Treatment and Surveillance of Superficial Bladder Cancer

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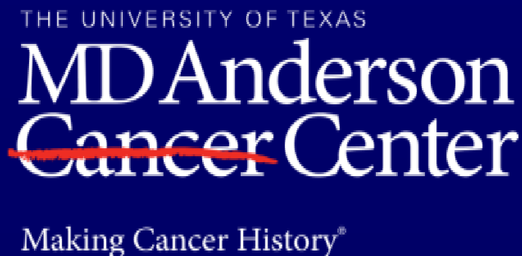
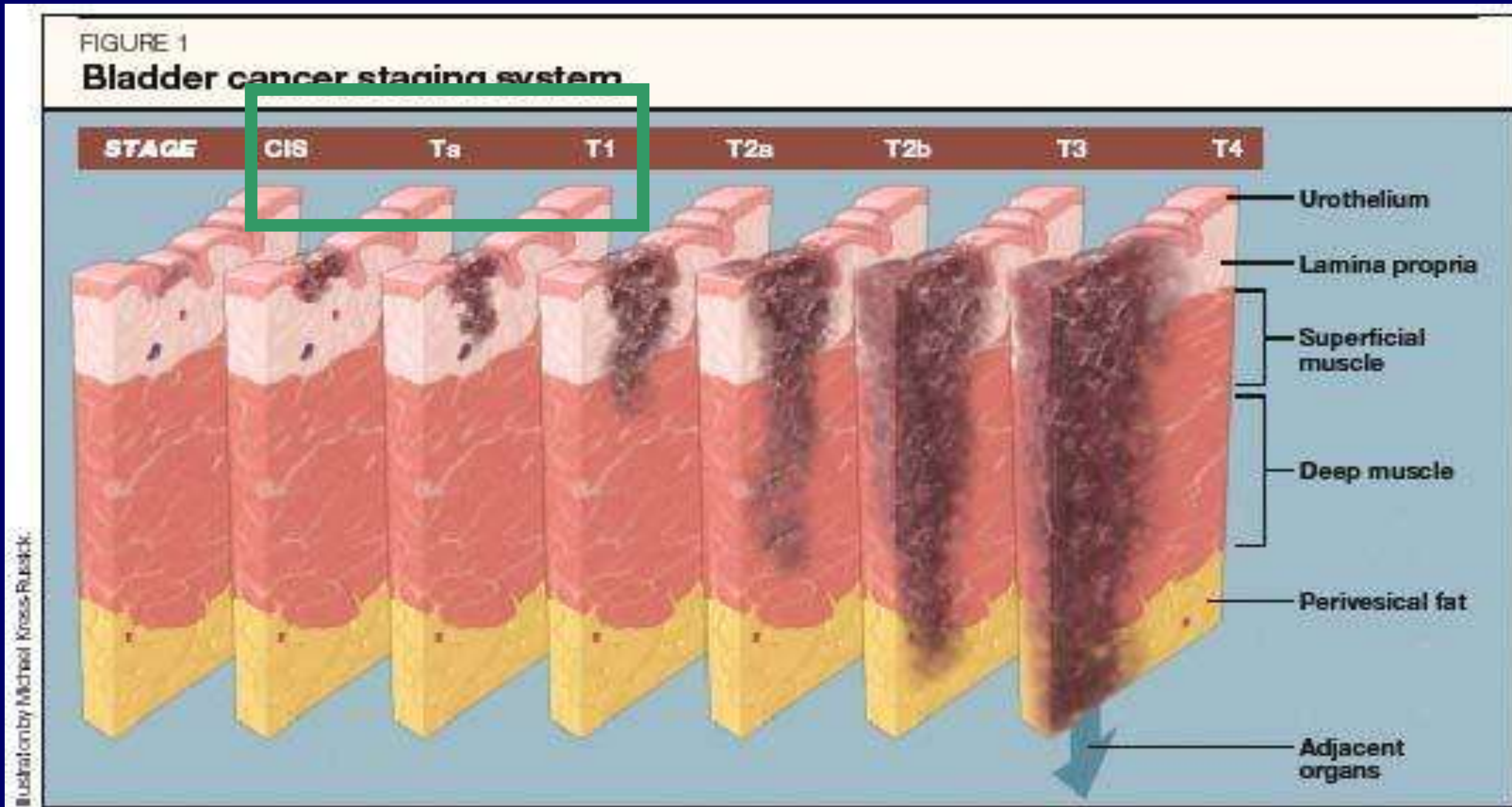


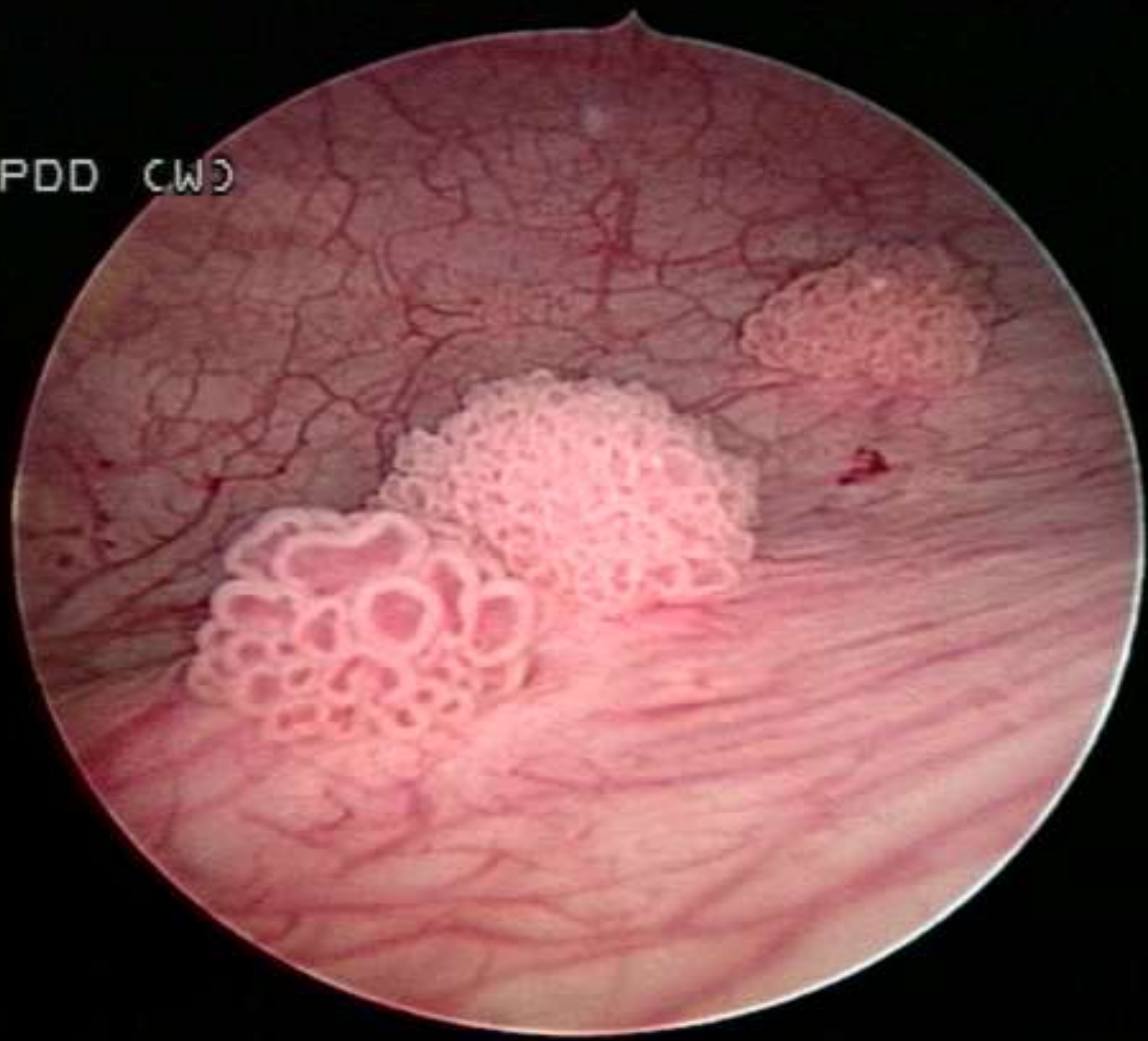
Houston, TX, 2011

Superficial Bladder Cancer

- The term ‘superficial’ refers to tumor above the muscle
- NOT a inconsequential tumor
- Also known as non muscle invasive bladder cancer

Bladder Cancer Staging





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Management of Superficial Tumors

- First thing after diagnosis is to remove the tumor
- This is done endoscopically
  - i.e. without an incision
- Instrument passed via urethra
- Fine cutting loop – using electric current

Good Tumor Resection

- Resection must be deep enough to obtain muscle
- Can lead to perforation and tumor spillage
  - Dependent on skill of surgeon

Abel & Kamat: Atlas of Bladder Surgery, 2010

Management of Superficial Tumors

- EUA – exam under anesthesia
  - Performed after tumor is resected
- Once the tumor is removed, it is studied under the microscope
- Determine ‘grade’ and ‘stage’
- Assessrisk of tumor recurrence and progression

Resection of Bladder Tumor

- Time: 10 - 60 minutes
- Usually outpatient surgery
- General anesthesia safer than spinal
- Risks:
  - Bleeding, Clot Retention
  - Infection
  - Perforation

Management

- After removal, most patients should receive one single dose chemotherapy in the bladder
- Low risk patients – this is all they need
- Some patients –
  - repeat tumor resection
  - further intravesical therapy
  - need to have bladder removed

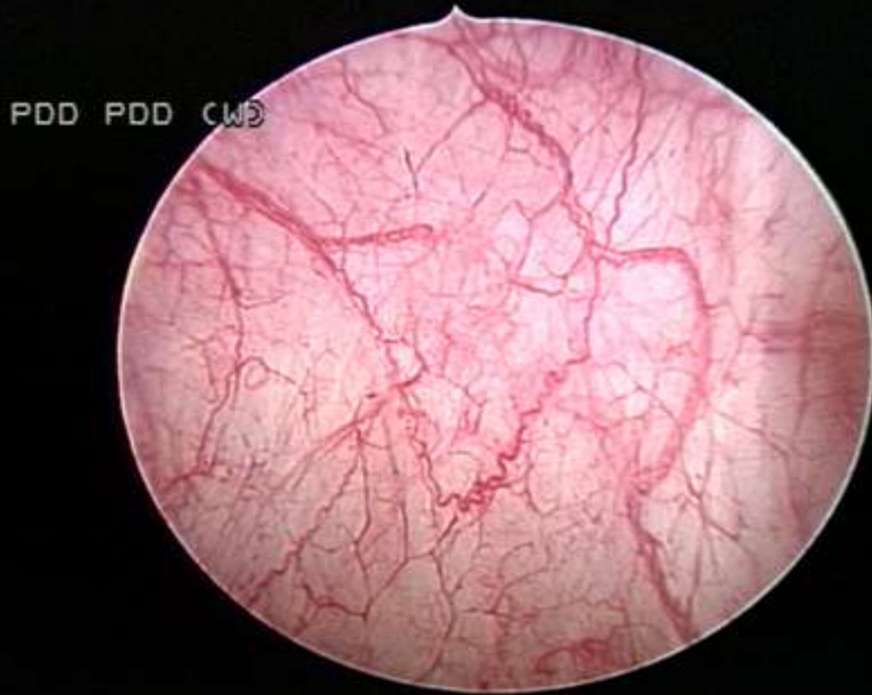
Post TUR Intravesical Therapy

- MUST consider instillation of chemotherapy into the bladder after resection of tumor
- ASK doctor if this will be done
  - Majority of patients do NOT have this done
- Some situations where not appropriate
  - But exception is not the rule!

Blue Light Cystoscopy (Cysview)

- Molecular Imaging of the Bladder
  - Special agent inserted into the bladder
  - Cancer cells selectively metabolize the agent
  - Appears pink under blue light
- Better visibility of tumors
- In wide use in Europe
  - Few centers in the US perform this

White Light vs Fluorescence



Papillary tumors: 95% vs 83% ($p=0.0001$) with fluorescence

Grossman et al, J Urol 178:62, 2007

CIS: 22% (4/18) detected only with fluorescence

Fradet et al, J Urol 178:68, 2007

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Repeat Resection

- Your doctor may elect to 'repeat the resection'
- Reason #1: no muscle present in the original specimen
- Likelihood of invasive disease on re-TUR
  - T1, muscle present – 14%
  - T1, no muscle present – 49%

Herr, J Urol, 1999

Intravesical Therapy

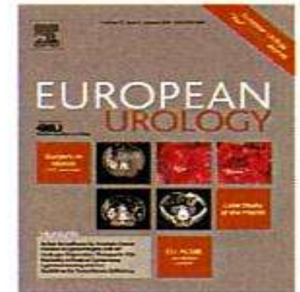
- Medication instilled into the bladder to PREVENT recurrences after complete TUR
- Chemotherapy – many choices, all relatively 'equal'
- Immunotherapy – BCG
  - BCG is the current gold standard for high risk tumors

Intravesical Chemotherapy or BCG?

EUROPEAN UROLOGY 56 (2009) 247–256

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology



Platinum Priority – Bladder Cancer

Editorial by Guido Dalbagni on pp. 257–258 of this issue

An Individual Patient Data Meta-Analysis of the Long-Term Outcome of Randomised Studies Comparing Intravesical Mitomycin C versus Bacillus Calmette-Guérin for Non–Muscle-Invasive Bladder Cancer

Per-Uno Malmström [a,], Richard J. Sylvester [b], David E. Crawford [c], Martin Friedrich [d], Susanne Krege [e], Erkki Rintala [f], Eduardo Solsona [g], Savino M. Di Stasi [h], J. Alfred Witjes [i]*

Intravesical Chemotherapy or BCG?

EUROPEAN UROLOGY 57 (2010) 766–773

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Bladder Cancer

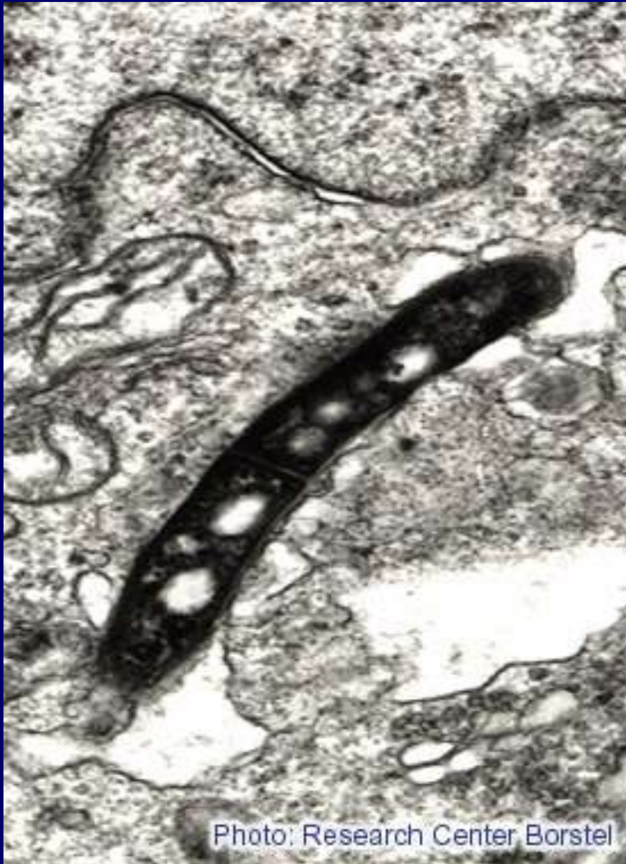
Editorial by Marko Babjuk on pp. 774–776 of this issue

Long-Term Efficacy Results of EORTC Genito-Urinary Group Randomized Phase 3 Study 30911 Comparing Intravesical Instillations of Epirubicin, Bacillus Calmette-Guérin, and Bacillus Calmette-Guérin plus Isoniazid in Patients with Intermediate- and High-Risk Stage Ta T1 Urothelial Carcinoma of the Bladder

Richard J. Sylvester[a,], Maurizio A. Brausi[b], Wim J. Kirkels[c], Wolfgang Hoeltl[d], Fernando Calais Da Silva[e], Philip H. Powell[f], Stephen Prescott[g], Ziya Kirkali[h], Cees van de Beek[i], Thierry Gorlia[a], Theo M. de Reijke[j]*

EORTC Genito-Urinary Tract Cancer Group

Intravesical BCG



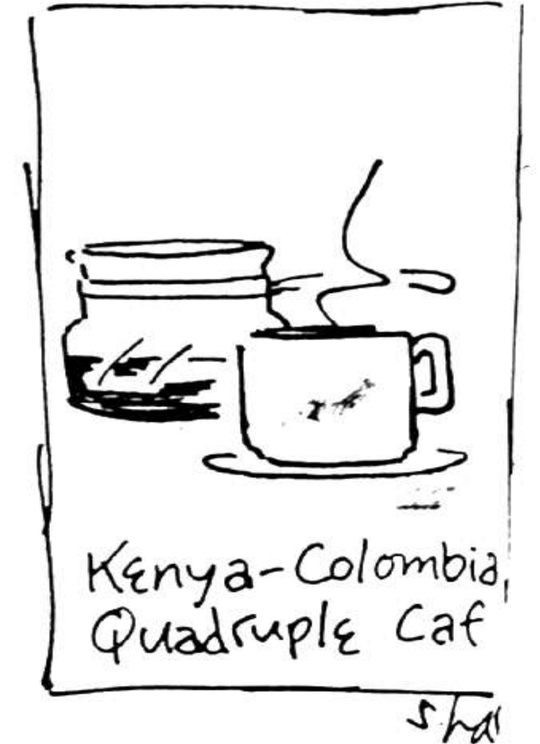
- Live attenuated bacteria
- Originally developed for vaccination against TB
- Seen that patients with TB had fewer cancers
- Tried for various tumors
- Bladder cancer – Gold Standard

BCG schedule

- 6 week induction at baseline
- 3 week maintenance
  - at 3mos, 6 mos, 12 mos and then
  - every 6 mos until 36 mos
- Cysto Schedule: q 3-6 mos for the first 36 mos.

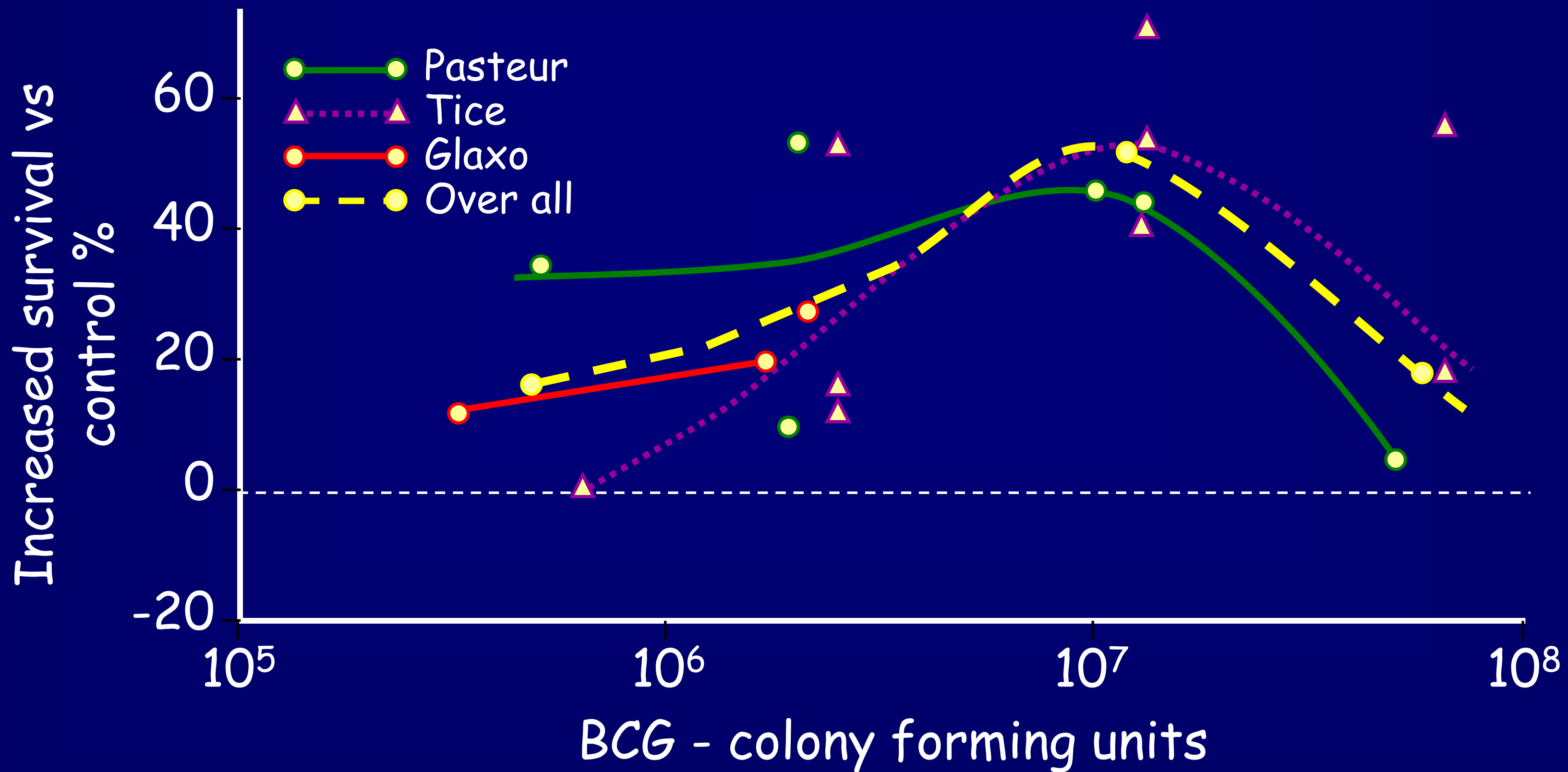
Dose-Response Relationship

THIS COFFEE CAN KEEP YOU UP

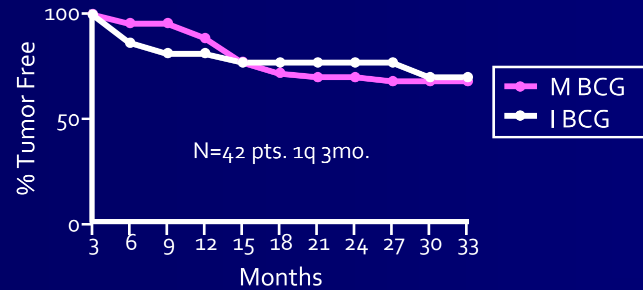


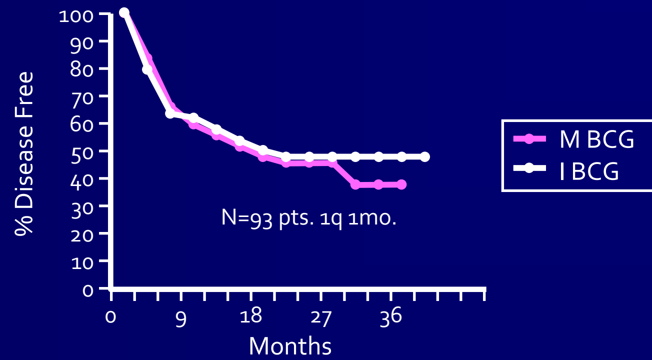
Dose-Response Curve to BCG

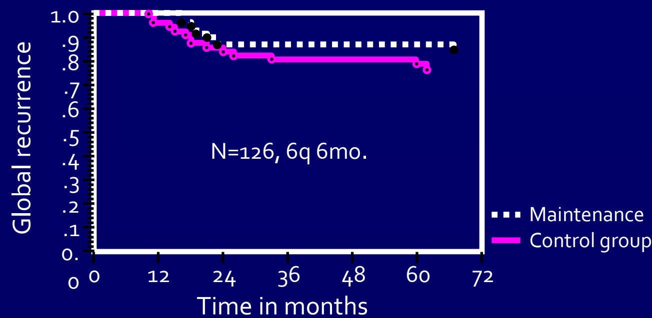
Individual responses vary, but
too little or too much BCG reduces effect

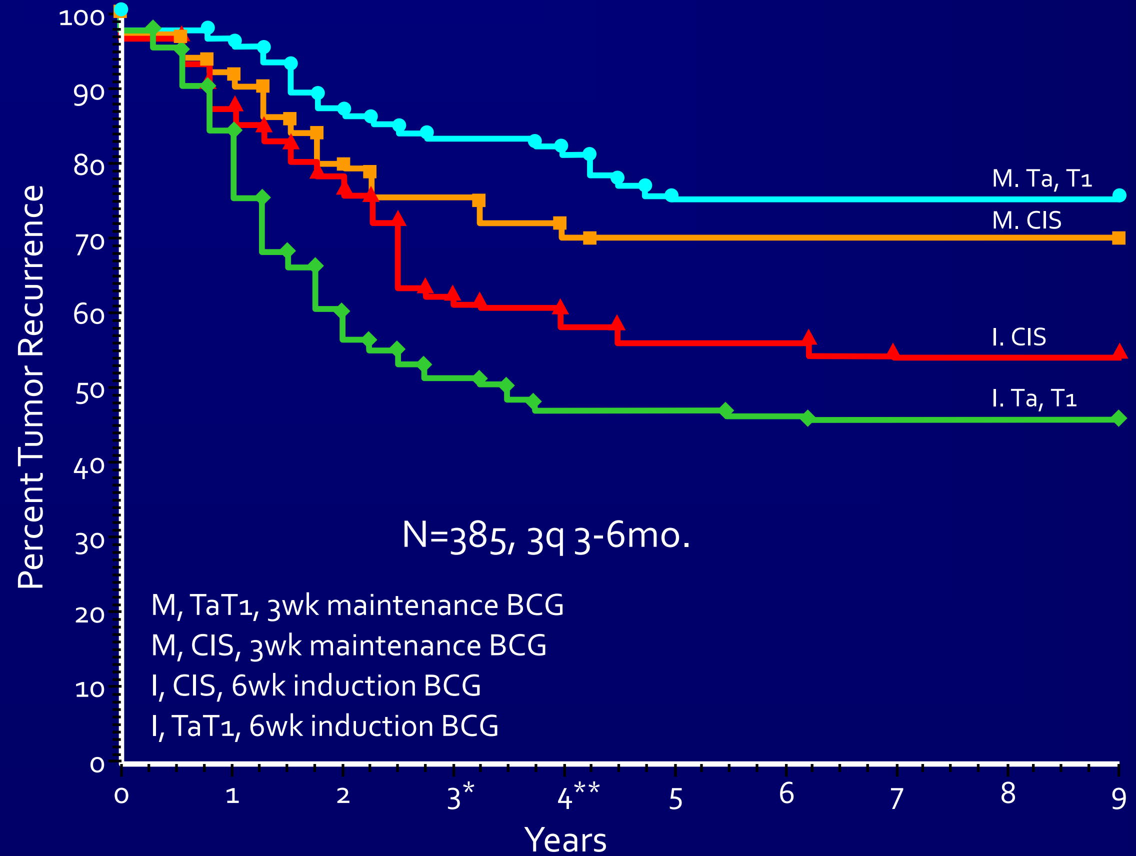


BCG Maintenance: Not Created Equal









Side Effects from BCG

Side Effects from BCG

- Common: Irritative symptoms, mild fever
  - Self limiting
  - Tylenol, antibiotics, antispamodics
- Uncommon:
  - 1 – 3%: Prolonged Fever,
  - Longer course of antibiotics
- Rare
  - < 1%: Sepsis, BCG infection

Practical Points with BCG

- Inform your doctor if your see blood in urine
- Stop if any blood or risk infecting blood stream
- Don't use too much KY – BCG clumps!
- Try to hold treatment in bladder for a min of 45 min but preferably 2 hours.
- Avoid antiplatelets eg ASA, Plavix
  - Discuss this with your doctor

- BCGs works very well
  - BUT – does not work for all tumors
- If tumor recurs after one induction plus one maintenance course of BCG
  - Must be considered a ‘dangerous’ tumor
  - Consider removing bladder

BCG plus 'X'
Interferon-α Combination

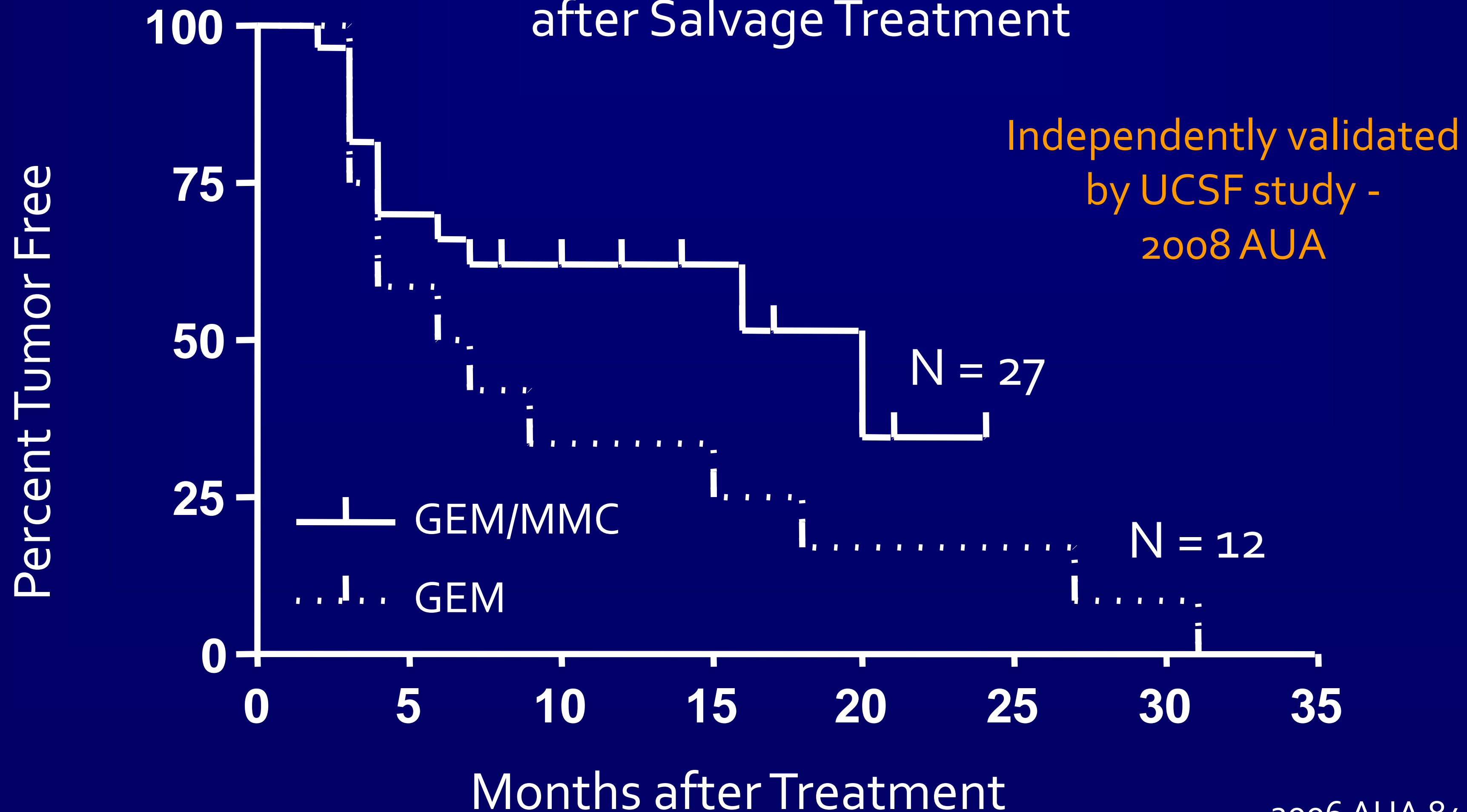
- Induction (1/3rd BCG + 50 MU IFN-α)
  - Maintenance
  - Dose Reduction BCG to 1/30th - 1/100th
- Results
  - Well tolerated (< 10% dropout rate)
  - Moderate efficacy
    - Not effective BCG failure X 2 +
  - Less effective in elderly patients (≥ 80 yr)

Dr O'Donnell, pers. comm.

VALSTAR for BCG Refractory CIS

- FDA approved in 1998 for BCG-refractory CIS
- For patients who are not candidates for cystectomy
- 800 mg/75ml weekly for 6 weeks

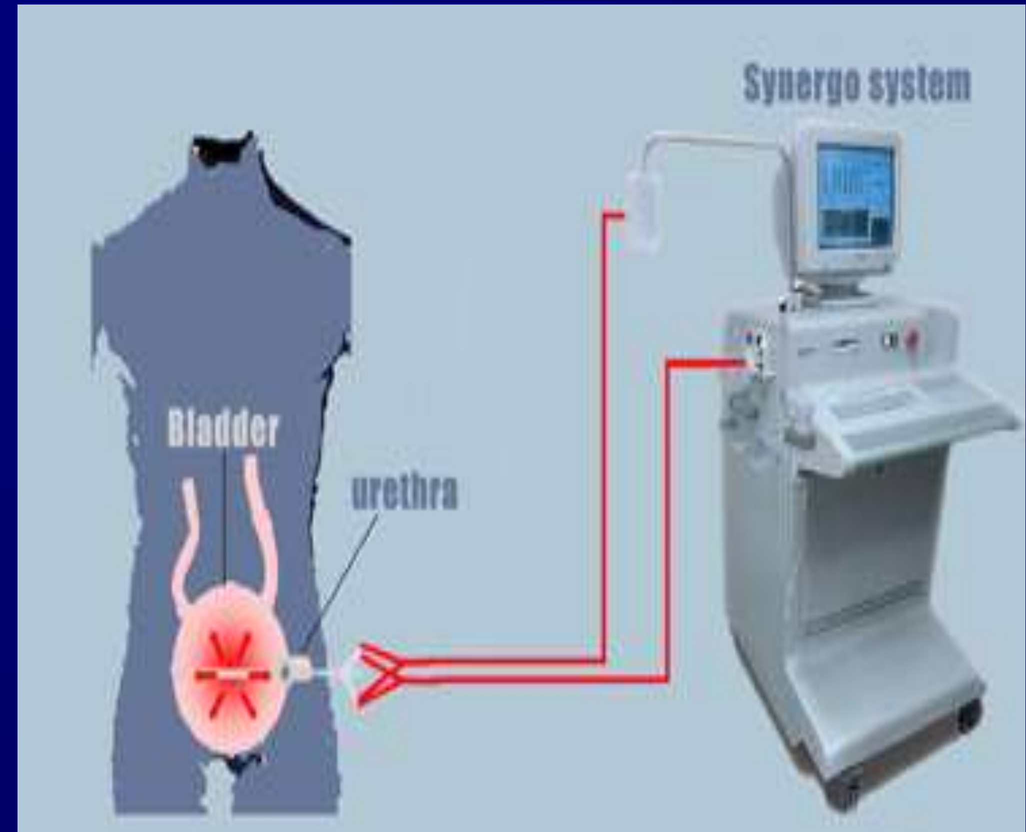
Combination Chemotherapy for BCG Failures



2006 AUA 840 (Maymi)

Microwave Chemothermotherapy

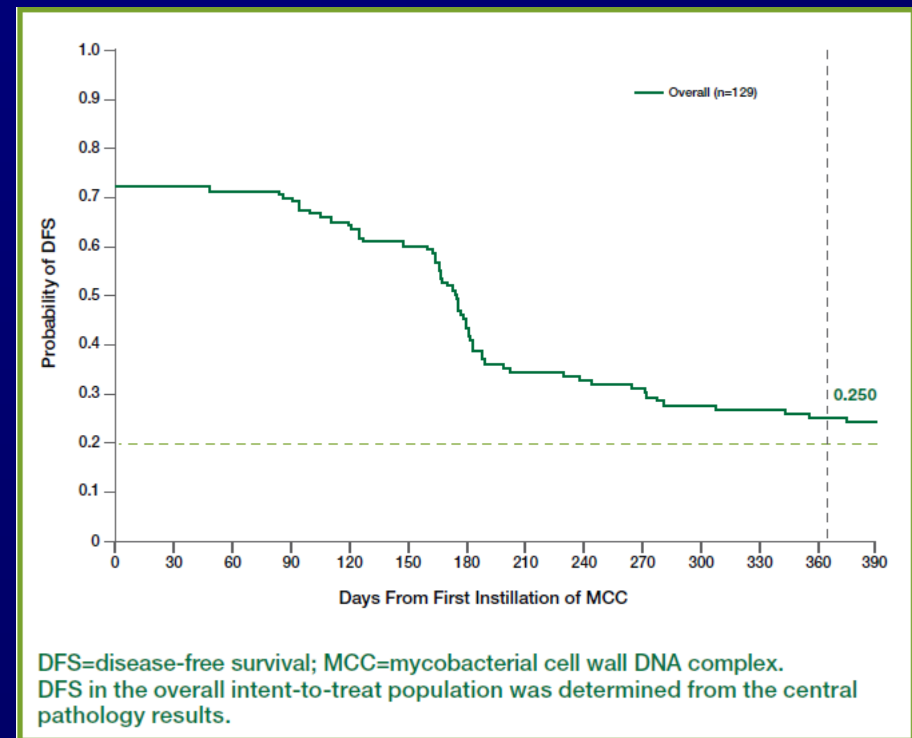
- Microwave catheter with chemotherapy
- Efficacy superior to MMC
- Early results for BCG failures
  - 76 BCG failures (EAU 2008)
    - 83% NED @ 1 yr; 62% 2 yr



Slide Courtesy Mike O'Donnell

Urocidin (Mycobacterial Cell Wall - DNA Complex)

- Phase 2/3 in BCG Refractory Patients (n = 129, 25 sites)
- Overall 1-year DFS rate was 25.0%
  - 35% with only papillary tumors
  - 21% with CIS (primary or concomitant with papillary)
- Well tolerated



DFS=disease-free survival; MCC=mycobacterial cell wall DNA complex.
DFS in the overall intent-to-treat population was determined from the central pathology results.

Presented at AUA 2011

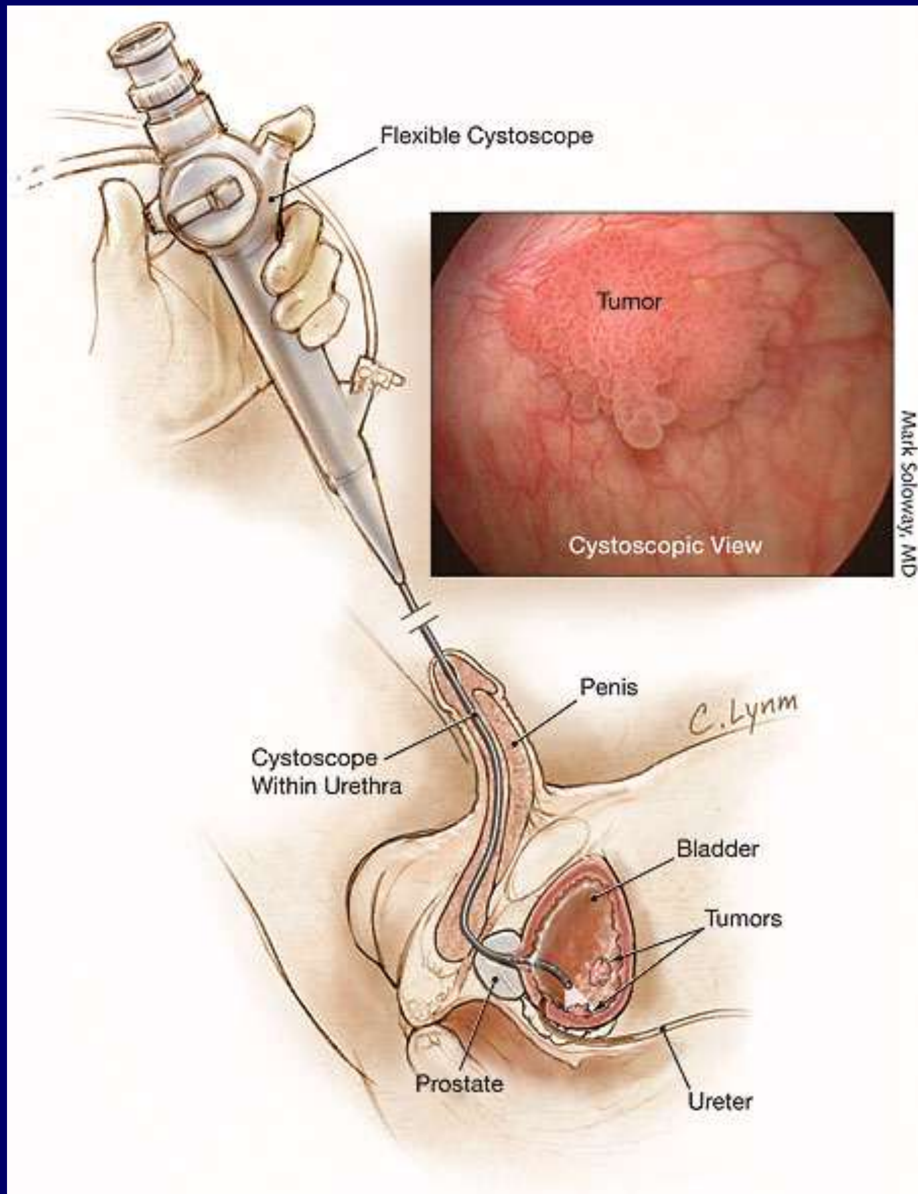
Other Agents Being Studied

- MD Anderson Ad-IFN Gene Therapy Trial
  - Phase 1 Completed, Phase 2 accruing

- Lytic Adenovirus w/GMCSF: (Cell-Genesis) Ph1 BCG failure
- Bexidem: (IDM) Autologous activated macrophage
- Chemophase: (Halozyme) + MMC
- Phase I, OGX-427Antisense Oligonucleotide Targeting Heat Shock Protein 27
- Pfizer: Sunitinib (Sutent) in BCG-Refractory TCC

Monitoring
Superficial Bladder Cancer

The Gold Standard for Bladder Cancer Detection



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Follow-up

- Frequency depends on the risk stratification
- Cystoscopy – i.e. look in the bladder
  - Every 3 months ….. every year …..
  - As bad to perform too often as it is to perform not often enough

Risk of Recurrence of Newly Diagnosed Superficial Bladder Cancer

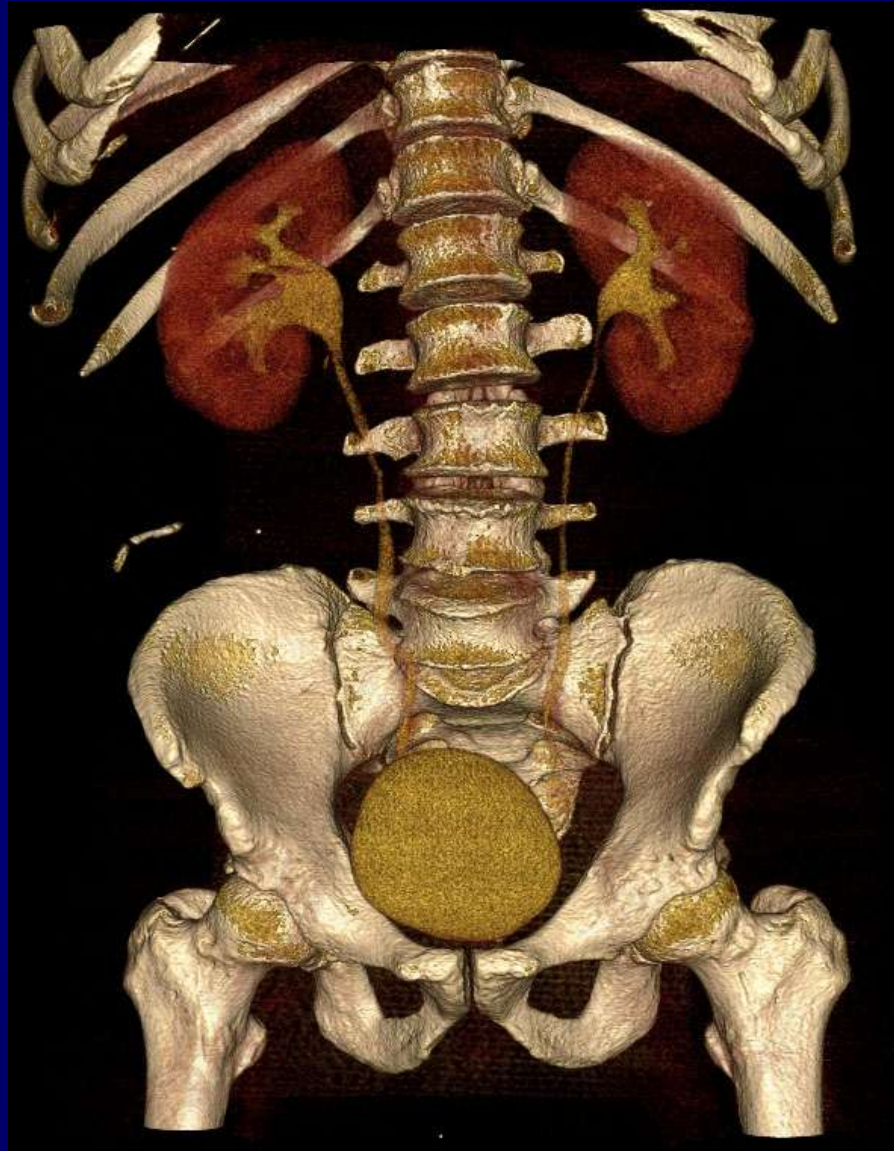
No. of Tumors	Recurrence at 3 mos cysto	1-year free of recurrence
Single	no	75%
Single Multiple	yes no	50%
Multiple	yes	20%

Not everyone needs cystoscopy every 3 months for 2 years!

Reading et al, *Br J Urol.* 1995.

Follow-up

- Imaging to evaluate the 'Upper Tracts'
  - Kidneys, ureters
  - IVP
  - CT Urogram
- Performed based on risk
  - Once every 12 to 36 months



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Follow-up: Urinary Markers

- Can use urine based tests
- False positives do exist
  - Can cause unnecessary anxiety, needless work-up
- Discuss with your doctor

Tumor Markers Available

- Cytology

Soluble

- NMP22, BladderChek
- BTA *stat*, TRAK
- AccuDx

Cellular

- ImmunoCyt
- DD23

FISH

- UroVysion

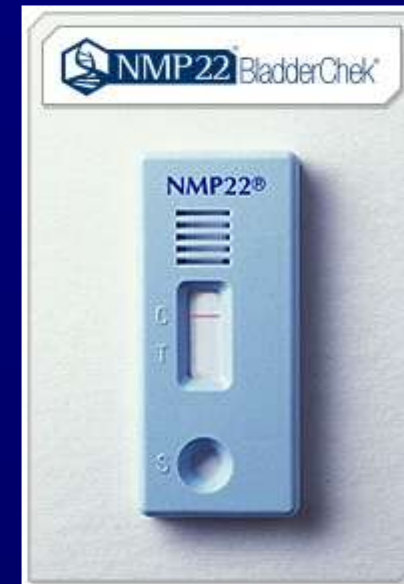
Others: HaHa, Survivin, TATI, sFas, BLCA-1, CYFRA21-1, etc ..

Urinary Cytology

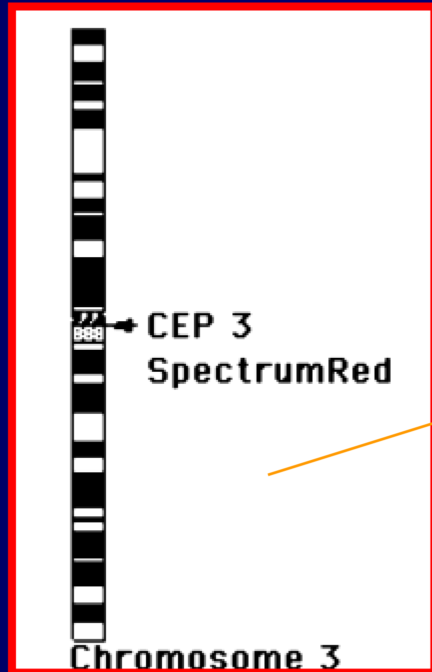
- Evaluate the urine for cells shed
- Study the architecture of cells to diagnose malignancy
- Depends on the expertise of the pathologist
- Very specific, but not very sensitive

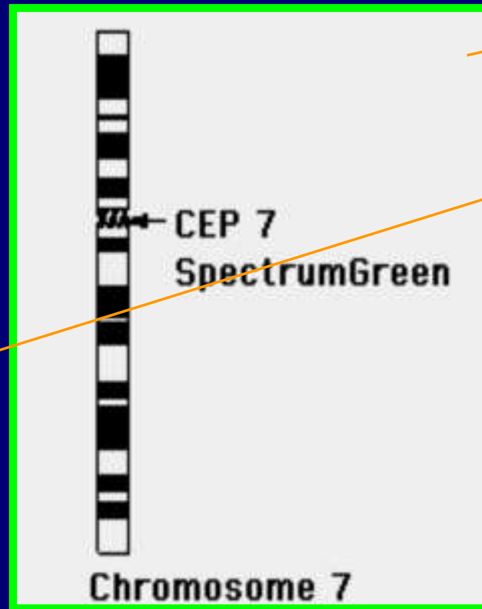
NMP22

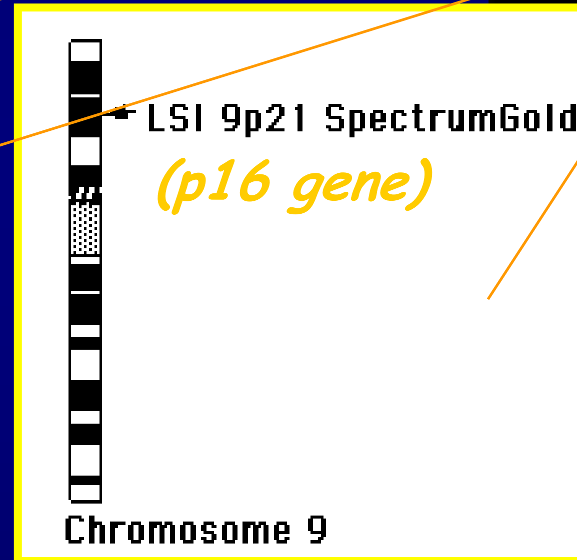
- Urine sample placed on test strip
- Colored line indicates test result
- Immediate results
- Many false positives
- High negative predictive value

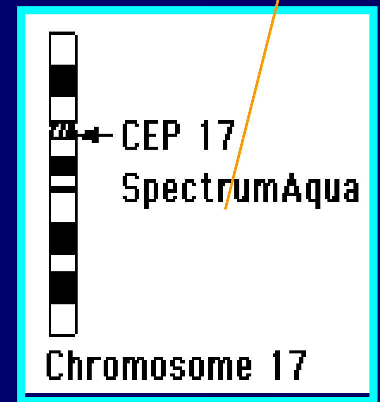


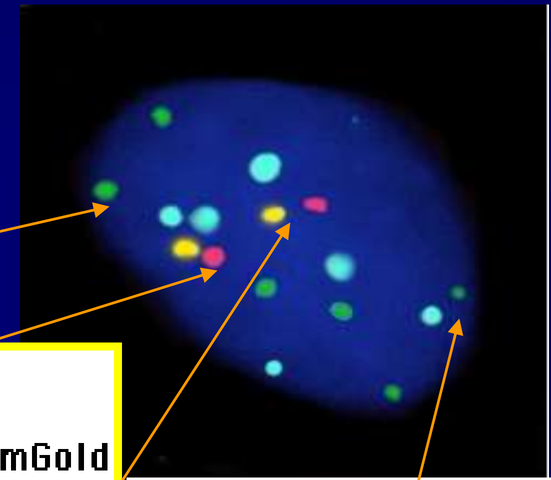
UroVysion™











Urinary Markers

- In a prospective trial, we found that cystoscopy alone was the most cost-effective strategy to detect recurrence of non-muscle invasive bladder cancer
- Addition of urinary markers added to cost, without meaningful improvement in detection of disease

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Non Muscle Invasive
(SUPERficial Bladder Cancer)

Ta, T1, CIS; G1, G2, G3, HG, LG

Complex Disease

Needs Diligent Urologist and Faithful Patient

Be Informed, Ask Questions

Questions?

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