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Bladder Cancer
Upper Tract Urothelial Carcinoma
Advanced Kidney Cancer

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Outline

- **NMIBC**
  - Risk adapted strategy
  - AUA guidelines
- **Muscle invasive bladder cancer**
  - AUA Guidelines
  - Perioperative chemotherapy
  - Perioperative management
  - Bladder sparing protocols

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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

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NCCN Guidelines Version 2.2016 Bladder Cancer

- APPROXIMATE PROBABILITY OF RECURRENCE

Pathology	Approximate Probability of Recurrence in 5 years
Ta, low grade	50%
Ta, high grade	60%
T1, low grade (rare)	50%
T1, high grade	50% - 70%
Tis	50% - 90%

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Urinary marker tests

NMP22®	Protein-based; identifies nuclear matrix protein involved in the mitotic apparatus
BTA®	Protein-based; identifies a basement membrane antigen related to complement factor H
UroVysion® FISH	Cell-based; identifies altered copy numbers of specific chromosomes using fluorescent probes
ImmunoCyt™	Cell-based; identifies three cell surface glycoproteins
Cxbladder™	Cell-based; identifies the presence of five mRNA fragments

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

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* 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

	Measured		Published	
	Sensitivity, % (95 % CI)	Specificity, % (95 % CI)	Sensitivity, % (95 % CI)	Specificity, % (95 % CI)
Cytology	45.5 (40.6–50.4)	96.3 (94.5–97.9)	56.1 (43.3–68.3) [18]	94.5 (91.9–96.5) [18]
NMP22	44.9 (37.4–52.3)	89.0 (86.5–91.5)	50.0 (37.4–62.6) [18]	88.0 (84.6–91.0) [18]
FISH	40.0 (22.7–52.3)	87.3 (83.7–91.6)	72 (69–75) [22]	83 (82–85) [22]
			61.9 [23]	89.7 [23]
			18 [24]	90 [24]
Cxbladder Detect	79.5 (71.1–87.8)	82.2 (79.2–85.0)	81.8 [18]	85.1 (fixed) [18]

* Cxbladder negative predictive value 97-98%

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Breen V, et al. *BMC Medical Research Methodology.* 2015;15:1-12.

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
Hyperplasia (flat and papillary)
Reactive atypia
Atypia of unknown significance
Urothelial dysplasia
Urothelial CIS
Urothelial papilloma
Papillary urothelial neoplasm of low malignant potential (PUNLMP)
Non-muscle invasive low-grade papillary urothelial carcinoma
Non-muscle invasive high-grade papillary urothelial carcinoma

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Clinical stage includes histologic findings at TURBT; physical exam, including bimanual exam under anesthesia; and findings on imaging

Staging of primary tumors (T) in bladder cancer	
TX	Primary tumor cannot be assessed
Ta	Noninvasive papillary carcinoma
Tis	Carcinoma in situ (CIS)
T1	Tumor invades lamina propria
T2	Tumor invades muscularis propria
T2a	Tumor invades superficial muscularis propria (inner half)
T2b	Tumor invades deep muscularis propria (outer half)
T3	Tumor invades perivesical tissue/fat
T3a	Tumor invades perivesical tissue/fat microscopically
T3b	Tumor invades perivesical tissue fat macroscopically (extravesical mass)
T4	Tumor invades prostate, uterus, vagina, pelvic wall, or abdominal wall
T4a	Tumor invades adjacent organs (uterus, ovaries, prostate stoma)
T4b	Tumor invades pelvic wall and/or abdominal wall

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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

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AUA Risk Stratification

Low Risk	Intermediate Risk	High Risk
LG[a] solitary Ta ≤ 3cm	Recurrence within 1 year, LG Ta	HG T1
PUNLMP[b]	Solitary LG Ta > 3cm	Any recurrent, HG Ta
	LG Ta, multifocal	HG Ta, >3cm (or multifocal)
	HG[c] Ta, ≤ 3cm	Any CIS[d]
	LG T1	Any BCG failure in HG patient
		Any variant histology
		Any LVI[e]
		Any HG prostatic urethral involvement

[a]LG = low grade; [b]PUNLMP = papillary urothelial neoplasm of low malignant potential; [c]HG = high grade; [d]CIS=carcinoma *in situ*; [e]LVI = lymphovascular invasion

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THE JOURNAL of UROLOGY®
Official Journal of the American Urological Association

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, Eila 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/burdens, and the Panel's judgment

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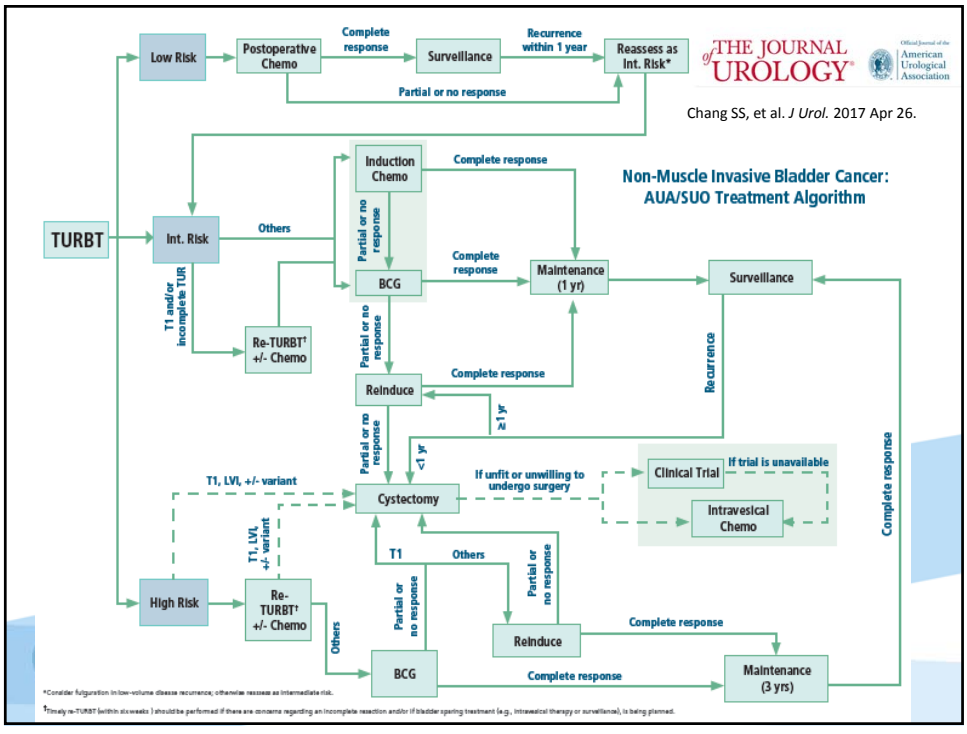

Chang SS, et al. *J Urol.* 2017 Apr 26.

NMIBC

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

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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, doxyorubicin, 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

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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)

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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.

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Histopathology

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

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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

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Micropapillary

- Most commonly found in association with high grade invasive UC
- Rare component but increasingly recognized
- Associated with aggressive disease

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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)

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AUA Guidelines- TURBT

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)

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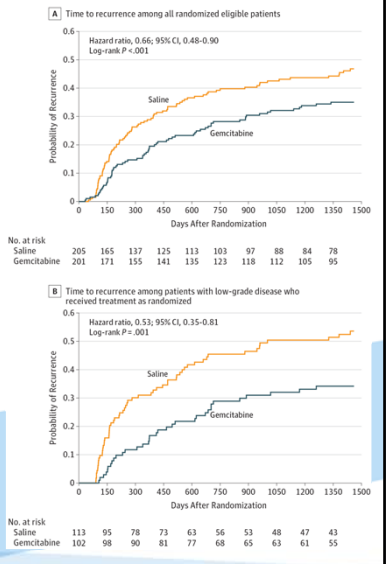
Post TUR gemcitabine - SWOG S0337

- 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.

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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

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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)

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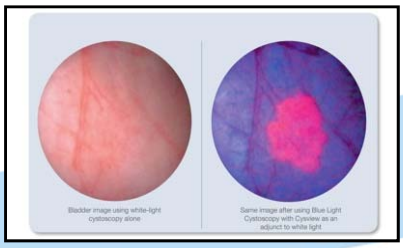
AUA Guidelines- Enhanced Cystoscopy

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)



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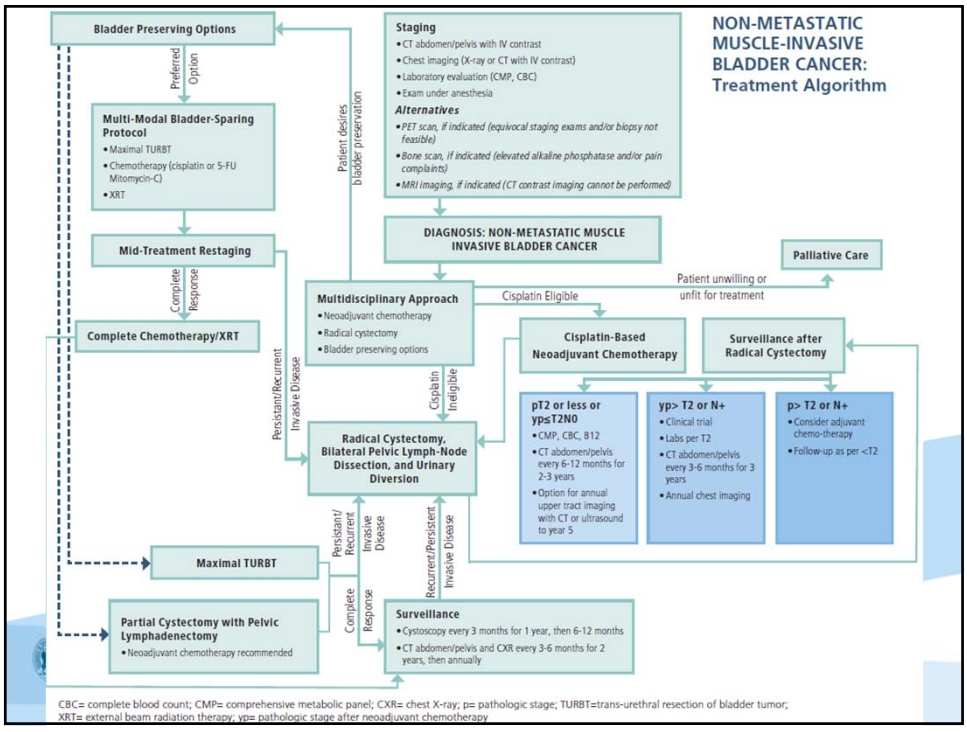
Daneshmand, Nature Reviews Urology 2014



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

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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)

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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.

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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.

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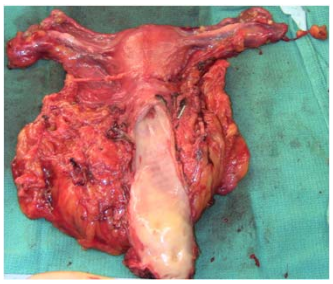
Bruins, Daneshmand :*J Urol.* Nov 2013
Bochner et al. European Eur 2015)

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

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Djaladat, Daneshmand: j Urol Dec 2012
AUA Guidelines, 2017

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**

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Hugen, Daneshmand WJU 2015
AUA Guidelines, 2017

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

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Median Hospital Stay 4 days- Daneshmand et al . Enhanced Recovery Protocol Following Radical Cystectomy, J Urology 2014

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

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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*

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Adjuvant chemotherapy

- Recommended for ≥ pT3, or N+ disease
- No Level 1 evidence available
- Meta-analysis shows survival benefit

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Bladder Preservation Strategies

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

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Radiation

- Usually administered along with radio-sensitizing single agent chemotherapy
  - Cisplatin most common
  - Gemcitibine, 5FU also may be used
- Trimodal approach requires radical TURBT (maximal debulking)
- Best candidates: smaller lesions, earlier stage, no hydronephrosis best candidates
- Not effective against CIS of the bladder

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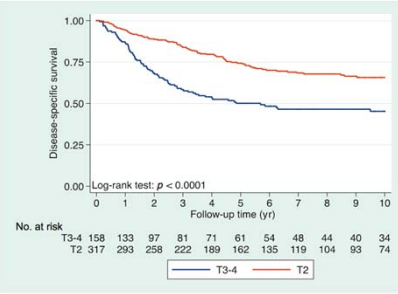
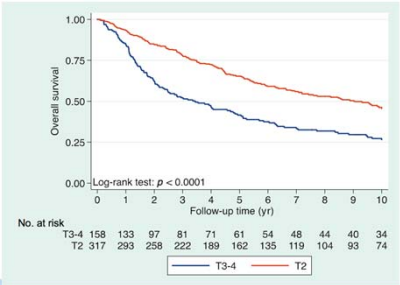
Trimodality therapy for bladder cancer-updated Mass Gen Hospital experience





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Giacalone NJ, et al. *Eur Urol*. 2017;71:952-960.

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 necessarioy ddMVAC)
  - Carbo/Gem alternative in cisplatin ineligible patients
    - Less efficacious than Gem/Cis

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Upper Tract Urothelial Cell Carcinoma

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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

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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

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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

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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)

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Surgical Treatment

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

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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

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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)

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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.

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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.

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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.

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Stenzl et al, 2017

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**

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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

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O'Brien et al 2011

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

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Neoadjuvant Chemotherapy

- Systematic Review and Meta-analysis of Neoadjuvant Chemotherapy for UTUC suggests improved survival
- Several prospective neoadjuvant trials ongoing

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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

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Roupret, et al. European Association of Urology Guidelines on Urothelial Carcinoma of the Upper Urinary Tract 2015

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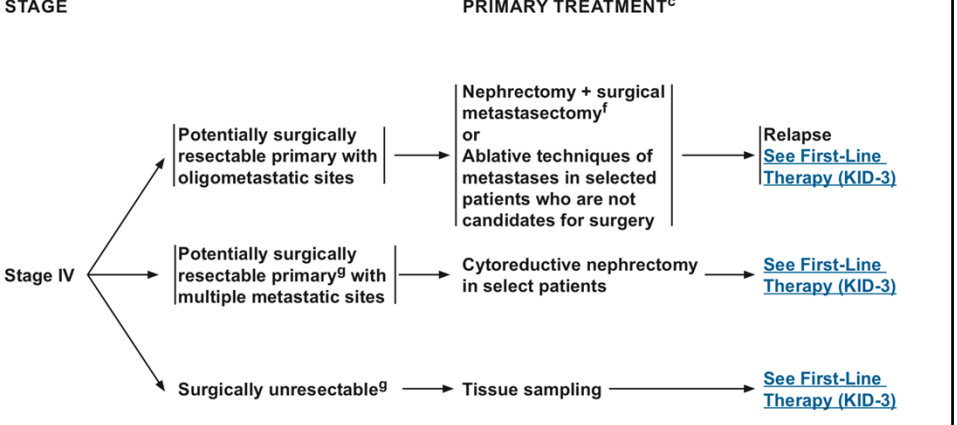
National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2018
Kidney Cancer



Principles of Surgery

- Nephron-sparing surgery (partial nephrectomy) is appropriate in selected patient
  - 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

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Rationale for cytoreductive nephrectomy

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

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Juan I. Martínez-Salamanca, SIU 2016

0022-5347/04/1713-1071/0
THE JOURNAL OF UROLOGY®
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Vol. 171, 1071–1076, March 2004
Printed in U.S.A.
DOI: 10.1097/01.ju.0000110610.61545.ae

CYTOREDUCTIVE NEPHRECTOMY IN PATIENTS WITH METASTATIC RENAL CANCER: A COMBINED ANALYSIS

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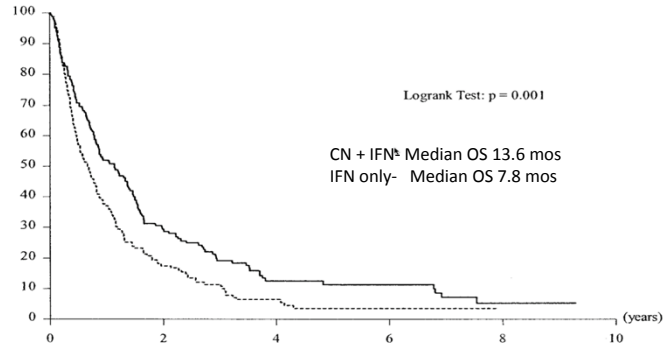
H. VAN POPPEL AND E. DAVID CRAWFORD

CYTOREDUCTIVE NEPHRECTOMY AND METASTATIC RENAL CANCER



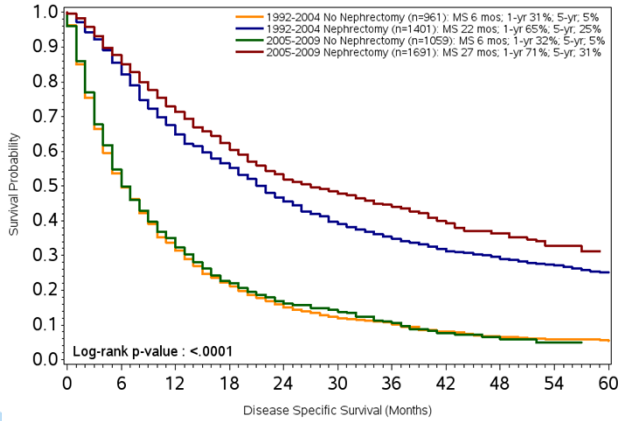
CN + IFN: Median OS 13.6 mos
IFN only- Median OS 7.8 mos

O	N	Number of patients at risk :				
141	161	46	13	9	3	Neph+IFN
152	163	26	7	1	0	IFN alone

FIG. 1. Duration of survival in combined SWOG and EORTC trials. *O*, observation. *N*, nephrectomy

Impact of cytoreductive nephrectomy

Disease Specific Survival by Time Period and Nephrectomy Status
Stage IV Renal Cancer Patients, SEER 1992-2009



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Nelson RA, Vogelzang NJ, Pal SK. Impact of cytoreductive nephrectomy on disease-specific survival (DSS) in the cytokine and targeted therapy eras: Age- and TNM-stage matched analysis of SEER data. ASCO Meeting Abstracts. 2013;31(15_suppl):4579

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

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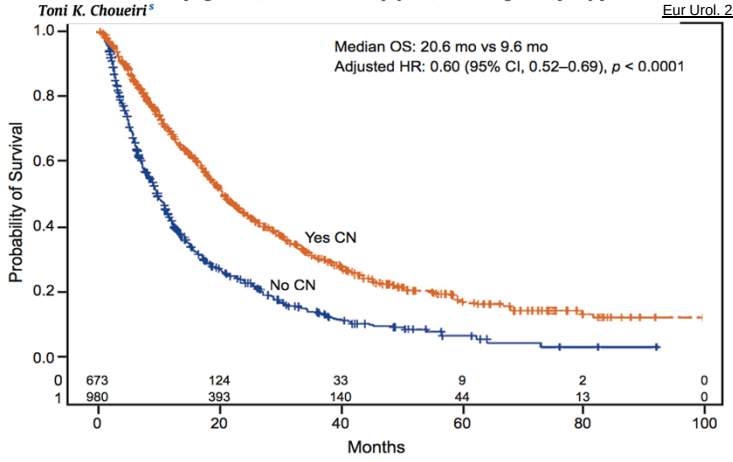
Eur Urol. 2014 Oct;66(4):704-10



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)

UL- upper limit of reference range
LL- Lower limit of reference range

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[1]*Motzer et al. J.Clin. Oncol. 2002;20:280-296.*
[2] *Heng et al. J Clin Oncol, 2009*

Prognostic factors

No. of IMDC criteria met	No CN OS, mo (*n*)	CN OS, mo (*n*)	*p* value
0	92% of patients (65/71) had CN, insufficient number to compare		
1	22.5 (*n* = 72)	30.4 (*n* = 178)	0.002
2	10.2 (*n* = 143)	20.2 (*n* = 253)	<0.001
3	10.0 (*n* = 113)	15.9 (*n* = 106)	<0.001
4	5.4 (*n* = 103)	6.0 (*n* = 67)	0.166
5	3.6 (*n* = 36)	2.8 (*n* = 14)	0.504
6	25% of patients (3/12) had CN, insufficient number to compare		

Overall, 1168 of 1658 subjects (70%) 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

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Heng, D. et al Eur Urol. 2014; 66(4): 704-710

Resection of Lung Metastases

Surgical resection of isolated lung metastases in carefully selected patients has been associated with a 20-50% 5Y survival.

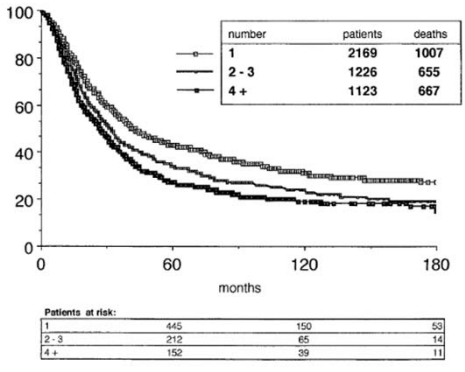

Fig. 3. Survival of patients having complete resections according to the number of pathologically proved metastases: single lesions, two to three lesions, and four or more lesions.

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Prognostic Factors: Resection of RCC Oligomets

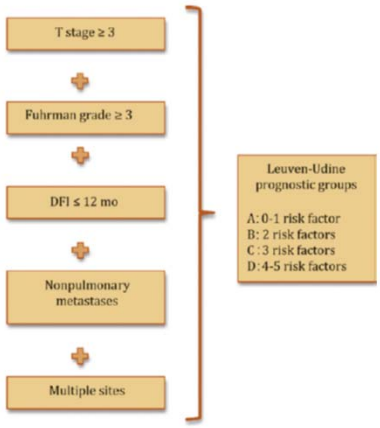

Fig. 1 – Leuven-Udine prognostic groups.

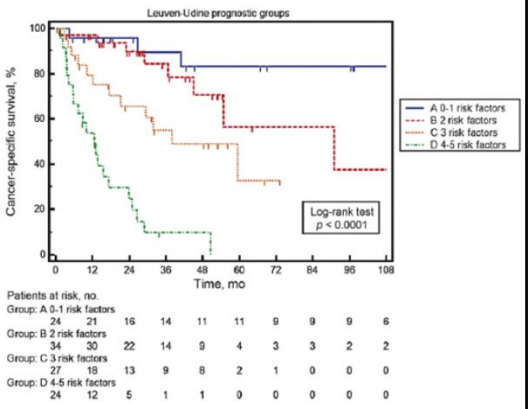

Fig. 2 – Cancer-specific survival stratified by Leuven-Udine prognostic groups.

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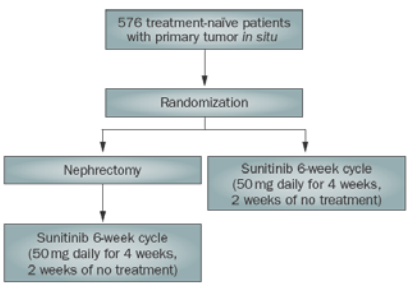
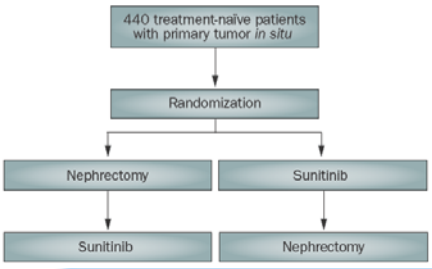
Slides courtesy of Dr. Monty Pal, M.D

Clinical trials

CARMENA



SURTIME



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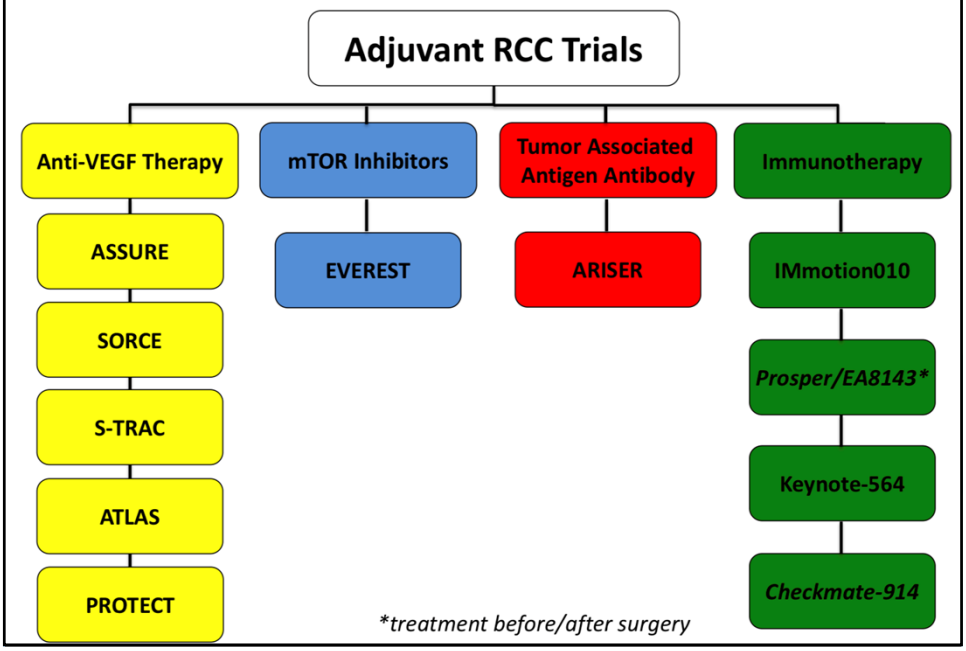
Abel EJ, Wood CG: Nat Rev Clin Oncol 6:375-383, 2009

Trial Overview



ASSURE ADJUVANT TRIAL

Trial	Phase	n	Drug	Route	Arms	Histology	Features	1° Outcome
ASSURE	III	1923	Sorafenib Sutent	PO	1-Placebo 2-Sorafenib-9 cycles 3- Sutent-9 cycles	All exept collecting duct or medullary	T1b, G3-4 T2,3,4 N+	DFS

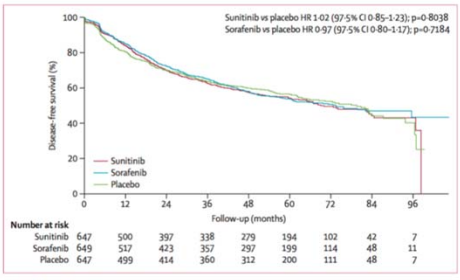


Figure 2: Disease-free survival
HR=hazard ratio.

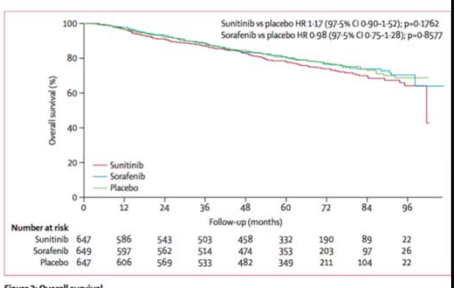


Figure 3: Overall survival
HR=hazard ratio.

Haas, N. B., et al. (2016). Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805)*Lancet*, *387*(10032), 2008–2016.

S-TRAC Trial

Trial	Phase	n	Drug	Route	Arms	Histology	Features	1° Outcome
S-TRAC	III	720	Sutent	PO	1-Placebo 2-Sutent-1 yr	Predominant clear cell	UISS High risk	DFS

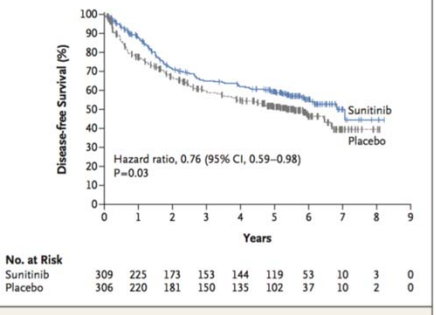


Figure 2. Disease-free Survival.
The median duration of disease-free survival according to independent central review was 6.8 years (95% confidence interval [CI], 5.8 to not reached) in the sunitinib group and 5.6 years (95% CI, 3.8 to 6.6) in the placebo group. At the time of data cutoff, an event of disease recurrence, a second cancer, or death had occurred in 113 of 309 patients (36.6%) in the sunitinib group and in 144 of 306 patients (47.1%) in the placebo group.

HR was 0.76 (p=0.003)

Median DFS (yrs)- 6.8 (5.8-NR) vs 5.6 (3.8-6.6)

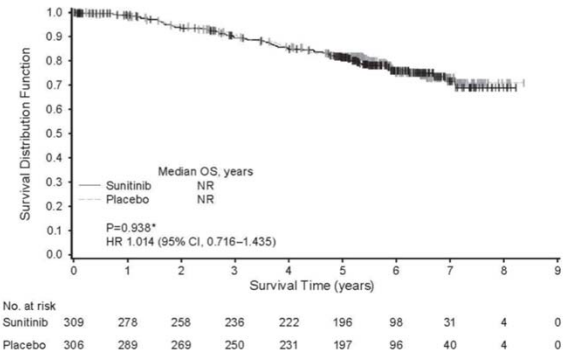
Improvement in DFS for Central Path review (not investigator review)

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

S-TRAC Trial

SUPPLEMENTARY FIGURES

Figure S1. Overall survival

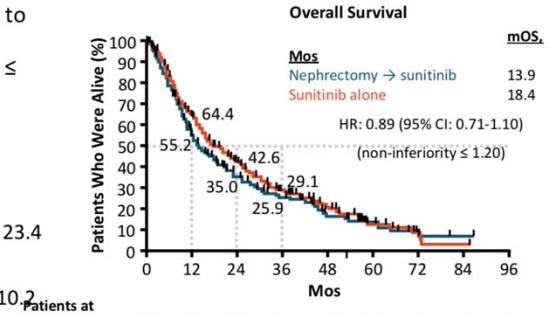


Data for overall survival, a 2° end point, were not mature at the time of the data cutoff, with deaths reported in 64 patients (20.7%) in the sunitinib group and 64 (20.9%) in the placebo group. The median overall survival was not reached in either group

However median survival already 5+ years…..

CARMENA: Overall Survival

- Sunitinib alone not inferior to nephrectomy → sunitinib (upper boundary of 95% CI ≤ 1.20)
- mOS longer with sunitinib alone vs nephrectomy → sunitinib:
  - MSKCC intermediate-risk: 23.4 vs 19.0 mos (HR: 0.92)
  - MSKCC poor-risk: 13.3 vs 10.2 mos (HR: 0.86)



Patients at Risk									
Nephrectomy → sunitinib	22	11	61	40	19	11	4	1	0
	6	0	76	44	26	8	3	1	0
Sunitinib alone	22	12							
	4	8							

Méjean A, et al. ASCO 2018. Abstract LBA3. Méjean A, et al. N Engl J Med. 2018;[Epub ahead of print].

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

•Méjean A, et al. ASCO 2018. Abstract LBA3. Méjean A, et al. N Engl J Med. 2018;[Epub ahead of print].

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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

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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 histooogy are all associated with a risk of tumor progression for T1 disease. Bladder neck involvement and age are not independent risk factors for progression.

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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

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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.

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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

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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.

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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

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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.

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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

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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.

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