



By Richard B. Thompson, MD
Ira M. Fielding, MD, FACS

A Retrospective Review of 2076 Prostate Ultrasonograms in One Urology Practice

Prostate cancer is the most common cancer in men, the second most common cancer-related cause of death, and has received a great deal of media attention. However, considerable controversy surrounds indications for screening asymptomatic patients for prostate cancer, and indications for urology referral (ie, in response to abnormal findings) have generated confusion.

We present an analysis of our experience with ultrasound evaluation of more than 2000 men for prostate carcinoma by the urology department in a staff-model health maintenance organization (HMO) whose cancer detection rate has averaged about 30%. This review suggests the clinical significance of using a number of parameters in evaluating the likelihood of cancer. These parameters are age; prostate volume; level of serum prostate-specific antigen (PSA), results of digital rectal and ultrasound examinations; and combined results of digital rectal examination, transurethral ultrasonography, and PSA analysis. We also present our experience with repeat biopsies.

Data are given in tabular form for easy reference by urologists and by primary care physicians. These data may help physicians to adjust their level of suspicion of cancer for each patient. For most cases in which prostate ultrasonography is done, we recommend that at least six biopsies be done.

Introduction

For men with suspicious results of digital rectal examination (DRE) or elevated serum levels of prostate-specific antigen (PSA), transrectal ultrasonography (TRUS) of the prostate with ultrasound-guided needle biopsy is the preferred procedure for diagnosis of prostate cancer. About 250,000 Health Plan members are served at the Kaiser Permanente Medical Center in Hayward and Fremont, California. Two thousand seventy-six men had prostate ultrasonography in the urology department between November 1989 and December 1997 to detect prostate cancer. We review the results of these 2076 ultrasound examinations to illustrate the evaluation of men in this clinical situation at a closed-panel HMO practice.

Materials and Methods

All ultrasound examinations were done using the Kretz Combison 310 instrument. Biopsy specimens were taken by using an 18-gauge, spring-loaded needle biopsy gun. Patients were given preoperative antibiotic prophylaxis, which consisted of two 500-mg doses of ciprofloxacin (one dose given the night before and one dose given on the morning of the procedure), and a Fleet enema given two hours before TRUS was done. After initially taking biopsy specimens from sites selected on the basis of suspicious ultrasound or DRE findings, we soon altered our technique to take biopsy specimens from at least six zones of the prostate selected by using a sextant or grid pattern as well as additional biopsy speci-

mens taken from suspect sites. For patients who had larger prostate volume and for patients who had repeat TRUS of the prostate in response to persistently rising PSA levels measured after negative initial biopsy results, eight or ten biopsy specimens were taken from representative zones of the prostate. This change in technique has increased our cancer detection rate substantially.

Results

In the early phase of our experience with prostate ultrasonography, biopsy was done less frequently, documentation was less careful, and some patients did not have PSA level or prostate volume recorded. In addition, as noted above, biopsy (when done) was done only at prostate sites for which ultrasound or DRE results were suspicious. During the first two years, the cancer detection rate (ie, men with positive biopsy results/total men biopsied) was approximately 18%, but thereafter, because of the changes in technique mentioned above, the cancer detection rate has averaged at least 30% each year.

Ultrasonography was done in men aged 39 years to 88 years (mean, 66 years). Most (1016) of these men were 61 to 70 years of age; of these 1016 men, 281 (28%) had a positive biopsy result. The cancer detection rate increased with each decade of age and varied from 17% (in men aged 41-50 years) to 43% (in men older than 80 years). Although 168 (8%) of the 2076 men did not have a biopsy, biopsy results were negative for >50% of men who did have biopsy.

“Prostates with volume <30 mL had the highest rate of cancer detected at biopsy (43%); the lowest rate (10%) was seen in prostates with volume >120 mL.”

RICHARD B. THOMPSON, MD (left), is a former Assistant Chief of Urology at Kaiser Permanente's Hayward-Fremont, California medical center. He retired from practice in June, 1999.

IRA M. FIELDING, MD, FACS (right), is a former Chief of Urology at the Hayward-Fremont medical center, and served as Chairman of the Chiefs of Urology from 1985 to 1997. He also retired from practice in June, 1999.



Prostate volume in the men studied varied from 8 mL to 324 mL (mean volume, 56 mL). In contrast to age and PSA level (which are directly related to incidence of cancer detected at biopsy), prostate volume shows an inverse relation to incidence of cancer detected at biopsy. Prostates with volume <30 mL had the highest rate of cancer detected at biopsy (43%); the lowest rate (10%) was seen in prostates with volume >120 mL.

Table 1 lists biopsy results grouped according to common PSA reference ranges. Of the 2076 patients who had TRUS of the prostate, 1815 (87%) had a serum PSA level recorded. As PSA values increased, the rate of positive biopsy results continued to increase and reached 98% (for PSA >90 ng/mL).

Calculating PSA density (serum PSA in ng/mL divided by prostate volume in mL) has been advocated as a method of increasing the sensitivity of cancer detection by correcting for the higher values of PSA that are due only to a larger prostate size. Because prostate cancer raises PSA level more per gram of tissue than benign prostate enlargement does, the concept of PSA density may be helpful in avoiding a biopsy when the elevated PSA is due to prostate size alone. A common recommendation is to avoid biopsy when PSA density is <0.15. Table 2 shows that a general increase in rate of positive biopsy results as PSA density increases. However, even at a density of 0.20-0.25, only about a third of men in the study had a positive biopsy result, and, conversely, 13% of men with PSA density ≤0.15 were found to have cancer that would not have been detected if biopsy had not been done.

Tables 3 through 6 show biopsy results correlated with the side of the prostate for which DRE or TRUS findings raised suspicion of cancer. Biopsy result for the suspect side was tabulated as negative even if the biopsy result for the contralateral, nonsuspect side was positive. This practice allowed more accurate evaluation of both the clinical significance of DRE and TRUS findings and the need for biopsy on the contralateral side. Only 35 patients had a negative biopsy result for the suspect side and a positive biopsy result for the contralateral, nonsuspect side. In cases where the laterality of DRE and TRUS does not play a role, these 35 positive results were tabulated with the other positive biopsy results.

Table 3 shows that 888 men with positive result of DRE had the highest positive biopsy rate (41%); 20% of men with negative results of DRE had positive biopsy results; and men with indeterminate results of DRE had an even lower rate of positive biopsy results (13%). The highest rate of negative biopsy results (72%) was seen in men who had negative results of DRE. However, 20% of men who had negative results of DRE did have cancer.

Table 4 relates biopsy results to ultrasound findings. Of the 591 men with a positive ultrasound result, 326 (55%) had a positive biopsy result, 262 (44%) had a negative biopsy result, and three (1%) had no biopsy.

Table 1. Positive biopsy result and level of serum prostate-specific antigen (PSA) in 1815 men^a

Serum PSA Level ^b	No. Positive Biopsy Results (% for same serum PSA level)	Percentage total population
≤ 4.0 (n=306)	26 (8)	17
4.1-10.0 (n=803)	207 (26)	44
> 10.0 (n=706)	340 (48)	39
Total (n=1815)	573 (32)	

^a Serum PSA level was not recorded for 261 (13%) of the 2076 men. For 46 (18%) of these 261 men, biopsy result was positive. Overall for the 2076 men, 619 (30%) had a positive biopsy result.

^b Expressed as ng/mL.

Table 2. Rate of positive biopsy results and PSA density in 1520 men.^a

PSA density ^b	No. positive biopsy results (% with same PSA density)	No. men with recorded PSA density (% all men with recorded PSA density)
≤ 0.15	92 (13)	698 (46)
0.16-0.30	162 (35)	463 (31)
0.31-0.45	71 (47)	152 (10)
0.46-0.60	40 (61)	66 (4)
0.61-153.0	110 (78)	141 (9)
Total	475 (31)	1520

^aPSA density not calculated for 556 men because PSA value or prostate volume not recorded.

^bSerum PSA in ng/mL divided by prostate volume in mL.



The highest rate of positive biopsy result (55%) was seen in the group of men who had positive results of TRUS. Only 16% of men who had negative results of TRUS and 30% of men with indeterminate results of TRUS had positive biopsy results.

Of the 2076 men who had TRUS, 1908 (92%) had a biopsy. Of these, 1584 (83%) had bilateral biopsy. Corrected for laterality, 584 (28%) of these 1584 men had positive results of ipsilateral biopsy on the suspect side. Of those 584 men, 262 (45%) were found to have cancer on the nonsuspect side as well, and 272 (47%) had negative results of contralateral biopsy. Only 35 (3%) of the 1324 men with negative results of ipsilateral biopsy had cancer on the contralateral, nonsuspect side only.

Positive biopsy result was related to PSA level and DRE result (positive or negative) and to PSA level and

TRUS result (positive or negative) (Tables 5,6). Combining PSA with positive DRE result gave a higher positive biopsy rate than PSA alone (Table 1) or DRE alone (Table 3) gave. Similarly, combining PSA and positive result of TRUS showed a higher positive biopsy rate than either measurement alone. The highest rate of positive biopsy result occurred in men with PSA >10.0 ng/mL and either a positive DRE result (75%) or a positive TRUS result (78%). The lowest rate of positive biopsy result was seen in men with PSA ≤4.0 ng/mL and negative DRE result (0%) or with PSA ≤4.0 ng/mL and negative TRUS result (3%).

Of the 26 patients with PSA ≤4.0 ng/mL prostate and cancer detected at biopsy (Table 1), 24 (92%) had a positive DRE result. However, those 24 men (Table 5) represent only 11% of the group of 214 men who had PSA ≤4.0 ng/mL and a positive DRE

“Positive biopsy result was related to PSA level and DRE result (positive or negative) and to PSA level and TRUS result (positive or negative).”

Table 3. Biopsy results correlated with results of digital rectal examination (DRE) in 2076 men.

DRE results	No. of biopsy results (% with same DRE result)			No. biopsy results (% total population)
	Positive	Negative	None	
Positive	361 (41)	473 (53)	54 (6)	888 (43)
Negative	201 (20)	735 (72)	85 (8)	1021 (49)
Indeterminate	22 (13)	116 (69)	29 (17)	167 (8)
Total	584 (28) ^a	1324 (64)	168 (8)	2076 (100)

^aAs noted in the text, 35 men had a positive biopsy result only on the negative side. Including these men results in an overall positive biopsy rate of 30% (619/2076).

Table 4. Biopsy results correlated with results of ultrasound examination in 2076 men.

Ultrasound result	No. biopsy results (% with same ultrasound result)			No. biopsy results (% total population)
	Positive	Negative	None	
Positive	326 (55)	262 (44)	3 (1)	591 (28)
Negative	204 (16)	933 (72)	165 (13)	1302 (63)
Indeterminate	54 (30)	129 (70)	0 (0)	183 (9)
Total	584 (28) ^a	1324 (64)	168 (8)	2076 (100)

^aAs noted in the text, 35 men had a positive biopsy result only on the negative side. Including these men results in an overall positive biopsy rate of 30% (619/2076).



Table 5. Positive biopsy results in 517 men correlated with PSA level and DRE result.^a

PSA level (ng/mL)	No. (%) of positive biopsy results ^b	
	Positive DRE result ^c	Negative DRE result ^d
≤4.0	24 (11)	0 (0)
4.1-10.0	92 (43)	89 (17)
>10.0	201 (75)	111 (28)
Total	317 (46)	200 (20)

^a 1514 men had indeterminate DRE result, negative biopsy result, no biopsy done, or a combination.
^b Percentage with same DRE result and level of PSA.
^c PSA level not recorded for an additional 44 men with a positive biopsy result.
^d PSA level not recorded for an additional one man with a negative biopsy result.

Table 6. Positive biopsy results in 490 men correlated with PSA level and ultrasound results.^a

PSA level (ng/mL)	No. (%) positive biopsy results ^b	
	Positive ultrasound result ^c	Negative ultrasound result ^d
≤ 4.0	19 (23)	5 (3)
4.1-10.0	80 (44)	93 (17)
> 10.0	198 (78)	95 (25)
Total	297 (57)	193 (17)

^a 1546 men had indeterminate ultrasound result, negative biopsy result, no biopsy done, or a combination.
^b Percentage with same ultrasound result and level of PSA.
^c PSA level not recorded for an additional 29 men with a positive biopsy result.
^d PSA level not recorded for an additional 11 men with a negative biopsy result.

result. Similarly, 19 (73%) of the 26 men with a positive biopsy result and PSA ≤4.0 ng/mL had a positive TRUS result; however, those 19 men represent only 23% of men with a PSA ≤4.0 ng/mL and a positive TRUS result (Table 6).
 Of the 2076 ultrasound examinations, 318 (15%) were repeat studies done on the same patient (seven days to seven years after the patient was first exam-

ined by ultrasound). Patients had any of five indications for repeated TRUS examination: 1) insufficient tissue specimen or nondiagnostic biopsy result; 2) no biopsy done at first TRUS examination; 3) presence of high-grade prostatic intraepithelial neoplasia (PIN); 4) only a small focus of low-grade cancer seen at first biopsy; or 5) rising PSA seen after initially negative TRUS or biopsy results. Of these 318 repeat ultrasound examinations, 312 (98%) were accompanied by biopsies, and 224 (72%) of these 312 biopsies showed no change from the previous biopsy results. Of the 272 men who previously had negative biopsy results, 208 had the same findings at repeat biopsies, and 60 (22%) converted to a positive biopsy result. Four men did not have biopsy done at repeat ultrasound examination. Of the 26 men who did not have biopsy done with the first TRUS examination, seven (27%) of these men had a positive biopsy result when TRUS was repeated, and 17 (65%) had a negative biopsy result when TRUS was repeated. Two men did not have a biopsy done at initial or repeat ultrasound examination. The cancer detection rate for both groups—22% for men with previous negative biopsy result and 27% for men with no previous biopsy result—was lower than the 30% detection rate for patients who had a biopsy at first TRUS examination.
 For each successive year after a negative biopsy result was obtained, the cancer detection rates seen at repeat TRUS and biopsy are also <30%. Among patients with initially negative biopsy results, repeat TRUS and biopsy produced an overall cancer detection rate of 23% when done for rising PSA density levels.
 How much weight should be given to positive or negative findings of DRE or TRUS examination, to a given serum PSA value, or to any combination of these three variables? Our experience correlating these important variables is presented (Tables 7,8,9).
 Different serum levels of PSA in relation to rate of positive biopsy result is shown (Table 7). Combining PSA data with data for positive DRE result or with positive TRUS result (ie, correlation with two variables) increased the percentage of positive biopsy results for each PSA level, but only when PSA was ≤4.0 ng/mL did TRUS (which showed a 23% rate of cancer detection) show a clinically significant diagnostic advantage over DRE (which showed an 11% rate of cancer detection). Combining all three variables (ie, positive DRE result, positive TRUS result, and PSA level) detected more cancer at each PSA level (Table 7). Negative DRE and TRUS findings were also correlated with PSA level (Table 8).

**Table 7. Percentage of positive biopsy results correlated with one, two, or three variables.**

		Percentage positive biopsy results		
		Correlated with two variables		Correlated with three variables
		Positive DRE result	Positive ultrasound result	Positive DRE and ultrasonography results
Alone				
Positive DRE result	41	--	62	--
Positive ultrasound result	55	62	--	--
PSA level ^a				
≤ 4.0	8	11	23	25
4.1-10.0	26	43	44	54
>10.0	48	75	78	89
-- = not applicable. ^a Expressed as ng/mL.				

Table 8. Percentage of positive biopsy results correlated with one, two, or three variables.

		Percentage positive biopsy result		
		Correlated with two variables		Correlated with three variables
		Negative DRE result	Negative ultrasound result	Negative DRE and ultrasonography results
Alone				
Negative DRE result	20	--	16	--
Negative ultrasound result	16	16	--	--
PSA level ^a				
≤ 4.0	8	0	3	0
4.1-10.0	26	17	17	14
>10.0	48	28	25	22
-- = not applicable. ^a Expressed as ng/mL.				

"As our experience increased and as our knowledge of prostate cancer increased,^{2,3} we began to do more biopsies, including biopsies on the side contralateral to the suspect side ..."

As shown in Table 9, a 16% incidence of cancer was detected among men for whom results of DRE and TRUS were both negative. Most of our patients had either a positive DRE result or a positive TRUS result to direct the focus of the biopsies. However, 805 patients had both a negative DRE result and a negative TRUS result. Of these men, 127 (16%) had positive biopsy results. Most men (423) had an intermediate PSA level (4.0–10.0 ng/mL). Biopsy result was positive among slightly less than half of this group; biopsy result was positive among slightly more than half of men with PSA >10.0 ng/mL.

Discussion

This review of >2000 ultrasound examinations of the prostate includes data from our initial years of using ultrasound for clinical diagnosis of prostate neoplasms. During the first two years, we detected a cancer incidence of 18% among men who had TRUS examination of the prostate. This result is similar to the rate found by Cooner et al¹ in their early, landmark study. As our experience increased and as our knowledge of prostate cancer increased,^{2,3} we began to do more biopsies, including biopsies on the side contralateral to the suspect side and then sextant-directed biopsies where biopsy of each lobe of the prostate was done at least three times regardless of the DRE or ultrasound findings. The result over the past few years has been a relatively stable 30% (mean) rate of positive biopsy result, a rate which is similar to those obtained in other published studies.^{4,5,6,7}

As we expected, our data showed an increase in incidence of cancer (ie, from 17% to 43%) with increasing age during the fourth through ninth decades of life.⁷

In addition, the positive biopsy rate decreases as prostate volume increases, as noted by others.^{5,6} This finding may be caused by two factors: 1) benign prostatic hyperplasia (the main cause of increased prostate volume) may increase serum PSA levels and thus lead to TRUS examination in many men with benign disease; 2) when sextant biopsies are done on a large gland, a small cancerous area is more likely to remain undetected than when the same number of sites are biopsied in a small gland.

Measurement of PSA density has been suggested as a method to correct for the effect of increased prostate volume on PSA levels.⁸ However, our experience (Table 2) has not shown that PSA density is a useful indicator for prostate biopsy.

Used as an indicator, a positive DRE or ultrasound result leads to more positive biopsy results, as does an elevated PSA level.^{4,9,10} In addition, the higher the PSA level, the higher the number of positive biopsy results; yet neither a negative result of DRE or ultrasound nor a "normal" PSA level assures absence of cancer.^{3,11,12} Combining variables increases the rate of positive biopsy result (Table 7) but could nonetheless fail to detect cancer in some patients (Tables 8, 9).

Given that many biopsy results for the contralateral, nonsuspect side were positive and that positive biopsy results were not precluded by either a "normal" PSA, a negative DRE result, or a negative ultrasound result, we advocate use of the sextant or multiple biopsies in addition to directed biopsies of suspect areas as identified at DRE or ultrasound examination.^{3,4,12,13}

In our experience, initial biopsies yielded the highest cancer detection rate (30%), whereas later, repeat biopsies yielded rates lower than 30%.¹⁴

Table 9. Biopsy results correlated with negative results of both DRE and ultrasonography in 805 men.

Biopsy result	No. (%) biopsy results correlated with PSA level ^a				Total
	≤4.0	4.1-10.0	>10.0	Not recorded	
Positive	0 (0)	60 (47)	67 (53)	0 (0)	127 (16)
Negative	27 (5)	324 (55)	231 (39)	11 (2)	593 (74)
None	20 (24)	39 (46)	3 (4)	23 (27)	85 (11)
Total	47 (6)	423 (53)	301 (37)	34 (4)	805

^aExpressed as ng/mL.



Summary and Conclusions

These data present the experience of a urology practice performing 2076 transrectal ultrasound examinations of the prostate to detect prostate carcinoma at a staff-model HMO. Our diagnostic techniques have improved over the years, resulting in a higher number of positive biopsy results. We now perform at least six biopsies of selected sites from both sides of the prostate for all patients whose serum PSA levels are higher than the age-adjusted norm; this procedure includes directed biopsy in men who have a definite nodule at DRE or a clearly delineated hypoechoic lesion seen at TRUS examination. If PSA level is within normal limits, we may elect biopsy only for palpable or visible lesions in otherwise low-risk patients. The high yield of positive contralateral biopsy results obtained in patients whose suspect side gives positive results shows that we may assign too low a stage to many cancers if contralateral biopsy is not done. We recommend that men with large prostate glands have eight or more biopsies of selected sites and that men with previous negative biopsy results but rapidly rising PSA levels have biopsy of the transition zone of the prostate as well. We do not use PSA density as an indicator for initial biopsy of the prostate. ❖

References:

1. Cooner WH, Mosley BR, Rutherford CL Jr, Beard JH, Pond HS, Terry WS, et al. Prostate cancer detection in a clinical urological practice by ultrasonography, digital rectal examination and prostate specific antigen. *J Urol* 1990;143:1146-52; discussion 1152-4.
2. Stamey TA. Diagnosis of prostate cancer: a personal view. *J Urol* 1992;147(3 Pt 2):830-2.
3. Stamey TA. Making the most out of six systematic sextant biopsies. *Urology* 1995;45:2-12.
4. Brawer MK, Chetner MP, Beatie J, Buchner DM, Vessella RL, Lange PH. Screening for prostatic carcinoma with prostate specific antigen. *J Urol* 1992;147(3 Pt 2):841-5.
5. Karakiewicz PI, Bazinet M, Aprikian AG, Trudel C, Aronson S, Nachabe M, et al. Outcome of sextant biopsy according to gland volume. *Urology* 1997;49:55-9.
6. Levine MA, Ittman M, Melamed J, Lepor H. Two consecutive sets of transrectal ultrasound guided sextant biopsies of the prostate for the detection of prostate cancer. *J Urol* 1998;159:471-5; discussion 475-6.
7. Orozco R, Kunnel B, O'Dowd GJ, Stamey TA. Positive prostate biopsy rate consistently increases with age at the same prostate-specific antigen level in patients with normal digital rectal examination. *Urology* 1998;51:531-3.
8. Beduschi MC, Oesterling JE. Prostate-specific antigen density. *Urol Clin North Am* 1997;24:323-32.
9. Catalona WJ, Richie JP, Ahmann FR, Hudson MA, Scardino PT, Flanigan RC, et al. Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: results of a multicenter clinical trial of 6,630 men. *J Urol* 1994;151:1283-90.
10. Partin AW, Carter HB. The use of prostate-specific antigen and free/total prostate-specific antigen in the diagnosis of localized prostate cancer. *Urol Clin North Am* 1996;23:531-40.
11. Flanigan RC, Catalona WJ, Richie JP, Ahmann FR, Hudson MA, Scardino PT, et al. Accuracy of digital rectal examination and transrectal ultrasonography in localizing prostate cancer. *J Urol* 1994;152(5 Pt 1):1506-9.
12. Hodge KK, McNeal JE, Terris MK, Stamey TA. Random systematic versus directed ultrasound guided transrectal core biopsies of the prostate. *J Urol* 1989;142:71-4; discussion 74-5.
13. Norberg M, Egevad L, Holmberg P, Sparen P, Norlen BJ, Busch C. The sextant protocol for ultrasound-guided core biopsies of the prostate underestimates the presence of cancer. *Urology* 1997;50:562-6.
14. Ellis WJ, Brawer MK. Repeat prostate needle biopsy: who needs it? *J Urol* 1995;153:1496-8.

"We recommend that men with large prostate glands have eight or more biopsies of selected sites and that men with previous negative biopsy results but rapidly rising PSA levels have biopsy of the transition zone of the prostate as well."

Positive Change

"If each of us were involved in some form of positive change, there wouldn't be enough problems to go around."

*Sam Harris,
Reclaiming Democracy*