Treatment of Prostate cancer – and why I refuse to know my PSA

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Princess Margaret Hospital and University of Toronto

Outline of Presentation

1. Requirements for screening to be effective in reducing mortality from a disease
2. Potential for screening to be harmful
3. Screening for prostate cancer; results of the screening trials
4. What did we gain from discovering PSA?
5. Advances in management of metastatic prostate cancer – hormonal therapy
6. Advances in management of metastatic prostate cancer – chemotherapy and other approaches

Potential conflicts of interest

City-wide Rounds, Toronto

Requirements for screening to be effective in reducing mortality from a disease

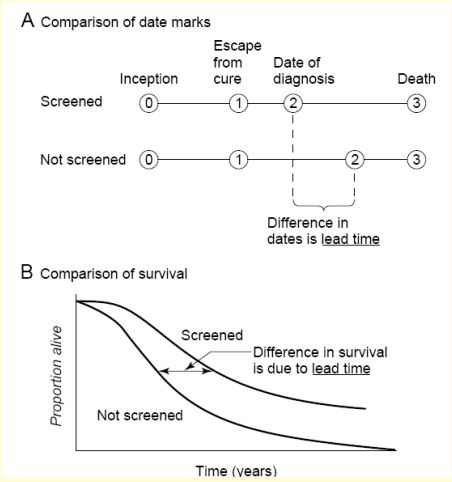
- A test that increases the probability of detecting cancer in an asymptomatic individual
  - Ideally the test should be simple, non-invasive, have high specificity, and be inexpensive
- Available treatment that leads to better outcome than treatment applied at onset of symptoms
- Survival from diagnosis will be improved by screening (lead time bias) but may not lead to improvement in overall mortality
- The disease must be common
- Benefits of screening must outweigh the harms

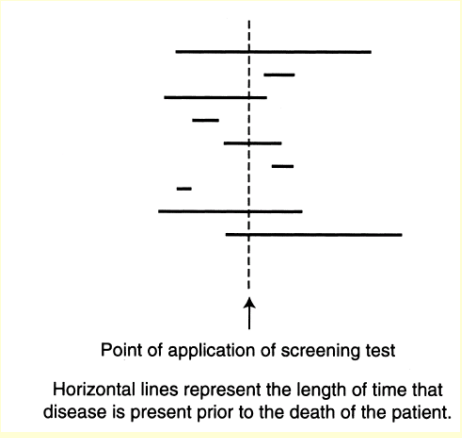
Various types of bias can influence the interpretation of screening

- **Selection bias:**
  - Individuals who present for screening may be more likely to have the disease (motivated, and often better general health)
- **Lead-time bias**
  - Screening will advance the date of diagnosis, and survival from diagnosis, even if it has no effect on course of disease
- **Length bias**
  - Screening is more likely to detect disease in those with a long pre-clinical history (i.e. those with indolent disease who might not need treatment) than in those with a short preclinical phase

Lead-time and length bias

(from Hodgson & Tannock, Basic Science of Oncology, 4th edition, 2005)





Rigorous trials to evaluate potential benefits of screening

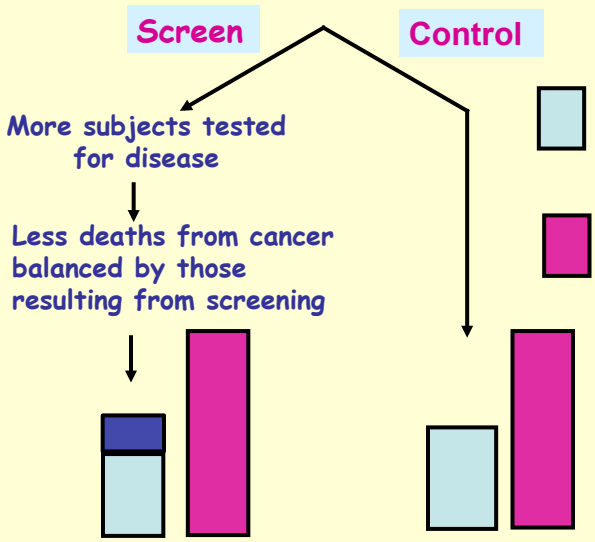
- Rigorous evaluation requires a large randomised controlled trial comparing screened and unscreened populations
- The primary endpoint is usually cause-specific mortality (i.e. deaths due to the cancer which is being screened)
- Ideally the endpoint should be overall mortality
  - It is not a successful strategy to save lives due to a cancer but to have an equal (or possibly greater) mortality as a result of investigations prompted by screening

Potential for screening to be harmful

- Complications of the test itself (including induced anxiety)
- Harms from investigations stimulated by positive tests (both false and true positives).
  - e.g. Complications from biopsy of breast, prostate, lung etc
- Detection and unnecessary treatment of cancers that would never have caused medical problems

N.B. Giving a diagnosis of cancer to someone who would never become aware of it, and the toxicity of treatment applied to produce a "pseudo-cure", are major potential harms due to screening

Slippery linkage bias in screening trials



Adapted from Black et al, JNCI 2002; 94:167-73

An example of slippery linkage

- Mr Jawal has PSA screening for prostate cancer. His PSA is 5ng/ml
- He undergoes trans-rectal biopsies which show normal prostatic epithelium
- He develops a pelvic abscess after the procedure which requires drainage and i.v. antibiotics
- Six months later he dies suddenly
- Autopsy shows a pulmonary embolus, a large clot in his internal iliac vein, and no evidence of prostate cancer
- Classification: Death unrelated to prostate cancer

Particular problems with screening for prostate cancer

- Many men have occult prostate cancer but die of other causes
  - detecting and treating their disease is a disservice
- Investigation is invasive
  - complications are rare, but so also is extending life through treatment
- Slippery linkage will occur
  - death from pulmonary embolus 6 mos after biopsy will be called "unrelated"
- Treatment is not very effective
  - and has considerable side-effects

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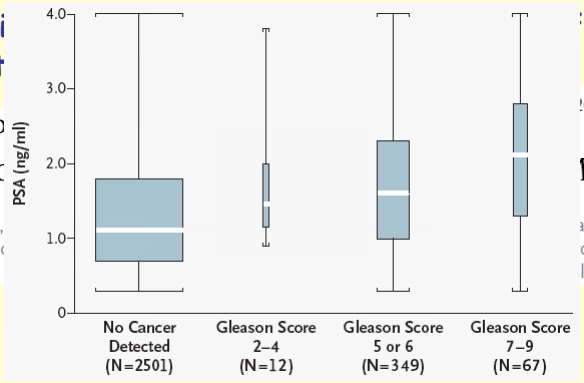
How good is PSA as a screening test?

It is diffi… to separat…

P… with a Pro… Milliliter

Ian M. Thompson, M. Scott Luc… Scott M. Lippman, … angen, Dr.P.H., …d, M.D., …ltman, Jr., M.D.

…004;350:2239-46.



CONCLUSIONS

Biopsy-detected prostate cancer, including high-grade cancers, is not rare among men with PSA levels of 4.0 ng per milliliter or less — levels generally thought to be in the normal range.

Prostate cancer

Jan-Erik Damber, Gunnar Aus

Lancet 2008; 371: 1710–21

Department of Urology, Sahlgrenska University Hospital, Gothenburg, Sweden

The disparity between reported incidence and mortality rates leads to the probable conclusion that only a small proportion of diagnosed low-risk prostate cancers will progress to life-threatening disease during the lifetime of the patient.

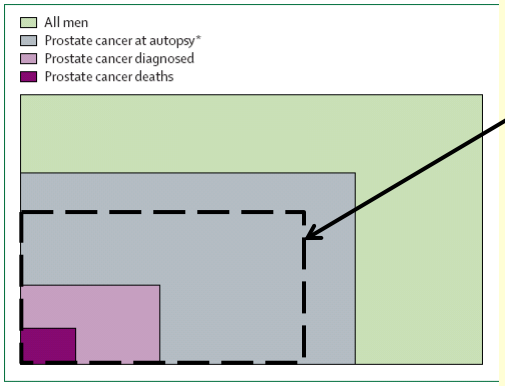


Figure 4: Relation between prevalence of prostate cancer at autopsy, clinically diagnosed, and prostate cancer deaths

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"Is cure necessary in those in whom it may be possible?"

"Is cure possible in those in whom it may be necessary"

W.F Whitmore Jr, 1990

N.B. The commonest cause of death in men with prostate cancer is..... Cardiovascular disease

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Moreover, because of length bias, PSA screening is more likely to detect men with slowly-progressive cancer

Rather than the small proportion of men who are destined to die as a result of their cancer

And how effective is radical treatment in preventing death due to prostate cancer?

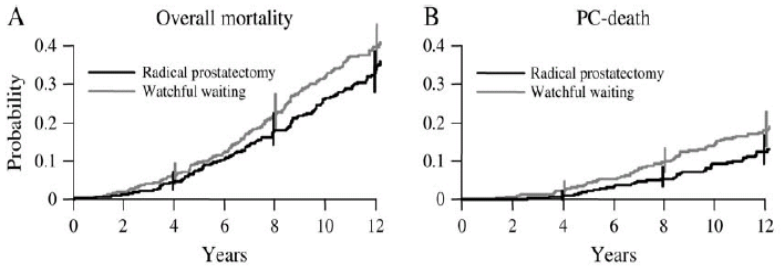
Scandinavian RCT of 695 men
(with clinical diagnosis)

Radical Prostatectomy versus Watchful Waiting in Early Prostate Cancer

N Engl J Med 2005;352:1977-84.

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

J Natl Cancer Inst 2008;100:1144–1154



No. At Risk							
Radical prostatectomy	347	343	332	311	284	220	142
Watchful waiting	348	341	326	306	267	201	127
Radical prostatectomy	347	343	332	311	284	220	142
Watchful waiting	348	341	326	306	267	201	127

The Scandinavian Trial…

J Natl Cancer Inst 2008;100:1144–1154

Median F/U=10.8 years	Radical prostatectomy (N=347)	Watchful waiting (N=348)	Relative risk
Number of deaths	137 (33%)	156 (40%)	0.82 (0.65-1.03) p=0.09
Deaths due to prostate cancer	47 (13.5%)	68 (19.5%)	0.65 (0.45-0.94) p=0.03
Deaths of men >65 yrs	42%	39%	1.04 (0.77-1.40) P=0.81

- Number needed to treat (NNT) to save one life is 19
- Benefit appears restricted to men with age<65
- NNT will be much greater for screen-detected cancer
- You don't buy immortality!

Current results of the prostate cancer screening trials

Mortality Results from a Randomized Prostate Cancer Screening Trial

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Screening and Prostate-Cancer Mortality in a Randomized European Study

N Engl J Med 2009;360:1320-8.

Fritz H. Schröder, M.D., Jonas Hugosson, M.D., Monique J. Roobol, Ph.D., Teuvo L.J. Tammela, M.D., Stefano Ciatto, M.D., Vera Nelen, M.D., Maciej Kwiatkowski, M.D., Marcos Lujan, M.D., Hans Lilja, M.D., Marco Zappa, Ph.D., Louis J. Denis, M.D., Franz Recker, M.D., Antonio Berenguer, M.D., Liisa Määttänen, Ph.D., Chris H. Bangma, M.D., Gunnar Aus, M.D., Arnauld Villers, M.D., Xavier Rebillard, M.D., Theodorus van der Kwast, M.D., Bert G. Blijenberg, Ph.D., Sue M. Moss, Ph.D., Harry J. de Koning, M.D., and Anssi Auvinen, M.D., for the ERSPC Investigators*

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The American (PLCO) trial

- 76,693 men (aged 55-74) randomised to screening or not between 1993 & 2001
- Screening: Annual PSA testing for 6 years and digital rectal exams for 4 years
- Follow-up determined by practitioners
- Primary analysis: Intent to screen comparison of prostate-specific mortality
- Analysis after 7 years of follow-up

The American trial....

... is unfortunately not interpretable due to adoption of PSA screening in the control group ("Contamination")

Compliance with screening:

In those assigned to screening: 85%

In the control group: 40% after 1 year

52% after 6 years

Not surprisingly there were no differences in low rates of death due to prostate cancer in the "screened" (N=50) and "control" (N=44) groups

The European trial

- 162,243 men in core age group of 55-69 randomised to screening or not
- Screening: PSA testing at an average interval of 4 years
- Most centres used a PSA threshold of 3ng/ml for bx
- Primary analysis: Intent to screen comparison of prostate-specific mortality
- 82% compliance in screened group"
  Low contamination in control group
- First analysis after median 9 years of follow-up

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Main results of the European trial

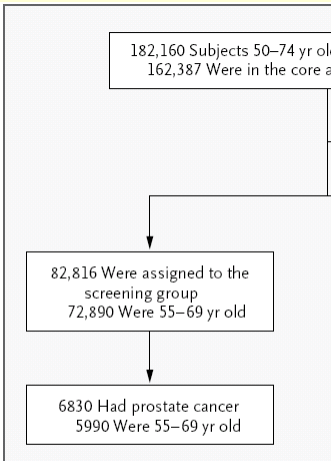
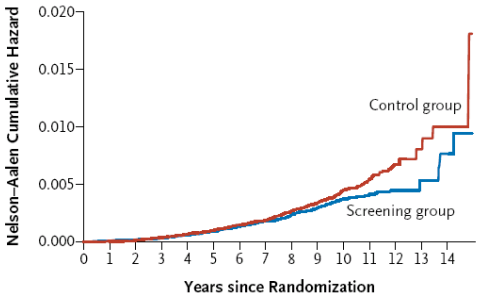


Figure 1. Enrollment and Outcomes, Acc
The predefined core age group for this
tween the ages of 55 and 69 years.



No. at Risk

Screening group	65,078	58,902	20,288
Control group	80,101	73,534	23,758

Figure 2. Cumulative Risk of Death from Prostate Cancer.
As of December 31, 2006, with an average follow-up time of 8.8 years, there were 214 prostate-cancer deaths in the screening group and 326 in the control group. Deaths that were associated with interventions were categorized as being due to prostate cancer. The adjusted rate ratio for death from prostate cancer in the screening group was 0.80 (95% CI, 0.65 to 0.98; P=0.04). The Nelsen–Aalen method was used for the calculation of cumulative hazard.

What do these results mean?

- Relative risk of dying of prostate cancer in the screened as compared to control group = 0.80 (0.65-0.98); p=0.04
- Absolute difference in risk of death from prostate cancer = 0.71 per 1000 men

1410 men would need to be screened and 48 additional cases of prostate cancer would need to be treated to prevent one death from prostate cancer

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Here is a man of a certain age who refuses to know his PSA

... and I will not change my mind even if the difference in prostate cancer-specific mortality increases with further follow-up of the European trial

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Reasons for not screening

- It leads to massive over-treatment with radical prostatectomy (RP) or radiotherapy in men who would never develop clinical prostate cancer
- Even for clinically diagnosed prostate cancer, the Scandinavian trial shows only small benefits for RP over watchful waiting, and only in younger men
- I do not believe that the toxicity of radical treatment (surgery or radiotherapy) warrant the small benefits for most men in this trial.
- And benefits will be less in screen-detected cancers

So what have we gained from discovery of PSA?

Different scenarios where PSA is often measured

- Screening of healthy men to detect occult prostate cancer
- To detect recurrence after primary treatment of localised prostate cancer
- As a marker of response or progression during treatment of advanced disease

Viewpoint

Eradication of a disease: how we cured symptomless prostate cancer

Lancet 2002; **359:** 1341–42

Ian F Tannock

All we are doing by measuring PSA and then not acting on the information is causing anxiety

We are converting healthy men into PSA cripples

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Management of Advanced Prostate Cancer

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A hypothetical patient

- Mr Eriksson is a 68 year old man with a 3-month history of pain in several bones
- On rectal examination his prostate is enlarged and hard
- A needle biopsy shows prostate cancer, Gleason grade 8/10
- His bone scan is "positive" and his serum level of PSA is 245ng/ml

How should Mr Eriksson be treated?

Which option for hormonal therapy would you recommend?

A. Orchiectomy

B. LHRH agonist (e.g. goserelin; leuprolide)
with short course of andiandrogen to prevent flare

C. Antiandrogen alone (e.g. bicalutamide)

D. Combined androgen blockade (LHRH agonist + antiandrogen)

E. Intermittent hormonal therapy

Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials

*Prostate Cancer Trialists' Collaborative Group**

Lancet 2000; **355:** 1491–98

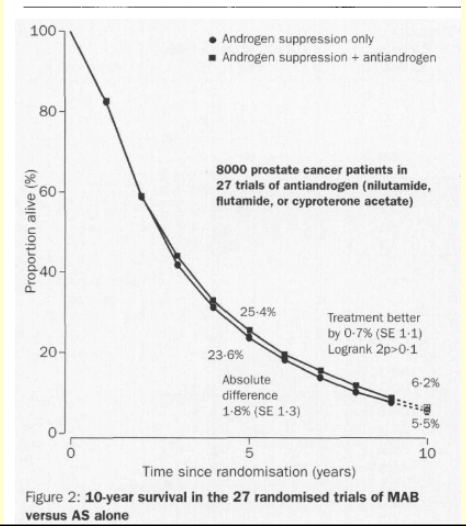

Figure 2: **10-year survival in the 27 randomised trials of MAB versus AS alone**

The patient-based meta-analysis showed no significant benefit of MAB after 8000+ pts and 27 trials

MAB is expensive, has increased toxicity and should not be used

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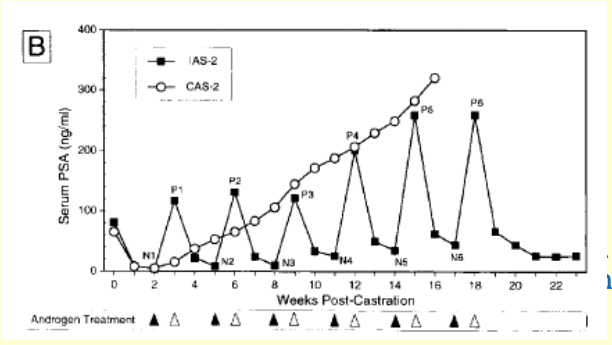
Intermittent Androgen Suppression Delays Progression to Androgen-independent Regulation of Prostate-specific Antigen Gene in the LNCaP Prostate Tumour Model

Naohide Sato,[1] Martin E. Gleave,[1,2] Nicholas Bruchovsky,[1] Paul S. Rennie,[1] S. Larry Goldenberg,[2], Paul H. Lange[3] and Lorne D. Sullivan[2]

J. Steroid Biochem. Molec. Biol., Vol. 58, No. 2, pp. 139–146, 1996



German study:
Miller et al:
ASCO 2007

Prostate cancer M+ and/or N+

Goserelin/Bicalutamide
x 24 weeks

PSA < 4 mg/dl
Decrease > 90%

N=335

Intermittent

PSA < 4 mg/dl
stop therapy

PSA > 10 mg/dl
resume therapy

Continous

PSA Progression
3 x rise

Second line
treatment

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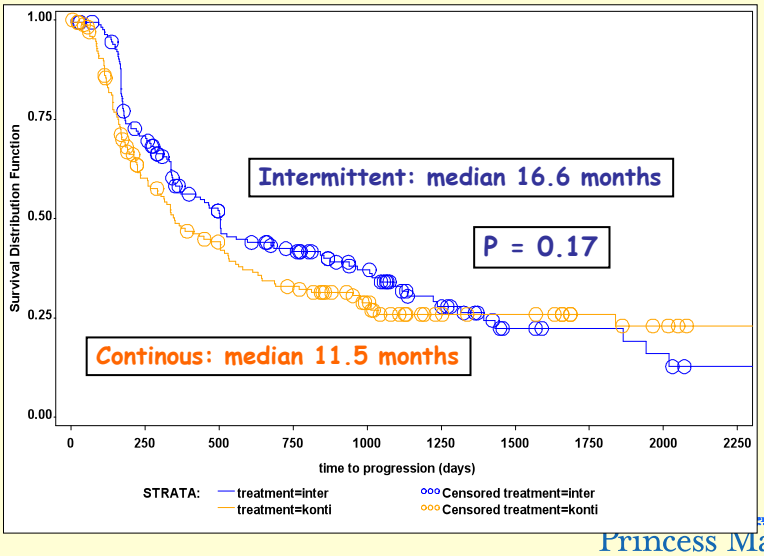
Time to Progression



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Randomized trials of intermittent vs continuous hormonal therapy

Trial	N	Setting	Treatment	Result
De Leval Clin Prost Cancer 2002	68	T3-4, N+, M+	goserelin+ flutamide	↓progression rate to androgen independence (AI)
Calais da Silva Europ Urol 2009	626	T3-4, N+, M+	triptorelin + cyproterone	similar time to AI & survival improved QoL
Miller ASCO 2007	335	N+, M+	goserelin + bicalutamide	similar time to AI improved QoL
Thun AUA 2007	167	rising PSA after RP	leuprolide	similar time to AI improved QoL

Should intermittent androgen blockade now be regarded as standard therapy?

In answer to the question:
"What would you do doctor if you were me?"

My response would be "Yes"

Advantages:
- Less time on a potentially toxic therapy
- Marked decrease in cost

Mr Eriksson's Treatment

- Mr Eriksson is treated with an LHRH agonist with short term bicalutamide to prevent flare
- He becomes pain free within 2 weeks, and one year later his PSA is 0.1
- However, he does have one or two side effects of treatment……..

Which of the following is NOT a known side effect of hormonal therapy?

A. Impotence
B. Gynecomastia
C. Hot flashes ("male menopause")
D. Loss of muscle and bone
E. Anemia
F. Thrombocytopenia
G. Increased risk of cardiovascular events

Prevention of Bone Loss for men on hormonal therapy

Exercise is probably the best protection against loss of bone and muscle

All men receiving ADT should be taking calcium and vitamin D

Several randomized trials have shown that bisphosphonates can prevent bone loss due to hormone treatment

A recent trial showed that Zoledronate given annually is effective in preventing bone loss

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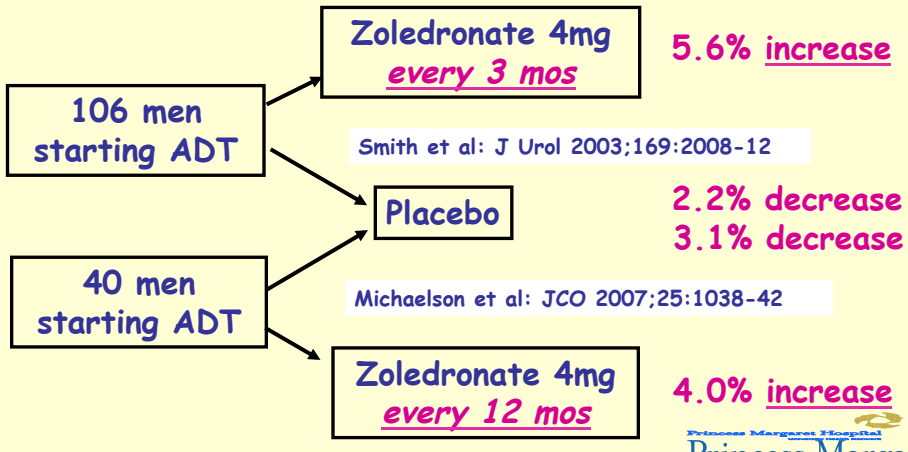
Role of Bisphosphonates in Preventing Bone Loss

Bone density at 1-year



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Androgen Deprivation Therapy (ADT) and Metabolic Syndrome

There is increasing evidence that ADT raises insulin levels and may increase diabetes and cardiovascular disease

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Diabetes and Cardiovascular Disease During Androgen Deprivation Therapy for Prostate Cancer

Nancy L. Keating, A. James O'Malley, and Matthew R. Smith

J Clin Oncol 24:4448-4456. © 2006

>73,000 men age>65 treated for localized Ca prostate 1992-1999, observed through 2001
>1 in 3 received ADT

Events per 1000 person-years	Diabetes	CHF	MI	Sudden death
No treatment	20.9	61.3	10.9	9.0
LHRH agonist	29.0	72.3	13.6	12.9
Orchiectomy	24.5	63.3	13.2	12.5

Other recent series have confirmed these effects

Castration Resistance

- 18 months after starting ADT, Mr Eriksson's PSA has increased to 5
- At 24 months the PSA is 50 and he is beginning to have some aching pain

He has a transient response of 6 months to adding bicalutamide.

He does not have further response to bicalutamide withdrawal

Subsequent hormonal therapy

Multiple small series indicate that Mr Eriksson, who has progressed after primary ADT, followed by addition and withdrawal of bicalutamide has a low but definite chance of responding to:

Other anti-androgens (e.g. nilutamide, flutamide)

Inhibitors of steroid synthesis (e.g. ketoconazole)

Estrogens such as DES

Glucocorticoids such as dexamethasone

For this reason the term "Castration-resistance" is more appropriate than "Hormone-refractory"

Androgen-dependent pathways remain important targets

- Several studies have shown substantial androgen levels ***within*** prostatic tissue (including cancer) which can stimulate androgen pathways in the face of very low levels of circulating androgens

Intraprostatic Androgens and Androgen-Regulated Gene Expression Persist after Testosterone Suppression: Therapeutic Implications for Castration-Resistant Prostate Cancer

Elahe A. Mostaghel,[1,2] Stephanie T. Page,[2,5] Daniel W. Lin,[3,5] Ladan Fazli,[6] Ilsa M. Coleman,[1] Lawrence D. True,[4] Beatrice Knudsen,[1] David L. Hess,[7] Colleen C. Nelson,[6] Alvin M. Matsumoto,[2,5] William J. Bremner,[2] Martin E. Gleave,[6] and Peter S. Nelson[1]

[1]Fred Hutchinson Cancer Research Center; Departments of [2]Medicine, [3]Urology, and [4]Pathology, University of Washington School of Medicine; [5]Veterans Affairs Puget Sound Health Care System, Seattle, Washington; [6]Vancouver General Hospital, Vancouver, British Columbia, Canada; and [7]Oregon National Primate Research Center, Beaverton, Oregon

Abstract

Androgen deprivation therapy (ADT) remains the primary treatment for advanced prostate cancer. The efficacy of ADT has not been rigorously evaluated by demonstrating suppres- efficacy will require testing of novel approaches targeting complete suppression of systemic and intracrine contributions to the prostatic androgen microenvironment. [Cancer Res 2007;67(10):5033–41]

Two promising new agents for hormonal treatment of CRPC

Abiraterone acetate, an inhibitor of androgen synthesis

MDV-3100, an irreversible inhibitor of the androgen receptor

Both drugs have shown high rates of PSA response in phase II trials for men with CRPC, both pre- and post-chemotherapy

Both drugs are being evaluated in large RCTs:
Abiraterone + prednisone vs prednisone,
MDV-3100 vs placebo,
in both pre and post-chemotherapy settings

Design and End Points of Clinical Trials for Patients With Progressive Prostate Cancer and Castrate Levels of Testosterone: Recommendations of the Prostate Cancer Clinical Trials Working Group

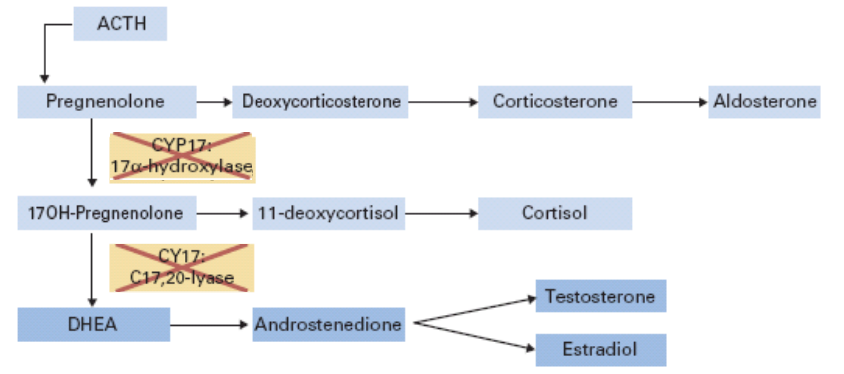
J Clin Oncol 26:1148-1159. © 2008

Howard I. Scher, Susan Halabi, Ian Tannock, Michael Morris, Cora N. Sternberg, Michael A. Carducci, Mario A. Eisenberger, Celestia Higano, Glenn J. Bubley, Robert Dreicer, Daniel Petrylak, Philip Kantoff, Ethan Basch, William Kevin Kelly, William D. Figg, Eric J. Small, Tomasz M. Beer, George Wilding, Alison Martin, and Maha Hussain

- **Increased emphasis on "time to event" endpoints as compared to "response" endpoints**
- **Early changes in PSA or pain to be ignored (unless overwhelming evidence of clinical progression) and treatment to be continued for at least 12 weeks**
- **No need to wait for anti-androgen withdrawal if there was no response to adding the anti-androgen**
- **Decreased emphasis on bone scans and rigorous requirements for defining progression by bone scan**

Abiraterone: a promising new drug

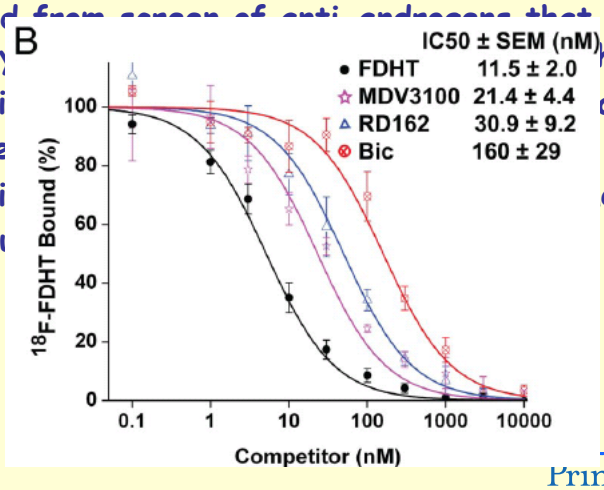
(from Attard et al, JCO 2008;26:4563-71)



MDV3100

(Tran et al: Science 2010;324:787-90)

- Derived from screen of anti-androgens that retain activity
- ↑ bindi
- ↓ nucle
- ↓ bindi
- ↓ recru



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Phase II results (PSA response rates in men with CRPC) for Abiraterone and MDV3100

Abiraterone, Chemotherapy-naïve

67% (28/42) (Attard et al: JCO 2009;27:3742-8)

Abiraterone, Post-chemotherapy

36% (22/57) (Danila et al: JCO 2010;28:1496-501)

51% (24/47) (Attard et al: JCO 2010;28:1489-95)

MDV3100, Phase I/II (54% post-chemo)

56% (78/140) (Scher et al: Lancet 2010;375:1437-46)

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How should Mr Eriksson be managed for castration-resistant prostate cancer (CRPC)

- Recognize that he has incurable cancer and Quality of life is important
- Optimize Mr Eriksson's pain control with regular dosing of narcotic medication, such as morphine
- Give regular laxatives to control the constipation that will be caused by morphine
- Give local radiotherapy to the right hip, his dominant site of pain
- Consider chemotherapy for men with diffuse symptoms or rapid PSA progression

Chemotherapy for castration-resistant prostate cancer

- Earlier trials showed that mitoxantrone + prednisone gave superior pain control and QoL compared to prednisone alone. There was no improvement in survival but the trials were too small to detect small differences (Tannock et al, JCO 1996:14;1756-64)
- Mitoxantrone remains a reasonable option and is very well tolerated.
- More recent trials have shown higher response rate (PSA and pain) and improved survival with docetaxel and prednisone, albeit with increased toxicity

(Tannock et al, NEJM 2004;351:1502-12
Petrylak et al, NEJM 2004;351:1513-20)

TAX 327 Study

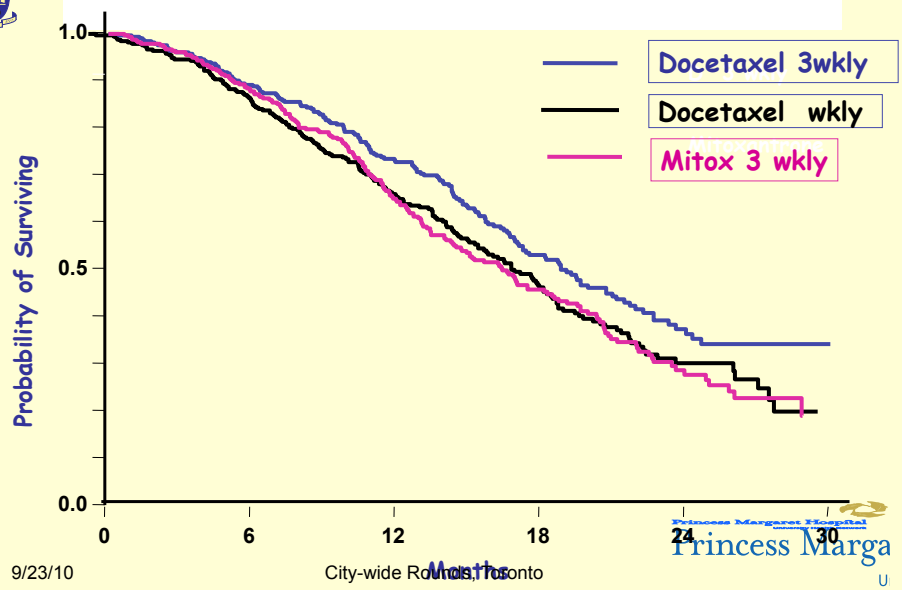
(Tannock et al, NEJM, 2004;351:1502-12)

1006 patients with HRPC

- Docetaxel 75 mg/m^2 q3wks x 10 cycles
- Docetaxel 30 mg/m^2 weekly for 5 of 6 weeks x 5 cycles
- Mitoxantrone 12 mg/m^2 q3 wks x 10 cycles

All patients received prednisone 10mg/day

Overall Survival



TAX 327: Secondary Endpoints

	Docetaxel q 3wk	Docetaxel weekly	Mitoxantrone q 3wk
Pain Response Rate	34.6% p=0.01	31.2% p=0.08	21.7%
PSA Response Rate	45.4% p=0.0005	47.9% p<0.0001	31.7%
QOL Response rate	21.9% p=0.009	22.6% p=0.005	13.1%

Mr Eriksson is treated with docetaxel every three weeks and prednisone

- He has relief of pain and by the 3rd course of treatment he is able to stop taking morphine
- His PSA declines steadily from 150 to 25 with the first 6 courses of treatment, but then begins to rise again to 70 after 8 courses
- He develops numbness in his hands and feet. His docetaxel is stopped because of this progression and to avoid further side effects

Should Mr Eriksson also receive a bisphosphonate?

Zoledronate Study

(Saad et al, JNCI 2002;94:1458-68 and 2004;96:879-82)

643 pts with HRPC

- Zoledronte 8mg q3wks
- Zoledronte 4mg q3wks
- Placebo q3wks

1. 8mg dose caused renal insufficiency and dropped
2. Less bone events with 4mg dose (44%) compared to placebo (33%, p=0.02) but no difference in QL
3. More low-grade toxicity with zoledronate

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Use of Zoledronate with Chemotherapy

- Zoledronate is a useful drug to decrease bone events in selected patients.
- Some cases of osteonecrosis of the jaw
- Annual zoledronate is sufficient to prevent osteopenia in patients on long-term anti-androgen therapy
- I know of no evidence to support use of this expensive drug at 3-weekly intervals with chemotherapy
- We are conducting a trial to evaluate duration of suppression of bone turnover after zoledronate

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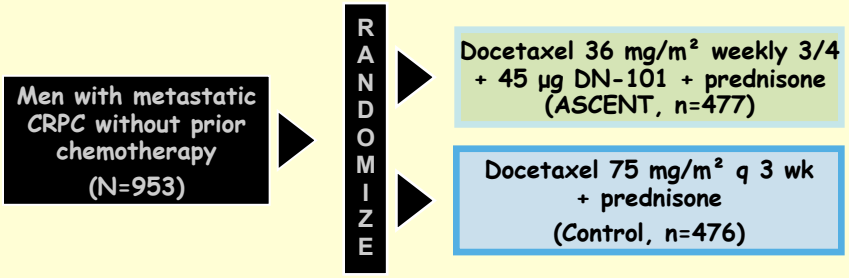
Is the RANK-ligand inhibitor Denosomab superior to Zoledronate?

- Denosomab is a fully humanized monoclonal antibody against RANK-L
- A RCT of 1901 patients compared denosomab with zoledronate (Fizazi et al, ASCO, 2010)
- Time to first Skeletal Related Event (SRE) was longer with denosomab – but there was no difference in survival or time to tumour progression.
- Adverse events were similar in both arms.
- Little to recommend this (undoubtedly) expensive drug

Might Mr Eriksson have greater benefit if treated with a molecular targeted agent in combination with docetaxel?

- Completed RCTs evaluating docetaxel plus:
  - High-dose calcitriol (DN-101)
  - Bevacizumab
  - GVAX (vaccine against common prostate cancer antigens)
  - …. have all been negative
- Other RCTs are evaluating docetaxel plus:
  - Aflibercept (VEGF-Trap)
  - Lenolidamide (Thalidomide analogue)
  - Atrasentan or Zibentan (Endothelin A antagonists)
  - Dasatanib (src/SFK inhibitor)
  - Custirsen (OGX-011, anti-clusterin, pro-apoptotic)

The ASCENT2 study: Docetaxel plus high-dose calcitriol versus docetaxel (plus prednisone) for patients with progressive CRPC (Scher et al, ASCO 2010)



Study was based on a placebo-controlled phase II study suggesting that docetaxel with DN-101 may increase survival compared to docetaxel alone

Results of ASCENT 2

	DN-101	Control	P-value
Median survival (months)	16.8	19.9	0.019 (0.002 by logrank)
Deaths due to prostate cancer	142	108	
Deaths due to other cause	32	30	
Dose modifications for docetaxel	229	160	

Trial was stopped early after an interim analysis showed more deaths in the DN-101 arm

What can we learn from this negative experience?

1. Docetaxel is a difficult partner – as yet, no drug has augmented its benefit for men with CRPC
2. Even large randomized phase 2 trials may be poor predictors of results in phase III
3. The role of dexamethasone

Some authors have suggested that the superior results of docetaxel compared to mitoxantrone in TAX327 and SWOG 99-16 might be due partly to dexamethasone

In ASCENT2 the experimental arm received greater exposure to dexamethasone (24mg weekly 3/4) compared to the control arm (24mg q 3 weeks) but had poorer survival

Docetaxel + prednisone +/- bevacizumab for CRPC (Kelly et al, ASCO, 2010)

Primary endpoint = Survival (OS)

Endpoint	DP + B (N=524)	DP (N=526)	HR	P-value
OS (mos)	22.6	21.5	0.91	0.18
PFS (mos)	9.9	7.5	0.77	<0.0001
PSA-RR	69.5%	57.9%		0.0002
Toxicity	↑↑			

Increase in OS and PFS are virtually identical to overview of 3 breast cancer trials – considered positive because primary endpoint was PFS

Three months after stopping docetaxel, Mr Eriksson is beginning to experience new pain in several areas and is back on morphine.

His PSA is fairly stable in the range of 60-80

Does this mean that his pain is due to causes other than progression of his disease?

NO – prostate cancer can evolve to a more aggressive form which produces less (or no) PSA during treatment

Should Mr Eriksson receive second-line chemotherapy?

- Mitoxantrone is often used second line, and is associated with ~15% PSA RR after docetaxel
- Some patients may respond to retreatment with docetaxel after an interval off-treatment
- Satraplatin was shown in a randomized trial to increase time to progression (but not survival) compared with prednisone alone – it was not approved by the FDA
- Cabazitaxel was shown recently to improve survival in an RCT compared to mitoxantrone

The TROPIC study: cabazitaxel or mitoxantrone with prednisone for metastatic CRPC previously treated with docetaxel (De Bono et al, ASCO 2010)

Men with metastatic CRPC progressing during and after docetaxel (N=755)

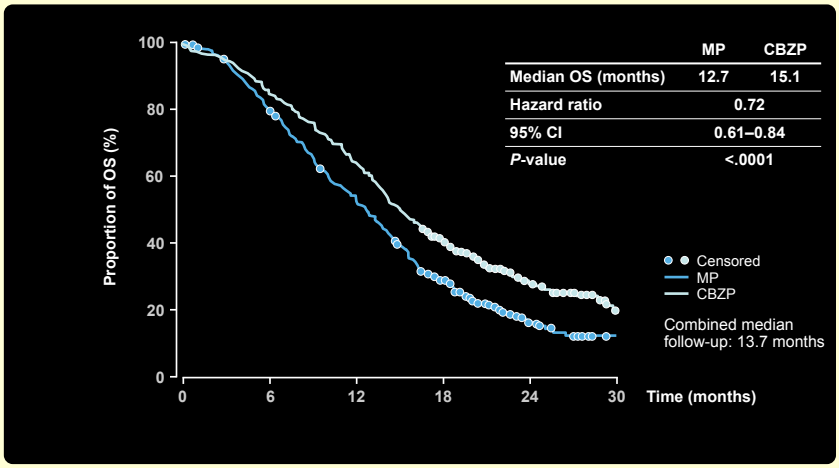
RANDOMIZE

- Cabazitaxel 25 mg/m² q 3 wk + prednisone for 10 courses (CBZP, n=378)
- Mitoxantrone 12 mg/m² q 3 wk + prednisone for 10 courses (MP, n=377)

Primary objective: Overall survival (To detect or R/O a HR<0.75)

Secondary objectives: PFS (tumor progression, pain progression, PSA progression, or death from any cause), response rate, safety

Overall Survival



	MP	CBZP
Median OS (months)	12.7	15.1
Hazard ratio	0.72	
95% CI	0.61–0.84	
P-value	<.0001	

The study met its primary objective

Important secondary results

Efficacy	MP	CBZP	p-value	Comment
Tumor response (%)	4.4	14.4	0.0005	
PSA response (%)	17.8	39.2	0.0002	MP consistent with other studies
Pain response (%)	7.8	9.2	0.63	Disappointing !

Toxicity	MP	CBZP	Comment
Toxic death	7 (1.9%)	18 (4.9%)	Concerning!
Neutropenic sepsis	1.3%	7.5%	
Diarrhea (≥ grade III)	0.3%	6.2%	Major impairment to quality of life
Neuropathy (%)		?????	

Other trials are evaluating various molecular targeted agents

Ongoing or completed phase III trials are evaluating:

Atrasentan and Zibotentan (Endothelin A antagonists)

Ipilumumab (anti-CTL4)

Sunitinib (multiple tyrosine kinase inhibitor)

Alpharadin (bone-seeking radioisotope)

Multiple targeted agents are in phase II evaluation

Mr Eriksson has treatment with mitoxantrone

He improves for about 4 months but then starts to have pain again and is tired.

His treatment is stopped, and he accepts that treatment will now be designed to minimize his symptoms.

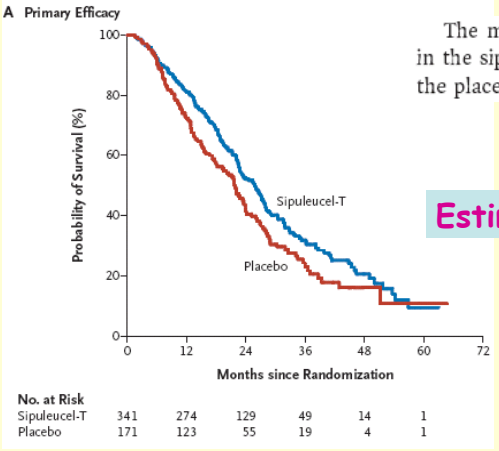
On his next visit to clinic, Mr Eriksson is clearly failing, but his wife brings a newspaper clipping about a new type of immunotherapy for prostate cancer

Couldn't this treatment be used to save my husband's life, she asks?

Sipuleucel-T Immunotherapy for Castration-Resistant Prostate Cancer

Philip W. Kantoff, M.D., Celestia S. Higano, M.D., Neal D. Shore, M.D., E. Roy Berger, M.D., Eric J. Small, M.D., David F. Penson, M.D., Charles H. Redfern, M.D., Anna C. Ferrari, M.D., Robert Dreicer, M.D., Robert B. Sims, M.D., Yi Xu, Ph.D., Mark W. Frohlich, M.D., and Paul F. Schellhammer, M.D., for the IMPACT Study Investigators*

N Engl J Med 2010;363:411-22.



The median survival was 4.1 months longer in the sipuleucel-T group (25.8 months) than in the placebo group (21.7 months) (Fig. 2A). The

Estimated cost = $93,000

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Thank you for your attention---and also to our international fellows who stimulate my ideas (but are not responsible for them)

ASCO 2007

Spain (2) Switzerland Australia (2)

Germany

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