

# Overview of superficial and Invasive Bladder Cancer

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# Bladder Cancer: Objectives

- Understand the Diagnosis, and characteristic presentation of the disease
- Stage and Histological grade of the Disease at the time of Diagnosis
- Epidemiology and Risk Factors for the Disease
- Treatment Guidelines and Prognosis

# Symptoms and Diagnosis

- Hematuria, gross or microscopic
- Voiding symptoms: Urgency, frequency, dysuria, and/or obstructive symptoms
- CT Urogram
- Cytology
- Cystoscopy

# Bladder Cancer

## Epidemiology/Etiology

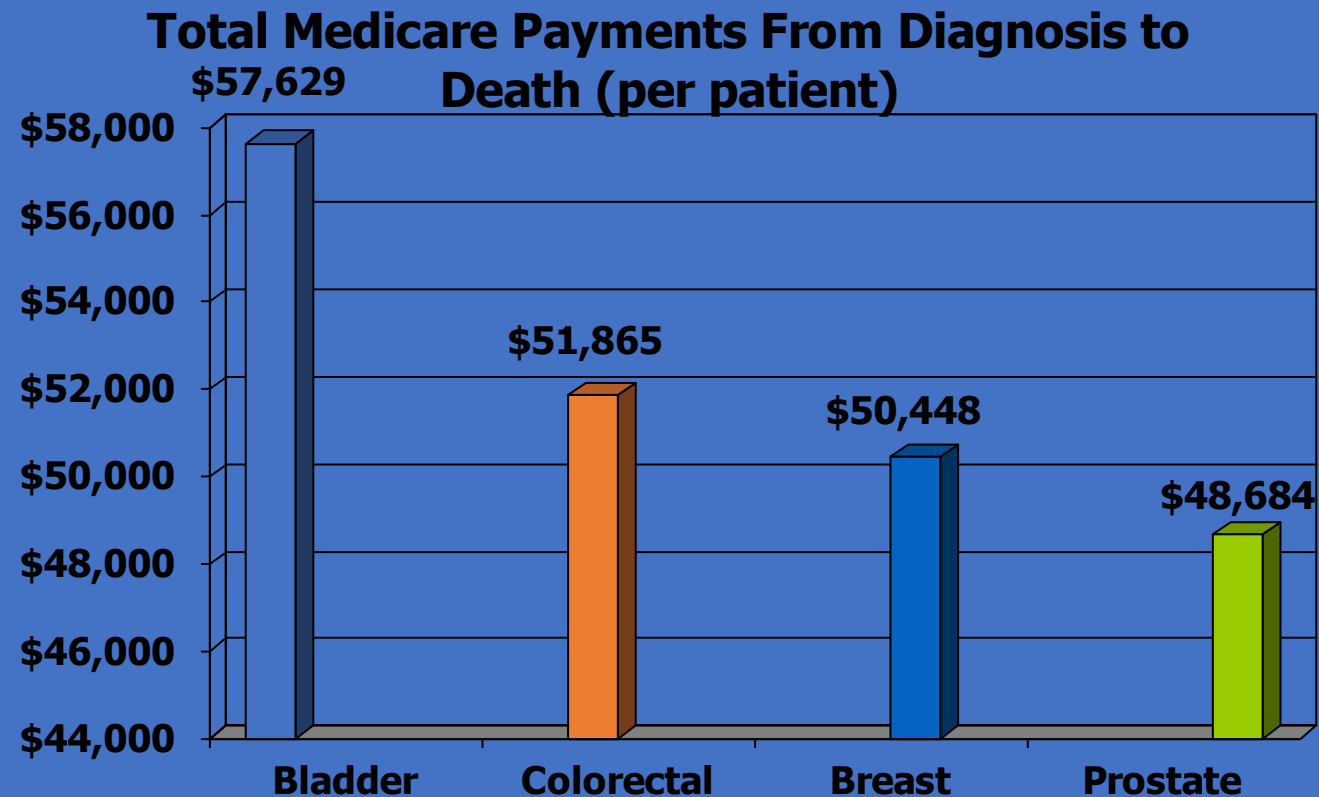
- Approximately 54,000 new cases and 12,000 deaths each year in the United States
- Fourth most common malignancy in men, second most common urologic malignancy.
- Male: Female ratio approximately 3:1
- Average age of onset: 68 years
- Cell types:
  - Transitional Cell = 90%
  - Squamous Cell = 5% to 7%
  - Adenocarcinoma = 2%
  - Rhabdomyosarcoma = 1%

# Bladder Cancer Risk Factors

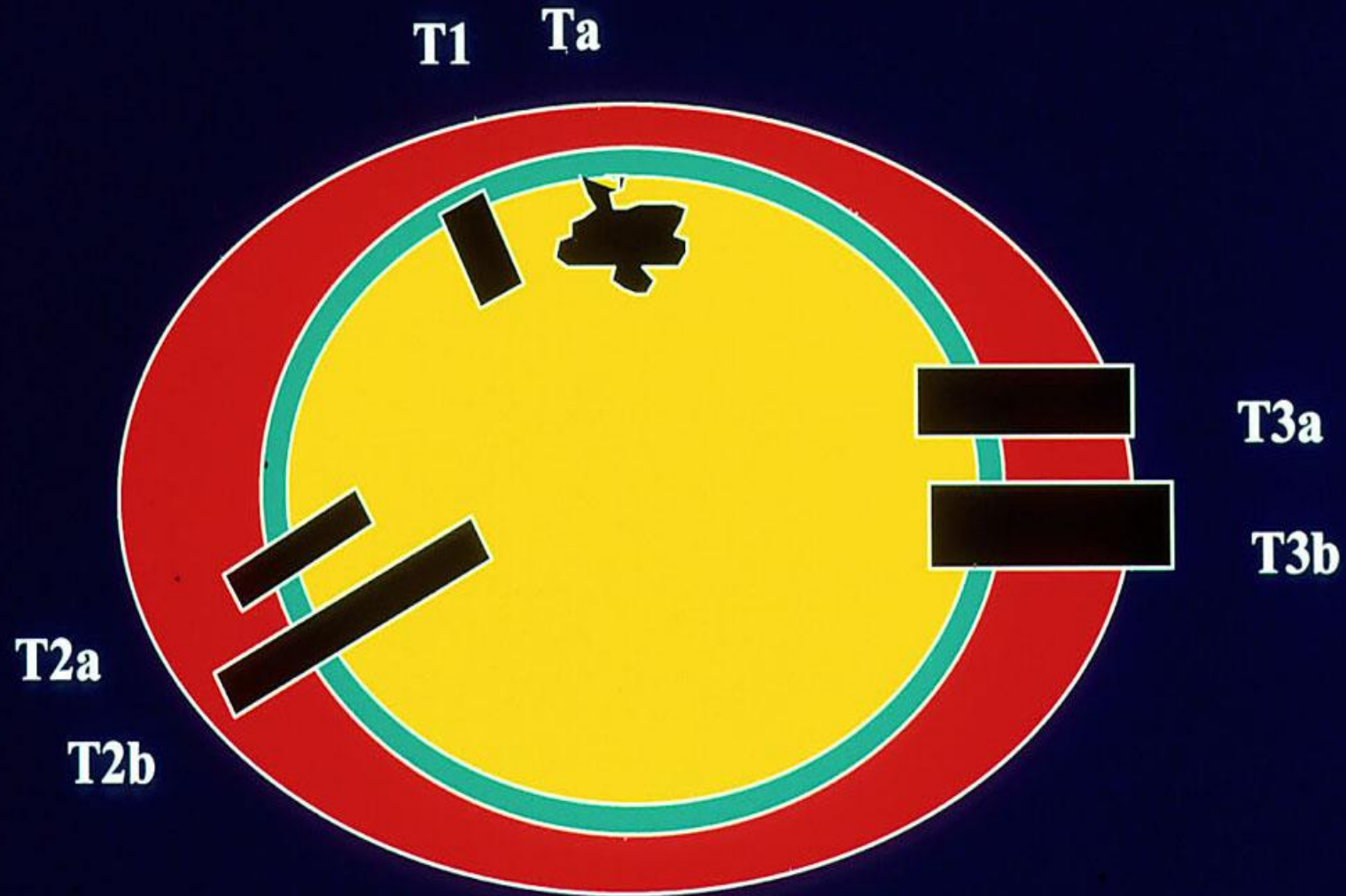
- Risk Factors you can change: Smoking, work place exposure, inadequate hydration, contaminated water supply, e.g., Arsenic, certain meds and herbals
- Risk Factors you can't change: race, ethnicity, gender, prior history of bladder cancer, birth defects, genetics, e.g., Lynch syndrome, Rb, prior chemotherapy and/or prior pelvic radiation

# Cancer Care Economics in the United States...

Current Standard of Care is aimed at  
Managing risk of recurrence



# Staging of Bladder Cancer



# TCC Pathology

Superficial Disease – 80% of TCC at initial presentation

Implies adequate tumor removal by TUR alone

Includes: Carcinoma in situ – CIS

Papillary tumors confined to the mucosa – Ta

Invasion into the lamina propria – T1



# TIS

Flat TCC of high cytologic grade

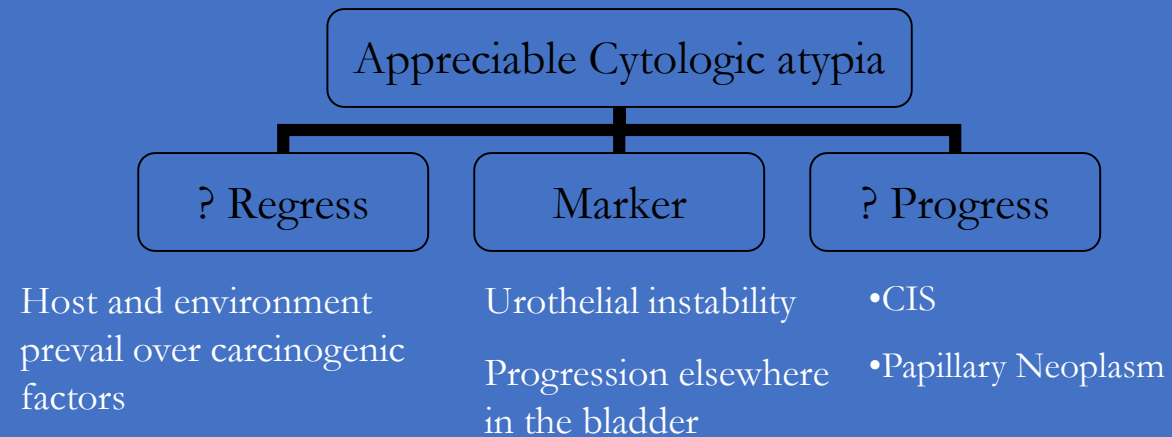
Severe dysplasia = Severe atypia = Carcinoma in situ.

# The who/ ISUP Consensus Classification of Urothelial (Transitional Cell) Neoplasms of the Bladder

## Flat lesions with atypia

- Reactive (inflammatory) atypia
- Atypia of unknown significance
- Dysplasia (low – grade intraurothelial neoplasia)
- CIS (high – grade intraurothelial neoplasia)

# Urothelial Dysplasia



Hence No Treatment

# CIS

Unequivocal anaplastic nuclear changes –

Neoplastic transformation

Stable Disease

Progress

DE NoVo

**Needs Treatment**

# Primary (DE NoVo) CIS

*(Orozco, et. Al, Cancer, 1994)*

- CIS sole abnormality in the bladder
- 1-10% of all CIS
- Favorable outcome

	Primary	Secondary
NED	62%	45%
Progression	28%	59%
Death	7%	45%

# Clinical Settings with Biological Significance

## DE NoVo CIS

- Potential to progress to invasive carcinoma and death
- Biologically appears to be more indolent than previously believed

## CIS in Patients with Non-Invasive or Superficially

## Invasive TCC

- Increased risk for recurrence
- Increased risk for invasion
- Increased risk for multifocal disease – renal pelvis prostatic urethra, etc.

# Ta lesions

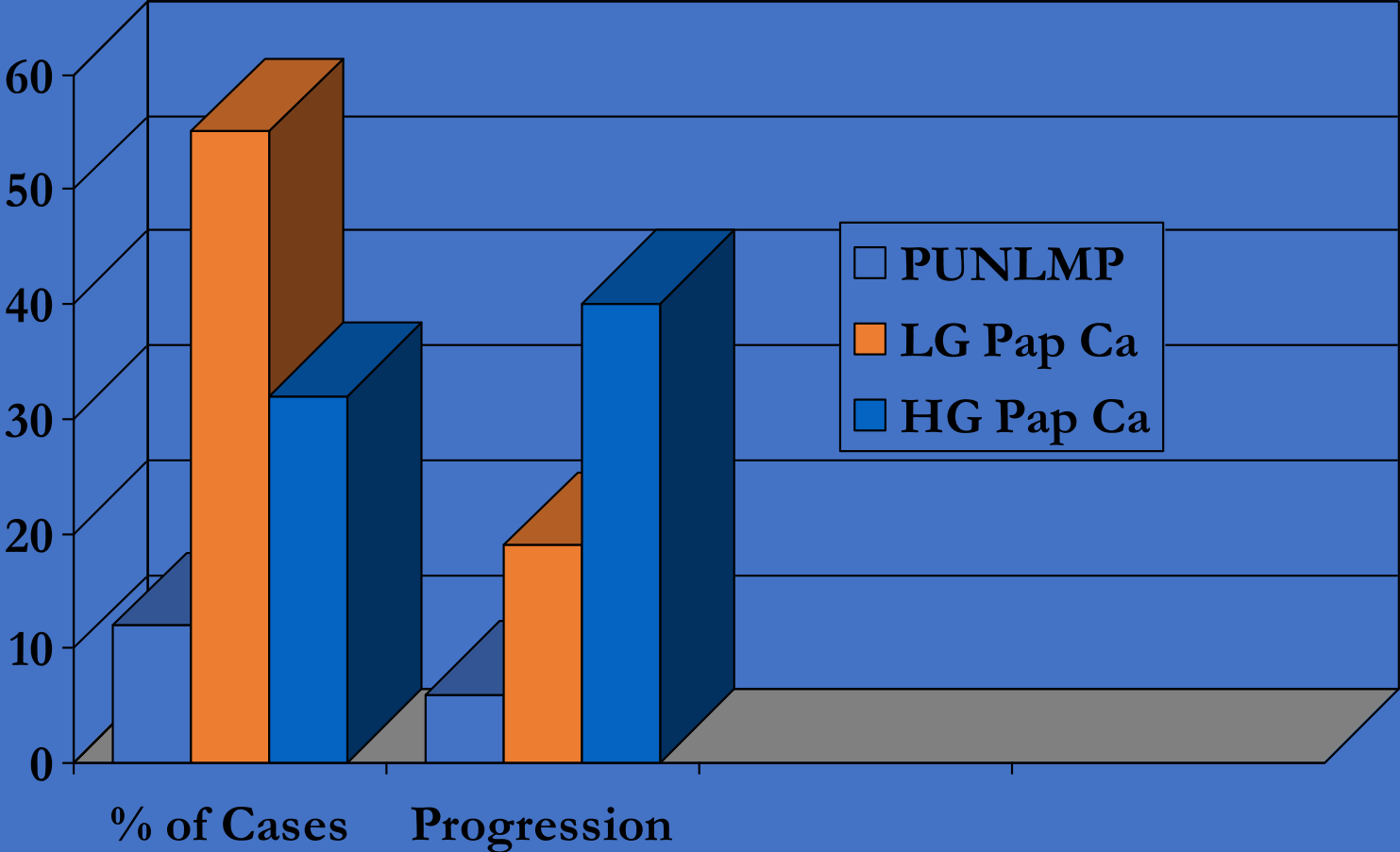
- 70% of superficial TCC
- Composed of branching fibrovascular core
- Greater than 8 cell layers displaying features of anaplasia

# Classification Scheme for Papillary Urothelial Tumors

Who 1973	Int. Soc. Urol Path (1998)	Murphy (AFIP, 1994)
Papilloma	Papilloma	Papilloma
G1	LMP	↓
G2	Low-grade	Low-grade
G3	High-grade	High-grade



# Who/ISUP (1998) Outcome Data



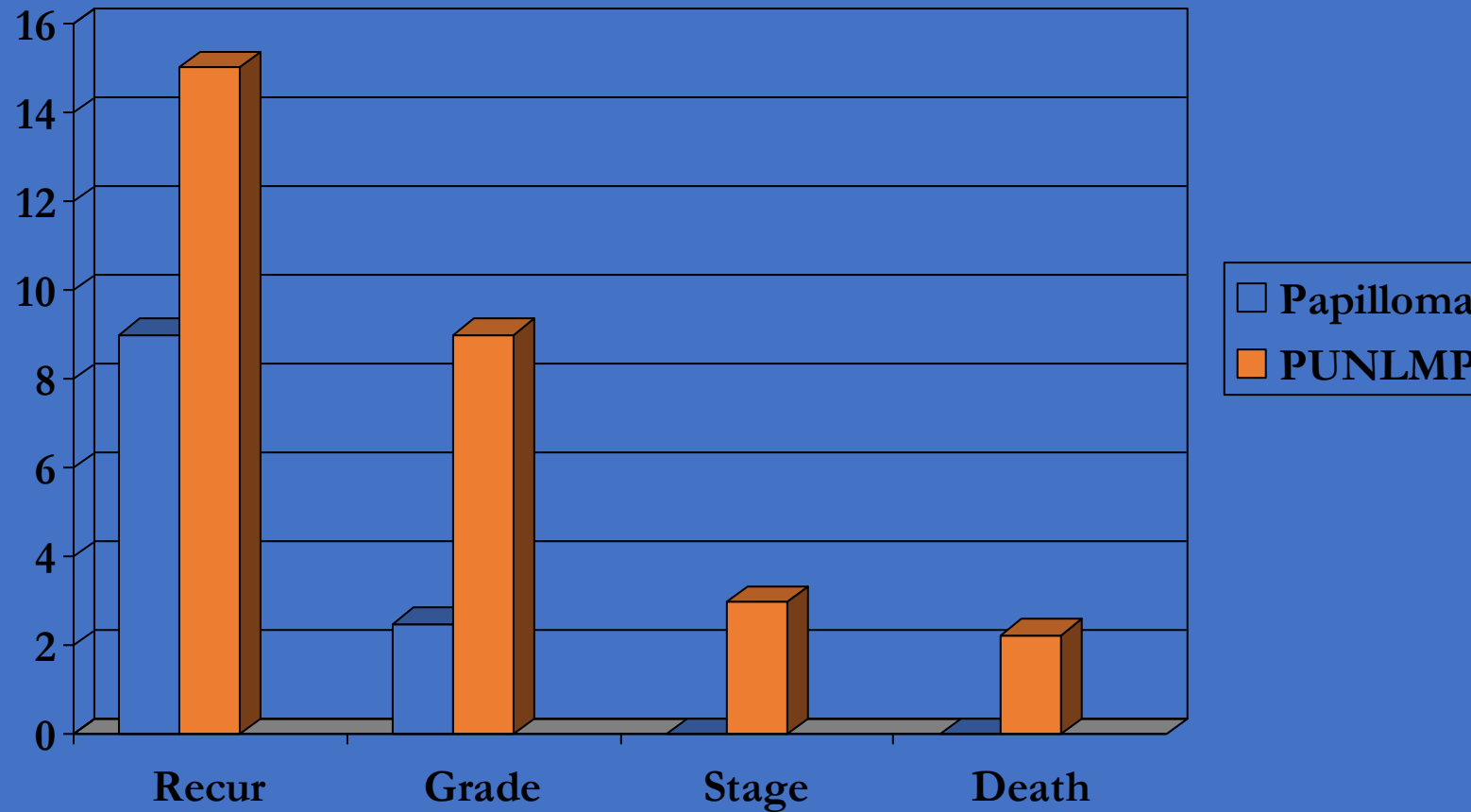
*Cheng et al, Cancer 88: 1663, 2000*

# Papillary Urothelial Neoplasm, LMP

## Biologic Behavior:

- Not usually associated with invasion or metastasis
- Patients at an increased risk of developing recurrences (new occurrences)
- May be of higher grade or may invade

# Papilloma vs. PUNLMP Outcome Comparison



**Papilloma (n=52):** Cheng et al, Cancer 86: 2098, 1999

**PUNLMP (n=112):** Cheng et al, Cancer 86:2102, 1999

# Papillary Urothelial Neoplasm, LMP

## Diagnostic Comment:

*“Patients with these tumors are at risk of developing new bladder tumors (“recurrences”), usually of similar histology. However, occasionally these subsequent lesions manifest as urothelial carcinoma, such that follow up of the patient is warranted.”*

Epstein, Amin, Reuter, Mostofi, and the Bladder Consensus Conference Committee Am. J. Surg Pathol (1998)

# T1 Lesions

- 30% of superficial TCC.
- Invade the lamina propria (muscularis mucosa).
- Papillary appearance but tend to be of higher grade.

# T1 Sub staging

Younes (1990)	T1 a, b vs. T1c	75% vs. 11% 5 yrs. Survival
Angulo (1995)	T1 a vs. T1b	85% vs. 52% 5 yrs. Survival
Hasul (1994)	T1a vs. T1b	6.7% vs. 53.5% Progression

# Transitional Cell Carcinoma

## Prognostic Features

### Category I:

- pTNM Stage
- Nuclear Grade
- Histologic type
- Carcinoma in situ
- Multicentricity
- Tumor Size
- Vascular-lymphatic invasion
- Depth of Invasion

### Category II:

- P53
- Blood Group antigens
- DNA ploidy

# Transitional Cell Carcinoma

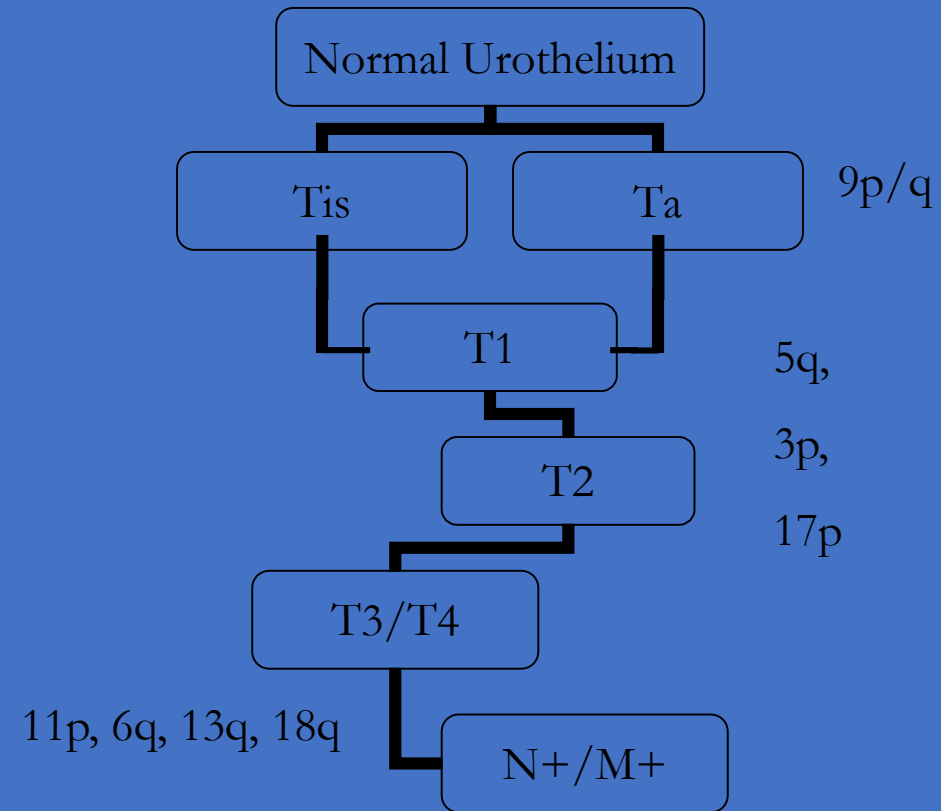
## Prognostic Features

### Category III:

- Bcl-2
- Nuclear Morphometry
- Growth Factors
- HLA antigens
- Basement Membrane Integrity
- EGFR
- Matrix Metalloproteinases
- Human Milk-Fat Globulin-2
- Transferring Receptor
- Ki-67
- BrdU
- S-phase fraction
- PCNA
- Mitotic Count
- Cytogenetics, LOH



# Transitional Cell Carcinoma



# Natural History (Superficial TCC)

60-90% of patients recur if treated by TUR alone.

Lutzeyer et al 1982

- Quality of life
- Recommendations for surveillance
- Adjuvant treatment
- Cost of treatment

No data on untreated superficial TCC, but the low frequency at autopsy suggests a short latent period.

# Bladder Cancer

## Primary Treatment of Superficial Bladder Cancer

- Surgery (primary therapy)
  - Transurethral resection
  - Partial cystectomy
- Laser therapy (Holmium laser)
- Photodynamic therapy
- Intravesical therapy
  - Chemotherapy (mitomycin C, thiotepa, doxorubicin, valrubicin, Gemcitabine/Docetaxel)
  - Bacillus Calomette-Gue'rin
  - Recombinant interferon alfa

# Superficial Bladder Cancer Rate of Progression and Survival by Tumor Grade

<u>Stage</u>	<u>Grade</u>	<u>Progression rate to muscle invasion following TUR, %</u>	<u>5-year survival rate, %</u>	<u>10-year survival rate, %</u>
Ta		2-5		
	I	0-2	100	95
	II	10-20	95	89
	III	45-50	95	84
T1		20-30		
	II	10-20	90	78
	III	45-50	70	50
Tis		50-80	70	55

Data from (Jakse, 1987) (Stanisic, 1987) (Utz, 1980) (Nuemann, 1999)

# Prognostic Factors in Patients with Superficial TCC

## Findings at Cystoscopy

- Tumor size
- Tumor number
- Tumor morphology

## Pathological Findings

- Stage
- Grade
- Presence of TIS
- Vascular and lymphatic invasion

## Response to Treatment

- Recurrence at first checkup cystoscopy
- Failure of BGG

## Biological Markers

- P53 status, especially in recurrent tumors following BCG therapy

# Superficial Bladder Cancer (TA, T1)

## TUR/Fulguration:

- 70-80% 5yr. Survival overall 10-15% ultimately require more aggressive therapy

## Progression:

- 46% in patients with L.V. involvement present in high grade lesions.
- 40% have residual tumor after “adequate resection” if re-resected at 6 weeks. (Klan et al 1991 J. Urol)
- 27-37% have residual tumor (Zurkichen et al. AUA 2001)

# Transurethral Resection

- Bimanual examination. Pre resection cystoscopy
- Resect large tumors piecemeal – nonfixed tumors are difficult to cut.
- Separate biopsy of tumor base to include muscle.
- Bimanual examination at completion.
- Random bladder biopsies of normal areas are controversial and are no longer recommended: limited impact on the clinical outcomes. They may be helpful at the dome and trigone if the malignant cell type suggests different embryonal origin other than TCC.
- 968 consecutive pts – Ta, T1, or Tis. 12% undergoing TUR for superficial TCC – multifocal disease or Tis.

Schwaibold et al. AUA 2001.

# Radical Cystectomy

Pre B.C.G.: Radical cystectomy for diffuse CIS, high grade T1 or prostatic involvement.

B.C.G. ERA: Cystectomy is still an option. Nerve sparing, continent neobladder techniques.

15-20% Death risk from high risk TCC even with B.C.G. Upstaging to muscle invasive disease – 30% Higher in a T1, High grade lesions.

5year survival post cystectomy for high grade lesions. 80-90%

Biological marker (P53) may help identify progressors.



# Who should be offered radical cystectomy as primary therapy?

- T1, High grade lesions have highest risk for progression.
- If coupled with lympho-vascular invasion or CIS risk further increased.
- Radical cystectomy discussed at the outset.

## Otherwise

- If resection seems complete – 6 weeks of B.C.G.
- Repeat cystoscopy “& random biopsies 3-6 weeks after B.C.G. and repeat resection of tumor site.
- Early recurrence: Consider cystectomy vs. repeat B.C.G.
- Consider Patient’s preference, available prognostic markers and clinical judgment.

# Superficial Bladder Cancer Intravesical Therapy Indications

- Diffuse papillary tumors
- Carcinoma in situ or severe dysplasia
- High grade Ta or T1 tumors
- Multiple tumor recurrences  
(Particularly multifocal recurrences)
- Positive cytology (after resection)

# Progression

- 176 patients post TUR no adjuvant treatment
- Followed to death or for 20 years
- 22% mortality
- Death related to tumor grade, number, and volume of recurrences
- 4 or more primary tumors – cystectomy or death
- Recurrences for more than 4 years continued to recur until death or cystectomy

# Intravesical Therapy

- TUR of superficial TCC – 60-90% recurrence rate.
- Intravesical therapy may eradicate existing remaining disease and prevent recurrences.
- Bacillus Calmette – Guerin (BCG) is the most frequently use intravesical agent in the U.S.
- Gemcitabine/Docetaxel –seems to have equal efficacy with less toxicity than BCG, still being evaluated

-Chemotherapy

-Interferons

-Gene Therapy

-Oral Therapy

-Keyhole Limpet Hemocyanin

-PDT

# Chemotherapy (Intravesical)

## Jones & Sweeney Lancet 1961

- Thiotepa
- Mitomycin C
- Doxorubicin Hydrochloride
- Epirubicin
- Gemcitabine/Docetaxel

### Criteria

- 1.) Activity vs. TCC – Non Phase specific
- 2.) Minimal systemic absorption.
- 3.) Minimal Local toxicity both acute and chronic.

# Efficacy

- Reduction of tumor recurrences.
- Prevention of tumor progression.
- Eradication of CIS.

Review of 4,000 patients – 23 controlled clinical trials.

Net benefit of intravesical chemotherapy over TUR alone.

14% at 1 to 3 years. 5 year recurrences with Thiotepa,

Doxorubicin and Mitomycin C. Same as nontreated controls.

Gemcitabine/Docetaxel still under evaluation

Traynelis & Lamm

Urology Annual 1996

# Regimens

- Single immediate post – TUR dose.
- Delayed induction course with or without maintenance therapy. Rationale (immediate) – Destroys viable tumor cells remaining in the bladder – preventing implantation and reducing recurrences.

Both regimens are effective but not addictive.

- Significant cost implication if in low or intermediate risk single dose is as effective as more detailed regimens.
- BCG should not be used at the time of TUR.

# EORTC and MRC

Analyzed randomized clinical trials of different chemotherapeutic agents.

No Clear Advantage:

- Progression
- Time to distant metastasis
- Duration of survival
- Progression-free survival.

Mean follow-up – 7-8 years.

Significant advantage: Duration of disease free survival

Pawinski, et al.

J. Urol. 1996

CIS response rate – 34-42% Gem/Doci initially similar results with less toxicity but maintenance unknown as yet



# Conclusions – Chemotherapy

- There is no clear superior intravesical chemotherapeutic agent
- Earlier is better than later
- Maintenance is of unclear benefit except perhaps with delayed therapy.
- Progression is not clearly altered
- Ablation can be achieved
- Failures occur in 2 phases: early and late (more constant)
- Local Toxicity is a common limiting feature
- Combination with BCG is potentially superior

# B.C.G.

- 1929 – Noted to have antineoplastic effects.
- 1939 – Luebeck Disaster. Babies given virulent BCG exaggerated the side effect of live attenuated TB vaccine.
- 1969 – Mathe et al – Reported encouraging results for treatment of A.L.L.
- 1976 – Morales et al – BCG useful in treatment of superficial TCC.
- 1999 BCG the Standard treatment for aggressive superficial TCC for comparison of new treatments.

# BCG Efficacy and Indications

1.) Prophylaxis against recurrence and progression.

- BCG & TUR – Recurrence Rate 31%
- TUR alone – 75%

Prospective randomized controlled study – 402 patients.

Lamm Urol Clin N. Am 1992

Most randomized studies show BCG is superior to chemotherapeutic prophylaxis, especially in higher grade lesions. SWOG Study comparing mitomycin C to BCG closed (1<sup>st</sup> interim analysis)

- Recurrence Rate 19.5 for BCG vs. 32.6%
- Time to recurrence 36 vs. 20 months

# Conclusions:

- Presenting symptoms: Hematuria/voiding sx
- Diagnosis: CT Urogram, Cytology, Cystoscopy
- Pathologic Stage and Grade: Higher predict Poorer prognosis
- Epidemiology and Risk factors: predict prognosis
- On the Horizon: Immunotherapy, currently Mayo phase II anti PD-L1, (atazolizumab) in metastatic bladder cancer