Historical Changes in Prostate Cancer Treatment

Dr. Leo Milleman
Urologist
McFarland Clinic
Motto

- Oh! Just go with the flow!
2009 Incidence of Prostate Cancer

• 192,280 new cases of prostate cancer
• 27,360 deaths from prostate cancer
History of Prostate Cancer

• Fun-Different type of talk
• Coach Rhoads
• Q & A
• Past, Present & Future
History of Prostate Cancer

- The last two decades have seen great advancements in our understanding of the prostate anatomy and approach including laparoscopic and robotic techniques. The history of developments in prostate cancer surgery, radiotherapy and hormonal therapy is fascinating and urologist through the ages had the quest to find an ideal treatment for prostate cancer in spite of their limitations of resources and understanding.
Cont., History of Prostate Cancer

• To the future, the matching of patients to the treatment modality most appropriate to their tumor, and quality of life outcomes are likely to become increasingly important in determining future practice. It is worthwhile to look at the evolution to plan for the future.
National Buick Show
Grandpa’s 1930 Buick
The Prostate

- First mentioned Herophilus
- First described: Niccolo Massa-1563
- Rilanus 1649- 1st known obstruction due to prostate
- 1834-1867, First surgeries, often to remove the bladder st?
- 1898 Hugh Young- 1st perineal surgery for BPH
Early History of Prostate

- 1536 - first described by Niccolo Massai
- 1853 - officially identified
- 1864 - Billroth, first transpubic prostatectomy
- 1873 - Demarquay, transrectal prostatectomy
- 1890 - Dittel, ischiorectal prostatectomy
1853, Adams

- Surgeon at The London Hospital, described the first case of prostate cancer
Prostate Cancer

- Team approach
- McFarland/Mary Greeley Medical Center
- Specialists
ADVOCACY AND SUPPORT ORGANIZATIONS

• American Cancer Society www.cancer.org (800) ACS-2345
• American Society of Clinical Oncology www.asco.org
• American Urological Association www.auanet.org
• CancerCare www.cancercare.org (800) 813-HOPE
• MaleCare www.malecare.com (212) 673-4920
continued

- Foundation for Cancer Research and Education
  www.cancer-foundation.org (434) 974-1303
  HRPCa.org. Developed by and for patients with
  hormone-refractory prostate cancer; frank,
  well-researched, patient-centered information
  www.hrPCA.org

- MaleCare www.malecare.com (212) 673-4920

- Man to Man, local groups of the American
  Cancer Society

- www.cancer.org (800) ACS-2345
continued

• National Alliance of State Prostate Cancer Coalitions www.naspcc.org (858) 459-0631
• National Comprehensive Cancer Network www.nccn.org
• National Prostate Cancer Coalition www.pcacoalition.org (888) 245-9455
• Patient Advocates for Advanced Cancer Treatments www.paactusa.org (616) 453-1477
• Prostate Cancer Education Council www.pcw.com (866) 477-6788
continued

• Prostate Cancer Foundation  
  www.prostatecancerfoundation.org (800) 757-CURE
• Prostate Cancer Research and Education Foundation  
  www.peref.org (619) 461-8181
• Prostate Cancer Research Institute  
  www.prostate-cancer.org Helpline: (800) 641-PCRI
• Prostate Forum www.prostateforum.com
• The Prostate Net www.prostate-online.org (888) 477-6763
• Us TOO International Prostate Cancer Education and Support Network www.ustoo.org Support hotline: (800) 808-7866
Promoting Wellness
For Prostate Cancer Patients

Promoting Wellness
for Prostate Cancer Patients
Mark A. Moyad, MD, MPH

William R. Bliss Cancer Center
A Service of Mary Greeley Medical Center and McFarland Clinic PC
Ames, Webster City and Outreach Clinics Throughout Central Iowa
Normal Prostate Cells
Gleason 3 pattern
Gleason 5 Pattern
Prostatectomy

- 1904-Hugh Hampton Young, John Hopkins Hospital
- Performed the first radical perineal prostatectomy
Retropubic Prostatectomy

• 1945
• Terrence Millin
• Easier to learn
• Access to pelvic lymph nodes
• Tumor staging
Prostate Cancer Surgery

• A. Multiple Approaches
  – 1904 Young first radical perineal for CA-P
    *All surgeries fraught with sepsis, hemorrhage, anesthesia issues plus incontinence/ED

• B. 1945- Miller Retropubic
  *In the 1970’s still only 7% with local CA-P had surgery
Androgen-ablation therapy

- 1930-Ethel and Alexander Gutman reported that serum acid-phosphatase levels increased in patients with metastatic prostate cancer.
- Charles Huggins found that castration or estrogen administration resulted in glandular atrophy.
Medical Treatment

• 1941-Charles Huggens
  – Published studies using estrogen to oppose testosterone production
  – “chemical castration”
  – 1966, won the Nobel Prize in Medicine
Androgen Ablation

- Provides palliative therapy
- Never curative
1960 Clinical Trial

- Veterans Administration Cooperative Urologic Research Group (VACURG)
- 2 randomized groups
  - Oral estrogen diethylstibesterol (DES)
  - Orchiectomy
- Both equally effective in treating prostate cancer
- Increased cardiovascular and thromboembolic toxicity
1960s-1980s

- Hormone treatment to block adrenal androgen production
- Luteinizing hormone or (LHRH)
- Synthetic LHRH agonist developed
  - Lupron
  - Zoladex
Prostate Specific Antigen

- Serum marker for prostate cancer
- Discovered around 1983
- FDA approved measurement of PSA levels to monitor prostate cancer progression and response to therapy
Dr. Patrick Walsh

- A. Director Hopkins, 1974
- B. 1982, first nerve sparing operation on a 52 y/o professor
- C. This is the basis of modern prostate cancer surgery

*Dr. Milleman came to Ames in 1978*
Radical Retropubic Prostatectomy

- 1983
- Patrick Walsh, John Hopkins
- Control of bleeding
- Reduced injury to the neurovascular bundles
- Improved erectile function
- Decrease incontinence
Prostate Cancer Improved Survival

- 1974-1993
- The number of radical prostatectomy's or radiation therapy for prostate cancer tripled

- 1990-1995
- Death rate in U.S. fell for first time in decades
Ultrasound Guided Biopsy

- Late 1980’s
- Prostate cancer screening
- Ability to obtain high quality core biopsies
Historical Tanks 1940
Historical Tank
Mash Unit
A Happy Wife is a Happy Life
**Radiation therapy**

- Beginning of twentieth century
- First reported the use of radiation to treat localized prostate cancer
- Limited to radium sources introduced into urethra and rectum as palliative therapy
Radiation Therapy

• A. 1897, First noted use of Radiation Treatment for therapy not just diagnostics
• B. 1912, Marie Curie published “Theory of Radioactivity”
• C. 1920, First Trials of Radiation Therapy (poor control)
• D. Radiation Therapy was largely abandoned for years due to androgen ablation discoveries
Rubin Flocks, M.D.

• In 1960, Flocks and his colleague, David A. Culp, published a textbook, *Radiation Therapy of Early Prostatic Cancer*.

• early 1950s, at the dawn of the age of nuclear medicine, Flocks published extensively on brachytherapy, using radioactive colloidal gold (Au 198).
Dr. Rubin Flocks

• A. 1952-Au\textsuperscript{198}
• B. Subsequent Brachytherapy techniques
• C. 1980’s Linear Accelerator
Brachytherapy

- 1970
- Willet Whitmore
- $^{125}\text{I}$ radioisotope of iodine
- Inserted into prostate
- Inconsistent dose distribution
Brachytherapy, continued

- 1983
- H. Holm
- Implanting the prostate with radioactive seeds
- Guidance of trans-rectal ultrasonography
External Beam Radiation

- 1950
- High energy cobalt machine
- Penetrate to deeper levels
- Malcolm Bagshaw
Computerized tomography

- Three dimensional conformal treatment plans
- High dose radiation
- Sparing surrounding tissues
Chemotherapy

- Treatment for hormone refractory prostate cancer
- National Prostate Cancer Project
- Gerald Murphy, evaluate efficacy of chemotherapy
Chemotherapy

• A. Avastin (Anti-angiogenesis) does not help
• B. Hazard ratio more severe
• C. Taxatere: Prednisone, helpful
History of the Gleason Score

- Donald F. Gleason, the Minnesota pathologist who invented the “Gleason score” for characterizing cancerous growths in the prostate.
- The Gleason score is now used almost universally to predict the likely outcome of prostate cancer.
- Gleason had been an unknown, junior-grade pathologist in 1962 when he was approached by his hospital's chief of urology to develop a standardized rating system for determining the grade of prostate tumors;
- measurement of how far prostate cancer had progressed and the likely course of the disease.
- Before the Gleason score was developed each pathologist pretty much used his own system, which made comparing research results among different groups nearly impossible."
Gleason Score

Gleason's Pattern

1. Small, uniform glands
2. More stroma between glands
3. Distinctly infiltrative margins
4. Irregular masses of neoplastic glands
5. Only occasional gland formation

Well differentiated

Moderately differentiated

Poorly diff./Anaplastic
# Gleason Scores

<table>
<thead>
<tr>
<th>Gleason Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 to 4</td>
<td>Well differentiated. Small glands that are closely packed. Cancer cells behave in &quot;predictable&quot; manner. Least aggressive, least likely to metastasize.</td>
</tr>
<tr>
<td>5 and 6</td>
<td>Moderately well differentiated. Variable-sized glands with little stroma. May also see a cribriform pattern of several cells fused together. Cancer cells behave in &quot;predictable&quot; manner. Most common grade.</td>
</tr>
<tr>
<td>7</td>
<td>Can be considered a moderately well differentiated or poorly differentiated cancer. Glands are incompletely formed.</td>
</tr>
<tr>
<td>8 to 10</td>
<td>Poorly differentiated. Single cells have broken away and may be found within vascular lumen. Cancers cells can behave in unpredictable manner. Aggressive cancer.</td>
</tr>
</tbody>
</table>


Source: Urol Nurs © 2004 Society of Urologic Nurses and Associates
Gleason Score = 6
Gleason Score = 9
TNM Staging of Prostate Cancer

**T1**
- Clinically apparent; tumor not palpable or visible by imaging
- T1a Incidental finding during transurethral resection of prostate (< 5% of tissue resected)
- T1c Tumor identified by needle biopsy (e.g., because of elevated PSA)

**T2**
- Tumor confined within prostate (palpable or visible on TRUS)
- T2a Involves half of a lobe or less
- T2b Involves more than half of a lobe but not both lobes
- T2c Tumor involves both lobes

**T3**
- Tumor extends through prostatic capsule, bladder neck or seminal vesicle
- T3a Unilateral extracapsular extension
- T3b Bilateral extracapsular extension
- T3c Tumor invades seminal vesicle(s)

**T4**
- The tumor has spread or attached to tissue next to the prostate (other than the seminal vesicles)
- T4a The tumor has spread to the neck of the bladder, the external sphincter (muscles that help control urination), or the rectum.
- T4b The tumor has spread to the floor or the wall of the pelvis.

**N0-3**
- Cancer has not spread to any lymph nodes.
- N1 Cancer has spread to a single regional lymph node (inside the abdomen) and is not larger than 2 centimeters
- N2 Cancer has spread to one or more regional lymph nodes and is larger than 2 centimeters (\( \leq 4 \text{ inch} \)), but not larger than 5 centimeters
- N3 Cancer has spread to a lymph node and is larger than 5 centimeters

**M0-1**
- The cancer has not metastasized (spread) beyond the regional lymph nodes
- M1 The cancer has metastasized to distant lymph nodes (outside of the pelvis), bones, or other distant organs such as lungs, liver, or brain
# TNM Staging

## Table 2: TNM Staging System

<table>
<thead>
<tr>
<th>T Categories</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TX:</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T1:</td>
<td>Clinically inapparent tumor neither palpable nor visible by imaging</td>
</tr>
<tr>
<td>T1a:</td>
<td>Tumor incidental histologic finding in 5% or less of tissue resected</td>
</tr>
<tr>
<td>T1b:</td>
<td>Tumor incidental histologic finding in more than 5% of tissue resected</td>
</tr>
<tr>
<td>T1c:</td>
<td>Tumor identified by needle biopsy</td>
</tr>
<tr>
<td>T2:</td>
<td>Tumor confined within prostate</td>
</tr>
<tr>
<td>T2a:</td>
<td>Tumor involves 50% or less of one lobe</td>
</tr>
<tr>
<td>T2b:</td>
<td>Tumor involves more than 50% of one lobe but not both lobes</td>
</tr>
<tr>
<td>T2c:</td>
<td>Tumor involves both lobes</td>
</tr>
<tr>
<td>T3:</td>
<td>Tumor extends through the prostate capsule</td>
</tr>
<tr>
<td>T3a:</td>
<td>Extracapsular extension (unilateral or bilateral)</td>
</tr>
<tr>
<td>T3b:</td>
<td>Tumor invades seminal vesicle(s)</td>
</tr>
<tr>
<td>T4:</td>
<td>Tumor is fixed or invades adjacent structures other than seminal vesicles</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N Categories</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NX:</td>
<td>Regional lymph nodes were not assessed</td>
</tr>
<tr>
<td>N0:</td>
<td>The cancer has not spread to lymph nodes</td>
</tr>
<tr>
<td>N1:</td>
<td>The cancer has spread to lymph nodes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M Categories</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MX:</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0:</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1:</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td>M1a:</td>
<td>The cancer has spread to distant lymph nodes</td>
</tr>
<tr>
<td>M1b:</td>
<td>The cancer has spread to bone(s)</td>
</tr>
<tr>
<td>M1c:</td>
<td>The cancer has spread to other organs (e.g., lungs, liver, brain)</td>
</tr>
</tbody>
</table>

TNM: tumor-node-metastasis.
## Partin Table

<table>
<thead>
<tr>
<th>Case One Data</th>
<th>Case One Predictions</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA Level</td>
<td>Confined to the Prostate: 83% (81% to 85%)</td>
</tr>
<tr>
<td></td>
<td>Extraprostatic Extension: 16% (14% to 17%)</td>
</tr>
<tr>
<td></td>
<td>Seminal Vesicle Invasion: 1%</td>
</tr>
<tr>
<td></td>
<td>Lymph Node Invasion: 0%</td>
</tr>
<tr>
<td>Gleason Score</td>
<td>5-6</td>
</tr>
<tr>
<td>Clinical Stage</td>
<td>T1c</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Case Two Data</th>
<th>Case Two Predictions</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA Level</td>
<td>Confined to the Prostate: 70% (66% to 74%)</td>
</tr>
<tr>
<td></td>
<td>Extraprostatic Extension: 27% (23% to 30%)</td>
</tr>
<tr>
<td></td>
<td>Seminal Vesicle Invasion: 2% (2% to 3%)</td>
</tr>
<tr>
<td></td>
<td>Lymph Node Invasion: 1% (0% to 1%)</td>
</tr>
<tr>
<td>PSA Level</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Gleason Score</td>
<td>5-6</td>
</tr>
<tr>
<td>Clinical Stage</td>
<td>T1c</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Case Three Data</th>
<th>Case Three Predictions</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA Level</td>
<td>Confined to the Prostate: 31% (26% to 37%)</td>
</tr>
<tr>
<td></td>
<td>Extraprostatic Extension: 56% (49% to 62%)</td>
</tr>
<tr>
<td></td>
<td>Seminal Vesicle Invasion: 9% (5% to 14%)</td>
</tr>
<tr>
<td></td>
<td>Lymph Node Invasion: 4% (2% to 8%)</td>
</tr>
<tr>
<td>PSA Level</td>
<td>6.1-10</td>
</tr>
<tr>
<td>Gleason Score</td>
<td>4+3=7</td>
</tr>
<tr>
<td>Clinical Stage</td>
<td>T2a</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Case Four Data</th>
<th>Case Four Predictions</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA Level</td>
<td>Confined to the Prostate: 12% (7% to 18%)</td>
</tr>
<tr>
<td></td>
<td>Extraprostatic Extension: 33% (22% to 46%)</td>
</tr>
<tr>
<td></td>
<td>Seminal Vesicle Invasion: 28% (16% to 42%)</td>
</tr>
<tr>
<td></td>
<td>Lymph Node Invasion: 26% (12% to 44%)</td>
</tr>
<tr>
<td>PSA Level</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Gleason Score</td>
<td>8-10</td>
</tr>
<tr>
<td>Clinical Stage</td>
<td>T2b/c</td>
</tr>
</tbody>
</table>
Pursuing a prostate cancer vaccine
Sipuleucel-T Immunotherapy for Castration-Resistant Prostate Cancer
Prostate Vaccine

- A. For hormone insensitive CAP
- B. 27,000-30,000 per infusion x3
- C. Patient own white cells
- D. 38% respond, 4 month increase in life
- E. Provenge, Dedreon: Stock $45
Stages of life
Dr. Dick Williams

• Dr. Williams’ influence on urology will not be forgotten, but his gifts as a human being will be cherished above all.
Dr. Richard Williams

• Urology Chairman of University of Iowa
• Dr. Williams was most recently granted the American Urological Association’s 2009 Hugh Hampton Young Award, for outstanding contributions to the study of genitourinary disease.
• In 2005, Dr. Williams received the International Volunteers in Urology Humanitarianism Award, for his missionary travels with the organization to Haiti.
• His volunteer work was also recognized with a U.S. Department of Health and Human Services Award in 2009.
Dick Williams: Great Urologist, Better Person

• I once watched Dr. Williams in the operating room as he helped remove a high-risk patient’s kidney tumor. I was awed by his surgical skill but also his concern about the patient and his family, wondering to myself whether all surgeons made this many calls from the OR to waiting family members.

• Richard R. Kerr, editor-in-chief of Urology Times
2010 Flood
Flood 2010
Robot Surgery

- A. Comments
- B. More complications
- C. Less blood loss
- D. Outcomes same/unknown
Evidence-Based Recovery of Sexual Function After Robotic Assisted Laparoscopic Prostatectomy
Ames McFarland Urology

- Dr. Jack Sibley
- Dr. Curtis Clark
- Dr. Leo Milleman
- Dr. Brad Thorgaurd
- Dr. Damon Dyche
A Patient

- 62 y/o male, history of septic prostatitis
- Hospitalized 5 times
- PSA <4, 5.2, 7.3, in 2 years
- Trans-rectal biopsy: Gleason 4 + 3 = 7, bilateral
- Bone scan
- All labs negative
Patient Treatment

• August 2009-RRP (Radical retro-pubic prostatectomy).
  – Left margin +
  – Right margin = bulk tumor
– PSA
  • 3 months = .12
  • 4 months = 1.9
  • 5 months = .31
– Lupron – Radiation therapy
Lambeau Field
The Future – Man Power

• A. 20 years ago AUA “Gallup” no predicted shortage
  – A. Huge oversight
• B. 30 million new baby boomers
• C. New Allied urology care
New Thoughts

A. French shepherd dogs sniff CA-P urine
B. U.S. Preventive Services: Stop PSA screening, Age 75
   1). Most men don’t agree
   2). Most men/M.D’s have not heard of the study
Diet Advice

• **Definite**
  – 0

• **Maybe**
  lycopenes
  Conc. Tomatoes
  Cherry Juice

• **No**
  apricots
  PC Spec.
  Laetrile

(Univ. of Iowa)
Alternative Treatments

- Lycopene
- Saw Palmetto
- Nettle weed
- Shark Cartilage
- Zinc-Sunflower Seeds
Radiation: for PSA Escape

• A. RT + ADT improves survival
  – 23% less deaths of Ca-P
  6 month longer survival
• B. Use ADT > 6 months with radiation therapy 1% versus 15% survival
• C. Neoadjuvant H.T. increase CAD risk if more than 1 risk factor (JAMA 8, 2009)
Final Thoughts

• A. Pat Walsh – like football
  – Films, review each operation

• B.
  – Partin tables
  – Gleason scores
  – MAYO Oesterling age PSA tables

• C. Be aware of PSA controversies
Future Studies

• Genetic & biochemical framework
  – Understanding sporadic and inherited prostate cancer

• Interactions between diet, environmental, inheritance and ageing

• Dietary and chemoprevention, to decrease risk

• Gene therapy vectors (prostate specific vectors promote lytic virus specific to prostate cells)

• Develop agents that induce apoptosis of prostate specific cancer cells
Do not forget little kindnesses and do not remember small faults.

Chinese Proverb
Conclusion

• RAY & Bubba
• Individualize – one size does not fit all
• Take your Test
Grandpa’s 1930 Buick
Gleason 4 Pattern
The End

- Questions
- Tour
Mash Unit
Mash Unit
Intro

• A. Dragon Fly Mosquitoes
• B. Ames Famous Summer
  – Buick Show
  – Tank Photos
  – Floods-sponge bath: bottled water
• C. Prostate cancer history
  -the old days
  -now
  -the future

SOME FUN AND QUESTIONS and a TEST