Genito-Urinary (GU) Cancers Overview

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Delaware Christiana Care CCOP

CALGB CRA Orientation, April 2008

CALGB GU CANCER PROTOCOLS

Topics

- **Prostate cancer (early)** - adjuvant and neoadjuvant protocols (prevent relapse)
- **Prostate cancer (intermediate)** - hormone-sensitive adjuvant trials (prevent symptoms/↑ survival in patients with early relapse)
- **Advanced GU cancer** - metastatic studies (control symptoms/↑ survival with the best QOL among patients with advanced prostate, kidney, testis, and bladder cancer)
- **Special populations** - pharmaco-kinetic, molecular genomics, psychosocial questions
2008 Estimated US Cancer Cases*

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Men</th>
<th>Women</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>745,180</td>
<td>692,000</td>
<td>25%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>14%</td>
<td></td>
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<tr>
<td>Colon &amp; rectum</td>
<td>10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td>5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis 4%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral cavity</td>
<td>3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Other Sites 20%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>26%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>14%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td>4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td>4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovary</td>
<td>3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Other Sites 23%</td>
<td></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, 2008.

Cancer Incidence Rates* for Men 1975-2004

*Age-adjusted to the 2000 US standard population and adjusted for delays in reporting.
Source: Surveillance, Epidemiology, and End Results Program, Delay-adjusted Incidence database:
2008 Estimated US Cancer Deaths*

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Percentage</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>31%</td>
<td>294,120</td>
<td>271,530</td>
</tr>
<tr>
<td>Prostate</td>
<td>10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophagus</td>
<td>4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All other sites</td>
<td>24%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ONS=Other nervous system.
Source: American Cancer Society, 2008.

Cancer Death Rates* Among Men, US, 1930-2004

*Age-adjusted to the 2000 US standard population.
National Center for Health Statistics, Centers for Disease Control and Prevention, 2006.
What is the Prostate?

- A male sex gland
- The size of a walnut below the bladder and in front of the rectum
- Produces the fluid that is part of semen
One out of seven American men age 55 and older will be diagnosed with prostate cancer in his lifetime.

Prostate Cancer Facts

• 1 in 6 to 7 American men will develop prostate cancer

• This year, more than 186,000 men will be diagnosed with prostate cancer

• Every 19 minutes, a man dies from prostate cancer
Risk Factors

- **Family History:** Men with a single first-degree relative – *father, brother, or even son* – with prostate cancer are more than twice as likely to develop the disease.

- **Age:** More than 65% of all prostate cancer cases are diagnosed in men older than 65.

- **Race:** African-Americans have the highest prostate cancer incidence of any race and are nearly 2.5 times as likely to die from the disease than Caucasian men.

Screening for Prostate Cancer

- **Prostate-Specific Antigen Blood Test (PSA)** – Measures substance made by the prostate gland.

- **Digital Rectal Exam (DRE)** – Physical exam of the Prostate Gland.
American Cancer Society Recommendations

- At age 50 and after, annual exam with DRE and Prostate Specific Antigen (PSA) blood test
- African American men and men who have first degree relatives diagnosed before age of 65 should start DRE and PSA at age 45
- Multiple first degree relatives effected at an early age should begin at age 40

CALGB GU Cancer Protocols

Diagnostic Studies

- **Physical examination** - measure nodules, assess tenderness, weight ↓, PS
- **Ultrasound** - measure nodules, solid v. fluid-filled, assess extent/depth
- **Scans/Xrays** - bone scan, CXR, CT scan, MRI
- **Laboratory studies** - tumor markers (PSA, AFP, BHCG, LDH)
- **Biopsy/definitive surgery** - histology, Gleason score, staging, margins
- **Others** - PET scan, IVP, cytology, etc.
**Gleason score by final pathological stage in 703 men with clinically localized prostate cancer**

<table>
<thead>
<tr>
<th>Gleason Score</th>
<th>No. Pts. (%)</th>
<th>Organ Confined Disease</th>
<th>Established Capsular Penetration No. (%)</th>
<th>Pos. Seminal Vesicles No. (%)</th>
<th>Pos. Lymph Nodes* No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-4</td>
<td>64 (9)</td>
<td>49 (77)</td>
<td>12 (19)</td>
<td>2 (3)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>5</td>
<td>168 (24)</td>
<td>116 (69)</td>
<td>43 (26)</td>
<td>3 (2)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>6</td>
<td>303 (43)</td>
<td>173 (57)</td>
<td>89 (30)</td>
<td>16 (5)</td>
<td>25 (8)</td>
</tr>
<tr>
<td>7</td>
<td>130 (19)</td>
<td>39 (30)</td>
<td>50 (38)</td>
<td>15 (12)</td>
<td>26 (20)</td>
</tr>
<tr>
<td>8-10</td>
<td>38 (5)</td>
<td>5 (13)</td>
<td>9 (24)</td>
<td>8 (21)</td>
<td>16 (42)</td>
</tr>
<tr>
<td>Totals</td>
<td>703 (100)</td>
<td>382 (54)</td>
<td>203 (29)</td>
<td>44 (6)</td>
<td>74 (11)</td>
</tr>
</tbody>
</table>

*Includes patients who did not undergo radical prostatectomy because of positive lymph nodes at pelvic lymph node dissection.

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**Figure 1.** Disease-Specific Survival among Untreated Patients with Localized Prostate Cancer, According to Tumor Grade. Data on patients who died of other causes were censored.
CALGB Prostate Studies
Diagnostic Studies

**History**
- difficulty urinating (IPS score)
- frequency, nocturia
- weak stream, urgency
- weight loss, pain
- hematuria

**Digital rectal examination (DRE)**
- size
- symmetry
- texture
- effect on rectal lumen
- nodules

**Trans-rectal ultrasound (TRUS)**
- size
- symmetry
- nodules

**Prostate specific antigen (PSA)**
- level
- rate of rise
- comparison to prior values

**Other laboratory tests**
- CBC
- CMP (alkaline phos, LDH)
- Testosterone

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Diagnostic and Staging Imaging for Prostate Cancer

- Bone Scan
- CT Scan Abdomen and Pelvis
- Endorectal Coil MRI
- Transrectal ultrasound and staging biopsy
- ProstaScint Scan
- Bone MRI
Includes patients who did not undergo radical prostatectomy because of positive lymph nodes at pelvic lymph node dissection.

**Distribution of serum PSA levels in 703 men with clinically localized prostate cancer by pathological stage**

<table>
<thead>
<tr>
<th>PSA ng./ml.</th>
<th>No. Pts. (%)</th>
<th>Organ Confined Disease No. (%)</th>
<th>Established Capsular Penetration No. (%)</th>
<th>Pos. Seminal Vesicles No. (%)</th>
<th>Pos. Lymph Nodes* No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4.0</td>
<td>284 (40)</td>
<td>211 (75)</td>
<td>65 (23)</td>
<td>4 (1)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>4.0-10</td>
<td>246 (35)</td>
<td>131 (53)</td>
<td>78 (32)</td>
<td>8 (3)</td>
<td>29 (12)</td>
</tr>
<tr>
<td>10-20</td>
<td>118 (17)</td>
<td>31 (26)</td>
<td>45 (38)</td>
<td>21 (18)</td>
<td>21 (18)</td>
</tr>
<tr>
<td>20-30</td>
<td>27 (4)</td>
<td>7 (26)</td>
<td>10 (37)</td>
<td>3 (11)</td>
<td>7 (26)</td>
</tr>
<tr>
<td>30-40</td>
<td>12 (2)</td>
<td>1 (8)</td>
<td>2 (17)</td>
<td>4 (33)</td>
<td>5 (42)</td>
</tr>
<tr>
<td>40-50</td>
<td>8 (1)</td>
<td>1 (13)</td>
<td>2 (25)</td>
<td>3 (37)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>&gt;50</td>
<td>8 (1)</td>
<td>--</td>
<td>1 (13)</td>
<td>1 (13)</td>
<td>6 (74)</td>
</tr>
<tr>
<td>Totals</td>
<td>703 (100)</td>
<td>382 (54)</td>
<td>203 (29)</td>
<td>44 (6)</td>
<td>74 (11)</td>
</tr>
</tbody>
</table>

*Includes patients who did not undergo radical prostatectomy because of positive lymph nodes at pelvic lymph node dissection.
CALGB Prostate Studies

Staging

• **Why stage prostate cancer?**
  – So CALGB investigators can compare apples-to-apples!
  – Prognosis is inversely related – the higher the stage, the lower the cure rate.
  – Treatment is conditional on stage – the higher the stage, the more aggressive the treatment.

• **How to stage prostate cancer?**
  – Tumor size
  – Nodal status
  – Metastases

• **Early Stage Risk Stratification**
  – PSA
  – Gleason Score
  – Clinical Stage (T1c,T2a,T2b,T2c)
  – Risk Nomograms

Identifying High-Risk Patients

• Predictive tools have been developed to identify the risk that a patient will fail definitive local therapy (surgery or RT)

• At diagnosis:
  – Partin Tables
  – Risk Groups
  – Pre-treatment Nomograms

• After radical prostatectomy:
  – Pathological Features
  – Post-treatment Nomograms
Pre-Treatment Risk Factors

- Serum PSA
- Clinical stage
- Biopsy Gleason score
- Other biopsy features
  - Number (%) cores with cancer
  - Length of cancer
- Pre-treatment PSA velocity

Pre-operative Nomogram for Prostate Cancer Recurrence

<table>
<thead>
<tr>
<th>Points</th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
<th>70</th>
<th>80</th>
<th>90</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA</td>
<td>0.1</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Clinical Stage</td>
<td>T1c</td>
<td>T1ab</td>
<td>T2a</td>
<td>T2b</td>
<td>T2c</td>
<td>T3a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopsy Gleason Grade</td>
<td>≤ 2+</td>
<td>3+</td>
<td>≤ 2</td>
<td>≥ 3+</td>
<td>≤ 2+</td>
<td>≥ 3+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Points</td>
<td>0</td>
<td>20</td>
<td>40</td>
<td>60</td>
<td>80</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>60 Month Rec. Free Prob.</td>
<td>.96</td>
<td>.93</td>
<td>.9</td>
<td>.85</td>
<td>.8</td>
<td>.7</td>
<td>.6</td>
<td>.5</td>
<td>.4</td>
<td>.3</td>
<td>.2</td>
</tr>
</tbody>
</table>
Patients who score < 60% may be eligible for the PUNCH 90203 Study.
CALGB Prostate Studies
Therapy - Standard and Investigational

- **Surgery - Radical prostatectomy**
  - Complications: impotence, incontinence, urethral narrowing
  - Advantages: one-time procedure
  - Questions: neoadjuvant or adjuvant hormonal therapy & chemotherapy

- **Radiation therapy - External beam, 3-D conformal, brachytherapy (seeds), IMRT, systemic radioisotopes**
  - Complications: fatigue, dermatitis, bladder/rectal irritation
  - Advantages: non-surgical, potency preserved, constantly improving
  - Questions: adjuvant hormonal therapy and chemotherapy

<table>
<thead>
<tr>
<th>Hormonal Therapy</th>
<th>Chemotherapy</th>
<th>Targeted Molecules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune Therapy</td>
<td>(Dendritic Cellular Rx)</td>
<td></td>
</tr>
</tbody>
</table>
“Carcinoma of the prostate gland is peculiarly favorable for endocrine manipulation... We shall demonstrate that the acid phosphatase of serum is reduced in metastatic carcinoma of the prostate through castration or estrogenic injections and that this enzyme is increased by injecting androgens. We have been unable to find any previous observations indicating any relationship of hormones to carcinoma of the prostate gland.”

Huggins, C and Hughes, CV, Cancer Research 1:293-7, 1941.
### CALGB Prostate Studies

#### Hormonal Therapy

**Advantages:**
- Highly effective in all stages
- Low toxicity (bone, muscle, hot flushes)
- Highly acceptable to patients
- Multiple options for Rx (Lupron, Oral, Orchiectomy)
- Improves survival

**Disadvantages:**
- Not curative in advanced stages
- Androgen-independent clones of cells develop, leading to treatment failure

**Questions:**
- Can it improve the cure rate for early disease?
- How to delay/prevent androgen independent clones?
- Once hormones fail, are there ways to restore sensitivity?
- Are there better 2nd or 3rd hormonal treatments than the ones currently available?
- When to start?

### CALGB Prostate Studies

#### Chemotherapy

**Advantages**
- Cytolytic (kills cells)
- Untargeted (potential for broad activity)
- Taxotere plus Prednisone

**Complications**
- Toxicity high, especially in elderly
- Many prostate cancer patients have bone marrow involvement &/or co-morbidities
- Late-stage patients

**Questions**
- Adjuvant or Neoadjuvant Benefits?
- Targeted Molecules (Avastin)?
- New Agents?
- Complementary Rx (Zometa)?
CALGB Prostate Studies

Follow-up/End-points

Relapse (Progression-free Survival)
- The problem of measurable end-points in prostate cancer
- Clinical indicators - performance status, weight, indirect lab indicators
- PSA

Survival
- From diagnosis to death
- From inception of study to death

Toxicity - judged by the physician and the CRA

Quality of life - judged by the patient

Renal Cell Cancer

Epidemiology

- 32,000 new cases per year
- 12,000 deaths per year
- Risk factors
  - Smoking
  - Obesity
  - Environmental exposures
  - Genetic predisposition (von Hippel-Lindau)
- Clear Cell Histology Most Common
Renal Cell Cancer

Metastatic disease

- Chemotherapy: ineffective
- Interferon alone
  - Response rate 15%, partial response and short
- High dose IL-2
  - Response rate only 15%, but ½ are CR’s and many of these patients may actually be cured
- Targeted Molecules
  - Sorafenib (Nexavar) and Sunitinib (Sutent)
  - Temsirolimus (Torisel)
  - Avastin?

Biology of RCC

- Von Hippel-Lindau (VHL) syndrome is characterized by germline mutation of chromosome 3p, development of renal cell carcinoma (RCC)
- Noninherited clear-cell RCC characterized by VHL gene tumor suppressor gene inactivation, leads to
  - Induction of hypoxia-inducible genes, including vascular endothelial growth factor (VEGF)
  - VEGF overexpression promotes tumor angiogenesis
Akt/PKB

PI3K

p38MAPK

Raf

MEK

Erk

Vascular permeability

Endothelial cell survival

Endothelial cell migration

Endothelial cell proliferation

Bevacizumab

VEGF

Vascular endothelial cell plasma membrane

Axitinib

Sorafenib

Sunitinib

Vascular permeability

Endothelial cell survival

Endothelial cell migration

Endothelial cell proliferation

RCC pathogenesis and progression
The New World of RCC

- VHL gene inactivation is a frequent event in clear-cell RCC leading to VEGF overexpression
- Therapeutic inhibition of VEGF via antibody or receptor blockade results in antitumor activity in metastatic RCC
- New clinical options that target VEGF ligand or VEGF receptor currently available
  - Both approaches appear effective

CALGB Prostate CA Clinical Trials

- **90202**: Early vs. Late Zometa with Bone Mets and 1st Line Hormonal Therapy for CaP *
- **90203**: Neoadjuvant Chemo + Hormonal Rx for High Risk CaP *
- **150201**: Correlative Science Studies for CaP
- *Schema to follow*
CALGB 90202
CaP Metastatic 1st Hormone RX

Randomize

- Double-Blinded
  - Zoledronic acid 4 mg IV Q 4 Wks
  - Placebo IV Q 4 weeks

- Open Label
  - Zoledronic acid 4 mg IV Q 3 wks

- SRE
  - End protocol treatment. Treat at physician's discretion

For CALGB Participants Only Slide 41

CALGB 90203 (PUNCH)
Neoadjuvant Chemohormonal Therapy Prior to CaP Surgery

Randomize

- 6 cycles of chemohormonal therapy
  - Docetaxel 75 mg/m² IV every 21 days
  - LHRH agonist therapy (18-24 weeks)

- Surgical Intervention
  - Staging pelvic lymphadectomy
  - Radical prostatectomy

For CALGB Participants Only Slide 42
Future GU Clinical Trials

- **90601**: Chemotherapy w/wo Avastin for TCC Bladder Mets

- **90602**: BCG w/wo IFNA for recurrent Superficial TCC of Bladder

CALGB GU Cancer Protocols

- Among the most common cancer-related causes of death for American males.
- Under-served populations are vulnerable & have the most to benefit from access to state-of-the-art care and therapy.
- Lots of diagnostic tools, measurements and clinical correlates to help define the best treatments for sub-populations.
- Very committed investigators

Exciting for the right CRA!
(Is it you?)