Bladder Cancer Diagnosis, Management, and Current Research

Piyush K. Agarwal, MD
Head, Bladder Cancer Section
Urologic Oncology Branch
National Cancer Institute
piyush.agarwal@nih.gov
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Agenda

• Overview of Bladder Cancer
  – Epidemiology
  – Risk Factors
  – Evaluation
  – Staging
  – Grading

• Current Treatment Strategies
  – Transurethral Resection of Bladder Tumor (TURBT)
  – Intravesical Therapy
  – Radical Cystectomy
    • Chemotherapy and Radiation
  – Urinary Diversions
  – Robotic Approaches

• Current Research
Important Facts: Bladder Cancer

- 4th most common cancer in men and 12th most common cancer in women in 2014
- 74,690 new cases and 15,580 deaths in 2014
- Represents 7% of all cancers and 3% of all cancer deaths
- Recurrence and routine surveillance/treatment make bladder cancer most expensive malignancy to treat from diagnosis to death ($187,241/patient in 2001)
- M:F = 3:1 (survival better in men)
- Peak incidence ages 60-70
- Majority (~93%) are urothelial cancer (transitional cell carcinoma)

Siegel et al. CA Cancer J Clin 2014.
## Risk Factors

<table>
<thead>
<tr>
<th>Exogenous</th>
<th>Industrial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schistosomiasis</td>
<td>Aniline dyes</td>
</tr>
<tr>
<td>Tobacco</td>
<td>Benzene derivatives</td>
</tr>
<tr>
<td>Phenacetin metabolites</td>
<td>(aromatic amines)</td>
</tr>
<tr>
<td>Cytostatics</td>
<td>Paints, oils, gasoline</td>
</tr>
<tr>
<td>(Cyclophosphamides)</td>
<td></td>
</tr>
<tr>
<td>? Sweeteners (Saccharin, cyclamate)</td>
<td></td>
</tr>
<tr>
<td>Pelvic radiation</td>
<td></td>
</tr>
<tr>
<td>Blackfoot disease (Taiwan)</td>
<td></td>
</tr>
<tr>
<td>A. Fangchi (Chinese herb)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Endogenous</th>
<th>Tryptophan metabolites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic irritations</td>
<td>Nitrosamines</td>
</tr>
<tr>
<td>(catheters) /Toxins</td>
<td></td>
</tr>
<tr>
<td>Chronic inflammation</td>
<td></td>
</tr>
</tbody>
</table>
Occupations at Risk

- Dry cleaners
- Painters
- Autoworkers
- Truck drivers
- Paper manufacturers
- Metal workers
- Plumbers
- Hairdressers
- Tire and rubber workers
- Chemical workers
- Petroleum workers
Presentation

• Gross hematuria most common
  • Most commonly intermittent
    – Gross 68-97%
    – Microhematuria 11%
• Timing of hematuria
  – Initial – suggests urethral source
  – Terminal – suggests posterior urethra, bladder neck, prostate
  – Continuous – suggests bladder etiology
• Irritative voiding symptoms (especially in absence of UTI)
Work-up for Hematuria

- Cystoscopy
- Urinary Tumor Marker  
  - Usually cytology
- Imaging  
  - Renal Ultrasound and IVP traditionally  
  - Now CT Urogram  
  - Even MR Urogram
- Transurethral Resection of Bladder Tumor (TURBT) and Exam Under Anesthesia (EUA)
Cystoscopy
CT Urogram – New Gold Standard

- Right ureteral tumor
- Several bladder tumors
EUA and TURBT
Bladder Cancer Staging

Stage 0 Bladder Cancer

- Bladder
- Ureter
- Fat around the bladder
- Muscle layers
- Connective tissue
- Inner lining

Stage Ta
- Papillary carcinoma

Stage Tis
- Carcinoma in situ
Bladder Cancer Staging

Stage T1
Bladder Cancer Staging

Stage T2
Stages of Bladder Cancer
Stage

- ~70% non-muscle invasive (superficial)
  - Despite adequate therapy, 60-70% recur and 10-20% progress
  - 70% Ta and 30% T1
- ~25% muscle-invasive
  - 5 year overall survival 78% (45% with + nodes)
  - Morbidity of treatment (cystectomy +/- chemotherapy)
  - Majority present as muscle-invasive initially
- 5% metastatic disease
  - Chemotherapy produces median survival of 18 months and long-term disease-free survival in 10-15%

Stein et al. JCO 2001.
Dinney CPN. Urology 2006.
Grade

Low Grade

High Grade
Disease Recurrence

- Up to 70% will recur within 5 years

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Probability of Recurrence in 5 years</th>
<th>Probability of Progression to Muscle Invasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ta, low grade</td>
<td>50%</td>
<td>Minimal</td>
</tr>
<tr>
<td>Ta, high grade</td>
<td>60%</td>
<td>Moderate</td>
</tr>
<tr>
<td>T1, low grade (rare)</td>
<td>50%</td>
<td>Moderate</td>
</tr>
<tr>
<td>T1, high grade</td>
<td>50-70%</td>
<td>Moderate-High</td>
</tr>
<tr>
<td>Tis</td>
<td>50%-90%</td>
<td>High</td>
</tr>
</tbody>
</table>

Disease Progression

Estimates of disease progression in superficial bladder cancer

<table>
<thead>
<tr>
<th>Tumor type(^a)</th>
<th>% Relative frequency</th>
<th>% Progression</th>
<th>% Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noninvasive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papilloma</td>
<td>10</td>
<td>0–1</td>
<td>0</td>
</tr>
<tr>
<td>PUNLMP</td>
<td>20</td>
<td>3</td>
<td>0–1</td>
</tr>
<tr>
<td>Papillary cancer low grade (TaG1)</td>
<td>20</td>
<td>5–10</td>
<td>1–5</td>
</tr>
<tr>
<td>Papillary cancer high grade (TaG3)</td>
<td>30</td>
<td>15–40</td>
<td>10–25</td>
</tr>
<tr>
<td>Invasive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papillary cancer (T1G3)</td>
<td>20</td>
<td>30–50</td>
<td>33</td>
</tr>
<tr>
<td>Carcinoma in situ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>10</td>
<td>&gt;50</td>
<td>—</td>
</tr>
<tr>
<td>Secondary</td>
<td>90</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: PUNLMP, Papillary urothelial neoplasm of low malignant potential.

\(^a\) World Health Organization/International society of Urological Pathology Consensus Classification of Superficial Bladder Cancer [9].

Data from Refs. [4,6,8,9].
Summary of Standard of Care Therapy

- Low grade, Ta or T1 disease
  - Surveillance
  - Possible intravesical therapy

- High grade (cIS, Ta, T1)
  - Repeat TURBT
  - Intravesical therapy

- Muscle-invasive disease (T2)
  - Cystectomy and urinary diversion

- Lymph Node/Distant Metastases (N+/M+)
  - Chemotherapy +/- radiation

High Cost
High Recurrence
High Cost
High Progression
High Cost
Morbid Operation
50% Live
High Cost
0% Live
Surgical Therapies for Bladder Cancer

- Transurethral resection of bladder tumor (TURBT)
- Intravesical Therapy
- Radical Cystectomy
  - *** +/- Neoadjuvant Chemotherapy
  - *** Trimodal Therapy (XRT, Chemo, Surgery)
- Urinary Diversions
- Robotic Approaches to Bladder Surgery
  - Partial Cystectomy
  - Radical Cystectomy

*** not to be discussed due to time
Man with Visible Blood in the Urine
TURBT
INTRAVESICAL THERAPY
Who is a Candidate for Intravesical Therapy?

- High Risk Disease
  - Multifocal disease
  - T1G3 (or all T1)
    - 70-80% recurrence rate and 30% progression
  - CIS
  - Tumors in Dome/Anterior Wall
  - High risk of progression
## Intravesical Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immunomodulatory Agents</strong></td>
<td></td>
</tr>
<tr>
<td>Bacillus Calmette-Guérin (BCG)</td>
<td>• Inflammatory host response; release of cytokines</td>
</tr>
<tr>
<td></td>
<td>• May be combined with interferons&lt;sup&gt;90-94&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Interferons</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Lymphocyte activation; cytokine release; phagocyte stimulation</td>
</tr>
<tr>
<td></td>
<td>• Antiproliferative actions</td>
</tr>
<tr>
<td></td>
<td>• Antiangiogenic&lt;sup&gt;31,90&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Chemotherapeutic Agents</strong></td>
<td></td>
</tr>
<tr>
<td>Thiotepa</td>
<td>• Alkylating agent; cross-links nucleic acids&lt;sup&gt;95&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mitomycin C</td>
<td>• Antibiotic; inhibits DNA synthesis&lt;sup&gt;76-78&lt;/sup&gt;</td>
</tr>
<tr>
<td>Doxorubicin, epirubicin, valrubicin</td>
<td>• Intercalating agents; inhibits DNA synthesis&lt;sup&gt;75,96-98&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>• Deoxycytidine analog; inhibits DNA synthesis&lt;sup&gt;99-103&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
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<thead>
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</tr>
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<tbody>
<tr>
<td><strong>Bacillus Calmette-Guérin (BCG)</strong></td>
<td>Prevent recurrence &amp; progression</td>
</tr>
<tr>
<td>Interferon</td>
<td>• Lymphocyte activation; cytokine release; phagocyte stimulation</td>
</tr>
<tr>
<td></td>
<td>• Antiproliferative actions</td>
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<td></td>
<td>• Antiangiogenic [31,90]</td>
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<td>Chemotherapeutic Agents</td>
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<td>Mitomycin C</td>
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<tr>
<td>Doxorubicin, epirubicin, valubicin</td>
<td></td>
</tr>
<tr>
<td>Gemcitabine</td>
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</tr>
</tbody>
</table>

**AUA Guidelines 2007.**
Intravesical Therapy: Mitomycin C (MMC)

- Cross linking agent inhibits DNA synthesis and other mechanisms (alkylating agent)
- Non-cell cycle specific but sensitive in G1
- Large molecule (334 kd) – minimal systemic absorption and effects
- Average CR: 36%; less in recurrence: 19-42%
- Higher response in CIS (58%) than papillary lesions (43%)
- Role of maintenance therapy uncertain
Mitomycin C: Side Effects

- Chemical cystitis: up to 40% pts
- Decreased bladder capacity
- Skin rash/palmer desquamation (contact dermatitis)
- Leukopenia or bladder contraction is rare
Post-TURBT MMC

- Single post-TURBT instillation of MMC can decrease the time to recurrence but does not affect progression (Sylvester 2004) – 39% decrease in odds recurrence compared to TURBT alone
- Data is particularly strong for patients with a single tumor:
  - 35.8% recurrence rate compared to 65.2% recurrence for patients with multiple tumors
- EUA and AUA guidelines – give post-TURBT intravesical therapy in majority of patients who undergo solitary or multifocal papillary tumors unless contraindication
History of BCG

- BCG has anti-tumor effects
  - 1929 autopsy study – lower frequency of cancer in patients with active or healed tuberculosis (TB)
  - 1950s – Old - mice infected with BCG increased resistance to tumor transplantation
    - Close contact between BCG and tumor cells
    - Immunocompetent host capable of mounting immunological reaction to mycobacterial antigens
    - Limited tumor burden
    - Adequate numbers of viable BCG organisms

HERR ET AL. J UROL 2008
BCG and Bladder Cancer

- 1975 – deKernion – treated isolated melanoma in bladder with intravesical BCG

- 1976 – Morales – first successful use of intravesical BCG for superficial TCC
  - Devised original protocol for induction
    - 6 doses because Frappier strain packaged in 6 vials
    - 120 mg/dose because tolerated by intradermal
    - Weekly instillation because adverse effects <1 week

- 1978 – Morales treated 10 patients and BCG reduced/eradicated tumor recurrences in 7
- 2 randomized controlled trials – SWOG (Lamm) and MSKCC conducted and confirmed reduced tumor recurrences compared to TURBT alone
- 1990 – FDA approved intravesical BCG
Effectiveness of BCG

- CIS
  - 60-80% complete remission
- Residual papillary disease
  - Eradicates in 45-60% but NOT substitute for good TURBT!
- Decreases Recurrence in all 20-65% (~40%)
- Response durable in 30% at 10 years
BCG Induction Therapy

• No Established Optimal Course
• Most use 6 week course
• An additional 6 week course advantageous in:
  – CIS: 30% additional response
How to Make BCG More Tolerable

- Can decrease side effects 30-50% by one of following:
  - Decrease dose to 1/3 or less
  - Space intervals to 2 weeks instead of 1 week
  - Decrease dwell time for BCG to 30 min
  - Administer fluoroquinolone 6 and 12 h after each dose
  - Use NSAID or COX-2 Inhibitor to potentiate favorable BCG immune response

BCG Failures

- **CIS and BCG**
  - 7% progression rate for untreated CIS
  - 20% progression rate after CR to BCG
  - 30% recurrence rate after BCG
- **Failure after one induction course for CIS**
  - 30% additional response in CIS with second course
- **Failure after two induction courses in NMIBC**
  - 30% progression over 3-5 years
  - Only 46.7% disease-free at 3.6 years
  - 50% metastatic disease over 3-5 years
- **Definitely consider alternate therapies or cystectomy**
  - 81% of surveyed US urologists reluctant to recommend cystectomy even for high risk cases of BCG failure x 2
    - Any CIS, high-grade, or T1

JOU DI ET AL. UROL ONCOL 2006.
RADICAL CYSTECTOMY

- First performed in 1887, 230 patients reported by Whitmore and Marshall in 1962 with 5 year survival rates of 21-49%
- Now 50% (78% if confined to muscle, 25% if lymph nodes involved)

= Removal of bladder, peri-vesical fat, overlying peritoneum, pelvic lymph nodes and in:
  Men - Prostate and seminal vesicles
  Women - Uterus and portion of anterior vaginal wall

However, recent movement for genital organ sparing surgery
Bowel Mobilization and Lymphadenectomy

- Mobilize cecum and small bowel to retroperitoneal attachments (ligament of Treitz)
- Mobilize sigmoid along line of Toldt
- Pack small bowel and right colon
- Identify ureters in RP just cephalad to common iliac vessels and ligate close to bladder
- Perform meticulous lymph node dissection (either before or after cystectomy)

• Divide lateral pedicles
• Denonvillier’s fascia formed by convergence of anterior and posterior peritoneal reflections
• Divide in plane between rectum and posterior sheath of Denonvillier’s fascia – “Don’t go down to Brownsville!”

URINARY DIVERSION
Urinary Diversion

- Bowel segment required
  - Each segment with unique metabolic consequences

- Types of Diversion
  - Conduit – non-continent “tubeless”
    - Jejunal
    - Ileal
    - Colon
    - Ureterostomy
  - Continent – “dry”
    - Non-orthotopic (e.g. Indiana Pouch)
      - Also known as continent cutaneous catheterizable pouches
    - Orthotopic (e.g. Studer ileal neobladder) – “can void”
Conduits (small bowel or large bowel)

- **Advantages:**
  - Simple and quick procedure (less OR time)
  - Few inherent complications
  - Time tested – longest F/U data
  - Can compensate for short ureters

- **Disadvantages:**
  - Visible stoma
  - Negative body image
  - Need for lifelong stoma care (external appliance)
  - Anxiety of urinary leakage/odor
Ileal Conduit
Nipple Stoma:

• 4 - 6 cm of intestine is brought through the abdominal wall
• Fascial sutures are placed
• Each suture is placed in the seromuscular layer 3 cm proximal
• placed through the full thickness of the distal end of the intestine, then secured to the dermis before it is tied.
Continent Urinary Diversion

**Patient Selection:**

- Serum creatinine < 2
- Adequate Liver function
- Adequate bowel function
- Adequate intellectual capacity, dexterity, and mobility
  - Able and willing to perform self-catheterization
- Patient compliance (agrees to lifelong f/u)
- Absence of short gut syndrome/IBD
  - Colonoscopy prior to using any colon for diversion
- Motivated patient
Indiana Pouch
Studer Pouch

**Pros**
- High capacity (500cc), low pressure (<20cm H2O)
- 92% day continence, 80% nighttime (in Studer’s hands!)
- No ileocecal valve involved

**Cons**
- Long ileal segment used
- 6% metabolic disturbance, B12 and bile salt
- 2% ureteral and 2% urethral stenosis
Neobladder - Post-op Care

- Irrigation of the neobladder regularly
- Peritoneal drainage
- Ureteral stents
- S/P tubes
- Teach the patient to void with abdominal pressure
- CIC if can’t void by himself
A French comic drawing from 1914 showing how the artist envisioned the operating room of year 2000
Robot-Assisted Laparoscopic Partial Cystectomy (RAPC)

14 year old boy with history of VHL and multiple pheochromocytomas s/p bilateral adrenal surgery
Now with elevated serum catecholamines and headaches with urination
Robot-Assisted Laparoscopic Partial Cystectomy (RAPC)

- When performed for TCC, recommend only if no CIS, negative margins possible, good resulting bladder capacity, and concomitant LN dissection
Robot-Assisted Laparoscopic Radical Cystectomy (RARC)

- Lymph node yield, OS, CSS, positive margin rate, and complications all similar to open series
- In most series, EBL, LOS, and time to bowel recovery quicker with RARC

Haber GP. BJU Int 2007
Pruthi RS. Urology 2008
Complications and Morbidity Still a Problem

• However, surgery has a 3% 90-day perioperative mortality rate
• Surgery can result in complication rate of 29-69% - most are grade I, II
• 5-year survival still ~50% for all muscle-invasive tumors at 5 years
  – Improves if final pathology favorable
  – Improvement seen with neoadjuvant chemotherapy
No Therapeutic Advance in Last Two Decades and 5-Year Survival Rates Dismal in Regional/Distant Disease

We Need New Drugs!

Siegel et al.  CA Cancer J Clin 2014.
PANVAC PROTOCOL
Rationale and Background

• HG NMIBC (Ta, T1, and/or CIS) is managed by BCG but still with ~35% initial failure rate after induction course in terms of progression and/or recurrence. Although 20-35% of cases that fail an initial course can benefit from a second induction course, patients best served by radical cystectomy if continue to fail to respond.

• Radical cystectomy is potentially morbid and so unmet clinical need for patients that still have NMIBC that fails to respond to BCG.
• BCG works by unclear immunologic mechanism:
  – Athymic animals only respond to BCG when T cells administered
  – BCG-induced macrophage cytotoxicity importanted and promoted by Th1 immune system (TNF-a, IFN-y, IL-12, IL-18) and inhibited by Th2 immune system (IL-4, IL-10) and Tregs
  – T cell infiltration important as degree of infiltration (CD3, CD4, and CD8) with immune cells is greater in patients with a complete response to BCG
Rationale for Panvac

- Pox viral vector-based vaccine than can induce CD4 and CD8 antigen-specific immune response against MUC-1 and CEA
  - Also contains 3 co-stimulatory molecules
  - Excellent safety record in other tumors
  - Administered subcutaneously
- MUC-1 expression in up to 93% bladder tumors
- CEA expressed in 76% of HG tumors and 59% of T1 bladder tumors
- Postulate that this drug may enhance an immune response in HG tumors that have not responded to BCG
Hypotheses/Objectives

• Primary: PANVAC will augment BCG-induced cytotoxic T lymphocyte response against bladder cancer cells expressing MUC-1 and/or CEA when given with BCG and will result in greater **12 month RFS** than BCG alone in patients who failed to respond to at least 1 previous induction course of BCG.

• Secondary: PANVAC+BCG will have greater **PFS** and greater **immune response** than BCG alone.
Eligibility

• Adults with histologically confirmed high grade (Ta, T1, and/or CIS) UC of bladder who “failed” at least one induction course of BCG (either progressed and/orrecurred)
• Patients who fail >1 induction course of BCG have been offered radical cystectomy and either refuse or are not surgical candidates for cystectomy
• ECOG PS 0-2
Immune Correlates

- Biopsy (compared day 0 and week 17 tissue) IHC for:
  - CEA and MUC-1
  - CD4, CD8, and Tregs (by DS for Foxp3 and CD4)
  - Myeloid derived suppressor cells (MDSC)
- PBMCs and sera at 4 time points (week 0 (prior to vaccination), week 3 (prior to BCG), week 8 (prior to last BCG), and week 17 (end of treatment)):
  - Flow cytometry for 23 markers (e.g. CD4, CD8, Tregs, MDSCs, and NK)
  - In HLA-A2 allele patients, ELISPOT for CD8 T-cell responses for CEA and MUC-1 and cascade antigen Brachyury
  - If sufficient sample available, CD4 specific responses to CEA will be measured
  - Study sera for Ab to CEA
- Urine
  - Check levels of urinary cytokines at week 3 and week 5 to assess cytokine production in response to BCG and PANVAC therapy
- PPD
  - See if any correlation with immunologic response
Benefits of Immunotherapy

• Ability to work in a variety of different cancers
• No cross-resistance to chemotherapy or XRT
• Multiple killing mechanisms
• Durable responses if patient responds
  – Potential for memory and single lifelong administration

Schlom et al. JNCI 2012.
MOLECULAR TARGETED PHOTOIMMUNOTHERAPY (PIT)
**Precision Targeted Therapy**

**PROS**
- Durable remission metastatic bladder noted after treatment with everolimus based on fs mutation in TSC1
  - [Pre-treatment](#)  [3-mo. interval](#)
- NY Times: young hematologist (Dr. Wartman) had ALL with FLT3 on whole-genome sequencing now in remission on sunitinib
- Certain lung cancers have an EGFR mutation making them susceptible to respond to monoclonal antibodies

**CONS**
- Not every patient can currently undergo whole genome sequencing
- Weak single-agent activity
- Heterogeneity in response to targeted therapy regardless of target expression
- Multiple downstream pathways

Photodynamic Therapy (PDT) in Bladder Cancer

- PDT utilizes a photosensitizer dye which targets the tumor. It absorbs light from an external source and delivers that energy to produce cytotoxic reactive oxygen species which results in necrosis and apoptosis.

- In standard photodynamic therapy, the sensitizer is instilled or injected which can lead to diffuse penetration of bladder tissue or nonspecific binding of dye.
  - **SIDE EFFECTS** (e.g. severe bladder contractures, cutaneous photosensitization)


### Table 5. Previous clinical studies of PDT for bladder cancer

<table>
<thead>
<tr>
<th>References</th>
<th>No. Pts</th>
<th>Photosensitizer</th>
<th>Light Dose (J/cm²)</th>
<th>Early (%)</th>
<th>Late (%)</th>
<th>AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neevoy et al.¹⁰</td>
<td>22</td>
<td>Photofrin II</td>
<td>15-20</td>
<td>83.30</td>
<td>30</td>
<td>Irritating LUTS, bladder shrinkage</td>
</tr>
<tr>
<td>D’Hallewin and Baert²⁵</td>
<td>18</td>
<td>Photofrin II</td>
<td>75, 100</td>
<td>Not applicable</td>
<td>60</td>
<td>Bladder capacity loss</td>
</tr>
<tr>
<td>Uchitayashi et al.⁵⁶</td>
<td>23</td>
<td>Hamatoporphyrin derivative</td>
<td></td>
<td>73.50</td>
<td>22</td>
<td>Skin photosensitivity, transient bladder capacity decrease</td>
</tr>
<tr>
<td>Walther et al.²⁷</td>
<td>20</td>
<td>Photofrin II</td>
<td>5.1-25.6</td>
<td>45</td>
<td>20</td>
<td>Asymptomatic reflux, bladder contraction, fibrosis</td>
</tr>
<tr>
<td>Neevoy et al.¹⁷</td>
<td>58</td>
<td>Photofrin</td>
<td>10-60</td>
<td>75-84</td>
<td>53</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Mavvek and Oganò²⁸</td>
<td>34</td>
<td>Porphyrin sodium</td>
<td>5-10</td>
<td>56</td>
<td>44</td>
<td>Bladder contracture</td>
</tr>
<tr>
<td>Berger et al.²⁹</td>
<td>31</td>
<td>5-ALA</td>
<td>30-50</td>
<td>Not applicable</td>
<td>52</td>
<td>Dysuria due to urinary tract infection, hematuria</td>
</tr>
<tr>
<td>Waidelich et al.³⁰</td>
<td>11</td>
<td>5-ALA</td>
<td>100</td>
<td>Not applicable</td>
<td>46</td>
<td>Transient frequency, urgency</td>
</tr>
<tr>
<td>Lee et al.¹¹</td>
<td>5</td>
<td>Fotolon (intravenous)</td>
<td>10 (intravenous), 24 (intravesical)</td>
<td>80 (6 mos)</td>
<td>60</td>
<td>Vesicoenteric fistula</td>
</tr>
<tr>
<td>Badar et al.³⁰</td>
<td>17</td>
<td>HAL</td>
<td>25 (PDT 1), 50 (PDT 2), 100 (PDT 3)</td>
<td>52.9 (6 mos)</td>
<td>11.8 (21 mos)</td>
<td>Irritative bladder symptoms, infection, gross hematuria</td>
</tr>
<tr>
<td>Present series</td>
<td>34</td>
<td>Radachlorin</td>
<td>15</td>
<td>90.9 (1 yr)</td>
<td>64.4 (2 yrs)</td>
<td>Irritative bladder symptoms, infection, hematuria</td>
</tr>
</tbody>
</table>
Molecular Targeted Photoimmunotherapy

- Photosensitizer: phthalocyanine dye, IR700, that uses near infrared light (NIR) conjugated to monoclonal antibody (mAb)

- Induces cell death after irradiating mAb-IR700-bound target cells with exposure to NIR

- Non-toxic except at thermal doses

- Hydrophilic dye will not associate with CM

Our Target: EGFR (epidermal growth factor receptor)

- EGFR amplified in UC
- Overexpression of EGFR is an independent predictor of decreased survival and stage progression in bladder cancer

Chaux et al. Hum Pathol. 2012 Oct;43:1590
**Method:** Expression in various Bladder Cancer cell lines analyzed using flow cytometry. Anti hEGFR – PE (Abcam) was used for these experiments. Rat IgG2a, kappa Mab-PE (Abcam) was used as a Isotype control.
• Two cell lines UMUC-5 (high expression of EGFR) and TCCSUP (low-moderate expression of EGFR) are used for further analysis. Breast cancer cell line MDA-MB-453 or Balb-3T3 (no expression of EGFR) are used as a negative control in certain assays.
Gel Electrophoresis and Infrared Imaging of Panitumumab and Conjugated Panitumumab

148 KDa

Marker  IRDye700  Panitumumab  Pan-IRDye700  IRDye700  Panitumumab  Pan-IRDye700

SDS-PAGE  Infrared
“Home-grown” Apparatus
Balb 3T3 – EGFR negative control

No light

Light (4J)
UMUC5 – EGFR ++ bladder cancer cell line

Untreated

Pan

Pan-IR700

Blocking

No light

Light (4J)
Trypan Blue Exclusion Assay

Photoimmunotherapy of UMUC5 bladder cancer cells

Percentage of viable cells by trypan blue exclusion

- Control
- Panitumumab
- Pan+IR700
- Blocking condition

No Light  Light (4J)
Necrosis is Potential Mechanism of Death: Annexin-V/PI Staining 60 min After PIT
Necrosis is Potential Mechanism of Death: Annexin-V/PI Staining 15 min After PIT

Untreated

4 J/cm²

Pan 10µg

4 J/cm²

Pan IR700 10µg
Caspase Assay: 15 min after NIR Exposure
In vivo PIT effects

**Graphs and Images:**
- **IR700 vs. IR700/White**
  - Pre, Day0, Day2
  - NIR light

**Graphs Details:**
- **Survival**
  - Time after Ab-IR700 injection (days)
- **Tumor volume (mm³)**
  - Time after Ab-IR700 injection (days)

**Legend:**
- No treatment
- Pan 300 μg iv, no PIT
- Pan-IR700 300 μg iv, no PIT
- No Mab, PIT 30 J/cm²
- Pan-IR700 300 μg iv, PIT 30 J/cm²

**References:**
Mitsunaga, Kobayashi, Nature Med 2011/12
Summary of PIT and Future Directions

- PIT platform works with EGFR based conjugate in EGFR expressing cell line
- In lines with less EGFR expression, increased energy can increase efficacy
- Mechanism is likely necrosis
- Current: Orthotopic bladder cancer model with UMUC-5
- Future: Conjugate other monoclonal antibodies targeting other receptors present in bladder cancer (FGFR3, MET, HER2, AXL) and Clinical Trial

→ Characterize Tumor Surface Receptor Expression and Conjugate Target-specific mAB-IR-700 and Instill in Bladder After Resection of Tumor
MET and AXL Expression in Cell Lines

**Met Expression in Bladder Cancer Cell Lines**

**AXL Expression in Bladder Cancer Cell Lines**
Other Projects

- High throughput screening of bladder cancer cell lines against 1900+ compounds

- Y-specific gene, SMCY, may be associated with male tumors and is associated with histone de-methylation

- IL-12/chitosan intravesical therapy
Conclusions

- Bladder cancer is common and has poor survival rates for non-localized disease
- Therapy requires surveillance, intravesical therapy, TURBT, surgery, radiation, chemotherapy
- Even though localized disease has good prognosis, recurrence is a problem making bladder cancer most expensive cancer
- Surgery evolving but still high rate of complications
- No new FDA-approved drugs in >20 years!
Conclusions

• PANVAC trial is currently open
  – 4 patients enrolled
  – Waiting for BCG to enroll more patients!
  – Greatly indebted to Day Hospital RNs for getting this trial off the ground!

• Molecular-targeted PIT has potential for effective treatment for non-localized disease and is translatable! (VPL better?)

• Other new potential intravesical agents may be identified from our screening project
Evolving Bladder Cancer Program

• Establishing a multi-disciplinary team that will see complex patients together:
  – Deborah Citrin, MD – Radiation Oncology
  – Andrea Apolo, MD – Medical Oncology

• Building a dream team:
  – Patient care coordinator
  – Nurse practitioner
  – Research nurse
  – Urologic oncology fellow
  – Data manager
  – Tissue procurement personnel
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