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MD Anderson Cancer Center
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The Impact of Variant Histology in Urothelial Carcinoma

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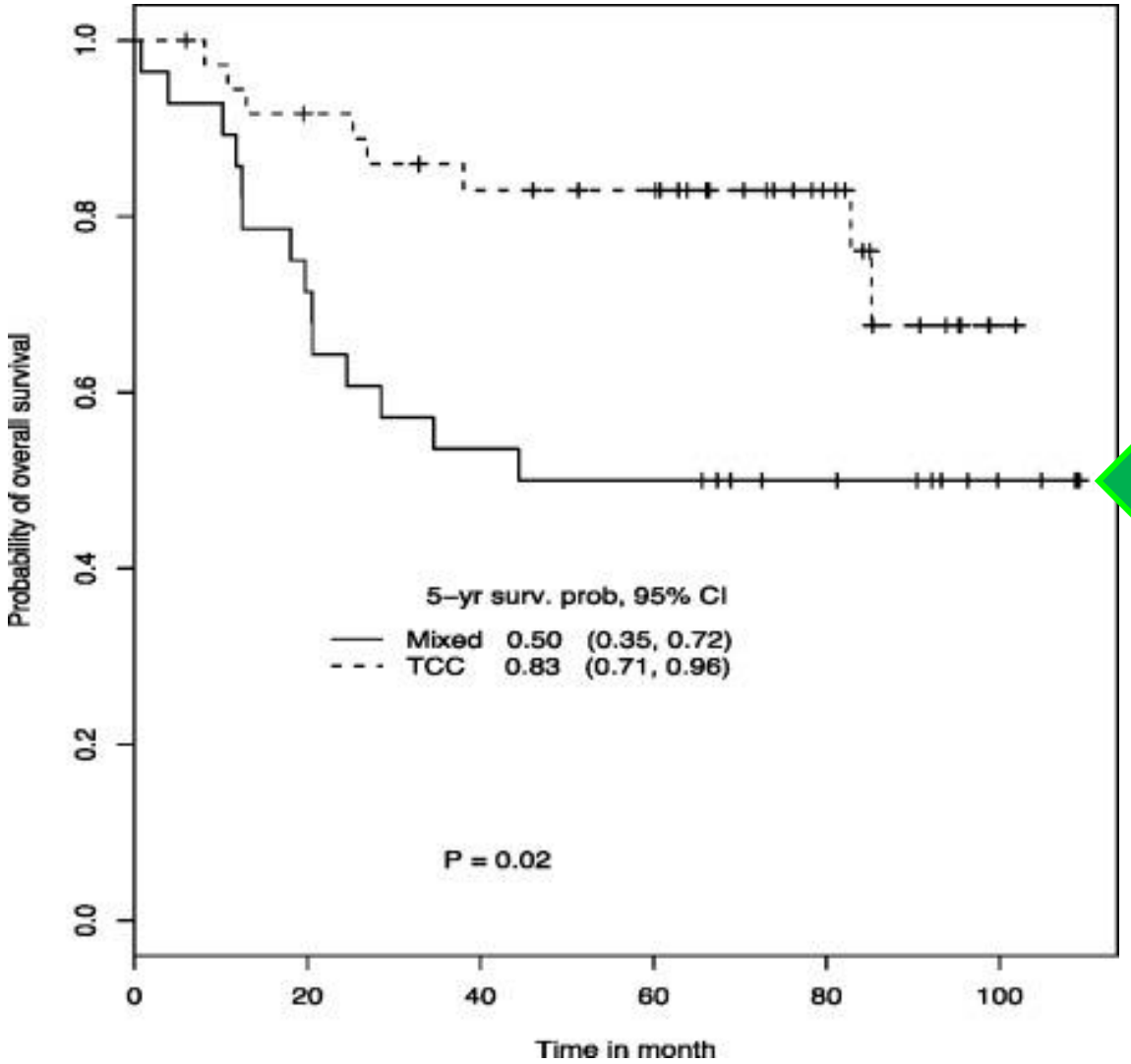
Variant Histology: Poor Prognosis



Neoadjuvant trial:

- Ifosfamide, Doxorubicin, Gemcitabine
- pT0N0 = 43%, pT1N0 = 50%
- 5-year DSS 68%
- 5-yr OS 63%

Worse DSS when variant histology present

- Mostly micropapillary as variant histology

Siefker-Radtke, et al. Cancer 2012

Adverse Prognosis: All Variants are not Equal

SWOG Intergroup Trial:

- MVAC vs GC
- Pure UC: n = 236
- Mixed UC: n=59
- Non urothelial cancer components included squamous and glandular differentiation
- “Mixed” tumors had evidence of improved survival benefit with chemotherapy (HR 0.46; 95% CI 0.25-0.87, p = 0.02)
- Marginal evidence that “mixed” tumors had survival benefit from chemotherapy than “pure” UC (interaction p = 0.09)

Estimated five-year survival probabilities

Stage	Treatment	Pure UC		Mixed Tumors	
		5-yr survival†	95% CI	5-yr survival†	95% CI
cT2	Cystectomy-only	0.61	(0.52,0.72)	0.54	(0.39,0.74)
cT2	MVAC + cystectomy	0.64	(0.55,0.74)	0.73	(0.62,0.86)
cT3-T4a	Cystectomy-only	0.42	(0.34,0.53)	0.34	(0.21,0.55)
cT3-T4a	MVAC + cystectomy	0.46	(0.37,0.56)	0.58	(0.45,0.75)

Do mixed squamous and mixed adenocarcinomas do better than pure UC with chemotherapy?

Scosyrev et al, BJU 2011

Role for Gene Expression vs. Variant Histology

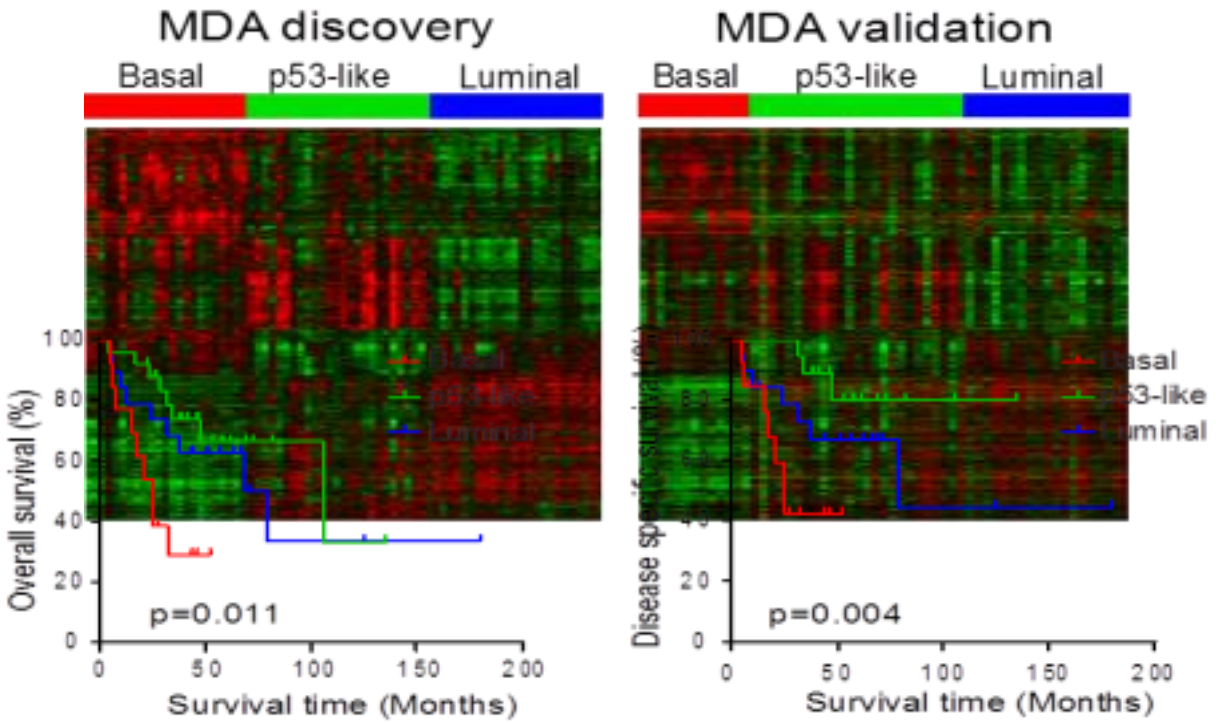
- Gene-expression profiling:
  - Differentiates tumours that differ in their prognosis

    and
  - Is predictive of benefit from treatment

Background: gene expression

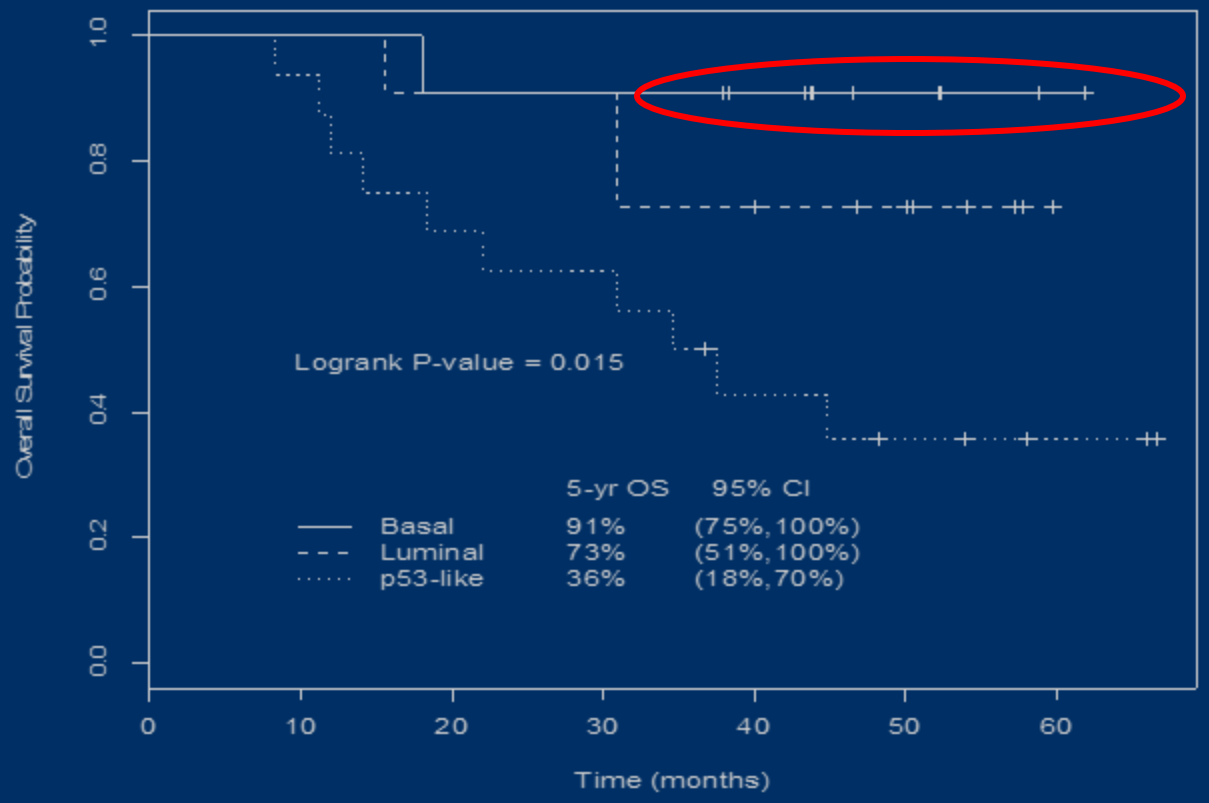
Three intrinsic subtypes:

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

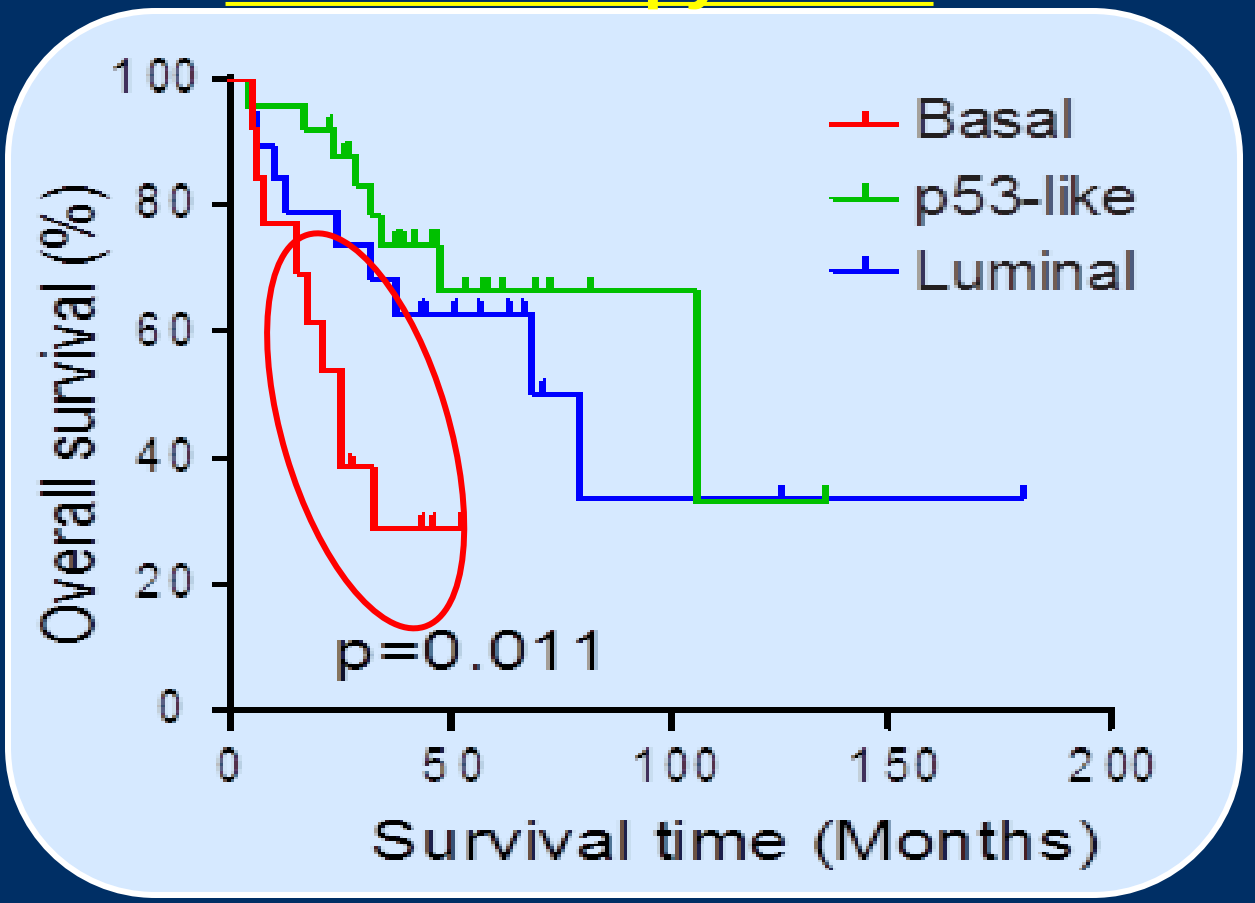


Basal tumors benefit from neoadjuvant chemotherapy: MDACC clinical trials

Neoadjuvant chemotherapy



Chemotherapy Naive



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

Paradigm Shift in Urothelial Cancer

- Urothelial cancer is no longer just 1 disease:

"Basal"

- Chemo-sensitive
- Immune signature

Therapies:

- GC/DDMVAC
- CTLA4?
- PD-1/PDL-1?
- Proteasome inhibitors + chemo?

"p53-like"

- Chemo-resistance
- Stromal enrichment
- Bone mets
- Immune signature

Therapies:

- PD-1/PD-L1?
- Met inhibitors?

"Luminal"

- Still some chemo-sensitivity
- "FGFR" signature

Therapies:

- GC/DDMVAC
- FGFR inhibitors?
- Proteasome inhibitors + chemo?

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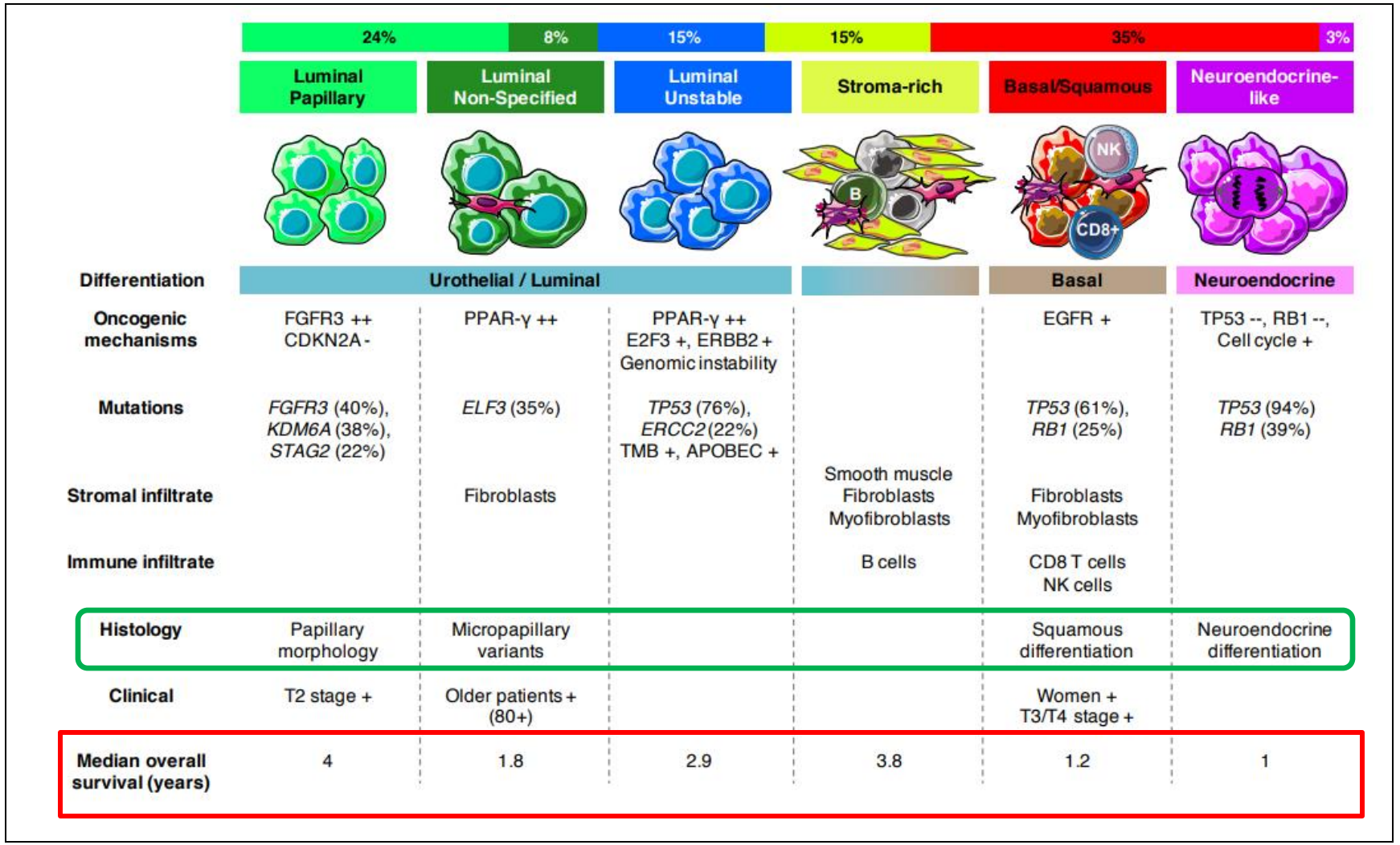
Variants within Subtypes

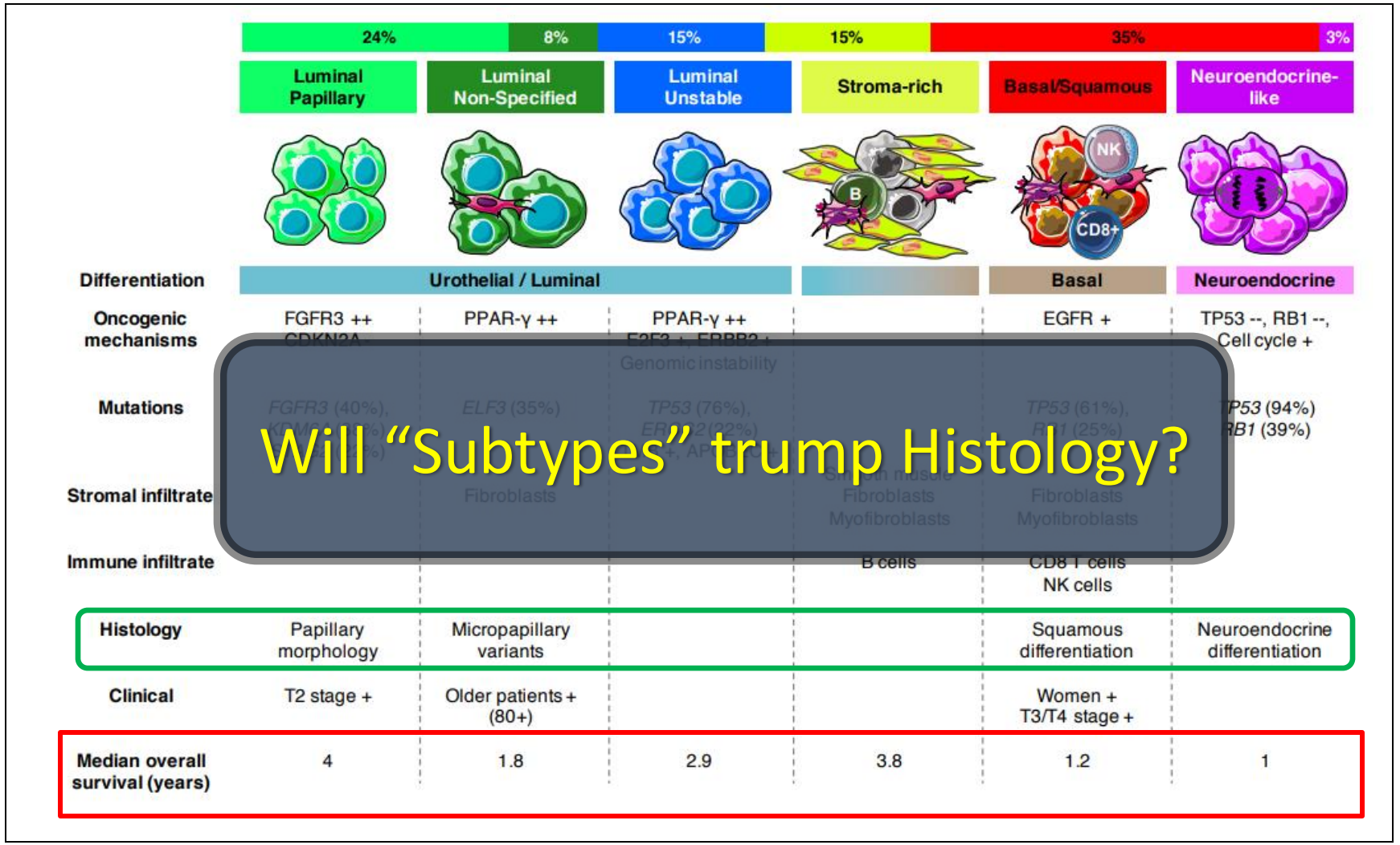


	Luminal Papillary	Luminal Non-Specified	Luminal Unstable	Stroma-rich	Basal/Squamous	Neuroendocrine-like
Differentiation	Urothelial / Luminal				Basal	Neuroendocrine
Oncogenic mechanisms	FGFR3 ++ CDKN2A -	PPAR-γ ++	PPAR-γ ++ E2F3 +, ERBB2 + Genomic instability		EGFR +	TP53 --, RB1 --, Cell cycle +
Mutations	*FGFR3* (40%), *KDM6A* (38%), *STAG2* (22%)	*ELF3* (35%)	*TP53* (76%), *ERCC2* (22%) TMB +, APOBEC +		*TP53* (61%), *RB1* (25%)	*TP53* (94%) *RB1* (39%)
Stromal infiltrate		Fibroblasts		Smooth muscle Fibroblasts Myofibroblasts	Fibroblasts Myofibroblasts	
Immune infiltrate				B cells	CD8 T cells NK cells	
Histology	Papillary morphology	Micropapillary variants			Squamous differentiation	Neuroendocrine differentiation
Clinical	T2 stage +	Older patients + (80+)			Women + T3/T4 stage +	
Median overall survival (years)	4	1.8	2.9	3.8	1.2	1

APOBEC, apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like; CDKN2A, cyclin-dependent kinase Inhibitor 2A; E2F3, E2F transcription factor 3; NK, natural killer; TMB, tumour mutation burden.

Kamoun A, et al. 2019. Epub ahead of print date

Variants within Subtypes



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Current Treatment: Histology

Urothelial Cancer

- Transitional cell (aka: urothelial cancer)
- Variants (often mixed)

  "Better prognosis"
  - Squamous with UC – infection/inflammation – treat as UC
  - Small cell – treat as small cell
  - Adenocarcinomas with UC – treat as UC

  "Poor Prognosis"
  - Sarcomatoid
  - Plasmacytoid – CDH1 mutations/loss, peritoneal
  - Micropapillary – early surgery/neoadjuvant

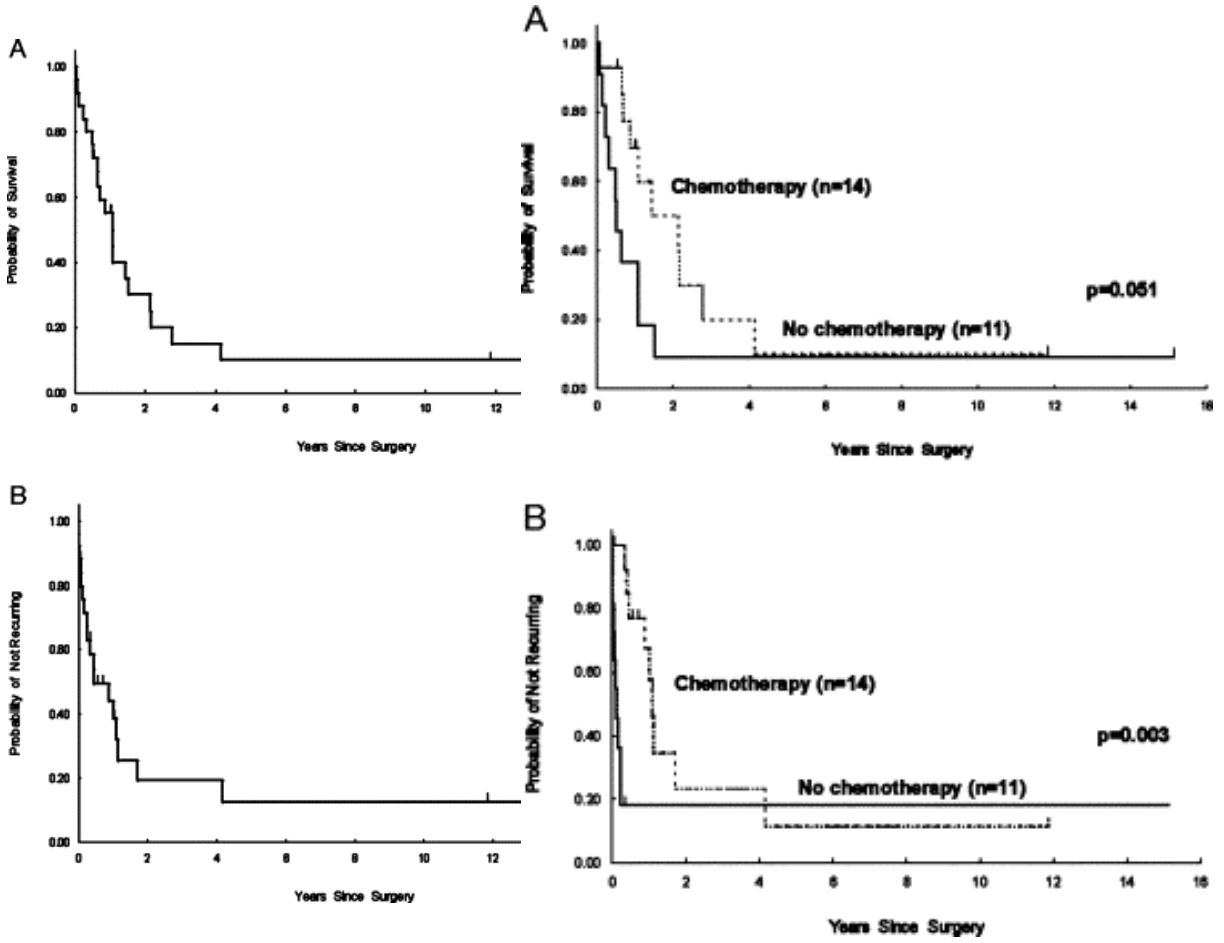
Small Cell Urothelial Carcinoma

Small Cell Urothelial Cancer: Initial Surgery

- Historically associated with poor prognosis
- Earlier recommendations for initial surgery, but “In most reported series, the prognosis is uniformly poor and most patients succumb to disease within 1 year (Principles and Practice of Genitourinary Oncology, 1996)

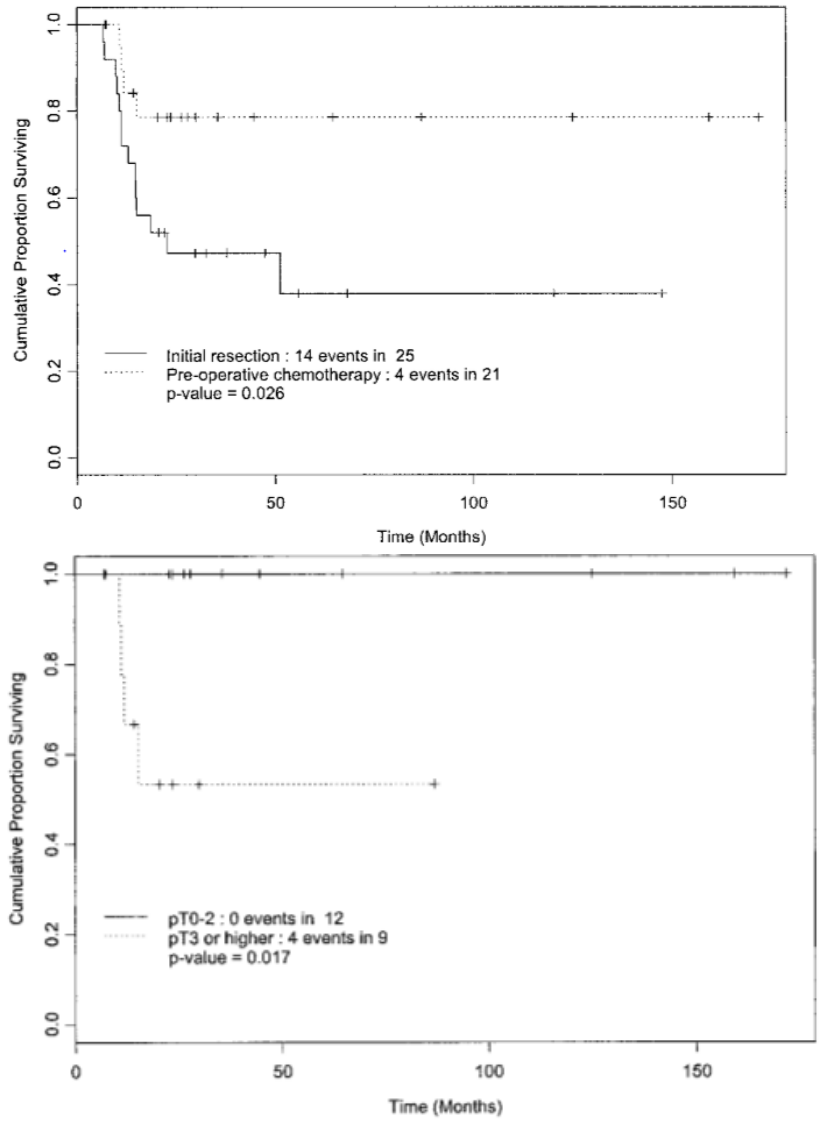
USC Norris: Initial Cystectomy

- n=25
- Only 4 (16%) had organ confined disease at resection
  - 2 (8%) pT3bN0
  - The majority (76%) had lymph node involvement or distant metastases
  - 14 patients received chemotherapy
    - 13 Adjuvant, 1 preoperatively
    - Median OS 13 months.



Quek et al. J Urol 174:93-96, 2005

Small Cell Benefit from Neoadjuvant Chemotherapy

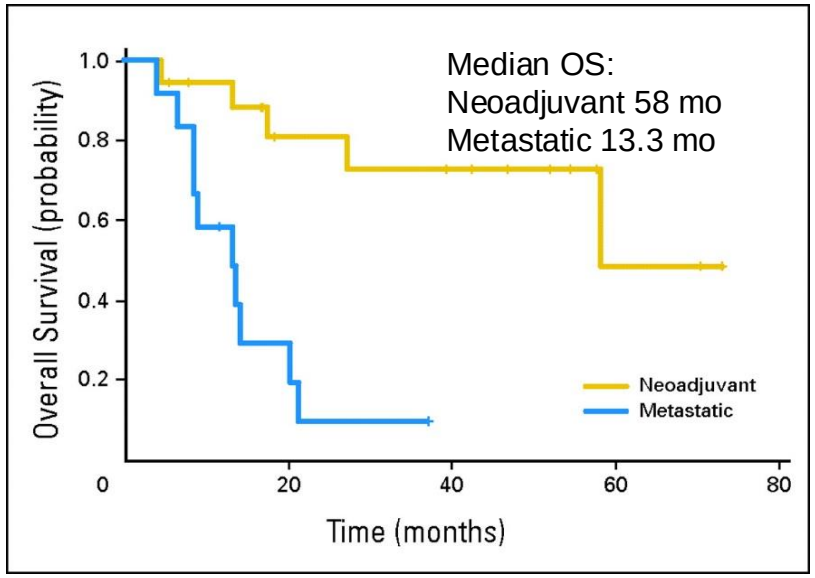


MDACC (retrospective)

- N=88; 46 surgery
- 25 neoadjuvant chemotherapy
- Only 2/12 treated with neuroendocrine regimen had small cell remaining at surgery
- 6/9 treated TCC regimen had small cell remaining
- 5-yr CSS: neoadjuvant 78%, initial surgery 36%
- Improved CSS with neoadjuvant therapy (p=0.026)
- Down-staging had a significant impact on outcomes

Siefker-Radtke et al. J Urol 2004

Phase 2 Trial: Small Cell Urothelial Cancer

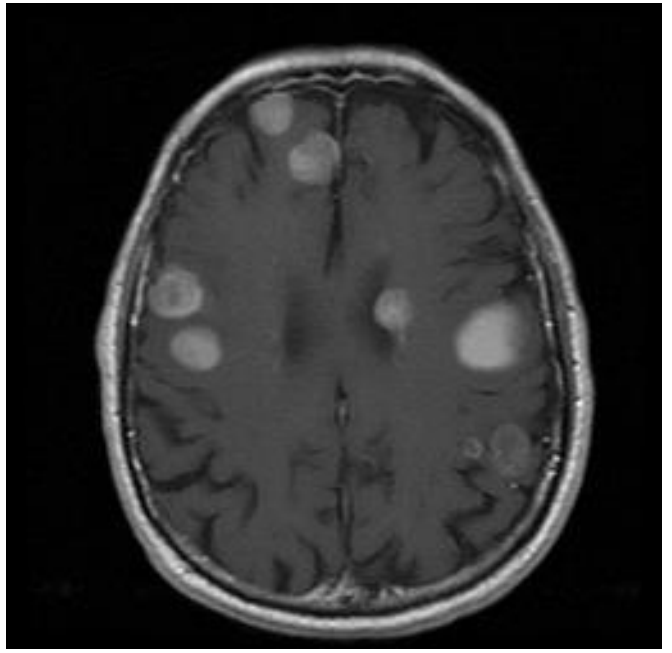


Siefker-Radtke, A. O. et al. J Clin Oncol; 27:2592-2597 2009
JOURNAL OF CLINICAL ONCOLOGY

50% incidence of brain mets in T3b or greater disease

MDACC

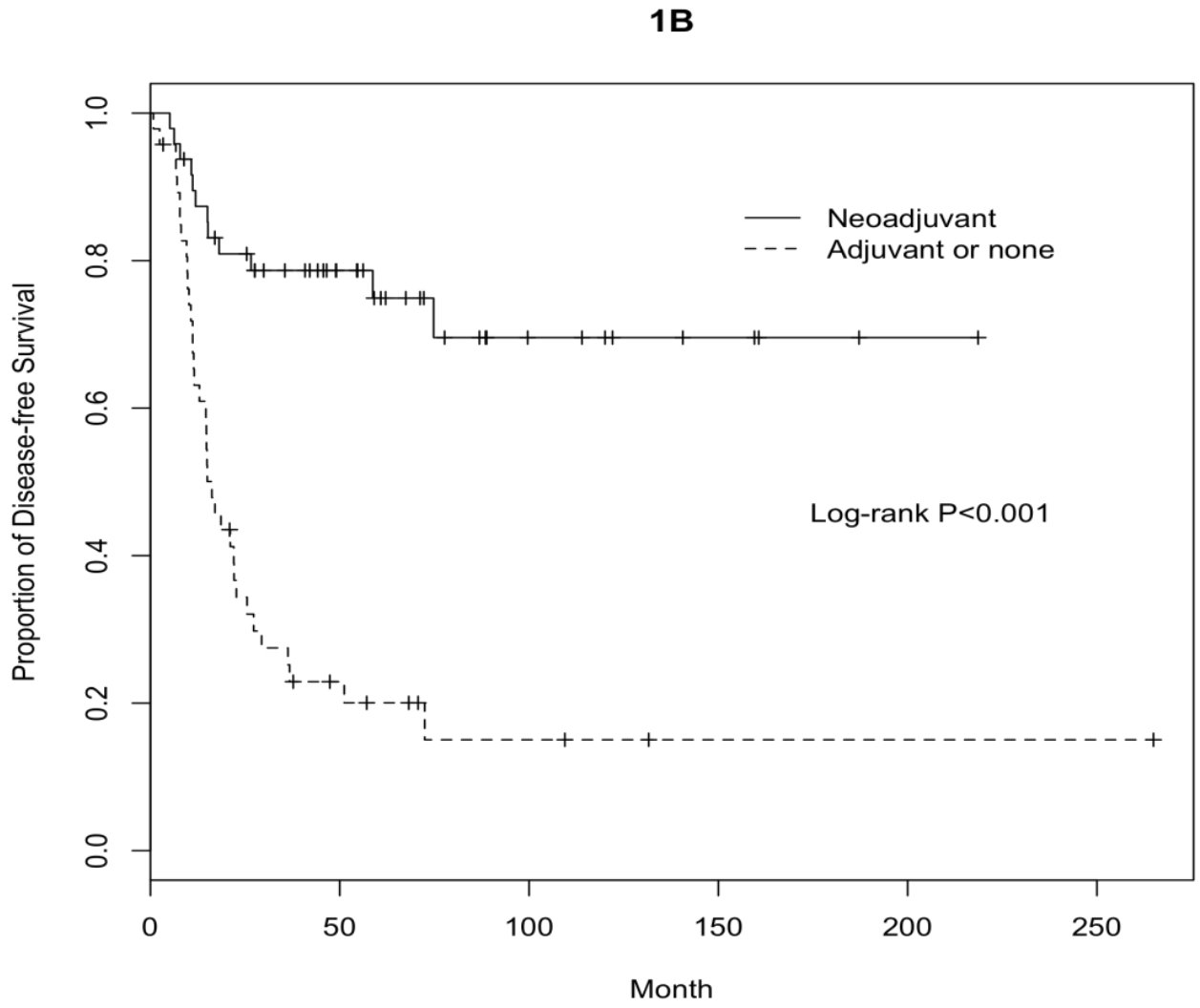
- N=30
- Alternating chemotherapy
  - Ifosfamide/doxorubicin alternate with etoposide/cisplatin
- Planned 4 cycles neoadjuvant
- 2 cycles beyond maximal response for metastatic disease



Small Cell Urothelial Cancer: Update

MDACC Retrospective

- cT2-T4aN0 small cell urothelial cancer
- 48 neoadjuvant
  - 71% Ifosfamide/Doxorubicin alt with Etoposide/Cisplatin
  - Median OS 159.5 month
  - 5-year DSS 79%
- 47 initial surgery
  - Half had adjuvant therapy
  - Median OS 18.3 months
  - 5-yr DSS 20%



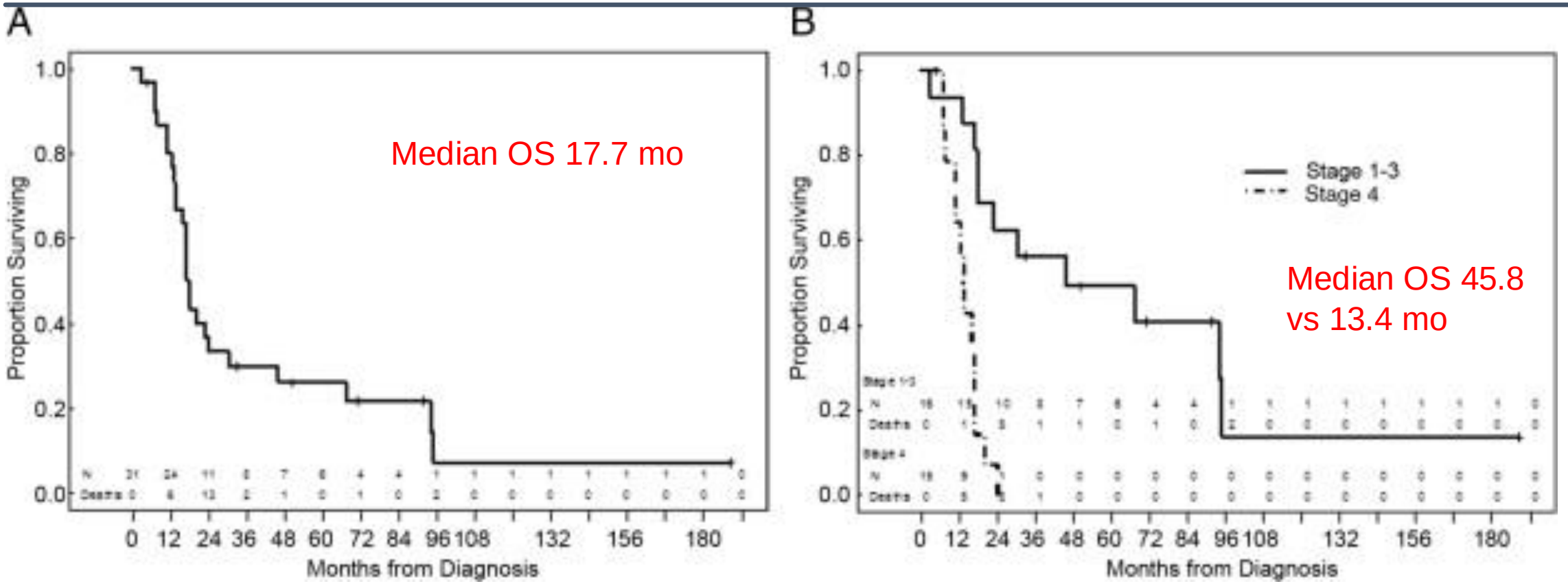
Lynch, Siefker-Radtke et al. Eur Urol 2013

Plasmacytoid Urothelial Carcinoma

Plasmacytoid Urothelial Cancer

- Appearance reminiscent of plasma cells
  - Eccentric nuclei with abundant eosinophilic cytoplasm
  - Can express CD138, a marker shared with myeloma cells
- Cell adhesion marker, E-cadherin, down-regulated or missing
  - CDH1 mutations
- Grows along tissue planes
- Can present with pencil-thin stools
  - Circumferential thickening around the rectum
- Pathognomonic appearance on CT?

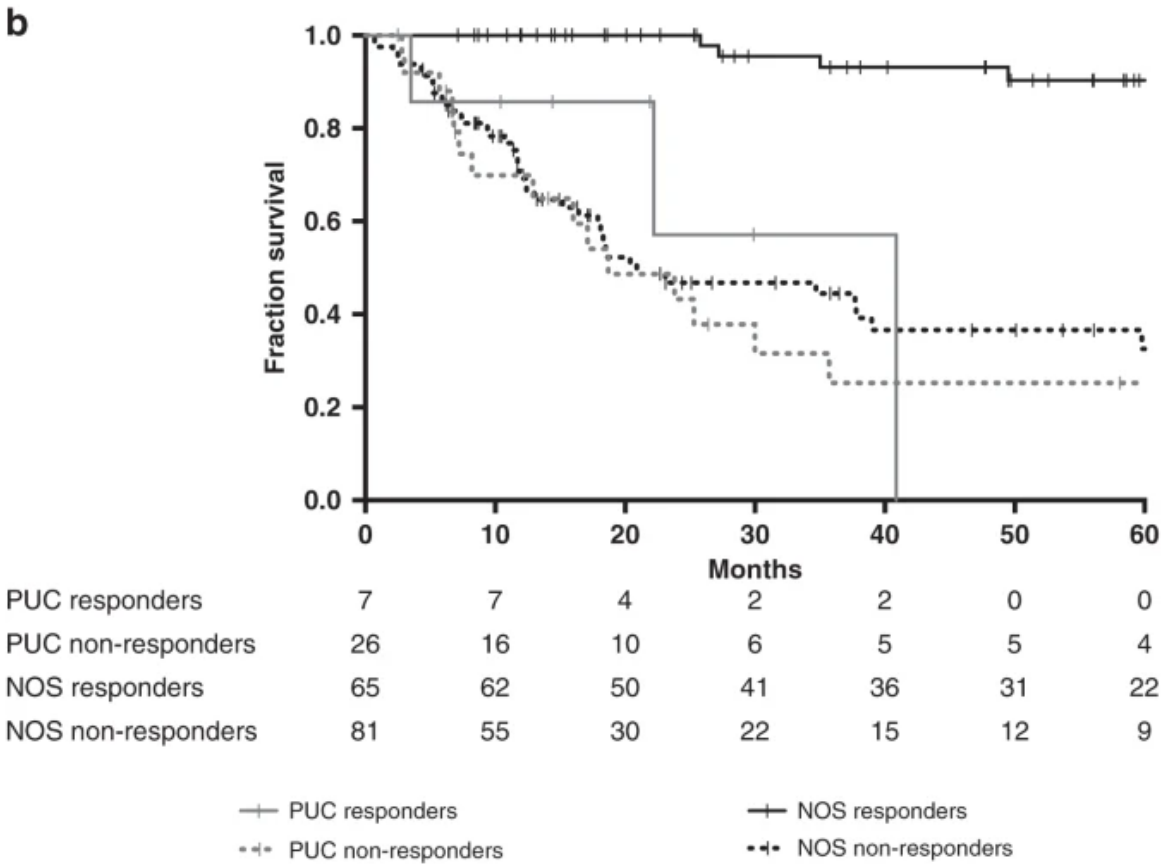
Plasmacytoid Urothelial Carcinoma, a Chemosensitive Cancer with Poor Prognosis, and Peritoneal Carcinomatosis



- N=31
- Few long-term survivors with neoadjuvant chemotherapy despite pathological downstaging
- Over 80% had peritoneal involvement on imaging during their disease course

Dayyani, Siefker-Radtke et al. JUrol 2013

Plasmacytoid Urothelial Cancer: MSKCC



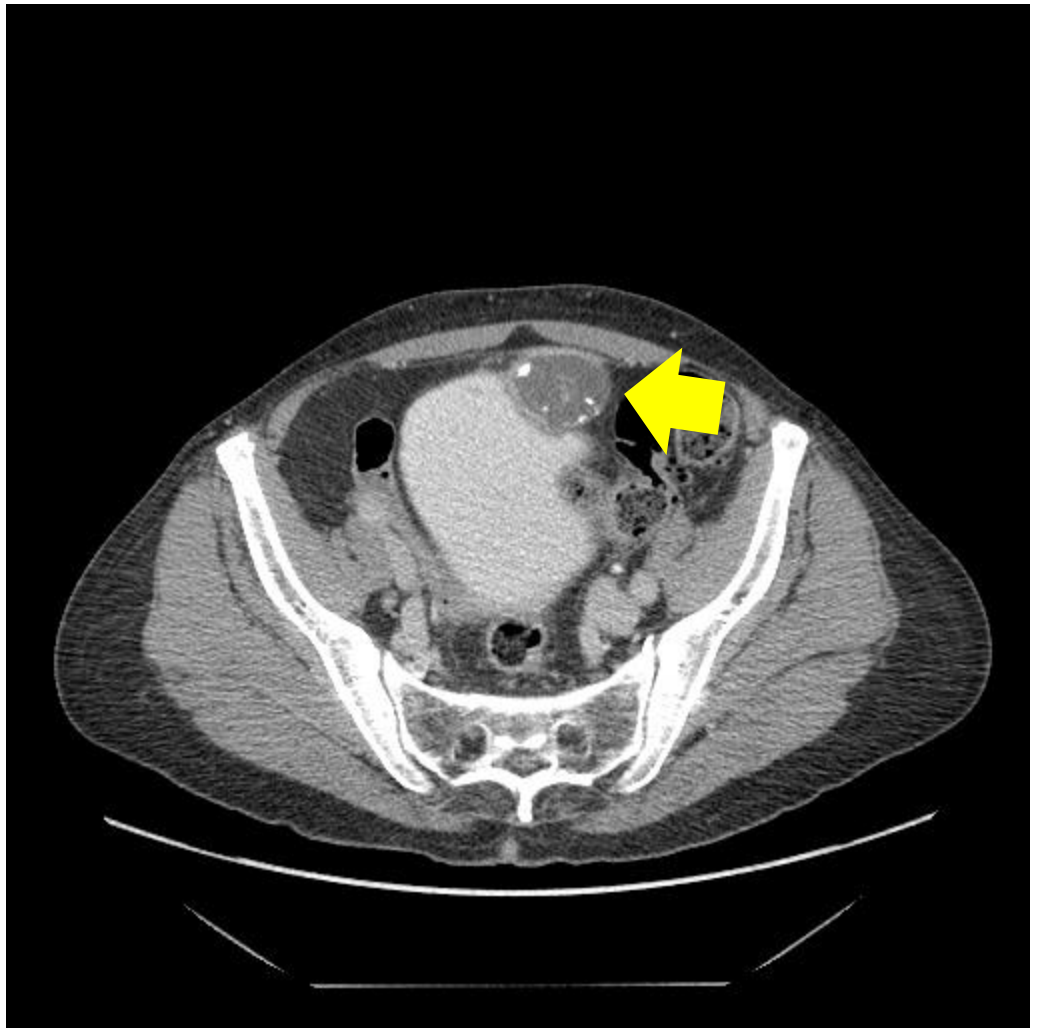
- N=81
- Localized/resectable n = 62
  - 12% pT0N0 neoadjuvant chemotherapy (gem/tax/cisplatin)
  - Med OS 30 months
- Unresectable/metastatic n=19
  - medOS 10.5 mo
- Few long-term responders despite aggressive therapy
- Inferior outcomes compared to typical UC

Teo et al. Br. J Can 2021

Urachal Carcinoma

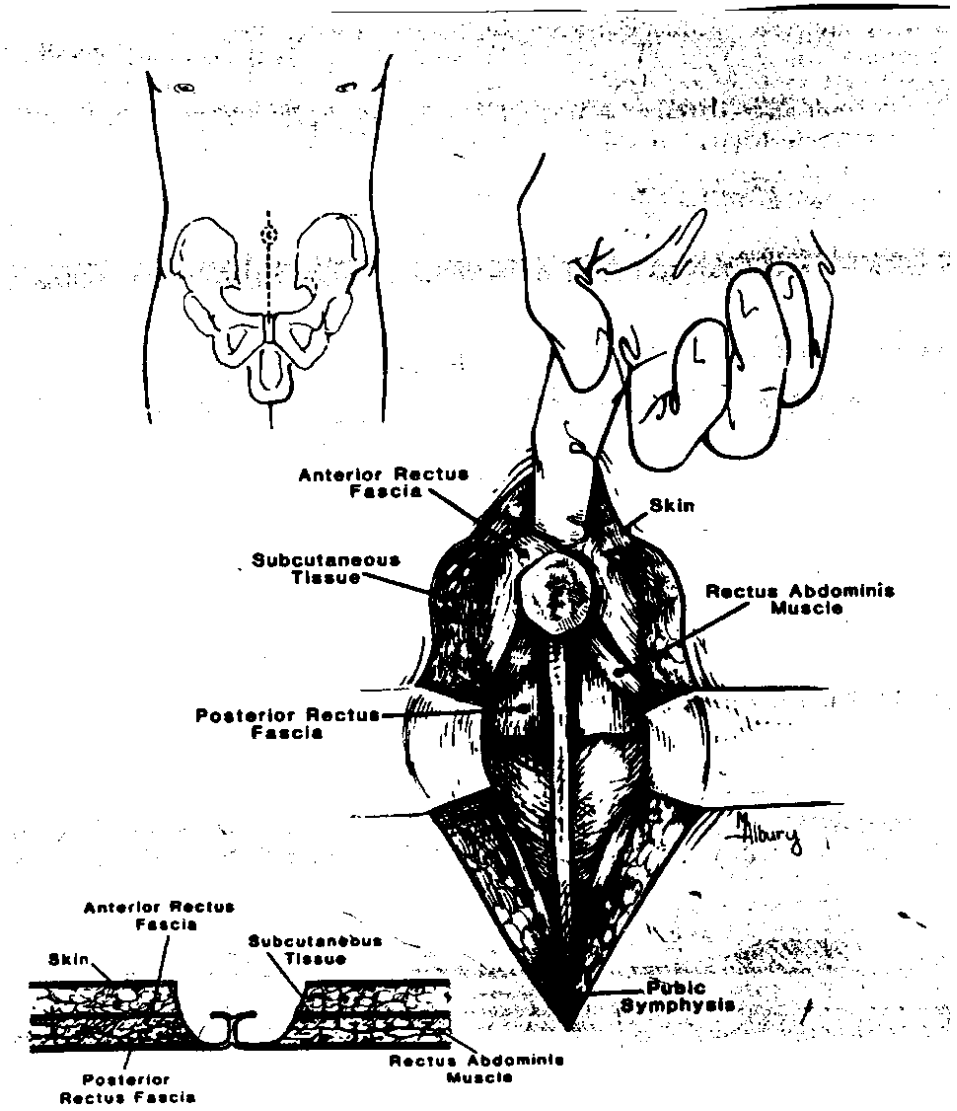
Urachal Carcinoma

- Pure adenocarcinomas are rare except when located in the bladder midline (urachal cancer), or along the urethra
- Consider evaluation for other primaries
- Midline cystic mass with calcifications if pathognomonic for urachal carcinoma



Siefker-Radtke et al. JUrol 2003

Urachal Carcinoma: Surgical Resection



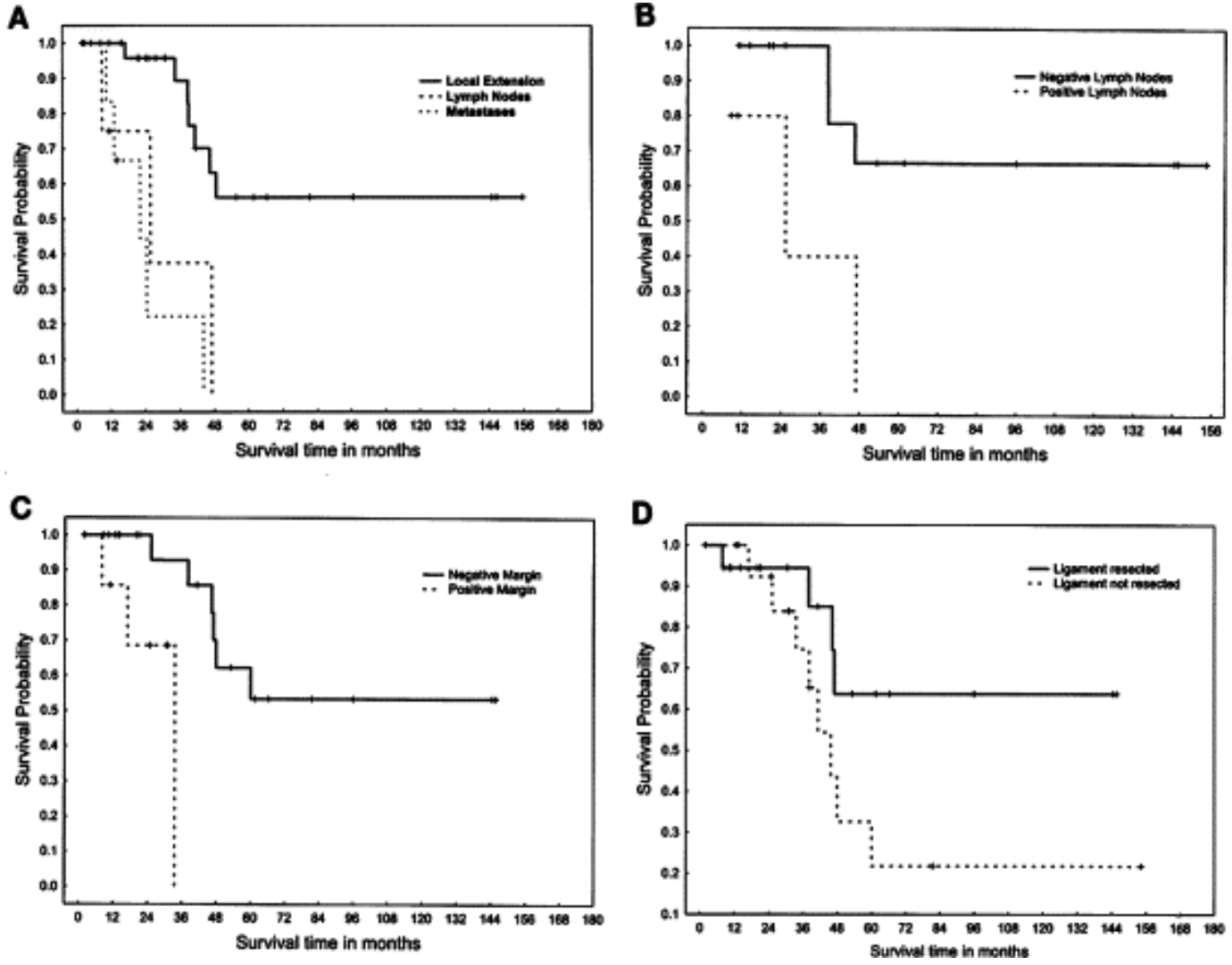
<u>En-bloc Resection is Required</u>

- Sheldon first proposed en-bloc resection of the umbilicus, urachal ligament, and bladder

<u>Partial vs Complete Cystectomy</u>

- Henly: no difference in survival between partial (n=30) and radical (n=4) cystectomy with en-bloc umbilectomy

Urachal Carcinoma: Risk Factors for Relapse



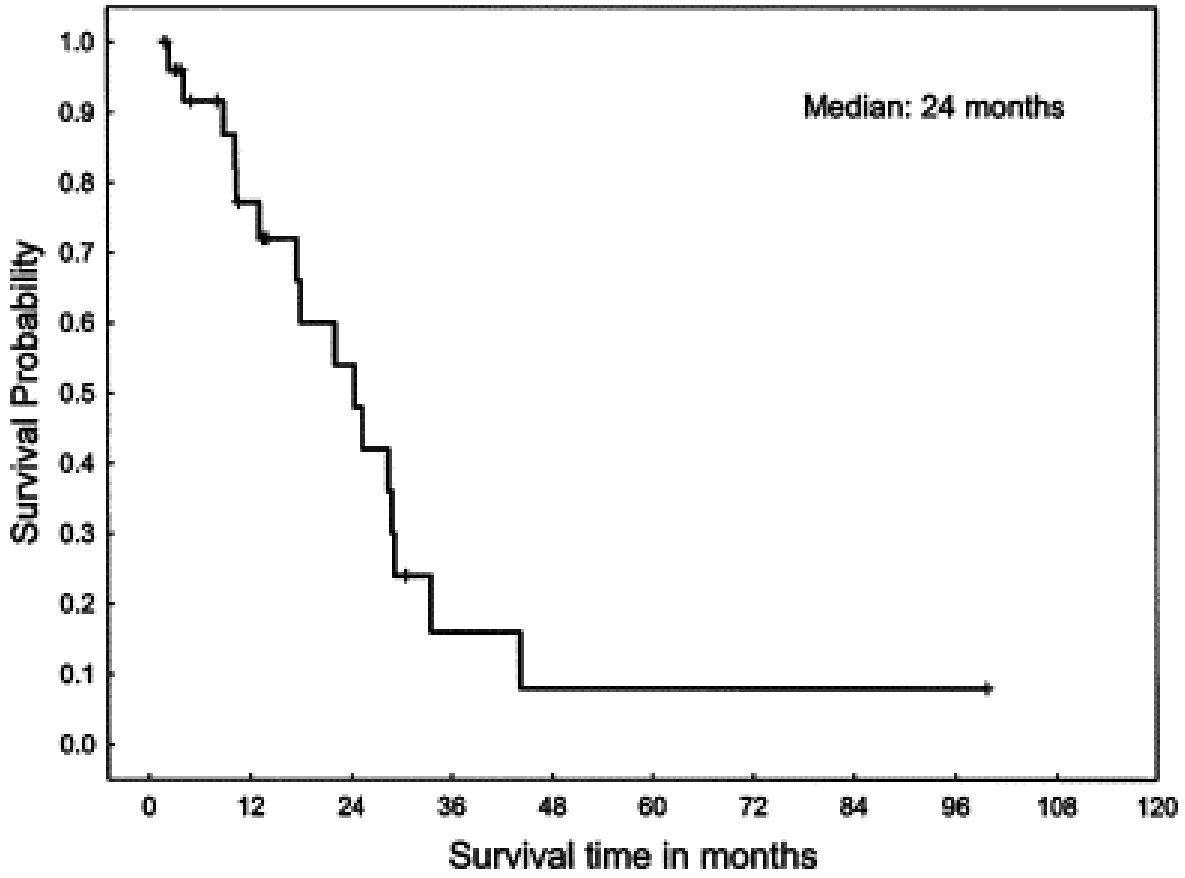
Risk Factors

- Node positive
- Peritoneal mets/extension at surgery
- Positive margin
- Lack of en-bloc resection of the umbilicus with the urachal ligament (the belly button is left behind)

Siefker-Radtke et al. JUrol 2003

Urachal Carcinoma: Chemotherapy

- N= 42
  - Surgery N=35
- Chemotherapy (for metastastases) N=26
  - 4 responses
    - 3/9 5-FU with cisplatin
    - 1/6 Taxol/methotrexate/cisplatin
    - MVAC: 0/5
  - Median OS 24 months



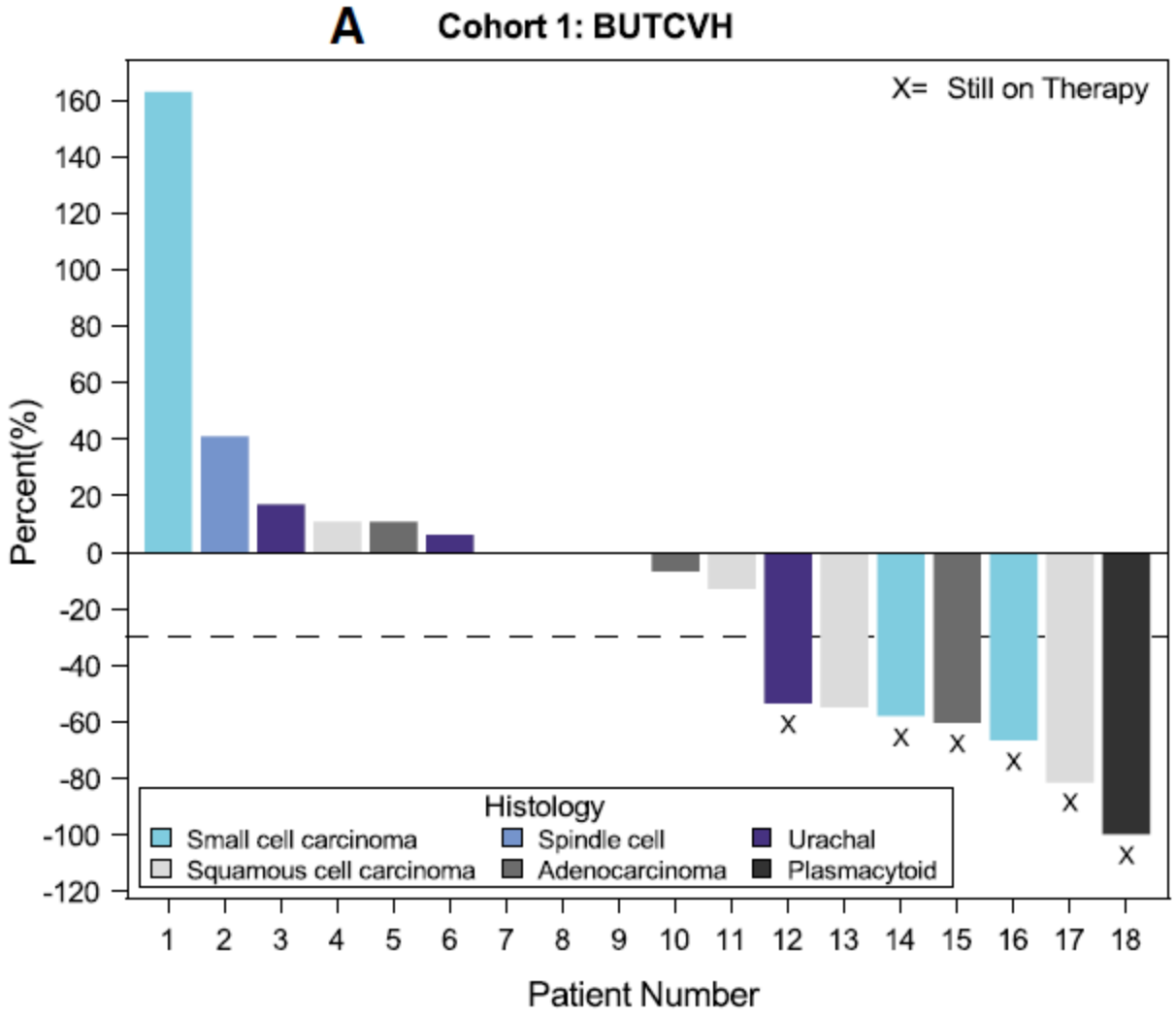
Siefker-Radtke et al. JUrol 2003

Immunotherapy and Variant Histology

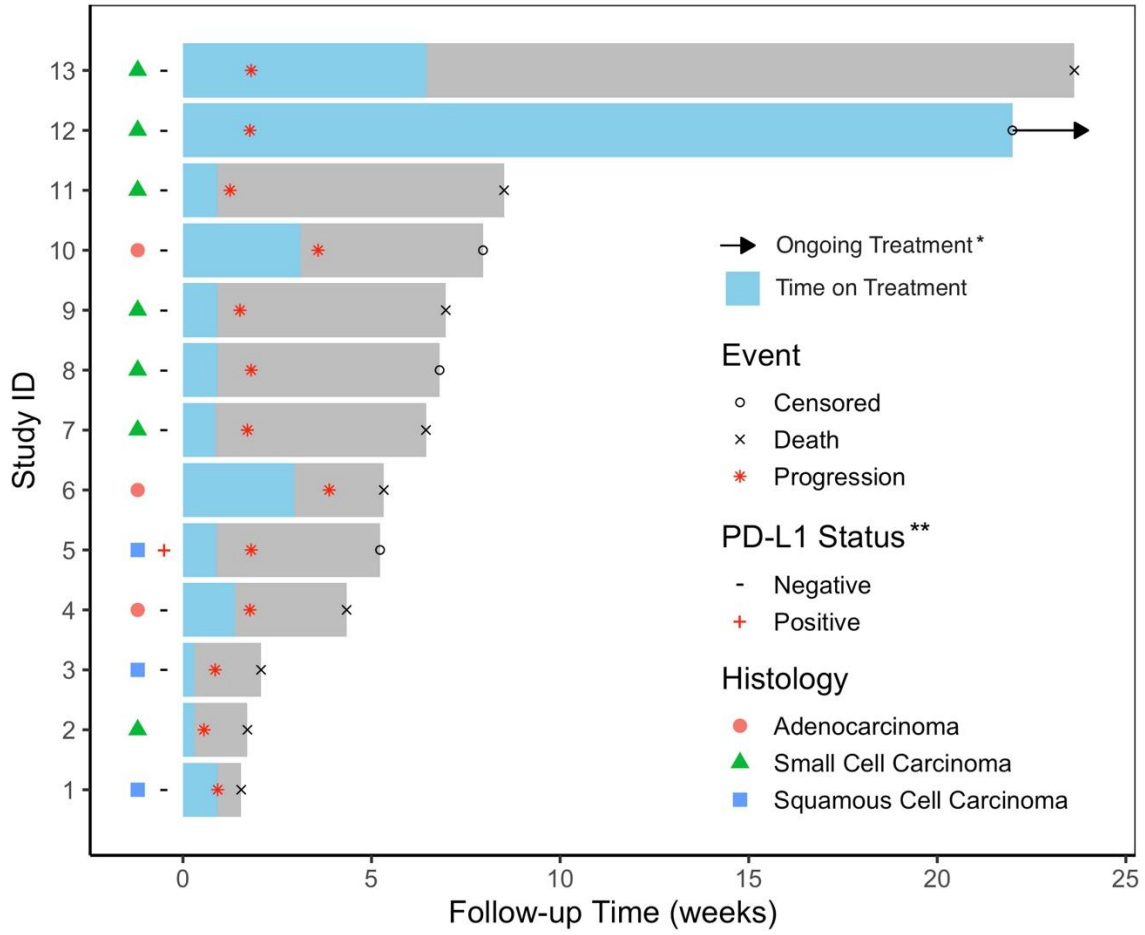
Checkpoint Inhibition in Variant Histology

Multi-institutional

- DFCI, MDACC, Emory, Ohio State, UCSD, Beth Israel
- N=55
- N= 19 (bladder, upper tract variant histology BUTCVH))
- Nivolumab 3 mg/kg, Ipilimumab 1 mg/kg x4 f/b maintenance nivolumab
- ORR 37% BUTCVH
  - 2/3 Small cell
  - 2/4 squamous cell
  - 1/3 urachal
  - 1/3 adenocarcinoma
  - 1/1 plasmacytoid



Checkpoint Inhibition in Variant Histology

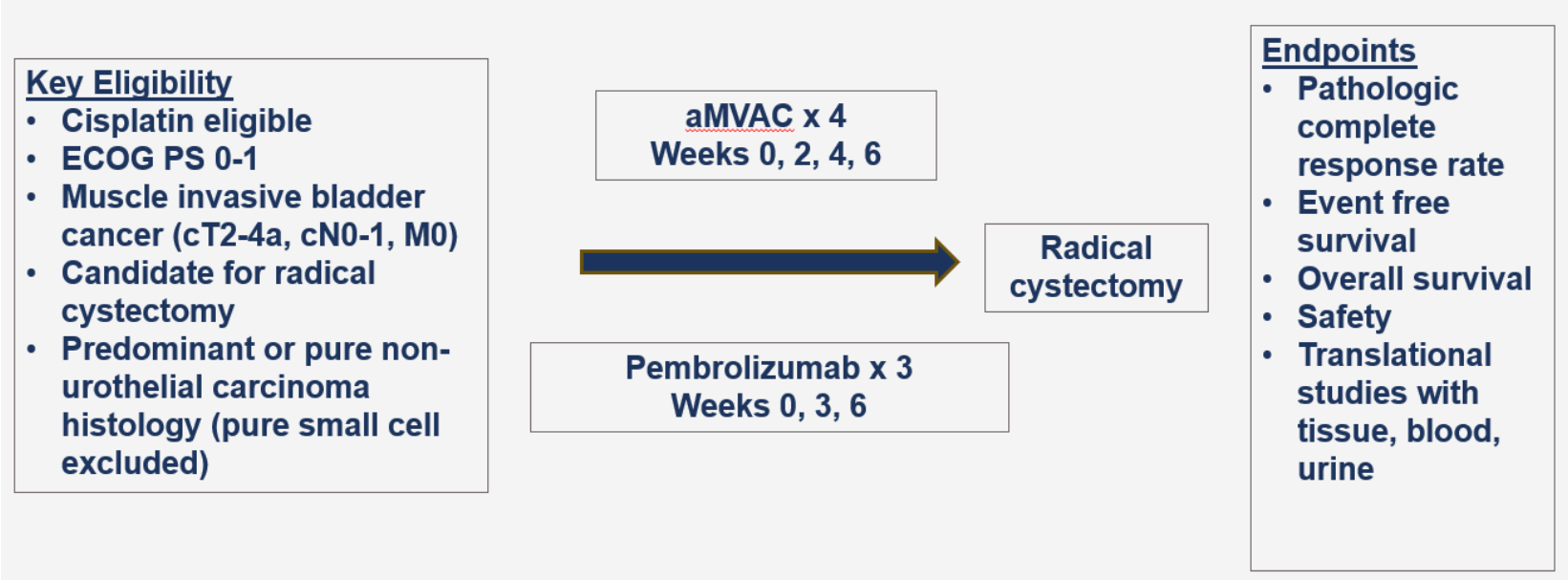


MSKCC

- N=13
- Durvalumab 1500 mg and Tremelimumab 75 mg f/u durvalumab maintenance
- ORR 0%, 2/13 with SD
- medOS 7 months

Sarfaty et al. Canc Med 2020

Checkpoint Inhibition + DDMVAC



Clinical T-Stage at diagnosis	
T2	10 (59)
T3-4*	7 (41)
Predominant histologic subtype (at TURBT)	
Squamous cell	5 (29)
Plasmacytoid	3 (18)
Micropapillary	3 (18)
Poorly differentiated	3 (18)
Glandular	2 (12)
Sarcomatoid	1 (6)

- N=17
- 9/17 (53%) ypT0N0
- 2-year OS 77%

Conclusions:

- Understanding the disease may guide to most appropriate therapeutic strategies
  - Neoadjuvant treatment for small cell
  - 5-FU based therapy for adenocarcinoma
  - En-bloc resection of the umbilicus with urachal ligament and bladder dome for urachal carcinoma
- Effects of checkpoint inhibition remain largely unknown due to exclusion from trials, small numbers of patients.
- Future strategies
  - Marker or subtype driven strategies to enhance outcomes across the spectrum of urothelial malignancies
  - Is it time to stop excluding these from urothelial cancer trials?


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