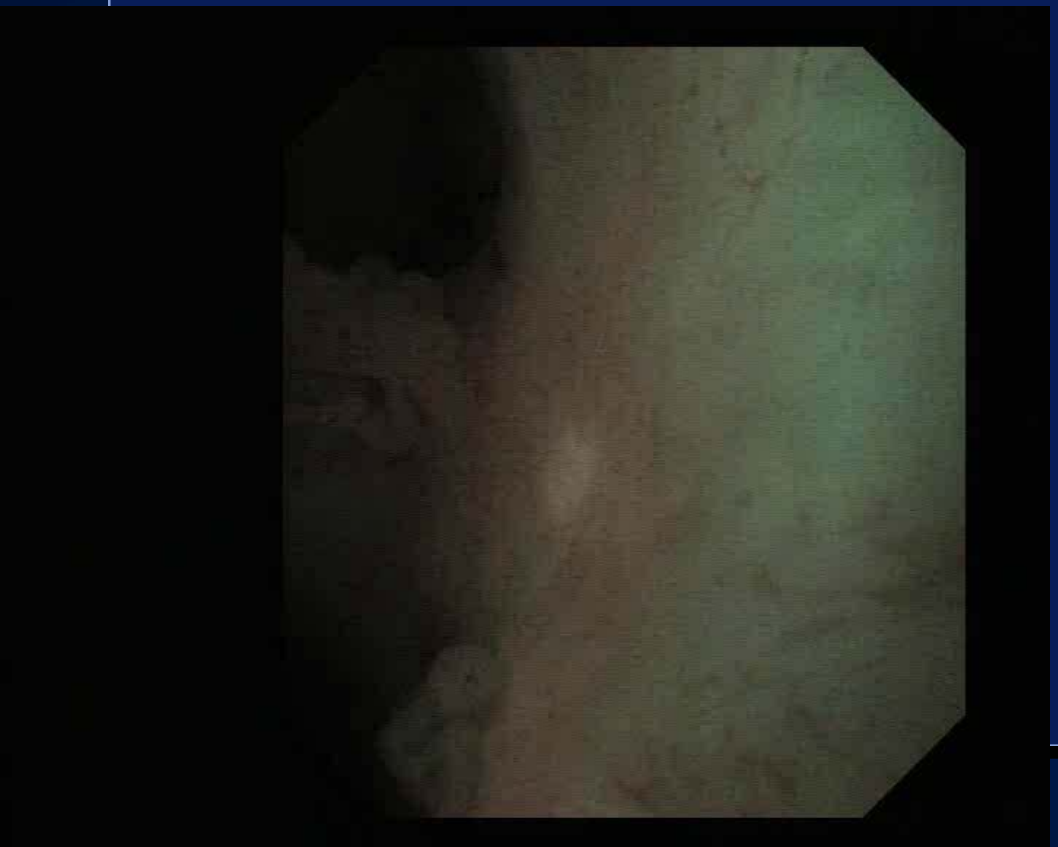
Lessons Learned in 15 years of Minimal Access Management of UTTCC



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Lessons Learned…

1. …from data & the literature
2. …from colleagues
3. …from patients
4. …from bitter (& sweet) personal experience

Background

- Standard treatment is NU
- No improvement in outcomes over 20 yrs*
- Lesson from the literature: there is no 'gold standard'

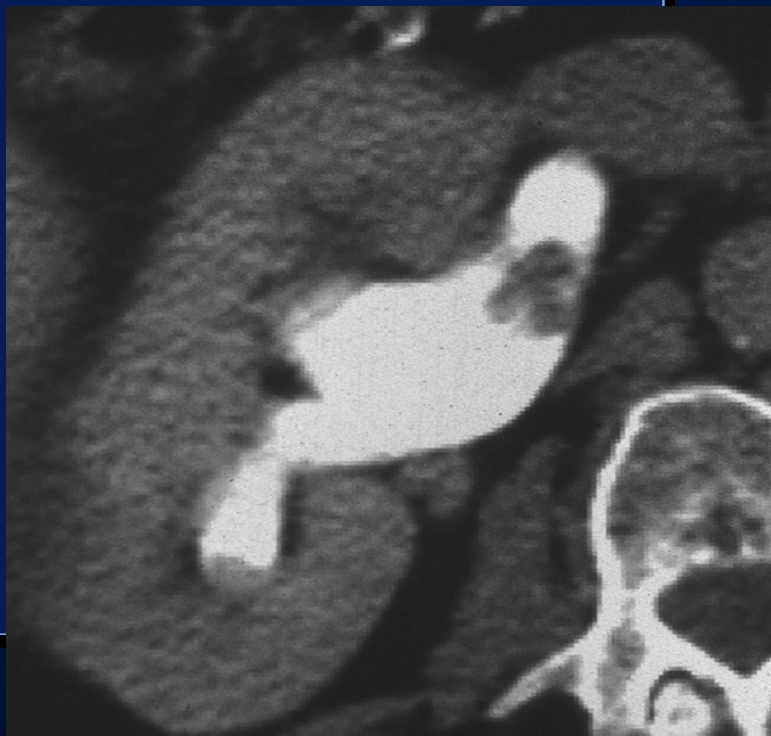
Discussion points:

- Advances in URS
- Nephron-sparing surgery
- Adjuvant Rx

*Brown et al. BJUI 2006

Case 1: 67 y.o. woman

- Investigated for visible hematuria
- Short for her weight
- Previous laparotomy x 4
- Normal renal function
- Cystoscopy: nl
- Cytology: negative
- CT urogram



Case #1: Questions

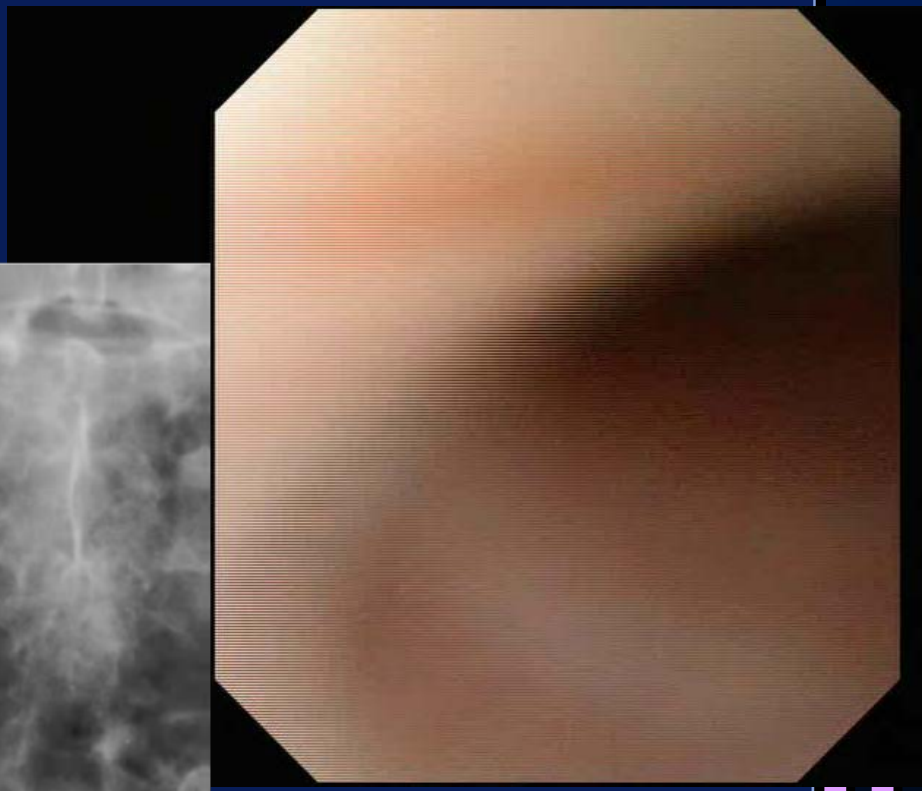
- Is the diagnosis in doubt?
- Is ureteroscopy necessary?
  - NU is standard Rx (nl contralateral kidney)
- A similar finding in the urinary bladder would be treated endoscopically
- Why not treat UTTCC like bladder TCC?
- What further information is needed?

Case #1: Answers

- Biopsy: Grade 2; Negative cytology from ureter
- Treated endoscopically in 2005
- Several recurrences in renal pelvis and bladder
- Alive and well
- Extremely happy to keep her kidney and travel long distance for endoscopic surveillance
- Lesson learned: Challenge the ‘gold standard’

Diagnosis: Technique

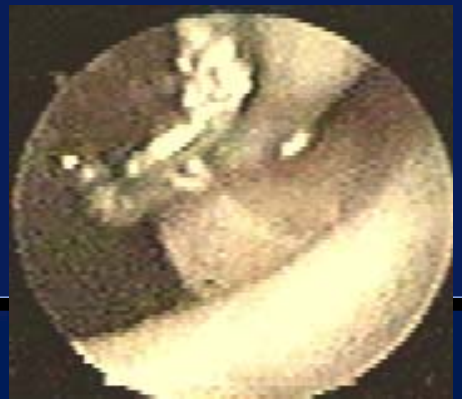
- Upper tract urine sample for cytology
- Retrograde
- Rigid & flexible ureteroscopy to inspect entire collecting system
- 'No touch' technique

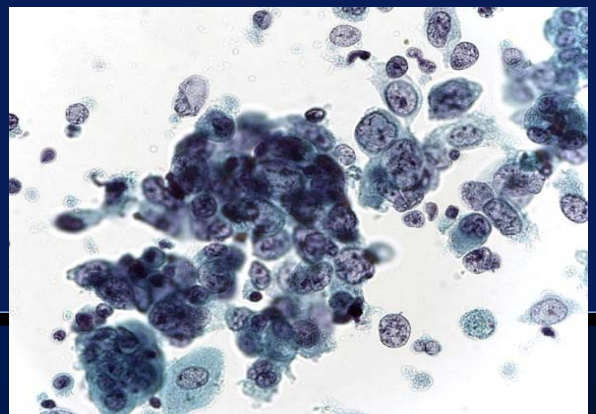


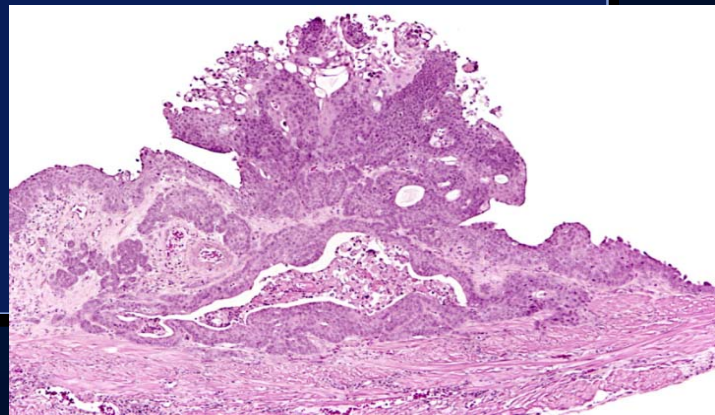
Diagnosis: Biopsy

- Flat wire basket or biopsy forceps
- Histology: 'The specimen did not survive'
- All specimens to cytology
  - Fragments stained & graded
- Case biopsy: G2 pTx
- Clinical staging very limited

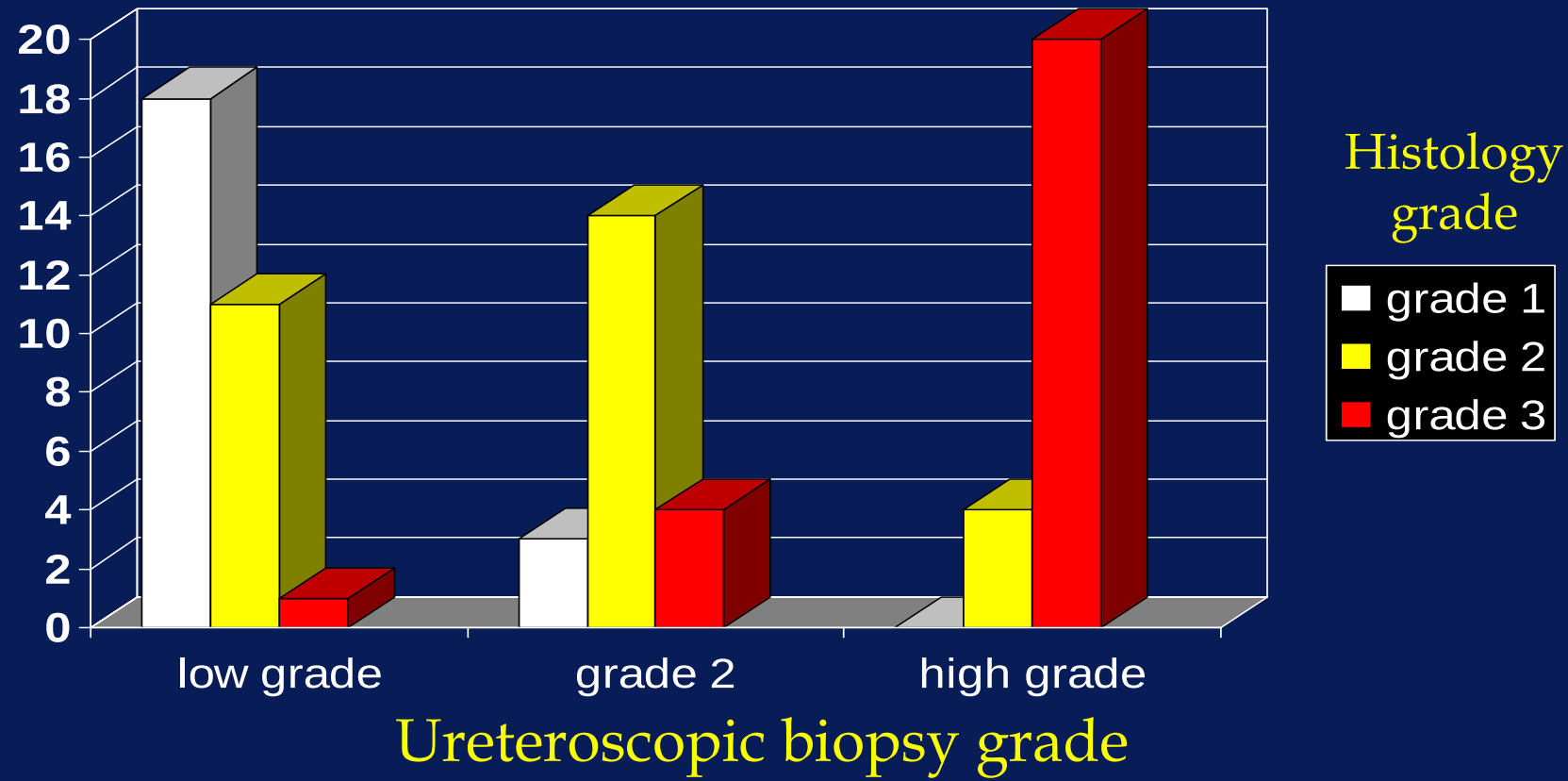
Q: Can biopsies determine grade and stage?







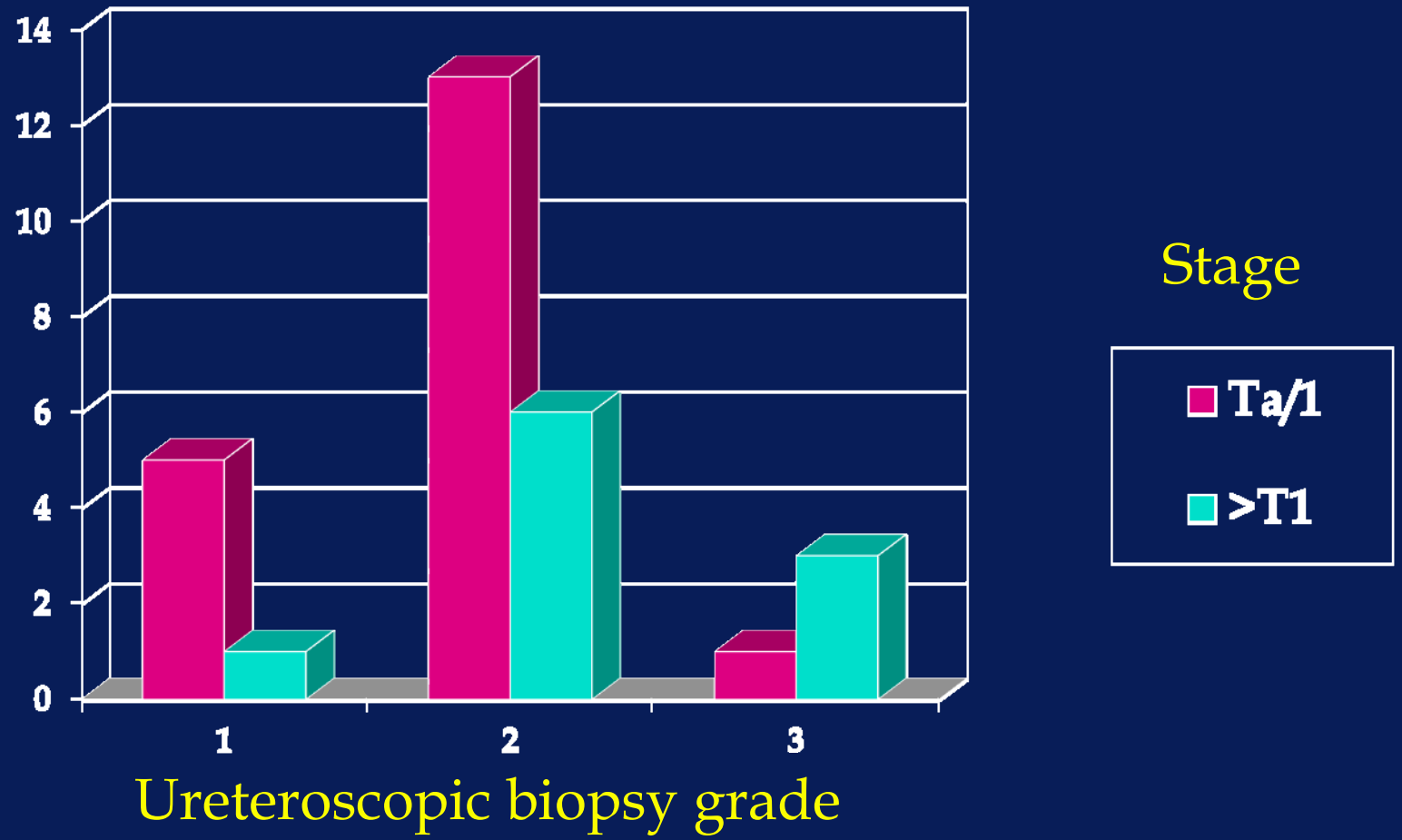
Biopsy Grade vs. Histology Grade



Lesson learned: UTTCC can be heterogeneous, especially if larger

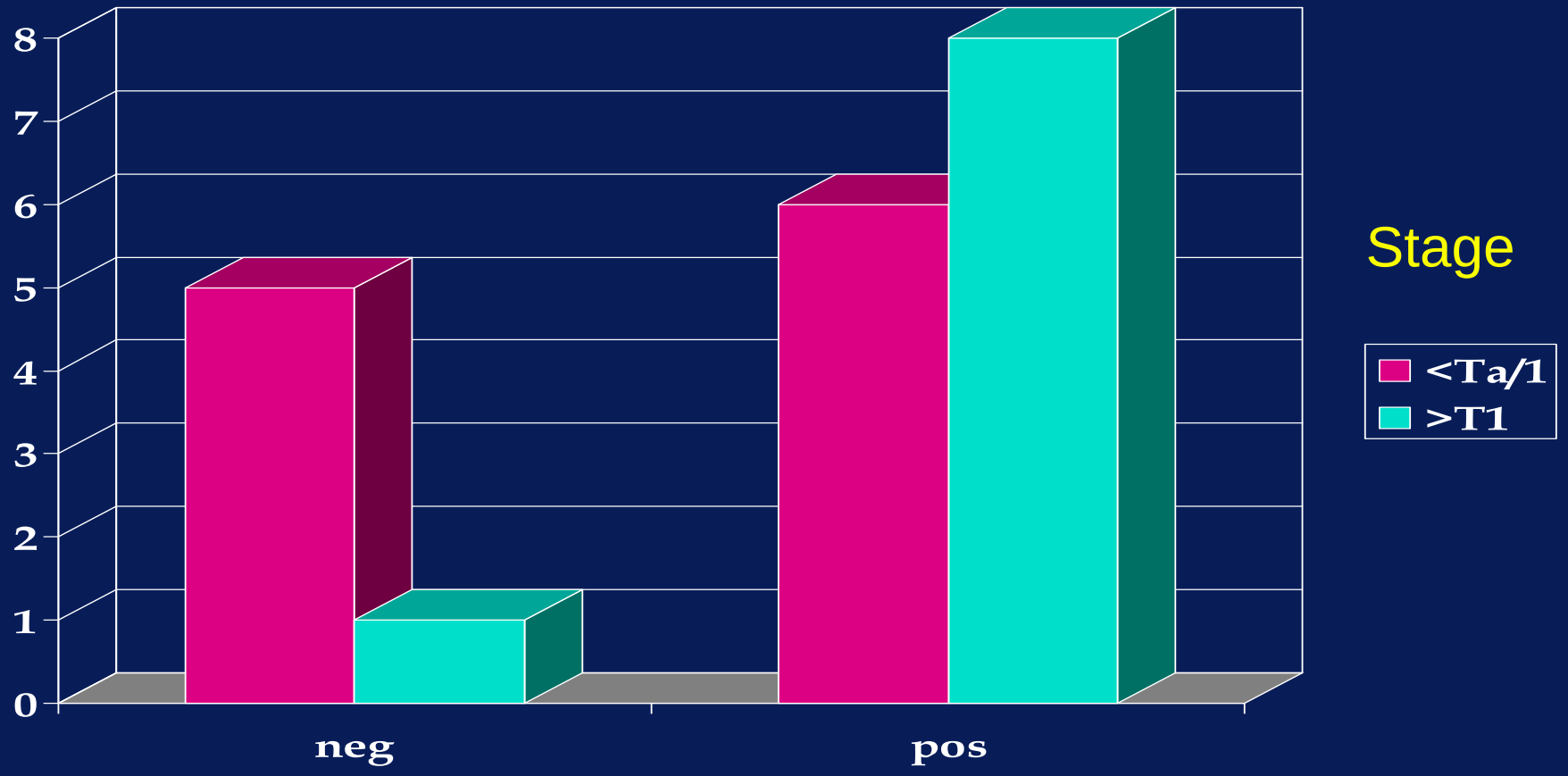
Keeley, Kulp, Bibbo, Bagley J Urol 1997

Biopsy Grade vs. Histology Stage



Williams, Minervini, Denton, Keeley, Timoney. J Endourol 2008.

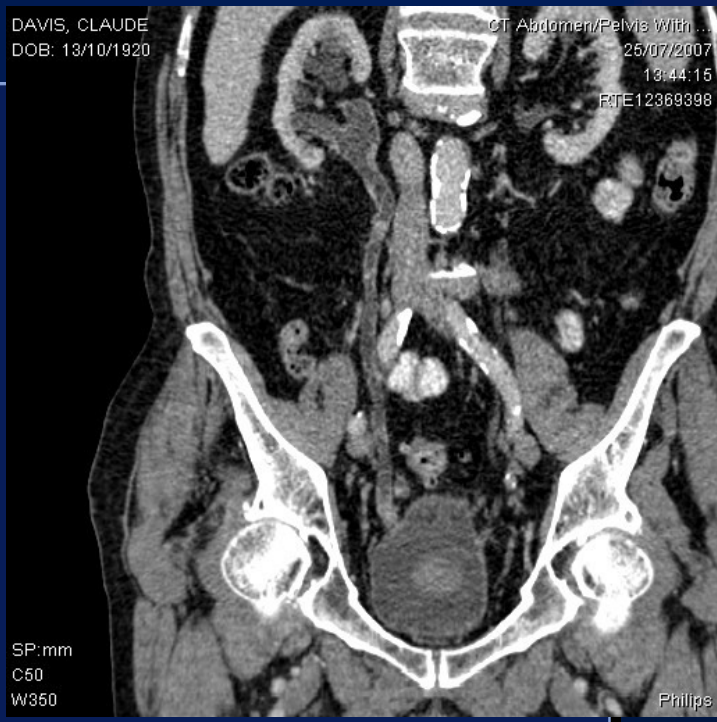
Biopsy Grade vs. Stage: Grade 2 +/- positive cytology

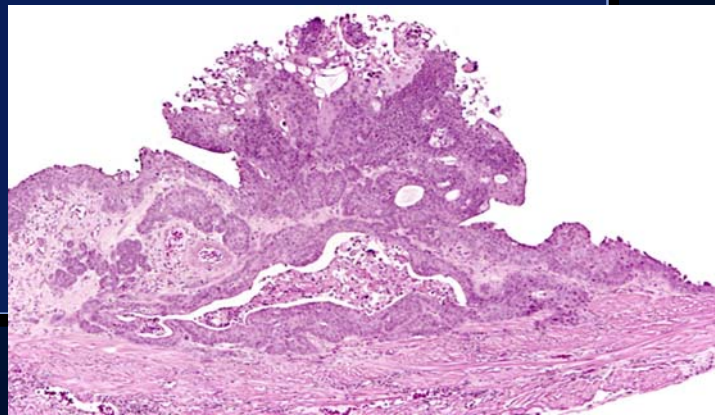


Williams, Minervini, Denton, Keeley, Timoney. J Endourol 2008

Predicting Stage

- Clinical staging (CT):
  - Hydronephrosis
  - Local invasion
  - Lymphadenopathy
  - Insensitive for early stage
- Histology: Limited pathological staging
  - Grade
  - Cytology





Diagnosis, Grading, and Staging

- Diagnosis essential before therapy
- Endoscopic biopsy allows grading
- Staging poor
- Grade correlates closely with stage
- Lesson learned: tissue essential
- Just like a good TURBT

Why biopsy an obvious tumor?

- Lesson learned: some are benign
- NU without biopsy carries risk

What's New in Ureteroscopy?

Narrow Band Imaging

- 2 discrete bands of light
  - Blue at 415nm
  - Green at 540nm
- Blue light displays superficial capillaries
- Green light displays subepithelial vessels
- Lesson learned: keep up with new technology

TREATMENT

Q: Should we treat upper tract TCC just like bladder cancer?

Indications for Organ Preserving/ Conservative Treatment

- Imperative
- Relative
- Elective
- Palliative

Indications for Organ Preserving/ Conservative Treatment

- Imperative
- Solitary kidney
- Bilateral tumors
- Poor renal function

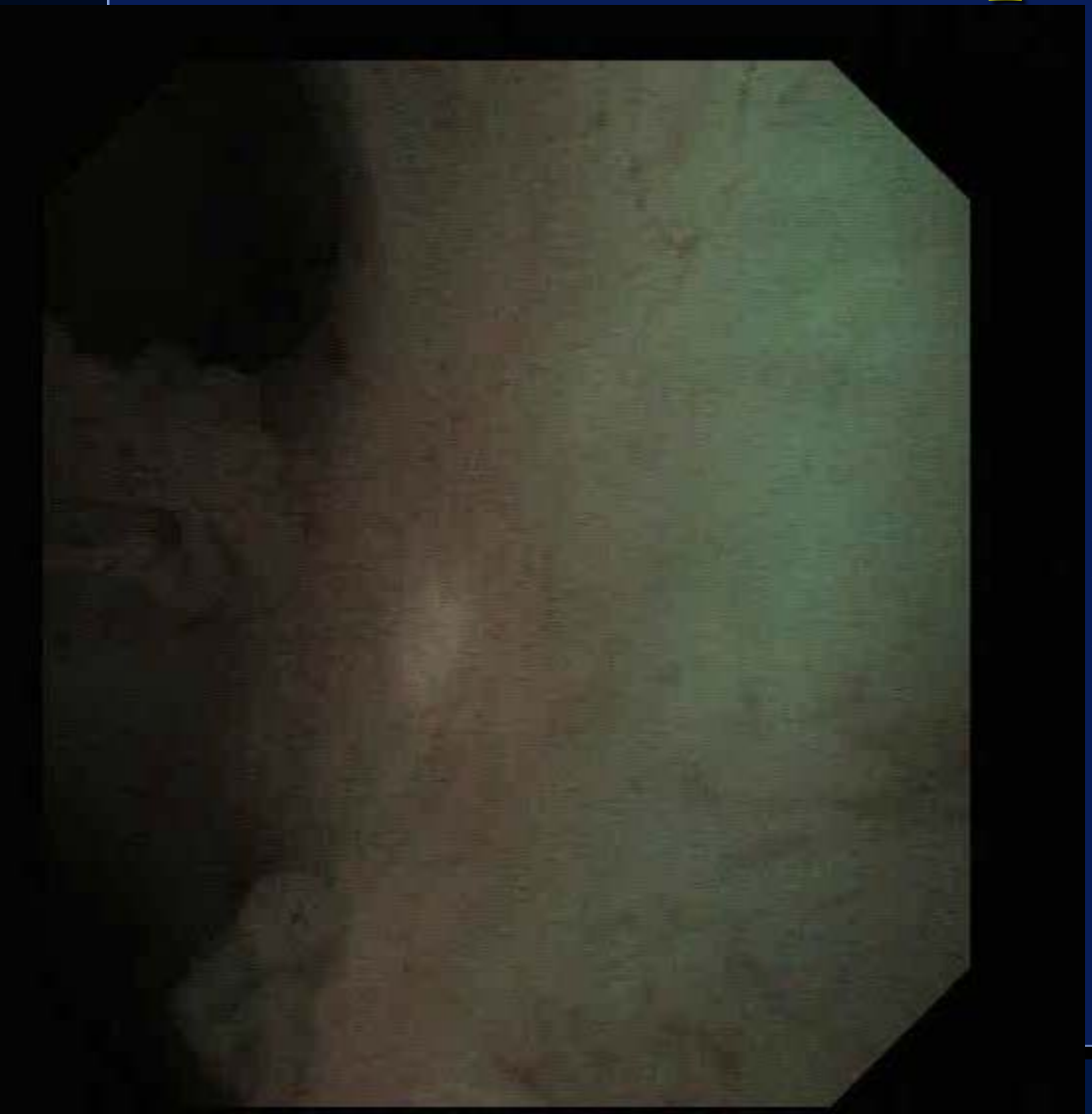
Indications for Organ Preserving/ Conservative Treatment

- Relative:
- High surgical risk
- Moderate renal impairment

Indications for Organ Preserving/ Conservative Treatment

- Elective
- 2 normal kidneys
- Low-grade, low-stage tumor
- Not multifocal
- Reasonable volume

Technique: Treatment



- Nd:YAG to coagulate
- Ho:YAG to ablate
- Repeat as necessary
- Avoid Nd in the ureter
- Avoid circumferential treatment in ureter

Surveillance Schedule

- Second look at 6 weeks
- Rigid and flexible ureteroscopy
  - Three-month intervals for first year
  - Six-month intervals for second year
  - Annually thereafter
- CT urogram annually
- Tailored to the individual depending on stage, grade, and indication
- Lesson learned: Get buy-in from patient
- Lesson learned: Not evidence based

Ureteroscopic Treatment: Outcome

Over 10 year period, 92 pts diagnosed

- 54 had nephroureterectomy
- 38 patients (41 kidneys) treated and followed endoscopically

Keeley Bibbo Bagley J Urol 1997

Patient Selection: Indications

Absolute	***# of patients***
Solitary kidney	7
Bilateral tumors	8
Renal insufficiency	2
Total Absolute	***17 (20 kidneys)***
Relative	
High surgical risk	***8***
Elective	
Low-grade disease	7
Patient choice	4
Total Elective	***11***
Palliative	***2***

Results: Philadelphia

- Mean follow-up 35 mo. (range, 3-116)
- > 200 procedures; > 90 treatments
- Tumor grading possible in 40/41 pts
- No local progression (grade or stage)
- No metastatic disease
- No cancer mortality

Keeley, Bibbo, Bagley J Urol 1998

Tumor Size

Size	N	tumor-free(%)	recur (%)	NED (%)
< 1.5 cm	22	20 (91)	5 (25)	20 (91)
> 1.5 cm	19	8 (42)	3 (37)	4 (21)

Keeley, Bibbo, Bagley J Urol 1998

Early Results: Bristol

- 33 elective endoscopic treatment
  - 12 delayed NUx after median 6 mo.
- 21 kept their kidneys
  - F/U 6 – 121 mo. (median 21)
  - No metastatic disease
- Bitter lesson learned: do not manage high-grade disease endoscopically
- Since 2006, we restricted endoscopic treatment to low-grade TCC

Painter, Denton, Timoney, Keeley J Endourol 2008

Bristol Update

- 1998-2006
- 33 patients
- 12 NUx
- 21 (63%) had NSS
- No metastatic disease

- 2006-2012
- 21 patients
- 1 Nux, 1 distal Ux
- 20 (95%) had NSS
- No metastatic disease

Adjuvant Therapy

- Survival post NU poor for high-grade disease
  - Has not improved with time

  Brown et al, BJUI 2006
- Local adjuvant therapy:
  - BCG
  - MMC
  - Radiotherapy
- Systemic chemotherapy
- No evidence of benefit from any of above

BCG Complications

- Fever in 39%
- Granulomas in up to 25%
  - Can lead to ureteral stricture
- BCG sepsis
- Bacterial sepsis

Adjuvant Mitomycin C

- Q: Why not treat just like bladder cancer?
- 19 pts. had 28 treatments
- Multifocal, recurrent tumors
- MMC in 3 doses instilled via 6F catheter
- Given the day after URS
- Compared to historical controls

Keeley, Bagley J Urol 1998

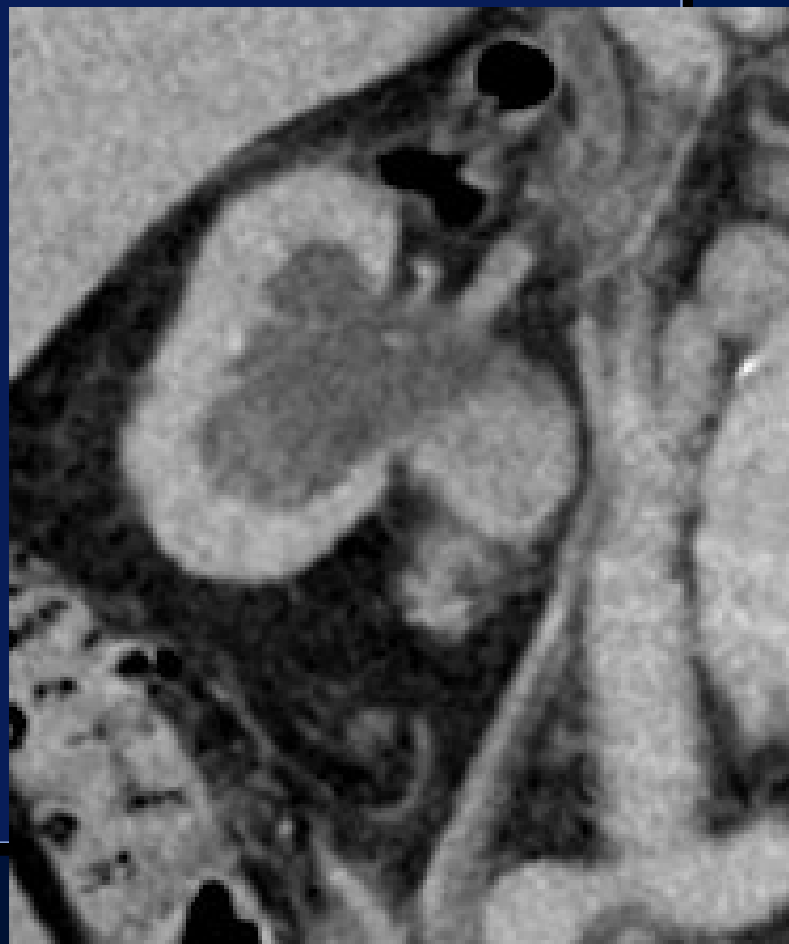
Adjuvant Mitomycin C

- Results: No systemic toxicity
  - 12/19 (63%) rendered disease-free
  - Better than historical control group
  - 37% recurred
  - No progression (mean FU = 26 mo)
- Conclusions: MMC safely given via catheter
  - Little hospitalization, no nephrostomy
- Lessons learned: ureteric strictures with BCG, MMC; BCG sepsis when given through nephrostomy; aplastic anemia
- Lesson learned: the anatomy of the upper tract does not allow for contact time or a safety margin

Keeley, Bagley J Urol 1998

Case 2: 74 y.o. Male

- Visible hematuria
- Normal renal function
- Cystoscopy: nl
- Cytology: suspicious
- CT urogram: clinical stage T2/3
- Retrograde




Abdomen with contrast
LIH 2
13.10.10
10.51
/2
274cGy cm²
ID: 20101013104146
SOUTHMEAD HOSPITAL
Siemens

Stage and Grade

- Clinical stage:
  - Biopsy: Grade 3, stage T2/3
- Laparoscopic nephroureterectomy
- Pathological grade and stage:
  - Grade 3, stage pT3, N0
- Q: How did endoscopic biopsy help?
- A: We would never do a cystectomy without tissue; over 10% of histology from NU is benign

What is the role of endoscopic biopsy when the imaging suggests an obvious TCC of the upper tract?

- My advice:

'Whenever there is an issue, get some tissue.'

Unanswered Questions

- Does he need a tissue diagnosis?
- What is the role of laparoscopy?
- ... Or lymphadenectomy?
- Why is prognosis so poor for high risk patients?
- What is the role of adjuvant or neo-adjuvant therapy?

POUT

- Adjuvant gemcytabine + cisplatin (or carboplatin) v observation
- Is this the right question?
- Will we be able to answer it?
- Should we study neo-adjuvant treatment?
- Oncologists say no due to lack of histology
- Combination of biopsy grade and imaging staging predicts invasive TCC
- Two kidneys are better than one for cisplatin
- Lesson learned: questiong the ‘gold standard’

Upper Tract TCC: Conclusions

- Late presentation, delayed diagnosis make endoscopic treatment inappropriate for many
- Accurate grading, effective endoscopic treatment possible
- Essential aspects of endoscopic treatment:
  - Proper patient selection
  - Accurate grading
  - Rigorous follow-up

Quiz

Q: Should we treat upper tract TCC just like bladder cancer?

A: NO

Q: Is nephroureterectomy the only effective treatment for upper tract TCC:

A: NO

- Lesson learned: There are many unanswered questions in UTTCC