A Competing Risk Analysis of Men Age 55-74 Years at Diagnosis Managed Conservatively for Clinically Localized Prostate Cancer

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Background

1998: md's will dx prostate ca. in 200,000 U.S. men.

Many will be offered treatments designed to cure and/or control progression of their disease.

No data from large randomized trials.

?? relative efficacy of

- aggressive treatment

    vs.

more conservative approach
(watchful waiting followed by androgen suppression for symptomatic metastatic disease)
Background ...
Long term outcomes with conservative management

- focus on older men
  modest cancer mortality if low/moderate grade tumors.

- little information on outcomes in younger men

Treatment selection based on data from 3º centers
  (radical prostatectomy; radiation therapy)

- little info on competing medical risks
  (increasingly important as men age)
Aims ...

Estimate survival based on competing risk analysis

• men diagnosed with clinically localized prostate ca.
• who did not receive surgery or radiation therapy.

Primary objective

Estimate probability of dying from prostate cancer or other competing causes given a patient’s tumor histology and age at diagnosis.
Patients selected to meet 4 criteria:

1) long term follow-up extending over 10-20 years after diagnosis to capture the impact of prostate cancer and competing medical hazards,

2) men age 55-74 years at diagnosis to identify a series of men who have an average life expectancy greater than 10 years,

3) availability of original histology material contemporary grading, Gleason scoring system

4) n sufficiently large stratification by biopsy Gleason score & age at dx
Subjects and Methods

*Patient Identification and Data Collection:*

Connecticut Tumor Registry

Patients age 55-74 years at diagnosis


Patients noted to have metastases excluded.

Attempted to locate hospital medical records

36 acute care hospitals /2 VA medical centers
Charts abstracted on site
- confirmed date of dx
- additional info re:
  - method of dx, metastatic evaluations,
  - method of tx, associated co-morbidities.

Abstractors blinded to the long term outcome of the patients as recorded by the Registry.

Original histology slides located & mailed to referee pathologist (blinded to the long term outcome)
- grading using the Gleason classification system.
Subjects and Methods

Data

Hospital record
- method of case finding (needle bx/turp/open prostatectomy),
- results of procedures performed to exclude metastases
- any treatment initiated within six months of diagnosis.
- other concomitant diseases : instrument by Charlson et. al

- Vital status as of March 1, 1997
- If patient deceased, attempted to retrieve the original death certificate.
  • Died from prostate cancer
    if any one of 3 causes listed was prostate cancer.
  • Died of competing medical conditions
    if prostate cancer did not appear on one of these 3 lines

- Patients not followed until death considered alive until date of last contact.
### 767 patients with putative localized prostate cancer

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (mean, years)</td>
<td>68</td>
</tr>
<tr>
<td>Year of diagnosis (mean)</td>
<td>1979</td>
</tr>
<tr>
<td>Years from dx to death or last contact (mean)</td>
<td>8.6</td>
</tr>
<tr>
<td>Caucasian</td>
<td>94%</td>
</tr>
<tr>
<td>Number followed until death</td>
<td>80%</td>
</tr>
<tr>
<td>Number followed alive for &gt; 15 years</td>
<td>10%</td>
</tr>
<tr>
<td>Number followed alive for 10-15 years</td>
<td>10%</td>
</tr>
<tr>
<td>Information available concerning cause of death</td>
<td>91%</td>
</tr>
<tr>
<td>Digital examination</td>
<td></td>
</tr>
<tr>
<td>not suspicious for cancer</td>
<td>51%</td>
</tr>
<tr>
<td>suspicious: confined within prostate</td>
<td>15%</td>
</tr>
<tr>
<td>suspicious: extending through capsule</td>
<td>5%</td>
</tr>
<tr>
<td>suspicious: no further information</td>
<td>24%</td>
</tr>
<tr>
<td>not done or result unknown</td>
<td>5%</td>
</tr>
<tr>
<td>Method of diagnosis</td>
<td></td>
</tr>
<tr>
<td>transurethral resection of prostate</td>
<td>60%</td>
</tr>
</tbody>
</table>
simple open prostatectomy 11%
needle biopsy of prostate 26%
other or unknown 3%

**Total acid phosphatase**
- normal 53%
- elevated, <2x upper limit of normal 6%
- elevated, >2x upper limit of normal 3%
- elevated, magnitude unknown 2%
- done, but result unknown 3%
- not done 33%

**Bone scan performed - no metastases** 30%
**Metastatic survey done; no metastases** 27%
**No tests for metastatic disease performed** 21%

**Treatment within six months of diagnosis**
- none 58%
- orchiectomy 16%
- estrogen therapy 22%
- both 4%
Concurrent medical conditions (if >5%)
- myocardial infarction 12%
- congestive heart failure 8%
- peripheral vascular disease 6%
- cerebrovascular disease 7%
- chronic pulmonary disease 20%
- diabetes 10%
- peptic ulcer disease 11%

Vital status at last contact
- alive 21%
- dead of other causes 46%
- dead of prostate cancer 26%
- dead, unable to ascertain cause 7%
Comorbidity & Immediate anti-androgen treatment

181 : several co-morbidity (Charlson score >2
- mortality rate ratio 95% CI 1.6-2.2 (adjusted for age).
- prostate ca. mortality rate ratio 95% CI 0.95-1.69.

586 : few or no comorbidities (Charlson score 0-1).

42% : received immediate anti-androgen treatment
- mortality rate ratio 95% CI 1.42-1.87
  after adjusting for age and comorbidity
- prostate ca. mortality rate ratio: 95% CI 2.19-3.60

58% : received no immediate anti-androgen therapy
Statistical Methods

Objective  probability of dying from prostate ca. or competing causes given pt’s age at dx & tumor histology.

1 Table: (20 age-histology combinations) numbers of men ...
    alive  dead from prostate ca  dead from other causes

2 More refined competing risk analysis, based on two inputs:
   
   • rate of death from prostate cancer
   • rate of death from other causes
   each rate fitted as smooth function of age at dx, Gleason score and year of follow-up

   (functions derived from regression models)
### Distribution, comorbidity scores and outcome of the 767 patients

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>55-59</th>
<th>60-64</th>
<th>65-69</th>
<th>70-75</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-4</td>
<td>11</td>
<td>35</td>
<td>42</td>
<td>50</td>
<td>138</td>
</tr>
<tr>
<td></td>
<td>10,1</td>
<td>30,5</td>
<td>29,13</td>
<td>35,15</td>
<td>104,34</td>
</tr>
<tr>
<td></td>
<td>5,6,0,0</td>
<td>15,16,4,0</td>
<td>14,22,3,3</td>
<td>16,28,1,5</td>
<td>50,72,8,8</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>24</td>
<td>43</td>
<td>43</td>
<td>118</td>
</tr>
<tr>
<td></td>
<td>8,0</td>
<td>19,5</td>
<td>7,36</td>
<td>33,10</td>
<td>96,22</td>
</tr>
<tr>
<td></td>
<td>8,0,0,0</td>
<td>13,9,0,2</td>
<td>16,22,1,4</td>
<td>4,29,6,4</td>
<td>41,60,7,10</td>
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<tr>
<td>6</td>
<td>25</td>
<td>45</td>
<td>84</td>
<td>140</td>
<td>294</td>
</tr>
<tr>
<td></td>
<td>18,7</td>
<td>37,8</td>
<td>65,19</td>
<td>103,37</td>
<td>223,71</td>
</tr>
<tr>
<td></td>
<td>12,6,2,5</td>
<td>15,16,5,9</td>
<td>20,37,5,22</td>
<td>8,87,10,35</td>
<td>55,146,22,71</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
<td>22</td>
<td>43</td>
<td>64</td>
<td>137</td>
</tr>
<tr>
<td></td>
<td>6,2</td>
<td>17,5</td>
<td>33,10</td>
<td>48,16</td>
<td>104,33</td>
</tr>
<tr>
<td></td>
<td>1,1,2,4</td>
<td>2,3,0,17</td>
<td>3,23,5,12</td>
<td>2,31,5,26</td>
<td>8,58,12,59</td>
</tr>
<tr>
<td>8-10</td>
<td>2</td>
<td>15</td>
<td>30</td>
<td>33</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>2,0</td>
<td>13,2</td>
<td>17,13</td>
<td>27,6</td>
<td>59,21</td>
</tr>
<tr>
<td></td>
<td>0,0,1,1</td>
<td>0,1,3,1,1</td>
<td>2,10,1,17</td>
<td>1,8,3,21</td>
<td>3,19,8,50</td>
</tr>
<tr>
<td>All</td>
<td>54</td>
<td>141</td>
<td>242</td>
<td>330</td>
<td>767</td>
</tr>
<tr>
<td></td>
<td>44,10</td>
<td>116,25</td>
<td>180,62</td>
<td>246,84</td>
<td>586,181</td>
</tr>
<tr>
<td></td>
<td>26,13,5,10</td>
<td>45,45,12,39</td>
<td>55,114,15,58</td>
<td>31,183,25,91</td>
<td>157,355,57,198</td>
</tr>
</tbody>
</table>

Sample Size: Number of patients with Charlson score 0-1, number of patients with Charlson score ≥ 2
Number still alive, number dead from other causes, number dead of unknown cause, number dead from prostate cancer
57 men known to have died, but cause not known ...

imputed cause for each, separately for each histology category using distribution of deaths of known cause in category.

e.g.: men with Gleason score 2-4 tumors

72 deaths from competing hazards
8 deaths from prostate cancer (ratio 9:1)

each of 8 deaths of undetermined cause counted as
0.9 of a death from competing hazards
0.1 of a death from prostate cancer.

In all..

218.6 (198 known + 20.6 imputed) deaths from prostate ca
391.4 (355 known + 36.4 imputed) deaths from competing medical hazards.
Estimation of rates of death from prostate cancer and rates of death from competing medical hazards

separate Poisson regression analyses for each cause

6626 man-years of follow-up

Poisson link in the GENMOD procedure in SAS
(allowing non-integer numbers of events)

rates as a function of age at dx, histology and time since dx:

Estimation of proportions of men

alive  dead from prostate ca  dead from other causes

at a given no. of years following diagnosis

applied two fitted rates to the proportion of men still alive at the beginning of each successive follow-up interval
Estimated 15-year outcomes (%) for patients with putatively localized cancer managed conservatively

**AGE AT DIAGNOSIS**

<table>
<thead>
<tr>
<th>Gleason SCORE</th>
<th>55-59</th>
<th>60-64</th>
<th>65-69</th>
<th>70-74</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-4</td>
<td>A 69  O 27  C 4</td>
<td>A 55  O 40  C 5</td>
<td>A 38  O 56  C 6</td>
<td>A 20  O 73  C 7</td>
</tr>
<tr>
<td>5</td>
<td>A 67  O 27  C 6</td>
<td>A 53  O 39  C 8</td>
<td>A 35  O 55  C 10</td>
<td>A 18  O 71  C 11</td>
</tr>
<tr>
<td>7</td>
<td>A 15  O 15  C 70</td>
<td>A 14  O 24  C 62</td>
<td>A 11  O 36  C 53</td>
<td>A 7   O 51  C 42</td>
</tr>
<tr>
<td>8-10</td>
<td>A 3   O 10  C 87</td>
<td>A 3   O 16  C 81</td>
<td>A 3   O 25  C 72</td>
<td>A 2   O 38  C 60</td>
</tr>
</tbody>
</table>

A Percent Alive
OD Percent Dead of Other Disease
CA Percent Dead of Prostate Cancer

percentages derived from regression-based competing risks model)
Other reports of outcomes following conservative management:

• 1997, Johansson (15 year analysis of population based cohort of 642 men)  
  300 localized disease; 85 < 70 years; approx 1/2 well differentiated tumors. 
  
    died from prostate cancer
    well differentiated disease                  6%
    moderately differentiated disease           17%
    poorly differentiated                        56%

• 1994 Chodak (828 men; pooled from six studies)  
  
    10-yr disease-specific survival
    well & moderately differentiated tumors      87%
    poorly differentiated tumors                 34%

• 1995 Albertsen:411 men age 65-75 years at diagnosis 1971-1976  
  (334 included in 1998 report)  
  
    15 year cum. mortality from prostate ca.
    Score 2-4                                  9%
    Score 5-7                                  28%
    Score 8-10                                 51%
Aus et. al.: 301 Swedish men diagnosed with localized prostate cancer who died during the period 1988-1990.

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>Aus</th>
<th>Us</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-5</td>
<td>33%</td>
<td>33%</td>
</tr>
<tr>
<td>6-7</td>
<td>39%</td>
<td>56%</td>
</tr>
<tr>
<td>8-10</td>
<td>28%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Disease-specific survival of patients who survive > 10 years following dx with prostate ca. 55%

Died from prostate cancer within next 5 ys 11%
Died from competing hazards 30%
Still alive 56%
• Lead time in contemporary PSA-detected cases

Gann et. al.: a single elevated PSA measurement can detect

- 80% of aggressive cancers 5 yrs < clinical appearance
- 50% of aggressive cancers 9-10 yrs < clinical appearance

Contemporary patients will having a seemingly longer survival following dx compared with our study population.

• Patients in this series did not undergo PSA testing
• Did not have modern imaging studies

- high probability that this series contains a number of patients with non-localized disease.

- our case fatality estimates are probably over-estimates

Modern practice of initiating anti-androgen therapy based upon a rising serum PSA
Some researchers suggest that early anti-androgen therapy improves patient survival especially among patients with minimal disease.

Δ's in screening, staging and use of anti-androgen therapy

=> contemporary patients with clinically localized prostate ca likely to have superior survival outcomes to our population

**TURP-detected vs PSA-detected cancers**

Walsh & Brooks: lead time bias (TURP) > lead time bias (PSA)

26% of men dx'ed following needle biopsy of the prostate
71% of men dx'ed following TURP/ open prostatectomy

=> after adjusting for Gleason score and pt. age, no significant difference in survival of these two groups.

=> Patients dx'ed with nonpalpable disease (PSA detected) and managed conservatively would probably have survival curves that are better than those in figure.
Study limitations:

Inadequate staging evaluations, so some men with regional or metastatic disease are probably included
(shorter survival for men receiving immediate vs delayed anti-androgen therapy)

Patients excluded because of incomplete or absent records, absent histology slides or documentation of aggressive treatments such as surgery, radiation or brachytherapy.

As part of our preliminary analysis, we evaluated office based medical records for a subset of the patients included in this analysis. No instances of aggressive interventions that were not also identified in the hospital medical record.

Chart reviews did not reveal why men chose conservative management as opposed to more aggressive alternatives.
Summary

Managed conservatively, men with well differentiated, localized disease on prostate biopsy (Gleason scores 2-4) face a minimal risk of death from prostate cancer within 15 yrs of dx.

Men with poorly differentiated disease (Gleason scores 7-10) face a high risk of death from prostate cancer when treated conservatively even when diagnosed as late as age 75 years.

Men with moderately differentiated disease (Gleason scores 5-6) face a modest risk of death from prostate cancer that increases slowly over at least fifteen years of follow up.

These men face a risk of dying from prostate cancer, but it is unclear from a population perspective what percentage of these men will actually benefit from treatment.

Only through randomized trials to measure tx efficacy and additional research on issues surrounding health related quality of life can we answer questions concerning which patients benefit from aggressive screening and tx of prostate cancer.