Johns Hopkins Hospital
Pioneers in Medicine
Fortieth Anniversary of King Faisal Prize

The Impact of Surgical Innovation in Reducing Death and Suffering from Prostate Cancer

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Why Is Prostate Cancer Important?

• In the United States:
  – Most common cancer in men - life-time risk 12% - 1 out of 8 men
  – Second most common cause of cancer death in men.

• Worldwide:
  – Second most common cancer and 5\textsuperscript{th} leading cause of cancer death in men
  – 1,100,000 men are diagnosed each year and more than 300,000 die from it.
Estimated age-standardised mortality
Prostate, all ages
GLOBOCAN 2008

Age-adjusted mortality/100,000
The Impact of Surgical Innovation in Reducing Death and Suffering from Prostate Cancer

• The rationale for surgery:
Prostate cancer is a multifocal disease that begins simultaneously in many different sites. To cure it, the entire prostate must be eliminated.
Radical Prostatectomy

• Historical Perspectives
• Anatomic Discoveries
• Perfecting the surgical technique
• Impact on:
  – Safety
  – Mortality from prostate cancer
  – Research in the field
Radical Prostatectomy

- Historical Perspectives
- Anatomic Discoveries
- Perfecting the surgical technique
- Impact on:
  - Safety
  - Mortality from prostate cancer
  - Research in the field
Historical Perspective

- 1904:
  - Radical **perineal** prostatectomy: H.H. Young at the Johns Hopkins Hospital
Historical Perspective

• 1904:
  – Radical perineal prostatectomy: H.H. Young at the Johns Hopkins Hospital

• 1947:
  – Radical retropubic prostatectomy: Terrance Millin
Historical Perspective

• 1904:
  – Radical perineal prostatectomy: H.H. Young at the Johns Hopkins Hospital

• 1947:
  – Radical retropubic prostatectomy: Terrance Millin

• 1970’s
  – Radical prostatectomy rarely performed, despite effective cancer control, because of side effects:
    • Major bleeding: often life threatening
    • Impotence: 100%
    • Total incontinence: 10–25%
Historical Perspective

- Urologists were frightened by the blood loss associated with the retropubic approach and did not want to operate.
Historical Perspective

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• Patients rightfully felt that the treatment was worse than the disease.
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- With the introduction of external beam radiation radical prostatectomy fell into disuse.
Historical Perspective

• Urologists were frightened by the blood loss associated with the retropubic approach and did not want to operate.
• Patients rightfully felt that the treatment was worse than the disease.
• With the introduction of external beam radiation radical prostatectomy fell into disuse.
• In 1974 when I arrived at Hopkins I wondered why these side effects occurred and if it was possible to prevent them.
These Side-Effect Occurred Because We Did Not Understand the Anatomy *Around* the Prostate
These Side-Effect Occurred Because We Did Not Understand the Anatomy *Around* the Prostate

- **Bleeding**
  - Anatomy of the veins surrounding the prostate was not charted.
These Side-Effect Occurred Because We Did Not Understand the Anatomy *Around* the Prostate

• **Bleeding**
  – Anatomy of the veins surrounding the prostate was not charted.

• **Impotence**
  – Every one believed that the *cavernous nerves ran through the prostate*, but the actual location of the nerves responsible for erection was not known.
These Side-Effect Occurred Because We Did Not Understand the Anatomy Around the Prostate

- **Bleeding**
  - Anatomy of the veins surrounding the prostate was not charted.

- **Impotence**
  - Every one believed that the cavernous nerves ran *through the prostate*, but the actual location of the nerves responsible for erection was not known.

- **Incontinence**
  - Anatomical understanding of sphincteric complex was incorrect.
Why? Use of Adult Cadavers
Why? Use of Adult Cadavers

The prostate is shrouded by dense fascia, which conceals the surrounding anatomy.

In the postmortem state, the abdominal viscera compress the pelvic organs into a thick pancake of tissue and formalin fixatives dissolve the fatty planes, making the identification of anatomic structures impossible.

Solution

– Using the operating room as an anatomy laboratory
– Dissections in stillborn infants.
Historical Article

The Discovery of the Cavernous Nerves and Development of Nerve Sparing Radical Retropubic Prostatectomy

Patrick Craig Walsh*

From the James Buchanan Brady Urological Institute, The Johns Hopkins Medical Institutions, Baltimore, Maryland

Purpose: This review is of the events that led up to the discovery of the cavernous nerves and the development of nerve sparing radical retropubic prostatectomy.

Materials and Methods: The correspondence between Pieter J. Donker and Patrick C. Walsh, along with the publication folders describing the anatomy of the dorsal vein complex, pelvic plexus and cavernous nerves, and pelvic fascia, are reviewed.

Results: Serendipity had a major role in the fateful meeting of Pieter J. Donker and Patrick C. Walsh on February 13, 1981 when they dissected out the cavernous nerves in a stillborn male infant. During the next year intraoperative observations identified the capsular arteries and veins of the prostate as the likely microscopic landmark that could be used in the adult male pelvis to identify the microscopic cavernous nerves. Twenty-five years ago, on April 26, 1982, the first purposeful nerve sparing radical prostatectomy was performed. One year following surgery patient sexual function was normal, and 25 years later he has retained his quality of life and an undetectable prostate specific antigen.

Conclusions: The events that led up to the first nerve sparing radical prostatectomy illustrate the influence of serendipity on discovery.

Key Words: prostatectomy, prostatic neoplasms, impotence

Anatomical Observations: **Bleeding**

- Venous complex over the top of the prostate is *beneath dense fascia* and cannot be seen during surgery.

- Because the anatomy was obscure, surgeons believed that excessive bleeding was inevitable.
Anatomical Observations: Bleeding

Using the operating room as an anatomy laboratory, I identified a common trunk over the urethra.
Anatomical Observations: Bleeding

This important observation led to a surgical technique that reduced blood loss and this bloodless field made it possible to perform a safer, more precise, and thorough cancer operation.
Soon after developing the technique for controlling bleeding, a 58 year old man returned 3 months following surgery and told me that he was fully potent!

How could that be? At that time, because all men were impotent following surgery, everyone believed that the nerves ran through the prostate and it would be impossible to preserve potency.

However, from this one case, I knew that this was not true. But where were the nerves? The answer, which was in not in any anatomy book, was found on a trip to Leiden.
Professor Pieter Donker – A Neurourologist - Professor and Chairman University of Leiden

• In 1977, while attending an International meeting, my wife and I went to dinner downtown.

• As we were walking to our table, I noticed an older man who looked lonely. For the first and only time in my life I approached a total stranger and asked if he would like to join us for dinner. His name was Pieter Donker. After a wonderful dinner, I thought that was the end of it.
But 4 years later and 4000 miles away we met for the second time – in Leiden
Four Years Later in 1981: Visiting Professor University of Leiden

• Donker was retired and I was invited by his successor to be a visiting professor. On Friday February 13 Pieter volunteered to show me around Leiden. Instead, at my insistence, we went to his laboratory where he was using a dissecting microscope to study the *innervation of the bladder* in a stillborn male infant.

• When I asked to see the branches to the *corpora cavernosa*, he said that he had never looked. 3 hours later we identified them—outside the prostate!
Deiter- anatomy of autonomic nerves in pelvis.

Bladder →
Prost →
Urethra →

Some of these fibers appear to go into the corpus cavernosa - the bundle is lateral to the prostate or urethra.

2-13-81 Leiden
February 13 1981

Cavernous nerves

Pelvic Plexus

Prostate
Anatomical Observations: IMPOTENCE

- Based on this observation, we knew where the cavernous nerves were located in a tiny fetus. But how could we identify these microscopic structures in the adult male pelvis?
Identification of the neurovascular bundles

- When I returned to Hopkins, again using the operating room as an anatomy lab, I realized that the capsular arteries and veins of the prostate travelled in the exact same location as the nerves in the fetus.
Based on this observation, I speculated that this **neurovascular bundle** could be used as the **intraoperative landmark** to identify the microscopic nerves.
First Purposeful Nerve-sparing Radical Prostatectomy

April 26, 1982 – the 25th anniversary
Detailed Neuro-anatomical Studies
Detailed Neuro-anatomical Studies
Detailed Neuro-anatomical Studies
Anatomical Observations: Incontinence

- The external sphincter was not where we thought it was!
Anatomical Observations: *Incontinence*

- Instead it is a vertically oriented tubular sheath (Oelrich, 1980) of which the dorsal vein complex is an important component.

- Refined techniques for control of bleeding without injury to the striated sphincter improved postoperative continence.
Application of these anatomic principles

• Today, these anatomical principles form the basis used world-wide for radical prostatectomy using open, laparoscopic, and robotic techniques.
Radical Prostatectomy

• Historical Perspectives
• Anatomic Discoveries
• Perfecting the surgical technique
• Impact on:
  – Safety
  – Mortality from prostate cancer
  – Research in the field
Perfecting the Technique:
Perfecting the Technique:
Using the Operating Room As An Anatomy Laboratory
Perfecting the Technique:
*Using the Operating Room As An Anatomy Laboratory*

- Database day 1: anatomical observations, changes in technique, cancer control and quality of life.
Perfecting the Technique: 
*Using the Operating Room As An Anatomy Laboratory*

- Database day 1: anatomical observations, changes in technique, cancer control and quality of life.
- Telephone appointments every 3 months evaluating outcomes and coaching the patient to recovery.
Perfecting the Technique: Using the Operating Room As An Anatomy Laboratory

- Database day 1: anatomical observations, changes in technique, cancer control and quality of life.
- Telephone appointments every 3 months evaluating outcomes and coaching the patient to recovery.
- I told myself the truth by dictating exactly what the patient said when asked “are you wearing a pad” and “have you been able to have intercourse more than 50% of the attempts”.

The correlation between the database and an independent 3rd party questionnaire was 95%.

Perfecting the Technique: 
Using the Operating Room As An Anatomy Laboratory

- Change one thing at a time: 28 major changes over 29 years in 4569 patients.
- Constant re-evaluation
- Video documentation
  - To teach others
  - To teach myself
When it became obvious that minor variances in surgical technique could have a major effect on outcomes, I videotaped 62 consecutive cases, and 18 months later reviewed the cases frame by frame and correlated specific steps with quality of life outcomes, which were collected by an independent third party.

4 steps correlated with the early recovery of sexual function.
Sphincter responsible for passive urinary control
To preserve as much of the striated sphincter as possible, it was divided close to the prostate.
We did not know that the neurovascular bundles were pulled into the midline and could be damaged at this point.
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Dividing dorsal v. complex
Perfecting the Technique:

Using the Operating Room As An Anatomy Laboratory

• Change one thing at a time: 28 major changes over 29 years in 4569 patients.

• Constant re-evaluation

• Video documentation
  – To teach others
  – To teach myself

• **Goal** – to have every patient continent and potent at 3 months.
Perfecting Nerve-sparing Radical Prostatectomy: Sailing in Uncharted Waters
<table>
<thead>
<tr>
<th>Date</th>
<th>Patient number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>September 1984</td>
<td>#110</td>
<td>Wide excision of the neurovascular bundle</td>
</tr>
<tr>
<td>March 1985</td>
<td>#160</td>
<td>Fine ligation of the branches of the NVB</td>
</tr>
<tr>
<td>April 1985</td>
<td>#166</td>
<td>Mucosal eversion at the bladder neck</td>
</tr>
<tr>
<td>September 1987</td>
<td>#474</td>
<td>Vicryl instead of chromic for anastomotic sutures</td>
</tr>
<tr>
<td>October 1987</td>
<td>#485</td>
<td>Bulldog clamps on hypogastric arteries</td>
</tr>
<tr>
<td>April 1988</td>
<td>#567</td>
<td>Accessory / Aberrant pudendal artery recognized</td>
</tr>
<tr>
<td>January 1989</td>
<td>#672</td>
<td>Direct division of the posterior striated sphincter</td>
</tr>
<tr>
<td>January 1989</td>
<td>#678</td>
<td>Lateral pedicle divided but not ligated</td>
</tr>
<tr>
<td>October 1989</td>
<td>#785</td>
<td>Intermittent compression devices on lower extremities</td>
</tr>
<tr>
<td>June 1990</td>
<td>#883</td>
<td>Preservation of aberrant anterior pudendal artery</td>
</tr>
<tr>
<td>February 1991</td>
<td>#989</td>
<td>Nerve graft series initiated</td>
</tr>
<tr>
<td>March 1995</td>
<td>#1680</td>
<td>Six urethral sutures</td>
</tr>
<tr>
<td>March 1995</td>
<td>#1688</td>
<td>Vicryl replaced by Monocryl</td>
</tr>
<tr>
<td>June 1996</td>
<td>#1497</td>
<td>McDougal clamp discontinued</td>
</tr>
<tr>
<td>July 1996</td>
<td>#1963</td>
<td>Refined division of the dorsal vein</td>
</tr>
<tr>
<td>March 1997</td>
<td>#2087</td>
<td>Video documentation; Viagra</td>
</tr>
<tr>
<td>September 1997</td>
<td>#2202</td>
<td>Pubic stitch</td>
</tr>
<tr>
<td>November 1998</td>
<td>#2425</td>
<td>Release of peritoneum</td>
</tr>
<tr>
<td>May 1999</td>
<td>#2545</td>
<td>Closure bladder neck/new stoma on anterior bladder</td>
</tr>
<tr>
<td>June 1999</td>
<td>#2553</td>
<td>2.5 power loupes</td>
</tr>
<tr>
<td>August 1999</td>
<td>#2587</td>
<td>Division umbilical ligament</td>
</tr>
<tr>
<td>August 2000</td>
<td>#2766</td>
<td>Stopped traction on bladder with malleable blade</td>
</tr>
<tr>
<td>October 2000</td>
<td>#2801</td>
<td>Bladder neck intussusception</td>
</tr>
<tr>
<td>May 2003</td>
<td>#3275</td>
<td>Babcock clamp to stabilize the anastomosis while tying the sutures</td>
</tr>
<tr>
<td>December 2004</td>
<td>#3558</td>
<td>4.5 power loupes</td>
</tr>
<tr>
<td>January 2005</td>
<td>#3581</td>
<td>8 cm incision</td>
</tr>
<tr>
<td>June 2005</td>
<td>#3649</td>
<td>High anterior release of the neurovascular bundle</td>
</tr>
</tbody>
</table>
Goal

• I stopped operating after performing 4569 operations.

• I did not reach my goal of having every patient potent and continent at 3 months,

• But over the last 2 years using all of these modification I had the best results I ever had.
Goal

- In potent patients, who underwent at least partial bilateral nerve-sparing during the last 18 months that I was operating.

<table>
<thead>
<tr>
<th>Months Post-op</th>
<th>Potent*</th>
<th>No Pad</th>
<th>&gt; 1 pad</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>60%</td>
<td>94%</td>
<td></td>
</tr>
<tr>
<td>18 months</td>
<td>92%</td>
<td>95%</td>
<td>2.5%</td>
</tr>
</tbody>
</table>

- In 1981:
  - 100% of men were impotent and
  - 10-25% were totally incontinent.
Radical Prostatectomy

- Historical Perspectives
- Anatomic Discoveries
- Perfecting the surgical technique
- Impact on:
  - Safety and popularity
  - Mortality from prostate cancer
  - Research in the field
1983 - 1993
1983 - 1993

- Safer:
  - Blood loss was dramatically less; as a result
  - 30 day mortality reduced 10 fold: 2% to 0.2%
  - Length of hospital stay declined
1983 - 1993

• Safer:
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• Fewer side-effects
1983 - 1993

- Safer:
  - Blood loss dramatically less
  - 30 day mortality reduced 10 fold: 2% to 0.2%
  - Length of hospital stay declined

- Fewer side-effects

- PSA (prostate specific antigen) testing:
  Identified more men with localized disease.
  Prostate cancer produces no symptoms until it is too late to cure. PSA testing made it possible to diagnose the disease at an earlier more curable stage.
Radical Prostatectomy

• Historical Perspectives
• Anatomic Discoveries
• Nerve-sparing surgical technique
• **Impact on:**
  – Safety and popularity
  – Mortality from prostate cancer
  – Research in the field
Accomplishments

• **Cancer control**: Over the last 2 decades, more men were subjected to potential curative therapy and deaths from prostate cancer in the U.S. have fallen 40%. Why?
Age-adjusted deaths rates from cancer in US men

Age-adjusted deaths rates from cancer in US men

Age-adjusted deaths rates from cancer in US men

Nerve-sparing radical prostatectomy
PSA Testing

Radical Prostatectomy versus Watchful Waiting in Early Prostate Cancer

*NEJM 2014;370:932*

Anna Bill-Axelson, M.D., Ph.D., Lars Holmberg, M.D., Ph.D.,

- **SPCG-4**: Scandinavian Prostate Cancer Group 4
- Sweden, Finland, Iceland
- Randomized trial of *watchful waiting* vs. radical prostatectomy
- Pre-PSA era.
- 695 T2 (75%); mean age 65
- Follow-up 18 years following randomization.
Radical Prostatectomy versus Watchful Waiting in Early Prostate Cancer

NEJM 2014;370:932
Anna Bill-Axelson, M.D., Ph.D., Lars Holmberg, M.D., Ph.D.,

<table>
<thead>
<tr>
<th>%</th>
<th>Metastases</th>
<th>Deaths From Any Cause</th>
<th>Deaths From Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>43%</td>
<td>39%</td>
<td>44%</td>
</tr>
<tr>
<td>&lt; 65 years of age</td>
<td>49%</td>
<td>50%</td>
<td>55%</td>
</tr>
<tr>
<td>Low risk</td>
<td>57%</td>
<td>43%</td>
<td>46%</td>
</tr>
</tbody>
</table>
Implications

• In 1983, only 7% of men with prostate cancer underwent surgery and radiotherapy was too underpowered to cure. Essentially no one was being treated with curative intent.
Implications

- In 1983, only 7% of men with prostate cancer underwent surgery and radiotherapy was too underpowered to cure. Essentially no one was being treated with curative intent.

- By 1993, 70% of men in their 50s and 55% of men in their 60s underwent surgery – 100,000 men that year.
Mortality Percent Change between 1994 and 2003
Numbers (burden) vs Rates (risk)
All Ages

Liver & IBD
Thyroid
Esophagus
Melanoma of the Skin
Corpus & Uterus, NOS
Pancreas
Kidney & Renal Pelvis
Urinary Bladder
Ovary
Leukemia
Myeloma
Lung & Bronchus
Testis
Brain & ONS
All Cancer Sites
Non-Hodgkin Lymphoma
Oral Cavity & Pharynx
Larynx
Colon & Rectum
Hodgkin Lymphoma
Breast (Female)
Stomach
Cervix Uteri

Prostate

Percent change (%)
-40 -30 -20 -10 0 10 20 30 40 50 60

Decreased
Increased

Burden
Risk
How can we be certain that **surgery** is responsible for this decline in mortality **1994-2003**?

- During this era, surgery was the most common form of treatment for localized disease for men in their 50s and 60s (55 – 70%).

- Radiation was **underpowered** - dose escalation, better targeting, and adjuvant hormonal therapy did not become standard practice until 2000 and after.

- There was no improvement in the survival of men with metastatic disease during this era. *(Wu, JN Cancer 2014; 120:818)*
## Cancer Deaths, U.S.

<table>
<thead>
<tr>
<th></th>
<th>Prostate</th>
<th>Breast</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>40,400</td>
<td>46,000</td>
</tr>
<tr>
<td>2007</td>
<td>27,050</td>
<td>40,460</td>
</tr>
</tbody>
</table>

% Decrease:
- Prostate: 33%
- Breast: 12%
Radical Prostatectomy

• Historical Perspectives
• Anatomic Discoveries
• Nerve-sparing surgical technique

• Impact on:
  – Safety
  – Mortality from prostate cancer
  – Research in the field
Impact on Research

• In breast and colon cancer, tissue was always available for clinical/pathologic correlation and biochemical/molecular study. This accelerated discovery in these fields.

• However, prior to the development of anatomic radical prostatectomy only 7% of men with localized disease underwent surgery. Thus, only small needle biopsy material was available for research.

• Today, tissue harvested from surgical specimens has galvanized research.
Clinical Discoveries From Surgical Specimens

• It is difficult to describe how little we knew prior to the surgical era. For example, we did not know who was cured after treatment.

• In the absence of pathologic stage, accurate serum markers, and imaging, we had to wait 10 to 15 years to see who developed metastases or died from the disease.

• However, once we had surgical specimens, we knew immediately following surgery who was likely to be cured.
Probability of Undetectable PSA Following Radical Prostatectomy Based on Pathologic Findings

- Organ confined
- Extracapsular extension
- Seminal vesicle invasion
- Positive lymph nodes

Likelihood of undetectable PSA vs. Years Postoperative
Clinical Discoveries From Surgical Specimens

• The next step was to predict who was curable at the time of diagnosis.

• By predicting pathologic stage, were able to inform patients prior to surgery whether they had curable disease.
The Use of PSA, Clinical Stage, and Gleason Score To Predict Curability
The Use of PSA, Clinical Stage, and Gleason Score To Predict Curability

![Graph showing the likelihood of undetectable PSA over analysis time for different PSA levels (ng/ml): < 4.0, 4.1 - 10.0, 10.1 - 20.0, > 20.0)]
The Use of PSA, Clinical Stage, and Gleason Score To Predict Curability

**PSA**

- PSA (ng/ml)
  - < 4.0
  - 4.1 - 10.0
  - 10.1 - 20.0
  - > 20.0

**Clinical Stage**

- T1a
- T1b
- T1c
- T2a
- T2b
- T2c
- T3a

Clinical TNM Stage
The Use of PSA, Clinical Stage, and Gleason Score To Predict Curability

PSA

Clinical Stage

Gleason Score
THE USE OF PROSTATE SPECIFIC ANTIGEN, CLINICAL STAGE AND GLEASON SCORE TO PREDICT PATHOLOGICAL STAGE IN MEN WITH LOCALIZED PROSTATE CANCER

ALAN W. PARTIN,* JOHN YOO, H. BALLENTINE CARTER, JAY D. PEARSON, DANIEL W. CHAN, JONATHAN I. EPSTEIN AND PATRICK C. WALSH

From the Departments of Urology, Pathology and Laboratory Medicine, The Johns Hopkins University School of Medicine and the James Buchanan Brady Urological Institute, The Johns Hopkins Hospital and The Longitudinal Studies Branch of the Gerontology Research Center, National Institute on Aging, Baltimore, Maryland
<table>
<thead>
<tr>
<th>PSA Range (ng/mL)</th>
<th>Pathologic Stage</th>
<th>2–4</th>
<th>5–6</th>
<th>3 + 4 = 7</th>
<th>4 + 3 = 7</th>
<th>8–10</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–2.5</td>
<td>Organ confined</td>
<td>95 (89–99)</td>
<td>90 (88–93)</td>
<td>79 (74–85)</td>
<td>71 (62–79)</td>
<td>66 (54–76)</td>
</tr>
<tr>
<td></td>
<td>Extraprostatic extension</td>
<td>5 (1–11)</td>
<td>9 (7–12)</td>
<td>17 (13–23)</td>
<td>25 (18–34)</td>
<td>28 (20–38)</td>
</tr>
<tr>
<td></td>
<td>Seminal vesicle (+)</td>
<td>—</td>
<td>0 (0–1)</td>
<td>2 (1–5)</td>
<td>2 (1–5)</td>
<td>4 (1–10)</td>
</tr>
<tr>
<td></td>
<td>Lymph node (+)</td>
<td>—</td>
<td>—</td>
<td>1 (0–2)</td>
<td>1 (0–4)</td>
<td>1 (0–4)</td>
</tr>
<tr>
<td>2.6–4.0</td>
<td>Organ confined</td>
<td>92 (82–98)</td>
<td>84 (81–86)</td>
<td>68 (62–74)</td>
<td>58 (48–67)</td>
<td>52 (41–63)</td>
</tr>
<tr>
<td></td>
<td>Extraprostatic extension</td>
<td>8 (2–18)</td>
<td>15 (13–18)</td>
<td>27 (22–33)</td>
<td>37 (29–46)</td>
<td>40 (31–50)</td>
</tr>
<tr>
<td></td>
<td>Seminal vesicle (+)</td>
<td>—</td>
<td>1 (0–1)</td>
<td>4 (2–7)</td>
<td>4 (1–7)</td>
<td>6 (3–12)</td>
</tr>
<tr>
<td></td>
<td>Lymph node (+)</td>
<td>—</td>
<td>—</td>
<td>1 (0–2)</td>
<td>1 (0–3)</td>
<td>1 (0–4)</td>
</tr>
<tr>
<td>4.1–6.0</td>
<td>Organ confined</td>
<td>90 (78–98)</td>
<td>80 (78–83)</td>
<td>63 (58–68)</td>
<td>52 (43–60)</td>
<td>46 (36–56)</td>
</tr>
<tr>
<td></td>
<td>Extraprostatic extension</td>
<td>10 (2–22)</td>
<td>19 (16–21)</td>
<td>32 (27–36)</td>
<td>42 (35–50)</td>
<td>45 (36–54)</td>
</tr>
<tr>
<td></td>
<td>Seminal vesicle (+)</td>
<td>—</td>
<td>1 (0–1)</td>
<td>3 (2–5)</td>
<td>3 (1–6)</td>
<td>5 (3–9)</td>
</tr>
<tr>
<td></td>
<td>Lymph node (+)</td>
<td>—</td>
<td>—</td>
<td>0 (0–1)</td>
<td>2 (1–3)</td>
<td>3 (1–5)</td>
</tr>
<tr>
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<td>Organ confined</td>
<td>87 (73–97)</td>
<td>75 (72–77)</td>
<td>54 (49–59)</td>
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<tr>
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<td>&gt;10.0</td>
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<td>80 (61–95)</td>
<td>62 (58–64)</td>
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<td>27 (21–34)</td>
<td>22 (16–30)</td>
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<td>12 (9–17)</td>
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</tbody>
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Key: PSA = prostate-specific antigen.

*Clinical Stage T1c (nonpalpable, PSA elevated)*
### TABLE I. Clinical Stage T1c (nonpalpable, PSA elevated)

<table>
<thead>
<tr>
<th>PSA Range (ng/mL)</th>
<th>Pathologic Stage</th>
<th>Gleason Score</th>
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<tbody>
<tr>
<td></td>
<td>2-4</td>
<td>5-6</td>
</tr>
<tr>
<td>0-2.5</td>
<td>95 (89-99)</td>
<td>90 (88-93)</td>
</tr>
<tr>
<td>Extraprostatic extension</td>
<td>5 (1-11)</td>
<td>9 (7-12)</td>
</tr>
<tr>
<td>Seminal vesicle (+)</td>
<td>1 (0-1)</td>
<td>2 (1-5)</td>
</tr>
<tr>
<td>2.6-4.0</td>
<td>84 (81-86)</td>
<td>68 (62-74)</td>
</tr>
<tr>
<td>Seminal vesicle (+)</td>
<td>15 (13-18)</td>
<td>27 (22-33)</td>
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<td>4 (2-7)</td>
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<tr>
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<td></td>
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<td>32 (27-36)</td>
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Key: PSA = prostate-specific antigen.
Identification of patients who did not need treatment.

• At autopsy, 50% of men will be found to have microscopic foci of prostate cancer that would never be of clinical significance.

• The next step was to identify which patients diagnosed with cancer did not need treatment?
Pathologic and Clinical Findings to Predict Tumor Extent of Nonpalpable (Stage T1c) Prostate Cancer

Jonathan I. Epstein, MD; Patrick C. Walsh, MD; Marné Carmichael; Charles B. Brendler, MD

• Non-palpable
• Good Pathology: < 3 cores and < 50% any core and < Gleason 7
• Correction for inadequate sampling: PSA less than 15% of the prostate volume.
• These criteria are used today to identify men with very low risk disease who are candidates for active surveillance, which represents 40% of US men diagnosed with the disease.
Impact on Research

• These are just a few of the hundreds of important clinical discoveries that resulted from the availability of surgical specimens.

• However I firmly believe that in the final analysis, the major impact of surgery on reducing death and suffering will conclude

• That the availability of surgical specimens made it possible to understand the fundamental biology of the disease leading to discoveries that made it possible to prevent and cure the disease.
Basic Science Discoveries –
Made possible by the availability of tissue from radical prostatectomies

• Cell lines
• Molecular insight into the role of known genes in initiation and promotion.
  – Methylation of GST\(\pi\)
  – Loss of heterozygosity
  – Hereditary genes
  – Androgen receptor mutations
• Identification of new genes
  – cDNA microarrays
  – Proteomics
The Impact of An Anatomical Approach to Radical Prostatectomy

• Reduction in blood loss
• Improvement in surgical margins
• Preservation of sexual function and continence
• Reduction in cancer deaths as demonstrated in a randomized trial
• Acceleration of research in the field
Acknowledgments

• To all residents, faculty, and support staff, past and present, at Johns Hopkins
• To my patients - who have been my partners in discovery.
• Special thanks to valued collaborators:
Valued Collaborators

- Donald Coffey
- William Isaacs
- Jonathan Epstein
- H.B. Carter
- Alan Partin
- Herb Lepor
- Peter Schlegel
- Matthew Nielsen

- Elizabeth Platz
- William Nelson
- Mario Eisenberger
- Daniel Chan
- Mario Eisenberger
- Deborah Meyers
- Jianfeng Xu
- Angelo DeMarzo
Advice on how to make important discoveries

• If you want to make an important discovery – pick an important problem (Dan Nathans)
• But, don’t work on the most popular current problem. Instead take Einstein’s advice.

Einstein said “The person who follows the crowd will usually go no further than the crowd, but the person who walks alone is likely to find himself in places no one has ever seen before”
How do you find important problems?

• **Listen to your patients** – if they ask you a question you cannot answer or tell you something that sounds incorrect – *this may be your opportunity to find an important problem.*

• If I had not listened to the patient who said he was fully potent following surgery and not wondered why, *I would not be here today telling you this story.*

• If you listen to your patients - *you too can walk alone.*