Bladder Cancer
Upper Tract Urothelial Carcinoma
Advanced Kidney Cancer

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Director of Clinical Research
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Outline

• NMIBC
  – Risk adapted strategy
  – AUA guidelines

• Muscle invasive bladder cancer
  – AUA Guidelines
  – Perioperative chemotherapy
  – Perioperative management
  – Bladder sparing protocols
Outline

- Upper Tract Urothelial Carcinoma
  - Endoscopic management
  - Management of high grade disease
  - Perioperative chemotherapy

- Advanced Kidney Cancer
  - Role of cytoreductive nephrectomy
  - Role of Metastatectomy
  - Adjuvant trials

NCCN Guidelines Version 2.2016 Bladder Cancer

- APPROXIMATE PROBABILITY OF RECURRENCE

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Approximate Probability of Recurrence in 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ta, low grade</td>
<td>50%</td>
</tr>
<tr>
<td>Ta, high grade</td>
<td>60%</td>
</tr>
<tr>
<td>T1, low grade (rare)</td>
<td>50%</td>
</tr>
<tr>
<td>T1, high grade</td>
<td>50% - 70%</td>
</tr>
<tr>
<td>Tis</td>
<td>50% - 90%</td>
</tr>
</tbody>
</table>
Urinary marker tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMP22®</td>
<td>Protein-based</td>
<td>Identifies nuclear matrix protein involved in the mitotic apparatus</td>
</tr>
<tr>
<td>BTA®</td>
<td>Protein-based</td>
<td>Identifies a basement membrane antigen related to complement factor H</td>
</tr>
<tr>
<td>UroVysion® FISH</td>
<td>Cell-based</td>
<td>Identifies altered copy numbers of specific chromosomes using fluorescent probes</td>
</tr>
<tr>
<td>ImmunoCyt™</td>
<td>Cell-based</td>
<td>Identifies three cell surface glycoproteins</td>
</tr>
<tr>
<td>Cxbladder™</td>
<td>Cell-based</td>
<td>Identifies the presence of five mRNA fragments</td>
</tr>
</tbody>
</table>

9. A clinician should not use urinary biomarkers in place of cystoscopic evaluation. (AUA Guidelines 2016, Strong Recommendation; Evidence Strength: Grade B)

* Performance of Urinary Marker Tests

Table 3 Measured and published sensitivity and specificity for each test in the integrated dataset before imputation, mean and 95% CIs.

<table>
<thead>
<tr>
<th>Test</th>
<th>Measured Sensitivity, % (95% CI)</th>
<th>Measured Specificity, % (95% CI)</th>
<th>Published Sensitivity, % (95% CI)</th>
<th>Published Specificity, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology</td>
<td>45.5 (40.6–50.4)</td>
<td>96.3 (94.5–97.9)</td>
<td>56.1 (50.3–62.0)</td>
<td>94.5 (91.9–96.3)</td>
</tr>
<tr>
<td>NMP22</td>
<td>44.9 (37.4–53.3)</td>
<td>88.0 (86.5–91.5)</td>
<td>50.0 (47.4–53.9)</td>
<td>88.0 (84.6–91.0)</td>
</tr>
<tr>
<td>FISH</td>
<td>40.0 (27.7–52.3)</td>
<td>87.3 (83.7–91.6)</td>
<td>72 (69–75)</td>
<td>83 (82–85)</td>
</tr>
<tr>
<td></td>
<td>61.9 [23]</td>
<td>89.7 [23]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cxbladder Detect</td>
<td>79.5 (71.1–87.8)</td>
<td>80.2 (79.2–85.0)</td>
<td>81.8 [18]</td>
<td>85.1 [fixed] [16]</td>
</tr>
</tbody>
</table>

* Cxbladder negative predictive value 97-98%

### Grade and Stage

- **Tumor grade** is an important prognostic factor for determining risk of recurrence and progression in bladder cancer.

- **The WHO/ISUP 2004 grading system** is now the most widely accepted and utilized system in the United States.

#### 2004 World Health Organization/ International Society of Urologic Pathologists: Classification of Non-muscle Invasive Urothelial Neoplasia

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperplasia (flat and papillary)</td>
<td></td>
</tr>
<tr>
<td>Reactive atypia</td>
<td></td>
</tr>
<tr>
<td>Atypia of unknown significance</td>
<td></td>
</tr>
<tr>
<td>Urothelial dysplasia</td>
<td></td>
</tr>
<tr>
<td>Urothelial CIS</td>
<td></td>
</tr>
<tr>
<td>Urothelial papilloma</td>
<td></td>
</tr>
<tr>
<td>Papillary urothelial neoplasm of low malignant potential (PUNLMP)</td>
<td></td>
</tr>
<tr>
<td>Non-muscle invasive low-grade papillary urothelial carcinoma</td>
<td></td>
</tr>
<tr>
<td>Non-muscle invasive high-grade papillary urothelial carcinoma</td>
<td></td>
</tr>
</tbody>
</table>

#### Staging of primary tumors (T) in bladder cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>Ta</td>
<td>Noninvasive papillary carcinoma</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ (CIS)</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor invades lamina propria</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades muscularis propria</td>
</tr>
<tr>
<td>T2a</td>
<td>Tumor invades superficial muscularis propria (inner half)</td>
</tr>
<tr>
<td>T2b</td>
<td>Tumor invades deep muscularis propria (outer half)</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades perivesical tissue/fat</td>
</tr>
<tr>
<td>T3a</td>
<td>Tumor invades perivesical tissue/fat microscopically</td>
</tr>
<tr>
<td>T3b</td>
<td>Tumor invades perivesical tissue fat macroscopically (extravesical mass)</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invades prostate, uterus, vagina, pelvic wall, or abdominal wall</td>
</tr>
<tr>
<td>T4a</td>
<td>Tumor invades adjacent organs (uterus, ovaries, prostate stoma)</td>
</tr>
<tr>
<td>T4b</td>
<td>Tumor invades pelvic wall and/or abdominal wall</td>
</tr>
</tbody>
</table>
Regional Lymph Nodes (N)

Regional lymph nodes include both primary and secondary drainage regions. All other nodes above the aortic bifurcation are considered distant lymph nodes.

NX  Lymph nodes cannot be assessed
N0  No lymph node metastasis
N1  Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)
N2  Multiple regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node metastasis)
N3  Lymph node metastasis to the common iliac lymph nodes

AUA Risk Stratification

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>LG² solitary Ta ≤ 3cm</td>
<td>Recurrence within 1 year, LG Ta</td>
<td>HG T1</td>
</tr>
<tr>
<td>PUNLMPᵇ</td>
<td>Solitary LG Ta &gt; 3cm</td>
<td>Any recurrent, HG Ta</td>
</tr>
<tr>
<td></td>
<td>LG Ta, multifocal</td>
<td>HG Ta, &gt;3cm (or multifocal)</td>
</tr>
<tr>
<td></td>
<td>HG³ Ta, ≤ 3cm</td>
<td>Any CIS⁴</td>
</tr>
<tr>
<td>LG T1</td>
<td>Any BCG failure in HG patient</td>
<td>Any variant histology</td>
</tr>
<tr>
<td></td>
<td>Any LVIf</td>
<td>Any HG prostatic urethral involvement</td>
</tr>
</tbody>
</table>

²LG = low grade; ⁣ᵇPUNLMP = papillary urothelial neoplasm of low malignant potential; ³HG = high grade; ⁴CIS = carcinoma in situ; ⁵LV = lymphovascular invasion
Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline

Sam S. Chang, Stephen A. Boorjian, Roger Chou, Peter E. Clark, Siamak Daneshmand, Badrinath R. Konety, Raj Pruthi, Diane Z. Quale, Chad R. Ritch, John D. Seigne, Elia Curlee Skinner, Norm D. Smith and James M. McKiernan

From the American Urological Association Education and Research, Inc., Linthicum, Maryland

Systematic review of all relevant published literature and 38 statements covering principles of management based on body of evidence strength, level of certainty, magnitude of benefit or risk/burden, and the Panel's judgment

NMIBC

- Papillary tumors confined to mucosa (Ta)
- Tumors involving subepithelial tissue- lamina propria (T1)
- Carcinoma in-situ (CIS)

Adjuvant therapy

- Immediate postop intravesical chemotherapy
  - Thought to eliminate implantation of tumor cells
- Given within 24 hours after TURBT
- Randomized studies demonstrate an 11.7% decrease in recurrence rate using a single post TURBT dose of chemotherapy (mito C, doxorubicin, epirubicin)
- Primary and solitary tumors benefit most, guideline recommendations are for all post TURBT
  - Do not give if perforation is suspected
  - NEVER give BCG in the immediate post TURBT setting
AUA Guidelines- Diagnosis

3. In a patient with a history of NMIBC with normal cystoscopy and positive cytology

- Prostatic urethral biopsies and upper tract imaging

- Enhanced cystoscopic techniques (blue light cystoscopy, when available), ureteroscopy, or random bladder biopsies. (Expert Opinion)

AUA Guidelines- Variant Histology

6. If a bladder sparing approach is being considered, should perform a restaging TURBT within 4-6 weeks of the initial TURBT. (Expert Opinion)

7. Due to the high rate of upstaging associated with variant histology, a clinician should consider offering initial radical cystectomy. (Expert Opinion)

There is a lack of evidence regarding the efficacy of intravesical therapy for NMIBC with variant histology.
Histopathology

- **Variant cell types and growth patterns**
  - Squamous cell differentiation
  - Glandular differentiation
  - Small cell (neuroendocrine)
  - Signet cell
  - Sarcoma
  - Plasmacytoid cell
  - Micropapillary
  - Nested

Small cell carcinoma

- ~1% of bladder tumors
- Chromogranin A, synaptophysin, neuron specific enolase stains useful for diagnosis
- Poor outcomes, high relapse rates after treatment
- Treated with **cisplatin/etoposide**
Micropapillary

• Most commonly found in association with high grade invasive UC

• Rare component but increasingly recognized

• Associated with aggressive disease

AUA Guidelines Urine markers

9. A clinician should not use urinary biomarkers in place of cystoscopic evaluation. (Strong Recommendation; Evidence Strength: Grade B)

10. In a patient with a history of low-risk cancer and a normal cystoscopy, a clinician should not routinely use a urinary biomarker or cytology during surveillance. (Expert Opinion)
12. HG Ta tumors - should **consider** repeat TURBT within 6 weeks (Mod Rec; Grade C)

13. T1 disease - should repeat TURBT to include muscularis propria within 6 weeks (Strong Rec; Grade B)

Post TUR gemcitabine - SWOG S0337

- 406 eligible patients post TUR Gem vs saline
  - 37% recurrent tumors
  - 68% solitary tumors

- Intent to treat:
  - HR 0.66 - recurrence at 4 years
  - LG tumors only: HR 0.5

- G3 toxicity
  - 2.4% gemcitabine
  - 3.5% saline

Messing, EM.  JAMA 2018; 319(18):1880.
AUA Guidelines- Intravesical therapy

16. In a low-risk patient, a clinician should not administer induction intravesical therapy. (Mod Rec; Grade C)

17. In intermediate-risk - 6 week course of induction intravesical chemotherapy or immunotherapy. (Mod Rec; Grade B)

18. In a high-risk patient with newly diagnosed CIS, high-grade T1, or high-risk Ta urothelial carcinoma - 6 weeks course of BCG. (Strong Rec; Grade B)

19. In an intermediate- or high-risk patient with persistent or recurrent Ta or CIS disease after a single course of induction intravesical BCG, a clinician should offer a second course of BCG. (Mod Rec; Grade C) *** Not more than 2 courses

20. Maintenance BCG
   - Intermediate risk - min 1 year
   - High risk – 3 years

AUA Guidelines- HGT1 disease

22. In a patient fit for surgery with high-grade T1 disease after a single course of induction intravesical BCG, a clinician should offer radical cystectomy. (Mod Rec; Grade C)

23. In a high-risk patient who is fit for surgery with persistent high-grade T1 disease on repeat resection, or T1 tumors with associated CIS, LVI, or variant histologies, a clinician should consider offering initial radical cystectomy. (Mod Rec; Grade C)

24. In a high-risk patient with persistent or recurrent disease within one year following treatment with two induction cycles of BCG or BCG maintenance, a clinician should offer radical cystectomy. (Mod Rec; Grade C)
AUA Guidelines- Enhanced Cystoscopy

30. Should offer blue light cystoscopy at the time of TURBT, if available, to increase detection and decrease recurrence. (Mod Rec; Grade B)

31. May consider use of NBI to increase detection and decrease recurrence. (Conditional Rec; Grade C)

Daneshmand, Nature Reviews Urology 2014
Staging

• The reported rate of post-surgical upstaging to EV disease is as high as 40%

• The false negative rate regarding nodal staging is even higher, up to 68%

• Hydronephrosis strong predictor of upstaging to extravesical disease and independent predictor of worse prognosis

Imaging

• CT with IV contrast or MRI
  – Evaluate upper tracts, lymphadenopathy

• Need chest imaging to rule out metastatic disease

• PET scan
  – 70% sensitivity and 90% specificity for LN mets not identified on CT or MRI
  – Limited in primary bladder stage- FDG pooled in bladder

• Bone scan only if clinically indicated (bone pain, ↑ alk phos)
Treatment

• Gold standard remains surgery +/- neoadjuvant chemotherapy

• Radical cystectomy

• Mainstay of local/regional therapy
  – **Male**: bladder, the perivesical fat, the prostate, the seminal vesicles and the prostatic urethra.
  – **Female**: (anterior pelvic exenteration): bladder, uterus, cervix, fallopian tubes, ovaries and the anterior vagina.

Radical cystectomy- Male

• Male: ~50% chance of cancer involvement of the prostate (either urothelial carcinoma or adenocarcinoma of the prostate)

• Total urethrectomy is rarely required
  – Vast majority of cases a negative urethral margin can be achieved
  – Pts with + urethral margin on final pathology can be considered for delayed urethrectomy

• A randomized trial showed no difference in complication rates between open and robotic cystectomy.
Radical cystectomy-female

- Reproductive organs often removed
  - Risk of involvement <10%
  - Vagina most commonly involved site

- Patients with low stage disease can be considered for vaginal sparing or female organ preserving techniques, which can potentially improve post-operative sexual function
  - Risk of positive margin posteriorly

Lymph Node Dissection

- A meticulous and thorough pelvic lymph node dissection must be performed at time of radical cystectomy
  - accurately staging
  - Improved survival with thorough lymph node dissection
  - Extent remains controversial - At minimum Standard LND
Peri-operative management- Enhanced Recovery After Surgery (ERAS)

ERAS protocols shown to decrease hospital length of stay and improve patient experience.

Includes:
• Alvimopan- mu receptor antagonist
• Avoidance of NG tubes
• Avoidance of bowel preparation
• Enforced early enteral feeding starting on POD#1


Neoadjuvant Chemotherapy

• Improves survival (level 1 evidence): 5% absolute improvement in survival found in randomized studies

• 14-25% reduction in risk of dying of bladder cancer in patients treated with neoadjuvant chemotherapy
TREATMENT: CHEMOTHERAPY (AUA Guidelines)

Cisplatin-based NAC to eligible radical cystectomy patients prior to cystectomy

• The decision regarding eligibility for cisplatin-based NAC should be based on comorbidities and performance status

Adjuvant chemotherapy

• Recommended for ≥ pT3, or N+ disease

• No Level 1 evidence available

• Meta-analysis shows survival benefit
**Bladder Preservation Strategies**

- Radical transurethral resection
- Partial cystectomy
- Radiation therapy
  - With systemic chemotherapy
  - Without systemic chemotherapy
- Systemic chemotherapy

**Radiation**

- Usually administered along with radio-sensitizing single agent chemotherapy
  - Cisplatin most common
  - Gemcitabine, 5FU also may be used
- Trimodal approach requires radical TURBT (maximal debulking)
- Best candidates: smaller lesions, earlier stage, no hydronephrosis
- Not effective against CIS of the bladder
Trimodality therapy for bladder cancer—updated Mass Gen Hospital experience

Metastatic disease

- Poor prognosis (median survival about 1 year)

- Chemotherapy
  - MVAC (methotrexate, vinblastine, Adriamycin [doxorubicin], and cisplatin)
  - Dose-dense MVAC (ddMVAC)
  - Gemcitabine + cisplatin (Gem-Cis)
    - comparable efficacy but less toxic than MVAC (but not necessarily ddMVAC)
  - Carbo/Gem alternative in cisplatin ineligible patients
    - Less efficacious than Gem/Cis
Upper Tract Urothelial Cell Carcinoma

Presentation

- **Hematuria**
- Back pain
- Anorexia / weight loss
- Fatigue
- Filling defect on imaging

- **Differential Diagnosis**
- Blood clots
- Stones
- Overlying bowel gas
- Sloughed papilla
- Fungus ball

Images courtesy of Dr. Stuart Wolf
Risk of Upper Tract Tumor

• Similar Risk Factors to Bladder Cancer:
  - Smoking
  - Prior bladder cancer (2-4% develop upper tract UC)
  - Analgesics /Arsenic
  - Chronic Inflammation
  - Cyclophosphamide
  - Occupational exposures (same as bladder)

• Lynch Syndrome II (autosomal dominant)
• Females > males
• Younger diagnosis (mean, 55 year)
• Balkan Nephropathy

Evaluation of Upper Tract

• Differential Cytology from upper tract
• Imaging (risk of understaging)
  – CT Urogram preferred
  – IVP
  – RPG
  – MR Urogram – risk of nephrogenic systemic fibrosis (CrCl <30 ml/min)

• Ureteronephroscopy for definitive diagnosis
  – Distinguish from Renal Cell Carcinoma
  – Biopsy (brush or basket)
  – Determine endoscopic versus surgical treatment
  – Consider neoadjuvant chemotherapy, if suspect invasive disease
Role of Upper Tract Tumor Biopsy

• Distinguish Urothelial Cell from Renal Cell
• Identify grade (correlated with stage)
• No definitive stage information
• Identify variant histology (rare given limited biopsy tissue)

Surgical Treatment

1. Endoscopic management
2. Segmental ureterectomy
3. Total ureterectomy with ileal interposition
4. Nephroureterectomy with bladder cuff
   - Open / Laparoscopic / Robotic
Endoscopic Management

- Appropriate for low grade tumors
- High grade tumors in solitary kidney
- Recurrence rates high and associated with grade of tumor.

Ureteroscopy

- Tumors >1cm difficult to manage
- Basket or biopsy forceps used to debulk tumor if large
- Laser or Bugbee used to ablate small tumors or base of larger tumors.

Percutaneous Approach

- Allows for treatment of larger tumors
- Access location is key, i.e. calyceal tumor, renal pelvis

Endoscopic Management

- Ureteroscopic biopsy of upper tract tumors usually does not allow microscopic determination of invasion.
  - Staging limited to the grade of tumor
  - Change in grade in up to 1/3 of patients

- ‘Key concern with endoscopic management is the risk of upgrading or upstaging’
- In large series:
  - Risk of grade migration = 4-19%
  - Risk of stage migration = 8-14%

Cutress et al (BJUI 2012)
Upper Tract Instillation Therapy

- Mitomycin-C and BCG are two most commonly used agents.
- BCG most successful when used for primary CIS
- Efficacy data is retrospective
- Delivery of these agents has always been challenging and likely limits efficacy.
  - Retrograde with stent or catheter
  - Antegrade via nephrostomy tract

- Lead to development of metronidazole topical
  - sustained release hydrogel-based formulation allowing for longer exposure of MMC to the urothelium.

Ureterectomy

**Segmental ureterectomy** with primary reanastamosis for smaller low-grade and focal high-grade tumors in the mid-ureter

**Total ureterectomy** with ileal interposition for upper ureteral tumors
  - Risk of recurrence high
  - Close endoscopic surveillance mandatory

**Distal Ureterectomy**
  - Tumors in the distal ureter not amenable to endoscopic management can be treated with segmental resection of the distal ureter with a bladder cuff and ureteroneocystostomy.
Radical Nephroureterectomy

- Radical nephroureterectomy includes the removal of the entire kidney, ureter and ipsilateral bladder cuff.
  - associated with decreased risk of subsequent intravesical tumor recurrence
- Open radical nephroureterectomy is the standard of treatment for high-grade or clinically infiltrating upper tract urothelial carcinoma.
- In experienced hands, laparoscopic radical nephroureterectomy is oncologically equally effective with decreased intraoperative blood loss and hospital stay compared to the open procedure.

Lymphadenectomy

- Lymphatic metastases are commonly found in UCUT
  - 30% to 40%
- No clear consensus on template or extent of lymphadenectomy
- Improves local staging, but the therapeutic role remains controversial
- Best candidates \( > \) pT2 or higher.
  - Because of the inaccuracy of preoperative staging, it’s justified to perform lymphadenectomy in all patient with high grade disease
Radical Nephroureterectomy

Postoperative intravesical chemotherapy

- **ODMIT-C Trial**: PI: Dr. Tim O’Brien
- 284 patients randomized, prospective non-blinded trial to receive single dose of MMC at time of catheter removal following nephroureterectomy.
  - ITT analysis: 21/120 (17%) recurrence in MMC arm vs 23/119 (27%) in standard arm, p=0.055
  - Per protocol analysis: 17/105 (16%) recurrence MMC vs 31/115 (27%) standard, p=0.03

Adjuvant Chemotherapy

POUT Trial – United Kingdom  PI: Dr. Alison Birtle

- 248 patients: 123 surveillance 125 chemotherapy
- Phase III Randomized Trial of Perioperative Chemotherapy versus surveillance in upper tract urothelial cell carcinoma.
- Patients with pT2-pT4 N0M0 or pTany N1-3M0 randomized to chemotherapy vs observation.
- Chemo Arm with Gemcitabine + Cisplatin or Carboplatin

- **Primary Endpoint**: Disease-Free Survival
- **HR 0.49** (95% CI= [0.31-0.76], log rank p=0.001
Neoadjuvant Chemotherapy

• Systematic Review and Meta-analysis of Neoadjuvant Chemotherapy for UTUC suggests improved survival

• Several prospective neoadjuvant trials ongoing

Surveillance following treatment

• After Nephroureterectomy, over at least 5 years

• Non-invasive tumor
  – Cystoscopy/urinary cytology at 3 months and then yearly
  – CT every year

• Invasive tumor
  – Cystoscopy/urinary cytology at 3 months and then yearly
  – CT urography every 6 months over 2 years and then yearly

• After conservative management, over at least 5 years
  – Urinary cytology and CT urography at 3 and 6 months, and then yearly
  – Cystoscopy, ureteroscopy and cytology in situ at 3 and 6 months over 2 years, and then yearly
Advanced Kidney Cancer

NCCN Guidelines Version 4.2018
Kidney Cancer

<table>
<thead>
<tr>
<th>STAGE</th>
<th>PRIMARY TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IV</td>
<td></td>
</tr>
<tr>
<td>Potentially surgically resectable primary with oligometastatic sites</td>
<td>Nephrectomy + surgical metastasectomy or Ablative techniques of metastases in selected patients who are not candidates for surgery</td>
</tr>
<tr>
<td>Potentially surgically resectable primary with multiple metastatic sites</td>
<td>Cytoreductive nephrectomy in select patients</td>
</tr>
<tr>
<td>Surgically unresectable</td>
<td>Relapse See First-Line Therapy (KID-3)</td>
</tr>
<tr>
<td></td>
<td>See First-Line Therapy (KID-3)</td>
</tr>
<tr>
<td></td>
<td>See First-Line Therapy (KID-3)</td>
</tr>
</tbody>
</table>

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Principles of Surgery

- Nephron-sparing surgery (partial nephrectomy) is appropriate in selected patients
  - Unilateral Stage I-III tumors
  - Solitary kidney, renal insufficiency, bilateral renal masses, familial renal cell cancer
- Open, lap or robotic techniques all acceptable
- Regional lymph node dissection is optional but recommended for patients with adenopathy

Rationale for cytoreductive nephrectomy

- Immune system plays an important role in RCC
  - Rare spontaneous regression of mets following cytoreductive nephrectomy (CN)
    (Garfield 1972, Bumpus 1928, Sarna 1983)
- Patients undergoing CN had better prognosis
  (De Kernion 1983, Muss 1987)
- Metastatic sites possibly respond better to systemic therapies than the primary tumor
  (Wagner 1999)
Impact of cytoreductive nephrectomy

Disease Specific Survival by Time Period and Nephrectomy Status
Stage IV Renal Cancer Patients, SEER 1993-2009

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Cytoreductive Nephrectomy in Patients with Synchronous Metastases from Renal Cell Carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium

- Median OS: 20.6 mo vs 9.5 mo
- Adjusted HR: 0.60 (95% CI 0.52-0.69), p < 0.0001

Prognostic factors

- Karnofsky index <80%
- Time from diagnosis <12 months
- Hemoglobin < LL
- LDH > 1.5 x UL
- corrected serum calcium > 10 mg / dl
- Neutrophils > UL
- Platelets > UL

- Favorable risk (0)
- Intermediate risk (1-2)
- Unfavorable risk (3-5)

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Prognostic factors

<table>
<thead>
<tr>
<th>No. of IMDC criteria met</th>
<th>No CN OS, mo (n)</th>
<th>CN OS, mo (n)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>92% of patients (65/71) had CN, insufficient number to compare</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>22.5 (n = 72)</td>
<td>36.4 (n = 178)</td>
<td>0.002</td>
</tr>
<tr>
<td>2</td>
<td>18.2 (n = 143)</td>
<td>20.2 (n = 253)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3</td>
<td>18.0 (n = 113)</td>
<td>15.9 (n = 106)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4</td>
<td>5.4 (n = 103)</td>
<td>6.0 (n = 92)</td>
<td>0.166</td>
</tr>
<tr>
<td>5</td>
<td>3.6 (n = 36)</td>
<td>2.8 (n = 14)</td>
<td>0.504</td>
</tr>
<tr>
<td>6</td>
<td>23% of patients (2/12) had CN, insufficient number to compare</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Overall, 1168 of 1608 subjects (72%) had complete information about prognostic factors, nephrectomy, and outcomes and were used in this complete case analysis; the rest were excluded. Shaded rows indicate patient groups that may not benefit from cytoreductive nephrectomy.

CN = cytoreductive nephrectomy; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; OS = overall survival.

≥4 do not benefit from cytoreductive nephrectomy


Resection of Lung Metastases

Surgical resection of isolated lung metastases in carefully selected patients has been associated with a 20-50% 5Y survival.
Prognostic Factors: Resection of RCC Oligometas

Clinical trials

**CARMENA**
- 570 treatment-naïve patients with primary tumor in situ
- Randomization
- Nephrectomy
- Sorafenib 6-week cycle (400 mg daily for 6 weeks, 2 weeks of no treatment)

**SURTIME**
- 440 treatment-naïve patients with primary tumor in situ
- Randomization
- Nephrectomy
- Sorafenib


Slides courtesy of Dr. Monty Pal, M.D
**Trial Overview**

**Adjuvant RCC Trials**

- Anti-VEGF Therapy
- mTOR Inhibitors
- Tumor Associated Antigen Antibody
- Immunotherapy

- ASSURE
- SORCE
- S-TRAC
- ATLAS
- PROTECT

*treating before/after surgery

**ASSURE ADJUVANT TRIAL**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>n</th>
<th>Drug</th>
<th>Route</th>
<th>Arms</th>
<th>Histology</th>
<th>Features</th>
<th>1^ Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASSURE</td>
<td>III</td>
<td>1923</td>
<td>Sorafenib</td>
<td>PO</td>
<td>1-Placebo</td>
<td>T1b, 63-4, T2,3,4 N+</td>
<td>DFS</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>297</td>
</tr>
<tr>
<td>Placebo</td>
<td>305</td>
</tr>
</tbody>
</table>

Figure 2: Disease-free survival

HR was 0.76 (p=0.003)
Median DFS (yrs) - 6.8 (5.8-NR) vs 5.6 (3.8-6.6)
Improvement in DFS for Central Path review (not investigator review)

1st end point was the duration of disease-free survival= first tumor recurrence, the occurrence of metastasis or a secondary cancer, or cancer death

Data for overall survival, a 2nd end point, were not mature at the time of the data cutoff, with deaths reported in 64 patients (20.7%) in the sunitinib group and 64 (20.9%) in the placebo group. The median overall survival was not reached in either group.

However median survival already 5+ years.....
CARMENA: Conclusions

In final analysis of CARMENA, sunitinib alone not inferior to cytoreductive nephrectomy followed by sunitinib in patients with mRCC

Median OS longer in sunitinib-alone arm for all patients and in intermediate-risk and poor-risk subgroups

Clinical benefit rate significantly higher in sunitinib-alone arm (47.9% vs 36.6% with nephrectomy followed by sunitinib; \(P = .02\))

Investigators concluded that **nephrectomy should no longer be part of standard of care for patients with mRCC requiring medical treatment**

ARS Q1:

Important risk factors for progression of T1 bladder cancer includes:

- a) Solitary tumor
- b) Bladder neck involvement
- c) Age
- d) Variant histology
- e) Associated HGTa papillary tumors

Answer: D

D. Variant histology

Size of tumor, multifocality, extent of invasion (T1a v T1b v T1c), lymphovascular invasion, associated CIS (not HGTa), inability to completely resect tumor (anterior bladder wall/bladder neck/dome), residual T1 disease identified on restaging TURBT pathology, and recurrent T1 disease despite intravesical BCG exposure and variant histology are all associated with a risk of tumor progression for T1 disease. Bladder neck involvement and age are not independent risk factors for progression.
ARS Q2:

The following that has definitively been associated with improved survival for muscle invasive bladder cancer is:

a) Adjuvant chemotherapy
b) Neoadjuvant cisplatin based chemotherapy
c) Extended pelvic lymph node dissection
d) Adjuvant radiation therapy
e) Neoadjuvant chemoradiation

Answer: B

B - Neoadjuvant cisplatin based chemotherapy

• Although meta-analyses of the multiple trials show an improvement in survival for patients receiving adjuvant chemotherapy, there is only Level 1 evidence available for use of neoadjuvant cisplatin based chemotherapy for patients with muscle invasive disease. There are numerous retrospective studies suggesting extended pelvic lymph node dissection may improve survival but at this time there is no level I evidence (SWOG S1011 is randomizing patient to ‘standard’ vs ‘extended’ pelvic lymph node dissection and results will not be available for another few years). There is some suggestion that adjuvant radiation may decrease pelvic recurrence rates and trials are underway. There is no role for ‘neoadjuvant’ chemoradiation prior to definitive therapy.
ARS Q3:

A 78 year old gentleman with renal insufficiency and coronary artery disease and a bladder tumor undergoes TURBT showing a high grade T1 urothelial carcinoma with muscle present but no involved. The next best step in management should be:

a) Surveillance cystoscopy at 3 months  
b) Induction BCG  
c) Re-TURBT at 6 weeks  
d) Immediate radical cystectomy  
e) Chemoradiation

Answer: C

C. Re-TURBT at 6 weeks.

Although induction BCG and immediate cystectomy are options, the best next step in this patient with comorbidities would be a re-TURBT to determine whether there is any muscularis propria invasion.
ARS Q4:

A 64 year old patient gross hematuria and is found to have a 2cm distal ureteral tumor on a CT scan. Ureteroscopy and biopsy of the mass reveal it to be a high grade lesion. No other lesions are found in the bladder. The next best step would be:

a) Ureteroscopic laser ablation of the tumor  
b) Distal ureterectomy followed by ureteroneocystostomy  
c) Nephroureterectomy  
d) Chemotherapy followed by distal ureterectomy  
e) Chemoradiation

Answer: B

B. Distal ureterectomy and ureteroneocystostomy

Although this is a high grade lesion, it is confined to the distal ureter and is not amenable to laser fulguration. This can be successfully managed with distal ureterectomy and ureteroneocystostomy, along with an ipsilateral pelvic lymph node dissection. Close surveillance is necessary.
ARS Q5:

A 56 year old patient with excellent performance status has flank pain and is found to have a 13cm mass in the right kidney. CT scan reveals a solitary 1.5cm nodule in the peripheral right upper lobe of the lung. The next best step for treatment is:

a) Oral TKI agent  
b) Immunotherapy  
c) Radical nephrectomy followed by lung wedge resection  
d) Chemotherapy  
e) Radical nephrectomy followed by Sutent

Answer: C

C. Radical nephrectomy followed by lung wedge resection

In a patient with excellent performance status and a solitary lesion in the lung, the next best step in management would be a cytoreductive nephrectomy followed by metastatectomy. Systemic treatment should be reserved for patients with unresectable disease with multiple sites of metastases.