Localized Prostate Cancer: A Primer for Herbalists

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2015
The Problem
Multiple Prostate Cancers

- Every tumor is heterogeneous
- Every tumor is monoclonal, frequently spread to multiple areas within prostate (Boyd 2012)
- Every tumor is unique (very likely)
- Genetic similarities and differences between each patient’s tumors
Epidemiology

- Most (70–80%) prostate cancer is localized and low-grade, non-metastatic, non-lethal (Eggener 2011)

- Put another way, only 20–30% of men with prostate cancer have aggressive disease that spreads, causes symptoms, and/or causes death
Definition of Low-Grade

- Gleason score 3+3 or 3+4 (possibly a single small focus of 4+3 that doesn’t change) — low grade
- At most 4 positive biopsy cores — localized
- <20% of cores are positive for cancer — localized
- No change over several years’ time
- PSA rises slowly (PSADT >2 yr, PSAV <1 ng/ml/yr)
Etiology

- Background environmental factors
- Diet and lifestyle
- Genetic mutations
- Genetics

Cancer
Overdiagnosis and Overtreatment

- Much low-grade prostate cancer is being diagnosed due to PSA screening = over diagnosed
- Many of these men are treated aggressively (surgery, radiation)
- This doesn’t extend life or improve quality of life = over treated
- Our job is actually to provide alternatives to ineffective, harmful conventional therapy in men with low-grade disease
PSA Debacle

- Richard Ablin, MD discovered PSA in 1970.
- By 2010 he said, in the New York Times, “PSA has been a hugely expensive public health disaster.”
- False positives very high, resulting in a LOT of unnecessary surgery and radiation
- False negatives are also sufficiently common to be a problem

Sensitivity: 67–80%
Specificity: 69–93%
PPV: 31–54%
NPV: 81–96%
NNS: >1,410
**NNT: 48**

References:
Schröder 2009;
Brawer 1999
<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>Method</th>
<th>Follow-Up</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andriole 2009 PLCO</td>
<td>US, n=76,693</td>
<td>DBR</td>
<td>7 yr</td>
<td>No benefit</td>
</tr>
<tr>
<td>Kjellman 2009 Stockholm</td>
<td>Sweden, n=1,782</td>
<td>DBR</td>
<td>12.9 yr</td>
<td>No benefit</td>
</tr>
<tr>
<td>Schröder 2009 ERSPC</td>
<td>Europe, n=182,160</td>
<td>DBR</td>
<td>9 yr</td>
<td>20% pr ca mortality decr</td>
</tr>
<tr>
<td>Labrie 2004 Quebec</td>
<td>Canada, n=46,486</td>
<td>R</td>
<td>15 yr</td>
<td>No benefit (also Ilic 2006)</td>
</tr>
<tr>
<td>Sandblom 2004 Norrköping</td>
<td>Sweden, n=9,026</td>
<td>R</td>
<td>11 yr</td>
<td>No benefit</td>
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Lifespan Issue

- How much time does this patient likely have left? (livingto100.com is one tool to decide)

- 50-yr-old man with 35 year life expectancy: that’s a long time for cancer to progress

- 75-year-old man with 10 year life expectancy: not much time for cancer to progress
What to Do
First Do Nothing

- Excellent site: http://www.prostatepointers.org/ww/wwopt.htm
- CT Tumor Registry: no need for aggressive tx for localized (Gleason <7) pr ca (Albertsen 2005)
- VACURG trial: RP vs placebo no difference (Iversen 1995)
- Modern tPSA screened patients with low-grade dz have very low pr ca mortality (Lu-Yao 2009)
- Scandinavian PCG-4 trial: most rigorous and unbiased; at 10 yr slightly improved pr ca and overall survival in RP vs WW group (Bill-Axelson 2005)
More Watchful Waiting

- No benefit for patient over 70 from aggressive tx; indeed, some indications of harm (Fleming 1993)
- 10-yr survival of British men with Gleason <7 and tPSA < 5 over 90% (Cuzick 2006)
- Meta-analysis--screen-detected pr ca pt with Gleason <7 and tPSA <10, no benefit of RP over WW (Alibhai 2004)
### Is Killing the Only Option?

<table>
<thead>
<tr>
<th>Medicinal mushrooms</th>
<th>Immune support</th>
<th>Re-differentiation</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Mahonia aquifolium</em></td>
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<tr>
<td><em>Convolvulus arvensis</em></td>
<td>Angiogenesis inhibition</td>
<td>Energy deprivation</td>
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<tr>
<td>Redox modulators</td>
<td>Prevent new mutations</td>
<td>Metastasis inhibition</td>
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<td></td>
<td>Reduce choline</td>
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<td>Modified citrus pectin</td>
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</table>
Ornish Approach Original Trial

- n=93 (with T1c pr ca, Gleason 7 or less) (Ornish 2005)

- Baseline tPSA 4–10 ng/ml; decline 4% on average

- Randomized to Ornish approach (pescovegan, stress reduction, exercise), vs watchful waiting

- No Ornish patient required invasive treatment after 6 mon of treatment (6 controls did)
Ornish Approach Trial 2

$n=14$, all T1c prostate cancer (Nguyen 2006)

6 mon duration

All on vegan diet, tai chi for stress reduction

PSADT change: 12 mon to 112 mon (average)

tPSA: fell in 9 of 10 evaluable patients
Additional Trials

- Two-year follow-up: 2 of 43 (5%) of Ornish group vs 13 of 49 (27%) of controls had definitive therapy; no differences in PSA kinetics between groups (Frattaroli 2008)

- Beneficial changes in risk factors with Ornish diet (Dewell 2008)

- Beneficial changes in gene expression with Ornish diet (Ornish 2008)
Vegan Diet Enhancements

- All organic food
- Include some fish (Ornish even says to do this now)
- Insulin sensitizing spices (cinnamon, cloves)
- Omega 3 fatty acids sources---hemp, walnut, fish
- Reduce omega 6 fatty acid intake
- It’s vegetarian not grainitarian: avoid sugar & starch
- Exercise, stress reduction
Camellia sinensis (green tea)

- Meta-analysis of epidemiologic studies shows it is protective (Zheng 2011)

- In particular protects against aggressive dz (Kurahashi 2007)

- Multiple mechanisms likely

- Clinical trial: n=60 men with HGPIN, green tea catechins 600 mg qd vs placebo x 1 yr, decreased progression to prostate cancer w/ treatment (Bettuzzi 2006)
Tomatoes

- Meta-analysis finds high-level intake protective (Etminan 2004)

- Is it really just a lycopene delivery vehicle?
Estrogen Catabolism

Cruciferous veggies preventative (Liu 2012)

- Androstenedione → Estrone → 2-hydroxy metabolites
- Testosterone → Estradiol → 4-hydroxy metabolites
- Estriol → 16-alpha-metabolites

Aromatase inhibitors??

Cyt P450 (Heath 2010; Kong 2012)

non-carcinogenic

carcinogenic (Markushin 2006)
carcinogenic (Barba 2009)

Glucosinolates

Aromatase inhibitors??

Cyt P450
Urine 2/16α Ratio and Soy

- Higher urine 2/16α-hydroxyestrone ratio protective against prostate cancer in at least two studies (Barba 2009; Muti 2002)

- Each point higher tPSA equates to 14% decrease in 2-hydroxyestrone in urine (Teas 2005)

- Soy protein raises 2/16α-hydroxyestrone ratio in men at risk of pr ca (Hamilton-Reeves 2007)

- Soy foods: meta-analysis found intake protective (Hwang 2009)
The Totality of Soy

- Isoflavones
- Protein
- Inositol hexaphosphate (phytic acid)
- Bowman-Birk protease

Glycine max (soy)
Legumes and Isoflavones

- Higher intake of legumes and higher serum genistein protective (Travis 2009)
- Soy protein intake (w/ or w/o isoflavones) reduces HGPIN compared to milk protein 40 g qd after 6 mon (Hamilton-Reeves 2008)
- Soy isoflavones 60 mg qd reduces tPSA in early prostate cancer (Kumar 2004)
Isoflavones Trial

❖ n=52, full range of past tx (WW, RP, RT, ADT), full range of Gleason scores, 6 months (deVere White 2004)

❖ 450 mg genistein w/ 450 mg other isoflavones w/ Ganoderma mushroom polysaccharides qd

❖ 8 of 13 with WW had no rise or >50% decline in tPSA
Importance of Equol Conversion

**Ref:** Matthies 2012

30-50% of adult population can form equol (Matthies 2008)

*Slackia isoflavoniconvertens*
Isoflavones

- Review of existing 11 clinical trials (Messina 2006)
- Dose range: 60–900 mg isoflavones/d from soy
- Sample sizes: 8–62
- Duration: 20–360 d
- 4 of 8 studies in prostate cancer patients showed PSAV slowing
Isoflavones in kudzu

- *Pueraria montana* (kudzu) -- 10x higher levels than soy (Kaufman 1997)

- Not present in pure white commercial starch (look for brown)

- Completely safe, widely used as food in Asia

- All legumes have isoflavones (black beans, navy beans good sources) -- not all have huge PR firms
Artemisia annua

- Case studies with various human neoplasms (Singh 2006; Berger 2005).
- Iron not necessary for antineoplastic activity.
- Autoinduces intestinal CYP2D6; requires pulsed dosing (see next slide).
- Also metabolized by intestinal CYP3A4 (non-inducible).
- Other compounds synergistic (pump inhibitors, absorption enhancers).
Pharmacokinetics

artemisinin and semi-synthetics

CYP2B6
CYP3A4 (if 2B6 is low)
CYP2A6 (minor)

Autoinduction (Simonsson 2003)
deoxyartemisinin, other breakdown products

Ref: Svensson 1999

CYP2A6 (artesunate)
CYP3A4/5 (artemether)
CYP3A4 (arteether)

UGT1A9
UGT2B7

α-dihydroartemisinin-β-glucuronide

red = inactive

(semisynthetics only)
Artemisinin dosing

- Initial: 300-400 mg tid x 7 d
- Grapefruit juice first 3-4 days
- Monitor for neuropathies (rare at 300 mg tid)
- Take with 3-5 ml tincture or 2-3 g capsules tid
- Enhanced by combination with butyric acid, 10+ g qd po (Anticancer Res 2005;25:4325-31)
Results with Artemisinin in non-RP Patients

- 6/10 (60%) overall met criteria for efficacy (PSA kinetics improvement or stabilization)
- 3/10 (30%) had negative PSADT and PSAV
- 1/10 (10%) had biopsy-proven elimination of HGPIN
- 2/10 (20%) lost to follow-up
- 1/10 (10%) chose RP, no sign of spread at surgery
- 1/10 (10%) provided no follow-up data
<table>
<thead>
<tr>
<th>Age, Race</th>
<th>Stage, Gleason</th>
<th>Cores Positive</th>
<th>tPSA post-RP</th>
</tr>
</thead>
<tbody>
<tr>
<td>61, W</td>
<td>T2a, 4+3, 4+4</td>
<td>5/12</td>
<td>0.03</td>
</tr>
<tr>
<td>54, W</td>
<td>T1c, 3+3</td>
<td>1/6</td>
<td>0.03</td>
</tr>
<tr>
<td>68, AA</td>
<td>T1c, ?</td>
<td>6/6</td>
<td>0.06</td>
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<tr>
<td>63, W</td>
<td>T1c, 3+3</td>
<td>?</td>
<td>0.2</td>
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<tr>
<td>51, W</td>
<td>T2b, 5+4</td>
<td>?</td>
<td>0.47</td>
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<tr>
<td>Patient</td>
<td>Tx Duration</td>
<td>PSADT (yr)</td>
<td>PSAV (ng/ml/yr)</td>
</tr>
<tr>
<td>---------</td>
<td>-------------</td>
<td>------------</td>
<td>----------------</td>
</tr>
<tr>
<td>61, W</td>
<td>10 mon</td>
<td>negative</td>
<td>negative</td>
</tr>
<tr>
<td>54, W</td>
<td>4 mon</td>
<td>1.07</td>
<td>0.12</td>
</tr>
<tr>
<td>68, AA</td>
<td>3 mon</td>
<td>unknown</td>
<td>unknown</td>
</tr>
<tr>
<td>63, W</td>
<td>22 mon</td>
<td>0.75</td>
<td>3.17</td>
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<tr>
<td>51, W</td>
<td>10 mon</td>
<td>0.38</td>
<td>1.77</td>
</tr>
</tbody>
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Immune Support

- Surprisingly little research (compared to other cancers) esp. w/ *Trametes versicolor* (clinical trials ongoing at Bastyr University right now)

- Lentinan (from *Lentinula edodes*) 2 mg IV q wk very helpful in advanced disease (Tari 1994)

- Mushrooms by themselves are clearly not sufficient (deVere White 2002; Sumiyoshi 2010), must be combined with other tx
Modified Citrus Pectin

- Anti-metastatic by blocking galectin receptors
- A reminder that metastasis is not random
- The only clinical study of this was a small one for prostate cancer
- Many preclinical studies
- Dose: 5 g qd-tid
Initial trial: All patients post-RP or radiation therapy, tPSA<5, 8 oz Pom Wonderful per day, PSADT increased from 15 to 54 mo. No significant adverse effects (Pantuck 2006)

Small randomized trial confirmed these results in men with low-grade cancer using 1 and 3 g extracts (Paller 2013)
Pomegranate Synergy?

- Seed oil, pericarp, and fermented juice
- DU145 human pr ca cells tested in vitro
- All fractions synergistic
- Food/herbs are not reducible without losing something.
- Ref: Lansky 2005
## Anticancer Herbs of Interest

<table>
<thead>
<tr>
<th>Annona muricata</th>
<th>Zizyphus spinosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catharanthus roseus</td>
<td>Cephalotaxus fortunei</td>
</tr>
<tr>
<td>Mahonia aquifolium</td>
<td>Dicentra formosa</td>
</tr>
<tr>
<td>Phytolacca americana</td>
<td>Trichosanthes kirilowii</td>
</tr>
<tr>
<td>Rheum palmatum</td>
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</tr>
</tbody>
</table>
Annona muricata
Catharanthus roseus

vinblastine

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Mahonia aquifolium
Phytolacca americana

Photo © 2015 Yarnell
Rheum palmatum
Zizyphus jujube
Taxus brevifolia

paclitaxel
Cephalotaxus harringtonii

Photo © 2015 Yarnell
Dicentra formosa
Trichosanthes kirilowii

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Glossary

ADT = androgen deprivation therapy

cdTRUSP = color Doppler transrectal ultrasound of the prostate

CRP = C-reactive protein

CTC = circulating tumor cells

DRE = digital rectal exam

E1 = estrone; E2 = estradiol

eMRS = endorectal magnetic resonance spectroscopy

fPSA = free PSA

GnRH = gonadotropin-releasing hormone

HGPIN = high-grade prostatic intraepithelial neoplasia

HIFU = high-intensity focused ultrasound

IGF-1 = insulin-like growth factor-1

NNS = number needed to screen

NNT = number needed to treat

NPV = negative predictive value

PAP = prostatic acid phosphatase

PPV = positive predictive value

PSA = prostate-specific antigen

PSADT = PSA doubling time

PSAV = PSA velocity

RP = radical prostatectomy

T1C = stage T1C of prostate cancer

(PSA detected only cancer)

tPSA = total PSA

TRUSP = transrectal ultrasound of the prostate

UTI = urinary tract infection

WW = watchful waiting