Contemporary Management of Upper Tract Urothelial Carcinoma (UTUC)

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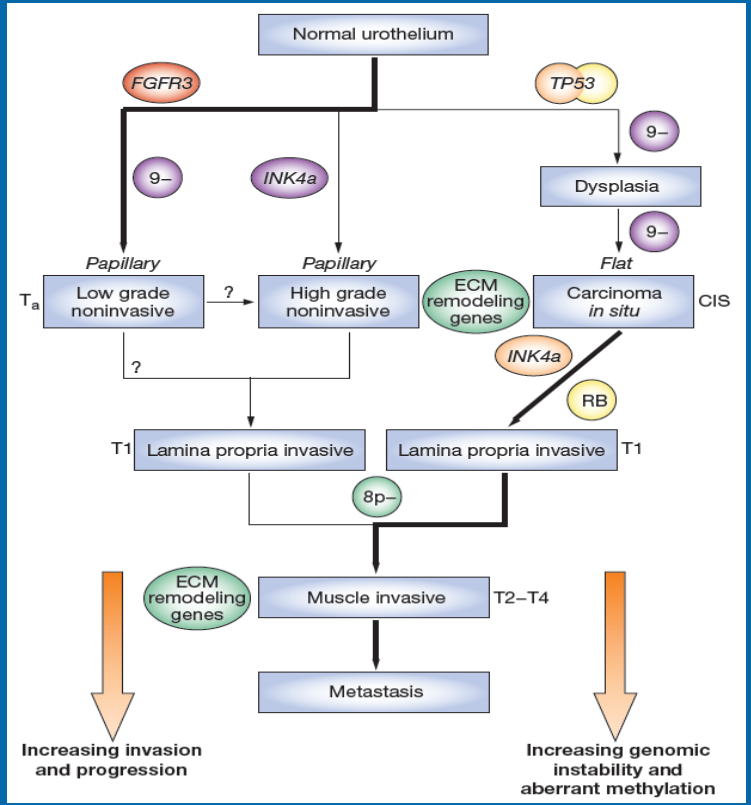
Upper Tract Urothelial Carcinoma (UTUC)

- Biologically indistinct from bladder urothelial ca
- Management follows paradigms developed for bladder cancer due to its relative rarity and absence of prospective ± randomized studies
- Low-grade → "non-lethal" → organ preservation
- High-grade → "potentially lethal" → multimodal therapy including organ removal
- Risks of under-grading and under-staging
- Consequences of organ removal

TaLG vs. T1 or HG: Different Species?

TaLG
FGFR3 mutations
↑Activation Ras-MAPK pathway
↓
Cell proliferation

“Non-lethal cancer”



TaHG, CIS, T1
Loss of p53 or pRB
Genetic instability
De-differentiation
↓
Progression

“Potentially-lethal cancer”

Wolff et al. *Nat Rev Urol* 2005

Low-Risk vs. High-Risk UTUC

Table 2. Commonly accepted risk-stratification criteria

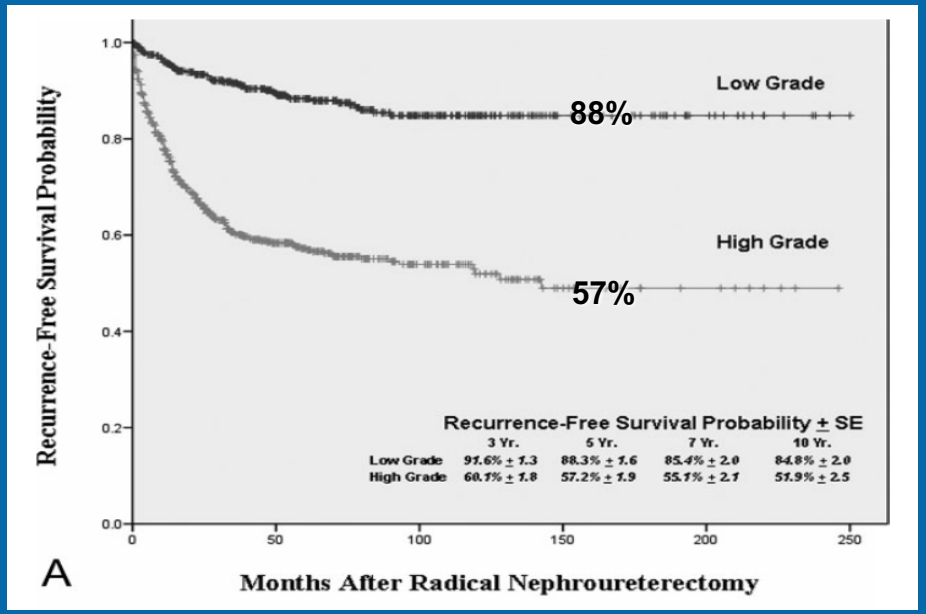
	Low-risk UTUC	High-risk UTUC
Biopsy tumor grade	Low grade	High grade
Architecture	Papillary	Sessile
Cytology	Negative	Positive/High grade*
Focality	Unifocal	Multifocal
Tumor size	≤1 cm	Unknown†
Hydronephrosis	Absent	Present
CTU findings	No findings of invasive disease	Parenchymal or fat invasion, enlarged lymph nodes

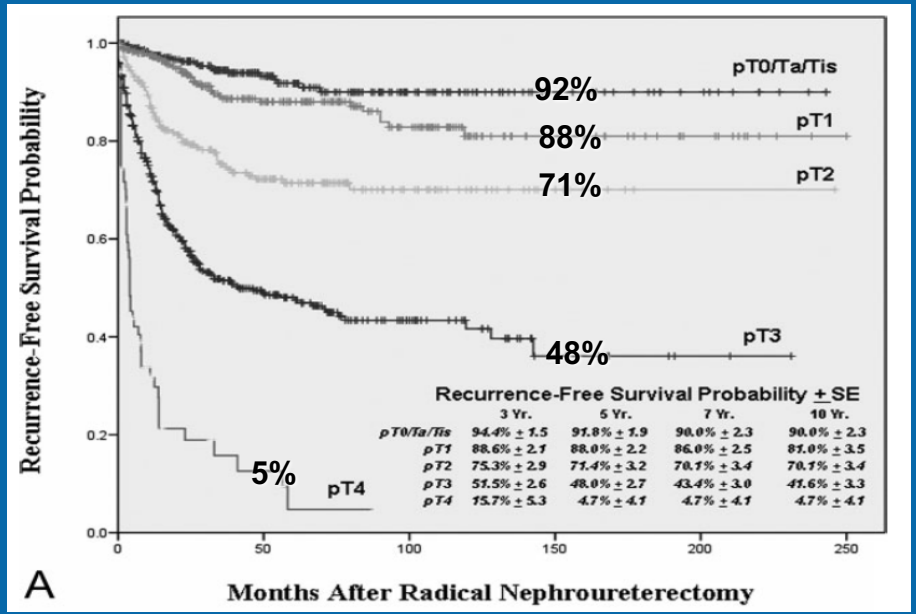
Mandalapu RS and Matin SF et al. *Urology* 2016

NU + LND: Gold-Standard for UTUC

- High-grade and/or invasive UTUC with normal contralateral kidney → NU + LND (RLND and/or ipsilateral PLND) with bladder cuff is gold-standard
- Optimizing outcomes:
  - Use of perioperative chemotherapy
  - Use of postoperative intravesical chemotherapy
  - Management of distal ureter and bladder cuff
  - Quality of lymphadenectomy
  - Patient factors

NU for UTUC: Outcomes





- N = 1363, 12 academic centers, 1992-2006, 16% periop chemo
- Similar stage-for-stage, grade-for-grade to RC for bladder ca

Margulis V et al. *Cancer* 2009

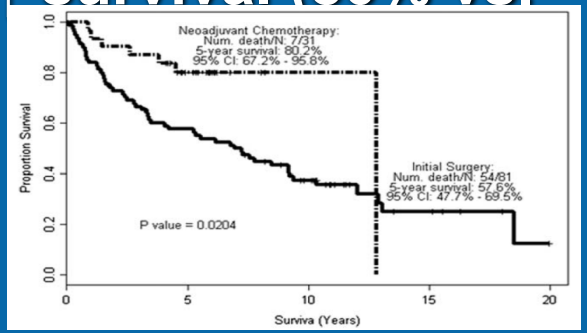
Upper Tract Urothelial Carcinoma: NU Patient Profile

- 50-60% > 70 years old
- 20-30% Charlson Comorbidity Index ≥ 2
- 25% LG, 75% HG
- 40-55% pT2-4 → up to half of patients under-staged or under-graded prior to nephroureterectomy
- pN+ 10%, pNX 57%
- 10-25% prior cystectomy

Lane BR et al. *Cancer* 2010; Margulis V et al. *Cancer* 2009; Smith AK et al. *Urology* 2011; Tinay I. et al. *BJU Int* 2015

Neoadjuvant Chemotherapy for UTUC

- Neoadjuvant favored over adjuvant for cisplatin-based perioperative chemotherapy
  - CKD (eGFR < 60) present in 52% preop vs. 78% postop
- MDACC: Matched-pair analysis, pts receiving neoadjuvant MVAC x 4 cycles had ↑ survival (80% vs. 56%)
  - ↑ pT0-TIS rate with chemo
  - 35% vs. 17%; *P* = 0.049



Lane BR et al. *Cancer* 2010; Porten S et al *Cancer* 2014

Role of Intravesical Chemotherapy

- 2-Yr Bladder cancer recurrence in 20-50% pts after NU
- Early clipping of distal ureter may ↓ risk
- Use of post-NU intravesical chemotherapy
  - 2 RCT showed non-statistically significant 40-60% ↓ in bladder cancer recurrence (absolute: 11-26%) with single post-NU installation of intravesical chemotherapy

O'Brien T et al. *Eur Urol* 2011; Ito A et al. *J Clin Oncol* 2013

NU: Role of Lymphadenectomy

- Poorly defined → NU series: > 50% pNX
- Probability of LN+ related to stage and grade
  - G1: 0%, G2: 11%, G3: 35%
- Poor prognosis for LN+ → 20-30% survival
  - Improved survival associated with removal of ↑ LN's
- Selection bias in studies where role of LND assessed
  - Multicenter study, N = 551, NU and LND, 61% pT3-4, 82% HG
    - Median No. LN: 5 (1-41) → LN+ 25%
    - ROC analysis: 13 and 8 LN removed assoc with 90% and 75% probability of finding 1 LN+

Kondo T et al. *Urology* 2007; Roscigno M et al *Urology* 2009; Roscigno M et al. *Eur Urol* 2009

NU: Extent of Lymphadenectomy

- Poorly defined

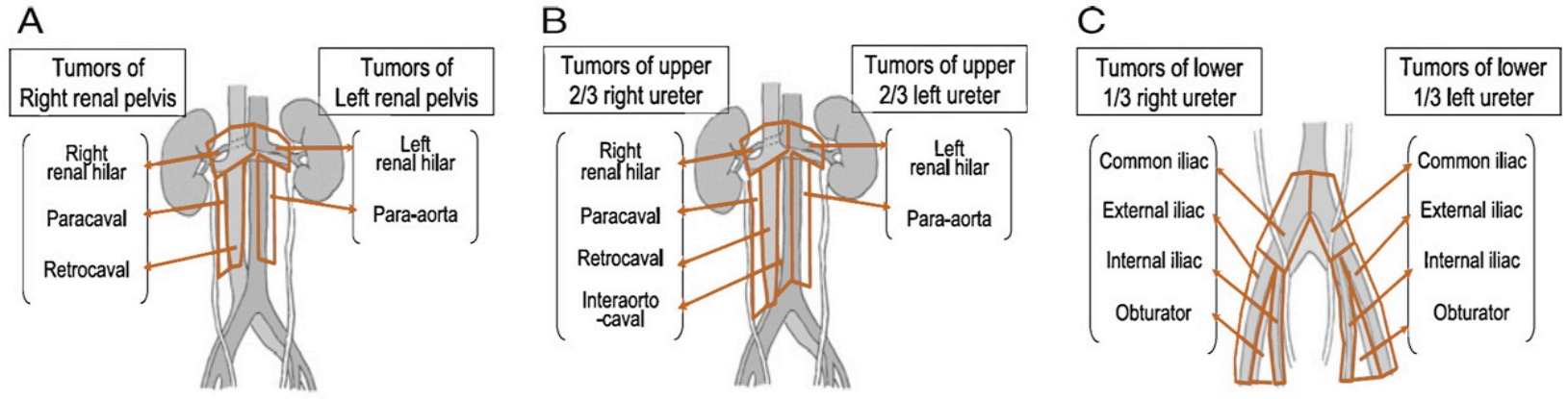


Fig. 1 – Regional lymph node template according to primary tumor location: (A) renal pelvis; (B) upper two thirds of ureter; (C) lower third of ureter [21].

Kondo T et al. *Urology* 2007; Matin SF et al. *J Urol* 2015

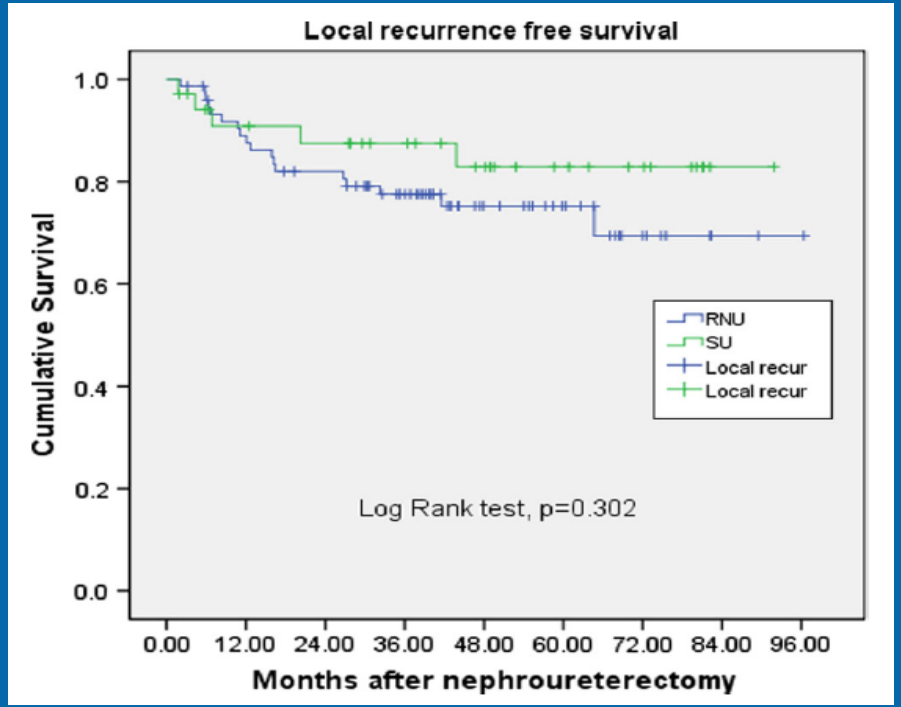
Special Considerations

- Distal ureteral tumors
- Low-grade tumors
- Solitary kidney or diminished renal function

Distal Ureteral UTUC: Role of Ureterectomy

Table 1 Patient characteristics

	RNU	SU	*p* value
Patient number	77	35	
Follow-up duration (months)	43.84 ± 20.64	48.26 ± 26.97	0.344
Age	66.71 ± 9.96	69.29 ± 9.44	0.201
Male/female	41/36	18/17	0.858
High grade	68 (88.3 %)	30 (85.7 %)	0.700
Multifocality	17 (22 %)	2 (5.7 %)	0.032
Preoperative eGFR	54.60 ± 28.78	56.31 ± 33.62	0.522
Postoperative eGFR change	−10.66 ± 24.5	1.18 ± 14.9	0.011
Bladder cancer history	16 (20.8 %)	8 (22.9 %)	0.804
Non-organ confined (>T2)	15 (19.5 %)	11 (31.4 %)	0.165
Bladder recurrence	28 (36.4 %)	12 (34.2 %)	0.832
Local recurrence	18 (23.4 %)	5 (14.3 %)	0.270
Distant metastasis	13 (16.9 %)	3 (8.6 %)	0.244
Cancer death	10 (13.0 %)	2 (5.7 %)	0.249



Hung SY et al. *Int J Urol* 2008

Management of LG UTUC

- Histological confirmation of grade is critical → management should parallel TaLG bladder cancer (organ-sparing)
- Mayo Clinic, 1983-2004, 22 pts UTUC managed endoscopically, all low-grade
  - 50% upper tract recurrence → 32% nephroureterectomy
  - 45% bladder cancer recurrence
  - 9% UTUC mortality
  - No patients with histologically-confirmed LG UTUC at diagnosis developed HG or invasive recurrence

Thompson HR et al. *BJU Int* 2008

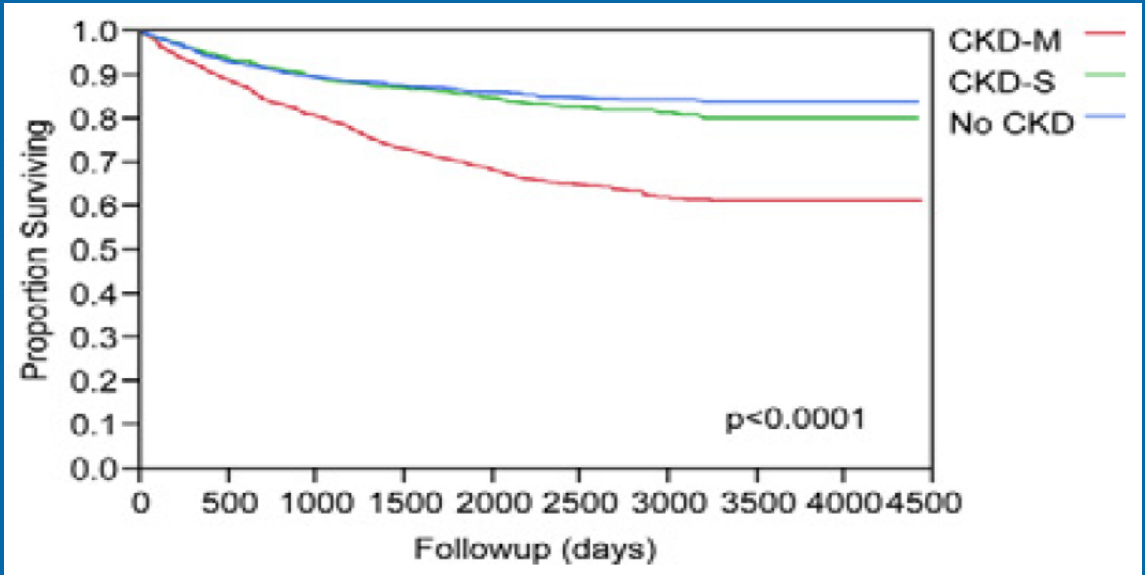
Consequences of Nephroureterectomy

- Cleveland Clinic, 1992-2009, 336 pts UTUC Rx by NU
  - 52% pts had pre-existing CKD (eGFR < 60 cc/min)
  - 78% pts had CKD after NU

- Implications re: long-term morbidity and mortality after NU and delivery of perioperative chemotherapy

Lane BR et al. *Cancer* 2009

Consequences of Nephroureterectomy



- Surgically-induced CKD not assoc with ↑ mortality

Lane BR et al. *J Urol* 2013

Management of LG UTUC

- High rate of pathological upgrading of UTUC at NU
- Mayo Clinic, 184 pts undergoing NU for UTUC with prior endoscopic biopsy
  - Median tumor size 3 cm, 60% HG, 40% invasive
  - 81 pts with Bx G1-G2 → 30 (37%) with G3 at NU

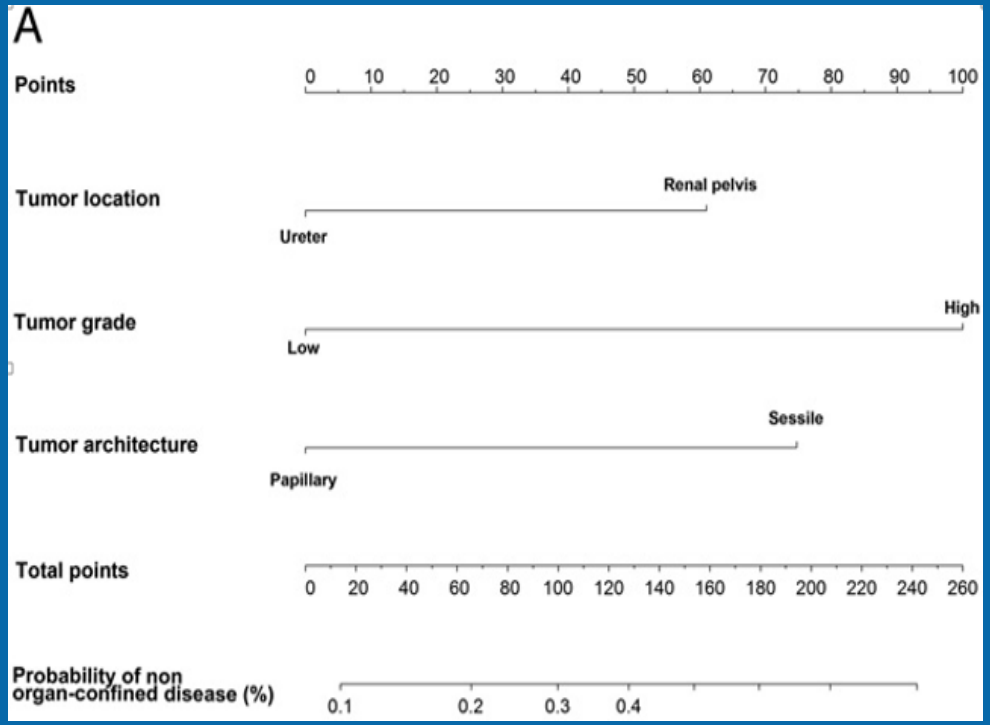
Table 3. Correlation of ureteroscopic biopsy grade with pathologic stage

	Pathologic Tumor/Nodal Stage (%)							
Biopsy Grade	Ta	Tis	T1	T2	T3	T4	Nx	N+
1	15/24 (63)	0/24 (0)	1/24 (4)	3/24 (13)	5/24 (21)	0/24 (0)	20/24 (83)	0/4 (0)
2*	25/57 (44)	3/57 (5)	12/57 (21)	5/57 (9)	8/57 (14)	3/57 (5)	48/57 (84)	4/9 (44)
3*	7/55 (13)	6/55 (11)	9/55 (16)	7/55 (13)	21/55 (38)	4/55 (7)	40/55 (73)	4/15 (27)

- CCF: 43% UTUC changed from Ta or LG → pT1-3 or HG

Wang JK et al. *Urology* 2012; Smith AK et al. *Urology* 2011

Nomogram Predicting Non-Organ-Confined UTUC

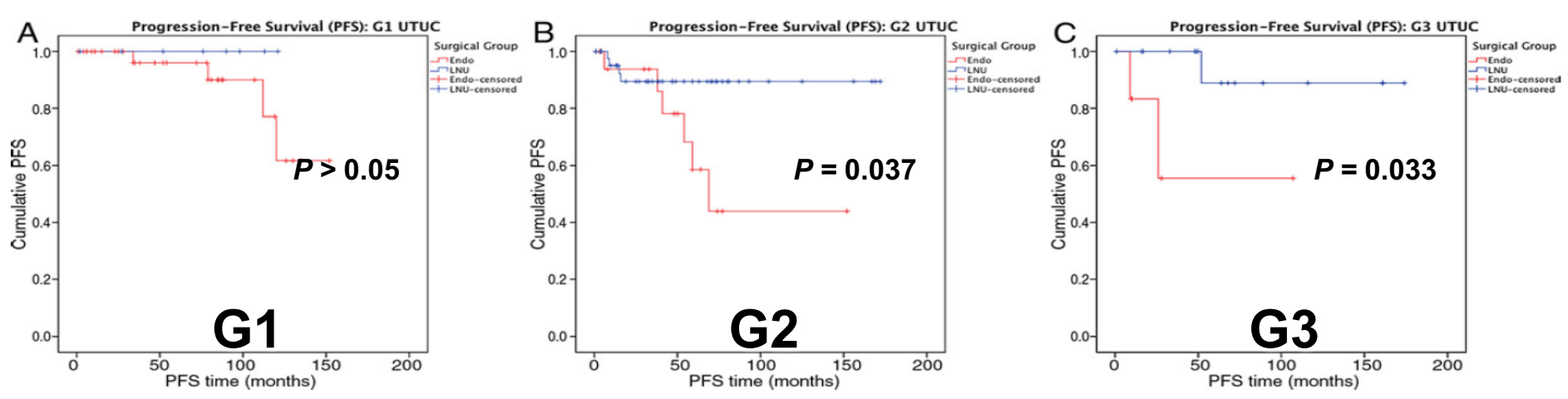


Other Prognosticators:

- Hydronephrosis
- Renal atrophy
- Cytology
- Tumor size
- Periureteric stranding

Margulis V et al. *J Urol* 2010; Favaretto RL et al. *BJU Int* 2012

Endoscopic Management vs. NU for UTUC

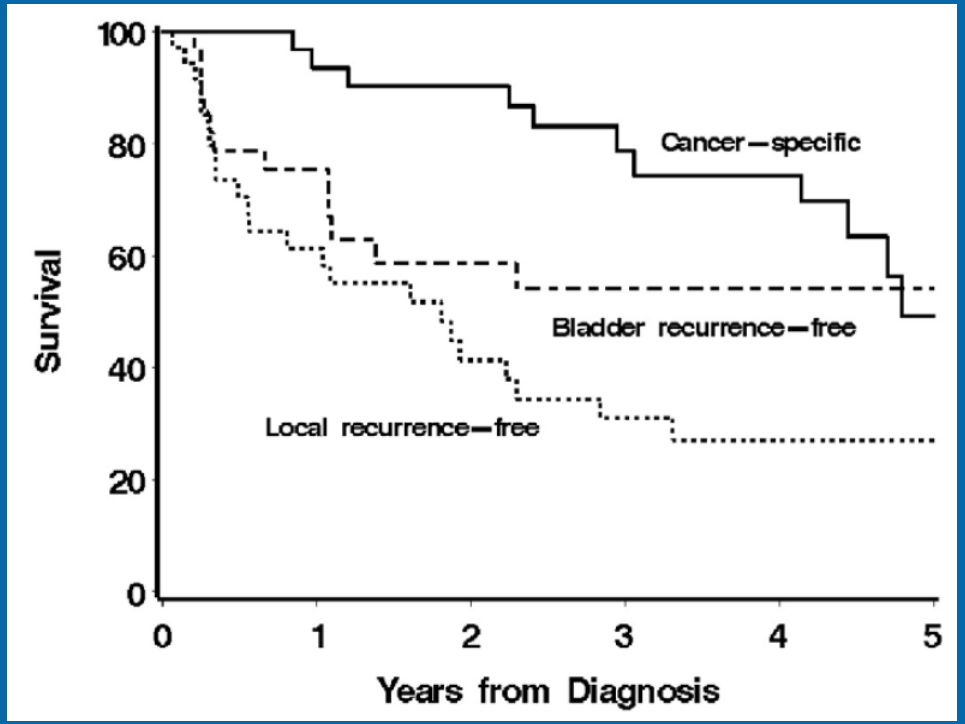


- 1991-2011, 59 pts managed endoscopically vs. 70 NU
- Endoscopic management:
  - 82% 5-year renal unit preservation, 51% recurrence rate

Cutress ML et al. *J Urol* 2013

Imperative Endoscopic Management UTUC

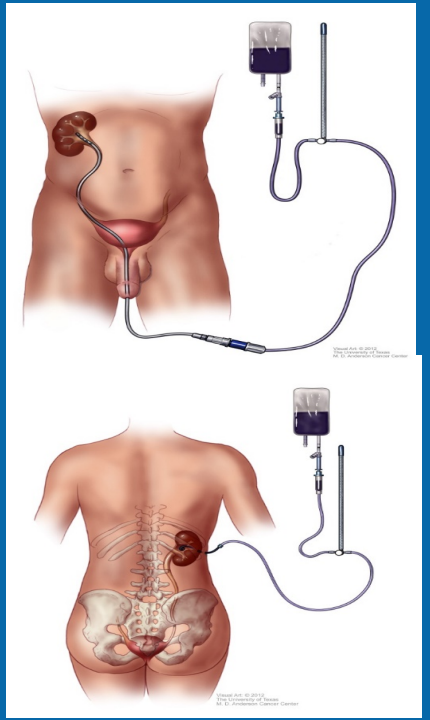
- 37 pts with imperative indications for endoscopic management
  - 32 solitary kidney, 3 bilateral UTUC, 2 CKD
- 23 (62%) developed upper tract recurrence
- NU avoided in 24 (75%) with solitary kidney
- 5-Yr UTUC Mortality: 51%



Krambeck AE et al. *J Urol* 2007

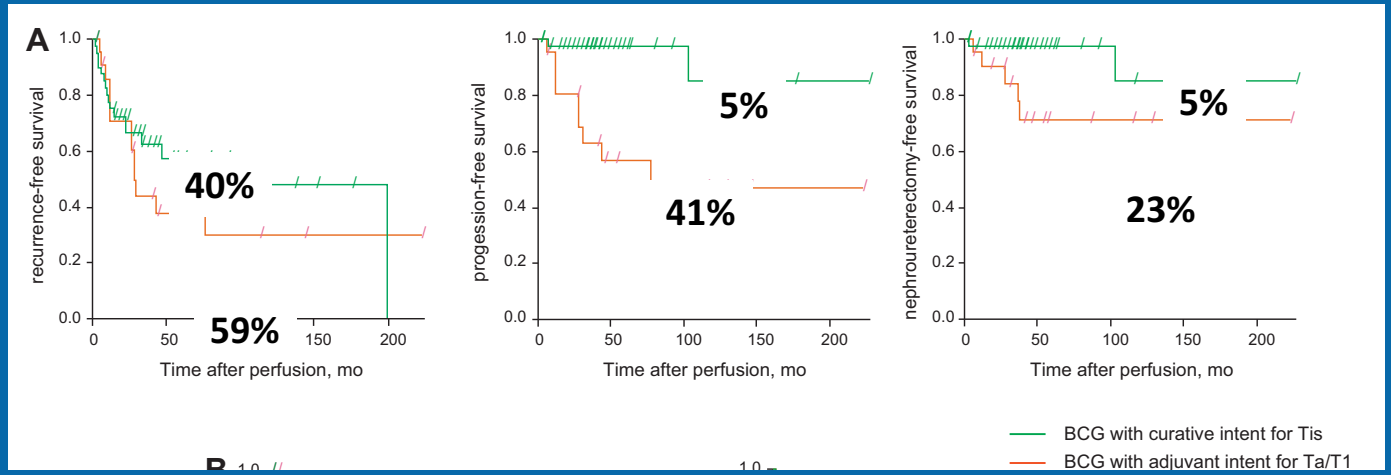
Intravesical or Percutaneous MMC Chemotherapy

- Risk factors for recurrence: grade, size, multifocality, prior bladder cancer Hx
- 28 pts treated with intravesical (71%) or percutaneous (29%) MMC for LG (N = 21) and HG (N = 7) UTUC
- 6 weeks induction + monthly (MMC)
- 3-Yr PFS: 67% (HG), 87% (LG)
- 3-Yr Kidney Preservation: 67% (HG), 82% (LG)



Wagenheim G et al. 2016 ASCO GU Cancer Symposium

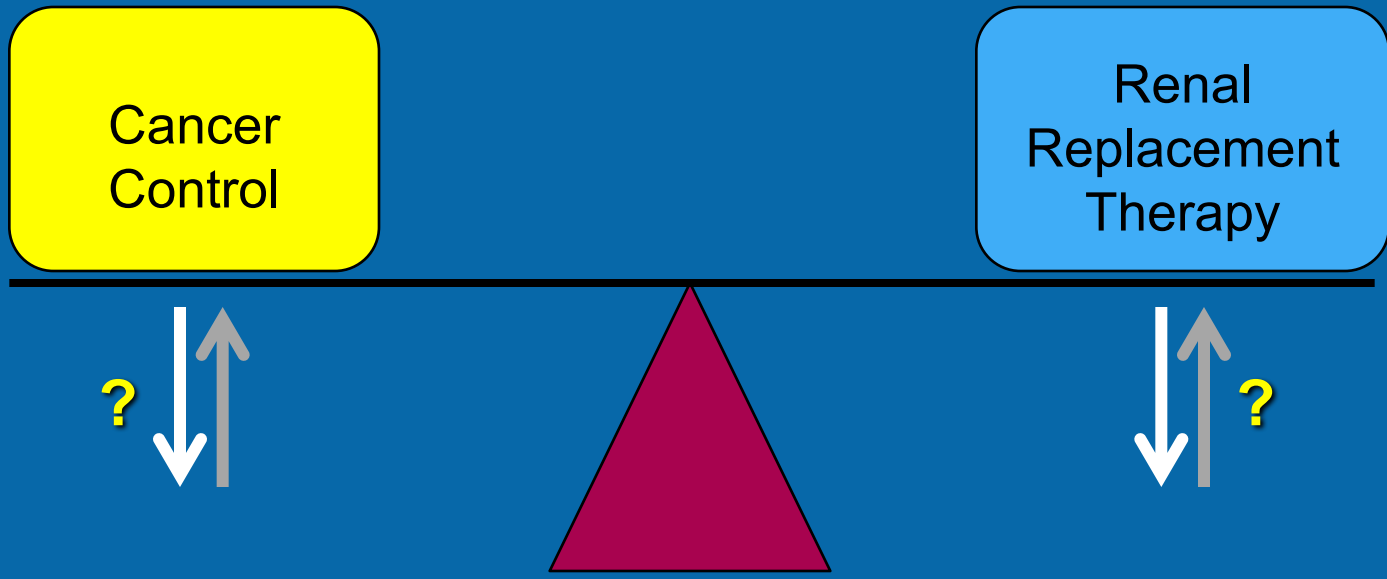
Percutaneous BCG for UTUC: Unproven



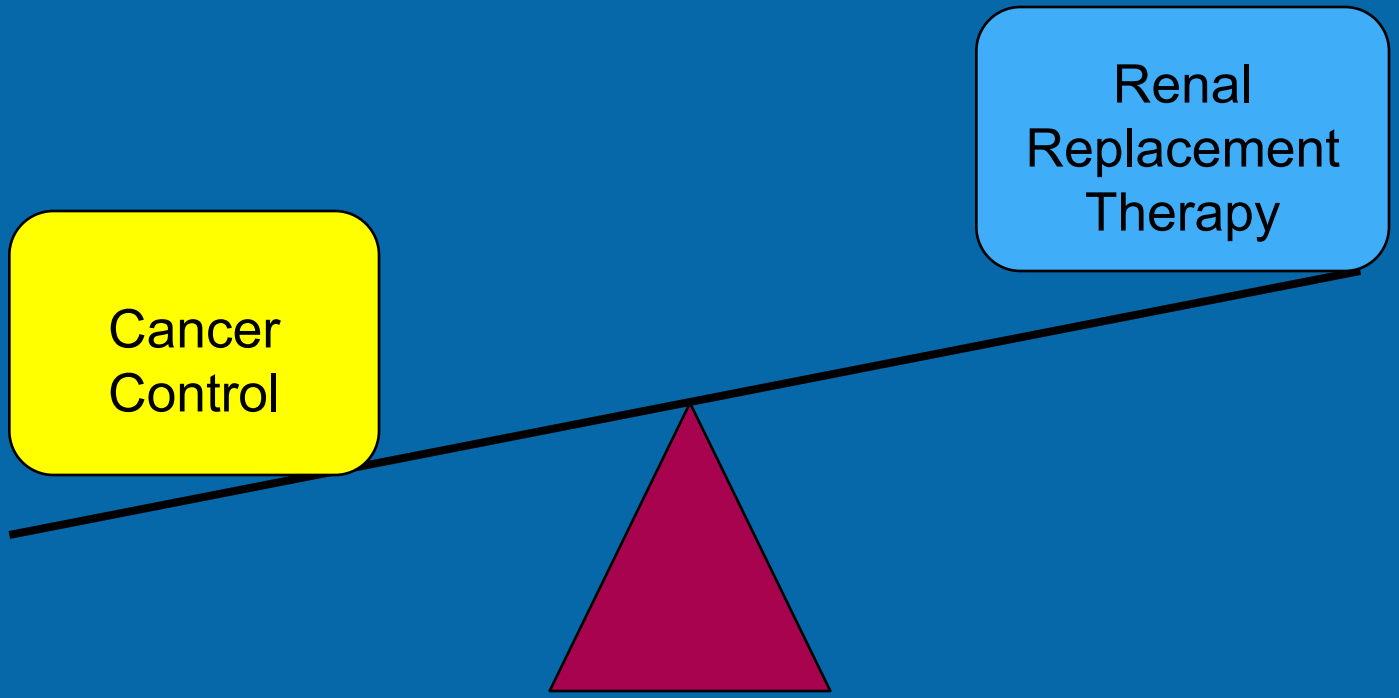
- N = 55, median FU 42 mos
- High rate of kidney preservation despite high recurrence rate → uncertain benefit

Giannarini G et al. *Eur Urol* 2011

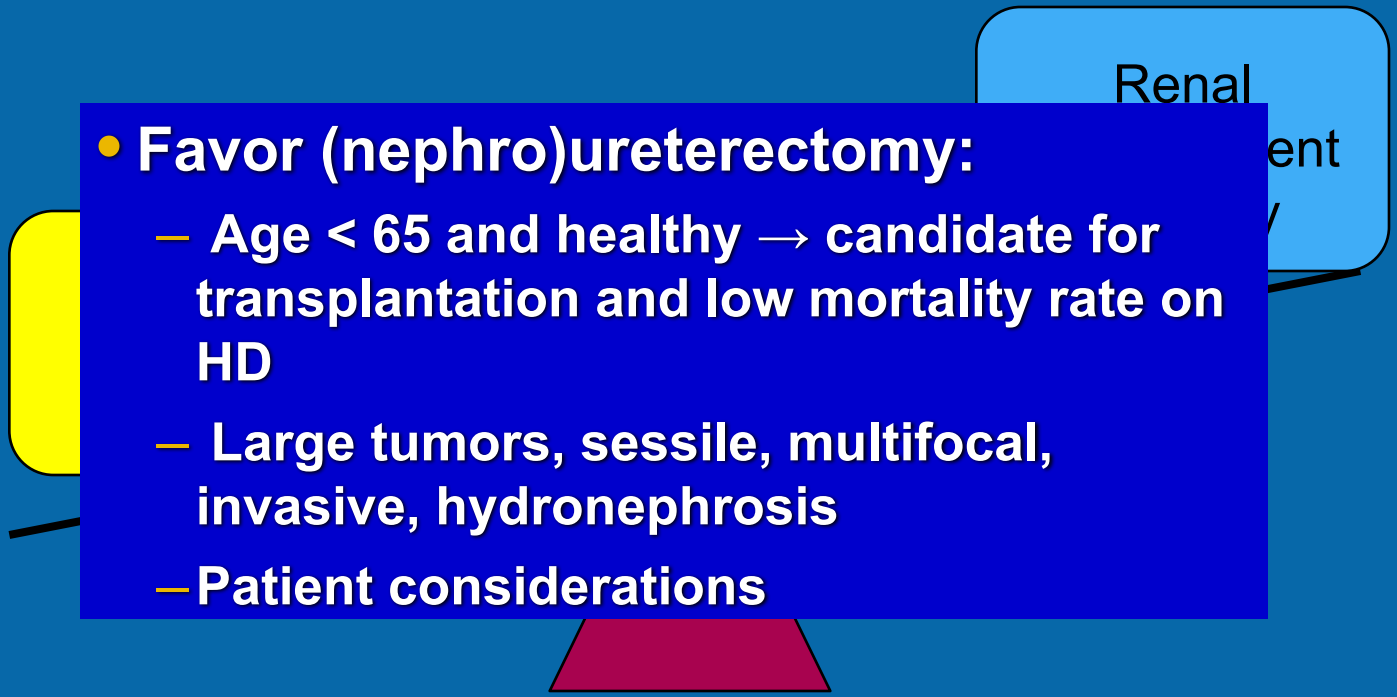
HG Upper Tract Urothelial Carcinoma, Solitary Kidney



HG Upper Tract Cancer, Solitary Kidney: NephroU

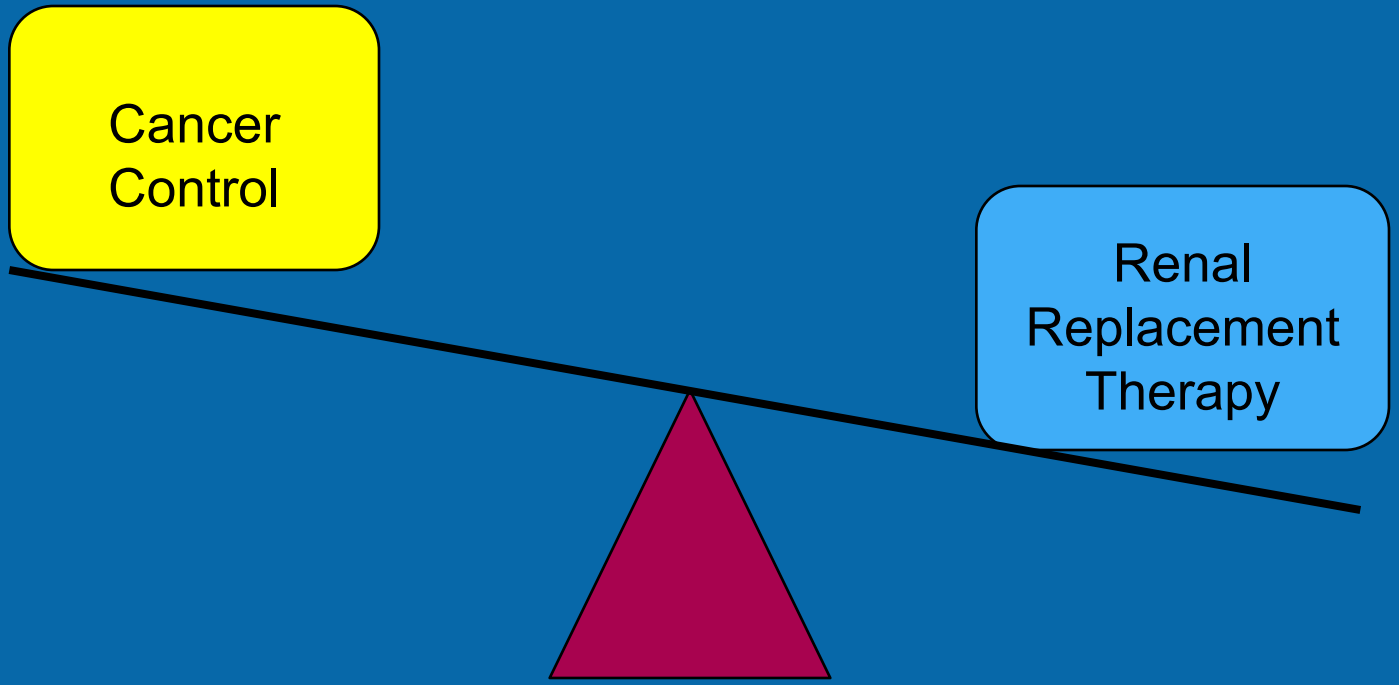


HG Upper Tract Cancer, Solitary Kidney: NephroU



- **Favor (nephro)ureterectomy:**
  - **Age < 65 and healthy → candidate for transplantation and low mortality rate on HD**
  - **Large tumors, sessile, multifocal, invasive, hydronephrosis**
  - **Patient considerations**

HG Upper Tract Cancer, Solitary Kidney: Endoscopy



HG Upper Tract Cancer, Solitary Kidney: Endoscopy

- **Favor endoscopic management:**
  - Age > 65-70 and presence of comorbid illness (diabetes, cardiovascular disease, obesity, smoking) → ↑↑↑ mortality rate on HD
  - Small, unifocal, papillary tumor amenable to complete resection
  - Patient considerations

Optimal Management of UTUC

- Treatment paradigms parallel those of bladder cancer
- Low-grade → organ preservation
- High-grade → organ removal ± multimodal therapy

Optimal Management of UTUC

- Cancer- and patient-related factors should be considered when selecting the best Rx strategy
- Normal renal function, normal contralateral kidney
  - NU and RPLND/PLND is gold-standard → consider postop intravesical chemo, consider neoadjuvant chemo for large high-grade cancer or suspicion of invasion
  - Endoscopic management may be considered for < 1 cm TaLG
- Solitary kidney, poor renal function
  - NU and RPLND/PLND for young, healthy pts → HD, transplant
  - Endoscopic management appropriate for older pts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Every life deserves world class care.