

Bladder Cancer Detection: BCAN meeting

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Bladder Cancer Natural History

- ◆ **Non Muscle Invasive Disease: 75%**
- ◆ **Invasive disease: 25%**
 - ◆ **Very different management for each**
 - ◆ **Cystectomy vs. TURBT**

The Problem in Non-invasive Cancers

- **Recurrence:**
 - 60-80% chance of recurrence at 5 years with surgery alone
 - Exception – first time, solitary, small, TaG1 papillary tumors

Progression

- **Aside from recurrent disease**
 - T1
 - High grade
 - Carcinoma-in-situ (CIS)
- **Progression to Muscle Invasive Bladder Cancer: 10-30%**

Field Effect

- **Toxins such as those in tobacco expose entire urinary tract**
- **Tumors arise at different times and sites in the urothelium**
- **Genetic changes occur throughout the urothelium in locations remote from actual tumors.**

Patterns of Spread

- **Lymphatic Spread**
 - The most common sites of metastases in bladder cancer are the pelvic lymph nodes.
- **Vascular Spread**
 - Liver: 38%
 - Lung: 36%
 - Bone: 27%
 - adrenal glands: 21%
 - Intestine: 13%

Initial Management

- TURBT – complete endoscopic resection with sampling of muscle (2nd look procedures for T1 disease)
- Perioperative intravesical cytotoxic chemotherapy (within 6 hours)
 - Low-risk patients – 40% decreased odds of recurrence
 - Multiple tumors – 56% decrease(Sylvester et al. JUrol 2004)

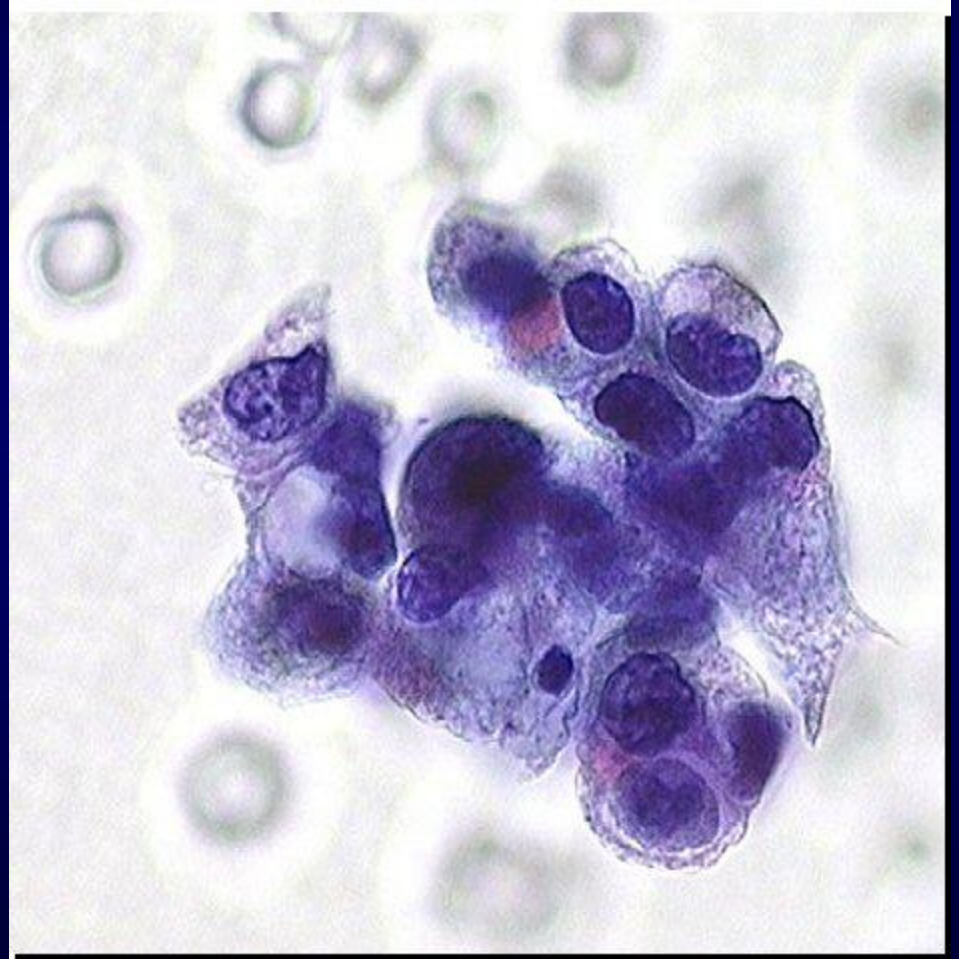
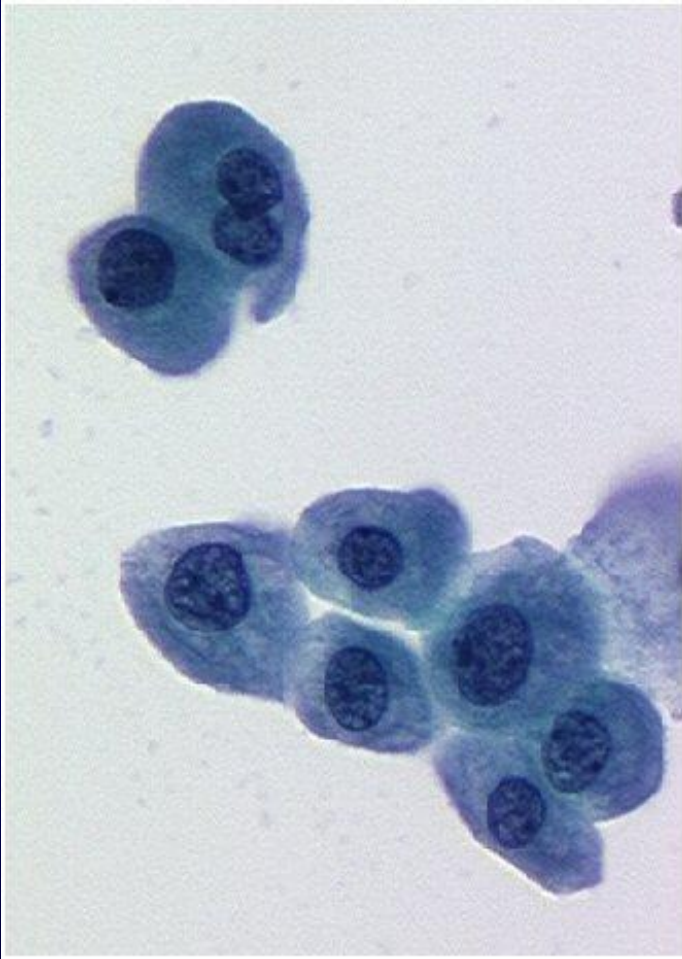
Bladder Cancer Surveillance : Non-invasive Disease

- **Cystoscopy: every 3 months**
 - **Sometimes Misses High-Grade CIS**
 - **Unable to Detect Upper Tract Disease**
- **Imaging**
 - **5% of patients with bladder cancer get cancer in lining of kidney and ureters**
 - **Patients with high grade disease get imaging every 2 years**

Urine Cytology

- **Detects High-Grade CIS**
- **Frequently Misses Low-Grade Papillary Tumors**
- **Overall Sensitivity 30%, Overall Specificity = 95%**

Urine Cytology



Tumor Marker Approaches

- **Biochemical** detection of proteins or other urinary compounds
 - NMP22
- Detection of cellular **antigen** by immunohistochemistry or cytochemistry
 - ImmunoCyt™
- Detection of **genetic alterations**
 - FISH

Sensitivity and Specificity of Common Markers

Marker	# studies	Sensitivity (95%CI)	# pts	Specificity (95% CI)	# pts
Cytology	18	.34 (.20-.53)	1255	.99 (.83-.997)	1512
NMP 22	15	.73 (.47-.87)	834	.80 (.58-.91)	1579
BTA Stat	10	.71 (.57-.82)	938	.73 (.61-.82)	1596
FISH	3	0.83	222	0.96	134
Telomerase	2	.77 (.53-.91)	104	.99 (.46-.99)	168
Immunocyt	1	0.86	79	0.79	170

Adapted from Lotan and Roehrborn: Urology
2003 61(1)

ImmunoCyt™ / uCyt+™

- **Uses antibodies labeled with fluorescent markers**
 - a mucin glycoprotein
 - carcinoembryonic antigen (CEA)
- **Any cells expressing tumor antigen are then detected by fluorescence microscopy.**
- **Recommended in combo with cytology**

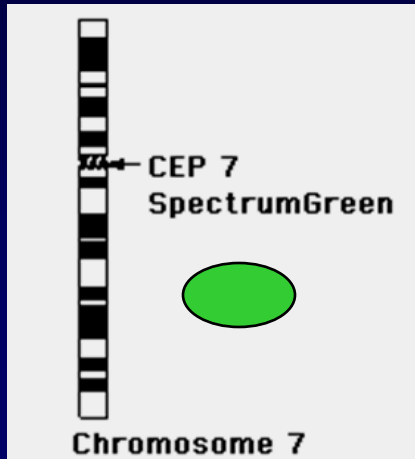
ImmunoCyt™ / uCyt+™

- **Multicenter French trial: Pfister et al. J Urol 2003**
- **694 patients: 458 (h/o TCC), 236 (symptoms)**
- **Sensitivity: 60.7% (gr1), 75.6% (gr2), 76.8% (gr3)**
- **Specificity: 84.2%**

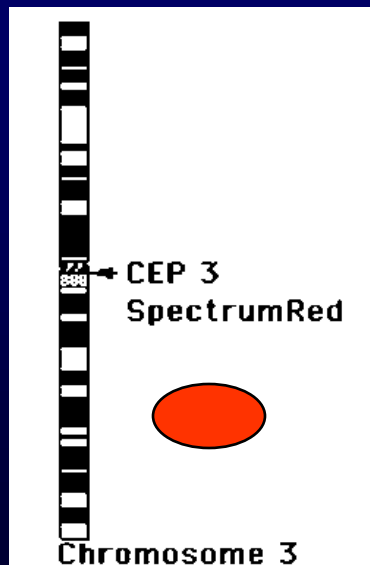
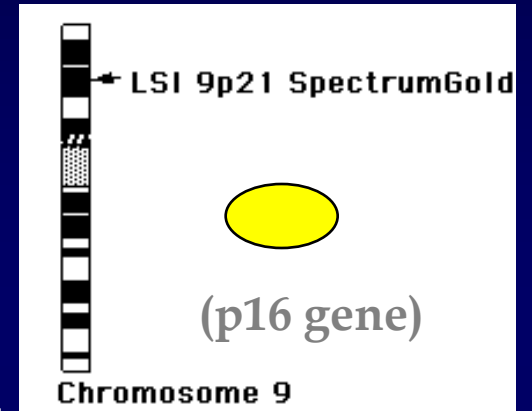
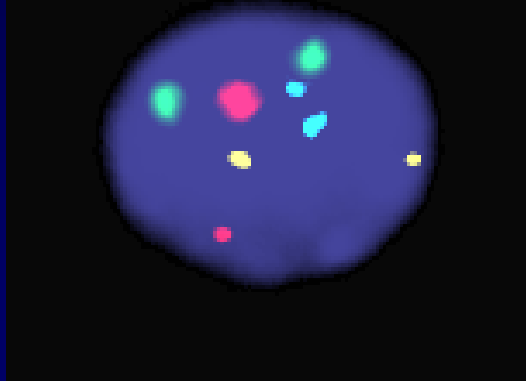
UroVysion

- **Detects aneuploidy via Fluorescence in situ Hybridization**
- **Abnormal result**
 - **More than 2-4 cells with multiple chromosomal gains**
 - **More than 9-11 cells with loss of both copies of 9p21**
- **Intended use**
 - **Monitoring for tumor recurrence in conjunction with cystoscopy**

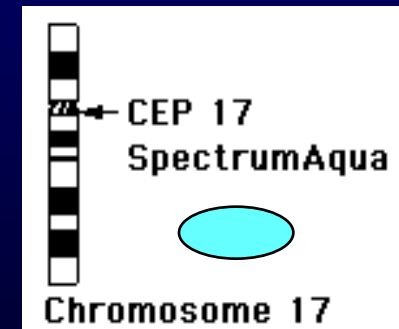
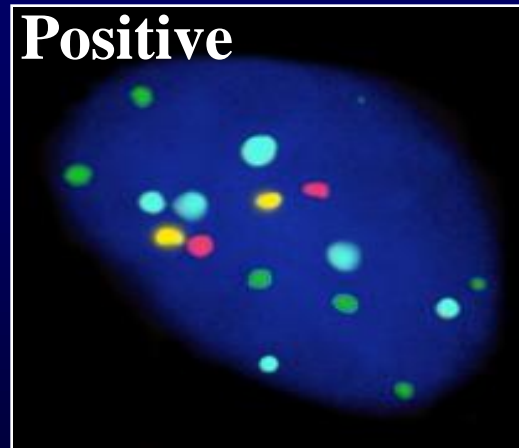
UroVysion

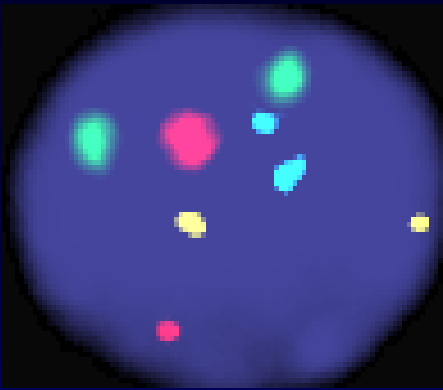


Normal

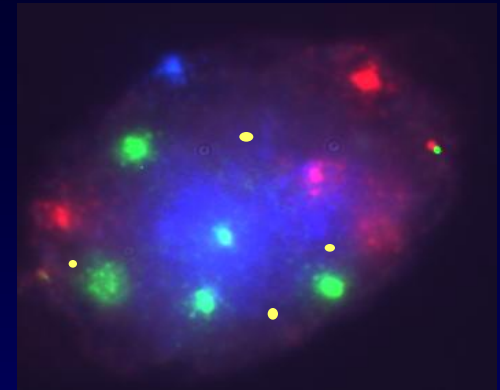


Positive

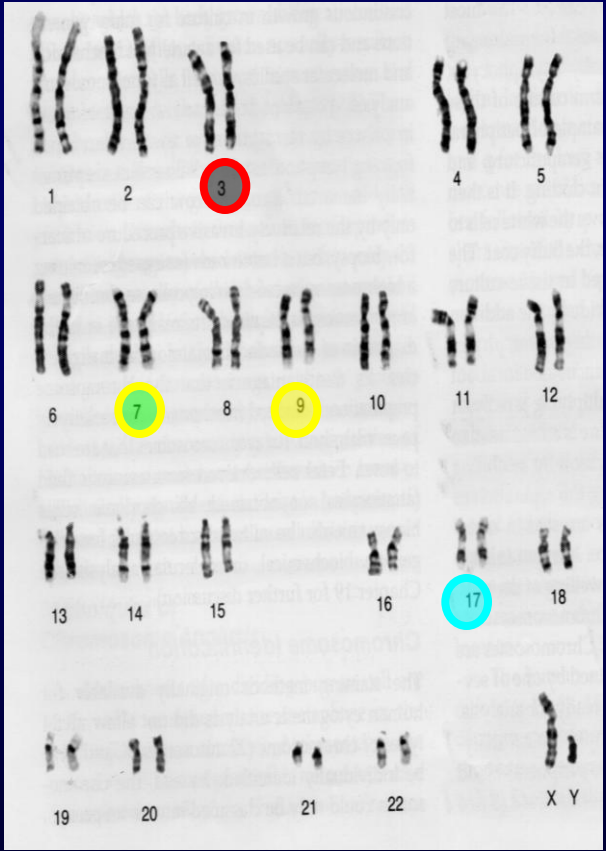




Normal Cell



Malignant Cell



NMP22® BladderChek™

- **On April 28, 2003: FDA approval for diagnosis of bladder cancer.**
- **Point-of-care test**
- **Medicare Reimbursement**
- **Detects nuclear matrix protein in the urine of patients**
- **What to do with “false positives”?**

Problems with Low Specificity

- 278 symptomatic patients:
 - 112: microscopic hematuria
 - 77: gross hematuria
 - 89: chronic symptoms of urinary frequency or dysuria.
- NMP22
 - True-positive in 28 cases
 - False-positive in 44 cases
 - Specificity of 82% and a PPV of 38.9%.
- BTA stat test
 - True-positive in 23 cases
 - False-positive in 43 cases
 - Specificity of 82.4% and a PPV of 34.9%.

Interpretation of False Positives

- False positive findings may indicate premalignant changes predating a finding of recurrent malignancy
- Mean f/u of 13.2 months after “false-positive” NMP22 test
- NMP22: 4/7 (57%) versus 2/18 (11%) [$P = 0.032$]
- Giannopoulos et al. Urology 55:871-5, 2000.

“Anticipatory Positive” FISH Results

- **7/11 (64%) recurrent TCC <12 months**
 - 4 progressed to a higher stage

Halling KC et al. - J Urol 2000; 165:1768-1175.

- **4/9 (44%) recurrent TCC <6 mo**

Junker K et al. - J Urol 2002; 167:164.

- **4/5 (80%) recurrence mean 7.9 months**
 - **0/5 (0%) FISH neg had recurrence**

Bubendorf L et al. - Am J Clin Pathol 2001; 116:79-86.