Localized Prostate Cancer

Relationship of Tumor Volume to Clinical Significance for Treatment of Prostate Cancer

Thomas A. Stamey, M.D., Fuad S. Freiha, M.D.,* John E. McNeal, M.D.,* Elise A. Redwine, M.S.,* Alice S. Whittemore, Ph.D.,† and Hans-Peter Schmid, M.D.**

Background. **Using the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute and American total mortality rates, the authors calculated the probability at birth of having a diagnosis of prostate cancer within a man's life to be 8.8% and then subtracted the incidence of microscopic Stage A cancers too small to ever be clinically significant. This gave a final probability of 8%.**

Methods. **Prostates were examined after 139 consecutive unselected cystoprostatectomies from patients with bladder cancers in whom it was unknown whether they had prostate cancer. Prostate cancer was found in 55 patients (40%); the volume of the largest cancer in each specimen was determined using histologic morphometry. The authors identified the 8% of these 139 cystoprostatectomy specimens with the largest volume of prostate cancer.**

Results. **The largest 11 of the 55 cancers represented 7.9% of the total 139 samples. These cancers ranged in volume from 0.5–6.1 ml, representing only 20% of all patients with prostate cancer.**

Conclusions. **If the strong evidence is accepted that cancer progression is proportional to cancer volume, it was concluded that prostate cancers larger than 0.5 ml appear to correspond to the 8% of men who will be diagnosed with a clinically significant carcinoma, as derived previously. Conversely, those 80% of prostate cancers smaller than 0.5 ml probably are not likely to reach a clinically significant size in view of the long doubling time of this cancer. *Cancer* 1993; 71:933–8.**

Key words: prostate cancer, significance, progression, volume.

Presented at the American Cancer Society National Conference on Prostate Cancer, San Francisco, California, February 13–15, 1992.

From the Departments of *Urology and †Health Research and Policy, Stanford University School of Medicine, Stanford, California.

Supported in part by the R. M. Lucas Cancer Foundation.

Address for reprints: Thomas A. Stamey, M.D., Chairman, Department of Urology (S287), Stanford University School of Medicine, Stanford, CA 94305-5118.

Accepted for publication August 6, 1992.

Prostate cancer is unique among human tumors in that the frequency of histologically confirmed invasive cancer at autopsy greatly exceeds the prevalence of clinically significant carcinoma during life. Several studies have shown a frequency of autopsy-detected cancer of 30–40% in men older than 50 years of age.[1,2] However, calculations from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute indicate that the lifetime probability of prostate cancer being diagnosed clinically is only 9.5%, and the probability of dying of prostate cancer is only 3%.[3] In no other malignancy is there such a vast reservoir of undetected cases that may never be clinically significant or cause death.

Two solutions to this unique enigma have been proposed. Nearly 40 years ago, it was concluded from autopsy studies that the majority of carcinomas in the prostate represent "latent carcinoma," tumors that are identical histologically to lethal cancer but are predestined never to acquire biologically aggressive features.[1] Such a category of histologically malignant but biologically benign tumors has not been shown for cancer in any other organ.

An alternative solution is that the clinically innocuous cancers are simply the smallest tumors of the set.[4] If intracapsular prostate cancer grows with a slow and constant doubling time, there would be an excess of very small tumors, and such an excess has been detected in a quantitative autopsy series.[2] If cancers only acquire the capacity to metastasize as a function of the passage of time and increasing volume, early small tumors might not be expected to behave aggressively. There is increasing evidence that such "biologic tumor progression" is a function of the mutational instability found in all cancers, which becomes manifest in proportion to the number of mitotic events (volume). Furthermore, in clinical prostate cancer treated by radical prostatectomy, we found that the frequency of lymph node metastases is linked closely to the cancer volume,[5]

as is the frequency of capsular penetration into the periprostatic fat[6] and seminal vesicle invasion.[7]

However, this second hypothesis has never been supported by quantitative data showing that the numeric values for the frequency of histologic, clinical, and lethal cancers are compatible with each other. If they are compatible, the practical utility of the concept should be demonstrable and testable by the identification of a threshold volume below which it would be expected that the length of time required for a tumor to reach a clinically significant size would exceed the patient's life. Tumors below this threshold volume could be regarded as latent in the practical sense that treatment would be contraindicated. At the same time, these findings would refute the concept of latency in the biologic or histologic sense.

To provide a quantitative test of the tumor-progression hypothesis, we studied 55 cancers that were found in 139 cystoprostatectomy specimens removed for bladder cancer. Because none of these patients had a previous diagnosis or suspicion of prostate cancer, they should represent an unselected sample of the population in the age range at risk for this disease. The volume distribution of these cancers was compared with figures representing our refinement of figures for lifetime diagnosis of a clinically significant cancer, based on SEER detection data. Our values support the tenability of the volume-based tumor-progression hypothesis. They also determine a threshold value of 0.5 ml of cancer volume; below this value, tumors can be regarded as clinically insignificant.

Materials and Methods

We used prostate cancer incidence rates for the period 1973–1977 from the SEER Program[8] and American total mortality rates for the year 1986[9] to calculate the probability at birth of a man having a diagnosis of prostate cancer made within his life. Specifically, for each 5-year age interval, we computed the probability of having a diagnosis of prostate cancer made within that interval. We did this by multiplying the probability of surviving to the start of the interval (estimated from the mortality rates) by the probability of having a diagnosis of prostate cancer made during the interval among those who were alive at its start (estimated from the SEER rates). Then we summed the results for all 5-year age intervals to obtain a lifetime probability of 0.088 (8.8%). However, the SEER program includes all those patients with clinical Stage A disease. This represents approximately 10–20% of all cancers diagnosed in the United States. By definition, these cancers are discovered by transurethral resection of prostates thought to be benign using digital rectal examination. Because transurethral surgical sampling of benign prostate hyperplasia (BPH) can detect and even completely remove small prostate cancers, most of these patients do not have progression of their disease during their lives, especially those with clinical Stage A1 (< 5% of chips involved with cancer), a substage that represents 60% or more of all patients with clinical Stage A disease. We estimated that allowance for these insignificant Stage A tumors constitutes approximately 9% of all SEER-reported patients, those that are unlikely to have clinical progression of their disease. Because all other patients detected in the SEER Program have serious cancers (clinical Stages B, C, D1, and D2), we reduced the 8.8% we calculated to 8% (8.8% minus 9% of 8.8%) and used this as the probability of having a significant cancer diagnosed.

All cystoprostatectomies for bladder cancer were consecutive and unselected in patients without a previous diagnosis of prostate cancer. At least two digital rectal examinations were done on each patient before this operation. Fifty-one patients underwent transrectal ultrasound examination of their prostates before surgery, the results of which have been reported previously.[10] Seventy-six of these 139 patients had ambulatory outpatient prostate specific antigen (PSA) determinations before their digital rectal examinations; the Yang polyclonal assay (Yang Laboratories, Bellevue, WA) was used.[11] All except one of the 139 cystoprostatectomies were done in white men.

After removing the cystoprostatectomy specimen, the prostate, seminal vesicles, and proximal bladder neck were dissected free from the specimen. The prostate and adjacent seminal vesicles were fixed overnight in full-strength formaldehyde, the surface was inked, and the specimen was cut in 3-mm sections according to the Stanford technique, as previously described.[12] After histologic marking of the capsule, all cancers were identified and traced along with the specific areas of BPH. Using special computer software and a digitalizing pad, the area of the tumor in each section was determined, and the sum of all areas was multiplied by the section thickness. Allowances were made for tissue shrinkage caused by tissue fixation. Because 50% of all prostate cancers are associated with a small separate cancer,[13] the secondary cancers also were identified.

Results

Fifty-five of the 139 men undergoing cystoprostatectomy (40%) had at least one prostate cancer, an incidence similar to previously reported unselected autopsy[1] and cystoprostatectomy specimen series.[14] The mean and median ages of the 55 patients with prostate cancer is contrasted with the age of the entire group of

Table 1. Mean Age, Median Age, and Age Range of 55 Patients With Unsuspected Cases of Prostate Cancer in 139 Cystoprostatectomy Specimens

Age	Prostate cancer (n = 55)	Cystoprostatectomy (n = 139)
Mean	66.0 yr	64.8 yr
Median	65.0 yr	65.0 yr
Range	31–84 yr	31–84 yr

139 men in Table 1. The age distribution of the 55 men with unsuspected prostate cancers (found during examination of the 139 cystoprostatectomy specimens) is shown in Figure 1. Only two cancers were discovered in men younger than age 50 years. One was 31, and the other was 44 years of age; both tumors were 0.1 ml in volume.

Fifty-three of the 55 men with prostate cancer had a normal or normal-feeling benign enlargement of their prostates during digital rectal examination done by two independent observers. Both of the abnormal-feeling prostates contained prostate cancer, although the palpable abnormality did not correspond with the area of the cancer. These two men were 58 and 67 years old with primary cancer volumes of 1.4 and 0.27 ml, respectively.

The volume distribution of the 55 unsuspected largest prostate cancers in the 139 cystoprostatectomy specimens is shown in Figure 2. Two of the cancers were more than 1.5 ml in volume (1.4% of the 139 patients), 6 were more than 1.0 ml (4.3% of all patients), 11 were 0.5 ml or greater (7.9%), and 17 were more than 0.2 ml (12.2% of the 139 patients).

Of the 76 cystoprostatectomy specimens from patients for whom we had ambulatory serum PSA determinations, 32 (42%) had prostate cancer, and 41 (58%) did not. The level of PSA ranged from 0.3–21.1 ng/ml. The average PSA value in patients with prostate cancer

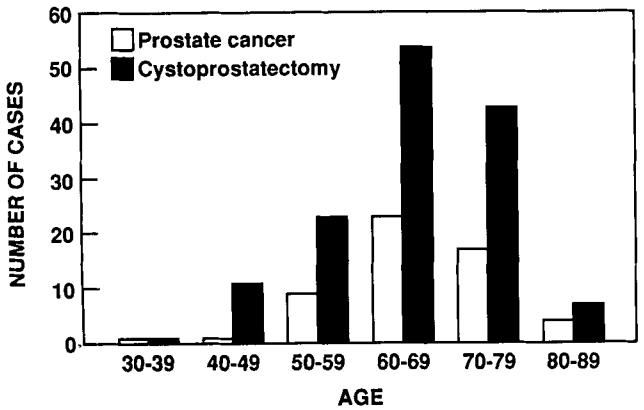

Figure 1. Age distribution of 139 patients undergoing cystoprostatectomy, 55 of whom were found to have prostate cancer.

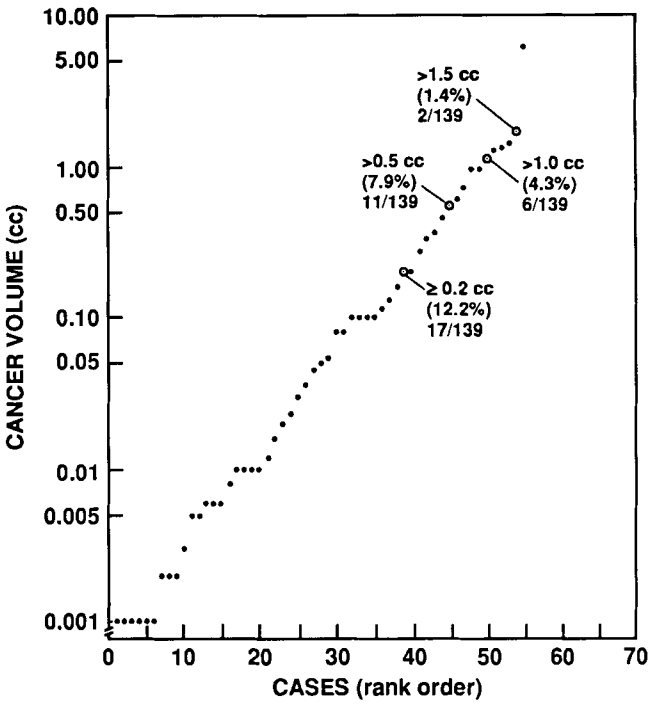

Figure 2. Volume distribution of 55 unsuspected largest prostate cancers in 139 cystoprostatectomies.

was 3.3 ng/ml (median, 2.5 ng/ml); it was 3.8 ng/ml (median, 1.6 ng/ml) in those patients without prostate cancer. Of the eight patients with undetectable PSA levels (< 0.3 ng/ml by the Yang assay), only one had cancer (tumor volume, 0.001 ml). Sixteen of the 32 patients with prostate cancer (50%) had PSA levels that were above the upper limits of the normal range for the Yang assay (2.5 ng/ml); 15 of the 44 patients (34%) without prostate cancer had PSA levels that were abnormal. However, the PSA level of only one patient with prostate cancer (3%) exceeded 10 ng/ml; this also occurred in six patients without prostate cancer (14%).

Discussion

A recent study of a closed population area in Sweden in which all 654 new patients with prostate cancer underwent modern bone scanning showed 24% of patients had bone metastases initially (Stage D2), 17% had clinical Stage A cancer, 30% had clinical Stage B, and 28% had clinical Stage C cancer.[15] This study is probably appropriate for the approximate clinical stages when patients are diagnosed with prostate cancer in the United States in the SEER Program.

The 8.8% lifetime probability of men in the United States ever having a diagnosis of prostate cancer made is, of course, an approximation, and we reduced this probability to 8% by excluding those clinical Stage A

cancers that were so microscopically small that they would be unlikely to progress or be clinically significant. That this 8% estimate is reasonable can be seen by its similarity to recent familial studies of men undergoing radical prostatectomy for prostate cancer in which the controls (often the spouses) had a 6–9.5% familial history for prostate cancer.[16–18]

Thus, because there is an 8% probability of a man in the United States having a prostate cancer large enough to be diagnosed during his life and because the probability of histologic progression (capsular penetration, seminal vesicle invasion, and microscopic metastases to the pelvic lymph nodes) is related directly to intracapsular cancer volume,[2,5–7,12] it was rational to ask, in the cystoprostatectomy specimens we studied, what were the largest volumes of cancer found in 8% of the 139 patients? Stated another way, if their prostates had not been removed because of their bladder cancer, who were the 8% of these men destined to have prostate cancer that would be diagnosed during their lives? As seen in Figure 2, only 7.9% (11 of 139) had a cancer volume of 0.5 ml or greater. At cancer volumes of 0.2 ml or more, 12.2% of men had cancers of this size, exceeding the 8% risk of having a significant cancer diagnosed during their lives. Unfortunately, cancers of 0.2 ml in volume can be detected easily both by rectal examination as very small palpable tumors[10] and certainly by transrectal ultrasound, where a 0.2-ml cancer, if a perfect sphere, would be 7 mm in diameter, well within the 4-mm lateral resolution of 7-MHz transducers. These data then, especially when combined with the extraordinarily slow growth rates of clinical Stage A and B cancers,[19] mean that the clinician must always ask the question, after making the diagnosis of cancer, "What is the volume of the intracapsular cancer?" If it is less than 0.5 ml, the patient probably does not need therapy and he will die with his cancer rather than of it. The alternative is to treat every patient whose prostate cancer is diagnosed without any consideration for the volume of the cancer. Carried to the extreme, 40% of all men might be treated for prostate cancer when only 8% will ever have a cancer large enough to be diagnosed and only 3% will die of it.[3]

From these data, after we realized that only cancer volumes of 0.5 ml or greater probably are significant, we examined our last 408 radical prostatectomies at Stanford for clinical Stage A and B disease to see what percent were less than 0.5 ml and what percent were even less than 0.2 ml. As seen in Table 2, 9% were less than 0.5 ml (37 of 408), and 2% were less than 0.2 ml. However, radical prostatectomies for clinical Stage A cancers, a stage in which it is known to be difficult to estimate the residual cancer volume,[20,21] included for 10 of these 37 cases (27%) cancer volumes that were less than 0.5 ml. Thus, it would appear from Table 2 that approximately 9% of the radical prostatectomies done at Stanford were unnecessary. To increase the accuracy of our preoperative volume estimates, we recently developed algorithms that include the preoperative serum PSA level, ultrasound volume of the cancer as measured by 2-mm axial step sections of the hypoechoic area, and the amount of cancer and Gleason grade of the cancer found in six systematic core biopsies. Although these four parameters have an excellent r^2 value of 0.76 for the logarithm of the intracapsular cancer volume, it is interesting that rectal examination for clinical Stage B disease adds no unique information in multiple-regression analyses, confirming the inaccuracies of digital rectal examination in defining intracapsular volume.

Table 2. Volume Distribution in 408 Radical Prostatectomy Specimens

Volume (ml)	No.	Percent
0–< 0.2	9	2
0.2–< 0.5	28	7
0.5–< 4.0	203	50
4.0–12	114	28
> 12	54	13
Total	408	100

In 1954, Franks,[1] faced with the problem of a 38% histologic incidence of prostate cancer in Great Britain that caused only 1.4% of all deaths in men older than 50 years of age, suggested that there were two forms of this cancer: a latent form and a clinical form that killed the patient. This separation was especially appealing because he could discern no differences in the microscopic appearance of these cancers. However, he did not recognize fully the importance of cancer volume as a measure of tumor progression, even though Leslie Foulds,[22] a pathologist in the same city (London) was beginning to elucidate his important concept of tumor progression. This important cancer principle currently includes the concepts that small tumors are incapable of metastases, the probability of metastasis increases with mass doublings (volume), and the mitoses that accompany the increase in volume generate heterogeneity in the new tumor cells, which ultimately cross the threshold for metastases. In prostate cancer, tumor volume and grade have been shown to be directly proportional to the probability of progression in a constant and linear fashion.[23] Thus, from our analysis of this cystoprostatectomy specimen series, prostate cancer latency is nothing more than a tumor with a volume less than 0.5 ml, a volume that included 80% of all cancers in our series. These cancers are unlikely to be of any clinical

significance during the patient's life and certainly will not be fatal. Our analysis of the extraordinarily slow doubling time for prostate cancer in an upcoming issue of *Cancer*[19] adds validity to this concept and, more importantly, identifies, for the first time, an objective measurement of the rate of progression (the serum PSA level).

PSA assays were obtained in 73 of 139 patients undergoing cystoprostatectomy; 44% had prostate cancer, and 56% did not. Because all except two patients with prostate cancer had normal rectal examination findings, these cancers would be expected to be small and low grade. All 55 were confined to the prostate, whereas only 40% of palpable lesions in our radical prostatectomy series similarly were confined. Although these cancers were small, in men with a mean age of 66 years (median, 65 years), substantial BPH was present in most prostates. We reported previously that 1 g of prostate cancer elevates the serum PSA level, on average, 3.5 ng/ml, and 1 g of BPH causes only a 0.3-ng/ml elevation in the serum PSA level,[11] and therefore, it is not surprising that, in the presence of small cancers and large amounts of BPH, PSA could not distinguish between patients with and without prostate cancer. Only 4.3% (6 of 139) of all patients had a cancer volume greater than 1.0 ml (Fig. 2).

Although screening for prostate cancer, at least from a cost–benefit ratio, remains controversial, there is important information in Figure 1 concerning when screening should begin. Both the American Cancer Society and the American Urological Association recommend that annual digital rectal examinations begin at 40 years of age. The American Cancer Society recommendation is a generic one because they include men and women and their concern extends beyond prostate cancer. For prostate cancer, however, Figure 1 clearly shows that this type of cancer is rare before the age of 50 years, and in the absence of a positive family history (which greatly increases the 8% probability of having prostate cancer diagnosed),[16–18] surely screening should not begin before age 50 years at least in white men. The results of our cystoprostatectomy specimen series agree with those of Franks'[1] 220 unselected autopsy cases, which were based on sudden or unexpected deaths in men that required a coroner's examination. Of 69 cancers in prostates sectioned at 4-mm intervals, not one was found in the 30 men who were younger than 50 years of age.[1] In two of our patients (ages, 31 and 44 years), microscopic cancers of 0.1 ml each were found. Thus, these two studies, especially in an era of escalating medical costs, argue strongly that screening for prostate cancer should not begin before age 50 years. If a first-degree relative, however, and especially if more than one first-degree relative or a first-degree and second-degree relative have prostate cancer, the sibling should probably undergo an annual PSA and digital rectal examination starting at 40 years of age. Because the SEER incidence rates for blacks 45 years of age is the same as that for whites 50 years of age,[8] it is possible that screening in blacks should begin at age 45 years.

Finally, it is interesting that the volume distribution of prostate cancer in these 55 cystoprostatectomy specimens was significantly smaller than that in our previous series of 100 consecutive autopsy-detected cancers.[2] For example, only 20% of the cystoprostatectomy specimen cancers were 0.5 ml or larger; 40% of the autopsy-detected tumors were this size. The explanation of this discrepancy is probably that the autopsy series was selected on the basis of 100 consecutive cancers rather than from a specific population unknown to have prostate cancer. Moreover, there were more blacks in the autopsy series. It is also possible that patients who die in the hospital may not reflect the true population incidence of prostate cancer.

References

1. Franks LM. Latent carcinoma of the prostate. *J Pathol* 1954; 68:603–16.
2. McNeal JE, Bostwick DG, Kindrachuk RA, Redwine EA, Freiha FS, Stamey TA. Patterns of progression in prostatic carcinoma. *Lancet* 1986; 1:60–3.
3. Seidman H, Mushinski MH, Gelb SK, Silverberg E. Probabilities of eventually developing or dying of cancer: United States, 1985. *CA Cancer J Clin* 1985; 35:36–56.
4. McNeal JE. Origin and development of carcinoma in the prostate. *Cancer* 1969; 23:24–34.
5. McNeal JE, Villers AA, Redwine EA, Freiha FS, Stamey TA. Histologic differentiation, cancer volume and pelvic lymph node metastasis in adenocarcinoma of the prostate. *Cancer* 1990; 66:1225–33.
6. McNeal JE, Villers AA, Redwine EA, Freiha FS, Stamey TA. Capsular penetration in prostate cancer: significance for natural history and treatment. *Am J Surg Pathol* 1990; 14:240–7.
7. Villers AA, McNeal JE, Redwine EA, Freiha FS, Stamey TA. Pathogenesis and biological significance of seminal vesicle invasion in prostatic adenocarcinoma. *J Urol* 1990; 143:1183–7.
8. Surveillance, Epidemiology, and End Results. Incidence and mortality data: 1973–1977. Bethesda (MD): National Cancer Institute Monograph 57; 1981 ; Publication No.: (NIH) 81-2330.
9. National Center for Health Statistics. Vital statistics of the United States. vol. 2. Hyattsville, MD: Public Health Service, 1986:10–1.
10. Terris MK, Freiha FS, McNeal JE, Stamey TA. Efficacy of transrectal ultrasound for identification of clinically undetected prostate cancer. *J Urol* 1991; 146:78–84.
11. Stamey TA, Yang N, Hay AR, McNeal JE, Freiha FS, Redwine E. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. *N Engl J Med* 1987; 317:909–16.
12. Stamey TA, McNeal JE, Freiha FS, Redwine E. Morphometric and clinical studies on 68 consecutive radical prostatectomies. *J Urol* 1988; 139:1235–41.

13. Villers AA, McNeal JE, Freiha FS, Stamey TA. Multiple cancers in the prostate: morphologic features of clinically recognized vs incidental tumors. *Cancer* 1992; 70:2313–8.
14. Montie JE, Wood DP Jr., Pontes JE, Boyett JM, Levin HS. Adenocarcinoma of the prostate in cystoprostatectomy specimens removed for bladder cancer. *Cancer* 1989; 63:381–5.
15. Johansson JE, Adami MD, Anderson SO, Bergström R, Krusemo UB, Kraaz W. Natural history of localised prostate cancer: a population-based study in 223 untreated patients. *Lancet* 1989; 1:799–803.
16. Steinberg GD, Carter BS, Beaty TH, Childs B, Walsh PC. Family history and the risk of prostate cancer. *Prostate* 1990; 17:337–47.
17. Keetch DW, Catalona WJ. Familial aspects of prostate cancer: a case control review [abstract]. *J Urol* 1991; 145:250A.
18. Babaian RJ, Spitz MR, Currier RD, Fueger JJ, Newell GR. Familial patterns of prostate cancer: a case-control analysis [abstract]. *J Urol* 1991; 145:213A.
19. Schmid H-P, McNeal JE, Stamey TA. Observations on the doubling time of prostate cancer as measured by serial prostate-specific antigen in untreated patients with prostate cancer. *Cancer.* In press.
20. Voges GE, McNeal JE, Redwine EA, Freiha FS, Stamey TA. The predictive significance of substaging stage A prostate cancer (A1 vs A2) for volume and grade of total cancer in the prostate. *J Urol* 1992; 147:858–63.
21. Greene DR, Egawa S, Neerhut G, Flanagan W, Wheeler TM, Scardino PT. The distribution of residual cancer in radical prostatectomy specimens in stage A prostate cancer. *J Urol* 1991; 145:324–9.
22. Foulds L. The experimental study of tumor progression: a review. *Cancer Res* 1954; 14:327–9.
23. Lowe BA, Listrom MB. Incidental carcinoma of the prostate: an analysis of the predictors of progression. *J Urol* 1988; 140: 1340–4.