Prostate cancer in 2016:
Current management, recent progress, and continuing controversies

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Beth Israel Deaconess Medical Center
Prostate Cancer

- 180,890 new cases estimated in 2016 (220,800 in 2015)
- 26,120 deaths estimated in 2016
- Recent decline in incidence & mortality
- 70% older than 65 years of age
- Majority of new cases have localized disease
Prostate Cancer Risk Factors

- **Age**
  - >70% by age 80; 1 in 6 lifetime risk

- **Family history**

- **Race**
  - Black > White > Asian

- Influence of diet unclear: ? role of fat

- **Vasectomy** ?

- **Smoking** not associated

- **Sexual activity** *may* be protective

- **Coffee consumption** *may* decrease risk and lethality
The PLCO Trial

• 16 yr randomized screening study for Prostate, Lung, Colorectal and Ovarian cancer

• 74,000 men ages 55-74 to be enrolled

• To determine whether screening with DRE + PSA can reduce mortality
  – DRE annually for 3 years
  – PSA annually for 5 years

Andriole GL. NEJM 2009; 361: 1310-1319
PLCO Trial Results

• Compliance with the protocol was 85% for PSA testing and 86% for DRE.

• At 7 years prostate cancer had been diagnosed in 2820 subjects in the screening group vs. 2322 subjects in the control group.

• This difference persisted at 10 years (3452 vs. 2974)
Figure 1. Number of Diagnoses of All Prostate Cancers (Panel A) and Number of Prostate-Cancer Deaths (Panel B).
PLCO Trial Results

- At 7 years there were 50 deaths from prostate cancer in the screening group and 44 in the control group (rate ratio 1.13; 95% CI 0.75-1.70)

- Through year 10 there were 92 deaths from prostate cancer in the screening group and 82 in control group (RR 1.11; 95% CI 0.83-1.50)
PLCO Trial Limitations

- Cutoff level of PSA testing (>4 vs. >3)
- Contamination
  - 44% of pts had prior PSA testing at baseline.
  - High level of screening in control group--85% over time while 15% of study group did not comply with testing
- Benefit of screening blunted by improvements in prostate cancer therapy.
- No quality of life analysis
- Few African Americans
- *Might need longer follow up to see an effect.*
Prevalence of Prostate Cancer Among Men with PSA < 4.0 ng/ml

Table 2. Relationship of the Prostate-Specific Antigen (PSA) Level to the Prevalence of Prostate Cancer and High-Grade Disease.*

<table>
<thead>
<tr>
<th>PSA Level</th>
<th>No. of Men (N=2950)</th>
<th>Men with Prostate Cancer (N=449)</th>
<th>Men with High-Grade Prostate Cancer (N=67)</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of men (%)</td>
<td>no. total no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤0.5 ng/ml</td>
<td>486</td>
<td>32 (6.6)</td>
<td>4/32 (12.5)</td>
<td>1.0</td>
<td>0.0</td>
</tr>
<tr>
<td>0.6–1.0 ng/ml</td>
<td>791</td>
<td>80 (10.1)</td>
<td>8/80 (10.0)</td>
<td>0.93</td>
<td>0.02</td>
</tr>
<tr>
<td>1.1–2.0 ng/ml</td>
<td>998</td>
<td>170 (17.0)</td>
<td>20/170 (11.8)</td>
<td>0.75</td>
<td>0.33</td>
</tr>
<tr>
<td>2.1–3.0 ng/ml</td>
<td>482</td>
<td>115 (23.9)</td>
<td>22/115 (19.1)</td>
<td>0.37</td>
<td>0.73</td>
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<td>3.1–4.0 ng/ml</td>
<td>193</td>
<td>52 (26.9)</td>
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* High-grade disease was defined by a Gleason score of 7 or greater. The population was restricted to men with a PSA level of 4.0 ng per milliliter or less throughout the study. Therefore, the definitions of sensitivity and specificity are restricted to cutoff values of less than 4.0 ng per milliliter (the cutoff values are equal to the lower value of the ranges in the PSA column [0.0, 0.6, 1.1, 2.1, and 3.1 ng/ml]). Sensitivity was defined as the proportion of men with cancer who had a PSA value above the cutoff among all men with cancer who had a PSA value of 4.0 ng per milliliter or less. Specificity was defined in a like manner.
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PLCO Trial Limitations

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Göteborg randomized population-based prostate-cancer screening trial: Diagnoses

Figure 2: Cumulative incidence of prostate cancer in the screening group and in the control group

Göteborg randomized population-based prostate-cancer screening trial: Mortality from Prostate Cancer

Figure 3: Cumulative risk of death from prostate cancer using Nelson-Aalen cumulative hazard estimates

Göteborg randomized population-based prostate-cancer screening trial: Mortality from Prostate Cancer

Absolute cumulative risk reduction of death from prostate cancer at 14 years
0.4% (from .9% in control to .5% in screened)

Risk ratio for death from prostate cancer death in screened vs. controls
HR = .56, 95% CI [.39-.82, p=0.002]

Prior to 2011:
• The USPSTF concluded that the current evidence was insufficient to assess the balance of benefits and harms of prostate cancer screening in men younger than age 75 years. Grade: I Recommendation.
• The USPSTF recommended against screening for prostate cancer in men age 75 years or older. Grade: D Recommendation.

Revised Recommendation:
• The USPSTF recommends against screening for prostate cancer in men at any age. Grade: D Recommendation
But the debate continues…

• Pros: reduction in morbidity and mortality

• Cons: overdiagnosis → overtreatment

• NNDx to save one life = 27 in European Randomized Study of Screening for Prostate Cancer (ERSPC); therefore, many treated for each death avoided

• ERSPC less contamination than PLCO and mortality reduction 25-30% in screened group, increasing over time as data matures

Klotz L. Oncology 2016: 30: 694
Screening becomes more acceptable if:

- New algorithms for risk-adapted frequency of testing: e.g. 40 yo with PSA <1 → test every 5 years; 60 yo with PSA <1 → no further testing

- Increasing use of MRI rather than bx as initial approach if PSA elevated—may separate aggressive vs. low-risk disease

- Increasing adoption of more conservative management of low-risk disease by active surveillance (up to 40% of all cases) and intermediate-risk low volume unilateral disease by focal therapy (reserving radical therapy for aggressive, large volume, intermediate-to-high-risk disease

Klotz L. Oncology 2016: 30: 694
USPSTF may be about to walk back its recommendation a bit—stay tuned!
Finasteride Prevention Trial

- An 5-alpha reductase inhibitor (blocks conversion of T to more potent dihydroT)
- 18,882 men > 55, nl DRE, PSA < 3.0
- 86.3% have completed 7 years of the study, end of study biopsy required
- Analysis with 4368 in finasteride group and 4692 in placebo group

Finasteride Prevention Trial

![Graph showing the probability of prostate cancer over years after randomization for Placebo and Finasteride groups.]

<table>
<thead>
<tr>
<th></th>
<th>Placebo group</th>
<th>Finasteride group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy rate (%)</td>
<td>3.0 2.8 2.2 2.9 2.8 2.6 7.1</td>
<td>3.3 2.0 2.1 2.5 2.1 2.2 7.0</td>
</tr>
<tr>
<td>Total no. of cancers diagnosed</td>
<td>48 71 60 80 92 96 124</td>
<td>42 35 39 68 78 51 122</td>
</tr>
<tr>
<td>No. of grade 7–10 cancers</td>
<td>5 6 15 35 24 24 38</td>
<td>11 11 17 31 28 26 64</td>
</tr>
</tbody>
</table>

Finasteride Prevention Trial

*but...*

- **1.27** relative risk factor for high grade cancers (Gleason > 7) in finasteride pts

- **280** high grade in finasteride pts vs. **237** control pts

Weighing the prevention trial data

- Oncology drugs advisory committee (ODAC) of FDA recommends **against** 5-alpha reductases for prevention of prostate cancer
Long-term survival of participants in the prostate cancer prevention trial

Table 1. Relative Risk of Prostate Cancer in the Finasteride Group, as Compared with the Placebo Group, According to Cancer Grade.*

<table>
<thead>
<tr>
<th>Prostate-Cancer Grade</th>
<th>Primary 2003 Report</th>
<th>Current Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relative Risk (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Any grade</td>
<td>0.75 (0.69–0.81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low grade</td>
<td>0.62 (0.56–0.68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High grade</td>
<td>1.27 (1.07–1.50)</td>
<td>0.005</td>
</tr>
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</table>

* Low-grade cancers had a Gleason score of 2 to 6; high-grade cancers had a Gleason score of 7 to 10.

Thompson IM. NEJM 2013; 369: 603-10.
Long-term survival of participants in the prostate cancer prevention trial

Thompson IM. NEJM 2013; 369: 603-10.
Pathology and Staging
Gleason patterns
Gleason patterns

3 + 3 = Gleason score of 6 is realistically lowest seen
## Staging TNM-Whitmore-Jewitt

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<tr>
<th>TNM</th>
<th>Whitmore</th>
<th>Description</th>
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<tbody>
<tr>
<td>Tx</td>
<td>-</td>
<td>Tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>-</td>
<td>No evidence of tumor</td>
</tr>
<tr>
<td>T1a</td>
<td>A1</td>
<td>Tumor at TURP(&lt;5%)</td>
</tr>
<tr>
<td>T1b</td>
<td>-</td>
<td>Tumor at TURP(&gt;5%)</td>
</tr>
<tr>
<td>T1c</td>
<td>B0</td>
<td>Nonpalpable, PSA only</td>
</tr>
<tr>
<td>T2a</td>
<td>B1</td>
<td>&lt;50% of one lobe</td>
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<tr>
<td>T3a</td>
<td>C1</td>
<td>Unilateral extracapsular extn</td>
</tr>
<tr>
<td>T3b</td>
<td>C1</td>
<td>Bilateral extracapsular extn</td>
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<tr>
<td></td>
<td></td>
<td>One or both seminal vesicles</td>
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<td>T4a</td>
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80% of American cases
Prostate Cancer: Pattern of Spread

• Extensive involvement of gland correlates with involvement of surrounding tissues

• Spread to regional nodes and bones

• Bone lesions usually in pelvis and spine and almost always sclerotic (osteoblastic)
Treatment
Therapy for Localized Disease

- Radical prostatectomy
- Image guided radiation therapy
- Brachytherapy
- Combination of two forms of radiotherapy
- Neoadjuvant hormone therapy $\Rightarrow$ XRT
- Watch and wait ("expectant management" $\Rightarrow$ "active surveillance")
Therapy for Localized Disease

- The choice of local therapy modality is hampered by a lack of randomized clinical trials
Prostate Testing for Cancer and Treatment (ProtecT) Trial

82,429 men ages 50-69 had PSA testing between 1999-2009

2664 diagnosed with localized prostate cancer

1643 randomized to active monitoring* (545), surgery (553) or radiotherapy** (545).

Primary endpoint = prostate cancer mortality at median follow-up of 10 years

*active monitoring= PSA follow up q 3 mo year 1, q 6-12 mo thereafter with “review” triggered by increase > 50%

**XRT included 3-6 mo. neoadjuvant/concurrent ADT

Prostate Testing for Cancer and Treatment (ProtecT) Trial

Patient Characteristics:

- Median PSA 4.6 (range 3.0-19.9)
- 77% Gleason 6
- 76% stage T1C (PSA elevation only)
- Arms well balanced in terms of Gleason scores and mean PSA at baseline and at first biopsy

Prostate Testing for Cancer and Treatment (ProtecT) Trial

Results:

• 17 prostate-cancer-specific deaths observed: 8 in active monitoring, 5 in surgery and 4 in radiotherapy arms (NS)

Prostate-cancer mortality:

• 1.5 deaths/1000 person-years in active monitoring
• 0.9 deaths/1000 person-years with surgery
• 0.7 deaths/1000 person-years with radiation therapy

  \[ P=0.48 \text{ (NS)} \] for overall comparison

Deaths from any cause also NS (p=0.87)

Results (cont’d):

Metastases
• 6.3/1000 person-years with active monitoring—33 events
• 2.4/1000 person-years with surgery group—13 events
• 3.0/1000 person-years with radiation therapy—16 events
  \[ P=0.004 \text{ for overall comparison} \]

Disease-progression rates
• 22.9 /1000 p-y for active monitoring—112 events
• 8.9/1000 p-y with surgery—46 events
• 9.0/1000 p-y with radiation therapy—46 events
  \[ P< 0.001 \text{ for overall comparison} \]
• 19% in active monitoring required treatment within 9 mo of randomization; overall 55% in active monitoring required treatment during the study

Figure 2. Kaplan–Meier Estimates of the Cumulative Probability of Undergoing Radical Intervention during the Follow-up Period, According to Treatment Group.

Radical intervention was defined as radical prostatectomy, per-protocol radiotherapy, nonprotocol radiotherapy (including brachytherapy), or high-intensity focused ultrasound therapy.
A Prostate-Cancer-Specific Survival

![Graph showing Prostate-Cancer-Specific Survival with data points for Surgery, Radiotherapy, and Active monitoring.]

<table>
<thead>
<tr>
<th>Follow-up (yr)</th>
<th>No. at Risk</th>
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<tbody>
<tr>
<td>0</td>
<td>1643</td>
</tr>
<tr>
<td>2</td>
<td>1628</td>
</tr>
<tr>
<td>4</td>
<td>1605</td>
</tr>
<tr>
<td>6</td>
<td>1575</td>
</tr>
<tr>
<td>8</td>
<td>1286</td>
</tr>
<tr>
<td>10</td>
<td>746</td>
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COPYRIGHT
*Disease Progression = metastases or death from prostate cancer or its rx
NNT in ProtecT

- **27** require prostatectomy vs active monitoring to prevent one patient from developing metastases

- **33** require XRT vs active monitoring to prevent one patient from developing metastases

ProtecT Trial: Patient-Reported Outcomes

Surgery:
• had greatest negative effective on sexual function and urinary continence, with some recovery from initial effects

Radiation Therapy:
• negative effect on sexual function at 6 months with some recovery and stability thereafter;
• little effect on urinary continence;
• voiding, nocturia and bowel function worse at 6 months with some recovery thereafter

Active monitoring:
• gradual decline in sexual and urinary function

Overall, no significant differences in anxiety, depression, or cancer-related quality of life among the 3 arms in the trial.

ProtecT: “bottom line”:

- “Men with newly diagnoses localized prostate cancer need to consider the critical trade-off between the short-term and long-term effects of radical treatments on bowel, urinary and sexual function and the higher risks of disease progression with active monitoring, as well as the effects of each of these options on quality of life.”

- “Further follow up with long-term survival data will be crucial to evaluate this trade-off in order to fully inform decision making for physicians and patients considering PSA testing and treatment options for clinically localized prostate cancer”.
Other studies examining “active surveillance” for newly diagnosed prostate cancer
Scandanavian Prostate Cancer Group Study 4
Estimated 15 yr data (Median Follow up = 12.8 yrs)

• 3rd NEJM update of this study
• 695 men <75, T1-2 with well or mod diff cancers
• T1c included after 1994
• PSA < 50, neg bone scan

• Cummulative incidence of death from prostate cancer is 14.6% with surgery vs. 20.7% with watchful waiting
• RR .62 (.44-.87, p=0.01)
• NNT to save one life is 15 overall, 7 for men younger than 65

Scandanavian Prostate Cancer Group Study 4
(Median Follow up = 18 yrs)

• 4\textsuperscript{rd} NEJM update of this study. 18 years of follow up (range 13.4 to 23.2 years)

• 63 deaths from prostate cancer in surgery group vs. 90 in watchful waiting. HR = 0.56 (95\% CI 0.21 to 0.77, \( p = 0.001 \))

• Absolute difference of 11\%.
• NNT to save one life is 8 overall.

• Benefit of surgery largest in men < 65 yrs old (HR 0.45)
• Reduced risk of metastases also seen in men > 65 (HR 0.68, \( p = 0.04 \))

• ADT used in 25\% fewer men in surgery group

Radical prostatectomy (RP) vs. Observation for localized prostate cancer: the PIVOT (prostate cancer intervention vs observation) trial

• Conducted between 1994 and 2002, reflecting the early era of widespread PSA testing

• 731 randomized, median age 67, median PSA 7.8; 48% Gleason >7
• Median follow-up 10 years

• Primary endpoint was all cause mortality
  – 47% mortality in radical prostatectomy gp vs. 49.9% in observation gp, HR .88 (95% CI 0.71-1.08, p=.22) **Absolute risk reduction 2.9%**

Wilt TJ, et al. NEJM 2012; 203-213
Radical prostatectomy (RP) vs. Observation for localized prostate cancer: the PIVOT trial

- Secondary endpoint was prostate-cancer mortality
  - 5.8% of men in radical prostatectomy group died of cancer or treatment vs. 8.4% in observation group, HR .63 (95% CI .36-1.09, p=0.09) Absolute risk reduction 2.6%
  - 21.4% of men in RP group had an adverse event within 30 d of surgery, with 1 death

- Subgroup analysis showed RP produced lower prostate-cancer mortality in those with PSA >10 (5.6% vs. 12.8%, p=0.02) and those with high-risk prostate cancer (9.1% vs. 17.5%, p=0.04)

- No difference in prostate-cancer mortality in those with PSA <10 (p=0.82)

Wilt TJ, et al. NEJM 2012; 203-213
SPCG 4 vs. PIVOT

- PIVOT lower tumor burden
- Reflects largely PSA-detected disease
- May introduce *lead time bias* in events so that much longer follow up may be required?
SPCG 4 vs. PIVOT

• *PIVOT* lower tumor burden

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• May introduce *lead time bias* in events so that much longer follow up may be required?

*Now we have ProtecT trial to include in this analysis*
Watchful Waiting -- in the U.S.

- The long term prognosis for T1c, Gleason score of 6 with less than 1/3 of cores positive is excellent.

- In this group, prostate cancer mortality may be so low that risk of dying of prostate cancer less than for other causes and 25-30% have chronic morbidity post rx.
What do you “watch” if you are pursuing a “Watchful Waiting” strategy?

• PSA not reliable

• Tumors may not be palpable and palpable change probably not “early” change

• Best strategy is follow up biopsies, integrating “volume” of tumor as represented by number of cores positive and Gleason score; repeat at 12 mo. and then q 18 mo.
  – (higher Gleason score on repeat bx likely reflects tumor heterogeneity rather than tumor transformation)
Clinical Results of Long-Term Follow-Up of a Large, Active Surveillance Cohort With Localized Prostate Cancer

• 450 patients observed, median 7.8 years (range 1-13)

• Patients had Gleason score $\leq 6$, PSA $\leq 10$ or over age 70 with Gleason score $\leq 7$ and PSA $\leq 15$.

• 30% of patients were reclassified as higher risk and offered radical intervention for the following criteria: PSA doubling time (DT) of less than 3 years; histologic upgrade on repeat prostate biopsy; or clinical progression (development of palpable nodule)

• Overall survival 78.6% and prostate-cancer actuarial survival 97.2%

• The hazard ratio for non prostate-cancer to prostate-cancer mortality was 18.6 at 10 years.

Endocrine Therapy—Androgen Deprivation
Androgen Deprivation Therapy (ADT)

- Prostate cancer is the most hormone dependent malignancy

- **Androgen deprivation benefits >80%**
  - Survival benefit not clearly demonstrated

- Medical gonadal suppression
  - Depot form of goserlin acetate, leuprolide
  - Diethylstilbestrol (historical interest only)

- Surgical castration
Side Effects of Androgen Deprivation

- Hot flashes
- Loss of libido and potency
- Loss of muscle mass
- Weight gain
- Fatigue
- Long term use leads to osteoporosis, likely preventable with bisphosphonates or denosumab
Castrate-Resistant Prostate Cancer
Castrate-Resistant Disease

- Demonstrated by PSA increase on androgen deprivation
- 18-24 months after initiation of hormonal therapy
- PSA progression precedes clinical progression by 6 months
- Median survival has been 12-18 months
- Castrate resistant prostate cancer is still frequently hormone driven
Abiraterone in castrate-resistant disease

- Abiraterone is a selective, potent, irreversible inhibitor of CYP 17 which blocks biosynthesis of both androgens and estrogens affecting both adrenal androgen production and intracrine production of androgen by prostate tumors.

- The use of concurrent low dose prednisone (5mg bid) or dexamethasone reduces mineralocorticoid-related toxicities of rx.

- Phase 3 trial: OS for abiraterone + prednisone 14.8mo vs. 10.9mo for placebo+ prednisone, RR .65, .54-.77, p<0.001.

Targeting the Androgen Receptor (AR) Pathway: Enzalutamide

- New anti-androgen which targets multiple steps in the AR signaling pathway; once a day, oral, no need for prednisone.

- Phase 3 trial vs. placebo shows statistically significant 5 month (18.4 vs. 13.6 mo) improvement in median overall survival for castrate-resistant prostate cancer after chemotherapy.

- Side effects: fatigue, diarrhea, hot flashes and rare (< 1%) seizures.

- To be evaluated with GNRH agonists or with abiraterone for complete androgen blockade.

The E3805 trial: chemohormonal therapy vs androgen ablation randomized trial for extensive disease in prostate cancer (CHAARTED): A potential game changer

• Strategy has been to use androgen deprivation as long as possible

• When castrate-resistant, now have new antiandrogens to even further extend hormonal therapy

• Chemotherapy traditionally reserved for patients who have exhausted all hormonal manoeuvres

Sweeney CJ. NEJM 2015; 373: 737-46.
CHAARTED Trial

- Randomized 790 men to ADT vs docetaxel x 6 + ADT as “first-line” therapy of metastatic disease

- 2/3 had “high volume” disease (≥ 4 bone lesions with at least one beyond pelvis and vertebrae or visceral disease (≈15% of patients)

- Median OS 57.6 months in combination arm vs 44.0 months in ADT arm (HR 0.61, 95% CI 0.47-0.80, p = 0.0003.)

- OS Benefit was 17 months for men with high volume metastatic disease (HR 0.60, 95% CI 0.45-0.81, p = 0.0006)

Sweeney CJ. NEJM 2015; 373: 737-46.
Prior adjuvant ADT was allowed if the duration of therapy was 24 months or less and progression had occurred more than 12 months after completion of therapy (≈ 4%).

72% no prior therapy local therapy for prostate cancer.

Patients who were receiving ADT for metastatic disease were eligible if there was no evidence of progression and treatment had commenced within 120 days before randomization (87% received brief ADT before randomization).
Kaplan–Meier Estimates of Overall Survival

Kaplan–Meier Estimates of Overall Survival by volume of disease

Sweeney CJ. NEJM 2015; 373: 737-46.
CHAARTED Trial: Tolerance and Safety of Combination Therapy

- 86% of those randomized to combination therapy completed 6 cycles of docetaxel.
- 74% required no dose reduction
- 9% Grade 4 neutropenia + 2.3% febrile neutropenia
- No infectious death
- 12.6% had any Grade 4 toxicity

Sweeney CJ. NEJM 2015; 373: 737-746.
CHAARTED Trial: Unanswered

• Chemotherapy in castrate-resistant patients generally adds 2-3 months of benefit. In first line setting, this was 13.6 months

• Should combined ADT and chemotherapy be new standard for first line therapy? High volume only?

• Given improvement in antiandrogen therapy with recently introduced agents, would a combination of GNRH analogue and abiraterone or enzalutamide be comparable?

Sweeney CJ. NEJM 2015; 373: 737-46.
New therapies for advanced prostate cancer (approved or in trials)

- Vaccines: sipuleucel-T, prostvac®
- Radium 223
- PD-1 and PDL-1 targeting?
- PARP inhibitors, platinums in BRCA+ patients?
Alpha Emitter Radium-223 in castrate-resistant prostate cancer with bone metastases

- 809 patients randomized (2:1) placebo controlled phase 3 trial
- Castrate resistant and progression on or declined docetaxel
- Q 4 week injection x6
- Median time to first skeletal event 15.6 mo vs. 9.8 mo.
- OS median 14.9 vs. 11.3 mo
- Mild myelosuppression, few non-hematologic adverse events

Alpha Emitter Radium-223 in castrate-resistant prostate cancer with bone metastases

A Overall Survival

Hazard ratio, 0.70 (95% CI, 0.58–0.83) 
P<0.001

Radium-223 (median overall survival, 14.9 mo)
Placebo (median overall survival, 11.3 mo)

No. at Risk
Radium-223 614 578 504 369 274 178 105 60 41 18 7 1 0 0
Placebo 307 288 228 157 103 67 39 24 14 7 4 2 1 0

Inherited DNA-repair gene mutations in men with metastatic prostate cancer

- Germline mutations in DNA-repair genes found in 11.8% of men with metastatic prostate cancer.

- Of 16 genes assessed, BRCA2 most common at 5.3%; (CHEK2 at 1.9% and ATM at 1.6%. All others < 1%)

- Only 1.2-1.8% of men with localized prostate cancer have BRCA2 mutations so these mutations are disproportionately represented in the advanced disease population.

- Therapeutic implications: platinums, PARP (poly ADP ribose polymerase) inhibitors

Conclusions

• No consensus on screening but currently a thumbs down-- but should it be ??

• Prevention efforts under evaluation—currently a thumbs down

• No consensus on best form of primary therapy

• Hormonal therapy has continuing role in castrate-resistant cases

• Can recent progress in castrate-resistant disease be extended to early disease?
Conclusions, contd.

• Hormonal therapy may lead to an improved survival if used earlier in the disease (but risk of over-treatment with considerable side effects in localized low risk patients).

• Will CHAARTED and STAMPEDE trials lead to re-thinking positioning of chemotherapy to early recurrence or ultimately even adjuvant setting?

• Continued development of new strategies for evaluation in early advanced disease