The 12th Annual Advances in Urology

Controversies in Prostate Cancer

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Disclosures

- None
Good News: Death Rates from Prostate Cancer Falling Dramatically
Age-adjusted death rate in US Men

Age-adjusted death rate in US Men

Bad News: The **Number of Deaths** From Prostate Cancer Will Triple
Bad News: The **Number of Deaths From Prostate Cancer** Will Triple. Why??

- The age at diagnosis for prostate cancer is higher than for any other cancer.
Prostate & Breast Cancer

1999 Age Specific Probability of Diagnosis

Years of Age

Prostate

Breast
Bad News: The Number of Deaths From Prostate Cancer Will Triple

• The age at diagnosis for prostate cancer is higher than for any other cancer.

• Although the death rate from prostate cancer (deaths per 100,000 men) is falling, if there are more older men in the population then there will be more total deaths. And that’s what’s happening.
Bad News: The **Number of Deaths From Prostate Cancer** Will Triple

- The age at diagnosis for prostate cancer is higher than for any other cancer.
- Although the death rate from prostate cancer (deaths per 100,000 men) is falling, if there are more older men in the population then there will be more total deaths. And that’s what’s happening.
- Why are there more older men:
  - Men are living longer
Cause of Death in Men Younger Than 85

Heart Disease

Cancer

Rate per 100,000 Population

Year of Death

1975-2004
• Change in average life expectancy between 1975-2000
  – White men: 69 $\rightarrow$ 76
  – Black men: 64 $\rightarrow$ 73

• Average age at death from prostate cancer: 80

• More men are living long enough to die from the disease
Figure 4. Annual age-adjusted cancer death rates among males for selected cancers, United States, 1930-2005.
Bad News: The Number of Deaths From Prostate Cancer Will Triple

• Age at diagnosis for prostate cancer is higher than for any other cancer.

• Although the death rate from prostate cancer (deaths per 100,000 men adjusted for age) is falling, if there are more older men in the population then there will be more total deaths. And that’s what’s happening.

• Why are there more older men:
  – Men are living longer
  – Baby boomers
The 80 Million Baby Boomers are Aging
Prostate & Breast Cancer
Projected New Cases

# of cases

2002 2005 2010 2015 2025 2045

Prostate
Breast
Prostate & Breast Cancer
Historical and Projected Deaths

Prostate
Breast

The Future

• Over the next 30 years, unless we are able to prevent the disease or cure it better, the number of new cases will double and the number of cancer deaths will triple, exceeding breast cancer.

• Worse. These estimates are based on the current improved survival rates. If the recommendations against PSA testing are widely accepted, the number of deaths from cancer could increase by more than 50%.
Strategy to Reduce Deaths and Suffering (Metastases)

- Primary prevention
- Secondary prevention – early diagnosis and effective treatment
- Improved management of advanced disease
Strategy to Reduce Deaths and Suffering (Metastases)

• Primary prevention
Strategy to Reduce Deaths and Suffering (Metastases)

• Primary prevention
  – Chemoprevention
  – Lifestyle changes
Rationale for Chemoprevention of Prostate Cancer

- Because prostate cancer is most common in older men, if it were possible to just delay its onset, this would reduce death and suffering.
Chemoprevention

• Antioxidants:
  – Selenium - no effect
  – Vitamin C - no effect
  – Vitamin E – no decrease but instead a 17% increase in the diagnosis of cancer

In men with high baseline selenium levels: selenium supplementation increased high grade disease by 91%.

In men with low baseline selenium levels: vitamin E supplementation increased total prostate cancer risk 63% and high grade disease 111%.

Conclusion: do not recommend vitamin E or selenium supplementation for prevention.
Chemoprevention

• Unfortunately, today there is no pill that will prevent the disease! That includes selenium, Vitamin E, Vitamin C, zinc, serenoa repens, and multivitamins
Chemoprevention

• Multivitamins:
  – Do not prevent the disease
  – They make it worse! Men who take more than one vitamin pill a day have an increased risk of being diagnosed with advanced prostate cancer and dying from it.

Lawson KA et al.; JNCI 2007; 99:754
Role of 5-alpha reductase inhibitors (5-ARIs) In Prostate Cancer Chemoprevention
PCPT: What We Have Been Told

Prostate Cancer Prevention Trial

• Finasteride reduces the risk of prostate cancer by 25%
• The increase in high grade disease is an artifact
• We should offer it to men over the age of 55 years for prevention.
• Is all this true?
On Dec 1, 2010 the FDA reviewed the use of finasteride for prevention of prostate cancer.

The FDA reanalyzed the PCPT data and found that in the first 7 years, men who were biopsied because of an abnormal PSA/DRE (as would occur in the clinical setting) finasteride reduced the risk of cancer by only 14% and all of this reduction could be explained by the fact that 15% of the men on finasteride refused to undergo their indicated biopsy. In men who underwent their indicated biopsy, there was no reduction.
• Thus, finasteride does not prevent prostate cancer; it only prevents men from knowing whether they have it.

• These men are fooled by their low PSA level into believing that their cancer has been prevented. They interpret it as if they were on a statin. “Look, my PSA has fallen 50%! My cancer has been prevented”.

• 5-ARIs do not prevent cancer – they just prevent men from undergoing biopsies.
The FDA also rejected the claim that the increase in Gleason 8-10 tumors was caused by prostate shrinkage or the improved ability of PSA to find it.

They concluded that the increase in high grade disease was real.
FDA Summary

• NNT: if 200 men were treated there would be a reduction of 3 men with small Gleason 6 tumors and an increase in 1 with Gleason 8-10 disease.

• Chemoprevention is administered to otherwise healthy individuals. Therefore, it must be risk free.

• The package inserts for Proscar and Avodart explicitly state that these drugs are not to be used for prevention – if they are prescribed for this purpose this is not an off label use – it is an against label use.
The Future: Search for root causes using genetic approaches

• Based on studies of twins, we know that 50% of the risk of prostate cancer is genetic and 50% is environmental.

• With recently developed high-throughput sequencing it should be possible to define the inherited genetic factors.

• Once explored, these leads may provide new approaches to prevention.

• Once we define genetic risk, it may be possible to dissect out the environmental factors that modify these genetic influences.
Strategy to Reduce Deaths and Suffering (Metastases)

• Primary prevention
  – Chemoprevention
  – Lifestyle changes
What Can We Tell Our Patients?

Lifestyle Changes

• Maintain a healthy weight through dietary restriction and exercise. Obesity is the number one cause of aggressive life threatening disease.
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Lifestyle Changes

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• **Eat** more fruits, vegetables, whole grains, fish
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• Avoid red meat, processed meat with preservatives (deli meats, bacon), charred meat and chicken (PhIP), refined sugars
What Can We Tell Our Patients?
Lifestyle Changes

• Maintain a healthy weight through dietary restriction and exercise. Obesity is the number one cause of aggressive life threatening disease.

• Avoid red meat, processed meat with preservatives (deli meats, bacon), charred meat and chicken(PhIP), refined sugars

• Stop smoking!! Smoking at the time of diagnosis increases the risk of advanced disease and dying from it.
Strategy to Reduce Deaths and Suffering (Metastases)

• Primary prevention

• Secondary prevention – early diagnosis and effective treatment
PSA testing saves few lives and leads to risky and unnecessary treatments for large numbers of men.

Study: Surgery for early prostate cancer doesn't save lives

Healthy men don’t need PSA testing for prostate cancer, panel says
Are the basic concepts obsolete?

- Patients are being told that early diagnosis and treatment have too many side effects, are ineffective, and are unnecessary.

- The very foundations for reducing deaths from prostate cancer are being seriously challenged.

- What should we be telling them?
Future of Cancer Care: Bert Vogelstein - 2013

• Vogelstein is a pioneer in cancer genomics and the world’s most cited scientist.
Future of Cancer Care: Bert Vogelstein - 2013

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- He is skeptical of scientists who talk about cures. “What we should be thinking about first is detecting and preventing cancer at a stage when it can be cured by conventional means”. 
Future of Cancer Care: 
Bert Vogelstein - 2013

- Vogelstein is a pioneer in cancer genomics and the world’s most cited scientist.
- He is skeptical of scientists who talk about cures. “What we should be thinking about first is detecting and preventing cancer at a stage when it can be cured by conventional means”.
- “I think 50 years from now, three-quarters of cancer deaths will be gone. That’s a realistic estimate, and I think most of that decrease will come from better prevention and early diagnosis, and the rest will come from better therapies.”
Early Diagnosis and Treatment

• **PSA Testing** – does it save lives and what is the American Urological Association saying?

• **Surgery** – does it save lives? Comparison of trials of radical prostatectomy versus watchful waiting - PIVOT versus Scandinavian SPCG-4.
PSA Controversy

Benefits
- Long-term
  - ↓ Metastasis
  - ↓ Mortality

Harms
- Short-term
  - Unnecessary biopsies
  - Overdiagnosis
  - Overtreatment
In medicine there are *always* two things that we should *never* say – always and never!
In medicine there are **always** two things that we should **never** say – always and never!

- Does PSA testing save lives?
  Yes and no.
- Can PSA testing do more harm than good?
  Yes and no.
- What is the difference? The viewpoint:
  - **Public Heath** - where the word PSA **screening** refers to populations.
  - **Patient Care** - where the word PSA **testing** refers to individuals.
In medicine there are always **always** two things that we should **never** say – always and never!

- Does PSA testing save lives? Yes
## Impact of PSA Testing on Clinical Stage at Diagnosis

<table>
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<th>Stage</th>
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<tr>
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Impact of PSA Testing on Clinical Stage at Diagnosis

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<td></td>
<td>1 out of 5</td>
<td>1 out of 25</td>
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Stage-specific incidence/100,000 men

The Prostate Cancer Conundrum Revisited

Treatment Changes and Prostate Cancer Mortality Declines

Cancer 2012

Ruth Etzioni, PhD; Roman Gulati, MS; Alex Tsodikov, PhD; Elisabeth M. Wever, MS; David F. Penson, MD; Eveline A. M. Heijnsdijk, PhD; Jeffrey Katcher, BS; Gerrit Draisma, PhD; Eric J. Feuer, PhD; Harry J. de Koning, PhD; and Angela B. Mariotto, PhD

Local and Distant PSA levels over time.
Effect of Three Decades of Screening Mammography on Breast-Cancer Incidence

Archie Bleyer, M.D., and H. Gilbert Welch, M.D., M.P.H.
Age-adjusted death rate in US Men

Age-adjusted death rate in US Men

Decline in deaths from prostate cancer since 1990

• If you apply the age-adjusted death rate of 39/100,000 in 1990 to the year 2007, if there had been no PSA testing nor improvement in treatment there would have been 59,000 deaths from prostate cancer.

• Instead in 2007 there were 35,000 and in 2013 29,700. If screening does not save lives why are there so many fewer deaths?
Change in Mortality from All Cancers in the U.S. between 1993 and 2003

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

Decrease | Increase
In medicine there are **always** two things that we should **never** say – always and never!

- Does PSA testing save lives? Yes and **no**.
In randomized trials PSA screening has had minimal/no effect
In randomized trials PSA screening has minimal/no effect

- **PLCO** (severely flawed for many reasons including 86% of controls had PSA testing) – no effect.
- **ERSPC** – 20% reduction in death from prostate cancer but to achieve this positive effect 1000 men must be screened to reduce one death.

- What’s the problem? Both studies are based on mortality at 10 years.
Why is 10 years of follow-up too short?

• It is generally understood that screening and treatment are not indicated in men with a life span of 10 years or less? Why?
Why is 10 years of follow-up too short?

- It is generally understood that screening and treatment are not indicated in men with a life span of 10 years or less? Why?

- Most men who die from prostate cancer within 10 years of diagnosis did not have curable disease at diagnosis and would not benefit from screening.
Why is 10 years of follow-up too short?

• It is generally understood that screening and treatment are not indicated in men with a life span of 10 years or less? Why?

• Most men who die from prostate cancer within 10 years of diagnosis did not have curable disease at diagnosis and would not benefit from screening.

• Most men with curable disease who are left untreated do not die from prostate cancer within 10 years.
Most men with curable disease who are untreated do not die within 10 years

- Observational study of 223 men with early, low-risk prostate cancer –
  - 47% non-palpable,
  - 66% Grade 1 and 15% Grade 2
- Followed expectantly for 30 years without initial treatment. Hormonal therapy administered at progression.
Most men with curable disease who are untreated do not die within 10 years.
Most men with curable disease who are untreated do not die within 10 years. If prostate cancer mortality is used as the end-point, the follow-up must be ≥ 20 years.
In medicine there are always two things that we should never say – always and never!

- Does PSA testing save lives?
  Yes and no.
- Can PSA testing do more harm than good?
The American Urological Association guideline on PSA testing takes the Public Health approach looking at population testing and does not separate screening from the side effects of treatment.

It is based on the premise that the current practice of widespread testing is doing more harm than good because of over diagnosis and overtreatment.

The new guideline is directed at men at average risk.
Today more men with low risk disease are being diagnosed.
However most of these low risk men are being treated aggressively.
However most of these low risk men are being treated aggressively: 1994 - 2007

Cooperberg J Clin Oncol 2010; 28: 1117-23
AUA Guideline - 2013

- The strongest evidence for screening is in men aged 55 to 69 years.
AUA Guideline - 2013

- The strongest evidence for screening is in men aged 55 to 69 years.

- “Screening may only occur after shared decision-making based on a man’s values and preferences weighing the benefits of preventing prostate cancer mortality in 1 man for every 1,000 men screened over a decade against the known potential harms associated with screening and treatment.”
• The strongest evidence for screening is in men aged 55 to 69 years.

• “Screening may only occur after shared decision-making based on a man’s values and preferences weighing the benefits of preventing prostate cancer mortality in 1 man for every 1,000 men screened over a decade against the known potential harms associated with screening and treatment”.

• The “benefit” doesn’t make any sense because men with a 10 year life span should not be tested at all! The benefit is grossly understated!
The Panel does not recommend routine screening in men between ages 40 to 54 years at average risk. For men younger than age 55 years at higher risk (e.g. positive family history or African American race), decisions should be individualized.
The Panel does not recommend routine screening in men between ages 40 to 54 years at average risk.

There is no information for or against testing at this age and for men in their forties, a single baseline PSA is useful in risk stratification.

The new NCCN guidelines recommend initiating screening at age 45.

AUA Guideline - 2013

• The Panel does not recommend routine PSA screening in men over age 70 years or any man with less than a 10 to 15 year life expectancy. Some men over age 70 years who are in excellent health may benefit.
AUA Guideline - 2013

- The Panel does not recommend routine PSA screening in men over age 70 years or any man with less than a 10 to 15 year life expectancy. Some men over age 70 years who are in excellent health may benefit.

- **The cutoff at age 70 needs to be revisited.**
  - 50% of deaths from prostate cancer occur in men who are diagnosed after age 75 (Scosyev et al Cancer 2012;118:3062)
  
  - 9 years after stopping PSA testing the incidence of potentially lethal cancers equals that of nonscreened men. (Bergdahl et al. Eur Urol 2013; Epub May 8, 2013)
<table>
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<th>AGE</th>
<th>Ave. Lifespan</th>
<th>&lt; 25&lt;sup&gt;th&lt;/sup&gt; Percentile in Health</th>
<th>&gt; 75&lt;sup&gt;th&lt;/sup&gt; Percentile in Health</th>
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<td>60 years</td>
<td>20 years</td>
<td>10 years</td>
<td>30 years</td>
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<td>65</td>
<td>17</td>
<td>9</td>
<td>26</td>
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<td>70</td>
<td>14</td>
<td>7</td>
<td>21</td>
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<tr>
<td>75</td>
<td>10</td>
<td>5</td>
<td>15</td>
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Prostate Specific Antigen Testing Among the Elderly—When To Stop?

Edward M. Schaeffer,* † H. Ballentine Carter,‡ Anna Kettermann,‡ Stacy Loeb,‡ Luigi Ferrucci,‡ Patricia Landis,‡ Bruce J. Trock‡ and E. Jeffrey Metter‡
Material and Methods

• BLSA longitudinal cohort study of 849 men:
  – 122 with
  – and 727 without prostate cancer
*None of the 154 men who had a PSA < 3 ng/ml at age 75 died of prostate cancer and only 1 man developed high risk disease but did not die of the disease; his PSA was 2.9 ng/ml at age 75.*
Conclusion Men with a PSA less than 3ng/ml at age 75-80 years are unlikely to die from or develop aggressive prostate cancer during their remaining life, suggesting that PSA testing might be safely discontinued for these men.
My approach to PSA testing

- **Who should be tested** – men with a 10-15 year lifespan who do not want to die from prostate cancer.

- **What can we as urologists do to improve screening?**
  
  
  – Avoid screening in men with a limited lifespan
  – Avoid treatment in men who do not need it.
  – Refer men who need treatment to high-volume centers so that the risk of treatment-related complications is reduced.
Early Diagnosis and Treatment

• PSA Testing – does it save lives and what is the AUA saying?

• Comparison of trials of radical prostatectomy versus watchful waiting - PIVOT versus Scandinavian SPCG-4.
Today’s Talk

• There is no better way to cure a cancer that is confined to the prostate than total surgical removal. But, does surgery save lives – conflicting information.

• Trials of radical prostatectomy versus watchful waiting -
  – Scandinavian SPCG-4 - YES
  – PIVOT – NO

• What is the true answer.
Radical Prostatectomy Reduces Prostate Cancer Deaths and Improves Overall Survival*

- **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 following randomization:
  - mean 18 years.
<table>
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<th>Metastases</th>
<th>Deaths From Any Cause</th>
<th>Deaths From Cancer</th>
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<tr>
<td><strong>All</strong></td>
<td>43%</td>
<td>39%</td>
<td>44%</td>
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<td><strong>&lt; 65 years of age</strong></td>
<td>49%</td>
<td>50%</td>
<td>55%</td>
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<tr>
<td><strong>Low risk</strong></td>
<td>57%</td>
<td>43%</td>
<td>46%</td>
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Relative Reduction at 18 years
Results in Men < 65 years at Randomization

Overall mortality

Cancer Deaths

= Watchful waiting men < 65 yo
Age-adjusted death rate in US Men

Nerve-sparing radical prostatectomy

Lung

PSA Testing

Colon
How can we be certain that surgery is responsible for this decline in mortality 1994-2003?
What about improvement in the management of metastatic disease?
What about improvement in the management of metastatic disease?

Conclusion: improvements in survival of men with metastatic disease have not contributed to the observed drop in mortality in the PSA era.
How can we be certain that surgery is responsible for this decline in mortality 1994-2003?

• Surgery was the most common form of treatment for men with localized prostate cancer during this era.
How can we be certain that surgery is responsible for this decline in mortality 1994-2003?

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

• By 1993, 70% of men in their 50s and 55% of men in their 60s underwent surgery. Why?

• More candidates with localized disease; less blood loss; 30 day mortality fell from 2.0% to 0.2%; continence rates were improved; and it was possible to preserve sexual function.

• And one decade later …
How can we be certain that surgery is responsible for this decline in mortality 1994-2003?

• Radiation was too underpowered to cure
  – 1970 -1990’s: limited dose (65-70 GY) 2 D
  – Dose escalation; better targeting; adjuvant hormonal therapy came later:
    • Late 1990s: 3D: (70-75 Gy)
    • 2004-07: IMRT (≥ 75 Gy)
    • 2005-09: IGRT (image guided)
    • 2000: neoadjuvant and adjuvant hormonal therapy for higher risk patients.
After 15 years of follow-up, there were 568 deaths, including 104 from PC. RP was associated with statistically significant advantages for overall (hazard ratio [HR] = 0.60, 95% confidence interval [CI] = 0.53 to 0.70, \( P < .0001 \)) and disease-specific mortality (HR = 0.35, 95% CI = 0.26 to 0.49, \( P < .0001 \)). Mortality benefits for RP were also observed within treatment propensity quintiles, when subjects were pair-matched on propensity scores, and in subgroup analyses based on age, tumor characteristics, and comorbidity.
Comparative effectiveness of radical prostatectomy and radiotherapy in prostate cancer: observational study of mortality outcomes 1996-2009; Sweden

Cancer-specific survival

<table>
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<th>Study</th>
<th>Risk group 1</th>
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<tr>
<td></td>
<td>All</td>
<td>Age &lt;64</td>
<td>Age ≥65</td>
<td>Charlson comorbidity index score 0</td>
<td>Charlson comorbidity index score ≥1</td>
<td>All</td>
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<tr>
<td>Favors: Radiotherapy</td>
<td>1.91 (1.16 to 3.14)</td>
<td>1.92 (0.96 to 3.82)</td>
<td>1.87 (0.94 to 3.69)</td>
<td>1.67 (0.93 to 2.99)</td>
<td>2.91 (0.88 to 9.59)</td>
<td>1.77 (1.37 to 2.29)</td>
</tr>
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BMJ 2014; 348
Sooriakumaran et al
The PIVOT trial (a randomized trial of surgery versus observation) concluded “radical prostatectomy did not significantly reduce all-cause or prostate cancer mortality, as compared with observation.”
Underpowered: although planned for 2000 healthy men with at least a 10 year lifespan, it actually recruited only 731 men and at 10 years 50% of these men were dead from other causes and at 14 years only 30% were still alive.
PIVOT
Prostate Cancer Intervention versus Observation Trial

• Underpowered: although planned for 2000 healthy men with at least a 10 year lifespan, it actually recruited only 731 men and at 10 years 50% of these men were dead from other causes and at 14 years only 30% were still alive.

• Although there was no reduction in deaths from prostate cancer in men with low risk disease at 10 years (something we have known for 30 years)
PIVOT
Prostate Cancer Intervention versus Observation Trial

• Underpowered: although planned for 2000 healthy men with at least a 10 year lifespan, it actually recruited only 731 men and at 10 years 50% of these men were dead from other causes and at 14 years only 30% were still alive.

• Although there was no reduction in deaths from prostate cancer in men with low risk disease at 10 years (something we have known for 30 years)

• There was a 60% decrease in metastases and a 40% reduction in cancer deaths in men with PSA > 10.
Yet the *New York Times* reported: “A new study shows that prostate cancer surgery, which often leaves men impotent or incontinent, does not appear to save the lives of men with early stage disease, who account for most of the cases, and many of these men would do just as well to choose no treatment at all.”
• Why were the results so different? The absolute results were different because there were fewer deaths in PIVOT – but the relative benefit was similar.

• “PIVOT should not be interpreted as evidence that RP is not efficacious in reducing prostate cancer mortality”
PIVOT: Summary

Prostate Cancer Intervention versus Observation Trial

- What did the authors actually do? They randomized older sick men who should have been observed to surgery, not healthy men who were candidates for surgery to observation.

- What should the authors have concluded?

- For the man with a life expectancy of 10 years or less who has low-volume disease, surgery is not an option.

- This study provides no useful information for a healthy man in his 40s, 50s, and early 60s. Unfortunately, most men and their general doctors do not understand this.
Summary

- There is no better way to cure a cancer that is confined to the prostate than total surgical removal. **But, does surgery save lives?**
- **Yes,** if the patient is diagnosed at a curable stage and lives long enough to be at risk for dying from the disease.
- **No** – in men with low risk disease who are too old or ill to live >10 years.
- In the patients who need it the most, healthy men with a 10-15 year life span who have intermediate/high risk disease, radical prostatectomy saves lives.
Strategy to Reduce Deaths and Suffering (Metastases)

- Primary prevention
- Secondary prevention – early diagnosis and effective treatment
- Improved management of advanced disease
Strategy to Reduce Deaths and Suffering (Metastases)

- Primary prevention
- Secondary prevention – early diagnosis and effective treatment
- Improved management of advanced disease
  - Radical prostatectomy in advanced disease
Radical Prostatectomy in Advanced Disease: Rationale

Patrick C. Walsh, M.D.
Journal Club January 30, 2014
Background: confession?

- I was always taught “big operations for little cancers and little operations for big cancers”. In other words, you only operated on patients that you thought were curable.

- The goal of the Partin tables was to refine the prediction of curability to optimize the selection of the ideal surgical candidate.
Recognizing the morbidity of the procedure, it seemed reasonable to operate only on patients where the chances of cure were high – but I was often criticized for only operating on highly selected cases – maybe the critics were right.

What about surgery in men with high-grade disease?
Preoperative characteristics of high-Gleason disease predictive of favourable pathological and clinical outcomes at radical prostatectomy

Phillip M. Pierorazio, Ashley E. Ross, Brian M. Lin, Jonathan I. Epstein, Misop Han, Patrick C. Walsh, Alan W. Partin, Christian P. Pavlovich and Edward M. Schaeffer
Evidence that treatment of the primary lesion is of benefit in advanced disease

• Even if it doesn’t cure!
Evidence that treatment of the primary lesion is of benefit in advanced disease

• In the SPCG-4 randomized trial of RP versus WW, the greatest benefit of surgery in reducing mortality and metastases was in young patients with high grade disease.

• This provides strong support for using maximal efforts to eliminate the primary lesion.

Evidence that treatment of the primary lesion is of benefit in advanced disease

• In locally advanced disease, treatment with ADT + radiation improves survival over ADT alone

Deaths From Prostate Cancer

ADT alone vs ADT + Radiation

Widmark A. Lancet 2009;373:301
Evidence that treatment of the primary lesion is of benefit in advanced disease

- In LN+ disease, men who undergo radical prostatectomy have improved survival over patients where the primary tumor was left in place.

Engel J Eur Urol 2010; 57:754
Why?

• In 1889 Paget proposed the seed and soil theory. Tumor cells (seeds) will selectively colonize in organs with favorable environment (soil).

• Preparing the “soil”: the premetastatic niche. Kaplan was the first to show that the initial event at the metastatic niche is not the arrival of tumor cells but of bone-marrow derived cells (BMDCs), which alter the microenvironment making it more receptive to tumor colonization.

• There is recent evidence that endocrine factors released by the primary tumor are responsible for their recruitment. Kaplan et al Cancer Res 2006;66:11089
Prostate Radiotherapy for Men with Metastatic Disease: A New Comparison in the STAMPEDE Trial
Prostate Radiotherapy for Men with Metastatic Disease: A New Comparison in the STAMPEDE Trial1

• In men with newly diagnosed M1 disease, a randomized trial of ADT vs. ADT +RT to prostate. Hypothesis: local radiotherapy to the primary tumor may retard distant disease progression and prolong survival in patients.

• But what about the role of surgery? Zelefsky et al showed that men with negative biopsies following radiation have improved survival over patients with positive biopsies and that radiation in doses of 81 Gy may not always be sufficient to completely eradicate local tumor.

Zelefsky J Clin Oncol 2010;28:1508
Cancer-specific Survival After Metastasis Following Primary Radical Prostatectomy Compared with Radiation Therapy in Prostate Cancer Patients: Results of a Population-based, Propensity Score-Matched Analysis  

Eur Urol; Epub May 21, 2013

(b)  

CSS in M1 disease in men who had prior surgery versus radiation
Using a propensity score-matched analysis this recent provocative paper suggests that in high risk patients who developed metastatic disease, men who had primary surgery had better PCSS than men who received primary radiation.
Surgery in advanced disease.

- Complete elimination of the primary lesion may improve survival in men with advanced disease even though it may not be curative. Is surgery more effective in some of these men?

- For this reason, biochemical and metastasis free survival may underestimate the ultimate value of any primary treatment to the prostate.
Strategy to Reduce Deaths and Suffering (Metastases)

• Primary prevention
• Secondary prevention – early diagnosis and effective treatment

• Improved management of advanced disease
  – Radical prostatectomy in advanced disease
  – Timing of salvage androgen deprivation - Early, Late, or Intermittent?
Who is a candidate for **salvage** hormonal therapy?

- Rising PSA following **radical prostatectomy**:
Who is a candidate for **salvage hormonal therapy**?

- Rising PSA following **radical prostatectomy**:
  - Who fail adjuvant or salvage radiation
  - Or who are too old/ill for radiation
  - Or who have **positive lymph nodes**
Who is a candidate for **salvage hormonal therapy**?

- Rising PSA following radical prostatectomy:
  - Who fail adjuvant or salvage radiation
  - Or who are too old/ill for radiation
  - Or who have positive lymph nodes

- Rising PSA following **definitive radiation therapy**, with or without attempt at local salvage therapy.
Who is a candidate for salvage hormonal therapy?

• Rising PSA following radical prostatectomy:
  – After failure of adjuvant or salvage radiation
  – Or in men who are too old/ill for radiation
  – Or in men with positive lymph nodes

• Rising PSA following definitive radiation therapy, with or without attempt at local salvage therapy.

• Today’s talk – when should hormonal therapy be initiated – early, intermittent, delayed?
Advantage of Immediate Hormonal Therapy
Advantage of Immediate Hormonal Therapy

- Your patient believes that he is doing something!
Advantage of Immediate Hormonal Therapy

• Your patient believes that he is doing something!

• *Delay in the time to the development of metastases.* However at that time, because patients have castration resistant disease, it does not prolong survival.
Disadvantage of Immediate Hormonal Therapy
Disadvantage of Immediate Hormonal Therapy

• Prolonged exposure to side effects
  – Hot flashes
  – Decreased bone mineral density
  – Decline in sexual function
  – Decreased muscle mass
  – Increased adiposity, serum lipid profile, fasting glucose $\rightarrow$ cardiovascular risk factors
  – Cognitive and mood change
  – Anemia
  – Gynecomastia
Advantage of intermittent androgen deprivation.
Advantage of **intermittent** androgen deprivation.

- Less exposure to the side effects of ADT
Advantage of **intermittent** androgen deprivation.

- Less exposure to the side effects of ADT
- The possibility that it may **prolong the time to androgen independent disease**. Data from animal models conflicting:
  - Trachtenberg – No. (J Urol 1987; 137:785)
  - Russo – No (Cancer Res 1987;47:5967)
  - Goldenberg – Yes (Cancer 1993; 71: 2782)
Advantage of intermittent androgen deprivation.

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  - Trachtenberg – No. (J Urol 1987; 137:785)
  - Russo – No (Cancer Res 1987;47:5967)
  - Goldenberg – Yes (Cancer 1993; 71: 2782)

- It became popular: medical oncologists had something to offer; patients liked fewer side-effects; drug companies loved it! Is it better?
Intermittent Androgen Suppression for Rising PSA after Radiotherapy  Crook et al. (NEJM 2012;367:10)

• At last we have an answer.
Intermittent Androgen Suppression for Rising PSA after Radiotherapy  Crook et al. (NEJM 2012;367:10)

• At last we have an answer.
• In a randomized trial, continuous versus intermittent androgen deprivation (IAD) resulted in identical overall survival.
Intermittent Androgen Suppression for Rising PSA after Radiotherapy  Crook et al. (NEJM 2012;367:10)

- At last we have an answer.
- In a randomized trial, continuous versus intermittent androgen deprivation (IAD) resulted in identical overall survival.
- Although men on IAD experienced a substantial decrease in exposure to hormonal therapy.
  - There was no delay in the development of androgen independence and
  - Only 29% of men who were potent at baseline had recovery of potency.
Intermittent versus Delayed

• This study clearly demonstrates that IAD achieves similar cancer control with fewer side effects than continuous treatment.
Intermittent versus Delayed

• This study clearly demonstrated that IAD achieves similar cancer control with fewer side effects than continuous treatment.

• However, because it did not delay the emergence of castrate-resistant disease and did not preserve sexual function in the vast majority of patients.

• Why not just delay the initiation of hormonal therapy in men with biochemical failure following primary treatment?
VACURG Study I: Early Orchiectomy vs Late Rx

Walsh, PC J Urol 166: 508-516, 2001
Delayed Hormonal Therapy

• 450 men with PSA recurrence following surgery at Hopkins, where treatment with hormonal therapy was delayed until the bone scan was positive.
### Immediate vs Delayed ADT

**Overall Survival**

<table>
<thead>
<tr>
<th>Study or Subcategory</th>
<th>Immediate ADT (n/N)</th>
<th>Deferred ADT (n/N)</th>
<th>RR (random); 95% CI</th>
<th>Weight</th>
<th>RR (random); 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>01 Untreated</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Byer VACURG 1</td>
<td>413/469</td>
<td>438/484</td>
<td>31.30</td>
<td>0.97</td>
<td>(0.93 to 1.02)</td>
</tr>
<tr>
<td>Kirk MRC PR03</td>
<td>434/469</td>
<td>438/469</td>
<td>43.43</td>
<td>0.99</td>
<td>(0.96 to 1.03)</td>
</tr>
<tr>
<td>Studer SAKK 98-08</td>
<td>87/96</td>
<td>85/92</td>
<td>9.68</td>
<td>0.98</td>
<td>(0.90 to 1.07)</td>
</tr>
<tr>
<td>Studer EORTC 30891</td>
<td>257/492</td>
<td>284/493</td>
<td>5.87</td>
<td>0.91</td>
<td>(0.81 to 1.02)</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>1,526</td>
<td>1,538</td>
<td>96.27</td>
<td>0.96</td>
<td>(0.95 to 1.01)</td>
</tr>
<tr>
<td><strong>Total events:</strong></td>
<td>1191</td>
<td>1245</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for heterogeneity:</strong> ( \chi^2 = 3.64 (P = .30) ) ( \chi^2 = 177 % )</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect:</strong> ( z = 1.46 (P = .14) )</td>
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<td></td>
</tr>
<tr>
<td><strong>02 N+ Postsurgery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Messing ECOG</td>
<td>17/47</td>
<td>28/51</td>
<td>0.38</td>
<td>0.66</td>
<td>(0.42 to 1.04)</td>
</tr>
<tr>
<td>Schroder EORTC 30846</td>
<td>72/119</td>
<td>71/115</td>
<td>1.86</td>
<td>0.98</td>
<td>(0.80 to 1.20)</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>166</td>
<td>166</td>
<td>2.25</td>
<td>0.85</td>
<td>(0.58 to 1.24)</td>
</tr>
<tr>
<td><strong>Total events:</strong></td>
<td>89 (Immediate ADT), 99 (Deferred ADT)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Test for heterogeneity:</strong> ( \chi^2 = 2.52 (P = .11) ) ( \chi^2 = 60.3 % )</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect:</strong> ( z = 0.86 (P = .39) )</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>03 Bicalutamide</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McLeod EPCP</td>
<td>458/1,114</td>
<td>462/1,170</td>
<td>7.48</td>
<td>1.04</td>
<td>(0.94 to 1.15)</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>1,114</td>
<td>1,170</td>
<td>7.48</td>
<td>1.04</td>
<td>(0.94 to 1.15)</td>
</tr>
<tr>
<td><strong>Total events:</strong></td>
<td>458 (Immediate ADT), 462 (Deferred ADT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for heterogeneity:</strong> not applicable</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Test for overall effect:</strong> ( z = 0.79 (P = .43) )</td>
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</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>2,806</td>
<td>2,874</td>
<td>100.00</td>
<td>0.98</td>
<td>(0.95 to 1.01)</td>
</tr>
<tr>
<td><strong>Total events:</strong></td>
<td>1,738 (Immediate ADT), 1,806 (Deferred ADT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for heterogeneity:</strong> ( \chi^2 = 6.63 (P = .36) ) ( \chi^2 = 9.5 % )</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect:</strong> ( z = 1.33 (P = .18) )</td>
<td></td>
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</tr>
</tbody>
</table>
In metastatic or progressive prostate cancer, immediate versus delayed institution of ADT results in a moderate decrease (17%) in prostate cancer mortality, moderate increase (15%) in non-prostate cancer-specific mortality, and no overall survival advantage.
Comments on Hormonal Therapy

• If early hormonal therapy produces a 17% reduction in prostate cancer mortality isn’t it worthwhile even if there is no improvement in overall survival?
Comments on Hormonal Therapy

• If early hormonal therapy produces a 17% reduction in prostate cancer mortality isn’t it worthwhile even if there is no improvement in overall survival?

• **NO** because the improved cancer-specific survival is an artifact – because hormonal therapy increases death from other causes men do not live long enough to die from their cancer!
Who should receive immediate hormonal therapy?

- Patients who are likely to develop metastases quickly. Who are they?
- Pathologic Gleason score 8-10 or PSADT < 12 months (Studer).
Protocol for Delayed Hormonal Therapy

• Evaluation every 6 months - with history (bone pain), physical exam for local recurrence, serum PSA and creatinine (to evaluate silent ureteral obstruction).

• Bone scan– every 6 – 12 months
25% of bone metastases occurred at PSA levels < 10 ng/ml
Protocol for Delayed Hormonal Therapy

• Evaluation every 6 months - with history (bone pain), physical exam for local recurrence, serum PSA and creatinine (to evaluate silent ureteral obstruction).

• Bone scan – every 6 – 12 months

• **Initiation of hormonal therapy** - if bone scan +, ureteral or urethral obstruction, or rapid *initial* PSADT (< 12 months)

• At that time – continuous or intermittent?
Continuous versus IAD: 1500 patients with metastatic disease.

IAD was associated with better erectile function for only the first 3 months.

Statistically inconclusive: however in this study 10% more men on IAD died of cancer.

In the discussion the authors state “the results suggest that IAD may compromise survival”.

Patients with extensive disease

<table>
<thead>
<tr>
<th>Therapies</th>
<th>No. of Deaths</th>
<th>Median Survival (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous therapy</td>
<td>225</td>
<td>4.4</td>
</tr>
<tr>
<td>Intermittent therapy</td>
<td>252</td>
<td>4.9</td>
</tr>
</tbody>
</table>
E3805
CHAARTED: ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer

Christopher Sweeney, Yu-Hui Chen, Michael Carducci, Glenn Liu, Mario Eisenberger, Yu-Ning Wong, Noah Hahn, Manish Kohli, Robert Dreicer, Nicholas Vogelzang, Joel Picus, Daniel Shevrin, Maha Hussain, Jorge Garcia, Robert DiPaola

ECOG-ACRIN
cancer research group
Reshaping the future of patient care

PRESENTED AT:
ASCO 50th Annual Meeting
Science & Society
E3805 – CHAARTED Treatment

STRATIFICATION

Extent of Mets
- High vs Low

Age
≥70 vs < 70yo

ECOG PS
- 0-1 vs 2

CAB> 30 days
- Yes vs No

SRE Prevention
- Yes vs No

Prior Adjuvant ADT
≤12 vs > 12 months

ARM A:
ADT + Docetaxel
75mg/m2 every 21 days for maximum 6 cycles over 18 weeks

Evaluate every 3 weeks while receiving docetaxel and at week 24 then every 12 weeks

Follow for time to progression and overall survival

Chemotherapy at investigator’s discretion at progression

ARM B:
ADT (androgen deprivation therapy alone)

Evaluate every 12 weeks

• ADT allowed up to 120 days prior to randomization.
• Intermittent ADT dosing was not allowed
• Standard dexamethasone premedication but no daily prednisone

Presented by: Christopher J. Sweeney, MBBS
In patients with high volume metastatic disease, there is a 17 month improvement in median overall survival from 32.2 months to 49.2 months. We projected 33 months in ADT alone arm with collaboration of SWOG9346 team.
Take home messages

• Unless we are able to prevent the disease or cure it better, over the next 30 years:
  
  • The number of new cases of prostate cancer in the U.S. will double and
  
  • The number of deaths from the disease will triple and will exceed breast cancer.
Take home messages

- There is no pill that will prevent prostate cancer. For this reason there is need for new approaches to prevention – new targets based on a better understanding of the root cause.

- Although the application of aggressive screening and effective therapy have achieved a significant reduction in mortality, this has been associated with over diagnosis, over treatment and unnecessary morbidity.
Take home messages

• Regardless, I believe that the AUA Guidelines will benefit from better clarification.

• In men over the age of 75 years, screening should continue only in very healthy men who have a PSA $\geq 3.0$

• In the patients who need it the most, healthy men with a 10-15 year life span who have intermediate/high risk disease, radical prostatectomy saves lives.
Take home messages

• Complete elimination of the primary lesion may improve survival in men with advanced disease even though it may not be curative. Is surgery more effective in some of these men?

• For this reason, biochemical and metastasis free survival may underestimate the ultimate value of any primary treatment to the prostate.
Take home messages

• In men who are candidates for salvage hormonal therapy, delayed therapy is safe, effective, less expensive, and associated with less exposure to hormonal therapy than continuous or IAD.

• In men with high volume metastatic disease, combined treatment with ADT plus Docetaxel provides a 17 month improvement in overall survival.