Hematuria

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Objectives

- Define hematuria and indications for evaluation
- Describe causes and differential diagnosis
- Indications for urologic evaluation/referral
- Advances in kidney cancer
- Update on bladder cancer

Examination of the Urine

"The ghosts of dead patients that haunt us do not ask why we did not employ the latest fad of clinical investigations; they ask why did you not test my urine?"

Sir Robert Hutchinson

1871-1960

Hematuria: Definitions

- Gross or microscopic blood in the urine
- 3 or more RBC/HPF in 2 of 3 specimens, or 4 or more RBC/HPF
- Normal: up to 100,0000 rbc excreted per 12 hours
- Microhematuria occurs in 2.5 to as much as 21% of the population
- 1ml or less of blood is visible

Hematuria

- Other causes of urine discoloration: pigment from beets, rifampin, pyridium. Porphyria
- Centrifuge: color in sediment
- Dipsticks are highly sensitive, as few as 1-2 RBC, confirm with microscopic examination

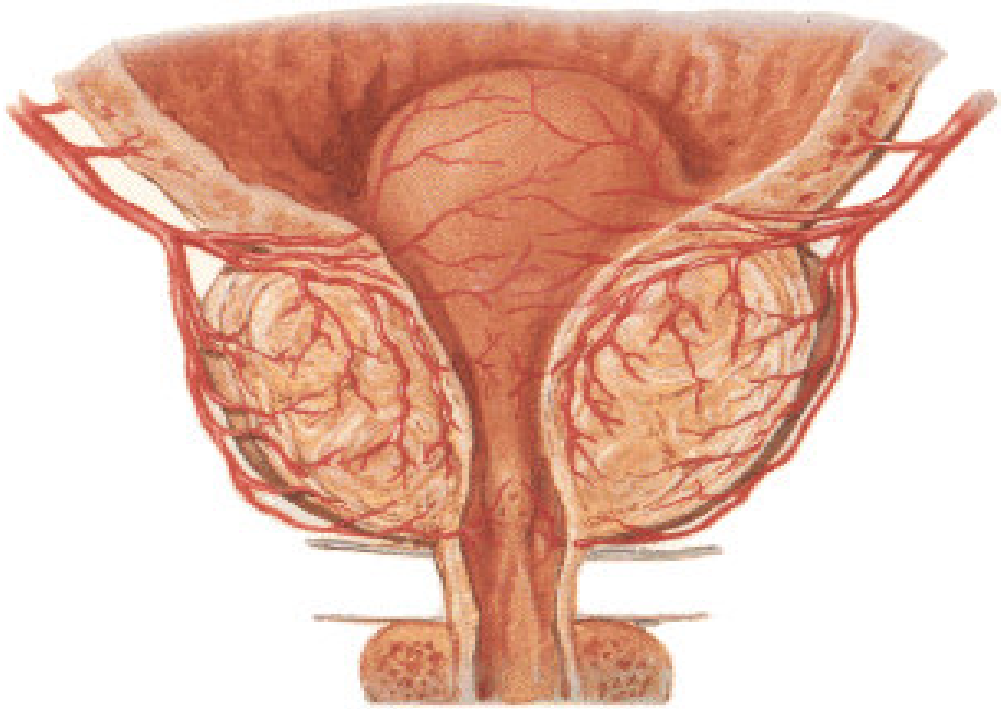
Hematuria

- 10% or more have benign hematuria or hematuria of unknown cause
- Symptom of bladder cancer, kidney cancer, infection, stones, etc. guide workup
- Risk factors for cancer: smoking, radiation, chemical exposure, age

Hematuria: Common Causes

- Bladder cancer
- Kidney cancer
- Ureteral cancer
- Urethral cancer
- Prostate cancer
- Stones
- Pyelonephritis
- Cystitis
- BPH
- Glomerulitis
- Radiation cystitis
- Chemical cystitis
- Prostatitis
- Exercise hematuria

Arterial Supply of Prostate



Benign hyperplasia specimen

Clues From the History

- Pyuria, bacteriuria and dysuria- suggest UTI, but beware, high grade bladder cancer causes dysuria and pyuria
- URI or skin infection 10-21 days ago or more suggest post-strep or IGa nephropathy
- Family history of kidney failure? Hereditary nephritis or polycystic kidney disease

Clues From the History

- Flank pain: renal/ureteral stone or blood clot. Rarely, persistent flank pain may occur: loin pain hematuria syndrome
- Spontaneous bleeding at other sites suggest coagulopathy, but hematuria still needs evaluation
- Lower tract obstructive symptoms
- Vigorous exercise, trauma

Clues From the History/ PE

- Cyclic hematuria in women: endometriosis of the urinary tract, menstrual contamination
- People of Mediterranean origin: sickle cell trait or disease
- Glomerular bleeding: RBC casts, protein>500mg/d without gross hematuria, dysmorphic RBC, renal insufficiency: nephrology rather than urology referral

Workup of Hematuria

- History and physical exam
- Urinalysis for protein, crenated RBC, RBC casts, bacteria
- Cytology
- Creatinine
- Imaging studies: ultrasound, IVP, CT, MRI, RPG
- Cystoscopy

Negative Evaluation?

- Found in at least 10% of cases
- Cancer later found in 1-3% of these patients
- Consider repeating UA and cytology in 6, 12, 24, 36 months
- Consider immediate repeat evaluation for recurrent gross hematuria, abnormal cytology, or lower urinary tract symptoms of frequency and dysuria

Unexplained Hematuria

- Focal glomerulitis
- Metabolic predisposition to stone formation
- Children: one third of idiopathic hematuria is due to hypercalciuria; 5-20% hyperuricosuria; rarely hypocitruria
- AV malformations/fistula- usually gross hematuria

Asymptomatic Microhematuria

- 100 consecutive cases
- 13% had significant urologic disease:
  - 8 urinary calculi
  - 3 kidney tumors
  - 2 bladder tumors
- 43/44 subjects (98%) with dysmorphic RBC or RBC casts had no significant urologic source, i.e. had a parenchymal source

Urology 46:484-9, 1995

Persistent Microhematuria

- 372 consecutive cases asymptomatic microhematuria evaluated with IVP and cystoscopy
- 43% had GU pathology found
- Of 212 with a negative workup, 75 (35%) had persistent microhematuria
- Repeat evaluation showed abnormalities in 11 of these 75 (15%)

Urology 56:889-94, 2001

CT for Microhematuria

- 115 pts: CT with 5mm cuts plus IVP
- Xray abnormalities: 38%. 100% sensitivity for CT and only 60% for IVP. CT specificity/accuracy 97%/98% vs 91%/81% for IVP
- 40 non-urological diagnoses were also made with CT
- CT is more sensitive and specific and detects other pathology

J Urol 268:2457-60, 2002

Renal Cancer Incidence, 2005

- 36,160 cases; 22,490 men, 13,670 women
- 3% of cancer in men
- 12,660 estimated deaths in 2005
- Relative mortality/incidence: 39%, compared with 23% for bladder, 17% prostate, and 5% testis

Renal Cancer, 1975 to 1995

JAMA. 1999;281:1628-1631

- Annual increase: 2.3% white men, 3.1% white women, 3.9% black men, and 4.3% black women; greatest for localized tumors but also advanced tumors
- In contrast, renal pelvis cancer declined among white men and remained stable among white women and blacks
- Mortality increased in all groups

Renal Cancer Etiology

- Tobacco, cadmium, radiation, dialysis
- Risk factors: hypertension, increased body mass index, and red meat intake; inverse relation with intake of carotenes
- Four-fold increased risk with family history

Seminars in oncol. 27:115-123, 2000

Curr opin oncol. 12:260-4, 2000

Renal Cancer Etiology

- Clear genetic factors: VHL gene on chromosome 3, mutation of VHL in **clear, granular and sarcomatoid RCC** but not papillary RCC
- Trisomy of 7 and 17 and loss of the sex chromosome: **papillary** tumors
- **Chromophobe RCC**: loss of chromosomes with a combination of monosomies
- Deletion (8p)/-8, +12, and +20: worse prognosis

Renal Cell Carcinoma

Urology, 55:31-5, 2000

- Onset age 62, 82% with localized disease
- 41% T1 disease, 15% T2, 39%T3, 4% T4
- Fuhrman grade 1 or 2 in 51% of patients and 3 or 4 in 45%. Prognosis correlated with Fuhrman grade
- Stage and grade associated with survival (P=.0001 and P = .0028, respectively)
- In stage M0, smokers had a significantly worse overall survival (P = 0.039)

Classification of Renal Carcinoma

Semin Oncol. 27:124-37, 2000

Tumor type	cell of origin	genetic abnormality
Clear cell (60%)	prox tubule	VHL, 3p
Papillary (10%)	distal tubule	7+ 17+3+Y-
Chromophobe (10%)	intercalated cells	Y-1-2-6-10-13-17-21-
Collecting duct carcinoma (1%)		1-6-14-15-22-8p-13q-
Medullary carcinoma (<1%)		sickle trait

Workup of Renal Masses

- Intravenous pyelogram is no longer the most common imaging study
- Most are diagnosed with CT, ultrasound, or MRI
- Angiography plays a less frequent role and is now used only for questionable cases or as an aid to partial nephrectomy

Controversies in Renal Tumors

- Partial nephrectomy
- Laparoscopic nephrectomy
- Nephrectomy in metastatic renal cell carcinoma
- Resection of solitary and multiple metastasis
- Medical treatment of metastatic disease

Bladder Cancer Statistics, 2005

- New cases: 63,210
  - Men: 47,010; #4 women: 16,200 #8
- Estimated deaths: 13,180
  - Men: 8,970; #9 women: 4,210
- Incidence/mortality: 20.8%
  - Men: 19% women: 26%
- Prevalence: more than 600,000 in US

Bladder Cancer Etiology

- Initial link to aniline dyes made in 1895
- Industrial exposure: rubber and textiles
- Aromatic amines: 30x risk
- Tobacco: 3x increased risk, 60% of cases
- Treatment complication: 9x risk with cyclophosphamide or ifosfamide; 4x RT
- Schistosoma hematobium, infection, foreign body: squamous cell carcinoma

Bladder Cancer Pathology

Transitional Cell:	94%
Squamous Cell:	5%
Adenocarcinoma:	<1%
Rhabdomyosarcoma:	<1%

Bladder Cancer, 2005

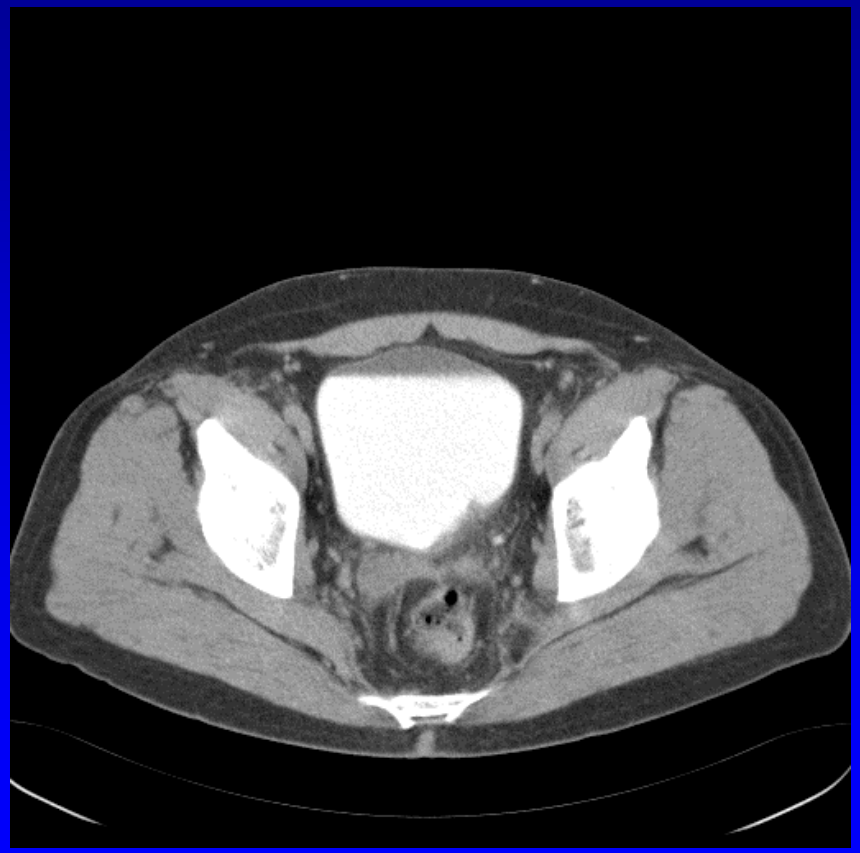
- Peak onset: 6th to 8th decades
- Men/women: 3 to 1
- Twice as common in white men compared with African American men
- Genetic mutations: genes on chromosome 9 including p16. Invasion p53, rb, p21
- Screening: hematuria detection reduces mortality

Bladder Cancer
Signs and Symptoms

- 85% present with gross or microscopic hematuria. Bleeding is ***typically*** intermittent and not related to grade/stage
- 20% have irritative voiding symptoms: burning, frequency. More commonly associated with CIS and higher grade tumors

“Recurrent” High Grade Bladder

58y/o man with 4 yr Hx micro-hematuria, not evaluated
Presented with gross hematuria
Cysto shows BT, resection G3,TA
No muscle in specimen
CT urogram shows normal upper tracts, lesion in bladder
Repeat resection confirms residual TCC, fortunately not invasive



66y/o with 4 year Hx of frequency, dysuria & hematuria.

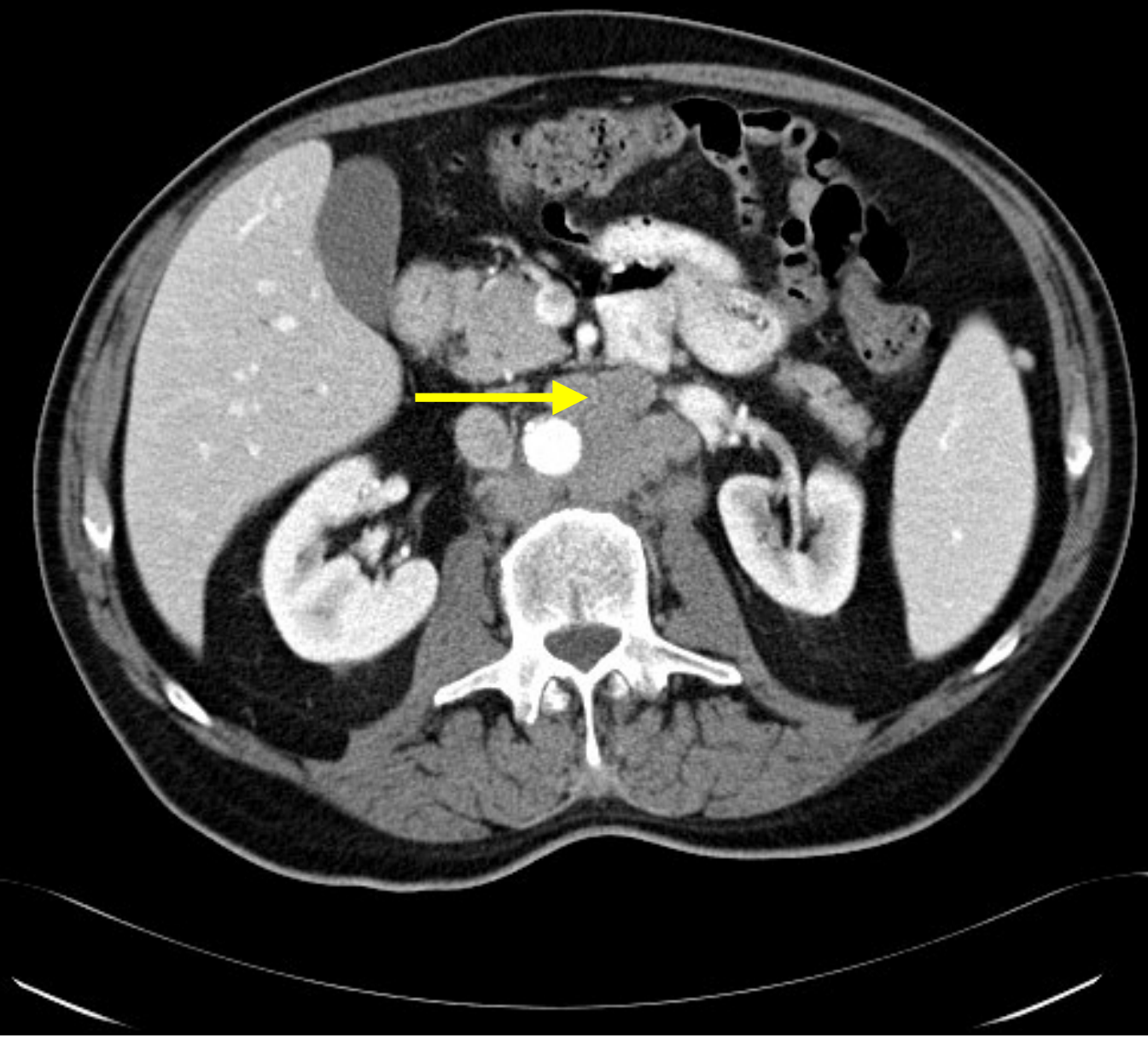
Suspicious DRE

Voided Cytology positive

Needle biopsy of prostate positive for TCC

Cysto/TUR: bladder neg. Invasive TCC prostate

CT scan: extensive nodal metastasis

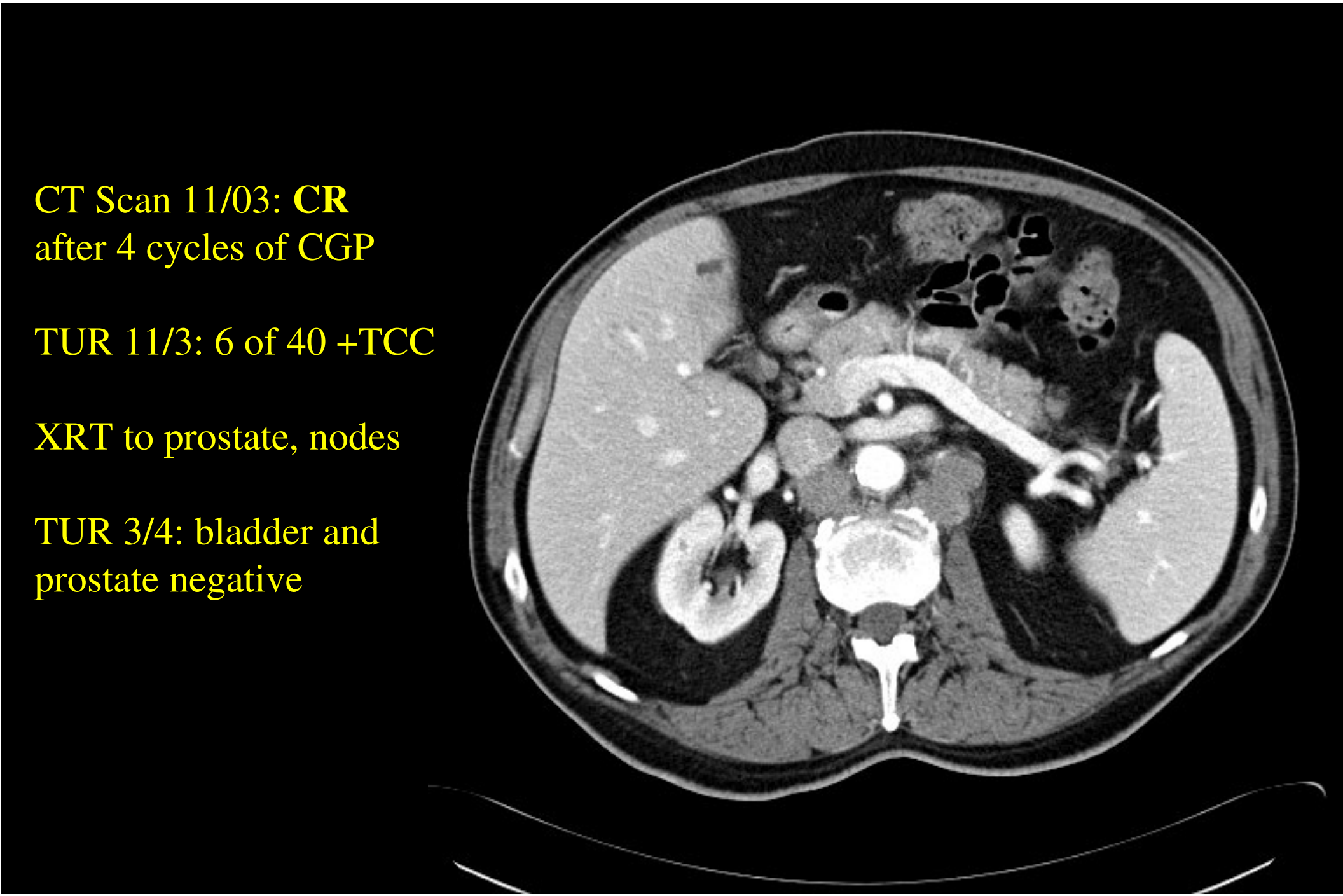


CT Scan 11/03: **CR**
after 4 cycles of CGP

TUR 11/3: 6 of 40 +TCC

XRT to prostate, nodes

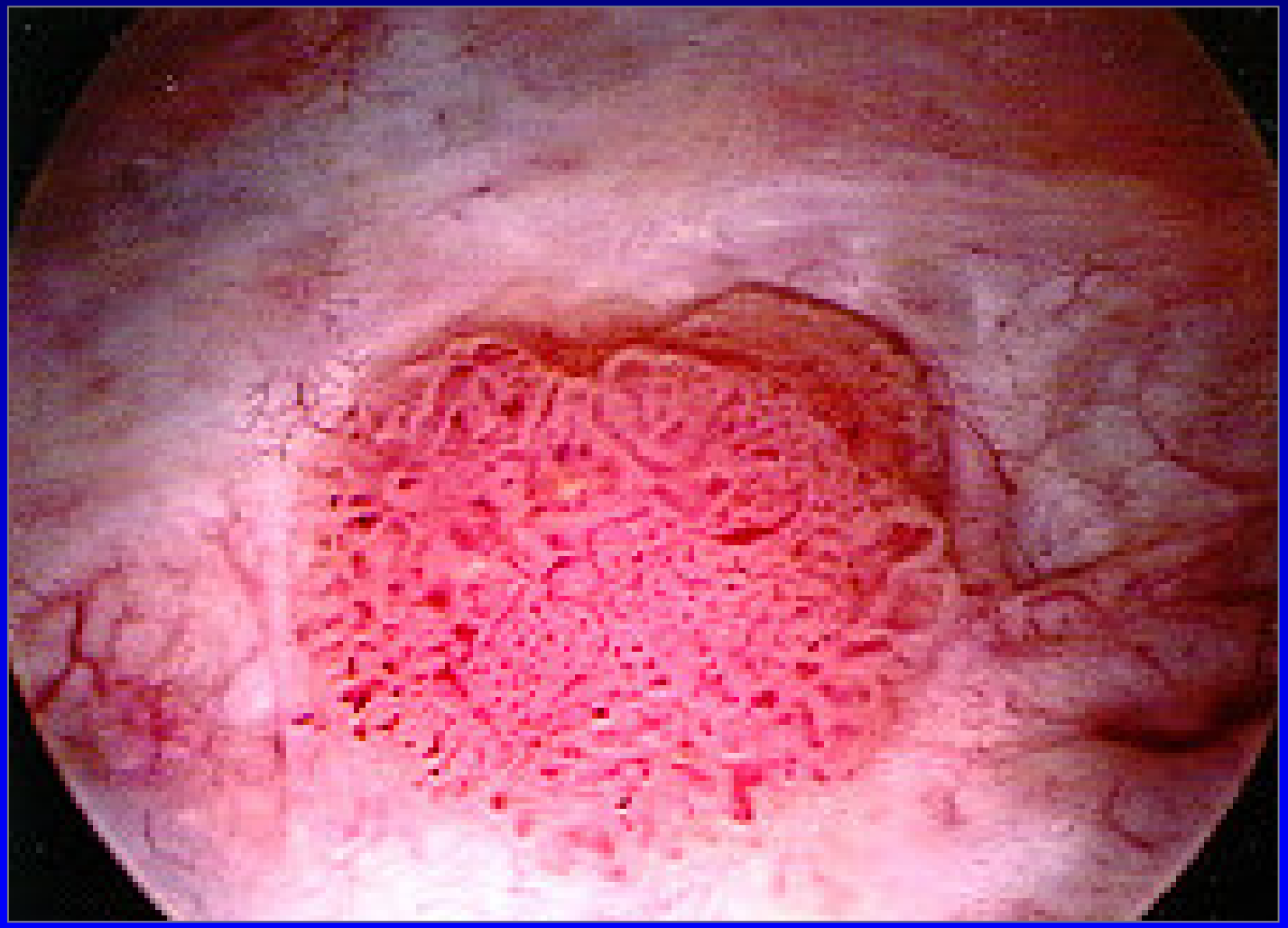
TUR 3/4: bladder and
prostate negative

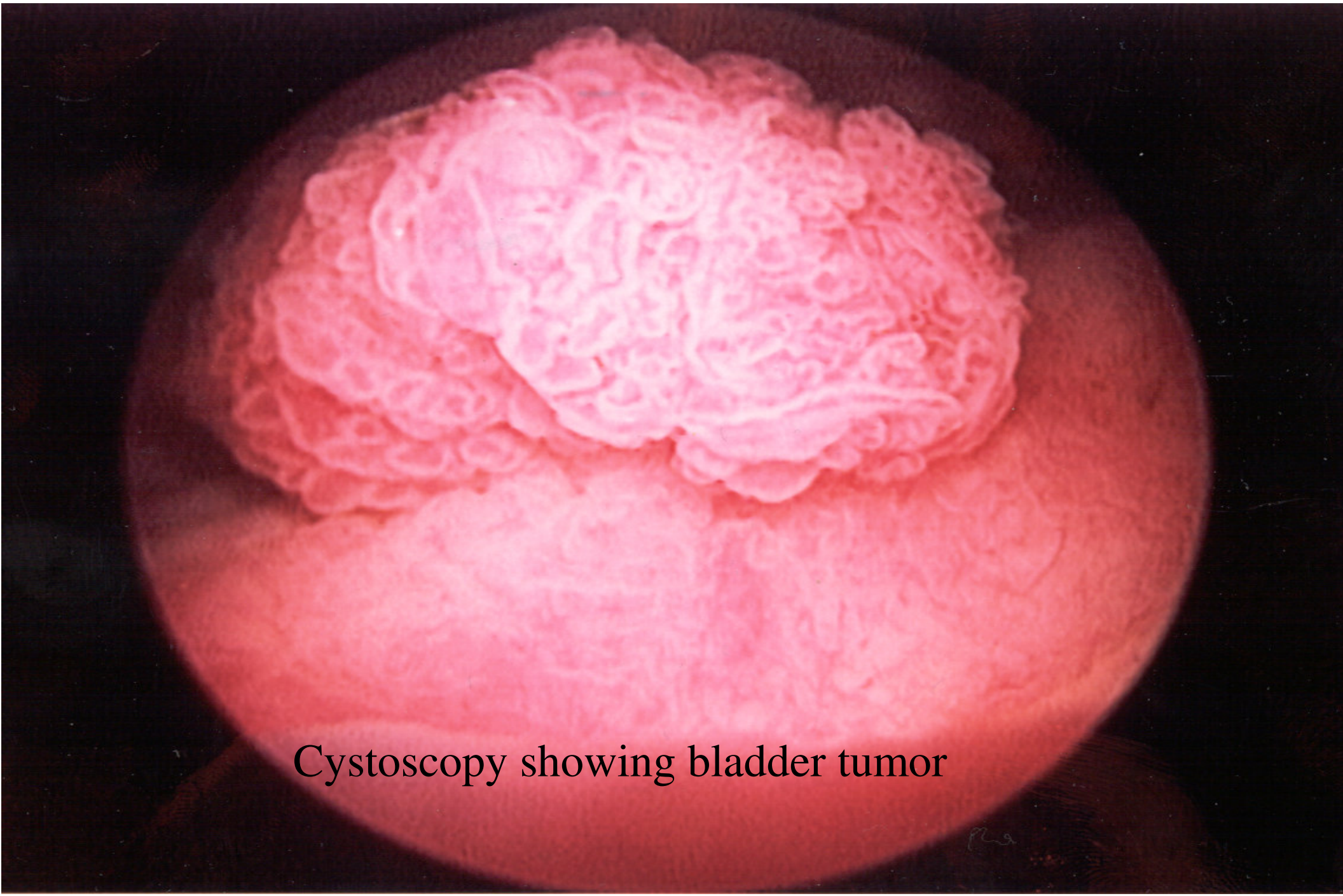


Diagnosis

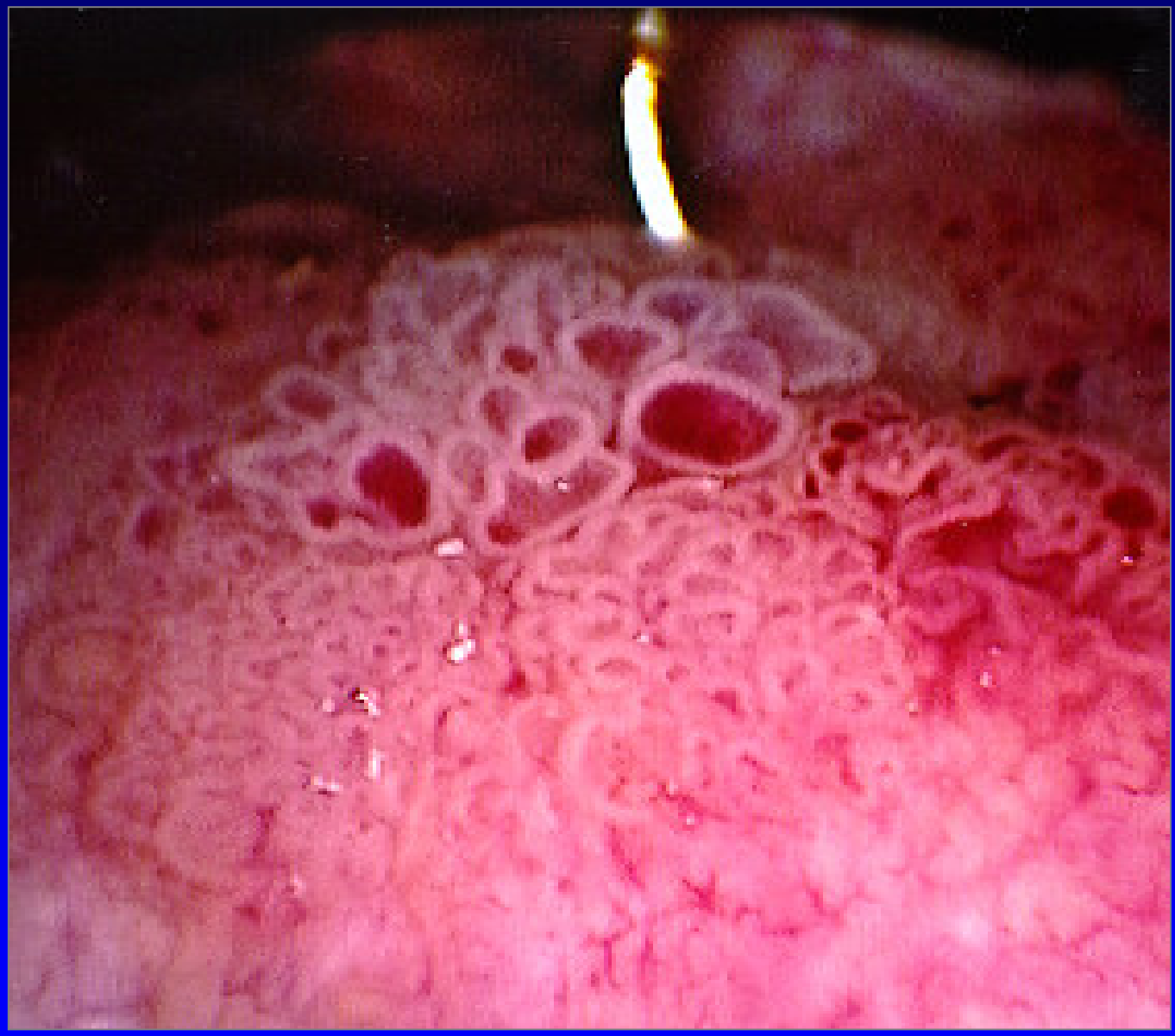
- Cystoscopy is key: papillary tumors are easily seen. High grade, solid, flat or in situ tumors may not be seen
- Urinary cytology: 80% + sensitivity in high grade tumors with 95% specificity. Sensitivity improved with FISH
- IVP, CT scan for upper tract evaluation

Grade I, Stage Ta TCC

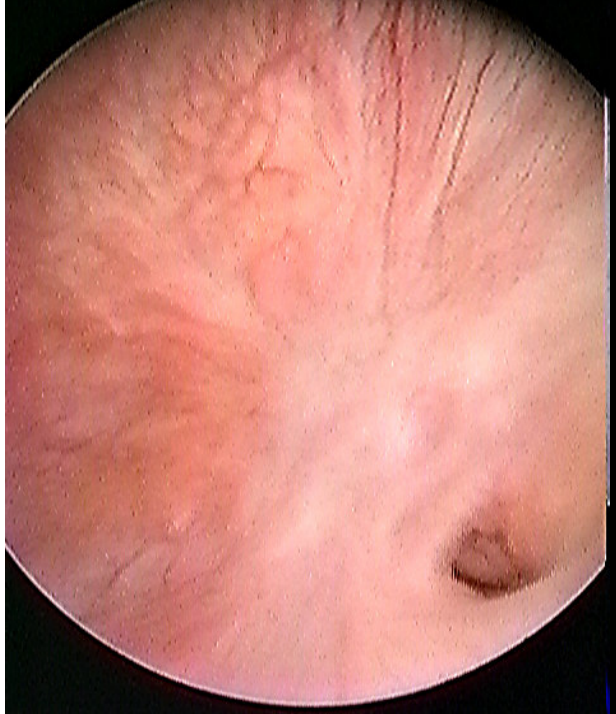


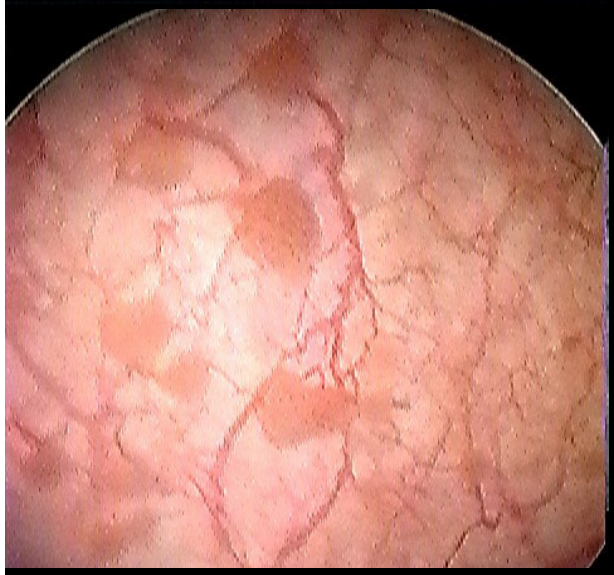
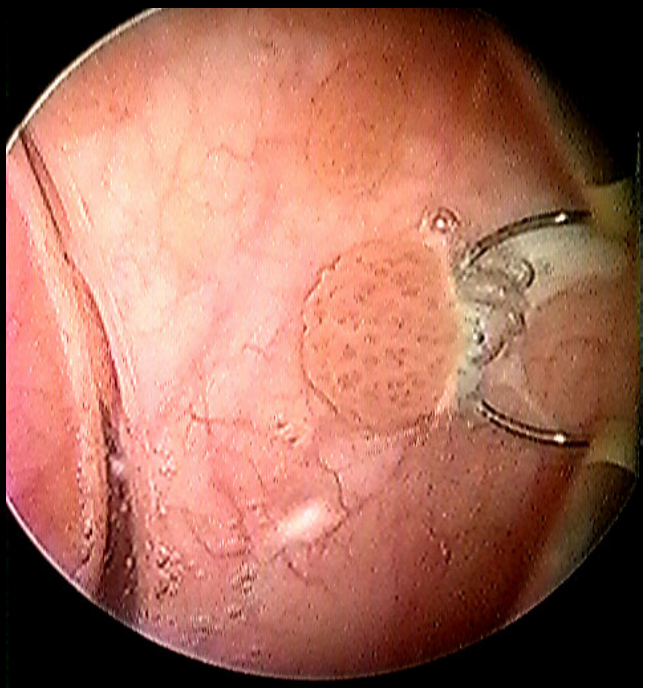
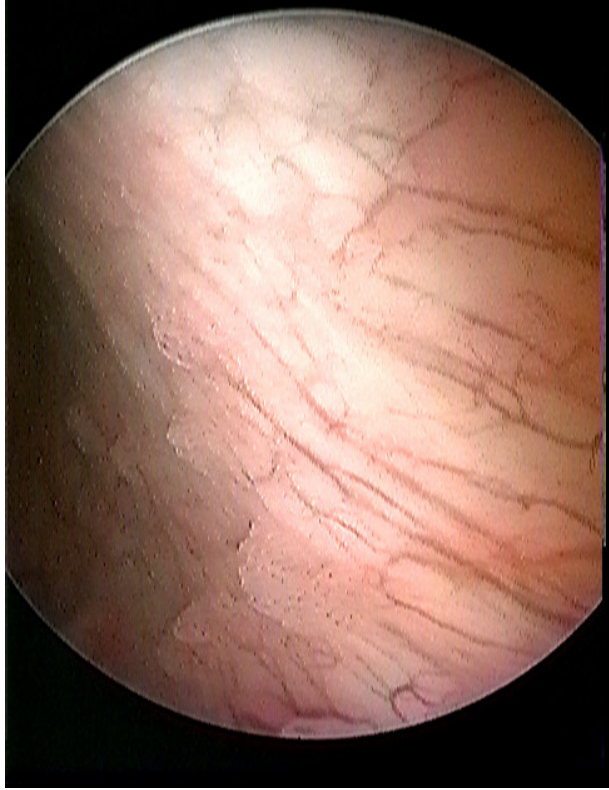
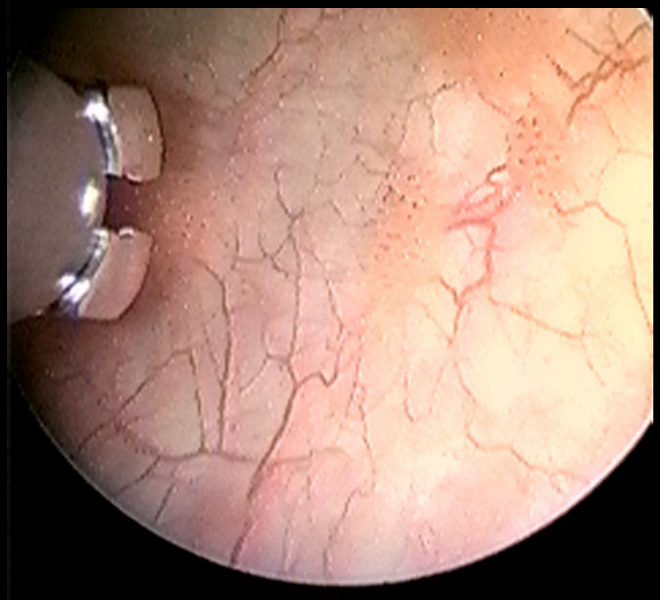


Cystoscopy showing bladder tumor

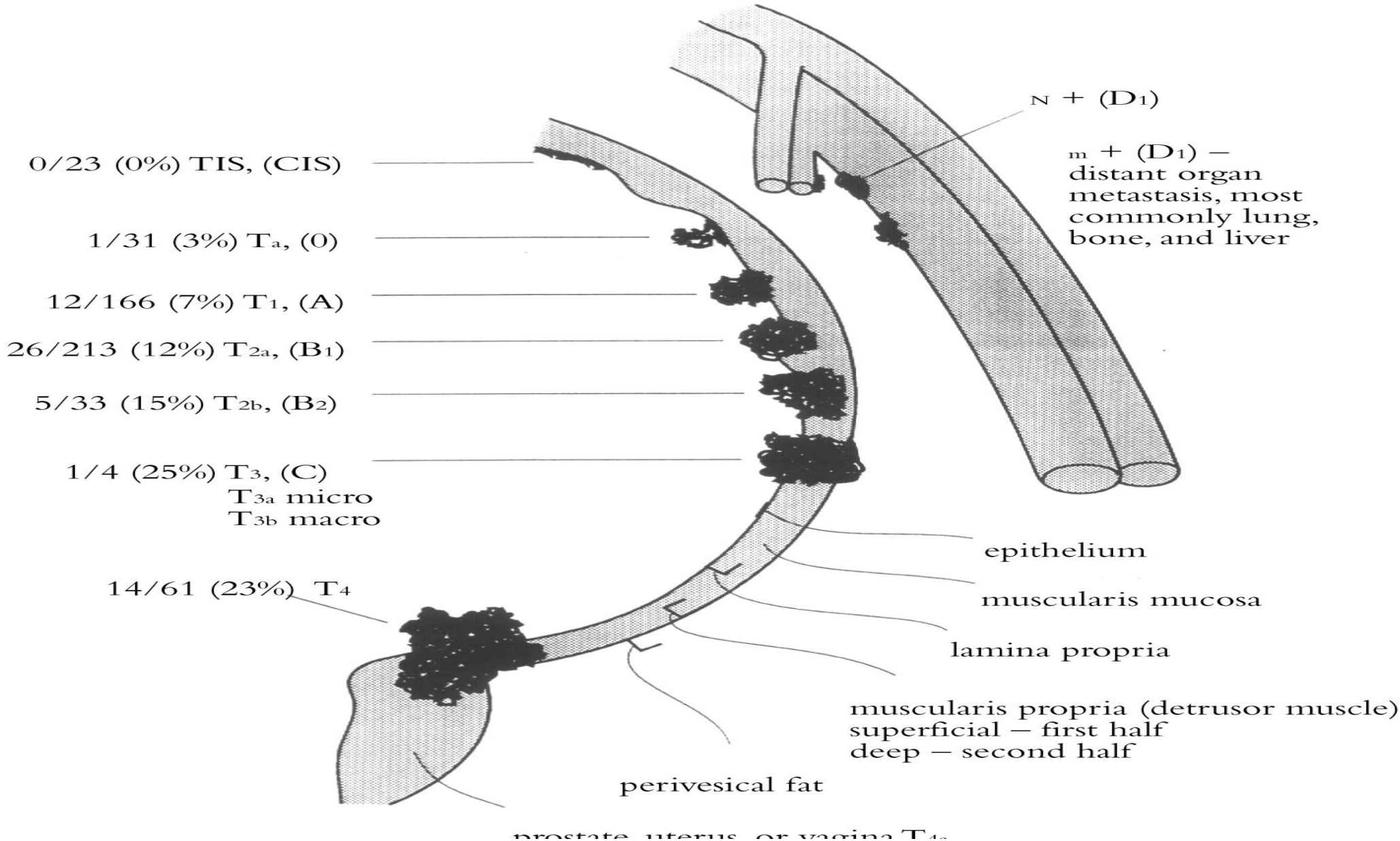


TURBT



Staging of Bladder Cancer



Bladder Cancer: Natural History

- About 70% present with resectable, superficial tumors, but up to 88% recur by 15 yrs
- Patients can and should be monitored with cystoscopic examination at frequent intervals to directly assess disease status
- Accessible for disease assessment, topical and systemic treatment

Risk Factors in Superficial Bladder Cancer

- Recurrence: 51% for solitary, 91% multiple; as low as 20% @ 5 years if 3month cysto clear
- Progression: 4% for TA, 30% for T1; 2% for G1,TA; 48% for G3,T1
- Mortality: 6% G1, 21% G3
- CIS: 52% progression T2 or higher if untreated
- T2(+): 45% 5yr survival with cystectomy

Risk Groups
Improve Treatment Selection

- Low risk: G1,TA solitary tumor with no recurrence at 3 months
- Intermediate risk: multiple or recurrent G1,TA; G2,TA
- High risk: any G3, lamina propria invasion (T1), CIS, or 3 month recurrence

Treatment Options in Superficial Bladder Cancer

- Transurethral resection: gold standard, but 88% 15 year recurrence
- Intravesical chemotherapy:
  - 20% reduction 2 year recurrence, 6% > 5 year
  - No reduction in disease progression
- Intravesical immunotherapy:
  - BCG: 40% reduction 2 yr recurrence, 20% >5 year
  - Alpha 2b interferon: 47% CR in CIS

Progress in Bladder Cancer

- Incidence up from 14.6/100,000 in 1973 to 16.5 in 1997 (adjusted to 1970 population)
- Mortality down from 4.2/100,000 in 1973 to 3.2 in 1997; 5 yr survival 53% in 1950, 82% 1997
- One of only 5 cancers (testis -5.1; bladder -1.3; breast -.3; ovary -.5; thyroid -1.1) with ***increased*** incidence and ***reduced*** mortality

Seer, 2000

Diet, Lifestyle and Environmental Factors

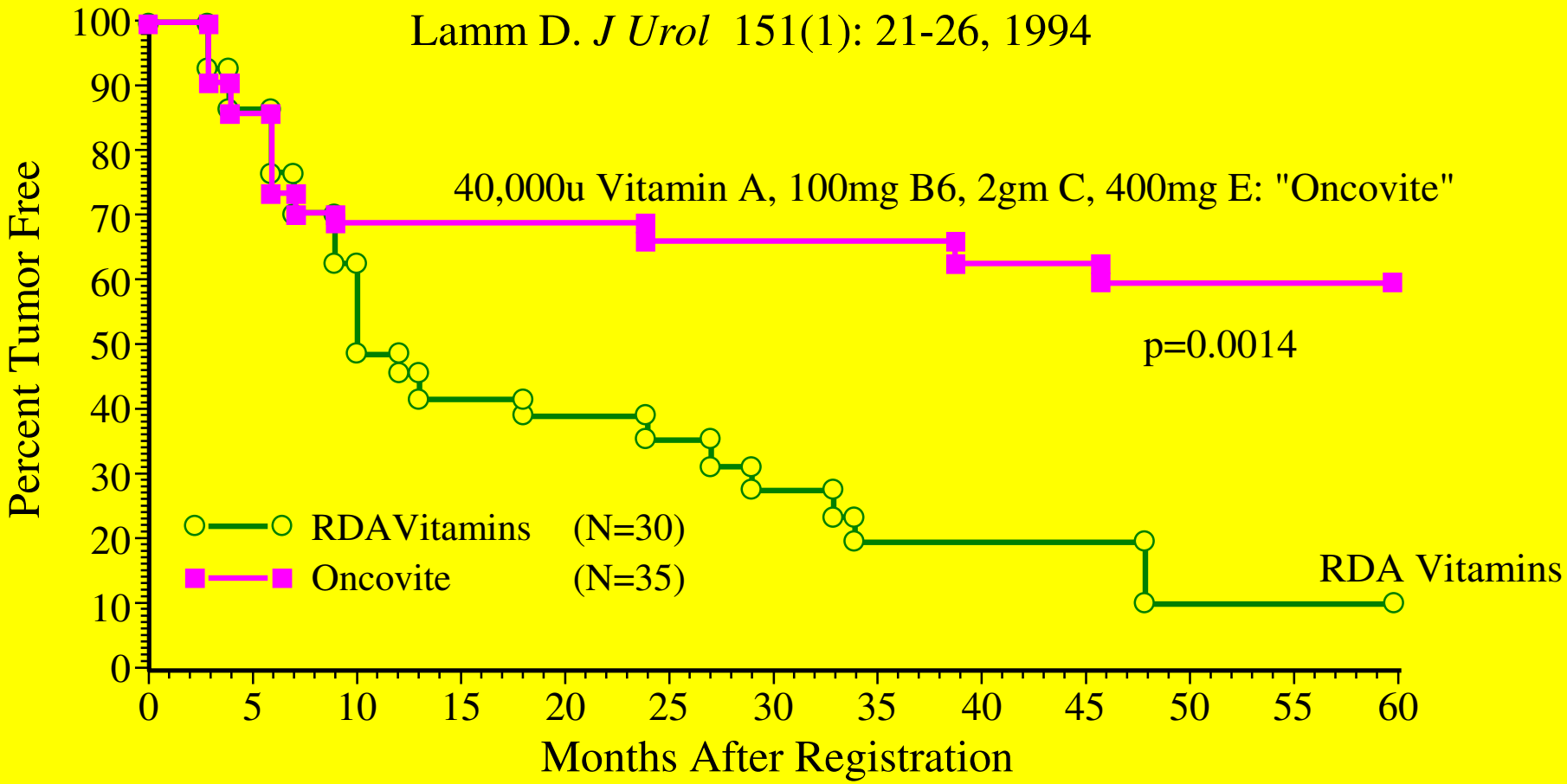
- Smoking increases risk of bladder cancer 3 fold, but more importantly it significantly increases risk of progression
- Chemical carcinogens: 20% of TCC in US
- Genetic factors: tumor suppressor genes: p53 (17p), proliferation genes: rb (13q), p 15 and p16 (chromosome 9), and growth factors such as erbb-2

Diet, Lifestyle and Environmental Factors

- Diet: low vitamin A, low serum carotene increase risk; increased fat increases risk; soy, garlic, selenium, NSAIDS, and green tea may reduce risk
- Vitamins may be protective: A (differentiating agent); B6; C (antioxidant); E (antioxidant), and possibly folic acid and D

Kaplan Meier Estimate of 5 Year Tumor Free Rate

In Patients Receiving Vitamin Supplement and BCG Therapy For Bladder Carcinoma



Mechanisms of Tumor Recurrence

- Implantation at the time of tumor resection
- Incomplete resection
- Stimulation by growth factors induced by surgery and the healing process
- Growth of transformed cells or CIS
- Continued induction and promotion due to continued carcinogen exposure

Principles of Intravesical Chemotherapy

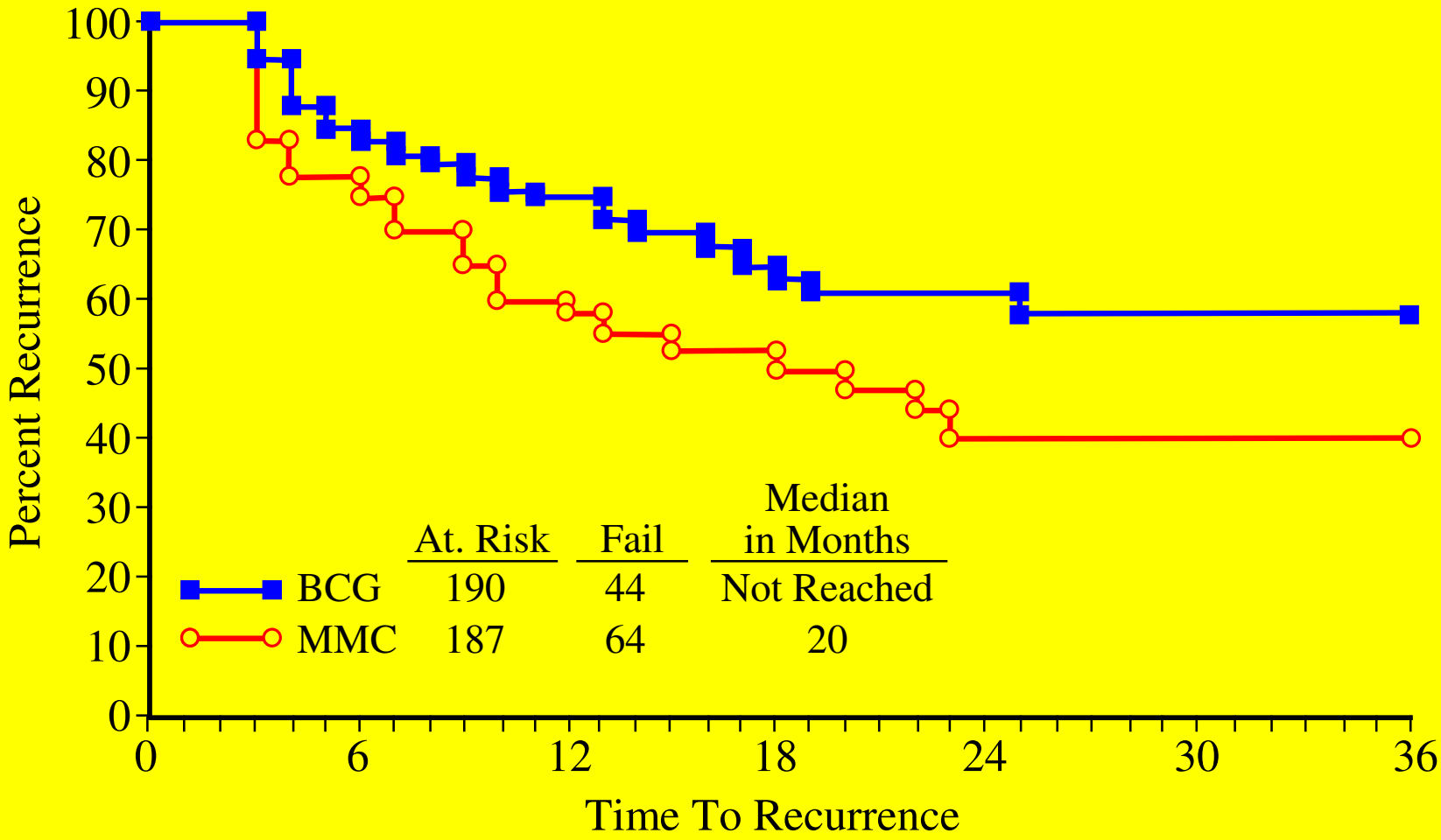
- Direct contact with cancer cells is required
- Tumor kill is proportional to **duration** of exposure and drug **concentration**
- Optimal response occurs with treatment within 6 hours of tumor resection
- Significant improvement with continued treatment or maintenance not reported
- Low-grade tumors respond best

Mitomycin C: Controlled Studies

Author	N	C	MMC	% Δ	P
Huland	79	52 %	10 %	42 %	0.01
Niijima	278	62 %	57 %	5 %	NS
Kim	43	82 %	81 %	1 %	NS
Tolley	452	60 %	41 %	19 %	0.0002
Krege	234	46 %	27 %	19 %	0.004
Akaza	298	33 %	24 %	9 %	NS
Total:	**1384**	**51.5 %**	**37.6 %**	**13.9 %**	

BCG Versus Mitomycin-C (SWOG 8795)

Lamm DL: *Urol Oncol* **1**:119-126, 1995



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Randomized BCG vs. Chemotherapy Studies

BCG	Rec	Chemo	Adv.	P value	Author
			Thiotepa		
0	vs	47%	+47	<.01	Brosman '82
7%	vs	43%	+35	<.01	Netto '83
13%	vs	36%	+26	<0.05	Martinez '90
			Doxorubicin		
53%	vs	78%	+21	<.02	Lamm '91
13%	vs	43%	+30	<.01	Martinez '90
24%	vs	42%	+18	<.05	Tanaka '94
			Epirubicin		
33%	vs	47%	+14	<.0001	vd Meijden '01

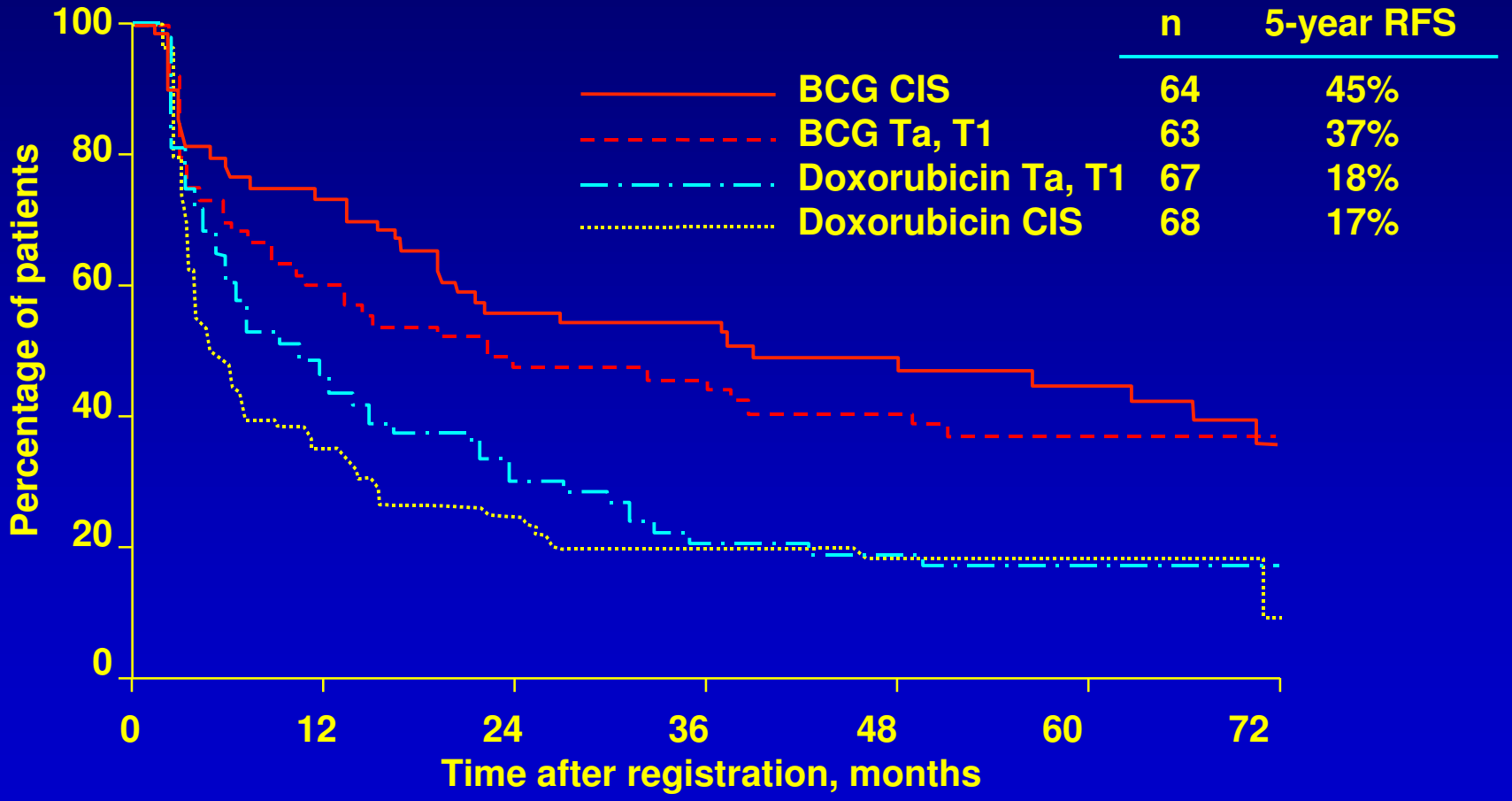
Summary of Controlled Chemotherapy Trials

Agent	series/n	% Δ (range)	P<0.05
Thiotepa	1257/11	16.6% (-3-41)	6/11
Doxorubicin	1751/8	16.2% (5-39)	4/8
Mitomycin	1384/6	13.9% (1-42)	3/6
Ethoglucid	226/1	20.0%	1/1
Epirubicin	985/6	19.6% (9-26)	3/6
Total:	2297/32	17% (-3-42)	17/32

Controlled BCG Trials

Author	no.	No rx	bcg	ben.	P
Lamm ' 85	57	52%	20%	32%	<.001
Herr ' 85	86	95%	42%	53%	<.001
Herr (CIS) ' 86	49	100%	35%	65%	<.001
Yamamoto' 90	44	67%	17%	50%	<0.05
Pagano ' 91	133	83%	26%	57%	<.001
Mekelos ' 93	94	59%	32%	27%	<0.02
Krege' 96	224	48%	29%	24%	<0.05
Total:	687	72%	28%	44%	

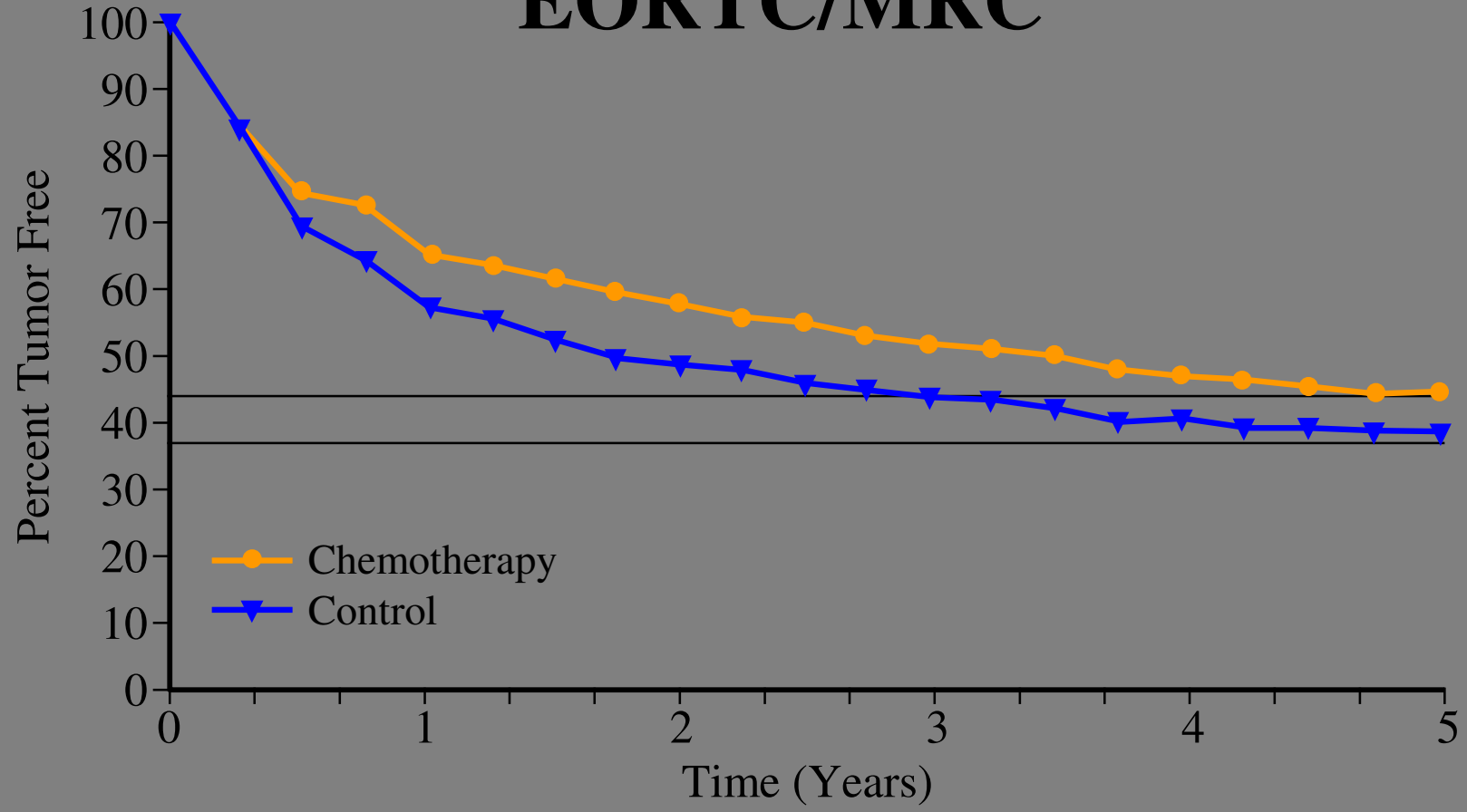
BCG Versus Doxorubicin: Time to Treatment Failure



Lamm DL: *N Engl J Med*. 1991;325:1205

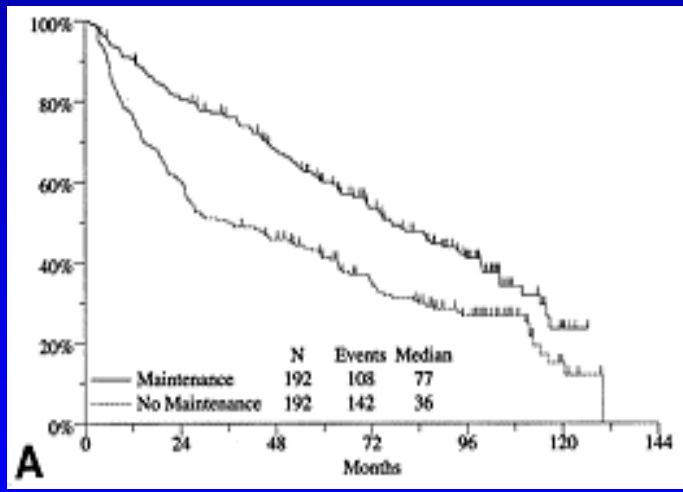
5 year Tumor Recurrence Curves With Chemotherapy vs Control

EORTC/MRC



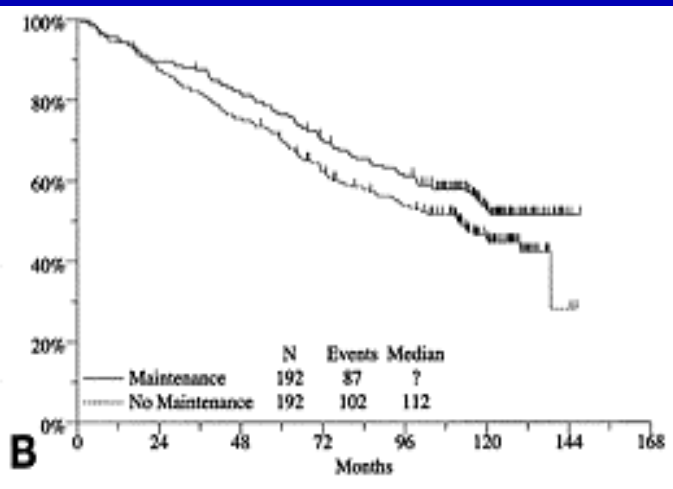
3 Week Maintenance BCG

Recurrence -free Survival



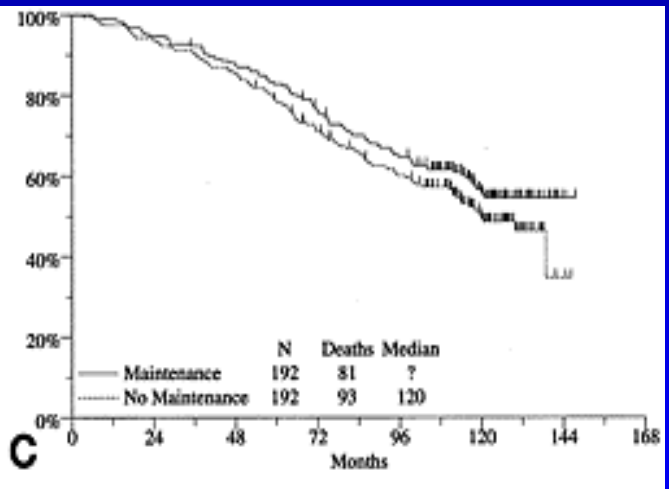
p < 0.0001

Worsening -free Survival



p = 0.04

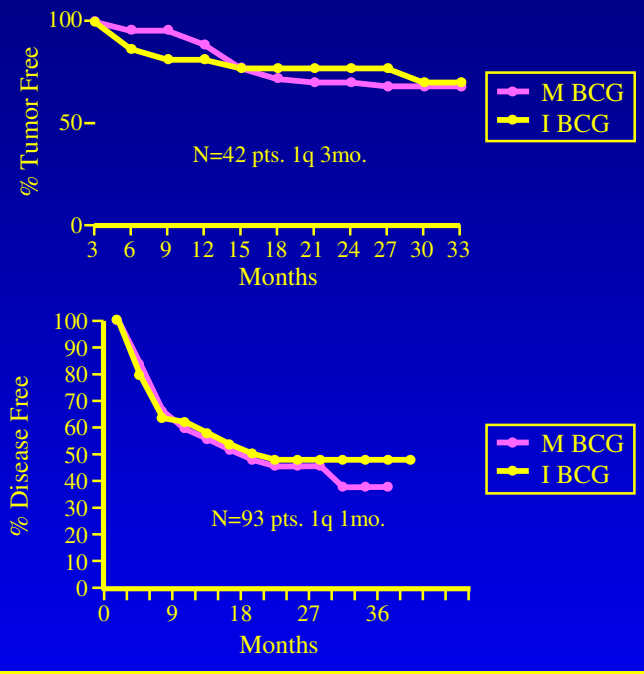
Survival



p = 0.08

Lamm DL et al, J Urol 163, 1124, 2000

BCG Maintenance: Not Created Equal



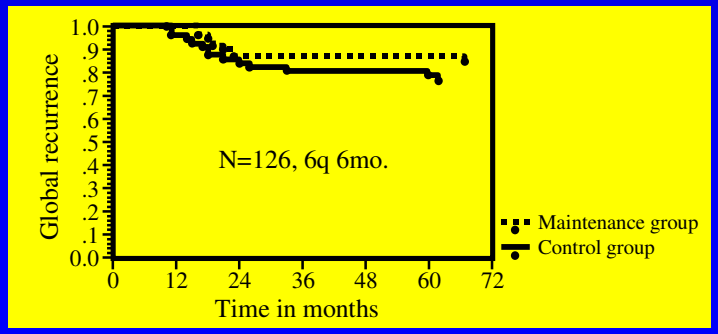
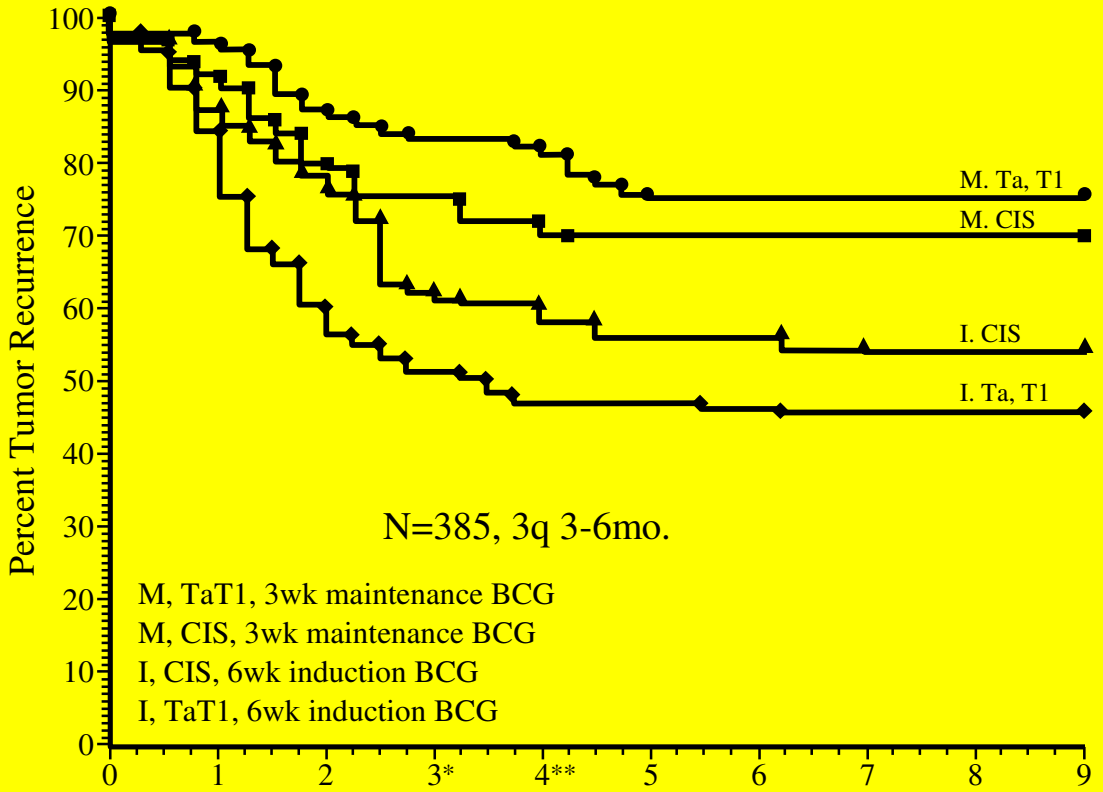


Figure 1:



* Completion of Therapy

** Apparent Increase in Rate of Recurrence One Year After Completion of Maintenance

Conclusions

- Hematuria is 3 or more RBC/HPF on urinalysis and should be evaluated
- Gross hematuria is significantly more likely to be associated with pathology
- Hematuria is the primary symptom of bladder and kidney cancer
- Early diagnosis of these malignancies improves survival

Arteries of Ureters and Urinary Bladder