

MORTALITY ANALYSIS

Recurrent PSA After Prostatectomy for Prostate Cancer: Implications of PSA Doubling Time

Thomas Ashley, MD

After radical prostatectomy for prostate cancer, men frequently develop detectable levels of prostate specific antigen (PSA). A slow rate of increase, as characterized by the PSA doubling time (PSADT) is the principal marker for a favorable prognosis. Data and results presented in 2 recent clinical articles studying cohorts of men with clinical stage T1/T2 prostate cancer are reviewed and used to develop mortality analyses. Life-table analysis shows a mortality ratio of 257% at 5 years for Gleason score <8, PSA recurrence >2 years after surgery for clinical stage T1/T2 disease, and PSA doubling time (PSADT) >10 months. Markov modeling using transition probabilities derived from the clinical articles to develop a life table analysis yields a mortality ratio of 145% at 10 years for similar patients.

Address: Gen Re LifeHealth, 695 East Main Street, Stamford, CT 06901; e-mail: tashley@genre.com.

Correspondent: Thomas Ashley, MD; Vice President and Chief Medical Director.

Key words: Prostate cancer, prostate specific antigen, prostatectomy, mortality, life insurance, Markov modeling.

Within 10 years after radical prostatectomy for prostate cancer, 35% of men develop detectable levels of PSA. Two studies^{1,2} of prostate specific antigen (PSA) recurrence after radical prostatectomy demonstrate an opportunity to offer insurance in selected cases for this common situation.

Roberts et al¹ reported 879 cases of PSA recurrence, comprising 31% of a Mayo Clinic cohort followed after prostatectomy for clinically localized disease, clinical stage T1/T2. Recurrence was defined as PSA >0.4 ng/mL. The endpoints after PSA recurrence evaluated in this study were local recurrence (LR; assessed by digital rectal examination, transrectal ultrasound and biopsy) or systemic progression (SP; assessed by metastasis on bone scan). In multivariate analysis, only PSA doubling time (PSADT) independently predicted either endpoint.

Roberts' Mayo Clinic study does not permit direct assessment of prostate cancer spe-

cific mortality after the local recurrence and/or systemic progression because the measured endpoints precede death and terminate observation. Patients who died from causes other than prostate cancer or who received adjuvant cancer treatment without evidence of LR or SP were censored.

The authors of this study depicted the systemic progression-free survival for patients grouped by several bands of PSADT levels. For those with PSADT of greater than 10 years, SP-free survival was $99 \pm 1\%$. For other PSADT bands, SP-free survival for those with PSADT of 0.5 to 1.0 year was $93 \pm 3\%$, for PSADT of 1.0 to 9.0 years was $95 \pm 3\%$, and for those with PSADT of less than 0.5 year, SP-free survival was $64 \pm 12\%$. Stated another way, among the 3 groups with PSADT over 0.5 year, SP-free survival was no worse than 7%. Since deaths from other causes were censored, this is disease-specific experience.

In the second paper reviewed for this ar-

Table 1. Life-table Analysis

	Survival			Mortality				
	<i>Cumulative (P)</i>			<i>Geometric Average Annual</i>				
	Observed (t to Δt = 0–5 years)			Expected		Comparative		
	Disease Specific	Population, Age 60–64	P (Total)	ṗ (Total)	q̇ (Total)	q̇'	EDR	MR (%)
Mayo ¹	0.93	0.9276	0.8626	0.9709	0.0291	0.0149	14.2	195
Hopkins ²	0.86	0.9106	0.7831	0.9523	0.0477	0.0186	29.2	257

ticle, Pound et al² followed the natural history of 304 cases of PSA recurrence, comprising 15% of a Johns Hopkins cohort followed after radical prostatectomy for stage clinical stage T1/T2 disease. PSA recurrence was defined as PSA ≥0.2 ng/mL. The study population excluded men who had adjuvant radiotherapy, and those who had postoperative radiation therapy to the prostatic bed who maintained a PSA response lasting over 2 years, as these were considered to have local recurrences only and cured of their cancer. No patients received adjuvant hormonal therapy, even after detection of metastatic disease. Deaths that occurred during the period of PSA recurrence, prior to metastatic disease, were apparently censored, as these were not specifically accounted for by the authors. For the endpoint of survival without systemic progression, the experience observed is disease-specific.

Pound's Hopkins group reported outcomes for many subgroups defined by Gleason score at operation, time to PSA recurrence, and PSADT. The portion of the study population of greatest interest to underwriting is defined by Gleason score <8, PSA recurrence >2 years after surgery, and PSADT >10 months. For this group, metastatic disease-free survival at 5 years is 86%.

Neither of these studies reports mortality after detection of PSA recurrence. To establish a maximum limit for mortality for life table analysis, I assumed no survival after SP and used the observed metastatic disease-free survival at 5 years as overall survival. This yields 7% mortality at 5 years for PSADT

>0.5 years in Roberts' Mayo study and 14% for the subgroup of Pound's Hopkins article that was described above.

Both studies censored deaths from other causes. One method to derive total mortality is to combine observed disease-specific mortality with background population mortality. The probability for survival of multiple simultaneous independent risks is the product of the separate survival rates. Total mortality is calculated in this way as:

$$P_{\text{total}} = P_{\text{population}} \times P_{\text{prostate cancer}}$$

$$Q_{\text{total}} = 1 - P_{\text{total}}$$

The reference populations for population mortality and for expected total mortality rates are 1990 Minnesota white males to reflect the Mayo Clinic demographics and 1991 US males for the Hopkins study.

The authors did not describe the age distribution of the subjects in either study. Correspondence with the author of the Hopkins paper disclosed that mean age = 59.9, median age = 60, and age range = 38–76. The Mayo study examined men with the same stage of disease and choice of treatment, so with no additional available information, I assumed mean age of 60 for both studies.

Life-table analysis (Table 1) yields a 5-year cumulative mortality ratio of 257% for Pound's Hopkins study and 195% for Roberts' Mayo study.

Markov analysis can test the life-table conclusions from the Pound article. This disease lends itself to a simple model with 3 states: PSA detected after radical prostatectomy,

Table 2. Markov Model of Disease-Specific Mortality for Clinical Stage T1/T2 After Radical Prostatectomy

Time	States			Annual Rates			
	PSA Recurrence	Systemic Metastasis	Death	Metastasis	Death		
0	1000	0.0	0.0	29.7	0.0		
1	970.3	29.7	0.0	28.8	3.3		
2	941.5	55.2	3.3	28.0	6.2		
3	913.5	77.0	9.6	27.1	8.7		
4	886.3	95.4	18.2	26.3	10.8		
5	860.0	111.0	29.0	25.6	12.5		
6	834.4	124.0	41.5	24.8	14.0		
7	809.7	134.9	55.5	24.1	15.2		
8	785.6	143.7	70.7	23.3	16.2		
9	762.2	150.9	86.9	22.6	17.0		
10	739.6	156.5	103.9				
Cumulative Exposure			9685.3 Years				
Cumulative Mortality			103.9 Deaths				
Average annual Mortality (\bar{q})			0.0107				
Survival					Mortality		
<i>Cumulative (P)</i>					<i>Annual</i>		
Observed (t to $\Delta t = 0-5$ years)					Expected	Comparative	
Disease Specific	Population, Age 60-69	P (Total)	\bar{p} (Total)	\bar{q} (Total)	\bar{q}'	EDR	MR (%)
0.989	0.9767	0.9664	0.9663	0.0337	0.0233	10.5	145

Model assumes mortality probability for men who develop metastasis 4-7 years post surgery (per Pound's Hopkins study²) and the transition probability of development of metastasis after PSA recurrence for cases with characteristics in this table.

systemic metastasis and death. Transitions follow a consecutive irreversible path.

The transition probability from PSA recurrence to metastasis is taken from Pound's Hopkins paper, based on survival in the subset Gleason score <8, PSA recurrence >2 years post-op, and PSADT >10 months, which was 0.0297/year. Pound's Hopkins article also provides a range of transition rates for death after systemic metastasis. Patients with metastasis that develop less than 4 years after surgery have a poor prognosis with approximately 30% survival at 5 years. Five-year survival after metastasis is 55% when metastasis occurs 4-7 years after surgery and is nearly 80% if metastasis occurs >8 years post-op. I used the 4-7 year data as the mortality rate after metastasis, 0.113/year. Table

2 summarizes the Markov model that was developed assuming 1000 cases as "starters." This shows the numbers of cases that are PSA recurrences, metastatic disease and deaths annually over 10 years modeled based on these probabilities. Cumulative 10-year mortality was then derived from the Markov model results.

DISCUSSION

The key parameter for selection of insurable risks among these patients is PSADT. Cancer mortality corresponds roughly to total tumor burden as measured by PSA. Long PSADT provides a marker for less aggressive disease. Calculation of PSADT from any 2 PSA measurements can be based on:

$$\text{PSADT} = (\text{time interval between tests}) \\ \times \ln 2 / (\ln \text{PSA}_2 - \ln \text{PSA}_1)$$

To determine the optimal PSADT cut-point, Pound's Hopkins group developed PSA models using many different sets of PSA values. The models fitted included ones that used all postoperative PSA values, only the first 2 values regardless of level, only the first 2 values after 0.2 ng/mL was reached, and all PSA levels within a 2-, 3- and 5-year period following an elevation. The optimal model was that which provided the best fit utilizing the most number of men with PSADT data. Ultimately, all PSA values within the 2 years of the initial documented PSA elevation provided the optimal combination of statistical significance and number of qualified men (median PSADT = 10 months). Roberts' Mayo group also used regression to assess optimal PSADT cut-point values using the multiple levels described above.

Roberts' Mayo study contains important weaknesses. Data were censored upon treatment of recurrent PSA alone. Attending physician discretion determined treatment, with no uniform protocol. Such additional therapy accounted for exclusion of 30% of patients with PSA recurrence after prostatectomy. These patients may have been sicker. If so, their exclusion improves the outcome for the patients who remained and formed the study population. Initiation of therapy precludes the endpoint of SP. By contributing exposure until the time of treatment, these patients depress the apparent rate of SP and, therefore, mortality.

Neither study allows examination of the effect of age. Disease behavior might differ with age, ie, the duration of biochemical PSA

recurrence and systemic metastasis states might diminish in older men.

Five years of observation limits the life-table analysis but does not match the duration of exposure to insurance risk. Excess mortality may lurk later in the course of prostate cancer relapse. The Markov model extended to 10 years shows no worse outcome, assuming the same transition probabilities for adverse events remain constant over this period.

The life-table analysis provides a conservative estimate of mortality ratio by the substitution of disease progression for death. The Mayo study did not report survival after disease progression (as defined in the study) using the same stratification by Gleason score and PSADT, so I could not incorporate those data in my analysis. As reported by Pound's Hopkins group, median survival is nearly 5 years after development of metastatic disease. Excess mortality among insured lives will reflect this delayed mortality. Most men with progressive disease will receive hormonal therapy, which should prolong life compared to the observations in both studies and the assumptions in both the life-table and Markov analyses. We can expect additional improvement from therapeutic advances in the future.

These data support carefully considered offers of life insurance for some men with recurrent prostate cancer.

REFERENCES

1. Roberts S, Blute M, Bergstralh E, Slezak J, Zincke H. PSA Doubling Time as a Predictor of Clinical Progression After Biochemical Failure Following Radical Prostatectomy for Prostate Cancer. *Mayo Clin Proc.* 2001;76:576-581.
2. Pound C, Partin A, Eisenberger M, Chan D, Pearson J, Walsh P. Natural History of Progression After PSA Elevation Following Radical Prostatectomy. *JAMA.* 1999;281:1591-1597.