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The Role of Digital Rectal Examination, Transrectal Ultrasound, and Prostate Specific Antigen for the Detection of Confined and Clinically Relevant Prostate Cancer

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Abstract In a study population, can digital rectal examination (DRE), transrectal ultrasound (TRUS), and prostate specific antigen (PSA) (monoclonal) effectively detect the majority of clinically relevant cancer? If this is possible, the remaining patients could then be considered for chemopreventive protocols.

The American Cancer Society/National Prostate Cancer Detection Project (ACS/NPCDP) had a cancer detection rate of 2.4% for its initial year utilizing PSA, DRE and TRUS. TRUS and PSA detected 73% more cancer than DRE alone. TRUS detected a greater percentage of cancers than DRE (85% vs. 64%).

PSA was ≥ 4 ng/ml for 66% of prostate cancer patients; 11% of cancer patients had PSA < 2 ng/ml. PSA decision levels based on gland volume detected a subgroup at the 95th percentile that had a nine-fold increased risk for cancer. In a separate study differentiating benign prostatic hypertrophy (BPH) and cancer, we found 0.12 ± 0.13 ng/ml/gm for serum PSA (sPSA)/gm BPH. This study proved that **predicted PSA (pPSA) = gland volume x 0.12**; this equation also functioned at the 95th percentile for any **individual** patient.

Individual patient assessment:

1. Entry level PSA = 2 ng/ml.
2. Those patients with PSA > 2 ng/ml have TRUS determination of gland volume (performed by technician).
3. pPSA = gland volume x 0.12.
   If sPSA > pPSA then:
4. (sPSA - pPSA)/2 = predicted volume (cc) of cancer;
5. $\sqrt[3]{}$ volume of cancer = mean diameter (cm) of cancer.

Thus, these results should detect the majority of clinically relevant cancer (>0.5 cc). PSA combined with TRUS and DRE can identify high risk groups for cancer.

Key words: DRE, predicted cancer volume, prostate cancer, PSA, TRUS

Cancer incidence and death from prostate cancer is projected to be 132,000 new cases and 34,000 deaths for 1992. It is the leading cancer in men and the second leading cause of death from cancer [1]. For men 50 years and older, the lifetime risk of developing clinically significant prostate cancer is estimated to be 10% [2]. In the USA, men are living longer; a large percentage live beyond 85 years, resulting in "aging of the aged" [3]. The risk for developing prostate cancer could increase dramatically and create major public health problems.

Clinical studies confirm long term survival and "cure" for localized disease when treated by either radiation therapy or radical prostatectomy [4,5]. The only non-invasive test for large scale screening of prostate cancer has been the digital rectal examination (DRE). However, detection rates for cancer have been quite low (0.8–1.5%), and the expected numbers of confined cancers are no better than those found for non-screened populations [6–11]. The focus of this paper is the application of recently acquired knowledge to properly complement prostate

specific antigen (PSA), transrectal ultrasound (TRUS) and DRE for early detection of clinically significant prostate cancer (>0.5 cc) [12,13].

TRANSRECTAL ULTRASOUND AND PROSTATE CANCER

In 1988, the application of TRUS proved to be more sensitive than DRE in early cancer detection. Overall, cancer detection rates by TRUS were two times higher as compared with DRE (2.6% vs. 1.3%). TRUS detected tumors of smaller size than those detected by DRE (13 vs. 17 mm). Seventy-seven percent of tumors were considered localized ($\leq$1.5 cm = 3 cc); TRUS detected 100% of these compared to 41% by DRE. These findings were confirmed by radical prostatectomy; 83% of those tumors $\leq$1.5 cm were confined to the prostate [14]. TRUS was capable of increasing not only cancer detection rates but, more importantly, detection of confined cancers. The American Cancer Society/National Prostate Cancer Detection Project (ACS/NPCDP), a multicenter, multidisciplinary study, showed 85% of cancers detected by TRUS versus 64% detected by DRE [12], confirming the superior sensitivity of TRUS over DRE.

Other reports comparing TRUS and DRE in screening settings are listed in Table I [9,15, 16]. Some of these studies included patients >70 years of age who are unlikely to benefit from early detection. When considering only men <70 years of age, the total detection rate for cancer was significantly greater for the ACS/NPCDP study (2.4%) as compared with other reported rates (1.4–1.7%) [9,12,16]. The ACS/NPCDP data from 10 centers also found TRUS to be of greater sensitivity in this age group. In contrast, Catalona *et al.* [16] detected fewer total cancers and found DRE to be of greater sensitivity than TRUS, highlighting the operator dependency of both examinations. Knowledge of cancer origin and technical expertise are important in TRUS; McNeal [17] has shown that 50% of cancers originate anterior to the midline of the prostate, out of reach of DRE.

PSA AND PROSTATE CANCER

PSA levels have shown correlation with tumor presence [18,19]. The results of the ACS/NPCDP study as compared with others utilizing PSA are summarized in Table II. The ACS/NPCDP study [12] may have detected cancer earlier, since 28% of those with cancer had PSA of 4–10 ng/ml as compared with 41% [19] and 51% [16] for two other studies. In a fourth series, Palken [15] related PSA levels of 2.8–10 ng/ml to 39% of those with cancer as compared with 50% for 2–10 ng/ml in the ACS/NPCDP study. The distribution of PSA was quite similar in both of these studies; however, the total detection rate for cancer was considerably higher in the Palken series (7%) as compared with the ACS/NPCDP study (2.4%) (see Table I). This may be explained, in part, by the limited cohort, advanced subject age (50–86 years) and use of systematic biopsy in the Palken series. The majority of cancers in the ACS/NPCDP study were detected by TRUS, and the earlier cancer diagnosis appears to be substantiated by lower levels of PSA. Again, a significant number of cancers (11%) have PSA

Table I. Screening/Early Detection

	ACS/NPCDP *et al.* [12]	Catalona *et al.* [16]		Palken *et al.* [15]	Chodak *et al.* [9]	
Cohort (n)	2,425	1,653	1,366	323	2,135	1,672
Ages	55–70	50–89	50–70	50–86	45–80	51–70
Cancer Detection	2.4%	2.2%	1.7%	7%	1.5%	1.4%
DRE	58%	68%		74%	100%	
TRUS	77%	57%		61%	0	

Table II. PSA and Cancer

PSA (ng/ml)	ACS/NPCDP *et al.* [12]	Catalona *et al.* [16]	Palken *et al.* [15]	Partin *et al.* [19]
0–2	11%	---		11%
0–2.7			22%	
2–4	22%	---	---	21%
4–10	28%	51%	(2.8–10) 39%	41%
>10	39%	49%	39%	27%

Table III. PSA Correlated With Pathology

PSA (ng/ml)	≤2	≤2.8	≤4.0	>4–10
Cancer	11%*	21%	32%	38%
Confined	68%**	73%	74%	54%
Non-confined	32%	27%	26%	46%

Partin *et al.* [19]

* Frequency of detected cancer
** Fraction of detected cancer which was confined to the prostate

Table IV. Screening Correlation With Pathologic State of Cancer

Stage of Cancer	DRE[1]	PSA of 4–10 ng/ml	
B (confined)	50%	59%[2]	54%[3]
C (non-confined)	50%	41%[2]	46%[3]

[1] Chodak *et al.* [9]
[2] Catalona *et al.* [16]
[3] Partin *et al.* [19]

levels <2.0 ng/ml. Brawn [20] has shown that cancers <1 cc in glands of <80 gm do not elevate PSA. These cancers are usually of low volume and the majority are biologically nonaggressive.

In the ACS/NPCDP, 33% of cancers had PSA <4 ng/ml; Palken [15] and Partin [19] reported similar levels (Table II). Cooner [21] advises that men younger than 65 years with PSA ≤4 ng/ml and negative DRE should not receive TRUS. This advice may not be appropriate in a screening setting. If we are to affect mortality rates, the entry PSA must be defined so that a significant number of confined cancers can be detected. This must be better than the national average (*i.e.*, 40–50% confined cancers) [10,11], equivalent to that found with DRE screening [7,9]. Table III correlates definitive histologic staging with PSA levels. For PSA of <4 ng/ml, 74% of cancers were confined as compared to 54% at 4–10 ng/ml. A comparison of Table III results with Catalona's series (Table IV) shows that a PSA of 4–10 ng/ml gives nearly the same results as DRE alone [16,19].

Should we accept results for PSA ≥4 ng/ml (*i.e.*, complementation of DRE by PSA), this would produce mainly an increased detection of non-confined cancer, a scenario not unlike that for DRE alone. Thus, this would not decrease current national mortality rates. Therefore an entry level of PSA ≥4 ng/ml in a screening setting would not be effective.

The ACS/NPCDP has the potential to produce the desired results since one-third of the cohort had PSA levels <4 ng/ml. If an entry level for PSA was 2 ng/ml it would eliminate 65% of TRUS and DRE exams and decrease the biopsy *rate to one-half*; however, 11% of the cancers would have been missed in the initial year of study [12].

PSA, GLAND VOLUME AND POSITIVE PREDICTIVE VALUE (PPV)

The relationship of prostate volume and PSA continues to be better defined [22,23]. Patients with PSA values above decision levels operating at the 95th percentile for selected gland volumes had an estimated nine-fold increased risk of prostate cancer. These decision levels objectively define a high risk group which influences biopsy decisions and PPV for TRUS and DRE.

Preliminary computation of ACS/NPCDP data indicates that a PSA (entry level) of 2 ng/ml selects 35% of the cohort for subsequent DRE and TRUS. Determination of gland volume with serum PSA (sPSA) then defines a high risk group with sPSA >95th percentile of normal. This high risk group approximates 10–15% of the study cohort.

We recently submitted data further refining the gland volume–PSA relationship in each individual patient [13]. This study was based on our finding of 0.12 ± 0.13 ng/ml/gm for PSA/gm of benign prostatic hypertrophy (BPH) with a coefficient of determination (R^2) = 0.59. The following formula functions at the 95th percentile for normal:

predicted PSA (pPSA) = gland volume × 0.12.

When pPSA was used to evaluate TRUS statistics, marked differences occurred in PPV for patients with sPSA > pPSA vs. patients with sPSA < pPSA (86% vs. 24%). For this series, those patients with pPSA > sPSA also had a proven 5% latent cancer (Stage A1). The TRUS PPV of 24% for patients with sPSA < pPSA emphasizes the importance of the hypoechoic lesion and the superior sensitivity of TRUS over pPSA.

The following is our protocol for detection of confined cancer.

1. Entry level for PSA = 2 ng/ml (monoclonal). Those men with PSA >2 ng/ml proceed to:
2. TRUS for gland volume + DRE.
   Gland volume [(w × h × l)cm] × 0.12 = pPSA.

This portion of the study could be done by a technician. Should pPSA > sPSA, then repeat PSA studies at 6 and 12 month intervals would be appropriate. Increasing levels of PSA would be an indication for re-TRUS and DRE.

3. If sPSA > pPSA, then (sPSA – pPSA)/2 = predicted volume (cc) of cancer, to be localized for biopsy by TRUS. The denominator of 2 is based on 1.8 ng/ml PSA (monoclonal)/gm of cancer [18].
4. Mean diameter of lesion = $\sqrt[3]{}$predicted cancer volume.
5. This value then allows the evaluator (M.D.) to focus on suspicious foci of appropriate size.

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