

Superficial Bladder TCC

Urology Grand Rounds
April 20 2005
John Morrell R4

OBJECTIVES

- To review the etiology, natural history, and conventional treatments for superficial bladder TCC
- To review new therapeutic strategies for superficial bladder TCC

OUTLINE

- Etiology
- Histopathology
- Natural history
- Prognostic factors
- Conventional treatments
- New treatment strategies

ETIOLOGY & RISK FACTORS

Campbell's 8th edition

- Cyclophosphamide (RR 9)
- Smoking (RR 4)
- Pelvic irradiation
- Occupational
- Schistosomiasis infection (SCC and TCC)

ETIOLOGY & RISK FACTORS

- Blackfoot disease (Taiwan)
- Renal transplant
- Chronically low fluid intake
- Chinese herb nephropathy
- Chronic cystitis (mostly SCC)

PATHOLOGY

1998 WHO/ISUP
consensus
classification

HYPERPLASIA

Flat Hyperplasia
Papillary Hyperplasia

FLAT LESIONS WITH ATYPIA

Reactive (Inflammatory) Atypia
Dysplasia
Carcinoma In-Situ**

PAPILLARY NEOPLASMS

Papilloma
Papillary Neoplasm of Low Malignant Potential (PUNLMP)
Papillary Carcinoma, Low-grade
Papillary Carcinoma, High-grade

**May include cases formerly diagnosed as "severe dysplasia"

Pathologic Grading

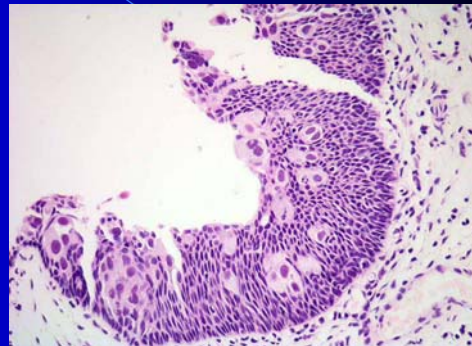
Relation of WHO '73 to WHO/ISUP '98

<u>WHO 1973</u>		<u>WHO/ISUP</u>
Papilloma	→	Papilloma
Grade 1	→	PUNLMP
Grade 2	→	Low Grade
Grade 3	→	High Grade

Carcinoma *in situ*

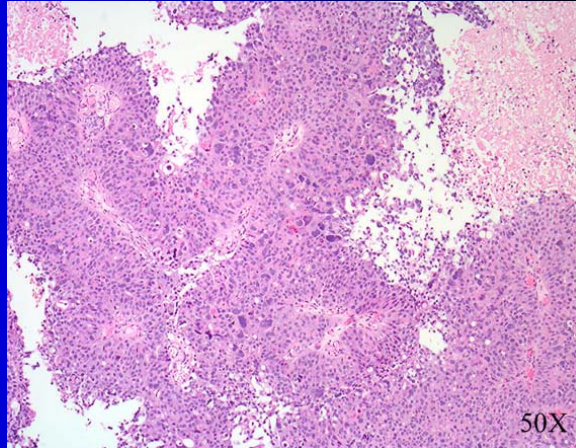
Flat intraurothelial lesion

- Increased cell layers and loss of polarity
- Nucleomegaly and increased nuclear-cytoplasmic ratio
- Irregular nuclear outlines
- Pleomorphism
- Increased number of mitoses



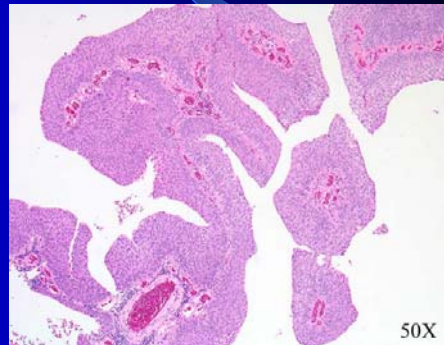
Papilloma

- Normal urothelium on a fibrovascular core
- Recurrence: 8%
- Grade progression: 2%
- Stage progression: 0%
- Survival: 100%



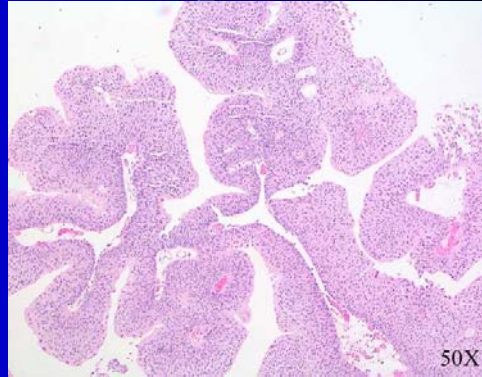
Papillary Urothelial Neoplasm of Low Malignant Potential

- Urothelium increased in thickness
- Recurrence: ~30%
- Grade progression: 10%
- Stage progression: < 5%
- Survival: 95%



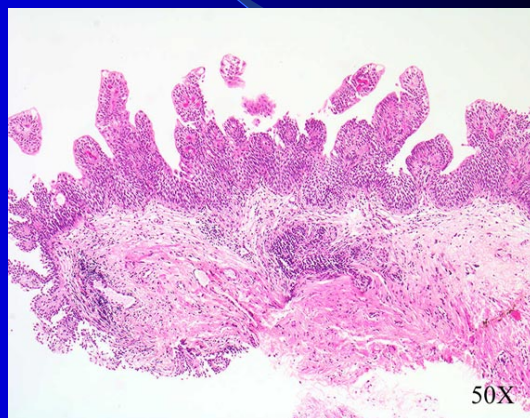
Papillary Urothelial Carcinoma, Low Grade

- Focal loss of polarity, nuclear abnormalities, absent pleomorphism
- Recurrence: ~70%
- Grade progression: < 10%
- Stage progression: < 10%
- Survival: ~ 90%



Papillary Urothelial Carcinoma, High Grade

- Marked disorder, marked nuclear abnormalities, pleomorphism, prominent nucleoli
- Necrosis may be present
- Stage progression: 15 – 40%



Pathologic Staging

Ta	Papillary, confined to epithelium
Tis	Carcinoma <i>in situ</i>
T1	Invasion of lamina propria
T2a	Superficial muscle invasion
T2b	Deep muscle invasion
T3a	Microscopic invasion of perivesical fat
T3b	Macroscopic invasion of perivesical fat
T4a	Invasion of pelvic viscera
T4b	Invasion of pelvic/abdominal wall

NATURAL HISTORY

Campbell's 8th edition

Newly diagnosed bladder cancers:

- 55% are low grade, superficial
- 45% are high grade lesions
 - 25% are invasive
 - 75% are superficial

NATURAL HISTORY

Campbell's 8th edition

- Majority develop recurrences
- ~ 25% of those recur with higher grade
- ~ 10% progress to invasive or metastatic disease

Risk Factors for Recurrence, Progression, & Mortality

Millan-Rodriguez et al., JU 163: 73, 2000

- 1529 patients with primary Ta – T1 treated with TURBT and random Bx
- Cold Bx of normal trigone, retrotrigone, lateral walls, dome, & prostatic urethra
- 32% received intravesical instillation, 1/2 was BCG
- Multivariate analysis

Risk Factors for Recurrence, Progression, & Mortality

Millan-Rodriguez et al., JU 163: 73, 2000

- F/U: cysto and cytology alternating with US and cytology q4m x 2 yrs then q6m, IVP
- Mean F/U: ~4 yrs
- End points: recurrence, progression (of stage), disease specific survival
- Prognostic factors: grade, stage, cis in random Bx, ≥ 2 tumours, tumour size ≥ 3 cm, dysplasia in random Bx, IV instillation

Recurrence

Millan-Rodriguez et al., JU 163: 73, 2000

- Kaplan-Meier Analysis
 - Difference in recurrence: multiple tumours, \uparrow size, grade, IV instillations
 - No difference in recurrence: stage, presence of cis
- Multivariate analysis
 - RFs for recurrence: multiplicity (2), size ≥ 3 cm (1.65), cis (1.6)
 - BCG protective effect (0.39)

Progression

Millan-Rodriguez et al., JU 163: 73, 2000

- Kaplan-Meier Analysis
 - Difference in progression: multiple tumours, ↑ size, grade, cis
- Multivariate analysis
 - Multiple OR 1.9
 - Grade 3 OR 19.9
 - Size ≥ 3 cm OR 1.7
 - cis OR 2.1

Disease Specific Survival

Millan-Rodriguez et al., JU 163: 73, 2000

- Kaplan-Meier Analysis
 - Difference in disease specific survival: high grade, cis, IV instillation
- Multivariate analysis
 - Grade 3 OR 14
 - cis OR 3

CONVENTIONAL TREATMENTS

Campbell's 8th

- TURBT ± site selected biopsy
- Neodymium:YAG laser ablation
- Cystectomy
- Intravesical chemotherapy
- Intravesical BCG

TURBT

Campbell's 8th edition

- Indication: treatment and staging of bladder cancer
- Indications for biopsies (controversial):
 - Suspicious areas
 - Planning for partial cystectomy
 - High grade cytology with no tumours/low grade tumours cystoscopically

Inadequacy of TURBT

AUAU XXII: 2, 2002

- 60% suffer recurrence within 5 yrs
- 80% suffer recurrence within 10 yrs
- 25% of those with superficial disease will progress and/or require radical treatment such as cystectomy

Mucosal Biopsy

May et al., Eur J Urol 2003

- 905 consecutive patients with Tis, Ta, or T1 tumours > 1 cm
- Random normal mucosal Bx → cancer 12%
- Upstaging in 7% based on biopsy
- Alteration of therapy in 7% (BCG, repeat TUR, cystectomy)

Neodymium: YAG Ablation

Campbell's 8th

- Lesions can be coagulated
- Little bleeding, no obturator reflex
- PRCT demonstrated no difference in recurrence (Beisland et al, J Urol Nephrol 1986)
- Drawbacks: no tissue, forward scatter of laser energy and perforation

Cystectomy

Campbell's 8th

- Optional indications for cystectomy in superficial disease: (Campbell's 8th)
 1. Polychronotropic disease rendering bladder non-functional
 2. High risk disease refractory to intravesical therapy
 3. High grade T1, especially if multifocal

Intravesical Chemotherapy

- Thiotepa, adriamycin/doxorubicin, epirubicin, valrubicin, mitomycin C
- Weekly instillations over 4 – 8 weeks starting > 1 week post TURBT
- Small decrease in recurrence rate < 15%
- Ablative activity on existing tumour

Inadequacy of Intravesical Chemotherapy

Lamm et al., JU 153: 1444, 1995

- Review of 22 (3899) randomized trials of IV chemo vs TURBT alone
- Thiotepa, MMC, doxorubicin, ethoglucide, epirubicin
- Average ↓ in incidence @ 2 yrs: 14%
- No advantage in long term (> 5 yrs)
- Progression data from 2011: no difference

John Morrell:

Intravesical BCG

Campbell's 8th edition

- Remains most effective intravesical therapy
- Efficacy:
 - Treating CIS
 - Treating residual papillary disease
 - Preventing recurrence of superficial disease

BCG Basics

- Attenuated strain of *M. bovis* (not *M. tuberculosis*)
- Exact MOA unknown but probably involves Th1 mediated immune response

BCG Administration

- Lyophilized powder, reconstituted with NS
- Administered by catheter
- Solution retained for ~ 2 hrs
- Weekly x 6 weeks
- Evaluate response at 3 months with cysto and bladder biopsy
- Repeat x 1 if failure

Indications for BCG

1. Primary treatment of CIS
2. Adjuvant treatment of residual papillary tumour
3. Prophylaxis against recurrence of:
 - T1
 - Recurrent high grade Ta
 - Multifocal disease

Campbell's 8th

Efficacy of BCG

- Initial tumour-free response rate in ~76%
- Compared to TURBT alone ~ 40% reduction in recurrence
- Two fold improvement in recurrence compared to intravesical chemo (thiotepa, doxorubicin)
- Number needed to treat to prevent recurrence: 3.3
- Better than all other IV agents

Campbell's 8th, AUAU XXII:2, Smith et al., JU 1999

Limitations of BCG

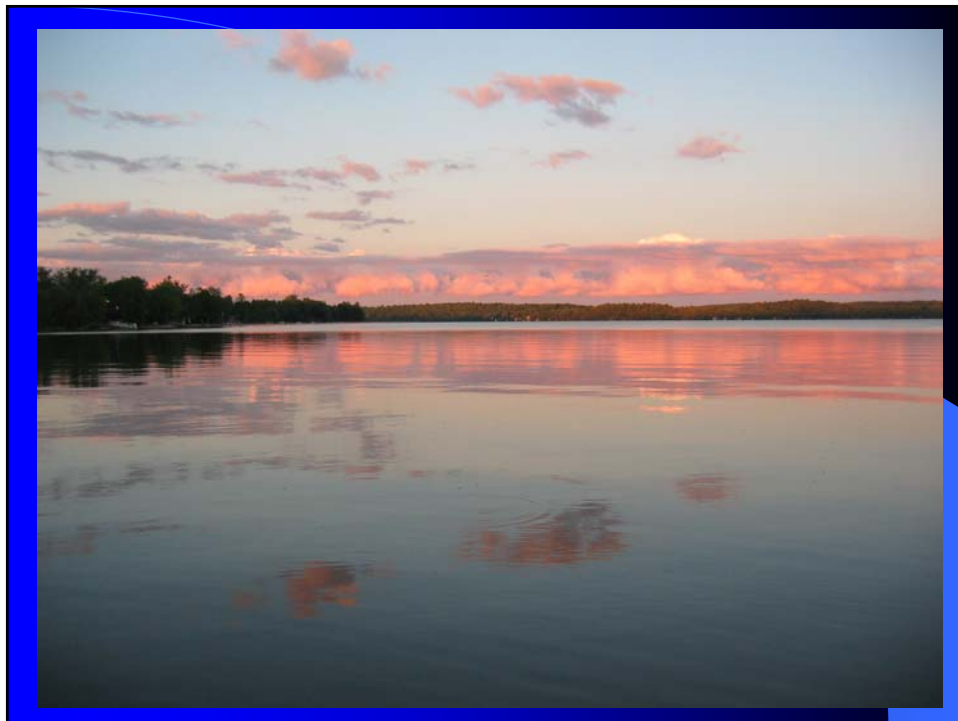
- Recurrence and/or progression in ~ 70%
- Use also limited by local/systemic side effects
- No effect on overall survival or death due to bladder cancer

Cookson et al JU '97,
Sylvester et al JU '02

Marginal Alternatives

- Intravesical interferons
- Intravesical interleukins
- Intravesical TNF
- Intravesical keyhole-Limpet Hemocyanin
(Cu containing protein from mollusc)

AUAU XXII:2, 2002



COMPLEMENTARY METHODS TO PREVENT RECURRENCE

- Macroablation
- Preventing re-implantation of tumour cells liberated during TURBT
- Microablation
- Prophylaxis

AUAU XXII:2, 2002

Macroablation

- Repeat TURBT
- Enhanced visual detection with 5-ALA and blue-light TURBT

Repeat TURBT

Grimm et al., JU 170: 433, 2003

- For big tumours, high grade tumours and high stage superficial tumours, 30% are upstaged on repeat TURBT
- Up to 1/3rd have residual tumour, 80% of time at initial TURBT site
- Rate of residual tumour independent of surgeon experience (Zurkirchen, Urol Int 2004)

Repeat TURBT

Grimm et al., JU 170: 433, 2003

- 124 patients with superficial tumour
- ReTURBT ~ 7 weeks for 78, no reTURBT for 36 (small, solitary TaG1)
- Tumour grade only independent factor predictive of residual tumour
- Kaplan-Meier 5 yr recurrence free survival: 63% reTURBT vs. 40% TURBT alone

5-ALA and Blue Light TURBT

- Conventional cysto may miss up to 1/3rd of tumours
- Pretreatment of bladder with 3% solution of 5-aminolevulinic acid (5-ALA) 2 – 3 hrs pre treatment
- 5-ALA is heme precursor

AUAU XXII:2, 2002

Filbeck et al., JU 2002

5-ALA and Blue Light TURBT

- Metabolite protoporphyrin IX accumulates after instillation in tumour tissue
- Accumulates in tumour vs. normal tissue 17:1
- Fluoresces red under excitation with violet light 375 – 440 nm
- Storz xenon white light with filter compatible with all scopes

AUAU XXII:2, 2002

Filbeck et al., JU 2002

5-ALA and Blue Light TURBT

Filbeck et al., JU 2002

- 301 patients underwent TURBT with either white light or 5-ALA & blue light
- Repeat TURBT 5 – 6 weeks later
- F/U white light cysto and cytology q3mo
- Residual tumour @ 6 weeks: 25% vs 5%
- 2 yr recurrence free survival: 90% vs 66%
- Hazard ratio for recurrence: 0.33

Preventing Reimplantation: Perioperative Cytotoxics

- Molecular fingerprints of recurrent tumours show most synchronous and metachronous tumours are of clonal origin
- Estimated that 50% of recurrences may be due reimplantation
- Multiple studies have shown efficacy of post TURBT intravesical chemo instillation with minimal side effects

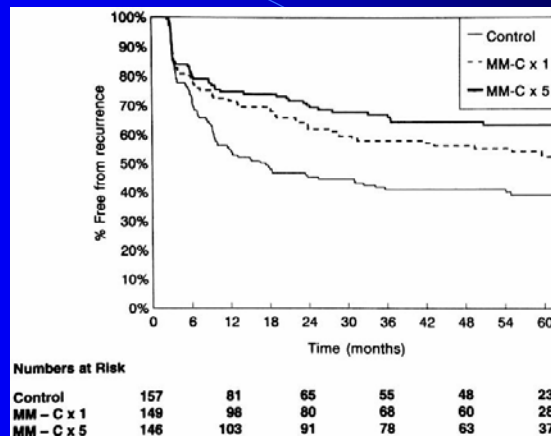
AUAU XXII:2, 2002

Perioperative MMC

Tolley et al., JU 1996

- 452 patients with Ta/1: TUR alone vs. TUR + immediate MMC vs. TUR + immediate MMC followed by MMC q3mo x 1 yr
- 40 mg/40 mL water given within 24 hrs
- Retained for 60 minutes
- Median F/U: 7 yrs
- Toxicity: well tolerated, no LUTS reported

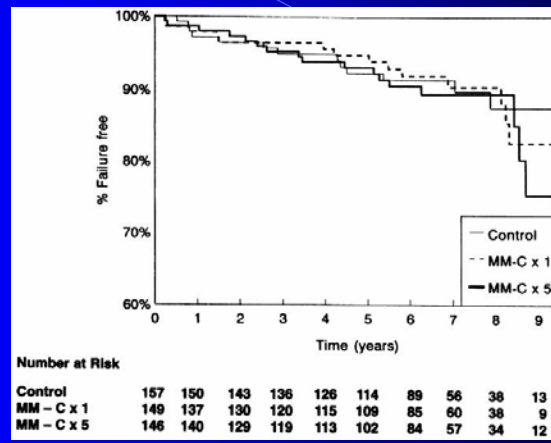
Kaplan-Meier recurrence



MMC x 1 ↓ recurrence by 34%

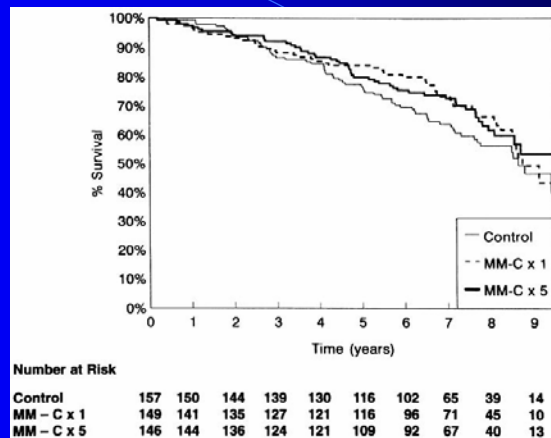
MMC x 5 ↓ recurrence by 50%

Kaplan-Meier progression



MMC had no effect on progression

Kaplan-Meier overall survival



MMC had no effect on overall survival

Microablation

- Enhancing chemotherapy
- Enhancing immunotherapy

Optimizing Chemo Pharmacology

Au et al., J Natl Canc Inst 2001

- Inducing relative dehydration
- Removing all residual urine at time of instillation
- Decreasing volume of diluent
- Increasing urinary pH (oral alkalinization to improve MMC stability)
- Five yr disease free rate: 41% vs. 25%

Combing Chemo with Synergistic Technologies

- Intravesical chemotherapy combined with intravesical hyperthermia
- Electromotive driven intravesical MMC

Intravesical chemo combined with intravesical hyperthermia

Colombo et al., J Clin Oncol, 2003

- Based on lab observation of tumour cell sensitivity to hyperthermia
- Prospective, randomized, multicentre
- Primary or recurrent Ta-T1, complete TUR
- TaG1 excluded
- 41 got MMC, 42 MMC + hyperthermia

Intravesical chemo combined with intravesical hyperthermia

Colombo et al., J Clin Oncol, 2003

- 8 weekly sessions and 4 x monthly maintenance
- Hyperthermia delivered via 915 Mhz intravesical microwave generator
- Hyperthermia: $42 \pm 2^\circ \text{C}$
- Min F/U: 24 months
- Primary outcome: recurrence free survival

Intravesical chemo combined with intravesical hyperthermia

Colombo et al., J Clin Oncol, 2003

- Recurrence @ 24 months: 17% vs. 58%
- Side effects: LUTS but no significant difference between groups
- Long term data required

Intravesical Electromotive MMC

Di Stasi et al., J Urol 2003

- G3 and T1 tumours may require higher concentrations of MMC than can passively diffuse
- Current → flow of water with solubilized MMC
- Prospective, randomized trial
- 108 patients with Tis and Ta – T1
- 40 mg MMC vs. 40 mg MMC + 20 mA vs. BCG

Intravesical Electromotive MMC

Di Stasi et al., J Urol 2003

- 6 weekly treatments
- additional 6 weeks for non responders
- Monthly x 10 for responders
- Well tolerated: more adverse effects in BCG group (frequency, cystitis, hematuria, fever, malaise, fatigue)

TABLE 3. *Treatment efficacy based on intent to treat analysis*

	BCG	Passive MMC	Electromotive MMC	p Value
% Complete response (95% CI):				
3 Mos	55.5 (38.1-72.1)	27.8 (14.2-45.2)	52.8 (35.5-69.6)	0.036 (Fisher exact test)
6 Mos	63.9 (46.2-79.2)	30.5 (16.3-48.1)	58.3 (40.7-74.4)	0.012 (Fisher exact test)
Crossover	35.0 (20.6-51.7)		23.1 (5.0-53.8)	0.511 (Fisher exact test)
Recurrence:				
% Pts (95% CI)	52.8 (35.5-69.6)	75.0 (57.8-87.9)	52.8 (35.5-69.6)	0.092 (Fisher exact test)
Median mos to recurrence (95% CI)	26 (21-37)	19.5 (12-27)	35 (21-46)	0.013 (Fisher exact test)
% Progression (95% CI)	16.7 (6.4-32.8)	22.2 (10.1-39.1)	16.7 (6.4-32.8)	0.861 (Fisher exact test)
% 5-Yr estimated survival probability (95% CI):				
Any cause	58.7 (35.9-75.8)	63.1 (41.6-78.5)	68.9 (46.6-83.4)	0.782 (likelihood ratio homogeneity test statistic)
Bladder Ca	78.0 (54.1-90.4)	75.3 (89.6-88.3)	78.5 (57.9-89.8)	0.943 (likelihood ratio homogeneity test statistic)

Alternative Chemo Regimens

AUAU XXII: 2, 2002

- Cis-platinum: anaphylactic reactions
- Mitoxantrone: not effective
- Etoposide: not effective
- Bleomycin: not effective
- MTX: not effective
- 5-FU: not effective
- Multi-agent regimens: not effective

Intravesical Gemcitabine

Gontero et al., Eur Urol 2004

- Phase II trial of ablative efficacy of intravesical gemcitabine
- 39 patients, marker lesion left after TUR of all other lesions
- 2 g of gemcitabine in 50 mL NS weekly x 6
- Repeat TUR 2 weeks after completion
- CR in 56%, stable disease in 44%

Intravesical Suramin

Uchio et al., J Urol 2003

- Polysulfonated naphthylurea
- Inhibits proliferation and DNA synthesis of TCC cell lines
- Large molecule with negative charge that inhibits absorption
- Safe dose identified

Mistletoe Lectin

Goebell et al., J Urol 2002

- 45 patients with Ta, low grade tumours
- TURBT vs. TURBT + SC mistletoe lectin
- Conclusion:
 - no effect on time to first recurrence
 - No effect on number of recurrences

Immunotherapy Enhancement

- Maintenance and reinduction BCG
- Dose reduction strategies
- Combination BCG and immune modifiers

Maintenance and Reinduction BCG

Lamm et al., J Urol 2000

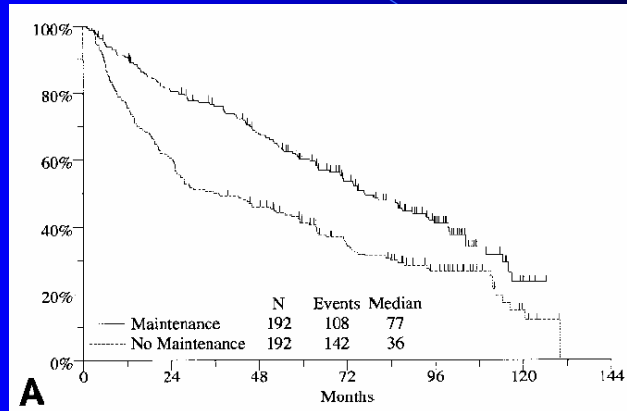
- 2nd 6 week course of BCG will induce CR in 30 – 50% of initial non-responders
- SWOG 8507 – Maintenance vs. no maintenance
- 550 patients with cis or recurrent Ta/1
- Induction 1 week post TURBT for 6 weeks
- Maintenance: 3 weeks @ 3, 6, 12, 18, 24, 30, 36 months

Maintenance and Reinduction BCG

Lamm et al., J Urol 2000

- Patients received standard IV BCG and percutaneous BCG
- Percutaneous BCG: inner thigh cleaned, 10 million CFU in 0.5 cc applied, skin punctured with 28 Ga needle x 3
- Benefit/futility of this extra step unknown

Recurrence-free survival



Median recurrence-free survival: 77 vs 36 months

%5 yr recurrence free survival: 60% vs 41%

Dose Reduction Strategies

- Dose currently used was never subject to same dose ranging phase I and II studies now required
- Several trials undertaken to test lower doses
- Goal: maximize activity while minimizing toxicity

Dose Reduction Strategies

Martinez-Pineiro et al., BJU Int 2002

- 500 patients Ta, T1, Tis randomized post TURBT to standard BCG 81 mg vs 27 mg
- Weekly x 6 then q2weeks x 6
- Median F/U: 69 months

Dose Reduction Strategies

Martinez-Pineiro et al., BJU Int 2002

- No difference:
 - time to first recurrence
 - % progression free @ 5 yrs
 - overall survival
- Significantly less toxicity in reduced dose group
- Trend towards ↓ recurrence/progression in std dose group for those with high-risk disease (G3, cis, relapsing, multifocal, large)

Combination Therapy Strategies: BCG + IFN- α

AUAU XXII:2, 2002

- BCG and IFN- α potentially synergistic
- IFN- α shown to potentiate and polarize in vitro human lymphocyte responses to BCG
- Preliminary results suggest combo may have improved efficacy over BCG alone
- Further studies required.
- Role in BCG failures

Prophylaxis

- Smoking cessation
- Dietary modification
 - Vitamin supplementation
 - Increased fluid intake

Smoking Cessation

- Late recurrences can result from continued carcinogenic exposure or prior field defects induced by past exposure
- Smoking is largest single RF for majority of patients
- Those continuing to smoke have highest risk for recurrence and progression

Smoking Cessation

Aveyard et al., BJU Int 2002

- Systematic review of evidence for smoking cessation
- Fifteen studies identified
- 3 examined influence of smoking on prognosis in incident cases, 1 high quality
- All papers suggested that quitting decreases recurrence but very weak evidence

Smoking Cessation

- Evidence insufficient for clinicians to inform patients that quitting will improve their prognosis
- Evidence insufficient for providing specialized services to assist patients with bladder cancer

Dietary Modification

AUAU XXII: 2, 2002

- Diets rich in fruits and vegetables impart the lowest RR
- Diets high in fats increase risk
- May be useful in reducing new BT formation

Vitamin Supplementation

- Randomized trial of supplemental high dose vitamins A, C, E, B6 and Zn versus std multivitamin
- Significant benefit in maintaining disease free state after successful BCG
- Small study (65 patients total)

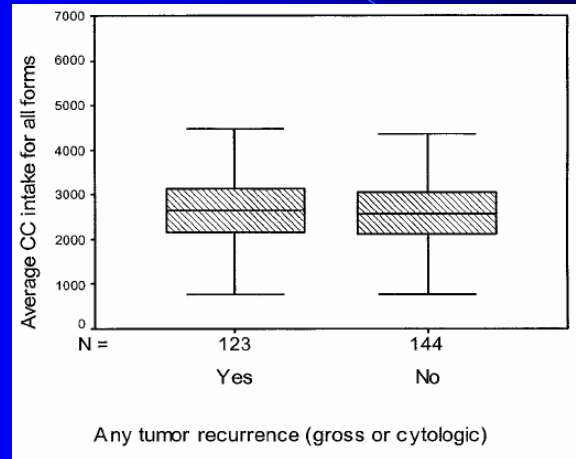
Lamm et al., JU 1994

Increased Fluid Intake

- High fluid intake yields decreased incidence of bladder cancer in men
- Prospective evaluation of effect of fluid intake on recurrence
- 267 patients on surveillance
- Fluid intake questionnaires at each F/U
- Minimum 2 yrs F/U

Donat et al., JU 2003

Increased Fluid Intake



Donat et al., JU 2003

SUMMARY

- Majority of superficial tumours recur
- Significant number progress in stage
- Current treatments are inadequate
- Recurrence can be decreased with complementary methods

POINTS FOR DISCUSSION

- Repeat TURBT
- Post-op MMC
- Maintenance BCG