Prostate Cancer: Radiation Therapy

Jordan Maier, MD
Radiation Oncologist
Karmanos Cancer Center
9/22/12
Prostate Cancer: Overview

- Most common cancer in US men
- Tx decision making:
  - Prostate cancer characteristics: PSA, Biopsy results, (Gleason Score), Exam
  - Patient characteristics: age, other illnesses, lifestyle
- Treatment options: Radiation Therapy, Radioactive seeds, Surgery, Cryotherapy, Hormones
- MDT approach
Karmanos Prostate Cancer Team
Advantages of Radiation Therapy

- Non-invasive
- Similar outcomes to surgery
- Easy to tolerate
- Minimal impact on quality of life
Disadvantages to Radiation Therapy
Disadvantages to Radiation Therapy

- Time commitment
- Irritative symptoms
- Side effects
Keys to Successful Treatment

- Goal: high dose to prostate, spare surrounding normal tissue (i.e., precision)
- Treatment Planning
- Treatment Delivery
- Buzz words: 3D Conformal, IMRT, IGRT
Treatment planning

- Fiducial marker placement
- CT scan + MRI
(molds, tattoos)
Varian IX
Varian IX: advantages

- Features:
  - Rapid Arc: faster, more conformal
  - Daily CBCT for prostate localization: (IGRT) – 3d imaging
Rapid Arc Advantages
Side effects

- **Short term:**
  - bladder irritation: increased frequency
  - rectal irritation: diarrhea
  - fatigue

- **Long term:**
  - erectile dysfunction
  - rectal irritation
Radiation or Surgery: What’s Best For Your Patients?

- No randomized trials comparing the two
- Data comparisons are retrospective
- Decision based on logistics and potential acceptable side effects
- MDT approach
Surgery vs Radiation

- Localized prostate cancer: radiation or surgery?
- Klein EA, Kupelian PA.
- Section of Urology Oncology, Urological Institute, Cleveland Clinic Foundation,
- The treatment of localized prostate cancer remains controversial because of the lack of conclusive well-controlled or randomized studies comparing outcomes of radiotherapy to outcomes of radical prostatectomy. A comparison of different therapies should include issues of cancer control, morbidity, quality of life (QOL), salvage of primary treatment failures, late effects, and cost. The available data suggest that these two modalities provide similar rates of cancer control at 10 years and choice of therapy should be based on toxicity and QOL issues.
**Surgery vs Radiation**

- Biochemical relapse free survival in a multi-institution series of 2991 men treated with prostatectomy, EBRT*, brachytherapy or combined brachytherapy/EBRT.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>BRFS*</th>
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<tbody>
<tr>
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<tr>
<td>EBRT ≥72 Gy</td>
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<td>EBRT &lt;72 Gy</td>
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<td>Brachytherapy</td>
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<td>83</td>
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<tr>
<td>Brachytherapy +EBR</td>
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</tbody>
</table>

BRFS: Biochemical relapse free survival.
* Results were similar in favorable-risk disease and a combined group of intermediate/high-risk disease.

Treatment Strategies for Patients with Advanced Prostate Cancer

Elisabeth I. Heath, MD
Associate Professor of Oncology
Director, Prostate Cancer Research
Karmanos Cancer Institute
Wayne State University School of Medicine
Prostate Cancer 2012

- Many exciting advances in treatment for men with castrate-resistant prostate cancer (CRPC)
- In past 2 years, several new agents have gained FDA approval for CRPC patients
- Inhibition of androgens signaling pathway remains foundation of therapy
- New questions emerging regarding the appropriate sequencing and combination therapy
Prostate Cancer Clinical States Model

- Clinically Localized Disease
- Rising PSA Non-Castrate
- Clinical Metastases: Non-Castrate
- Rising PSA: Castrate
- Clinical Metastases: Castrate
- Death From Other Causes
- Death From Disease

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FDA Approved Agents in Castrate-Resistant Prostate Cancer

- Docetaxel (Sanofi-Aventis)(2004)
- Sipuleucel-T (Dendreon)(2010)
- Cabazitaxel (Sanofi-Aventis)(2010)
- Abiraterone (Janssen Biotech)(2011)
- Enzalutamide (Medivation)(2012)
- Zoledronic Acid (Novartis)(2002)
- Denosumab (Amgen)(2010)
Androgens Drive Prostate Cancer Growth

- Androgens cause prostate epithelial and stromal cells to proliferate through the androgen receptor
- Majority of androgens produced in testes (~90%)
- Adrenal glands secrete ~10% circulating androgens
- Testosterone and dihydrotestosterone (DHT) are two major growth factors in circulation and prostate tissue, respectively
Androgen Biosynthesis

Cholesterol → Cholesterol

Pregnenolone → Progesterone → Corticosterone → Aldosterone

CYP17

17α-OH-pregnenolone → 17α-OH-progesterone → 11-Deoxycortisol → Cortisol

CYP17

DHEA → Androstenedione → Testosterone → DHT

5α-reductase

Estradiol

Mineralocorticoids

Glucocorticoids

Androgens/estrogens

Androgen Deprivation Therapy (ADT)

• Orchietomy

• Medical Castration
  – Gonadotropin-releasing hormone (GnRH) agonists (leuprolide, goserelin)
  – GnRH receptor antagonist (degarelix)
  – Androgen receptor antagonists (bicalutamide, flutamide, nilutamide)

• Medical therapy
  – Estrogen therapy (diethylstilbestrol)
  – Anti-androgen (ketoconazole)

• Intermittent vs Continuous ADT in CSPC (S9346)
  – Intermittent ADT inferior to continuous ADT in patients with minimal disease
  – Intermittent ADT noninferior to continuous ADT in patients with extensive disease

Castrate-Resistant Prostate Cancer

- Hormone-refractory, androgen-independent, castrate-resistant
  - Terms to reflect the concept that serum androgen levels represent androgen levels in prostate tissue
- Prostate cancer capable of de novo androgen synthesis
  - Higher levels of testosterone and DHT in prostate cancer primary and metastatic tissue compared to benign prostate tissue
- Intracrine signaling
  - Low levels of androgen enough for growth due to AR gene mutations, AR gene amplification, ligand-independent activation of AR
- Combined androgen blockade is not enough to prevent tumor progression; need to block third source

Androgen Biosynthesis

Abiraterone acetate targets CYP17 enzyme complex, inhibits androgen biosynthesis in the testes, adrenal glands, and the prostate tumor.

Cholesterol → Pregnenolone → Progesterone → Corticosterone → Aldosterone

17α-OH-pregnenolone → 17α-OH-progesterone → 11-Deoxycortisol → Cortisol

DHEA → Androstenedione → Testosterone → DHT (5α-reductase)

Estradiol

Mineralocorticoids
Glucocorticoids
Androgens/estrogens

Abiraterone Acetate Prolongs Overall Survival

- 1195 patients who previously received docetaxel therapy
- 2:1 randomization
- Abiraterone 1000 mg (797 patients) vs placebo (398 patients) PO daily and prednisone 5 mg PO BID
- Prolonged overall survival by 4 months in men who have metastatic CRPC that had progressed with docetaxel chemotherapy (COU-AA-301)
  - Median follow-up: 12.8 months
  - OS of 14.8 vs 10.9 months; hazard ratio (HR) 0.65; 95% confidence interval (CI), 0.54 to 0.77; P<0.001
  - Prostate-specific antigen (PSA) response rate (29% vs 6%, P<0.001)

Abiraterone Acetate Effective Prior to Chemotherapy

- COU-AA-302, 1088 men received abiraterone vs placebo prior to docetaxel
- Median follow-up 22 months, interim analysis results, abiraterone produced statistically significant improvement in
  - rPFS (HR = 0.43; 95% CI: [0.35, 0.52], p<0.0001)
  - Strong trend in OS (HR = 0.75; 95% CI: [0.61, 0.93], p = 0.0097)
- Secondary endpoints clinically and statistically significant
  - Time to PSA progression (11.1 vs 5.6 months)
  - Time to chemotherapy initiation (25.2 vs 16.8 months)
  - Time to ECOG-PS deterioration (12.3 vs 10.9 months)
  - Time to opiate use (NR vs 23.7 months)

rPFS, radiographic progression-free survival; ECOG-PS, Eastern Cooperative Oncology Group performance status

CYP17 Inhibitors in Prostate Cancer

• Abiraterone use can lead to side effects due to elevated mineralocorticoid levels including
  – Hypertension
  – Hypokalemia
  – Hypophosphatemia
  – Edema

• TAK 700 (orteronel)
  – Phase III orteronel, pre and post chemo
  – Role of concomitant steroids not yet defined

Enzalutamide (MDV3100)

- Androgen receptor signaling inhibitor: Inhibits binding of androgens to AR, AR nuclear translocation, and association of AR with DNA

Enzalutamide Prolongs Survival
AFFIRM Phase III Study

- 1199 men with progressive CRPC who failed docetaxel
- Randomized 2:1
- Enzalutamide 160 mg (800 patients) vs placebo (399 patients) PO daily

**Enzalutamide: 18.4 months**
(95% CI: 17.3, NYR)

**Placebo: 13.6 months**
(95% CI: 11.3, 15.8)

**HR = 0.631 (0.529, 0.752) P<.0001**
37% reduction in risk of death

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AFFIRM Secondary Endpoints

- Radiographic PFS = 8.3 months vs 2.9 months
- Time to PSA progression = 8.3 months vs 3.0 months
- PSA response = 54% vs 2%
- Time to first SRE = 16.7 months vs 13.3 months
- Adverse events of special interest include fatigue, seizure (.6%)

Graphs showing
- Radiographic progression-free survival
- PSA progression-free survival

Placebo: 2.9 months (95% CI: 2.8, 3.4) vs Enzalutamide: 8.3 months (95% CI: 8.2, 9.1)
Placebo: 3 months (95% CI: 2.9, 3.7) vs Enzalutamide: 8.3 months (95% CI: 5.8, 8.3)

RECIST, Response Evaluation Criteria in Solid Tumors; PCWG2, Prostate Cancer Clinical Trials Working Group

Androgen Receptor Targeting Agents

- The PREVAIL Phase III Study (enzalutamide)
  - Pre-chemotherapy study, completed enrollment in June 2012 of 1680 men (selected Asia sites to remain open)
- ARN 509 (4548, TPS4697)
- TOK-001 [(galeterone) (4665)]
Sipuleucel-T

- Administration of three doses of autologous antigen-presenting cells stimulated by a chimeric protein comprising prostate acid phosphatase and granulocyte-macrophage colony-stimulating factor over 1-month period
- Improved Overall Survival by 4 months as compared with placebo

Huber ML et al. JNCI 2012;104:273-279.
Future Agents in Clinical Trials

• Phase III *Ipilimumab* versus placebo
  • 800 patient trial (TPS4691)
• Phase III *PROSTVAC* versus placebo
  • 800 patient trial (TPS4699)
• Autologous *PSMA-directed CAR*+ T cells
  • TPS4700
• Phase II *L-BLP25* vaccine
  • 42 patients with radiation and ADT (TPS4701)
Sequence Versus Combination

• *Docetaxel plus*
  – Abiraterone (NCT01400555)
  – Enzalutamide (NCT01565928)
  – Orteronel (#4656)

• *Cabazitaxel plus*
  – Abiraterone (NCT01511536)
Cabazitaxel

Phase III TROPIC trial: OS\textsuperscript{a} versus mitoxantrone + prednisone

<table>
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<tr>
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<th>mitoxantrone + prednisone</th>
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<tr>
<td>n</td>
<td>378</td>
<td>377</td>
</tr>
<tr>
<td>Median OS (months)</td>
<td>15.1 (14.1–16.3)</td>
<td>12.7 (11.6–13.7)</td>
</tr>
<tr>
<td>Hazard Ratio (HR)\textsuperscript{b} (95% CI)</td>
<td>0.70 (0.59–0.83)</td>
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<tr>
<td>(P) value</td>
<td>&lt;.0001</td>
<td></td>
</tr>
<tr>
<td>Number of deaths</td>
<td>234 (62%)</td>
<td>279 (74%)</td>
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</tbody>
</table>

\(\text{OS}^a\) Primary endpoint.
\(\text{HR}^b\) Estimated using COX model; an HR of <1 favors cabazitaxel

RANK Ligand Inhibition may interrupt the “Vicious Cycle” of Cancer-Induced bone destruction

Tumour Cells

Formation Inhibited

Osteoblasts

Apoptotic Osteoclast

PT-Hp, BMP, TGF-β, IGF, FGF, VEGF, ET-1

PDGF, BMP, TGF-β, IGF, FGF

Ca²⁺

CFU-M=colony forming unit macrophage
M-CSF=macrophage colony stimulating factor

Denosumab

* 18% risk reduction in first SRE vs zoledronic acid
* Approved for prevention of SREs in patients with bone metastasis

Denosumab

- Approved to increase bone mass in patients at high risk for fracture including ADT for nonmetastatic prostate cancer

Denosumab

• Denosumab significantly delayed time to first bone metastasis, but no difference in overall survival in men who are nonmetastatic but high risk of bone metastasis (PSA ≥8 ug/L or PSA doubling time ≤ 10 months)(#4510)

• ODAC voted no to recommend new indication: denosumab for treatment of men with nonmetastatic CRPC at high risk of developing bone metastasis

• FDA also did not approve new indication

Radium-223 Targets Bone Metastases

- Alpha-particles induce double-strand DNA breaks in adjacent tumour cells\(^1\)
  - Short penetration of alpha emitters (2-10 cell diameters) = highly localised tumour cell killing and minimal damage to surrounding normal tissue

Radium-233

• Data previously presented at ASCO GU 2011 and European Multidisciplinary Cancer Congress (ECCO/ESMO/ESTRO) 2011
• ALSYMPCA trial of 921 patients with metastatic CRPC showed significant delay in time to first SRE (13.6 months versus 8.4 months) and median overall survival of 14 months versus 11.2 months (placebo)
• Fewer patients had ECOG PS deterioration in Radium arm
• Updated analysis (LBA4512, #4551)
XL-184 (Cabozantinib)

- Cabozantinib inhibits MET and VEGFR2
- Previous Phase II trials reported high rates of bone scan resolution, pain relief and disease control independent of PSA
- Phase II nonrandomized expansion cohort at 100 mg PO daily (#4513)
- Dose finding study reported 40 mg dose achieves a high bone scan resolution with improved tolerability (#4566)

ASCO 2011 and ASCO GU 2011
Strategies for therapeutically targeting the AR. The hypothalamus-pituitary-gonadal axis controls androgen synthesis as part of a negative feedback loop.

Summary

• Growing list of FDA approved agents
• Pipeline of agents in Phase III is robust
• Biomarker development and validation ongoing
• Combination of agents not necessarily synergistic
• Sequence of treatment will continue to evolve
• Consideration for quality of life issues remain very important in determining treatment plan
Prostate Cancer Screening, Diagnosis and Treatment Decisions

US Preventive Services Task Force Recommendation and The Pivot Trial

Isaac Powell, MD
U.S. Preventive Services Task Force 2011, Draft

Recommends against screening healthy men!
This recommendation applies to men in the U.S. population that do not have symptoms that are highly suspicious for prostate cancer, regardless of age, race, or family history. The Task Force did not evaluate the use of the PSA test as part of a diagnostic strategy in men with symptoms that are highly suspicious for prostate cancer. This recommendation also does not consider the use of the PSA test for surveillance after diagnosis and/or treatment of prostate cancer.
The task force, which is sponsored by the government to make independent recommendations on preventive medical services, analyzed the research on PSA tests and concluded outside of any economic considerations that the “harms” of PSA tests outweigh the benefits to patients.

"We have to face the reality of what the “science” is telling us," LeFevre said. "You're more likely to be hurt than to be helped.“

The screenings can be useful for men in higher risk categories including African-Americans and those with a family history of prostate cancer, said Dr. Gerald Andriole, chief of urologic surgery at Barnes-Jewish Hospital.
The American Urological Association issued a statement saying that the recommendation “will ultimately do more harm than good.” Many urologists reacted angrily.

“All of us take extraordinary issue with both the methodology and conclusion of that report,” said Dr. Deepak Kapoor, chairman and chief executive of Integrated Medical Professionals, a group that includes the nation’s largest urology practice. “We will not allow patients to die, which is what will happen if this recommendation is accepted.” He and other urologists said that the P.S.A. test is just one part of an overall strategy that, in the hands of well-trained doctors, can help prevent death and other consequences of cancer.
Key Issues of Screening and Early Treatment

- Does screening extend men’s lives (are there benefits)?
- Does screening lead to health problems (are there harms)?
- Do the benefits outweigh the harms?
What Are the Potential Benefits of Screening?

Three issues to consider:

- Does PSA testing lead to earlier detection?
- Does earlier treatment help men live longer?
- What happens to mortality rates as screening rates increase?
Are There Harms From Screening and Early Treatment?

- Three issues to consider:
  - False-positive screening tests.
  - Overdiagnosis (men who do not benefit from diagnosis).
  - Side effects of treatment.
Summary

Potential Benefits
- PSA screening detects cancers earlier.
- Treating PSA-detected cancers may be effective but we are uncertain.
- PSA may contribute to the declining death rate but we are uncertain.

Potential Harms
- False positives are common.
- Overdiagnosis is a problem but we are uncertain about the magnitude.
- Treatment-related side effects are fairly common.

Bottom line: Uncertainty about benefits and magnitude of harms
Reduction in Mortality Rate 1995-2005 in the U.S.

AAM  39%  (10 years)  3.9% per year

CM  41%  (10 years)  4.1% per year
United States Prostate Cancer Screening Clinical Trial

The PLCO trial is designed to answer the question of whether screening for prostate cancer followed by appropriate treatment saves lives.

Randomization

- PSA and DRE
- DRE
Characteristics of the Subjects at Baseline

| Table 1. Characteristics of the Subjects at Baseline.² |
|---------------------------------|------------------|------------------|
| Variable                        | Screening Group  | Control Group    |
| Age                             | (N = 38,343)      | (N = 38,350)     |
| 55–59 yr                        | 32.3%            | 32.3%            |
| 60–64 yr                        | 31.3%            | 31.3%            |
| 65–69 yr                        | 23.2%            | 23.2%            |
| 70–74 yr                        | 13.2%            | 13.2%            |
| Race or ethnic group†           |                  |                  |
| Non-Hispanic white              | 86.2%            | 83.8%            |
| Non-Hispanic black              | 4.5%             | 4.3%             |
| Hispanic                        | 2.1%             | 2.1%             |
| Asian                           | 4.0%             | 3.9%             |
| Other                           | 0.8%             | 0.9%             |
| Missing data                    | 2.4%             | 5.0%             |
| Enlarged prostate or benign prostatic hyperplasia | 21.4% | 20.5% |
| Previous prostate biopsy        | 4.3%             | 4.3%             |
| Family history of prostate cancer | 7.1%          | 6.7%             |
| PSA test within past 3 yr       |                  |                  |
| Once                            | 34.6%            | 34.3%            |
| Two or more times               | 9.4%             | 9.8%             |
| Digital rectal examination within past 3 yr |            |                  |
| Once                            | 32.8%            | 31.9%            |
| Two or more times               | 22.2%            | 22.0%            |

² PSA denotes prostate-specific antigen.
† Race or ethnic group was self-reported.

Design

1. The monitoring board supported follow-up of the subjects until all of them had reached at least 13 years of follow-up.

2. Target mortality reduction of 20%

3. Contamination of no greater than 20% of the control arm and compliance of 90% of the screen arm to achieve a mortality reduction of 20%.
In Nov. 2008, the board unanimously recommended that the current results of PCa mortality be reported.

Rationale:

a. data showing a continuing lack of a significant difference in the death rate between the two study groups
b. information suggesting harm from screening
c. concern that men and their physicians were making decisions on screening on the basis of inadequate information
d. data available from the trial were complete up to 7 years.
Clinical Results

1. Compliance with the screening protocol over-all 85% for PSA testing and 86% for DRE.

2. In the control group, the rate of PSA testing (contamination) was 40% in the first year and increased to 52% in the sixth year. (the original design estimate was 20%)
Histological Results at 7 years

1. PCa had been diagnosed in more subjects in the screening group (2820) than in the control group (2322).
2. More than 50% had a Gleason score of 5 or 6.
3. Overall, the numbers of subjects with advanced (stage 3 or 4) tumors were similar in the two groups, 122 in the screening group and 135 in the control group.
4. Gleason score of 8 to 10 was higher in the control group (341 subjects) than in the screening group (289 subjects).
Number of Diagnoses of All Prostate Cancers (Panel A) and Number of Prostate-Cancer Deaths (Panel B)

Screening-Related Risks (“Harm”)

• 1. The PSA blood test led to complications at a rate of 26 per 10,000 screenings (0.26%) primarily dizziness, bruising, and hematoma and 3 episodes of fainting.

• 2. Medical Complications from the diagnostic process occurred in 68 of 10,000 (0.68%) diagnostic evaluations after positive results on screening. (primarily infection, bleeding, clot formation, and urinary difficulties)

• 3. Treatment related complication evaluations are incomplete.
“Overdiagnosis”

• Among men with PCa at 10 years, 312 in the screening group and 225 in the control group died from causes other than PCa, and the excess in the screening group that was possibly associated with “overdiagnosis” of PCa. <1%
Conclusion

• The U.S. study reports that after 7 to 10 years of follow-up, the rate of death from PCa was very low and did not differ significantly between the two study groups.
• There are significant limitations to this study:
  • a. Contamination
  • b. Premature reporting of data
• Therefore in my opinion and the opinion of many others the study is flawed!
PCa Mortality (European Study)

• 1. Median follow-up times of 8.8 and 9.0 years in the screening and control groups.

• 2. The unadjusted rate ratio for death from PCa in the screening group was 0.80 (95% CI) p=0.01.

• 3. The rates of death in the two study groups began to diverge after 7 to 8 years and continued to diverge further over time.

• 4. Recently reported contamination rate of 15%.
European Study

Update of the European Randomised PCa Screening Study addresses the issue of compliance and contamination. There was 15% contamination of the control arm and 23% non-compliers. After adjusting for contamination and non-compliance, PSA screening reduced the risk of dying of PCa by up to 30%.

As this trial approaches follow-up of 13 years according the study design, the reduction of death may be as high as 40%.
European Screening Study Statement

• “To prevent one Prostate cancer death, 1410 men would have to be screened, and an additional 48 men would have be treated.” (NNT)

• But “The number needed to screen in this study is similar to that in studies of mammographic screening for breast cancer and fecal occult-blood testing for colorectal cancer.”
Mortality results from the Göteborg randomised population-based prostate-cancer screening trial (Swedish study)

- Prof Jonas Hugosson MD, Sigrid Carlsson MD, Gunnar Aus MD, Svante Bergdahl MD, Ali Khatami MD, Pär Lodding MD, Carl-Gustaf Pihl MD, Johan Stranne MD, Erik Holmberg PhD and Hans Lilja MD
Method

• In December, 1994, 20 000 men born between 1930 and 1944, randomly sampled from the population register, were randomised by computer in a 1:1 ratio to either a screening group invited for PSA testing every 2 years (n=10 000) or to a control group not invited (n=10 000).
Men in the screening group were invited up to the upper age limit (median 69, range 67–71 years) and only men with raised PSA concentrations were offered additional tests such as digital rectal examination and prostate biopsies. The primary endpoint was prostate-cancer specific mortality.
Cumulative incidence of prostate cancer in the screening group and in the control group

<table>
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<th>Number at risk</th>
<th>Time from randomisation (years)</th>
<th>Screening group</th>
<th>Control group</th>
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Cumulative risk of death from prostate cancer using Nelson-Aalen cumulative hazard estimates.
Results

- The rate ratio of death from prostate cancer for attendees (PSA group) compared with the control group was 0.44 (95% CI 0.28–0.68; \( p=0.0002 \)). Overall, 293 (95% CI 177–799) men needed to be invited for screening and 12 to be diagnosed and treated to prevent one prostate cancer death. (NNT)
PCa Screening/Early Detection

Summary

PCa guidelines recommend that men should be informed of the risks and benefits of prostate cancer screening before biopsy. Age, race, family history and co-morbidities are important factors in determining who and when one should be tested. The option of active surveillance in lieu of immediate treatment for certain men diagnosed with prostate cancer is available.
CLINICAL TRIALS

The PIVOT Trial (Prostate Cancer Intervention Versus Observation Trial)

Radical

PCa

Randomization

Radical

Prostatectomy with additional treatment if necessary.

Observation

Management with treatment for symptomatic local progression with metastasis.
Radical Prostatectomy versus Observation for Localized Prostate Cancer
July 19, 2012
Timothy J. Wilt et al.
Conclusions

Among men with localized prostate cancer detected during the early era of PSA testing, radical prostatectomy did not significantly reduce all-cause or prostate-cancer mortality, as compared with observation, through at least 12 years of follow-up.
Methods

From November 1994 through January 2002, we randomly assigned 731 men with localized prostate cancer (mean age, 67 years; median PSA value, 7.8 ng per milliliter) to radical prostatectomy or observation and followed them through January 2010. The primary outcome was all-cause mortality; the secondary outcome was prostate-cancer mortality.

(90% VA Hospital population)
Results

During the median follow-up of 10.0 years, 171 of 364 men (47.0%) assigned to radical prostatectomy died, as compared with 183 of 367 (49.9%) assigned to observation (hazard ratio, 0.88; 95% confidence interval [CI], 0.71 to 1.08; P=0.22; (overall survival). Among men assigned to radical prostatectomy, 21 (5.8%) died from prostate cancer or treatment, as compared with 31 men (8.4%) assigned to observation (hazard ratio, 0.63; 95% CI, 0.36 to 1.09; P=0.09);
Problems with this Study

• 1. Olded population: Average 67, < 10% under age 60. (Karmanos average age 61)
• 2. Unhealthy population: Almost 50% died < 10 years.
• 3. Median follow-up of 10 years is too short for men undergoing radical prostatectomy and progression to death.
• 4. Lack of stratification by age and disease aggressiveness.
Radical Prostatectomy versus Watchful Waiting in Early Prostate Cancer

Anna Bill-Axelson, M.D., Ph.D., Lars Holmberg, M.D., Ph.D.,
Mirja Ruutu, M.D., Ph.D., Hans Garmo, Ph.D., Jennifer R. Stark, Sc.D.,
Christer Busch, M.D., Ph.D., Stig Nordling, M.D., Ph.D.,
Michael Häggman, M.D., Ph.D., Swen-Olof Andersson, M.D., Ph.D.,
Stefan Bratell, M.D., Ph.D., Anders Spångberg, M.D., Ph.D.,
Juni Palmgren, Ph.D., Gunnar Steineck, M.D., Ph.D.,
Hans-Olov Adami, M.D., Ph.D., and Jan-Erik Johansson, M.D., Ph.D.,
for the SPCG-4 Investigators*
Methods

- prospective randomized trial of 695 men in Sweden, Iceland and Finland

- included if
  * age <75 years
  * life expectancy >10 years
  * no other cancers
  * T1 or T2 disease
  * PSA <50
  * negative bone scan
  * well to moderately well differentiated on bx or fna
Methods

- WW group
  * no immediate treatment
  * BOO --> TURP
  * hormone deprivation if
    - mets on bone scan
    - PSA elevation (2003)

- f/u for both groups
  * q 6 months for 2 years
Results

- subgroup analysis
  * age <65 vs 65 or older was significant (<65 NNT = 7)
Results

- low-risk pre-op prostate cancer (psa<10, gleason<7)
  * 124 men in RP group, 139 men in WW group

  * 13.2% absolute reduction in risk of overall mortality
  * 4.2% absolute reduction in risk of PCA mortality
    (p=0.14)
  * 11.4 % absolute reduction in risk of distant metastasis

  * 6 of 7 deaths upstaged on final path
The Next Challenge

• To determine the aggressive prostate cancers that need treatment from non-aggressive cancers that may not need treatment.