Estimating/reporting profile-specific risk functions from clinical trial data

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OUTLINE

- Profile-specific risk estimates
- Our survey of reporting practices
- How to obtain profile-specific risk estimates from Cox model
- A heuristic for estimator of the “baseline survival function” from Cox model
- Reporting an entire set of estimated profile-specific risks in a compact form

20-Year Outcomes Following Conservative Management of Clinically Localized Prostate Cancer

Peter C. Albertsen, MD, MS
James A. Hanley, PhD
Judith Fine, BA

Context The appropriate therapy for men with clinically localized prostate cancer is uncertain. A recent study suggested an increasing prostate cancer mortality rate for men who are alive more than 15 years following diagnosis.

Objective To estimate 20-year survival based on a competing risk analysis of men who were diagnosed with clinically localized prostate cancer and treated with observation or androgen withdrawal therapy alone, stratified by age at diagnosis and histological findings.

Design, Setting, and Patients A retrospective population-based cohort study using Connecticut Tumor Registry data supplemented by hospital record and histology review of 767 men aged 55 to 74 years with clinically localized prostate cancer diagnosed between January 1, 1971, and December 31, 1984. Patients were treated with either observation or immediate or delayed androgen withdrawal therapy, with a median observation of 24 years.

Main Outcome Measures Probability of mortality from prostate cancer or other competing medical conditions, given a patient's age at diagnosis and tumor grade.

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Table 2. Age Distribution, Comorbidity Scores, and 20-Year Outcome of 767 Patients With Clinically Localized Prostate Cancer Followed Up for a Median of 24 Years

	Age at Diagnosis, y				
	55-59	60-64	65-69	70-74	Total No. (%)
Gleason Score at Diagnosis of 2-4					
Sample size	11	35	42	50	138 (100)
Charlson score*					
0-1	10	30	29	35	104 (75)
≥2	1	5	13	15	34 (25)
No. of patients deceased due to					
Prostate cancer	0	1	3	6	10 (7)
Other causes	8	25	32	38	103 (75)
Unknown causes†	0	2	2	4	8 (6)
No. of patients alive	3	7	5	2	17 (12)
Gleason Score at Diagnosis of 5					
Sample size	8	24	43	43	118 (100)
Charlson score*					
0-1	8	19	36	33	96 (81)
≥2	0	5	7	10	22 (19)
No. of patients deceased due to					
Prostate cancer	1	3	6	6	16 (14)
Other causes	3	16	32	35	86 (73)
Unknown causes†	1	1	1	1	4 (3)
No. of patients alive	3	4	4	1	12 (10)
Gleason Score at Diagnosis of 6					
Sample size	25	45	84	140	294 (100)
Charlson score*					
0-1	18	37	65	103	223 (76)
≥2	7	8	19	37	71 (24)
No. of patients deceased due to					
Prostate cancer	5	13	24	39	81 (27)
Other causes	11	25	53	98	187 (64)
Unknown causes†	0	2	3	3	8 (3)
No. of patients alive	9	5	4	0	18 (6)
Gleason Score at Diagnosis of 7					
Sample size	8	22	43	64	137 (100)
Charlson score*					
0-1	6	17	33	48	104 (76)
≥2	2	5	10	16	33 (24)
No. of patients deceased due to					
Prostate cancer	4	18	14	26	62 (45)
Other causes	2	3	29	36	70 (51)
Unknown causes†	2	0	0	1	3 (2)
No. of patients alive	0	1	0	1	2 (2)
Gleason Score at Diagnosis of 8-10					
Sample size	2	15	30	33	80 (100)
Charlson score*					
0-1	2	13	17	27	59 (74)
≥2	0	2	13	6	21 (26)
No. of patients deceased due to					
Prostate cancer	1	13	18	21	53 (66)
Other causes	0	1	11	12	24 (30)
Unknown causes†	1	1	0	0	2 (3)
No. of patients alive	0	0	1	0	1 (1)

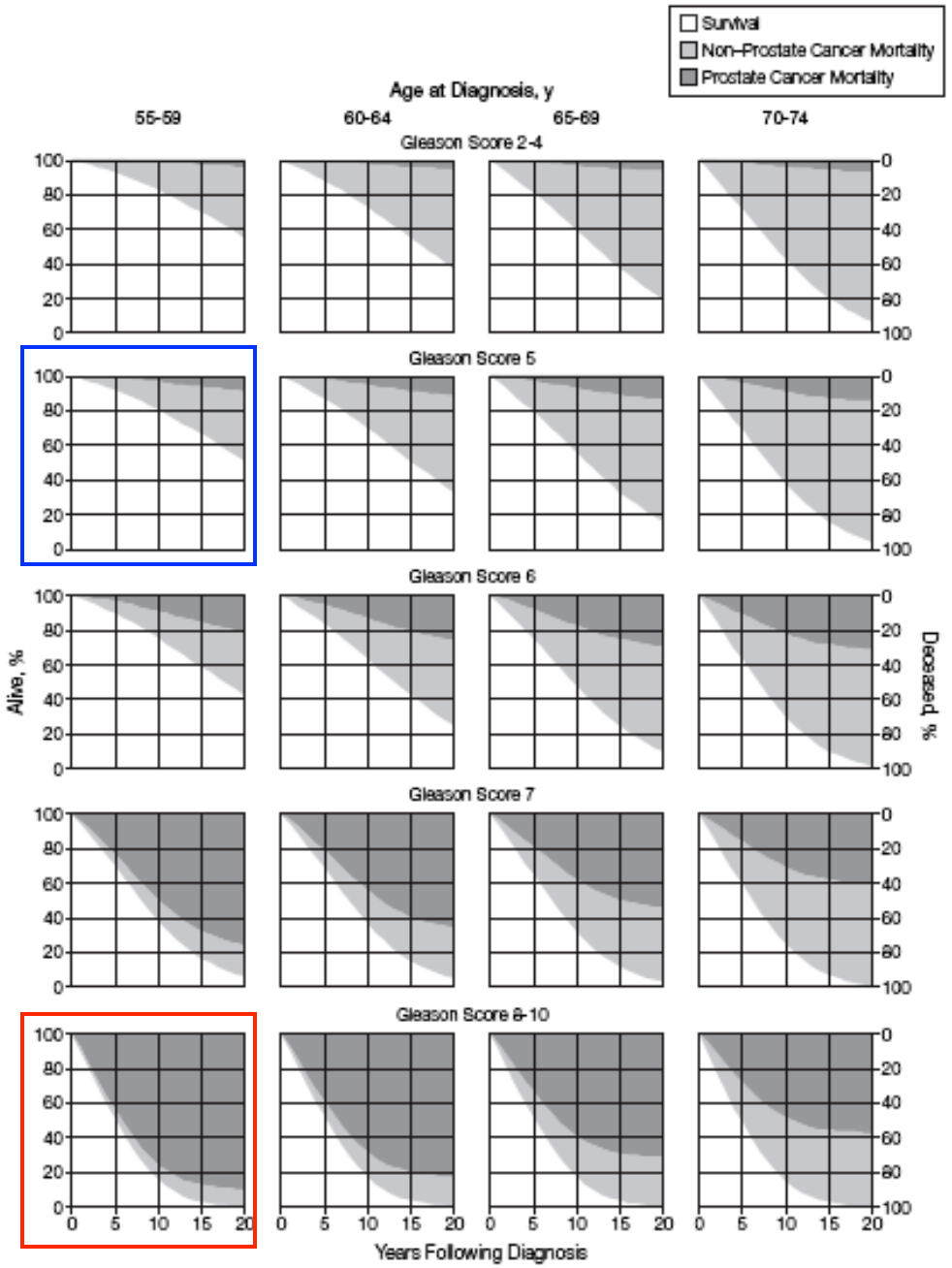
Gleason Score at Diagnosis of 5

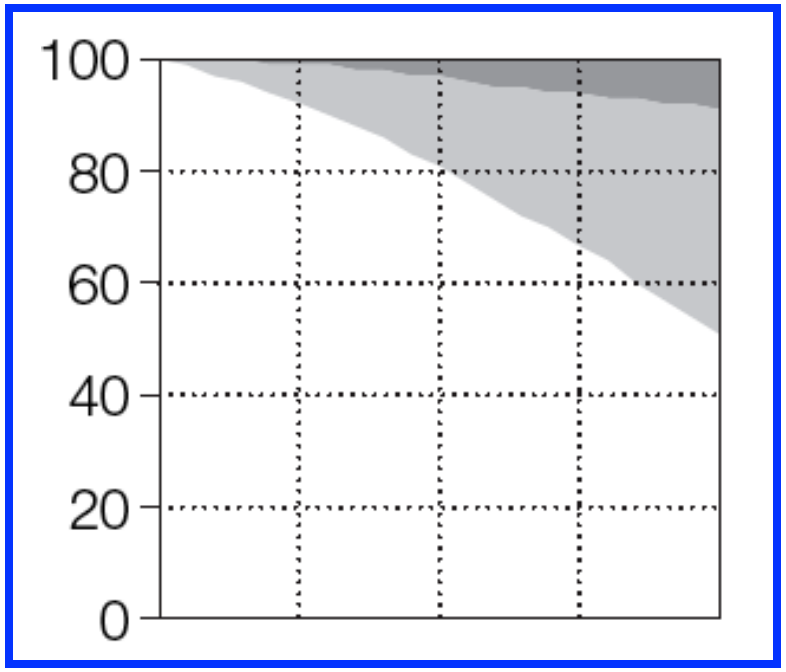
Sample size	8
Charlson score*	
0-1	8
≥2	0
No. of patients deceased due to	
Prostate cancer	1
Other causes	3
Unknown causes†	1
No. of patients alive	3

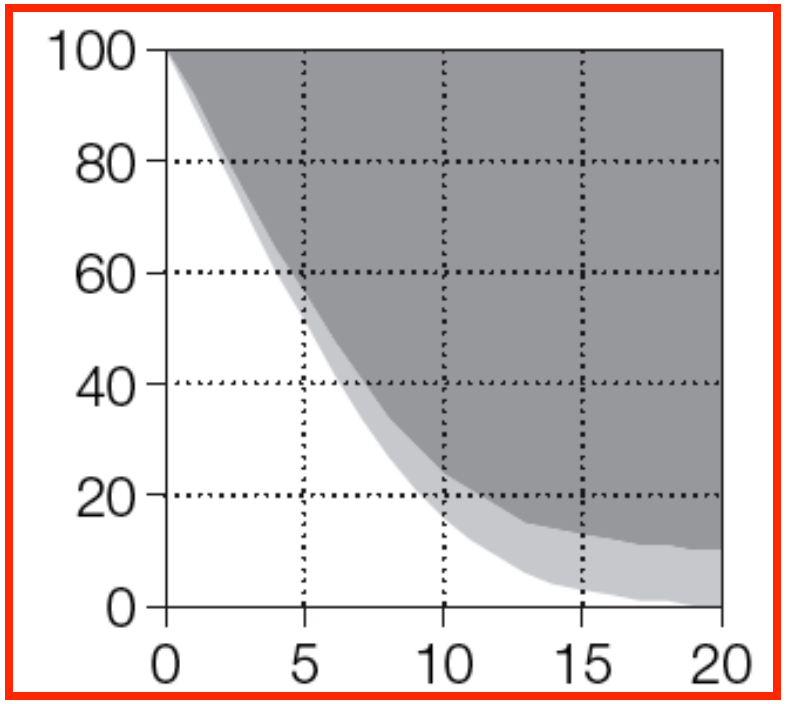
Gleason Score at Diagnosis of 8-10

Sample size	2
Charlson score*	
0-1	2
≥2	0
No. of patients deceased due to	
Prostate cancer	1
Other causes	0
Unknown causes†	1
No. of patients alive	0

Figure. Survival and Cumulative Mortality From Prostate Cancer and Other Causes Up to 20 Years After Diagnosis, Stratified by Age at Diagnosis and Gleason Score







The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Radical Prostatectomy versus Watchful Waiting in Early Prostate Cancer

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BACKGROUND

In 2002, we reported the initial results of a trial comparing radical prostatectomy with watchful waiting in the management of early prostate cancer. After three more years of follow-up, we report estimated 10-year results.

METHODS

From October 1989 through February 1999, 695 men with early prostate cancer (mean age, 64.7 years) were randomly assigned to radical prostatectomy (347 men) or watchful waiting (348 men). The follow-up was complete through 2003, with blinded evaluation of the causes of death. The primary end point was death due to prostate cancer; the secondary end points were death from any cause, metastasis, and local progression.

RESULTS

During a median of 8.2 years of follow-up, 83 men in the surgery group and 106 men in the watchful-waiting group died (P=0.04). In 30 of the 347 men assigned to surgery (8.6 percent) and 50 of the 348 men assigned to watchful waiting (14.4 percent), death was due to prostate cancer. The difference in the cumulative incidence of death due to prostate cancer increased from 2.0 percentage points after 5 years to 5.3 percentage points after 10 years, for a relative risk of 0.56 (95 percent confidence interval, 0.36 to 0.88; P=0.01 by Gray's test). For distant metastasis, the corresponding increase was from 1.7 to 10.2 percentage points, for a relative risk in the surgery group of 0.60 (95 percent confidence interval, 0.42 to 0.86; P=0.004 by Gray's test), and for local progression, the increase was from 19.1 to 25.1 percentage points, for a relative risk of 0.33 (95 percent confidence interval, 0.25 to 0.44; P<0.001 by Gray's test).

CONCLUSIONS

Radical prostatectomy reduces disease-specific mortality, overall mortality, and the risks of metastasis and local progression. The absolute reduction in the risk of death after 10 years is small, but the reductions in the risks of metastasis and local tumor progression are substantial.

Table 1. Baseline Characteristics of the 695 Men Enrolled in the Study.*

Characteristic	Radical-Prostatectomy Group (N=347)	Watchful-Waiting Group (N=348)
Age — yr	64.7±5.1.	64.7±5.1
Mean PSA — ng/ml	13.5	12.3
Tumor stage — no. (%)†		
T1b	33 (9.5)	50 (14.4)
T1c	43 (12.4)	38 (10.9)
T2	270 (77.8)	259 (74.4)
Unknown	1 (0.3)	1 (0.3)
WHO grade — no. (%)		
1	168 (48.4)	166 (47.7)
2	178 (51.3)	182 (52.3)
Unknown	1 (0.3)	0
Gleason score — no. (%)‡		
2–4	45 (13.0)	46 (13.2)
5–6	165 (47.6)	166 (47.7)
7	77 (22.2)	82 (23.6)
8–10	14 (4.0)	21 (6.0)
Unknown§	46 (13.3)	33 (9.5)
Method of detection — no. (%)		
Screening	18 (5.2)	18 (5.2)
Coincidental	87 (25.1)	91 (26.1)
TURP	40 (11.5)	56 (16.1)
Symptoms	152 (43.8)	138 (39.7)
Other	49 (14.1)	44 (12.6)
Unknown	1 (0.3)	1 (0.3)
PSA level — no. (%)		
<4 ng/ml	43 (12.4)	63 (18.1)
4–6.9 ng/ml	60 (17.3)	60 (17.2)
7–10 ng/ml	68 (19.6)	67 (19.3)
10.1–20 ng/ml	100 (28.8)	95 (27.3)
>20 ng/ml	69 (19.9)	60 (17.2)
Unknown	7 (2.0)	3 (0.9)

RESULTS

During follow-up, fewer men in the radical-prostatectomy group than in the watchful-waiting group died of prostate cancer (30 vs. 50, P=0.01). As for causes of death other than prostate cancer, the numbers were similar in the two groups (53 and 56, respectively). However, among men who died from causes other than prostate cancer, a larger number in the watchful-waiting group had metastases or local progression. In terms of death from any cause, 23 more men in the watchful-waiting group than in the radical-prostatectomy group died (106 vs. 83, P=0.04) (Table 2).

Table 2. Causes of Death, According to the Final Consensus of the End-Point Committee.

Cause of Death	Radical-Prostatectomy Group	Watchful-Waiting Group
	no. of patients	
Prostate cancer	30*	50†
Other causes	53	56
Other main cause, with metastases	1	8
Other main cause, without metastases but with local progression or recurrence	6	13
Other main cause, with unknown status regarding metastases but with local progression	0	0
Other main cause, with no evidence of metastases or local progression or recurrence	45	34
Other main cause, within first month after randomization	1	1
Any cause	83	106

DISEASE-SPECIFIC MORTALITY

The difference between the two groups in the cumulative incidence of death from prostate cancer increased over time, from 2 percentage points (95 percent confidence interval, −0.6 to 4.7) after five years of follow-up to 5.3 percentage points (95 percent confidence interval, −0.3 to 11.0) after 10 years, in favor of radical prostatectomy. The relative risk among men assigned to radical prostatectomy, as compared with those assigned to watchful waiting, was 0.56 (95 percent confidence interval, 0.36 to 0.88) (Fig. 1A and Table 3).

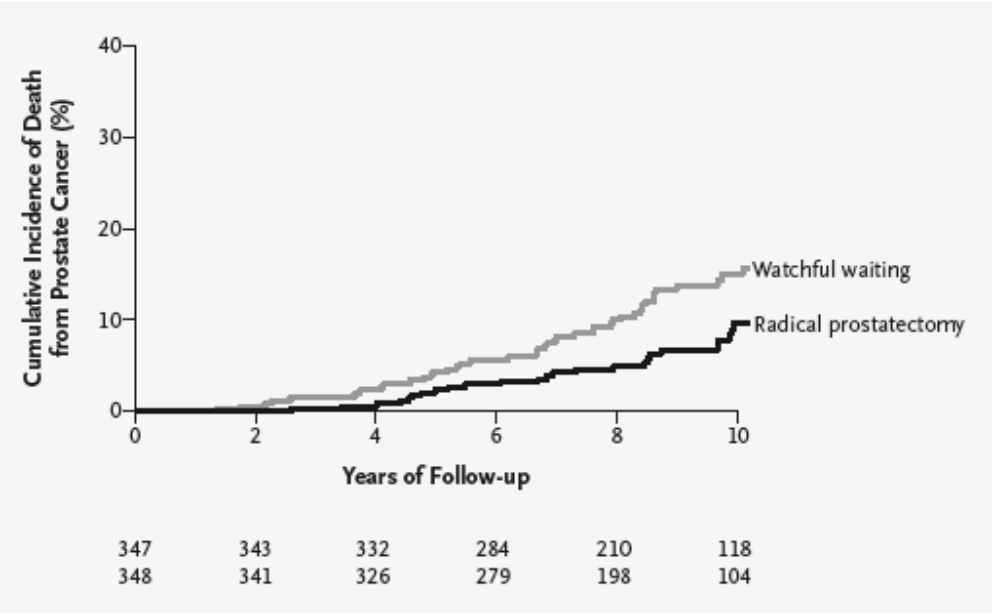


Table 3. Cumulative Incidence of the Main End Points and Corresponding Relative Risks.*

End Point	Cumulative Incidence				Absolute Risk Reduction (95% CI)	Relative Risk (95% CI)	P V
	Radical-Prostatectomy Group		Watchful-Waiting Group				
	total no.	*% (95% CI)*	*total no.*	*% (95% CI)*			
Disease-specific mortality	30		50				
At 5 yr		2.3 (1.2 to 4.6)		4.3 (2.6 to 7.1)	2.0 (−0.6 to 4.7)		
At 10 yr		9.6 (6.5 to 14.2)		14.9 (11.2 to 19.8)	5.3 (−0.3 to 11.0)	0.56 (0.36 to 0.88)	0
Distant metastases	50		79				
At 5 yr		8.1 (5.7 to 11.6)		9.8 (7.1 to 13.5)	1.7 (−2.5 to 6.0)		
At 10 yr		15.2 (11.4 to 20.3)		25.4 (20.4 to 31.5)	10.2 (3.1 to 17.2)	0.60 (0.42 to 0.86)	0
Local progression	64		149				
At 5 yr		8.1 (5.7 to 11.5)		27.2 (22.8 to 32.3)	19.1 (13.6 to 24.6)		
At 10 yr		19.2 (15.0 to 24.6)		44.3 (38.8 to 50.5)	25.1 (17.6 to 32.6)	0.33 (0.25 to 0.44)	<0
Overall mortality	83		106				
At 5 yr		7.8 (5.4 to 11.2)		9.8 (7.1 to 13.5)	2.0 (−2.2 to 6.2)		
At 10 yr		27.0 (21.9 to 33.1)		32.0 (26.9 to 38.2)	5.0 (−2.8 to 13.0)	0.74 (0.56 to 0.99)	0

Distant Metastasis

Death from Any Cause

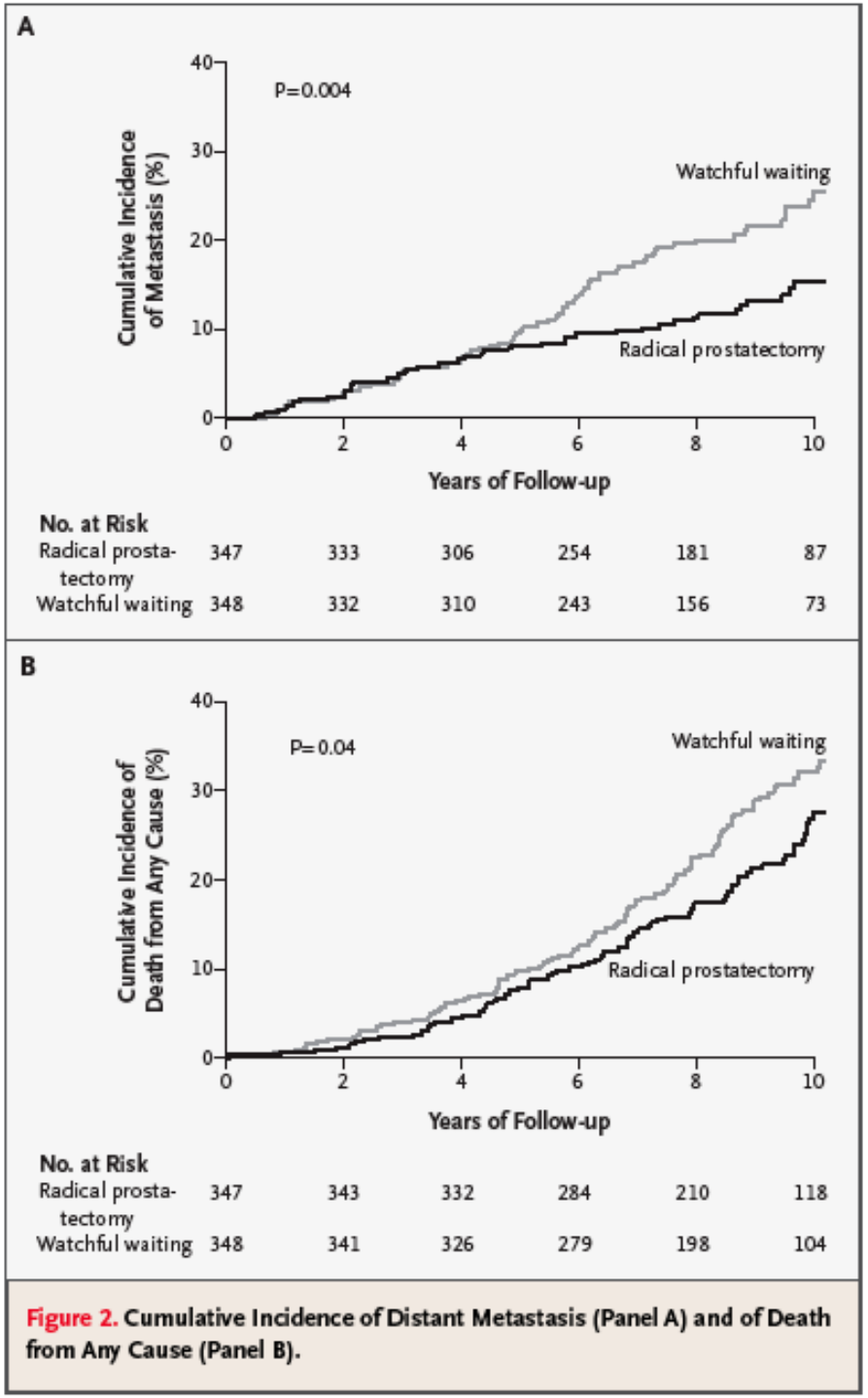
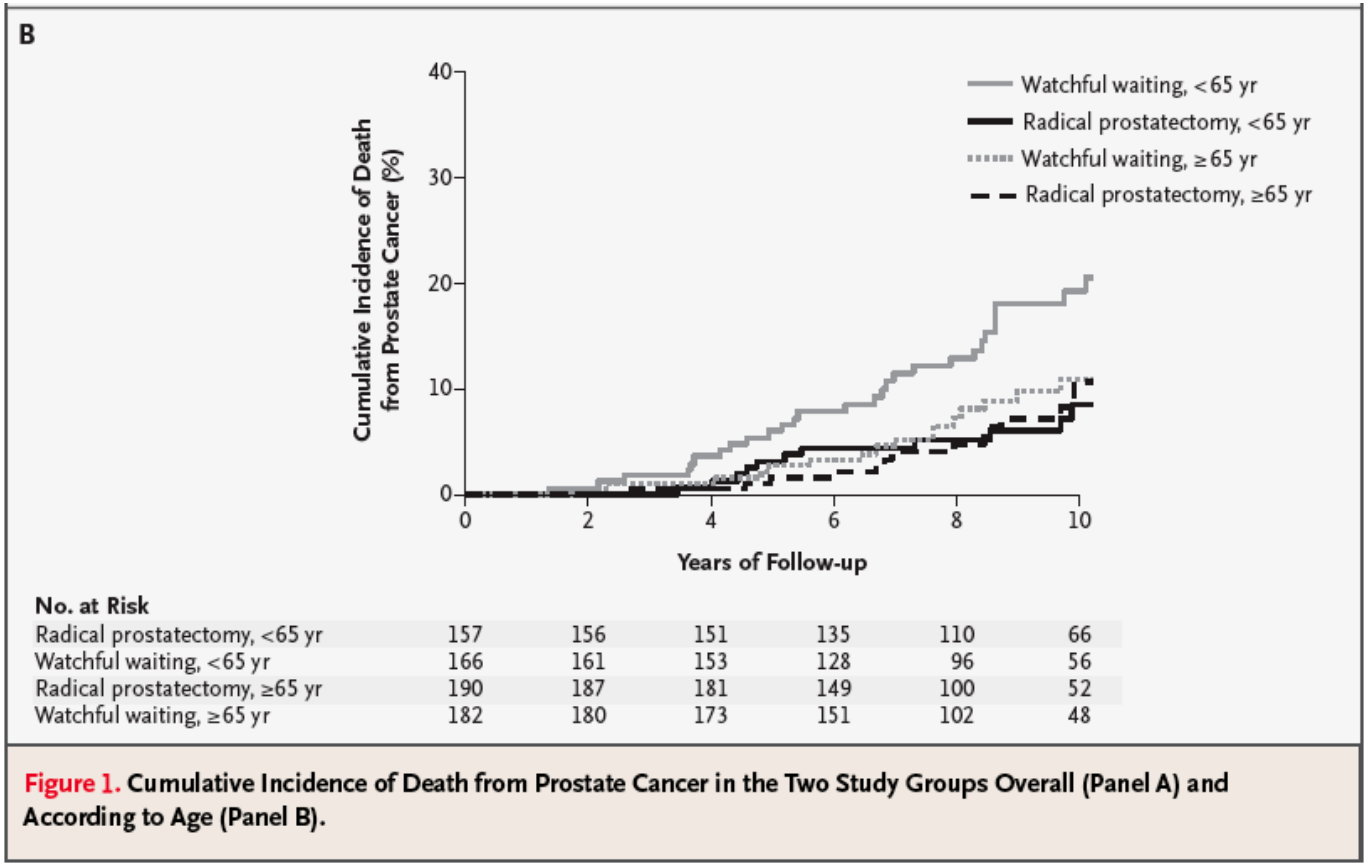


Figure 2. Cumulative Incidence of Distant Metastasis (Panel A) and of Death from Any Cause (Panel B).

SUBGROUP ANALYSES

In planned, simple stratified analyses, we found that the benefit of radical prostatectomy in terms of disease-specific mortality differed according to age group but not according to the PSA level at diagnosis or the Gleason score. A further investigation of disease-specific mortality with the use of a Cox proportional-hazards model that included the randomization group, the patient's age as a continuous variable, and an interaction term showed that the interaction term was statistically significant (P=0.03). When the same model was augmented with the PSA level at diagnosis, the tumor stage, the Gleason score, and the year at inclusion, the P value for the interaction term shifted to 0.08. For overall

The cumulative incidence of death from prostate cancer in men under 65 years of age in the watchful-waiting group was 19.2 percent at 10 years. This was markedly higher than the cumulative incidence of death in the other subgroups defined according to randomization group and age, for which the incidence varied from 8.5 percent to 11.5 percent (Fig. 1B).



No. at Risk						
Radical prostatectomy, <65 yr	157	156	151	135	110	66
Watchful waiting, <65 yr	166	161	153	128	96	56
Radical prostatectomy, ≥65 yr	190	187	181	149	100	52
Watchful waiting, ≥65 yr	182	180	173	151	102	48

Figure 1. Cumulative Incidence of Death from Prostate Cancer in the Two Study Groups Overall (Panel A) and According to Age (Panel B).

13-Year Outcomes Following Treatment for Clinically Localized Prostate Cancer in a Population Based Cohort

0022-5347/07/1773-0932/0
THE JOURNAL OF UROLOGY®
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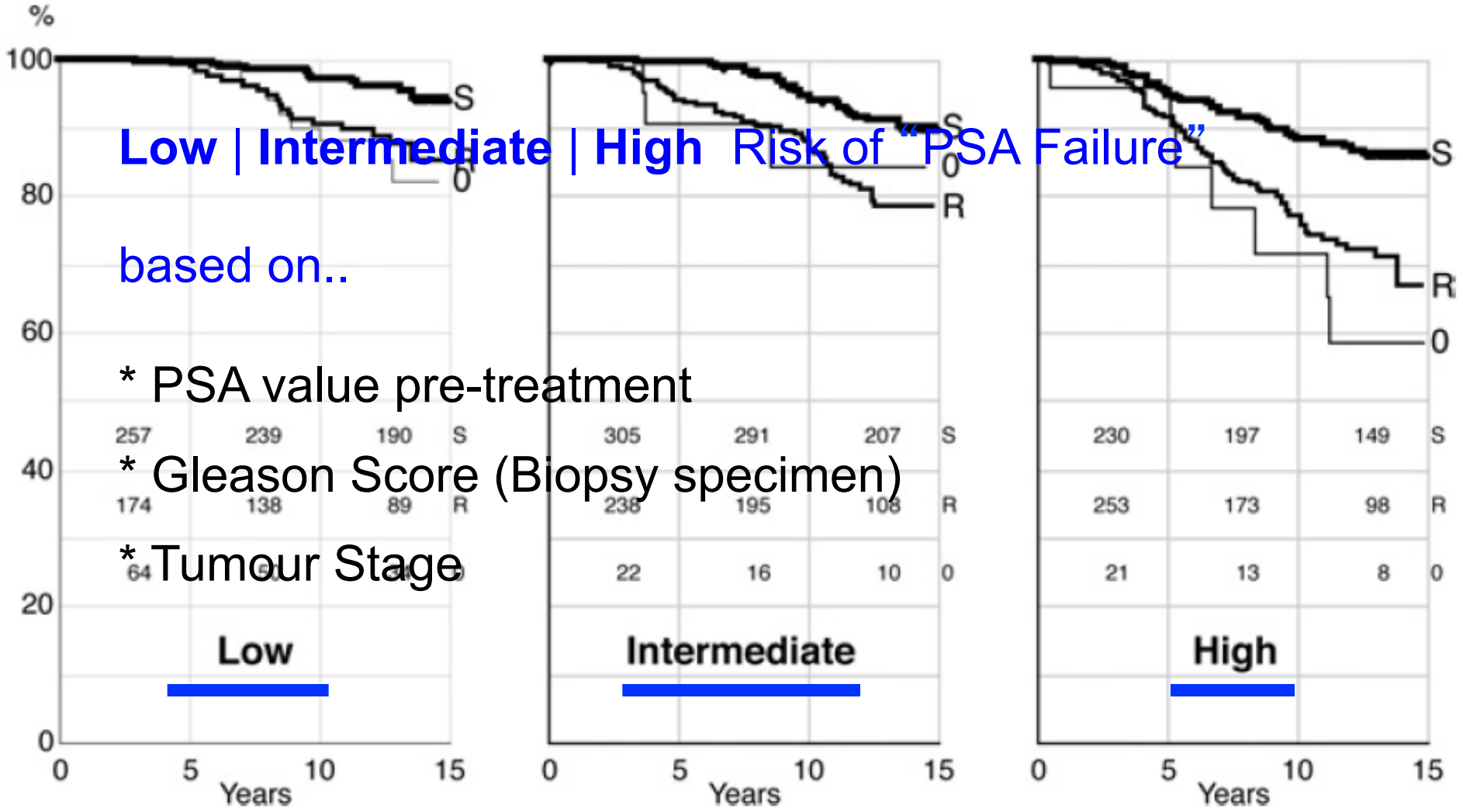
From the University of Connecticut Health Center, Farmington and St. Francis Hospital and Medical Center, Hartford, Connecticut, McGill University, Montreal, Quebec, Canada, and University of Southern California, Los Angeles, California

n = 1,618



Low | Intermediate | High Risk of "PSA Failure"

based on..

* PSA value pre-treatment
* Gleason Score (Biopsy specimen)
* Tumour Stage

FIG. 1. Cause specific survival in 3 treatment groups stratified by D'Amico risk category. *S*, surgery. *R*, radiation therapy. *O*, observation.

Survival Associated With Treatment vs Observation of Localized Prostate Cancer in Elderly Men

JAMA. 2006;296:2683-2693

Context Prostate-specific antigen screening has led to an increase in the diagnosis and treatment of localized prostate cancer. However, the role of active treatment of low- and intermediate-risk disease in elderly men is controversial.

Objective To estimate the association between treatment (with radiation therapy or radical prostatectomy) compared with observation and overall survival in men with low- and intermediate-risk prostate cancer.

Design and Setting Observational US cohort from Surveillance, Epidemiology, and End Results Medicare data.

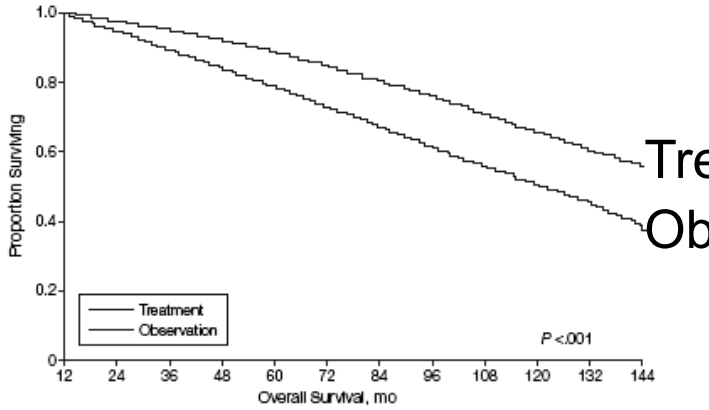
Patients At total of 44 630 men aged 65 to 80 years who were diagnosed between 1991 and 1999 with organ-confined, well- or moderately differentiated prostate cancer and who had survived more than a year past diagnosis. Patients were followed up until death or study end (December 31, 2002). Patients were classified as having received treatment (n=32 022) if they had claims for radical prostatectomy or radiation therapy during the first 6 months after diagnosis. They were classified as having received observation (n=12 608) if they did not have claims for radical prostatectomy, radiation, or hormonal therapy. Patients who received only hormonal therapy were excluded.

Main Outcome Measure Overall survival.

Results At the end of the 12-year study period, 4663 men (37%) in the observational group and 7639 men (23.8%) in the treatment group had died. The treatment group had longer 5- and 10-year survival than the observation group. After using propensity scores to adjust for potential confounders (tumor characteristics, demographics, and comorbidities), there was a statistically significant survival advantage associated with treatment (hazard ratio, 0.69; 95% confidence interval, 0.66-0.72). A benefit associated with treatment was seen in all subgroups examined, including older men (aged 75-80 years at diagnosis), black men, and men with low-risk disease.

Conclusions This study suggests a survival advantage is associated with active treatment for low- and intermediate-risk prostate cancer in elderly men aged 65 to 80 years. Because observational data cannot completely adjust for potential selection bias and confounding, these results must be validated in randomized controlled trials of alternative management strategies in elderly men with localized prostate cancer.

Figure. Kaplan Meier Survival Curves for Full Cohort



No. at Risk												
Treatment	32022	31378	30546	26519	22630	18724	15148	11674	8755	5805	2522	226
Observation	12608	11986	11308	9696	8124	6587	5163	3769	2608	1527	685	82

Patients who survived less than 12 months were excluded from the analysis.

Treatment

Observation

Table 3. Patient Distribution and 5- and 10-Year Overall Survival by Treatment and Propensity Score Strata

	Entire Cohort (0.06-0.97)	Quintile (Range) of Propensity Score*				
		1 (0.06-0.59)	2 (0.59-0.72)	3 (0.72-0.80)	4 (0.80-0.86)	5 (0.86-0.97)
Observation group						
No. of patients						
Overall survival (95% CI), y						
5						
10						
Treatment group						
No. of patients						
Overall survival (95% CI), y						
5						
10						

Abbreviation: CI, confidence interval.
*Propensity scores were rounded to 2 decimal points. There was no overlap of propensity scores across quintiles.

Table 4. Association Between Active Treatment and Overall Mortality

Propensity Score Quintile	Mean Propensity Score (Range)	HR for Death (95% CI)*
Entire cohort*	0.72 (0.06-0.97)	0.69 (0.66-0.72)
Entire cohort stratified by quintile	0.72 (0.06-0.97)	0.67 (0.65-0.70)
1†	0.43 (0.06-0.59)	0.69 (0.64-0.74)
2	0.66 (0.59-0.72)	0.70 (0.65-0.76)
3	0.76 (0.72-0.80)	0.66 (0.61-0.73)
4	0.83 (0.80-0.86)	0.67 (0.60-0.75)
5‡	0.89 (0.86-0.97)	0.57 (0.50-0.65)

Abbreviations: CI, confidence interval; HR, hazard ratio.
*Adjusted for tumor size, grade, and number of comorbidities.
†Lowest propensity for treatment.
‡Highest propensity for treatment.

Had information on Tumour Size and Grade, but not on PSA

Table 5. Association Between Active Treatment and Overall Mortality Among Subgroups

Subgroup	No. of Patients		HR for Death (95% CI)*
	Observed	Treated	
Year of diagnosis			
1991-1994	6085	15 299	0.74 (0.70-0.78)
1995-1999	6523	16 723	0.62 (0.57-0.66)
Black race	1256	2175	0.65 (0.58-0.74)
Elderly†	5073	6802	0.73 (0.69-0.78)
Good risk‡	3084	2553	0.79 (0.72-0.88)
No comorbidities for 90 days before diagnosis	4644	12 433	0.71 (0.66-0.77)
Radiation	12 608	18 249	0.81 (0.78-0.85)
Radical prostatectomy	12 608	13 292	0.50 (0.47-0.53)
Survival after diagnosis, y			
>2	11 975	31 356	0.72 (0.69-0.75)
>3	11 291	30 504	0.75 (0.71-0.78)

Abbreviations: CI, confidence interval; HR, hazard ratio.
*Adjusting for propensity score only.
†Those between 75 and 80 years at diagnosis.
‡Those with low-risk cancers have tumors that are classified as T2a and lower and well differentiated.

For all the data & all the analysis..

Most the reports do not inform us about the probability of treatment benefit for a particular patient profile, especially if the aggressiveness and stage of the patient's cancer are not near the typical of the cancers in the trial / study.

Is this an isolated example?

Survey

- Original articles, 1 January 2006 to 30 June 2006

  New England Journal of Medicine (NEJM),
  Journal of the American Medical Association (JAMA)
  The Lancet

- RCTs with significant treatment effect on 1º outcome.

- Survival analysis

- Yield: 20 articles.

Treatment Effect Measures: *Summary(aggregate)* and *Profile-specific*

Effects on stated 1º outcome [or 1st one reported in abstract]

1. Profile-specific effects: anywhere in article

(via graphs, tables, other).

2. All effect measures reported in abstract

	NEJM	JAMA	The Lancet	Total (%)
No. of articles	**10**	**3**	7	**20**
MEASURES IN ABSTRACT	19	9	16	**44**
Hazard ratio	5	3	2	**10** (50)
Two crude %'s (Risks)	4	2	4	**10** (50)
Relative risk	2	0	4	**6** (30)
Two x-year survival %'s	3	1	1	**5** (25)
Two rates	2	1	1	**4** (20)
Absolute risk difference	0	1	2	**3** (15)
Two median durations	2	0	0	**2** (10)
One rate with % reduction	0	0	1	**1** (5)
Two adjusted %	0	0	1	**1** (5)
Prevented fraction	1	0	0	**1** (5)
x-year survival difference	0	1	0	**1** (5)

	NEJM	JAMA	The Lancet	Total (%)
No. of articles	**10**	**3**	7	**20**
MEASURES IN ABSTRACT	19	9	16	**44**
Hazard ratio	5	3	2	**10** (50)
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Relative risk	2	0	4	**6** (30)
Two x-year survival %'s	3	1	1	**5** (25)
Two rates	2	1	1	**4** (20)
Absolute risk difference	0	1	2	**3** (15)
Two median durations	2	0	0	**2** (10)
One rate with % reduction	0	0	1	**1** (5)
Two adjusted %	0	0	1	**1** (5)
Prevented fraction	1	0	0	**1** (5)
x-year survival difference	0	1	0	**1** (5)
PROFILE-SPECIFIC RESULTS	0	0	0	**0** (0)

Profile-specific Treatment Effect Measures

No instances of profile-specific estimates of risks or risk differences

No tables or graphics from which they could be derived.

Semi-parametric ‘Cox model’

These reporting practices stem, in part, from the use of a model in which…

time is considered a non-essential element

the primary focus is on hazard ratios

Semi-parametric ‘Cox model’

Model leaves unspecified the form of the hazard per se as a function of time.

BUT…

Cox in his ‘72 paper, and software packages for survival analysis under this model, do in fact allow the user to address profile-specific cumulative incidence (risk).

Authors are either unaware of this possibility, or choose not to use it.

Obtaining Profile-specific Risks from Cox Regression

Use Fundamental Relation between

Survival function S[t] & hazard function h[t] :

$$S[t] = \exp\left[-\int h[u]\, du \right].$$

So, if $h_{X=x}[u] = h_{X=0}[u] \times HR_{x \text{ vs } 0}$

then $S_{X=x}[t] = \exp[\{ -\int h_{X=0}[u]\, du\} \times HR_{x \text{ vs } 0}]$

$= \{ S_{X=0}[t] \}$ to power of $HR_{x \text{ vs } 0}$

with… $HR_{x \text{ vs } 0} = \exp[\beta x]$

$\text{Risk}_{X=x}[0 \text{ to } t] = 1 - S_{X=x}[t]$

A heuristic for the estimator of the "baseline survival function" $S_{X=0}[t]$ from Cox model

See handout on Breslow estimator
(comments welcome)

Obtaining Profile-specific Risks from Cox Regression

SAS

```
DATA profiles;
INPUT psa gleason age tx ;
LINES;
      8.2    5      62  0
      8.2    5      62  1
;
PROC PHREG DATA = xxx ;
MODEL time*event(0) = psa gleason age tx ;
BASELINE OUT = s COVARIATES = profiles SURVIVAL =  s_hat;
```

Then… estimated risk (cumulative incidence) = `1 - s_hat ;`

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Stata [from UCLA website www.ats.ucla.edu/STAT/stata/seminars/]

```
input psa gleason age tx time event ;
stset time, failure(event)
stcox psa gleason age tx , nohr basesurv(surv0)
```

Cumulative incidence (CI)

Cut-and-paste regression coefficients b.psa, b.gleason… **into**

```
gen CI.tx0 = 1 - surv0^exp(b.psa*8.2 + .. + b.age*62          )
gen CI.tx1 = 1 - surv0^exp(b.psa*8.2 + .. + b.age*62 + b.tx*1)
```

Uses S_hat[t|x] = S_hat[t | x = 0] to power of exp[Linear Predictor]

{ Linear Predictor = b.1*x1 + b.2*x2 + . . . }

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R

```
require(survival)
ph.fit <- coxph(Surv(time,event) ~ psa + gleason + age + tx)
```

Cumulative incidence (CI)

```
Curves = survfit(ph.fit,
  newdata = data.frame(psa=c(8.2,8,2), .. , tx=c(0,1) ) )

CI.tx0 = 1 - c(1,curves$surv[,1] );
CI.tx1 = 1 - c(1,curves$surv[,2] );
```

STUDY for ILLUSTRATION

Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). (SHEP Cooperative Research Group, JAMA. 1991 Jun 26;265(24):3255-64).

OBJECTIVE. To assess the ability of antihypertensive drug treatment to reduce the risk of nonfatal and fatal (total) stroke in isolated systolic hypertension.

DESIGN. Multicenter, randomized, double-blind, placebo-controlled.

SETTING. Community-based ambulatory population in tertiary care centers.

PARTICIPANTS. 4736 persons (1.06%) from 447,921 screenees aged 60 years and above were randomized (2365 to active treatment, 2371 to placebo). Systolic blood pressure ranged from 160 to 219 mm Hg and diastolic blood pressure was less than 90 mm Hg. Of the participants, 3161 were not receiving antihypertensive medication at initial contact, and 1575 were. The average systolic blood pressure was 170 mm Hg; average diastolic blood pressure, 77 mm Hg. The mean age was 72 years, 57% were women, and 14% were black.

INTERVENTIONS.--Participants were stratified by clinical center and by antihypertensive medication status at initial contact. For **step 1** of the trial, dose 1 was chlorthalidone, 12.5 mg/d, or matching placebo; dose 2 was 25 mg/d. **For step 2**, dose 1 was atenolol, 25 mg/d, or matching placebo; dose 2 was 50 mg/d.

MAIN OUTCOME MEASURES. **Primary. Nonfatal and fatal (total) stroke.** Secondary. Cardiovascular and coronary morbidity and mortality, all-cause mortality, and quality of life measures.

RESULTS. Average follow-up was 4.5 years. The 5-year average systolic blood pressure was 155 mm Hg for the placebo group and 143 mm Hg for the active treatment group, and the 5-year average diastolic blood pressure was 72 and 68 mm Hg, respectively. **The 5-year incidence of total stroke was 5.2 per 100 participants for active treatment and 8.2 per 100 for placebo. The relative risk by proportional hazards regression analysis was 0.64 (P = .0003).** For the secondary end point of clinical nonfatal myocardial infarction plus coronary death, the relative risk was 0.73. Major cardiovascular events were reduced (relative risk, 0.68). For deaths from all causes, the relative risk was 0.87.

CONCLUSION. In persons aged 60 years and over with isolated systolic hypertension, **antihypertensive stepped-care drug treatment with low-dose chlorthalidone as step 1 medication reduced the incidence of total stroke by 36%, with 5-year absolute benefit of 30 events per 1000 participants.** Major cardiovascular events were reduced, with 5-year absolute benefit of 55 events per 1000.

DATA for ILLUSTRATION

Data, without subject identifications, obtained under program

"NHLBI Datasets Available for Research Use"

4,701 with complete data on :

age, sex, race, SBP and Tx {active , placebo}.

20,894 person-years of follow-up ;

263 events of stroke identified.

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http://www.nhlbi.nih.gov/resources/deca/default.htm

Table 1: For each of the two intervention groups ($I = 1$ for Active, $I = 0$ for Placebo), distributions of prognostic indicators; also shown are the respective numbers of subjects and strokes.

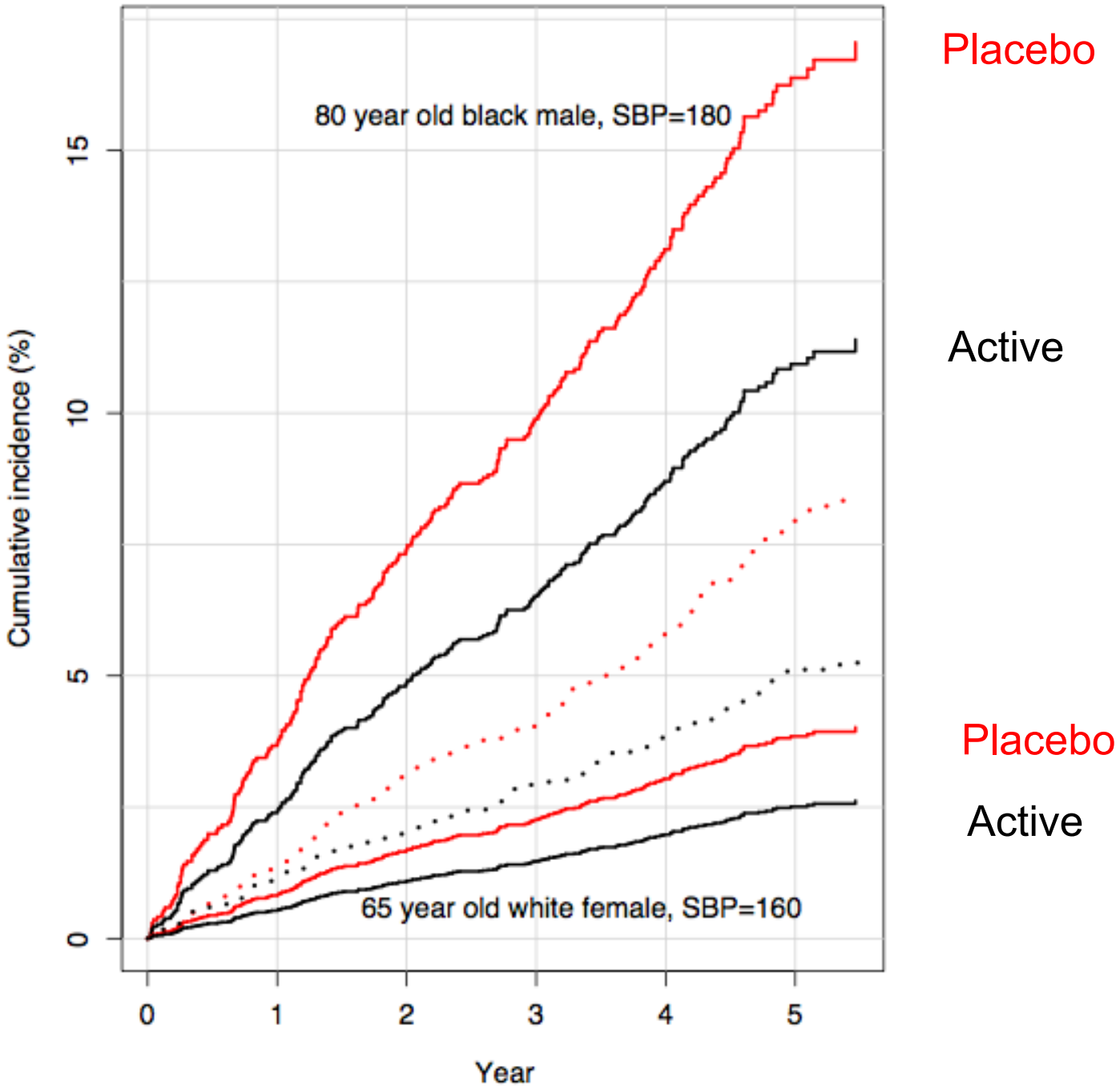
	Age:			Sex:	Race:	SPB:			No. of	No. of
I	Q_{10}	Q_{50}	Q_{90}	% male	% Black	Q_{10}	Q_{50}	Q_{90}	subjects	strokes
0	64	72	81	43	14	161	168	183	2351	158
1	64	72	81	44	14	161	168	185	2350	105

Q_{10}, Q_{50} and Q_{90} are the 10th, 50th and 90th centiles.
Person-years of follow-up: 10391.67 for $I = 0$ and 10502.68 for $I = 1$.

Table A2 Fitted values for the coefficients of Cox regression model: data from SHEP study

Age-60	I_{Male}	I_{Black}	SBP − 140	$I_{ActiveTreatment}$
0.041	0.259	0.303	0.017	−0.435[a]

Note: [a]Hazard ratio = exp(−0.435) = 0.65 (35% reduction).



Placebo

Active

Placebo

Active

Table 3: Risk (%) estimate for stroke in next $1, \ldots, 5$ years, if the SBP is untreated and if it is treated, as a function of the four prognostic indicators incorporated in the Total Score [Cox model].

	Total Score	Tx	Year 1	2	3	4	5
	200	0	3.4	6.8	9.1	12.1	15.1
		1	2.2	4.5	6.0	8.0	10.1
(No. Years beyond 60) × 4 ___							
	150	0	2.1	4.2	5.7	7.6	9.5
		1	1.3	2.8	3.7	5.0	6.3
Black ... 25 ___							
	100	0	1.3	2.6	3.5	4.7	5.9
		1	0.8	1.7	2.3	3.1	3.9
Male ... 30 ___							
	50	0	0.8	1.6	2.1	2.9	3.7
		1	0.5	1.0	1.4	1.9	2.4
(Every 10 mm SBP above 140) × 17 ___							
	0	0	0.5	1.0	1.3	1.8	2.2
		1	0.3	0.6	0.8	1.1	1.5
Total Score ___							

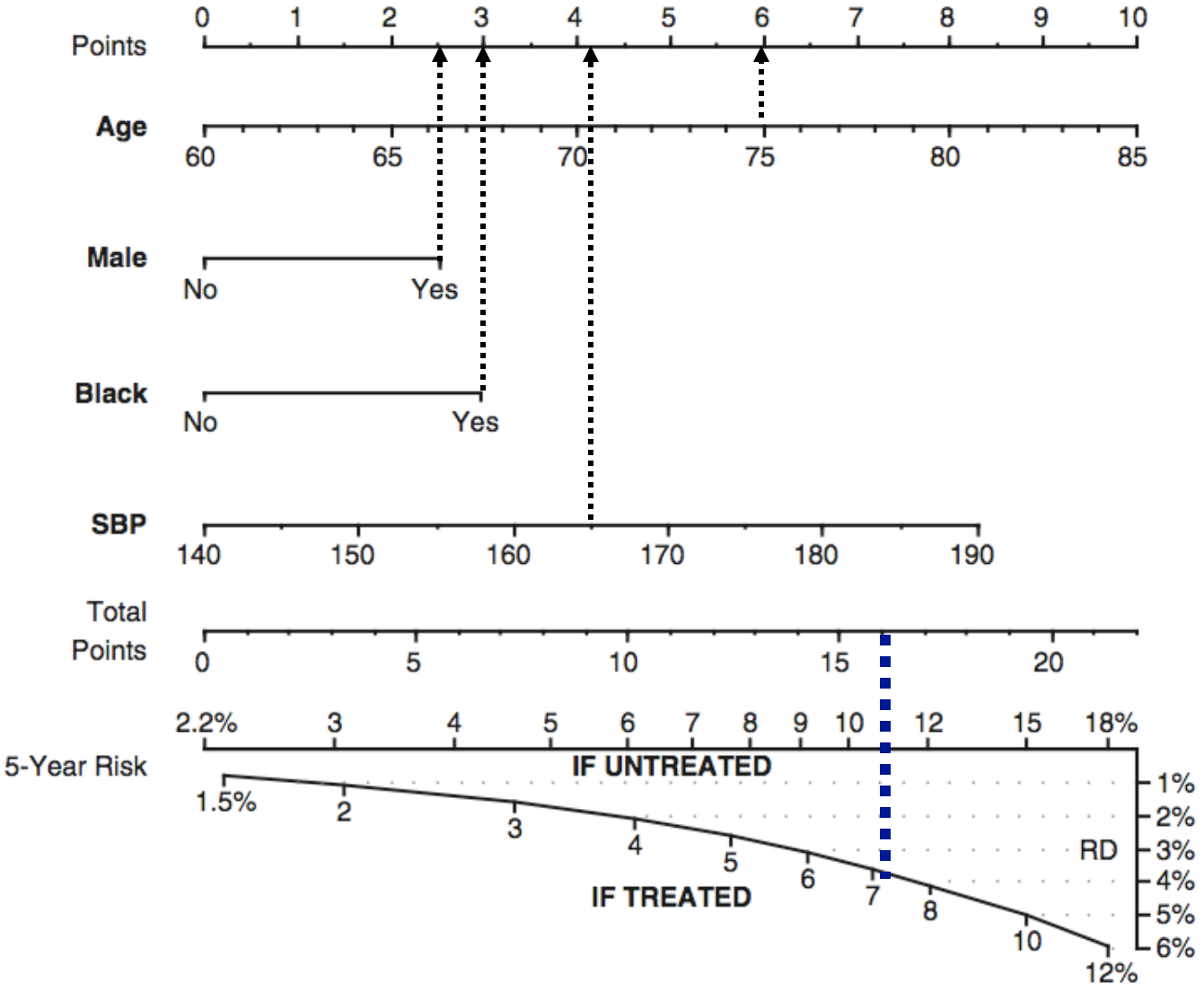


Figure 2 Nomogram to calculate estimated 5-year risk of stroke if untreated, or if treated. Points – proportional to fitted Cox regression coefficients – for the four factors (Age to SBP) are summed and transferred to 'Total Points' scale. The corresponding risks and Risk Difference (RD) are read from the bottom two scales. Data from SHEP study (see text)

SUMMARY

Profile-specific risk estimates are..

- Practice-relevant
- Almost never reported
- Estimable from Cox model
- Easy to report in a compact form

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