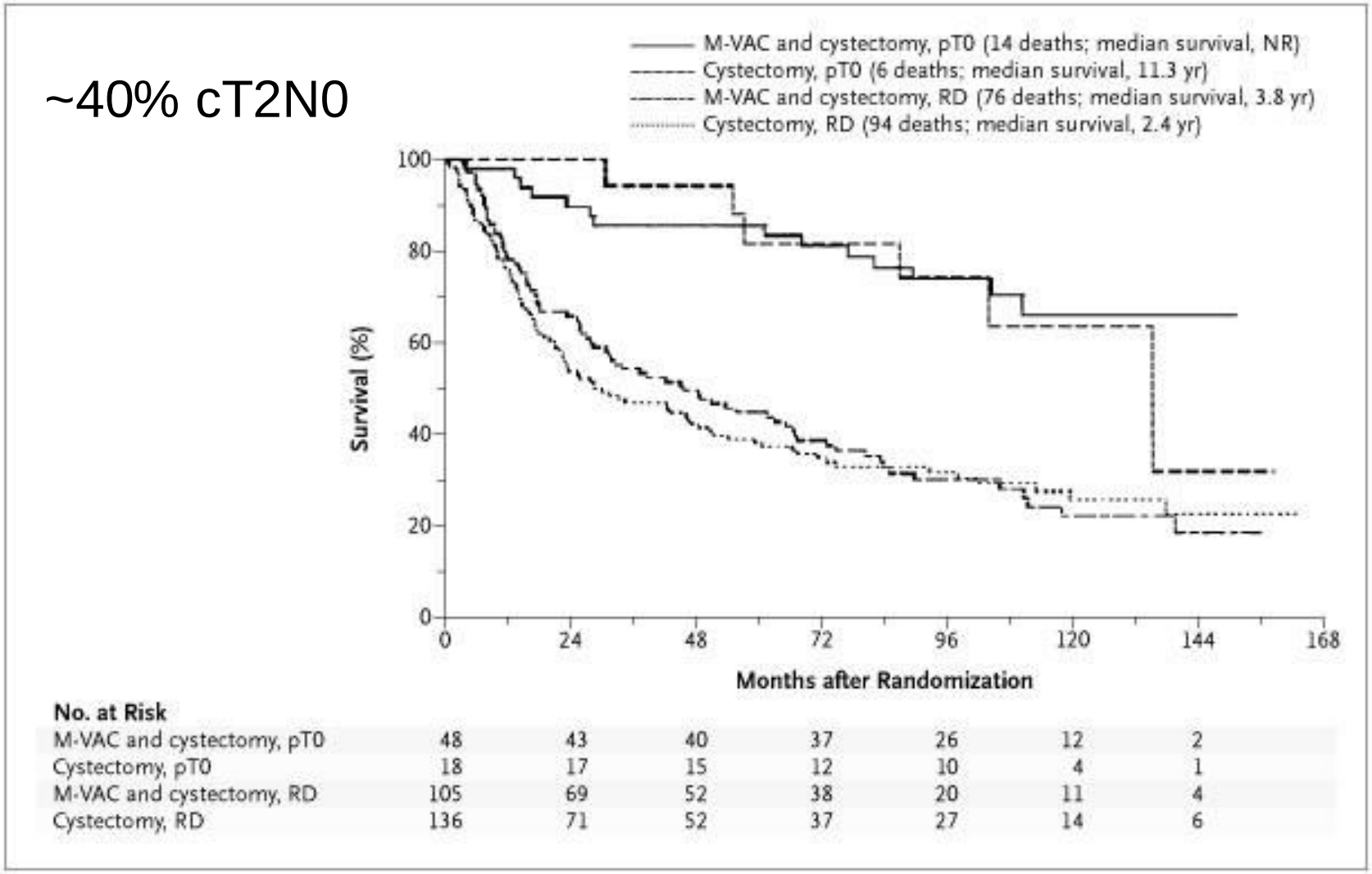
~40% cT2N0



Grossman et al. NEJM 349;9: 859-866, 2003

SWOG Intergroup Trial: 12% downstaging TUR alone, similar outcomes

~40% cT2N0



No. at Risk							
M-VAC and cystectomy, pT0	48	43	40	37	26	12	2
Cystectomy, pT0	18	17	15	12	10	4	1
M-VAC and cystectomy, RD	105	69	52	38	20	11	4
Cystectomy, RD	136	71	52	37	27	14	6

Grossman et al. NEJM 349;9: 859-866, 2003


Bladder Preservation:
The Art of Selection

Not all T2 tumors are equal…

Bladder “Preservation”

The “Optimal” patient

- Tumor is completely resected on TUR
- No mass on EUA
- Solitary tumor (no multifocal disease)
- No ureteral obstruction
- No disease near the urethra bladder neck
- No CIS

Chemo XRT vs XRT

- N= 360 pts.
- 80% cT2N0

XRT

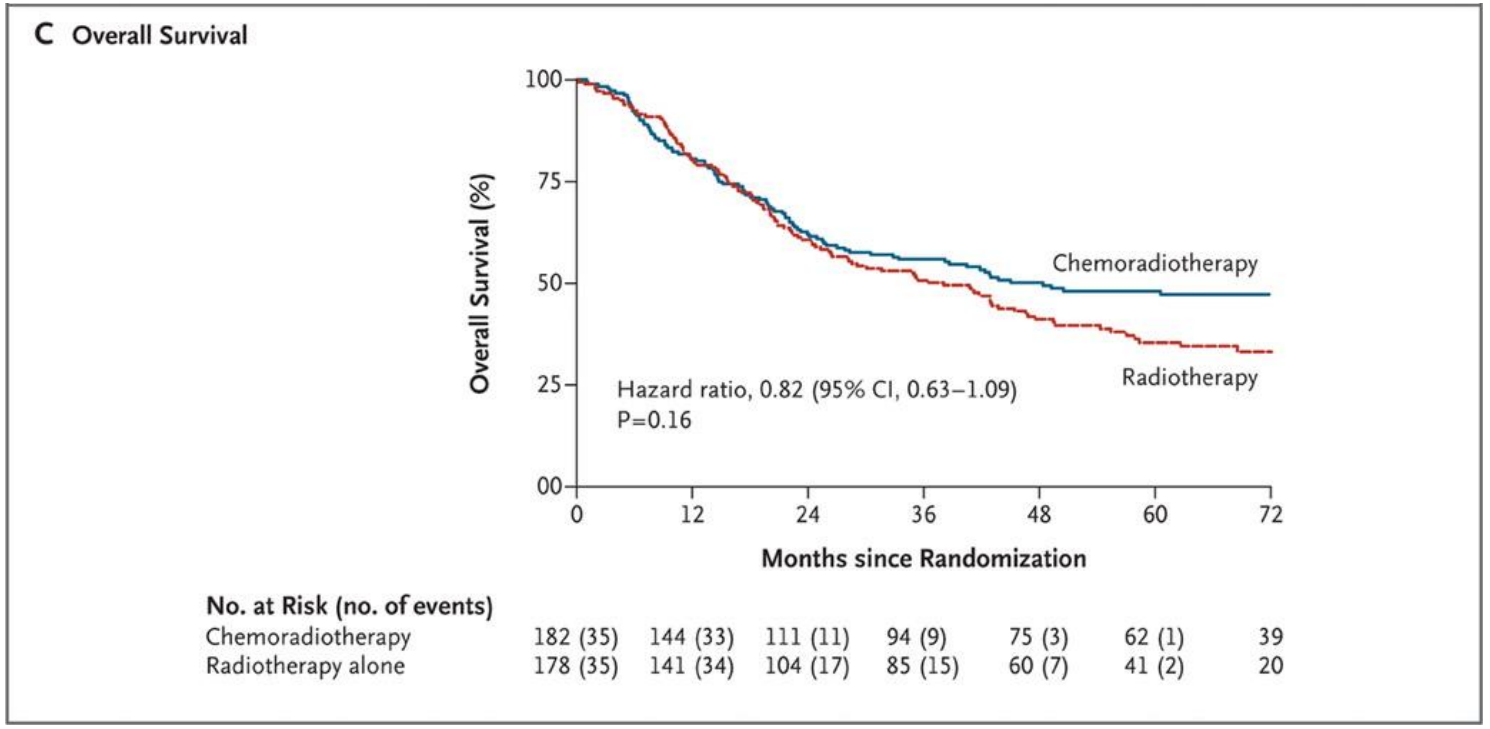
- 55 Gy in 20 fx or
- 64 Gy in 32 fx

Chemotherapy

- 5FU CI 500 mg/m2 per day

days 1-5, 16-20, and

- Mitomycin C 12 mg/m2 day 1



	2-yr "locoregional" DFS	5-year survival	2-yr cystectomy rate
XRT alone	54%	35%	16.8%
Chemo-XRT	67%	48%	11.4%
	HR 0.68, p = 0.03	HR 0.82, p=0.16	p = 0.07

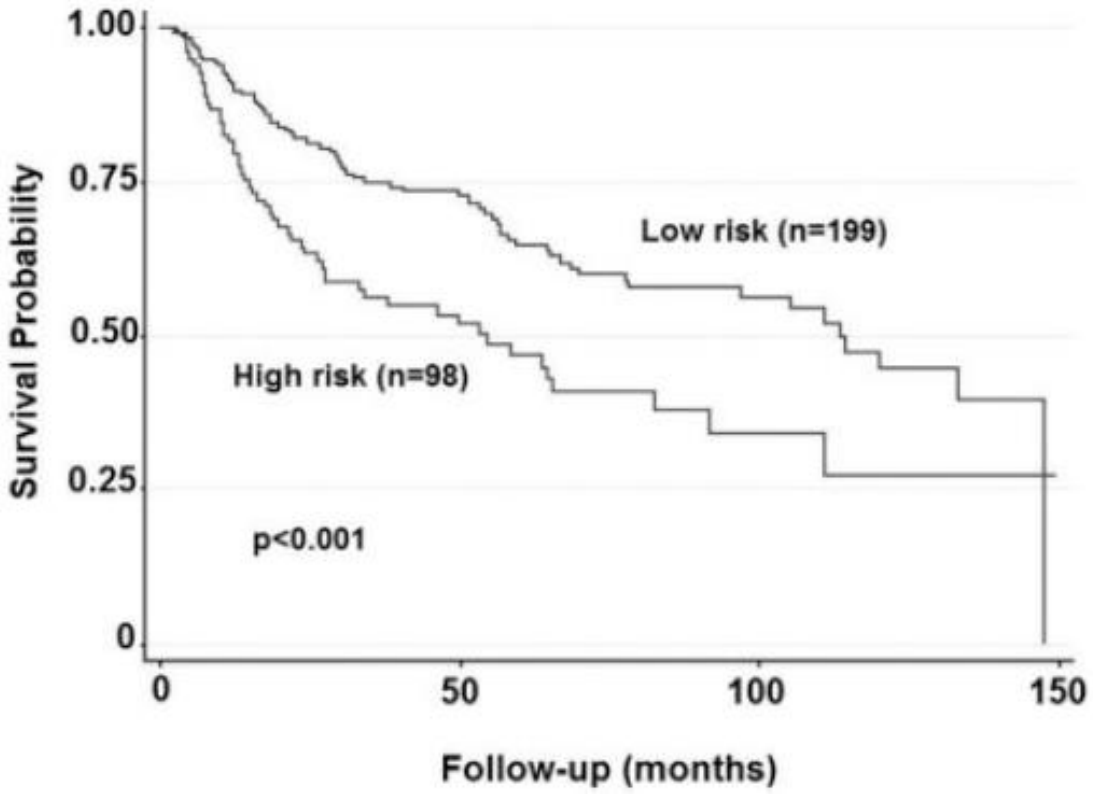
James, et al. NEJM 2012

MDACC: High-risk vs low-risk MIBC

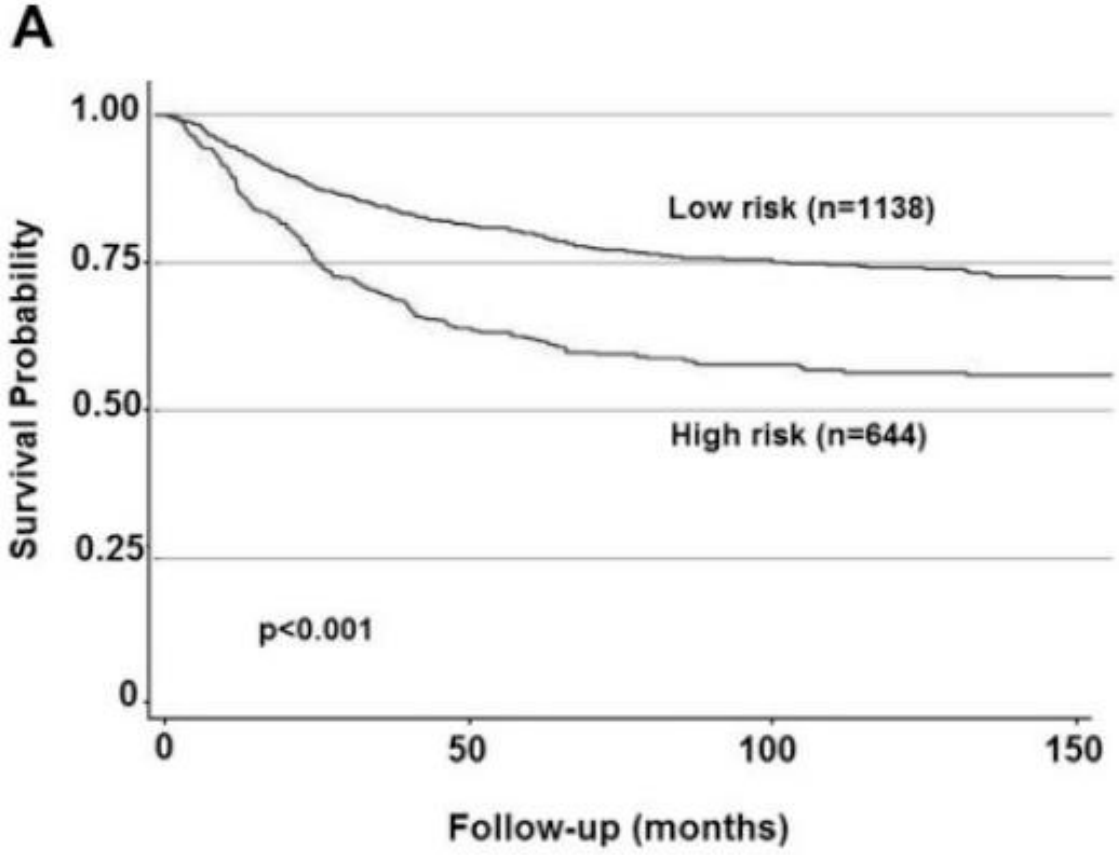
- Adverse prognostic factors
  - Lymphovascular invasion (LVI)
  - Positive EUA
  - Tumor at ureteral orifice/hydronephrosis
  - HG upper tract
  - Extension to local but resectable organs

Cystectomy Outcomes: Low Risk (no neoadjuvant chemotherapy)

MDACC



USC



5-year OS~75-80%

Culp J. Urol. 2015

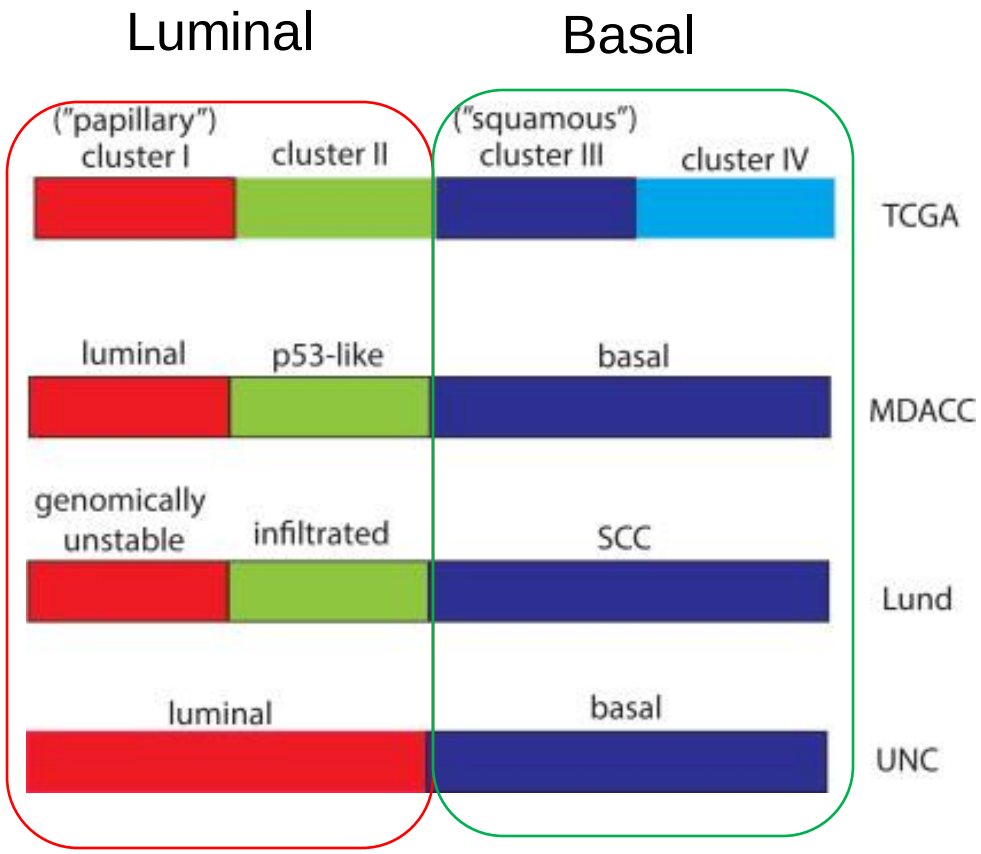
Bladder “Preservation”: Neoadjuvant + Partial Cystectomy/TUR

- 60/111 (54%) patients pT0 following 4 cycles MVAC
  - Tumor site biopsy negative, urine cytology negative
- 43/60 managed by TUR alone (n=28) or partial cystectomy (n=15)
- 74% of these well-selected patients alive at 10 years median follow-up
- 58% alive with bladder in place

Herr et al. JCO, 1998


Bladder Preservation:
The Science of Selection

Gene Expression



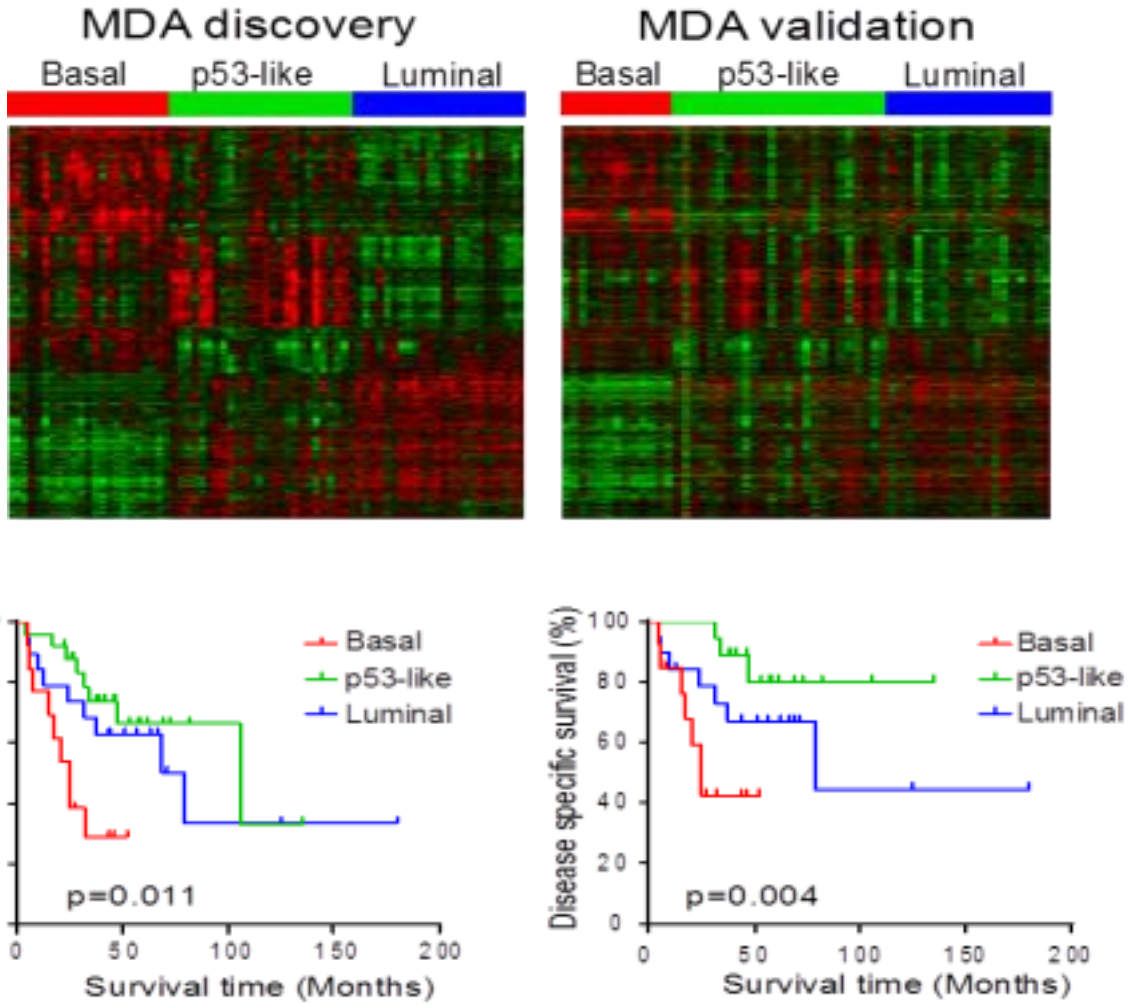
Relationships between the intrinsic subtypes identified by the groups at Lund University, MD Anderson Cancer Center, University of North Carolina, and TCGA centres

David J. McConkey, Woonyoung Choi, Andrea Ochoa, Arlene Siefker-Radtke, Bogdan Czerniak, Colin P.N. Dinney
Therapeutic Opportunities in the Intrinsic Subtypes of Muscle-Invasive Bladder Cancer
Hematology/Oncology Clinics of North America, Volume 29, Issue 2, 2015, 377–394
http://dx.doi.org/10.1016/j.hoc.2014.11.003

Background: Gene Expression

Three intrinsic subtypes:

- Basal
  - Highest proliferation
  - “Stemness”
  - Worst clinical outcomes
- Luminal
  - Intermediate proliferation
  - *FGFR3* mutations
- p53-like
  - Lowest proliferation
  - Stromal markers

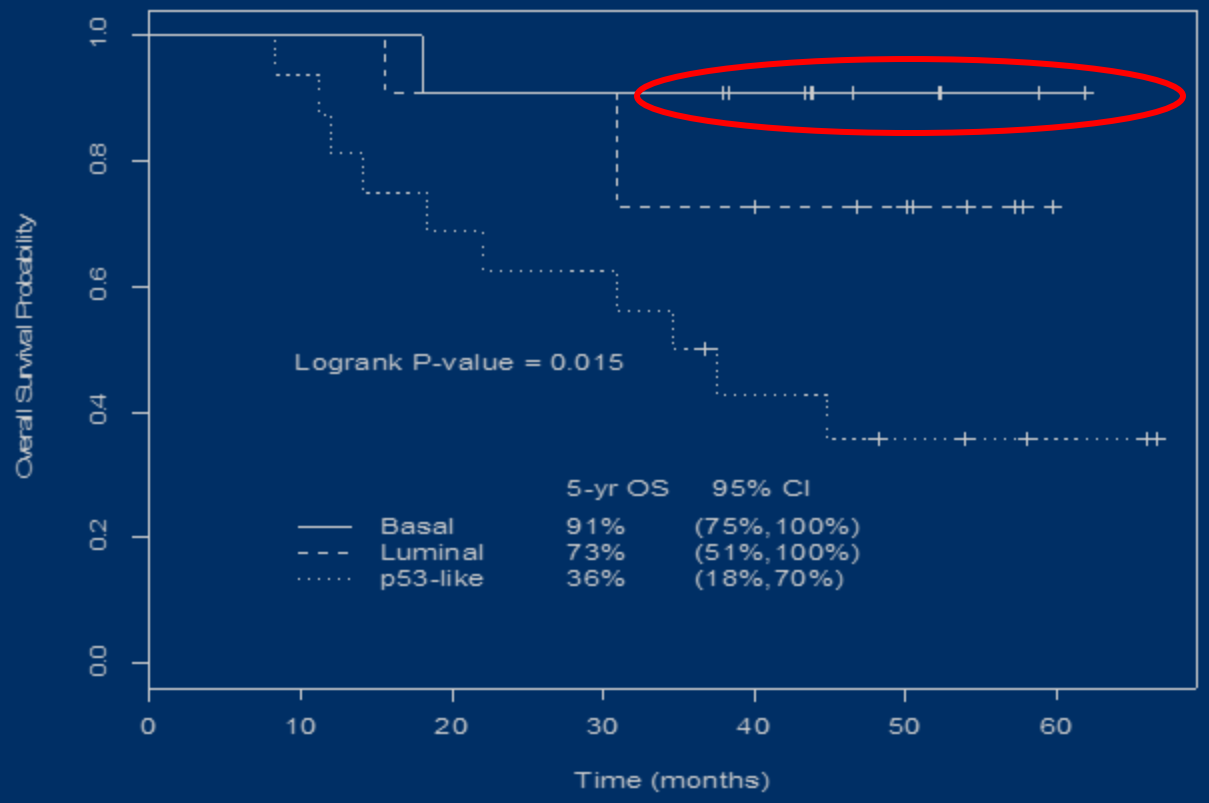


MDA, MD Anderson.

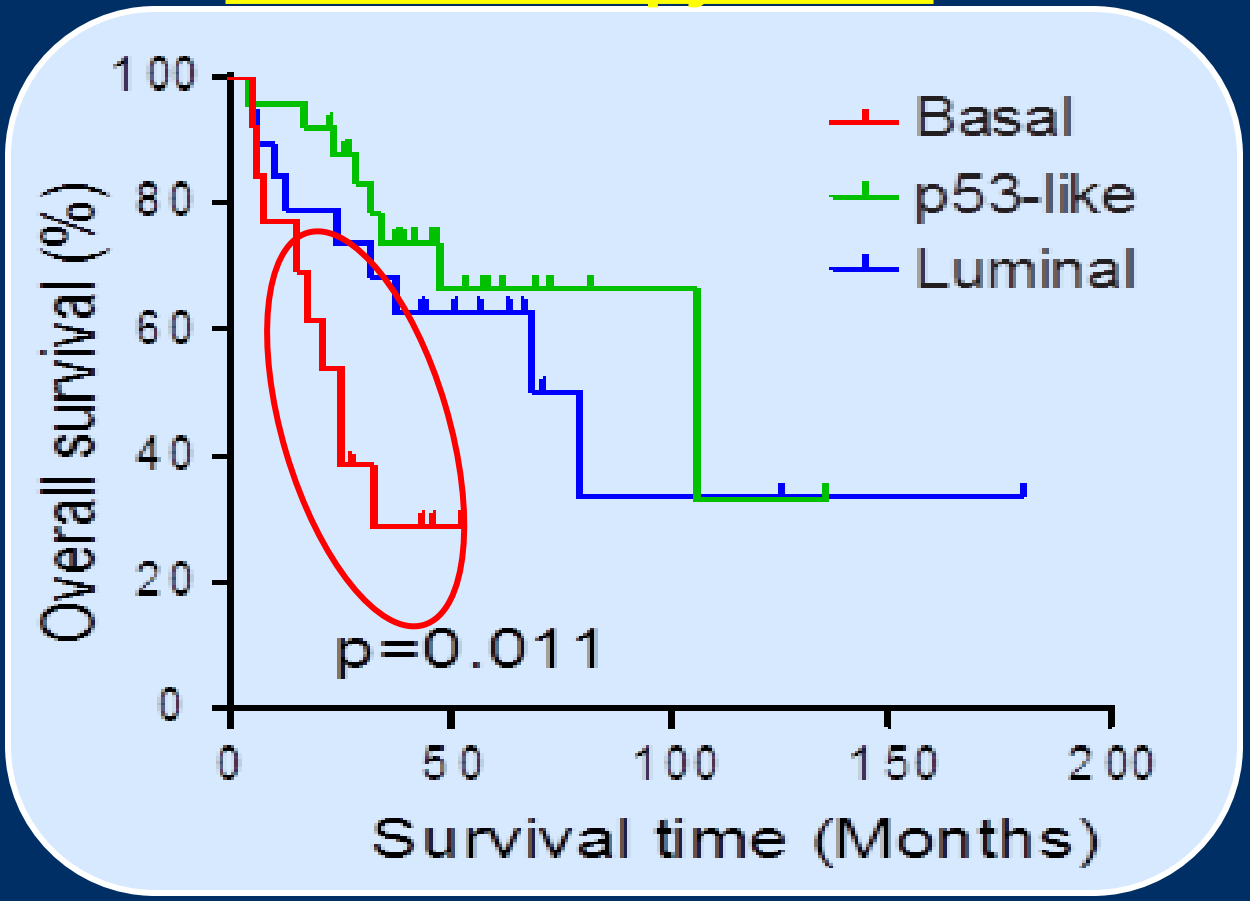
Choi W, at al. Cancer Cell. 2014;25:152-65.

Basal tumors benefit from neoadjuvant chemotherapy: MDACC clinical trials

Neoadjuvant chemotherapy



Chemotherapy Naive



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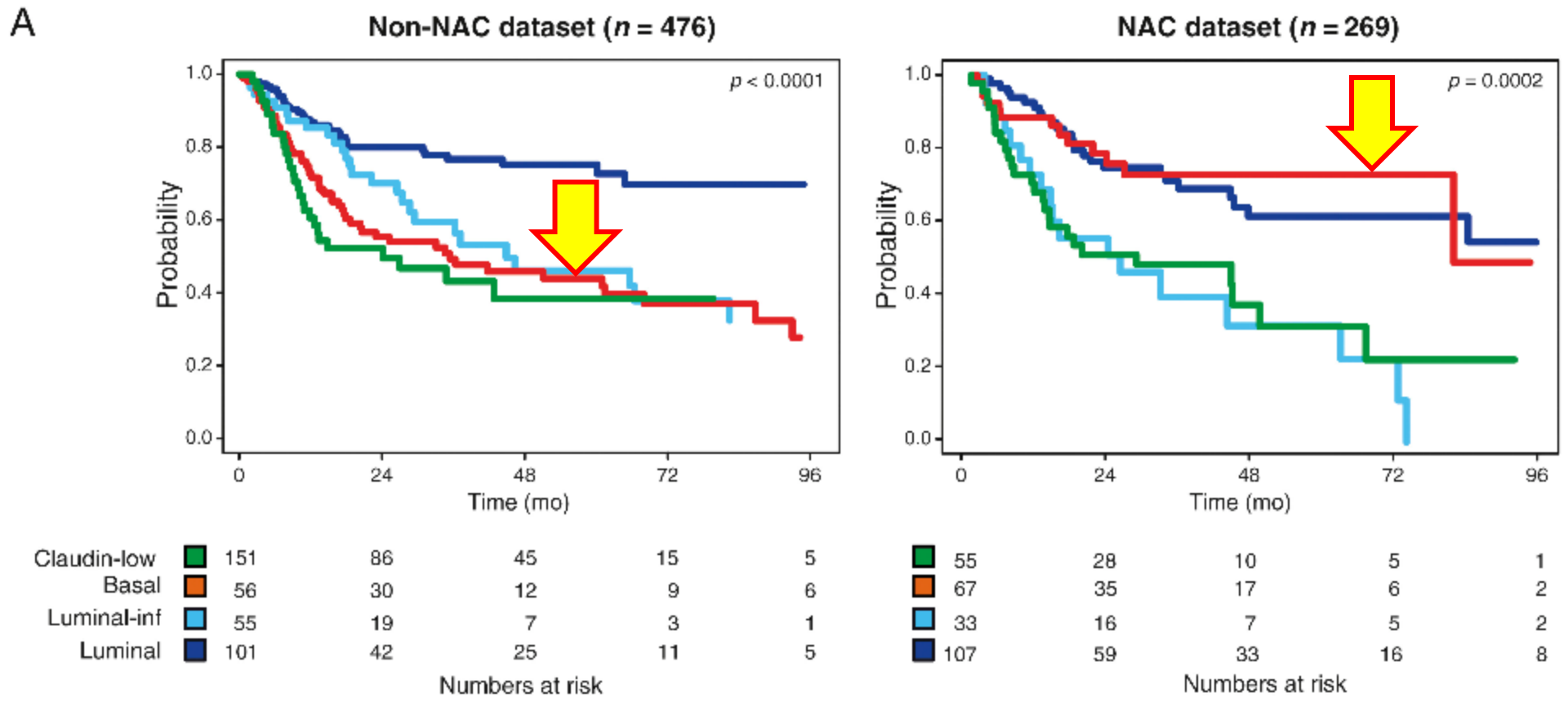
Siefker-Radtke, Choi, McConkey et al. GUASCO 2015, European Urology 2016

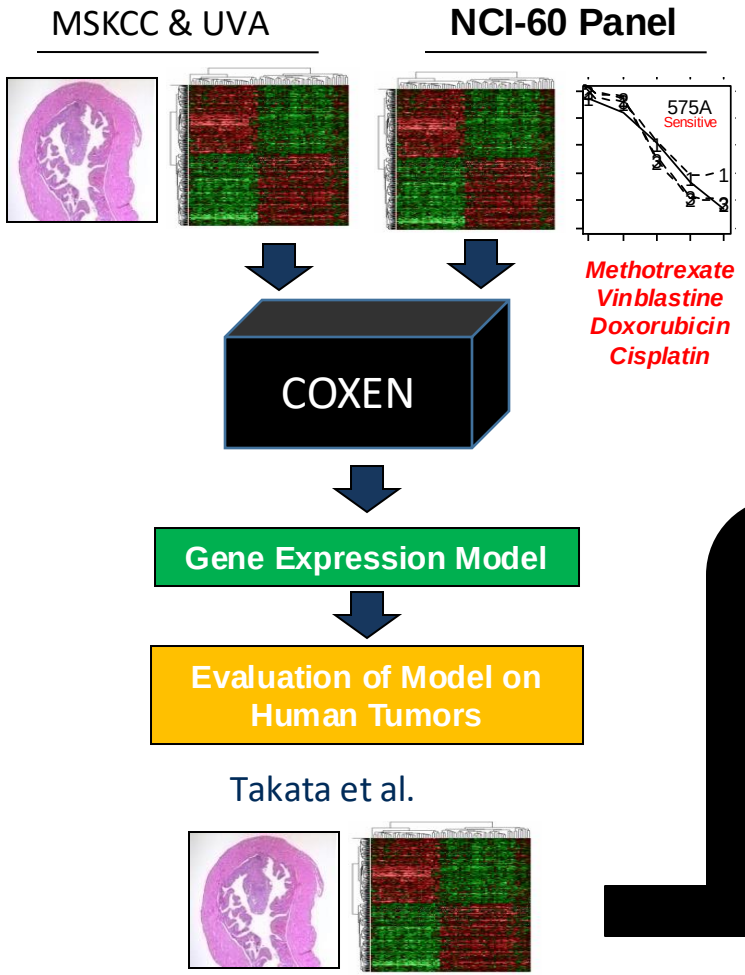
Additional retrospective analysis: basal tumours benefit from chemotherapy

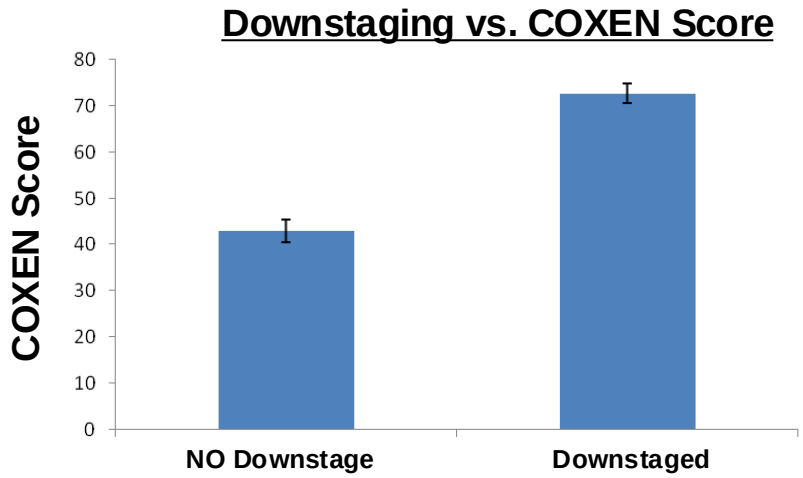


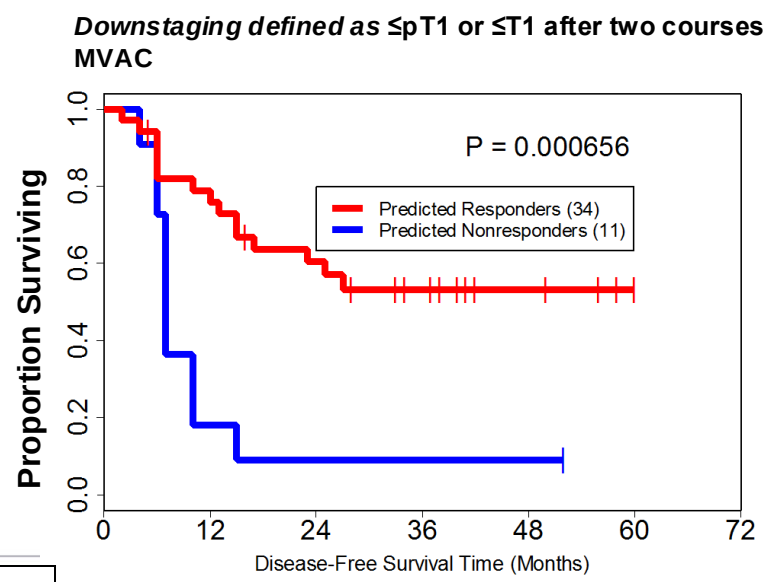
Luminal inf, luminal infiltrated, mo, months; NAC, neoadjuvant cisplatin-based chemotherapy.

Seiler R, et al. Eur Urol. 2017;72:544-554.

S1314: COXEN background



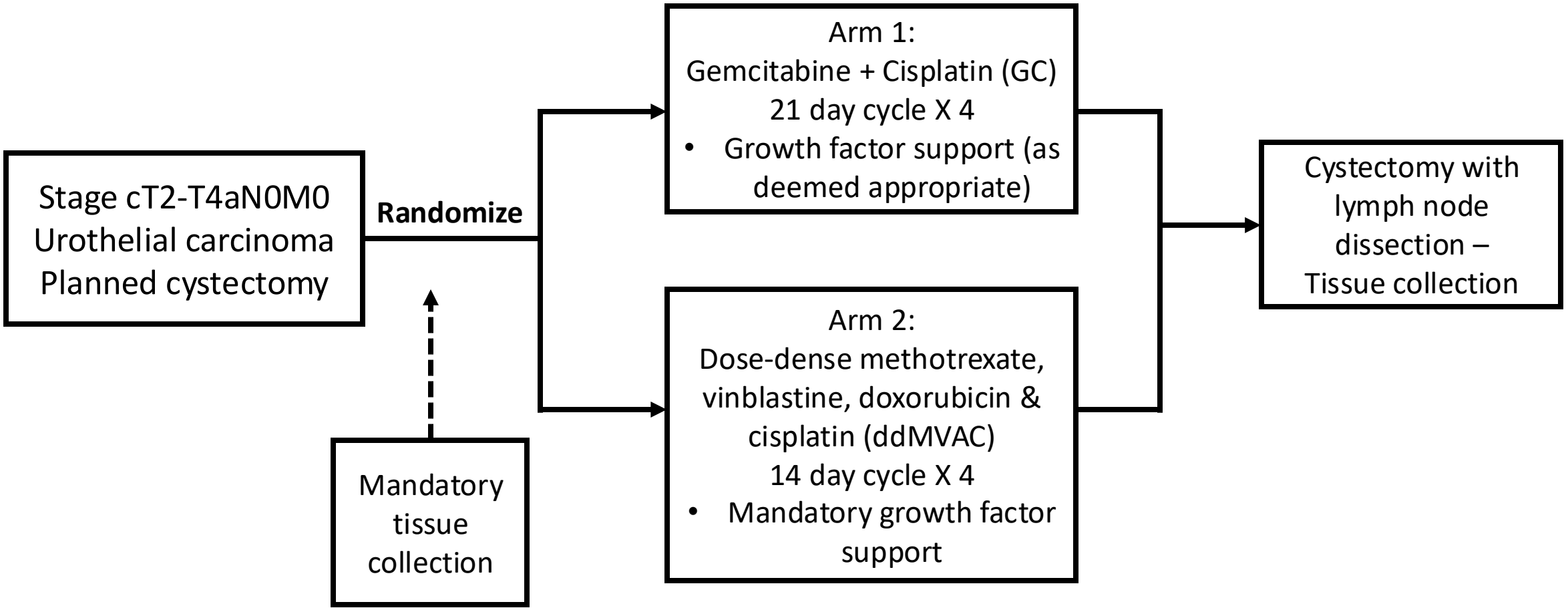




Ref: Clin Can Res 2005;11(7): 2625
Tx: Neoadjuvant MVAC (N=45) + surgery or XRT
Outcome: Downstaging, Overall survival

Slide courtesy of Tom Flaig, MD

S1314: Schema



Coxen Trial Results

Table 3. Results of logistic regression modeling of COXEN score and pathologic response at cystectomy.

COXEN score	Outcome	Arm	*N*	OR (95% CI)[b]	*P*[b]	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
GC[a]	pT0	GC	82	2.63 (0.82–8.36)	0.10	29% (13%–49%)	81% (69%–91%)	44% (22%–69%)	69% (56%–80%)
GC[a]	≤pT1	GC	82	1.75 (0.60–5.34)	0.30	25% (13%–41%)	81% (66%–91%)	47% (34%–60%)	53% (40%–66%)
ddMVAC[a]	pT0	ddMVAC	85	1.12 (0.42–2.95)	0.82	37% (19%–58%)	63% (46%–78%)	33% (17%–53%)	44% (17%–53%)
ddMVAC[a]	≤pT1	ddMVAC	85	0.92 (0.37–2.27)	0.86	34% (21%–49%)	63% (46%–78%)	53% (34%–72%)	69% (55%–81%)
GC[a]	pT0	Pooled	167	1.84 (0.88–3.83)	0.10	33% (21%–47%)	78% (69%–85%)	42% (27%–58%)	70% (61%–78%)
GC[a]	≤pT1	Pooled	167	2.33 (1.11–4.89)	0.02	32% (23%–43%)	81% (71%–89%)	65% (49%–79%)	52% (43%–61%)
ddMVAC[a]	pT0	Pooled	167	0.99 (0.49–2.02)	0.99	31% (19%–45%)	68% (58%–76%)	32% (20%–46%)	67% (58%–76%)
ddMVAC[a]	≤pT1	Pooled	167	0.90 (0.46–1.75)	0.76	30% (21%–41%)	66% (55%–76%)	49% (35%–63%)	46% (37%–56%)

Abbreviations: NPV, negative predictive value; Pooled, GC + ddMVAC arms; PPV, positive predictive value.
[a]Favorable based on prespecified COXEN algorithm and cut-off point.
[b]Adjusted for two stratification factors: clinical stage at baseline (T2 vs. T3, T4a), PS (0 vs. 1) in logistic regression model.

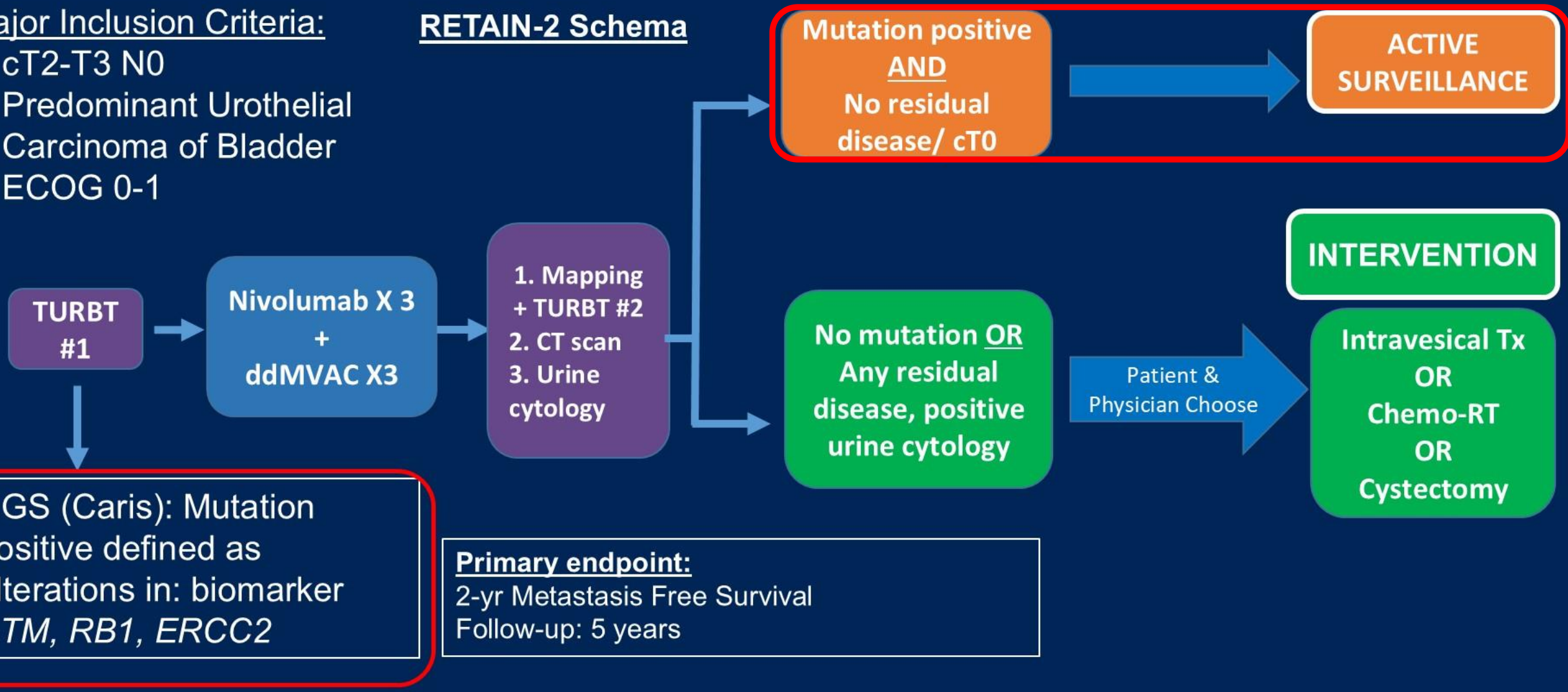
- Individual GC and MVAC coxen scores were not predictive of benefit
- The GC Coxen score predicted benefit when pooling GC and DDMVAC data

Flaig et al. ClinCanRes, 2021

Major Inclusion Criteria:

- cT2-T3 N0
- Predominant Urothelial Carcinoma of Bladder
- ECOG 0-1

RETAIN-2 Schema



NGS (Caris): Mutation positive defined as alterations in: biomarker *ATM, RB1, ERCC2*

Primary endpoint:
2-yr Metastasis Free Survival
Follow-up: 5 years

Metastasis free survival (MFS) is defined as the absence of a recurrence of urothelial carcinoma that is >cN1 (more than one clinically suspicious pelvic lymph node) or surgically unresectable local recurrence (e.g., >cT4a) or M1 disease).

PRESENTED BY: Pooja Ghatalia, MD
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Results: Baseline Characteristics

Characteristic	N = 71	(%)
Age		
Median	69	
Range	68-86	
Gender		
Male	55	77%
Female	16	23%
ECOG PS		
0	57	80%
1	14	20%
Histology		
Pure UC	48	68%
UC/Variant histology	23	32%
Clinical Stage		
cT2	41	58%
cT3	30	42%
Mutation		
positive	31	44%
negative	40	56.3%

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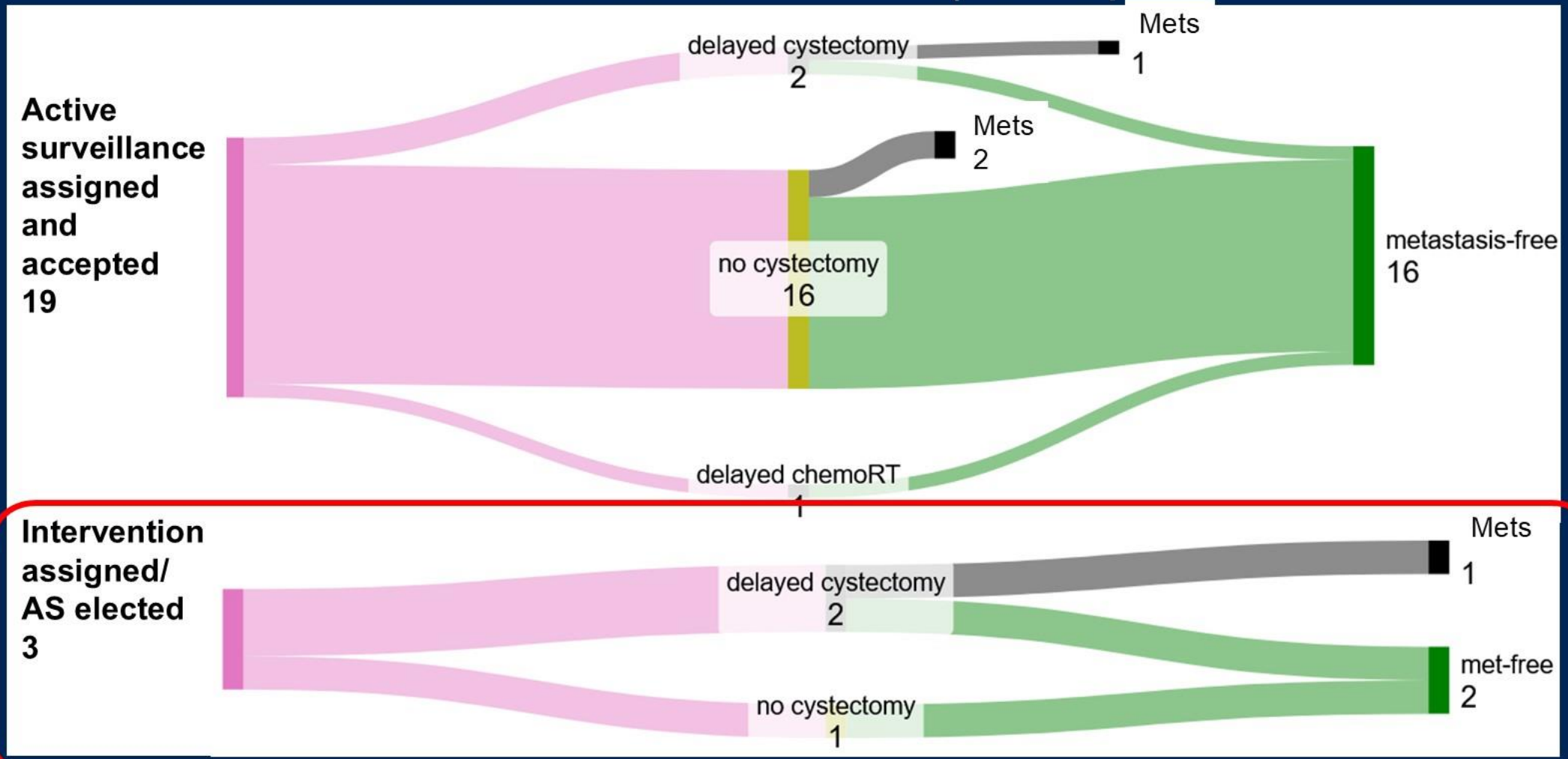
Results: Active Surveillance

Median follow-up: 21.7 months (25th-75th percentile: 13.6 – 30.3 months)



Among AS pts, 82% are metastases-free, 60% metastases-free and with an intact un-radiated bladder

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Conclusion:

Surgically resectable urothelial cancer:

- Selection matters!
  - The “artful” clinical factors for selection can be challenging
    - High risk/low risk
    - Assessing clinical responses
  - Scientific factors are not there yet
    - Gene expression
    - Coxen model
    - DNA repair
- Neoadjuvant chemotherapy with cystectomy remains the standard


Thank you!
“All bladder, all the time!”
Arlene Siefker-Radtke, MD