Management of Non-Invasive & Invasive Bladder Cancer

PRESENTED BY:
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Types, Grades, & Staging
Epidemiology of Transitional Cell Carcinoma
Symptoms & Diagnosis
Treatment of Superficial Transitional Cell Carcinoma
Surveillance & Follow Up
Treatment of Invasive Transitional Cell Carcinoma
Surveillance & Follow Up

Overview
- Types, Grades, & Staging
- Epidemiology of Transitional Cell Carcinoma
- Symptoms & Diagnosis
- Treatment of Superficial Transitional Cell Carcinoma
- Surveillance & Follow Up
- Treatment of Invasive Transitional Cell Carcinoma
- Surveillance & Follow Up

Overview
- 90% - 95% TCCa in United States & Europe.
- 5% SCCa.
- 0.5% - 2% Adeno Carcinoma.
- <1% small cell, micropapillary, carcinosarcoma, & sarcomatoid.
- Micropapillary
  - Median overall survival is 19 months.
  - >70% in one study with mets, 9 month survival.
  - Carcinosarcoma & Sarcomatoid
    - 41 pts. @ Mayo between 1936 & 1995.

HISTOLOGY
- Spinal cord patients
- Indwelling catheter, chronic UTI, stones.
- Most common bladder cancer in Egypt, Sudan, Arabia, & Africa 80%.
- Schistosoma haematobium major causative agent.
- Most squamous cell carcinomas are invasive.
- In the United States, about 2.2% of bladder cancers are squamous cell carcinomas.

SQUAMOUS CELL CARCINOMA
- Adenocarcinoma usually arises from urothelial or trigonal region.
- Prevalent with prior bladder exstrophy.
- Most common cancer associated with incontinence.
- Represents 0.3% - 2% of bladder cancer in U.S.

ADENOCARCINOMA
- 41% poorly differentiated.
- 100% invasive.
- 40% T3+
- 5 year survival, 18%
PHAEOMYOSARCOMA
- <0.5% of all bladder tumors.
- Most common tumors of the lower urogenital tract in children.
- Often children 2-6 years old; 75% male.
- Adult tumors are usually alveolar or unclassified, commonly with anaplasia, and resemble small cell carcinoma.
- Usually in trigone.
- Infiltrates adjacent tissue but distant metastases are rare.
- 5 year survival for embryonal subtype is 50-80%.
- Adult tumors are uniformly aggressive.

RHABDOMYOSARCOMA

BENIGN TUMORS
- Squamous Metaplasia
  - 50% of females; 10% of males.
  - White, flaky appearance, nearly always related to trigone.

INVERTED PAPILLOMA
- 1.5% risk of prior bladder cancer.
- 5% risk of present bladder cancer.
- 1.5% risk of future bladder cancer.
- Male:female ratio: 6:1
- Bladder neck or trigonal region, uniformly benign.

BENIGN TUMORS
- Nephrogenic Adenoma
  - Metaplastic response to trauma, infarction, RT, or immunosuppression.
  - TURBT & conservative cystoscopic follow up.
  - Pseudosarcoma: spindle cell tumor association with prior surgery.

TRANSITIONAL CELL CARCINOMA
- Men: TCCa cases are much higher in men than women with a 3:1 ratio.
- Caucasian men have double the risk than African American men.
- Women are twice as likely to die from TCCa because of advanced stage at time of diagnosis.

EPIDEMIOLOGY
- 14,000 deaths/year.
- 75% non muscle invasive
- 20% muscle invasive
- 5% metastatic
- 70,000 cases/year.
- 4th most common cancer in men, 10th in women.
- 66% of TCCa cases are diagnosed at age 65 years and older.
- Highest rates are in industrially-based cities, especially in the north eastern United States.
- Men: TCCa cases are much higher in men than women with a 3:1 ratio.
- Caucasian men have double the risk than African American men.
- Women: Women are twice as likely to die from TCCa because of advanced stage at time of diagnosis.
RISK FACTORS
- Smoking - responsible for 50% of cases in men & 30% in women.
- 15-30 year latency period.
- Sphingolipid storage disease.
- Analgesic abuse.

OCCUPATIONAL EXPOSURE
- 15% of cases.
- Inorganic arsenic, rubber paste, textile printing, petroleum.

RISK CLASSIFICATION SCHEME
- Low Risk (~50% of cases)
  - Any low grade (1 or 2).
  - Solitary
  - Primary T1
  - Reccurrence rate <5%.
  - Intermediate Risk (15% of initial cases)
  - Any high grade Ta or T1.
  - Any CIS.
  - Progression rate 25-50%.
  - High Risk (50% of cases)
  - Any high grade Ta or T1.
  - Any CIS.
  - Progression rate 25-50%.
  - Afrer 3 months of disease.
  - Progression rate >50%.

SIGNS & SYMPTOMS
- Hematuria:
  - 80% - 90% of cases.
  - Bladder cancer is the most common cause of gross hematuria in patients >50 years of age.
  - Intermittent symptoms without UTI.

WORK UP
- Urinalysis:
  - >3 RBC's/HPF on 2/3 UA's.
  - Culture & Sensitivity.
- Cystoscopy & CTU:
  - 2% with early upper tract disease at time of presentation.
  - 25% with advanced disease with upper tract TCC.
CT UROGRAM: NORMAL
CT UROGRAM: TCCA
CYSITOSCOPY VIDEO

DIAGNOSIS
- Cytology:
  - 35-48% sensitivity (70% with grade 3).
  - 94% specificity.
- Fish:
  - Tetraploidy in >12/25 cells.
  - 79-84% sensitivity.
  - 70-95% specificity.

BIOPSY & FULGURATION OR TURBT.
- Instill Mitomycin 20-40mg intravesically within 6 hrs post TURBT.
- 12% absolute reduction in recurrence out to 3 years.
- 25-50% relative reduction in recurrence.

STAGE TA
- Treatment of Superficial TCCa
- Transurethral Resection of Bladder Tumor (TURBT) Video

CHEMOTHERAPY
- Mitomycin:
  - Antibiotic isolated from Streptomyces.
  - Weekly instillations of 40mg via catheter.
  - Dwell time 1-2 hours.
  - 10% with genital/palmar paresthesia.
  - Chemical cystitis 2%.
  - 15% - 30% absolute reduction in recurrence to 3 years.
  - Severe tissue necrosis with perforation.
- Thiotepa:
  - Alkylating agent related to Nit. Mustard.
  - Low molecular weight (189).
  - 13% with myelosuppression.
  - Weekly pre-induction CBC.
  - Questionable benefit <12% reduction in recurrence.
BCG BACKLIT CAMELITE-STREAM

- Multifocal T1/T2 papillary tumors
- High grade T1 tumors
- Multifocal high grade tumors
- BCG to be done within 6 weeks of initial cystectomy

BCG MECHANISM OF ACTION
- Type 1 immune response
- Involves T cells, neutrophils, & NK cells
- Irritative?

- Cystitis - 50% (10% dropout due to intolerance)

Techniques to improve tolerance:
- Anticholinergics, pyridium
- Dose reduction
- Spacing treatments every 2 weeks
- Decrease dwell time
- Post BCG quinolone

( INH x 3days will not reduce side effect risk of BCG infection )

BCG TOXICITY
- Fever, chills, myalgia, arthralgia in 25%
- Fever > 39.5 in < 5% patients: sepsis 0.5%
- Severe infections require 3-6 months therapy
- INH alone x 6-8 months, or INH/Rifampin/EMB/ethambutol
- Vitamin B6 supplementation recommended
- Cycloserine ineffective
- Fluoroquinolones 3rd line agents

- 30% - 60% reduction in recurrence
- 30% reduction in progression risk
- 2nd course BCG, 30-50% response
- 3rd course BCG, < 20% response
- After 2nd failure, vulpectomy or cystectomy

Maintenance BCG (3, 6, 12, 18, 24, 30, & 36 months) doubles recurrence free survival from 36 to 77 months

BCG EXPECTED BENEFITS

- Low grade (grade 1-2), solitary, primary Ta papillary tumors
- If initial 3 month cystoscopy is negative, then it is safe to wait 12 months for the next cystoscopy, then 1-2x/year.

LOW RISK
- Recurrent Ta-T1, low grade.
- Multifocal Ta-T1, low grade.
- Cystoscopy every 3 months x2 years.
- Then every 6 months x2 years.
- Then annually.

INTERMEDIATE RISK
- Any high grade Ta or T1.
- Any CIS.
- Cystoscopy every 3 months x2 years.
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HIGH RISK

TC Ca Follow Up

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- Then annually.
**SUPERFICIAL TCCa RECURRENCE @ 4/8 YEARS**

- Papilloma: 20%
- PUNLMP: 40%
- LG TCC: 60-70%
- HG TCC: 80%

**SUPERFICIAL TCCA PROGRESSION @ 4/8 YEARS**

- Papilloma: 20%
- PUNLMP: 40%
- LG TCC: 60-70%
- HG TCC: 80%

**SUPERFICIAL TCCA RECURRENCE @ 2 YEARS**

- Invasion into lamina propria.
- Mitomycin post TUR.
- 12%-25% reduction in recurrence.
- Requires repeat TURBT.
- Residual tumor, or upstaging in 28% - 35%.
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**Radical Cystectomy**

- Includes bladder, prostate & SV’s in men.
- Bladder, uterus, cervix, & anterior vaginal wall in women.
- Internal iliacal lymph nodes.
- Extended LND becoming more common place.
- IMA
- For T2, T3, & refractory CIS
- Platinum based chemos for all T+ tumors.

**Open vs Robotic Cystectomy**

<table>
<thead>
<tr>
<th>Grade: 3-5</th>
<th>Complication</th>
<th>Time</th>
<th>Blood Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open</td>
<td>22%</td>
<td>328 mins.</td>
<td>679cc</td>
</tr>
<tr>
<td>Robotic</td>
<td>24%</td>
<td>454 mins.</td>
<td>518cc</td>
</tr>
</tbody>
</table>

**Surival Following Radical Cystectomy**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Node Negative</th>
<th>Node Positive</th>
<th>Node Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT2</td>
<td>34-66%</td>
<td>64-83%</td>
<td>34-66%</td>
</tr>
<tr>
<td>pT3</td>
<td>11-27%</td>
<td>17-46%</td>
<td>11-27%</td>
</tr>
<tr>
<td>pT4</td>
<td>11-27%</td>
<td>0-33%</td>
<td>11-27%</td>
</tr>
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</table>


**Node Management**

- Bilateral pelvic lymphadenectomy including external & internal iliacal & obturator nodes is now mandatory.
- Extended dissection from IMA for all T3-T4 tumors. (Nodes above iliac bifurcation).
- For grossly positive N2 or N3 disease, 18-20% long term survival with extended LND.

**Cystectomy Complications**

- 1,145 patients at MSK.
- 15-25% complication rate.
- Prolonged ileus, bowel obstruction, incontinence, & UI.
- Mortality 1.6 - 3.3%, almost all from PE, MI, or sepsis.
• 5% - 9% overall survival advantage for platinum based multi-dosing regimen, none for single agent.

NEoadjuvant Chemotherapy

- All invasive disease prior to cystectomy.
- Ta – T4a: node positive disease
- MVAC x3
- Carboplatin/gemcitabine

Research Evidence

• All invasive disease prior to cystectomy.
• Ta – T4a node positive disease
• MVAC x3
• Carboplatin/gemcitabine

Advantages (NEoadjuvant Chem)

• Treat micrometastatic disease in order to reduce rate of, or delay emergence of measurable metastatic disease and improve long term survival.
• Response to chemotherapy can be objectively assessed.
• Down staging unresectable disease to resectability.

Advantages (NEoadjuvant Chem)

• Potential for overestimating patients who would benefit from surgery alone.
• Inductive chemotherapy may alter definitive local therapy and delay progression.

5 Year Survival

Cystectomy:
- T2: 64%-83%
- T3: 17%-46%
- T4: 0%-33%

Trimodal Therapy:
- T2 - 5 yr. survival: 61%
- T3 - 5 yr. survival: 41%
- 25% - 29% require cystectomy
- 9% incidence of contracted bladder.
- 2% require cystectomy for contracted bladder.

Radiation Therapy as Primary Therapy for TCCA

• 55-65 Gy.
• Contraindicated with hydronephrosis, T3b, T4.
• 5 year survival T2 26% - 59%
• T3: 30% - 40%
• Outcome poorer when total dose <57.5 Gy.

Trimodal Therapy

- MVAC chemotherapy
- Cisplatin 100 mg/m² weekly
- Carboplatin 600 mg/m² weekly

So what type of diversion do we choose after cystectomy?
HISTORY OF URINARY DIVERSION

- 1951: First diversion with trigonal reimplant into rectum on 13 year old boy who died one year later.
- Lloyd repeated this and patient died in 7 days.
- 1878: Thomas Smith formed ureterosigmoid fistulas in a 7 year old patient who also died.
- 1911: Payter experimented with multiple bowel segments and settled on distal ileum.
- 1950: Bricker popularized ileal loop.

CRITERIA FOR RESERVOR SELECTION

- Nephrostomy
- Less pressure/high volume, low surface area.
- Ease of non-obstructing, non-obstructing ureteral stents.
- Stable urothelium.
- Recognized normal tract
- Simply acceptable, non-disguising.

TYPES OF CONTINENT DIVERSION

- Heterotopic with a continent, catheterizable stoma.
- Orthotopic, emptying through a native urethra.

METABOLIC SEQUELAE

- Colon conduit syndrome.
- Juxta-renal conduit syndrome.
- Bone demineralization.
- Hyperammonemia: encephalopathy.
- Megablastic anemia.
- Diarrhea.
- Stone formation (20 yrs – 20%).
- Renal function: GFR <25-25% after 11 years.

INTRINSIC FACTOR

- Secreted by parietal cells in fundus & body of stomach.
- Binds to B12 & protects it from digestion during passage thru small intestine.
- Absorbed in ileum.
- 15 cm of terminal ileum with highest concentration of IF-B12 absorption sites.
- Hepatic stores can last 3-5 years.

COLON

- Less absorptive surface area than small intestine.
- Highly efficient Na+, Cl-, water absorption due to active transport.
- Luminal concentration of Cl <15mEq, explaining large HCO3 excretion.
- K+ excreted passively to luminal concentration of >90mEq.
- <150ml of water lost per day from human colon.

COLON AS URINARY RESERVOIR

- Transverse & Ascending Colon:
  - 1% - 50% incidence of hyperchloremic metabolic acidosis.
- Sigmoid Colon:
  - 30% - 80% of hyperchloremic metabolic acidosis.
  - Hypernatremia, hyperchloremia, hypokalemia, metabolic acidosis.
  - Thirst, weakness, diarrhea, N/V, coma.
**JEJUNUM**
- 3.5 cm dia., 260 cm length.
- Largest pores and mucosal folds in small intestine.
- 8x greater water flux than ileum.
- Passive K flux, active Na transport (13mEq gradient).
- Isotonicity achieved rapidly/rapid water/solute movement.

**JEJUNUM AS URINARY RESERVOIR**
- Jejunal Conduit Syndrome:
  - N/V, anorexia, muscle weakness.
  - Hyponatremic, hypochloremic, hyperkalemic metabolic acidosis.
  - Azotemia
  - Clark et al – 40% of pts. demonstrated JCS.
  - Golimbu & Morales – 43% of pts. demonstrated JCS.
  - Treatment: sodium chloride and hydration, rarely bicarb.

**ILEUM**
- 3.1 cm dia., 390 cm length
- Smaller mucosal surface area, active Cl absorption.
- 20% of lumen reaches isotonicity with plasma.
- Separate anion & cation exchangers, i.e., when Na & Cl absorption equal, no HC03 loss.
- When Cl absorption > Na absorption, a net loss of HC03 into ileal lumen results.
- Bile salts & Intrinsic Factor absorbed in distal ileum.
- 1.6-10% incidence of hyperchloremic acidosis.
- NaHCO3 or citrate therapy.

**URETERAL REMPLANTS**
- 1853 – Sir John Simon developed iatrogenic uretero-rectal fistula.
- Lloyd replicated this with various bowel segments with 100% mortality.
- Coffey’s tunneled re-implant in 1911.
- Subsequently, multiple new methods have evolved, with varying degrees of difficulty and success.
- Simplicity, speed, non-refluxing, non obstructing.
**URETERAL RE-IMPLANTS**

- 201 Feofile pouches.
- Tunneled VS Non-tunneled:
  - Absence of reflux in 84 vs 87%, respectively.
  - Obstruction in 13 vs 4.2%, respectively.

**STOMA FORMATION**

- 1909 - Verhoogen, appendiceal continence mechanism.
- 1950 - Gilchrist claimed 100% continence with ileo-cecal valve in 29/29 pts.
- Multiple new techniques have evolved.
- Continence, ease of catheterization, minimal disfigurement.

- First used in 1980.
- Revison appendiceal safely.
- Continence in 42 out of 44.
- Difficult catheterization in 42%
- Surgical revision 28%-60%
MONTREAL SEGMENT

- Readily available
- Double joined tubes extend length when needed
- 24% stenosis rate
### Volume & Pressure Relationships with Various Intestinal Segments

<table>
<thead>
<tr>
<th>intestinal segment</th>
<th>mean vol. (cc)</th>
<th>mean pres. (cm H20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>tubular right colon</td>
<td>630</td>
<td>63</td>
</tr>
<tr>
<td>detubularized right colon</td>
<td>641</td>
<td>42</td>
</tr>
<tr>
<td>tubular ileum (40 cm)</td>
<td>311</td>
<td>81</td>
</tr>
<tr>
<td>detubularized ileum</td>
<td>403</td>
<td>28</td>
</tr>
</tbody>
</table>

### continent urinary diversion
- Continent, orthotopic ileal neobladder is the preferred urinary diversion.
- Continent heterotopic ileal or right colon urinary reservoir.
- 45-80% of patients are candidates for continent diversion.
- Rates of continent diversion vary from 90% to as low as 15%, depending on center.

### continent urinary diversion contraindications
- Past diversions: What we’ve learned.
  - CR > 2.0 mg/dL
  - GFR < 40 ml/min
  - Short gut, IBD, colon Ca.
  - Short mesentery, RT.
  - Positive urethral margin.
  - Question grossly positive nodes with need for adjuvant chemotherapy.

### ureterosigmoidostomy
- Hyperkalemic metabolic acidosis in 30% of pts.
- fecal & urinary incontinence in 100%
- Babcock et al. - 5% incidence of tumors with average incubation time of 20 years.
- Sandy & Steward - 40% incidence of proximal tumors with incubation time between 1 & 40 years.
Another diversion no longer performed but many patients are still alive and will need periodic re-exploration.

- First performed 1962
- First patient 1967
- First nipple valve 1975
- First series in 1982, 7/12 pts. Required re-operation.
- Kock - 60 cm of ileum (36 cm pouch, 12 cm valved).
- Skinner - 84 cm of ileum (44 cm pouch, 17 cm valved, 4 cm discarded proximally).

**Kock Pouch - Characteristics**

- Capacity - 800 - 1000 cc at 6 mo.
- Straight cath. Q 4-6 hr. during day; q 8 hrs. during night.
- Pouch pressure 15 - 20 cm at 350 cc.
KOCK POUCH COMPLICATIONS

Effluent Valve Malfunction
- 25% reoperation in world experience in 1980's.
- 35% reoperation in USC experience of 1,250 pts.

Causes of effluent valve malfunction include:
- Fistulae
- Abdominal wall detachment
- Lack of serosity
- Inadequate fixation to pouch wall
- Prolapse
- Para-anastomotic hernia
- Vasovagov tail
- Peritoneal leak

GASTROCYSTOPLASTY

Based on gastroepiploic artery.
- 20% - 60% Hematuria/dysuria syndrome.
- >20% with hyperchloremic alkalosis.
- 20% - 30% still with bacteriuria.
- Still utilized with renal insufficiency pts. with chronic metabolic acidosis.
- KCL supplementation superior to H2 blockers.

Currently favored continent diversions with low pressure/high volume reservoir & minimal metabolic sequelae.

HETEROTOPIC T-POUCH

- 20cm cecum & right colon.
- 35cm terminal ileum.
- Ileal patch or Heineke – Mikulicz.

INDIANA POUCH

- 20cm cecum & right colon.
- 35cm terminal ileum.
- Beal patch or Heineke – Mikulicz.
INDIANA POUCH RESULTS

- Capacity >400cc.
- Continence 87 – 95%
- Day time cath. Q4hrs.
- Night time cath. Q6hrs.
- Rare pouchitis.
- Ureteral obstruction rare.

STUDER NEOBLADDER

- 60 cm ileum.
- 20 cm afferent limb.
- 40 cm "U" shaped reservoir.
- Post-op capacity 125cc, expanding over time to 400 – 500cc.

STUDER COMPLICATIONS

- Pyelo/leisis - 14.7%
- Abdominal or inguinal hernia - 8%
- Outlet obstruction - 8%
- Ureteroileal anastomotic stricture - 7%
- Metabolic acidosis - 4%
- Fistula - 1%
ILEAL NEOBLADDER CHARACTERISTICS

- Avg. capacity 400-500cc.
- Avg. post void residual 12ml.
- Avg. pressure at capacity 24.4 cm (16-40 cm).
- Max. pressure during straining 60 cm.
- Max. flow rate 28ml/sec.
- 93% daytime continence.
- 86% nighttime continence.
- 4% require intermittent straight cath.
- 6% ureteral stricture.

Superficial TCCa has a high recurrence rate and needs close follow-up.
Most patients are candidates for some form of continent urinary diversion.
Unique metabolic sequelae occasionally seen from all forms of urinary diversion, can usually be easily corrected.

In Conclusion