

# Should Variant Histology Change Management of Bladder Cancer?

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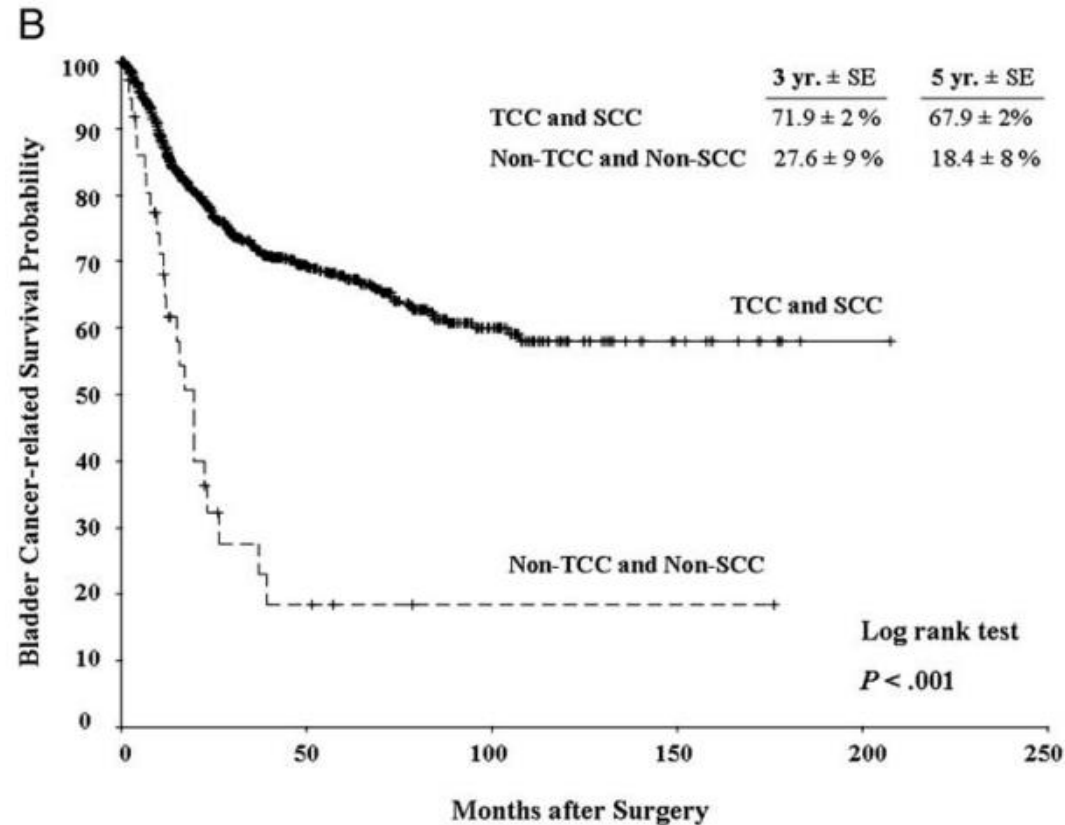
# Background/Missed Cases

- Bladder variant histology: 7,500 – 18,000 per year
  - 10%-25% of cases
- Discordance between TUR and Cystectomy as high as 39 - 47%
- ~ 44% cases of variants not recognized by community pathologists
- In order of decreasing frequency of missed diagnosis:
  - lymphoepithelial, plasmacytoid, nested variant, micropapillary and small cell histology

# Do histologic variants matter?

- Multitude of retrospective studies suggests that variant histology portends **worse outcomes**
- Higher propensity of locally advanced disease
  - Greater degree of **lymph node metastasis**
- **Upstaging** at radical cystectomy: HR 2.77
- Different **responses** to therapy – BCG, chemotherapy or radiotherapy

# Do histologic variants matter?



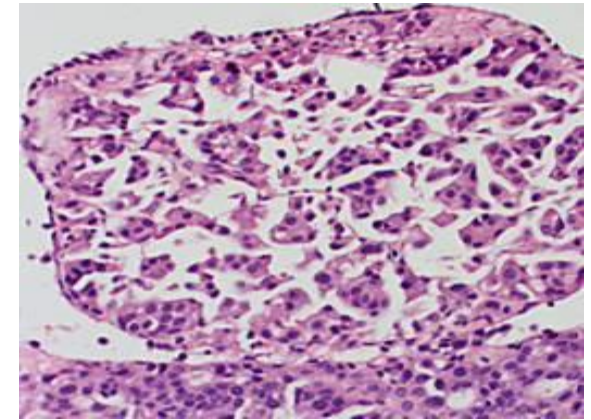
**Multi-institutional study ~ 1,000 patients;  
Histologic variants (nonTCC + SCC) increased risk of progression  
and death (OR 2.272 and 2.585, p 0.001); accounting for stage,  
adjunctive Rx, and LVI**

# Micropapillary Bladder Cancer

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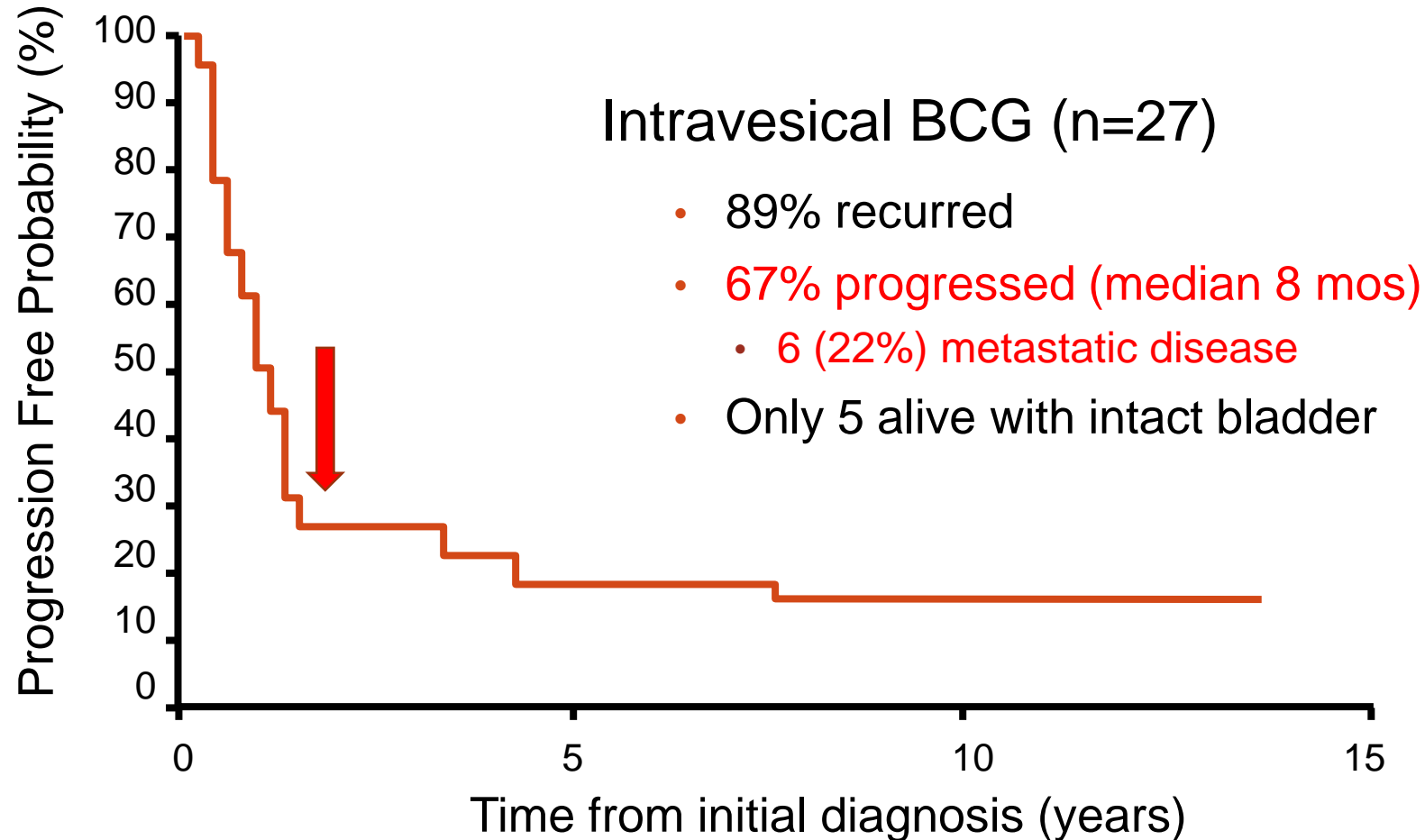
# Micropapillary Bladder Cancer

- A rare subtype of urothelial carcinoma
- First described from MDACC in 1994
- Micropapillae without central vascular cores
- LVI consistently present in the micropapillary areas.



# The Case for Early Cystectomy in the Treatment of Nonmuscle Invasive Micropapillary Bladder Carcinoma

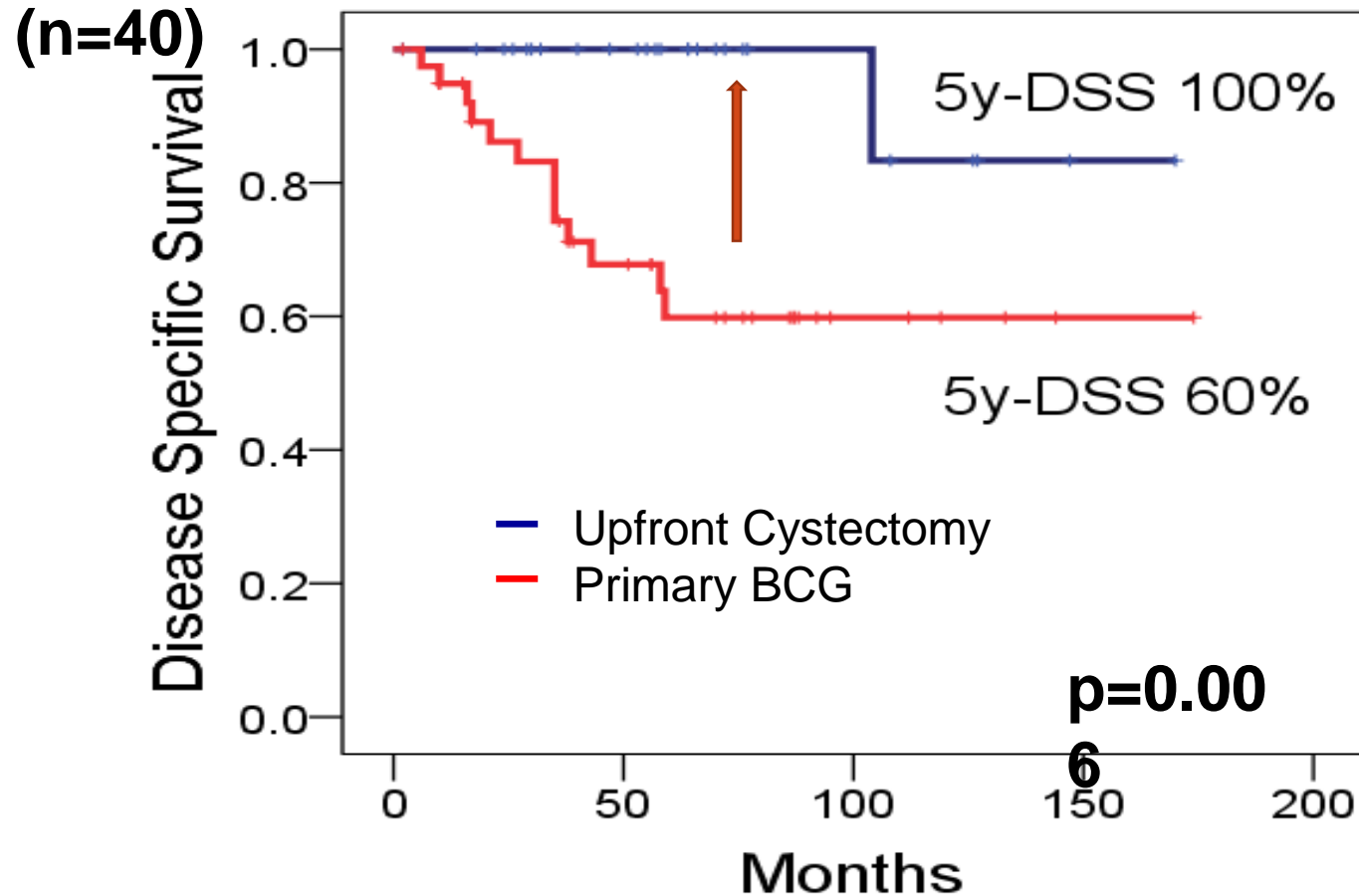
Ashish M. Kamat,<sup>\*,†</sup> Jason R. Gee,<sup>‡</sup> Colin P. N. Dinney,<sup>§</sup> H. Barton Grossman,<sup>||</sup> David A. Swanson,<sup>¶</sup> Randall E. Millikan,<sup>\*\*</sup> Michelle A. Detry,<sup>‡</sup> Tracy L. Robinson<sup>‡</sup> and Louis L. Pisters<sup>††</sup>



# MD Anderson Experience: Update 2015

N = 238 total; 72 patients with cT1

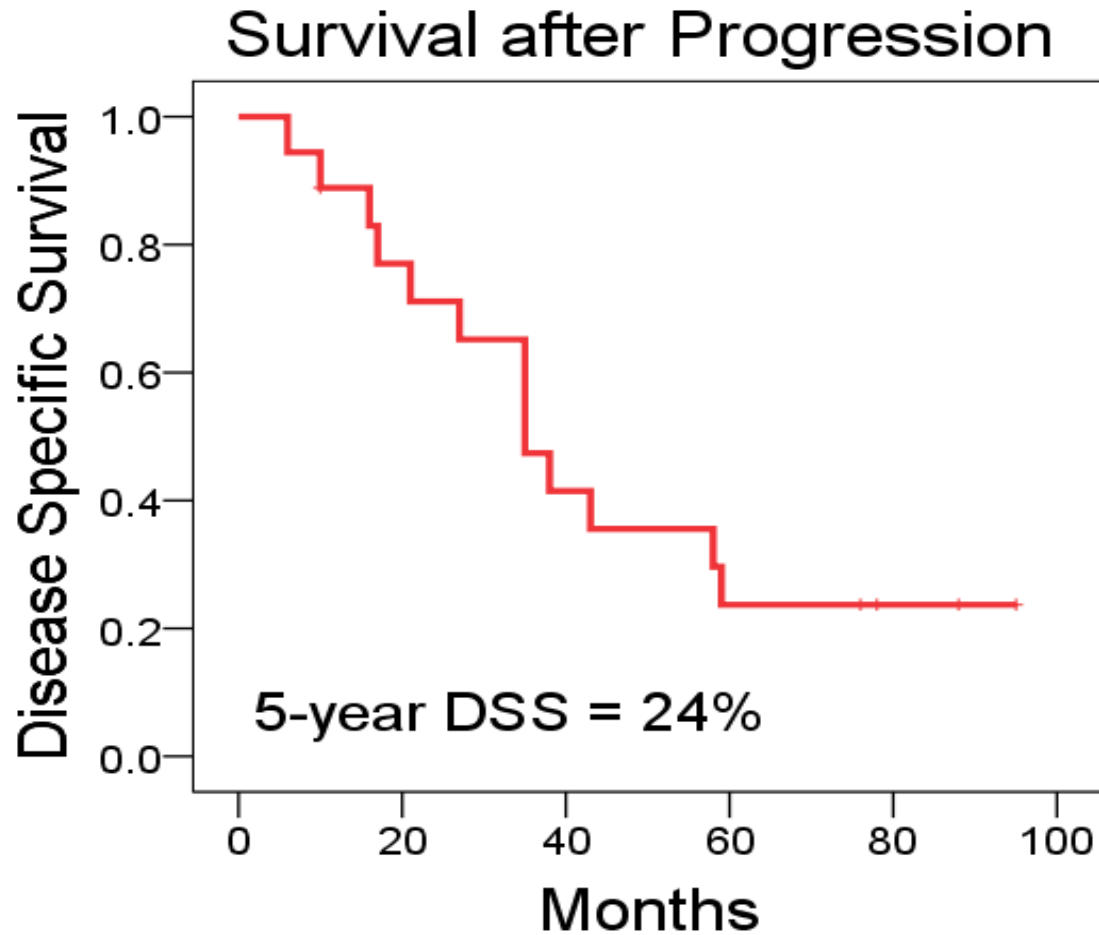
## Upfront Cystectomy (n=36) versus Primary BCG (n=40)





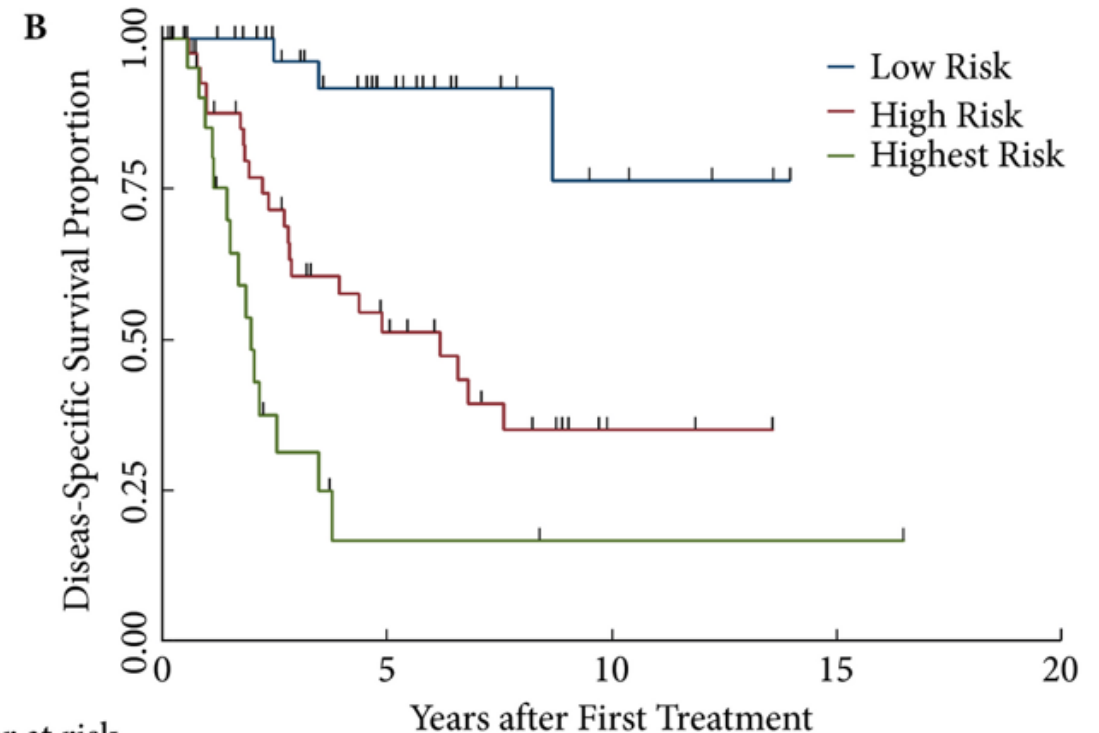
# MD Anderson Experience: Update 2015

N = 238 total; 72 patients with cT1



# Clinical risk stratification in patients with surgically resectable micropapillary bladder cancer

- Analysis of 103 patients
- 3 risk groups
  - low-risk: cT1
  - high-risk:  $\geq$ cT2
  - highest-risk: cTany with tumor associated HN
- 5-year DSS
  - low-, high-, and highest-risk groups
  - 92%, 51%, and 17%, ( $p < 0.001$ )



Number at risk		Years after First Treatment				
		0	5	10	15	20
Low Risk	35	15	4	0	0	0
High Risk	44	16	2	0	0	0
Highest Risk	22	2	1	1	0	0

# Supporting Series

- Cleveland Clinic Series; 38 MPBC cases (2000-2010)
- 10 presented with cTis-cT1
  - 7 BCG therapy
  - 100% underwent radical cystectomy
    - recurrence (n = 3) and/or progression (n = 4)
  - median of 12 months
- At cystectomy
  - all 7 patients had  $\geq$  pT3a disease
  - 6 had lymph node metastases!



## RUSSIAN ROULETTE

Inexhaustible needs of human being move us to  
uncertainty. Do we have to run this risk?  
Now, it's your turn!

## BOULETTE RUSSIAN

Now it's your turn!  
uncertainty. Do we have to run this risk?  
of us even need to be an individual?

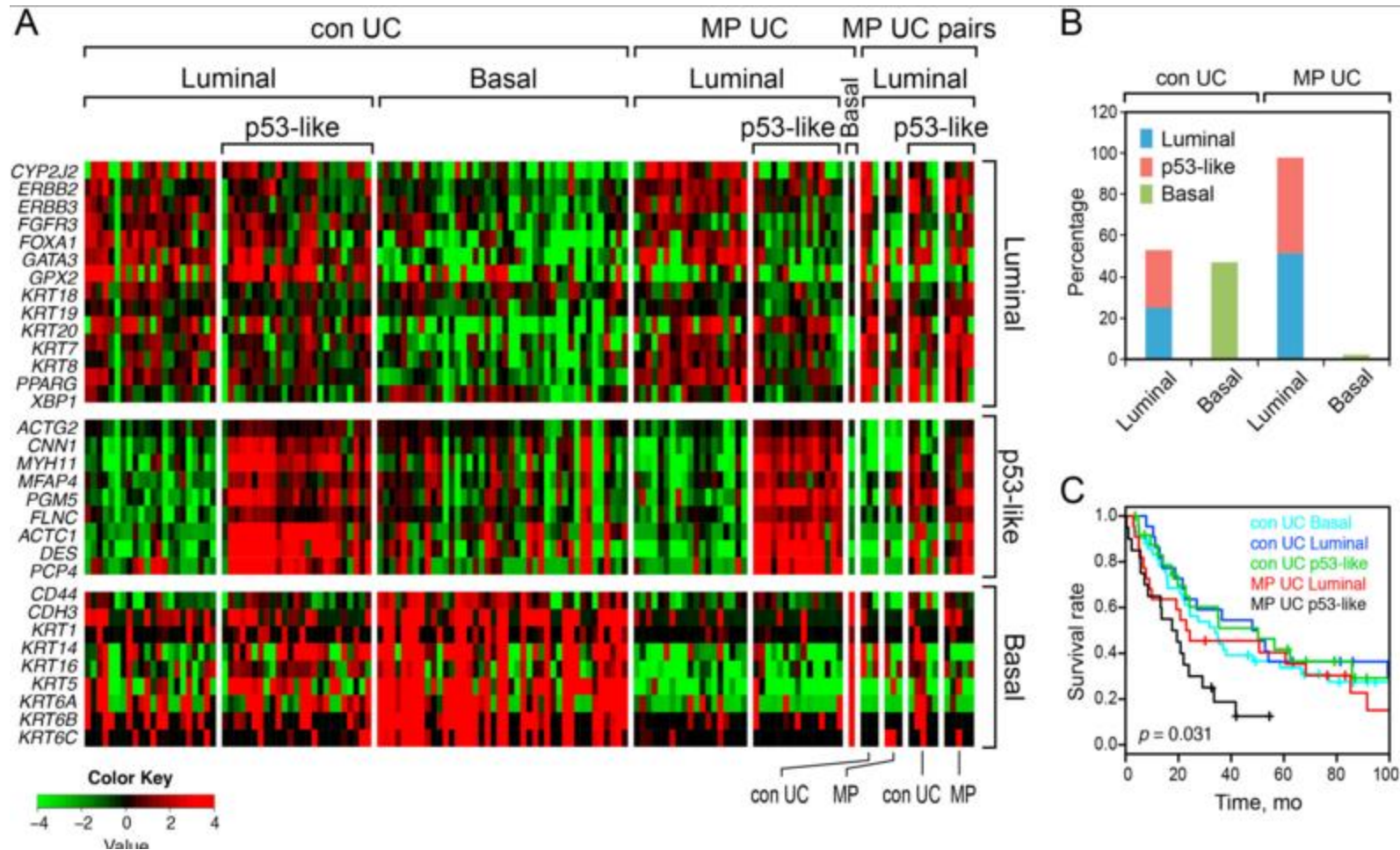
- Odds in Russian Roulette
  - 1 in 6: 16%
- Odds of Metastases with BCG for MPBC
  - 1 in 4.5: 22% (MDA-06)
  - 1 in 3.7: 27% (MDA-13)
  - **6 in 7: 85% (CCF)**

# BCG For Micropapillary Bladder Cancer





# Micropapillary Bladder Cancers clusters with Luminal Type Urothelial Carcinoma



**Radical Cystectomy  
Best (Safest) Option  
Micropapillary Bladder  
Cancer**

Risk



# Survey of SUO Members

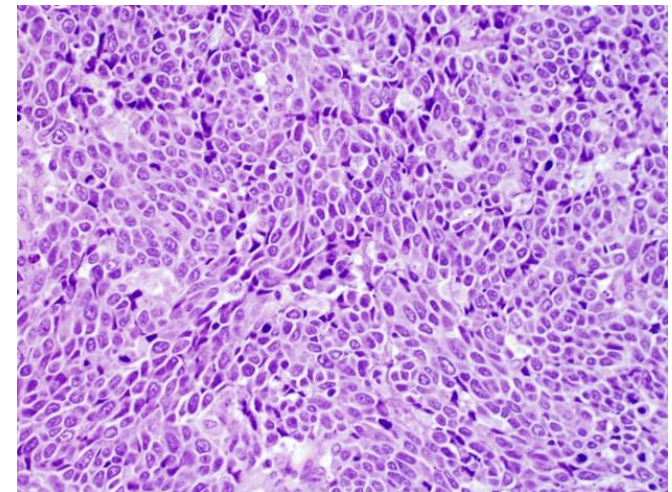
How would you treat cT1 MPBC?



# Small Cell Carcinoma

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- SmCC differs biologically from conventional UC
  - early metastasis, rapid growth
  - unique metastatic sites (brain and bone)
  -
- ~ 50% of patients have metastasis at cystectomy despite clinically organ confined disease
- SmCC ~ a systemic disease



# Brain Metastases for SmCC

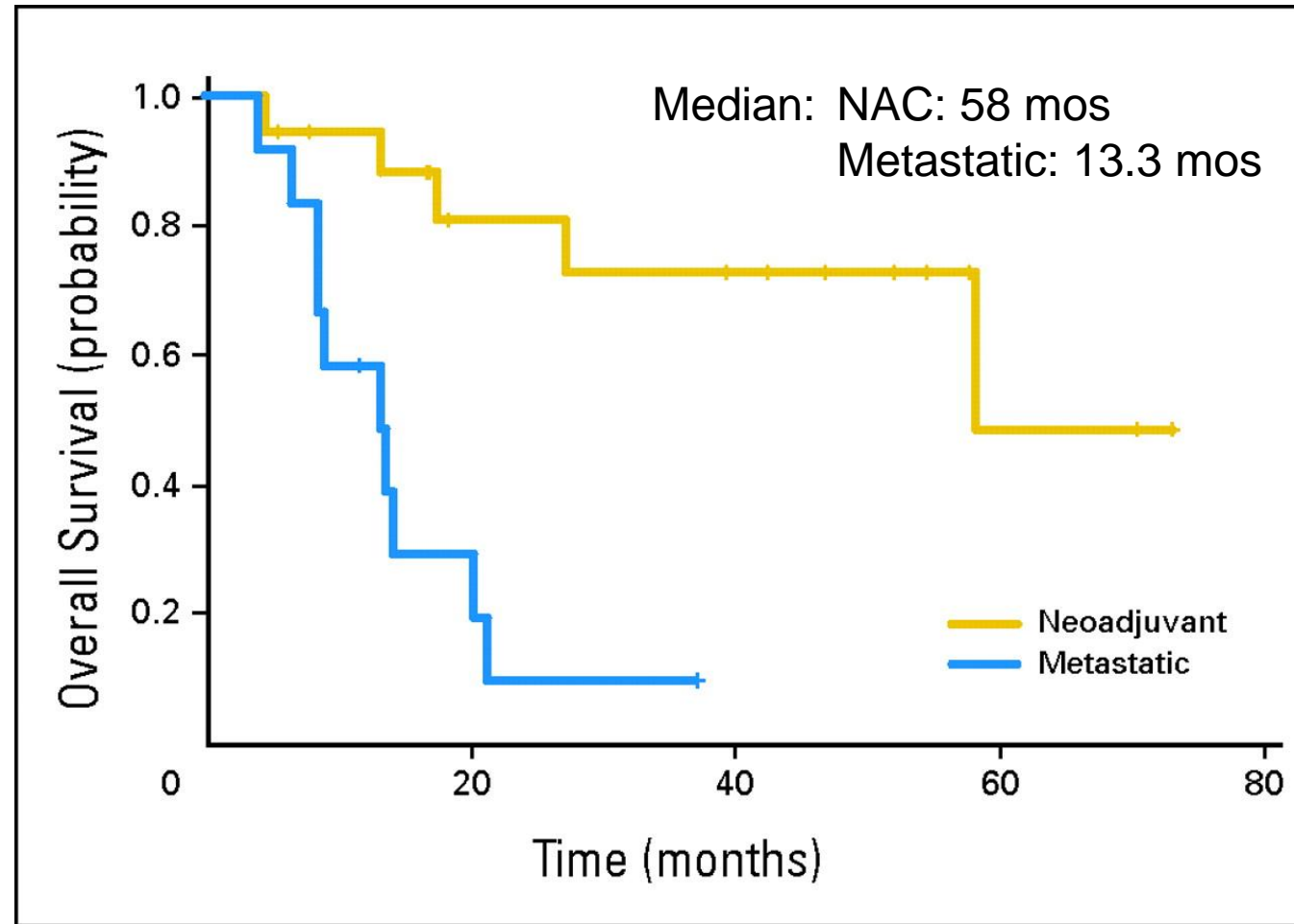
**Table 3.** Association Between Disease Stage and Brain Metastases

Brain Metastasis	Disease Stage (No. of patients)		
	II	III	IV
No	14	2	6
Yes	0	2	6

NOTE. Generalized Fisher exact test:  $P = .004$ .

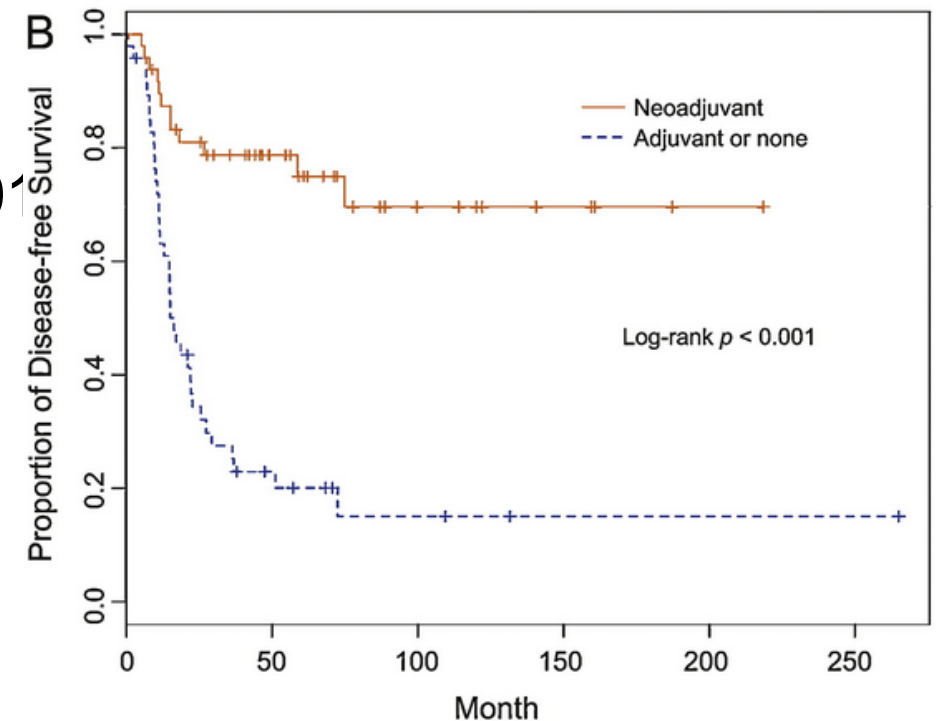
50% Incidence in  $\geq$ T3b, N+ or M+

# Phase II Trial of Neoadjuvant Alternating Doublet Ifosfamide/Doxorubicin ; Etoposide/Cisplatin in SmCC



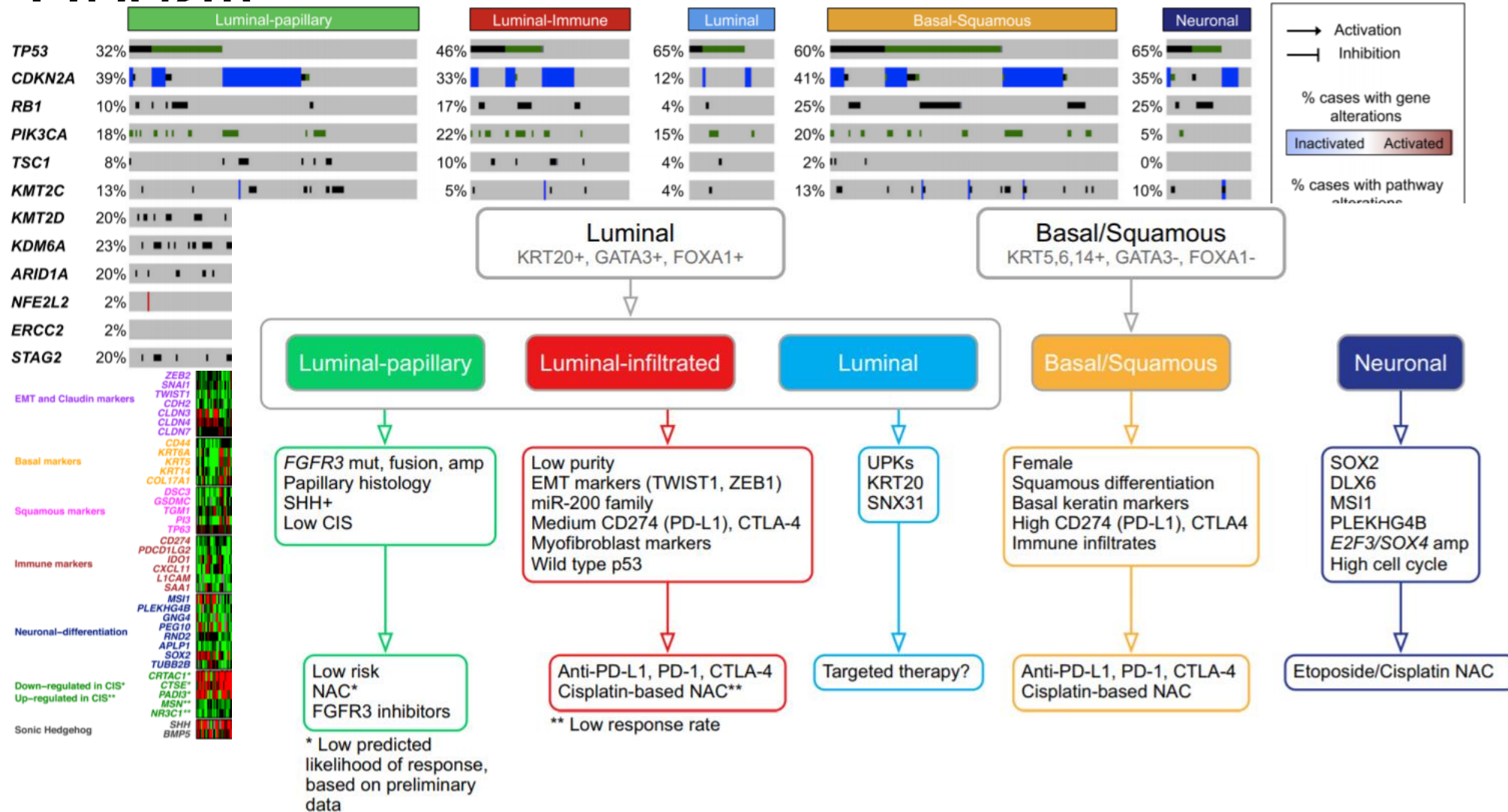
# MD Anderson Series (1985 – 2010)

- 172 Patients; 125 patients resectable ( $\leq$ cT4aN0M0)
- 95 surgical candidates: 48 NAC; 47 Upfront RC
- **NAC improved OS and DSS**
  - Median OS: 159.5 mo vs 18.3 mo,  $p < 0.001$
  - 5-yr DSS: 79% vs 20%,  $p < 0.001$ .
- **NMI**: 6 patients
  - 50% - upstaged to T3 or N+



# Separate GEP Category in TCGA – Oct 2017

## I Indate



# Small Cell Variant- Treatment Summary

- **Primary chemotherapy with a SmCC specific regimen** (cisplatin with etoposide) followed by RC
  - any %, at any stage
- **CNS imaging is standard** for all patients
  - High propensity for the tumor to recur intracranially
  - Clinical trial of prophylactic cranial irradiation (NCT#00756639) those who present with T3b or higher
- For patients unable to undergo cystectomy, NAC followed by chemoradiotherapy is an alternative

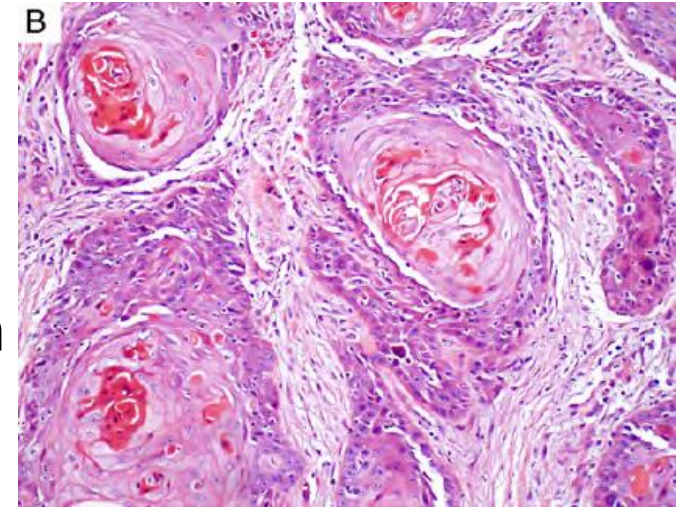
# Squamous Differentiation

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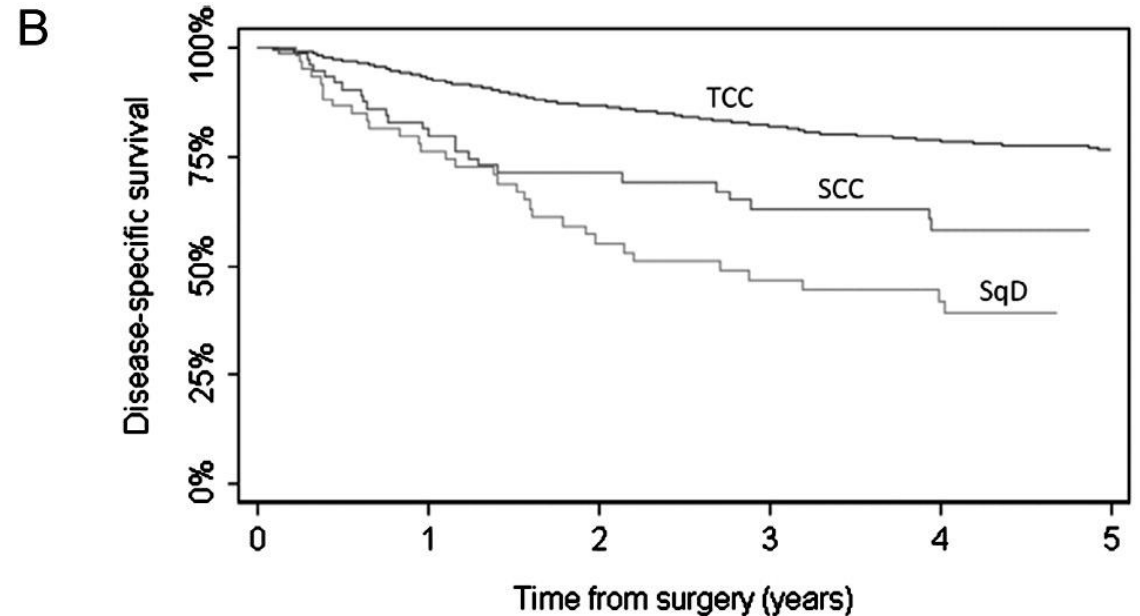
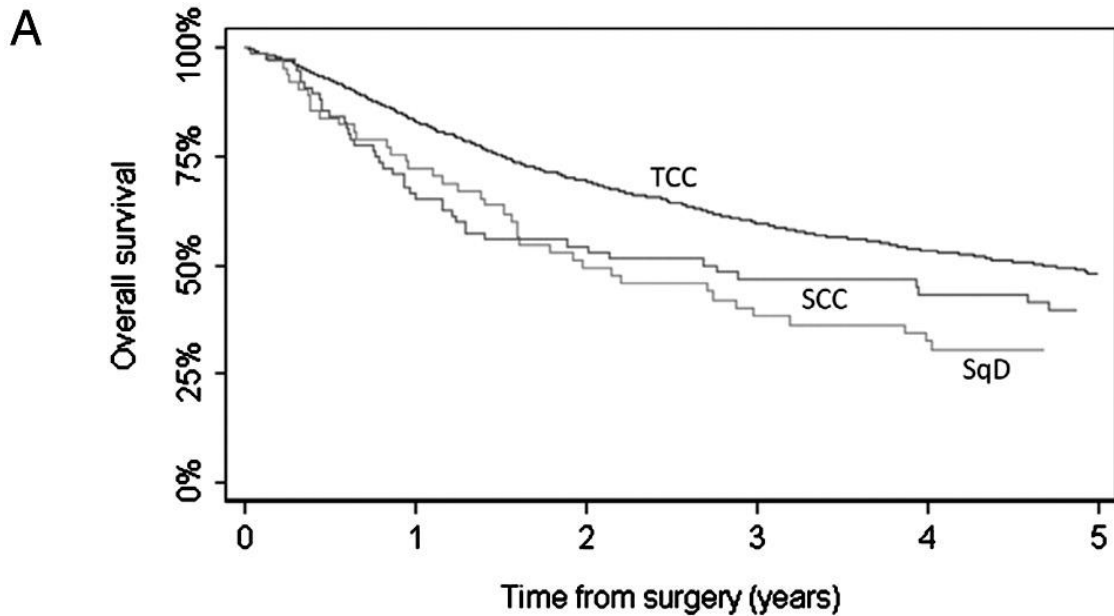


# Squamous differentiation

- Squamous differentiation
  - found in up to 60% of UCs
  - mostly reported when it predominates the specimen
  - often mixed with glandular differentiation
- Biology of these tumors remains poorly understood
  - portends more aggressive behavior
  - ? extensive SD may resemble pure SCC with similar response to chemotherapy, radiation, and a predisposition for local recurrence



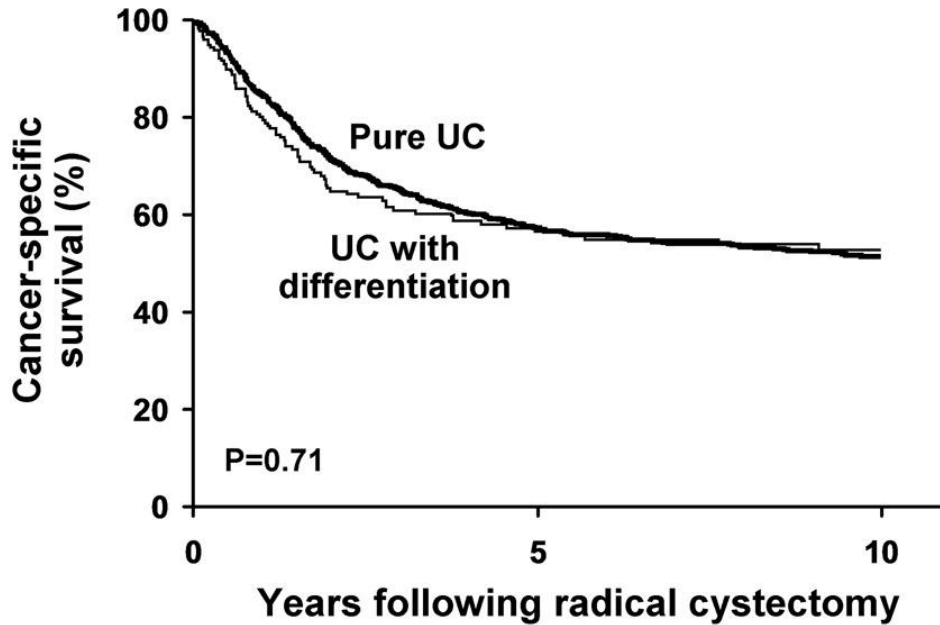
# Squamous differentiation – Worse Outcomes



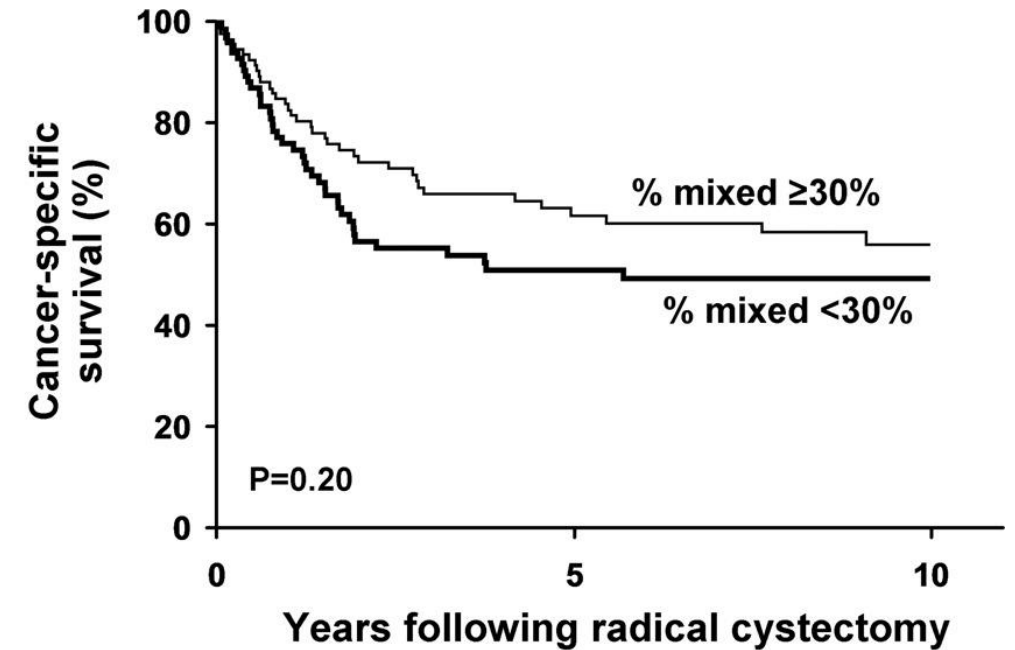
Number at risk						
TCC	1867	1498	1177	932	744	605
SqD	67	43	27	20	17	14
SCC	78	48	37	30	25	20

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# Squamous differentiation – No impact



Group	% survival (no. at risk)	5	10
— Pure UC	100 (827)	57 (362)	51 (194)
- - UC with differentiation	100 (186)	56 (71)	53 (36)



Group	% survival (no. at risk)	5	10
- - % mixed $\geq 30\%$	100 (99)	62 (41)	56 (19)
— % mixed $< 30\%$	100 (87)	51 (30)	49 (17)

# Squamous differentiation

- Urothelial tumors with squamous or glandular differentiation
  - potentially more aggressive
  - risk for understaging
- BUT
  - should be treated similarly as stage-matched urothelial bladder cancer
  - neoadjuvant chemotherapy should be considered



# Should histologic variants alter definitive treatment of bladder cancer?

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*Daniel L. Willis\*, Sima P. Porten\*, and Ashish M. Kamat*

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Curr Opin Urol 2013, 23:435–443



# Variant histology: role in management and prognosis of nonmuscle invasive bladder cancer

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*Sima P. Porten\*, Daniel Willis\*, and Ashish M. Kamat*

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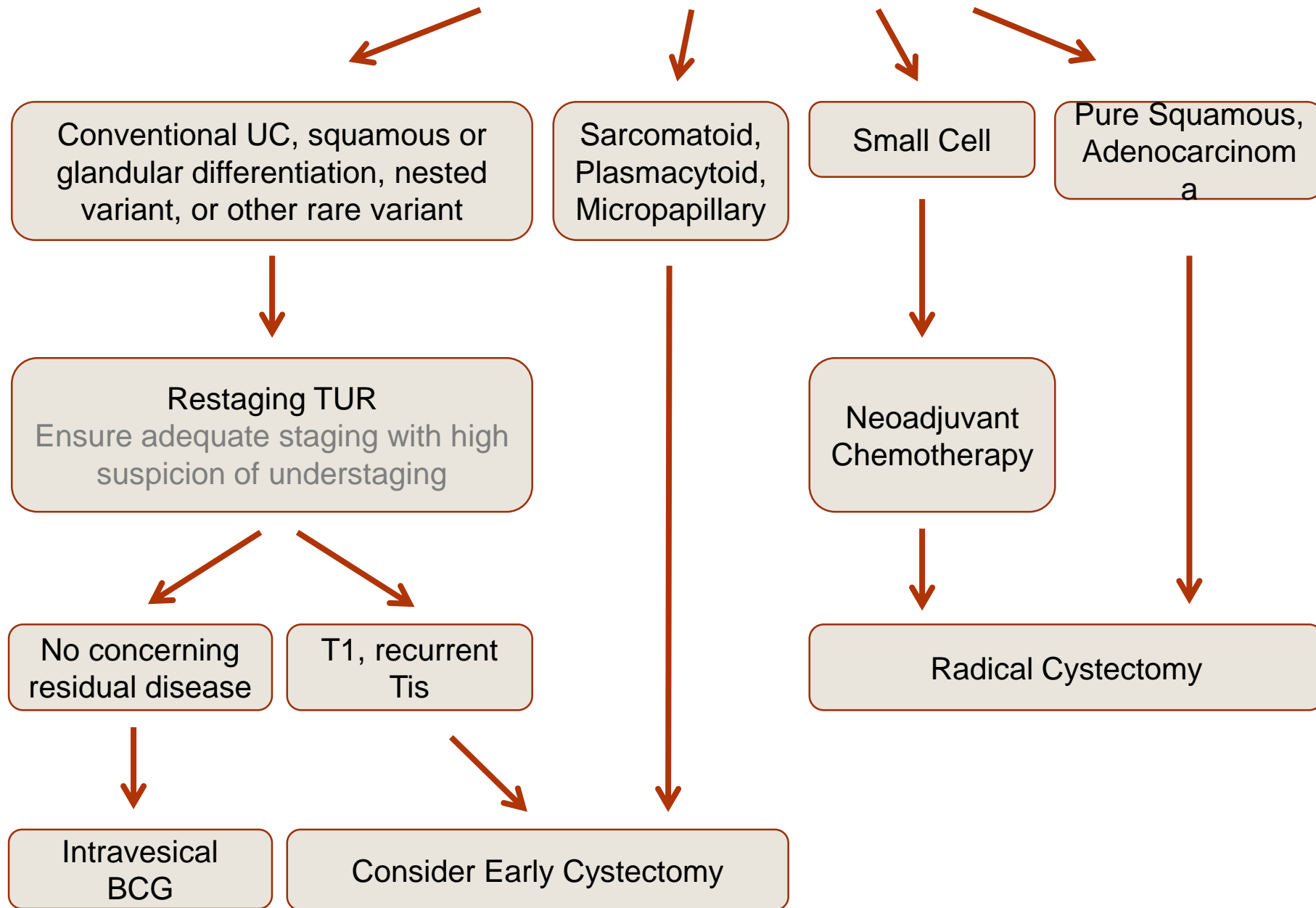
Curr Opin Urol 2014, 24:517–523

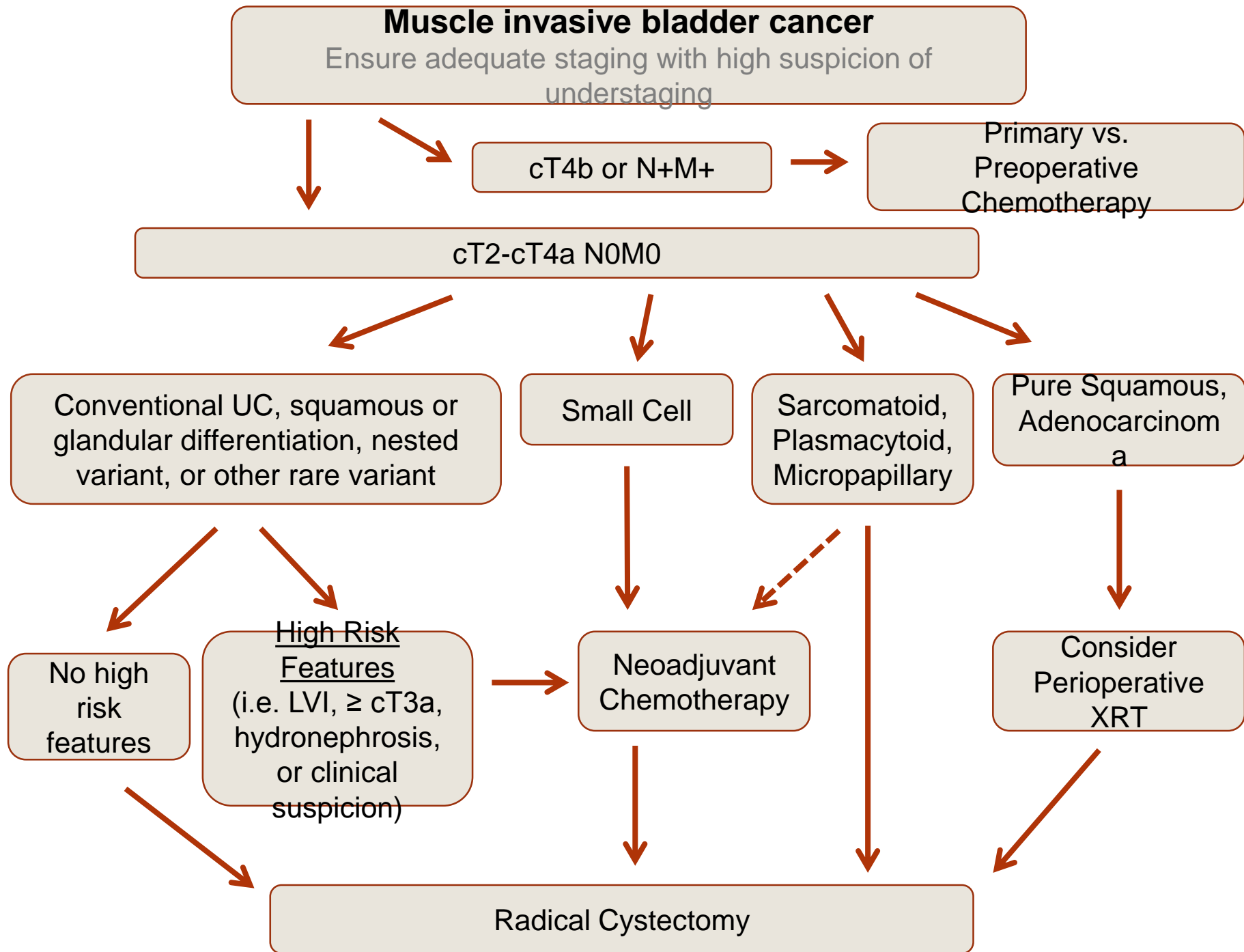
# Nonurothelial Bladder Cancer and Rare Variant Histologies

Hematol Oncol Clin N Am 29 (2015) 237–252

Daniel Willis, MD, FACS, Ashish M. Kamat, MD, MBBS\*

# Non-muscle invasive bladder cancer (Ta, T1, Tis)







# Thank you!



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 @UroDocAsh