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

Newly dxed prostate ca. between 1971 and 1984.

Patients noted to have metastates 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

CTR & Vital Statistics Bureau of CT Dept of Health.

- 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

Age at diagnosis (mean, years)	68
Year of diagnosis (mean)	1979
Years from dx to death or last contact (mean)	8.6
Caucasian	94%
Number followed until death	80%
Number followed alive for > 15 years	10%
Number followed alive for 10-15 years	10%
Information available concerning cause of death	91%
Digital examination	
not suspicious for cancer	51%
suspicious: confined within prostate	15%
suspicious: extending through capsule	5%
suspicious: no further information	24%
not done or result unknown	5%
Method of diagnosis	
transurethral resection of prostate	60%

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

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

Sample Size ; Number of patients with Charlson score 0-1, number of patients with Charlson score $\geq$ 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
(allows non-integer numbers of events)

rates as 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

Gleason SCORE	55-59			60-64			65-69			70-74		
	A	OD	CA	A	OD	CA	A	OD	CA	A	OD	CA
2-4	69	27	4	55	40	5	38	56	6	20	73	7
5	67	27	6	53	39	8	35	55	10	18	71	11
6	57	25	18	41	36	23	25	48	27	11	59	30
7	15	15	70	14	24	62	11	36	53	7	51	42
8-10	3	10	87	3	16	81	3	25	72	2	38	60

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 diseasedisease	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.

		Aus	Us
Gleason score	2-5	33%	33%
	6-7	39%	56%
	8-10	28%	10%

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.