Bladder Cancer

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Objectives

- Bladder Cancer
- Epidemiology
- Pathology
- Risk factors
- Presentation and clinical findings
- Staging
- Natural history

2012 Estimated New Cancer Cases*

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>848,170</td>
<td>790,740</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary bladder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Other Sites</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2012 Estimated Cancer Deaths

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>301,820</td>
<td>275,370</td>
</tr>
<tr>
<td>Prostate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophagus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary bladder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney &amp; Renal Pelvis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All other sites</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.
Source: American Cancer Society, 2012
**Epidemiology**

- Bladder cancer in the United States:
  - Estimated 73,510 new cases and 14,880 cancer related deaths in 2012
  - Whites > Blacks (2:1)
  - M>F (3-4:1)
  - A disease of the elderly (6th-7th decades)
  - Rising incidence (20% over the last 20-yr)

- In U.S., the second most prevalent cancer in men≥60
- Bladder cancer has significant financial impact on healthcare
  - Requires intensive, life-long cystoscopic, radiologic, and cytologic surveillance
  - Most expensive malignancy in the U.S.*


**Bladder Cancer Pathology: Histologic Subtypes in the U.S.**

- 90-95% Transitional Cell Carcinoma
- 3% Squamous Cell Carcinoma
- 2% Adenocarcinoma
- 1% Small Cell Carcinoma
- 1% Others

**Risk Factors**

- Gene abnormalities
- Chemical exposure
- Chronic irritation
Risk Factors

- Gene abnormalities
  - Proto-oncogenes: Ras
  - Tumor suppressor genes: p53, pRB, p16, p21, p27
  - Cell cycle regulatory proteins: cyclin D1
  - Tumor-specific growth factor pathways, angiogenesis and COX-2

Risk Factors

- Chemical exposure
  - Tobacco (rich in aromatic amines and acrolein)
  - Industrial contact to chemicals, plastics, coal, tar, asphalt, aromatic amines, aniline dyes, nitrites, and nitrates
  - Ifosfamide and Cyclophosphamide (long-term use)
  - Analgesic abuse, particularly phenacetin

Risk Factors

- Chronic irritation
  - Indwelling catheters, calculi (SCC)
  - Schistosoma haematobium (SCC, TCC)
  - Irradiation (SCC)

Signs and Symptoms

- Hematuria
  - Gross or microscopic
- Irritative symptoms
  - Frequency
  - Dysuria
  - Urgency
- Bladder outlet obstruction
- Ureteral colic
Physical Findings

- Palpable mass
- Bladder fixation to the pelvic wall
- Prostate induration
- Related to metastatic disease

Diagnostic Testing

- Urine Cytology (Sensitivity 67%, specificity 96%)
- Cystoscopy
  - Transurethral resection of bladder tumor (TURBT)
  - Ureteroscopy
  - Retrograde pyelography
- Radiographic Imaging (CT, MRI, IVP)
- Bone Scan (if elevated Alk Phos or bone pain)

TNM Staging of Bladder Cancer

TNM Staging, cont.

- Nodal disease
  - N1 Single regional LN mets in the true pelvis (hypogastric, obturator, external iliac, or presacral LN)
  - N2 Multiple regional LN mets in the true pelvis
  - N3 LN metastasis to the common iliac LNs
- Metastatic disease
  - M0 no distant mets
  - M1 distant mets

Colquhoun AJ, et al.
Postgrad Med J. 2002

American Joint Committee on Cancer (AJCC); 7th ed., 2010
TNM Staging, cont.

- **0** Ta, Tis
- **I** T1 only
- **II** T2a, T2b
- **III** T3a, T3b (perivesical tumor), T4a (prostate, uterus or vagina)
- **IV** T4b (pelvic or abdominal wall)
  Any N or M

Stages at Presentation

- 75% Superficial cancer
- 20% Muscle-invasive cancer
- 5% Metastatic disease

Bladder Cancer Stage: Prognosis

<table>
<thead>
<tr>
<th>Location</th>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>Survival (5 yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial</td>
<td>0a</td>
<td>Ta</td>
<td>0</td>
<td>0</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>Lamina</td>
<td>1</td>
<td>T1</td>
<td>0</td>
<td>0</td>
<td>65-90%</td>
</tr>
<tr>
<td>Early Disease</td>
<td>1</td>
<td>T1a</td>
<td>0</td>
<td>0</td>
<td>20-40%</td>
</tr>
<tr>
<td>Deep Muscle</td>
<td>1</td>
<td>T2b</td>
<td>0</td>
<td>0</td>
<td>20-40%</td>
</tr>
<tr>
<td>Perivesical Fat</td>
<td>1</td>
<td>T2b</td>
<td>0</td>
<td>0</td>
<td>15-25%</td>
</tr>
<tr>
<td>Lymph Nodes</td>
<td>IV</td>
<td>Any</td>
<td>0-3</td>
<td>0</td>
<td>5-28%</td>
</tr>
<tr>
<td>Metastatic</td>
<td>IV</td>
<td>Any</td>
<td>0-3</td>
<td>Any</td>
<td>&lt;2%</td>
</tr>
</tbody>
</table>

AJCC Cancer Staging, 1998

Natural History of Bladder Cancer

Superficial Bladder Cancer

Kamal Pohar, MD, FRCSC
Assistant Professor
Department of Urology
The James Cancer Hospital and
The Ohio State University Wexner Medical Center

Objectives

- Superficial Bladder Cancer
  - Surgical management
  - Prevention of recurrence and progression
    - Intravesical chemotherapy
    - Intravesical immunotherapy
  - Surveillance: Follow-up and early detection of recurrence

Bladder Cancer Staging Superficial Cancer

<table>
<thead>
<tr>
<th>AJCC Cancer Staging Manual 7th Edition</th>
</tr>
</thead>
</table>

American Joint Committee on Cancer (AJCC)
TNM Staging System For Bladder Cancer

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0 No evidence of primary tumor</td>
</tr>
<tr>
<td>Ta Noninvasive papillary carcinoma</td>
</tr>
<tr>
<td>Tis Carcinoma in situ “flat tumor”</td>
</tr>
<tr>
<td>T1 Tumor invades subepithelial connective tissue</td>
</tr>
<tr>
<td>T2a Tumor invades superficial muscle (inner half)</td>
</tr>
<tr>
<td>T2b Tumor invades deep muscle (outer half)</td>
</tr>
<tr>
<td>T3 Tumor invades perivesical tissue</td>
</tr>
<tr>
<td>T3a Microscopically</td>
</tr>
<tr>
<td>T3b Macroscopically (extravesical mass)</td>
</tr>
<tr>
<td>T4 Tumor invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall</td>
</tr>
<tr>
<td>T4a Tumor invades prostate, uterus, vagina</td>
</tr>
<tr>
<td>T4b Tumor invades pelvic wall, abdominal wall</td>
</tr>
</tbody>
</table>

Papillary Bladder Tumors
Flat Bladder Tumors (Carcinoma in situ (CIS))

Most often is a flat red spot(s) in the bladder

Superficial Bladder Tumors
Most Are Cured Endoscopically

- Transurethral resection (TUR) based on thermal energy
- May require more than one procedure for larger tumors

Cancer recurrence in the bladder
This is the real problem

<table>
<thead>
<tr>
<th>Author</th>
<th>Tumor No.</th>
<th>Patients</th>
<th>% Recurrence</th>
<th>% Progression</th>
<th>F/U (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herr Ta</td>
<td>Low Grade</td>
<td>23</td>
<td>90</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>Holmang et al</td>
<td>22</td>
<td>59</td>
<td>59</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>Holmang et al</td>
<td>255</td>
<td>71</td>
<td>71</td>
<td>2.4</td>
<td>10</td>
</tr>
<tr>
<td>Leblanc et al</td>
<td>152</td>
<td>55</td>
<td>55</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Haukass et al</td>
<td>59</td>
<td>40</td>
<td>40</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Herr Ta</td>
<td>High Grade</td>
<td>125</td>
<td>95</td>
<td>39</td>
<td>15</td>
</tr>
<tr>
<td>Holmang et al</td>
<td>55</td>
<td>73</td>
<td>73</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>Haukass et al</td>
<td>81</td>
<td>60</td>
<td>60</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Lebret et al</td>
<td>32</td>
<td>72</td>
<td>72</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>Herr T1</td>
<td>High Grade</td>
<td>121</td>
<td>90</td>
<td>52</td>
<td>15</td>
</tr>
<tr>
<td>Holmang et al</td>
<td>99</td>
<td>88</td>
<td>88</td>
<td>39</td>
<td>20</td>
</tr>
<tr>
<td>Haukass et al</td>
<td>80</td>
<td>74</td>
<td>74</td>
<td>30</td>
<td>10</td>
</tr>
</tbody>
</table>

When the cancer comes back it may be worse
This is not as common but worsens prognosis

<table>
<thead>
<tr>
<th>% Recurrence</th>
<th>90</th>
<th>59</th>
<th>71</th>
<th>55</th>
<th>40</th>
<th>95</th>
<th>73</th>
<th>60</th>
<th>72</th>
<th>90</th>
<th>88</th>
<th>74</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Progression</td>
<td>4</td>
<td>18</td>
<td>2.4</td>
<td>3</td>
<td>7</td>
<td>39</td>
<td>16</td>
<td>10</td>
<td>25</td>
<td>52</td>
<td>39</td>
<td>30</td>
</tr>
</tbody>
</table>
Europe and Organization for Research and Treatment of Cancer
Tables to Predict Bladder Cancer Recurrence and Progression

European Urology 49:466, 2006

European Organization for Research and Treatment of Cancer
Tables to Predict Bladder Cancer Recurrence and Progression

European Urology 49:466, 2006

Recurrence and Progression
Superficial Bladder Cancer

<table>
<thead>
<tr>
<th>Factor</th>
<th>Recurrence</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of tumors</td>
<td>Single</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>&gt; 5</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Tumor size</td>
<td>&lt; 5 cm</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 5 cm</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Prior recurrence rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 yr</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&gt;1 yr</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>T category</td>
<td>T3</td>
<td>0</td>
</tr>
<tr>
<td>T1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>GS</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Grade</td>
<td>G1</td>
<td>0</td>
</tr>
<tr>
<td>G2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>G3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Total score</td>
<td>0-3*</td>
<td>0-23</td>
</tr>
</tbody>
</table>

European Urology 49:466, 2006

FOCUS

- Review of medical evidence on therapeutic opportunities to reduce tumor recurrence in superficial bladder cancer patients
Therapeutic Opportunities
Reducing Bladder Cancer Recurrence

- Persistent/unrecognized tumor at the time of endoscopic resection of grossly visible tumors (residual cancer)
- Tumor implantation
- Urothelial Field Change

Residual Cancer After Endoscopic Resection

Variability in the Recurrence Rate at First Follow-up Cystoscopy after TUR in Stage Ta T1 Transitional Cell Carcinoma of the Bladder: A Combined Analysis of Seven EORTC Studies

Brausi, Maurizio; Collette, Laurence; Kurth, Karlheinz; van der Meijden, Adrian P.; Oosterlinck, Wm; Witjes, J.A.; Newling, Donald; Bouffioux, Christian; Sylvester, Richard J.

European Urology 41: 523 - 531, 2002

Promise of Improved Diagnostics

A New Generation of Optical Diagnostics for Bladder Cancer: Technology, Diagnostic Accuracy, and Future Applications

Evelynne C.C. Courtois*, Donald M. de Bree*, Dirk J. Füller*, Ton G. van Leeuwen*, Jean J.M.C.H. de la Roche+, Thijs M. de Ruijter*

*Department of Urology, Academic Medical Center Amsterdam, Amsterdam, The Netherlands
+Department of Benign Expanding and Peritoneal, Academic Medical Center Amsterdam, Amsterdam, The Netherlands

- Photodynamic Diagnosis (PDD) – Fluorescence (ALA or HAL)
- Narrow-band Imaging (NBI)
- Optical Coherence Tomography (OCT)

## Improvements in Technology Lead to Better Outcomes

### Repeat Endoscopic Resection Within 6 Weeks Reduces Tumor Recurrence

- Many studies confirm for high grade tumors a repeat endoscopic resection of the area where the original tumor was removed often removes residual microscopic cancer and leads to better clinical outcomes

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## Tumor Implantation

### Theories of Why Bladder Cancers Recur

- Hoglund M, Seminars in Cancer Biology 17:225,2007

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<table>
<thead>
<tr>
<th>Tumor Implantation</th>
<th>Theories of Why Bladder Cancers Recur</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hoglund M, Seminars in Cancer Biology 17:225,2007</td>
</tr>
</tbody>
</table>
Single Dose Instillation of Chemotherapy After Surgery In The Bladder

- Patients with a single tumor in the bladder reduced their risk of recurring from 47.1% to 35.8%
- Patients with more than one tumor in the bladder reduced their risk of recurring from 81.5% to 65.2%

Journal of Urology 171:2186–2190, 2004

Urothelial Field Change

Field Defect – Slaughter’s Concept of Field Cancerization

Hoglund M, Seminars in Cancer Biology 17:225, 2007
Urothelial Field Change

- Rationale for the use of intravesical chemotherapy and immunotherapy
- Drugs administered in liquid form via a urethral catheter allowing direct instillation into the bladder
- Drugs have a direct effect on the bladder epithelium (urothelium)

Reducing Risk of Recurrence
Intravesical Chemotherapy
Prophylaxis

<table>
<thead>
<tr>
<th>Intravesical Chemotherapeutic Agents*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiotepa</td>
</tr>
<tr>
<td>Doxorubicin</td>
</tr>
<tr>
<td>Ethoglucid</td>
</tr>
<tr>
<td>Mitomycin C</td>
</tr>
<tr>
<td>Epirubicin</td>
</tr>
<tr>
<td>Valrubicin</td>
</tr>
<tr>
<td>Gemcitabine</td>
</tr>
</tbody>
</table>

*Wide range of doses and schedules – most common weekly for 6-8 weeks

Reducing Risk of Recurrence
Intravesical Immunotherapy
Prophylaxis

History of BCG Vaccine

- BCG initially isolated by Calmette and Guerin (Pasteur Institute)
- Complete attenuation achieved through 231 sequential passages over 13 years (Mycobacterium bovis)
- Immunologists discovered the stimulatory effect of mycobacteria on the immune response to heterologous antigens (tumor cells)
- First tested in bladder cancer in the early 1980's

### Bladder Cancer Recurrence Risk Adapted Groups To Determine What Drug Is Best

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
</tr>
</thead>
</table>

### Maintenance Intravesical Therapy Reduces Cancer Recurrence

- Some studies support periodically giving additional intravesical chemotherapy or BCG when the patient is tumor free for an extended period of time (1-3 years)
- As an example, maintenance included 3 successive weekly intravesical instillations of BCG at 3, 6, 12, 18, 24, 30, and 36 months (SWOG 8507)

### Bladder Cancer Follow-up Detecting Recurrences

- **Office Cystoscopy**
  - Normal

### Bladder Cancer Follow-up Detecting Recurrences

- **Urinary Tumor Markers**
  - Urine cytology
  - UroVysion FISH
  - NMP-22
  - BTA
**Summary of Typical Timeline of Management**

**Superficial Bladder Cancer Patient**

- Tumors removed by endoscopic resection in OR leading to cure
- One dose of intravesical chemotherapy given in the recovery room after surgery
- High probability of bladder cancer recurrence can be reduced by administering weekly intravesical chemotherapy or immunotherapy for a few weeks
- Maintenance intravesical therapy can further reduce the probability of cancer recurrence when the patient is tumor free

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**Muscle-Invasive and Advanced Bladder Cancer**

Amir Mortazavi, MD
Assistant Professor
Department of Internal Medicine
Division of Medical Oncology
The Ohio State University Wexner Medical Center

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**Objectives**

- Muscle-invasive and Advanced Bladder Cancer
  - Management of metastatic disease
  - Management of muscle-invasive disease

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**Metastatic Disease**
Introduction

- Metastatic sites: regional and distant lymph nodes, lungs, bones, liver, brain, skin and elsewhere.
- Median survival with Best Supportive Care: 4-6 months
- Median survival with cisplatin-based combination chemotherapy: 12-14 months, 20% 3-yr survival

Introduction

- Many chemotherapy drugs have shown activity in bladder cancer, such as cisplatin, carboplatin, gemcitabine, methotrexate, vinblastine, doxorubicin, paclitaxel, docetaxel, ifosfamide, etc.
- TCC is a chemosensitive solid tumor
  - Phase II clinical trials: RR 70-80%
  - Phase III clinical trials: RR 50%
- Short duration of response: 4-6 mo

Prognostic Factors & Survival
Univariate and Multivariate Analysis (n=203) Bajorin, JCO 1999

<table>
<thead>
<tr>
<th># of PF</th>
<th>MS (mo)</th>
<th>CR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>33</td>
<td>35</td>
</tr>
<tr>
<td>1</td>
<td>13.4</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>9.3</td>
<td>0</td>
</tr>
</tbody>
</table>

# of PF
MS (mo)
CR (%)

p = 0.0001

Systemic Chemotherapy

- Till 2000, MVAC, the combination chemotherapy of methotrexate, vinblastine, doxorubicin, and cisplatin, was the standard of care for metastatic bladder cancer, based on phase II(1) and randomized phase III(2, 3) studies.

(2) Loehrer et al. JCO 10:1066, 1992
(3) Logothetis et al. JCO 8:1050, 1990
Advanced Bladder Cancer:
Gemcitabine Plus Cisplatin vs. MVAC

Stratification
- Stage
- Visceral mets
- PS
- Prior radiotherapy
- Investigator site
- Disease measurability
- Alkaline Phosphatase

MVAC: Methotrexate, Vinblastine, Doxorubicin, Cisplatin

Von der Maase, JCO 2000

GC vs. MVAC
G3/4 Toxicities

<table>
<thead>
<tr>
<th></th>
<th>GC</th>
<th>MVAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia (Grade 3/4)</td>
<td>71%</td>
<td>82%</td>
</tr>
<tr>
<td>Neutropenic sepsis</td>
<td>1%</td>
<td>12%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>1.5%</td>
<td>13.4%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>57%</td>
<td>21%</td>
</tr>
<tr>
<td>Mucositis</td>
<td>1%</td>
<td>22%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>11%</td>
<td>55%</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>22%</td>
<td>21%</td>
</tr>
<tr>
<td>Drug-toxicity death rate</td>
<td>1%</td>
<td>3%</td>
</tr>
</tbody>
</table>

GC vs. MVAC
Response and Survival

<table>
<thead>
<tr>
<th></th>
<th>GC (203)</th>
<th>MVAC (202)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>49.4%</td>
<td>45.7%</td>
</tr>
<tr>
<td>CR</td>
<td>12.2%</td>
<td>11.9%</td>
</tr>
<tr>
<td>PR</td>
<td>37.2%</td>
<td>33.8%</td>
</tr>
<tr>
<td>MS</td>
<td>13.8</td>
<td>14.8</td>
</tr>
<tr>
<td>(12.3-15.8)</td>
<td>(13.2-16.8)</td>
<td></td>
</tr>
</tbody>
</table>

Von der Maase, JCO 2000

Summary

- Cisplatin-based combination chemotherapy improves survival for patients with advanced bladder cancer.
- First-line treatment
  - Good PS, adequate GFR: Cisplatin-based
  - Poor PS, declined GFR, elderly: Carboplatin-doublets, or single agent
- Second-line treatment (Cisplatin-resistant)
  - Gemcitabine, paclitaxel, docetaxel, ifosfamide, nab-paclitaxel, vinflunine, and pemetrexed.
New agents

- Immune Modulation (Tumor Vaccines)
- Pemetrexed (Sweeney, 2006 JCO)
- Trastuzumab (Hussain, 2007 JCO; Single-agent CALGB study)
- Gefitinib (Galsky, 2007 Invest New Drugs; Philips, 2009 Ann Oncol)
- Erlotinib (Ongoing studies)
- Sorafenib (Sridhar, 2008 ASCO GU, #340)
- Sunitinib (Gallagher, 2007 ASCO, #5080; Bellmunt, 2008 ASCO GU, #291)
- Bevacizumab (With GC: Ongoing CALGB study; Hahn, 2009 ASCO, #5018)
- Vinflunine (Vaughn, 2008 ASCO GU, #316)
- FGFR3 Inhibitors (Ongoing studies)
- Histone Deacetylase Inhibitors (Vorinostat, AR42)

Muscle-Invasive Disease

- Who needs cystectomy?
- Who can be cured with bladder preservation?
- Who needs multimodality treatment (neoadjuvant/adjuvant treatments)?

Surgical treatment outcome

- In the U.S., the Gold Standard Treatment of muscle-invasive disease is radical cystectomy with bilateral pelvic lymph node dissection.
- After surgery, 40-50% of these patients develop metastases within 2-5 years and most die of their disease.
How to improve outcome?

- Bladder cancer is a radio- and chemo-sensitive disease.
- Cisplatin-based chemotherapies have 40-75% RR with 12-20% CRs.
- Multimodality treatment with neoadjuvant/adjuvant chemotherapy and/or radiation therapy can potentially improve outcome.

Randomized Neoadjuvant Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Neoadjuvant</th>
<th>Standard</th>
<th>Patients</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC/MRC</td>
<td>MVAC</td>
<td>Surgery</td>
<td>307 pts, 1987-1998; 126 centers in the U.S., f/u 8.7 yrs</td>
<td>Median Survival 77 mos, 46 mos, 0.05</td>
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<tr>
<td>SWOG Intergroup</td>
<td>MVAC</td>
<td>Surgery</td>
<td>307 pts, 1987-1998; 126 centers in the U.S., f/u 8.7 yrs</td>
<td>Median Survival 77 mos, 46 mos, 0.05</td>
</tr>
</tbody>
</table>

CR (pT0) 33% for CMV vs. 12% in surgery
HR=0.85 (95% CI 0.72-1.00)
5.5% improvement in survival p=0.048

Grossman NEJM 2003
Meta-analysis Studies

**Neoadjuvant Chemotherapy in Invasive Bladder Cancer: Update of a Systematic Review and Meta-Analysis of Individual Patient Data**

Eur Urol 48:202, 2005

- 11 randomized trials, 3005 pts

- **Overall survival benefit:**
  - 14% reduction in the risk of death (HR=0.86, p=0.003)
  - 5% (45% to 50%) at 5 years

- **Disease-free survival benefit:**
  - 22% reduction in the risk of recurrence (HR=0.78, p=0.0001)
  - 9% absolute improvement at 5 years

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**The impact of surgical factors**

Herr, et al. JCO 22:2781, 2004

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**Meta-analysis Studies**


- 8 randomized trials with cisplatin-based combination chemotherapy
  - HR for death 0.87 (p=0.006) and 6.5% absolute improvement in five-year OS (50% to 56.5%).

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**Meta-analysis Studies**

Eur Urol 48:202, 2005

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- Overall survival benefit: Overall survival benefit:
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- Disease-free survival benefit:
  - 22% reduction in the risk of recurrence (HR=0.78, p=0.0001)
  - 9% absolute improvement at 5 years
The impact of optimal combined modality treatment: Analysis of INT-0080

Summary

• The quality of radical cystectomy and the extent of pelvic lymph node dissection have a major impact on invasive bladder cancer survival*

• Radical surgery alone does not provide long-term survival for about half of the patients with invasive bladder cancer


Summary

• Adjuvant cisplatin-based chemotherapy (~4 cycles) can be offered to high-risk patients (>T2) and it improves disease-free survival and prevent recurrence, but its benefit for overall survival, yet to be determined (level 2)

Summary

• Neoadjuvant cisplatin-based combination chemotherapy can be delivered safely, significantly improves P0 rate (no evidence of cancer at cystectomy), and disease-free and overall survivals (level 1 evidence)
In Conclusion

- Patients with muscle-invasive bladder cancer require multimodality care and the optimal curative strategy for most of them is neoadjuvant cisplatin-based combination chemotherapy followed by radical cystectomy and complete pelvic lymph node dissection.