The digital rectal examination (DRE) remains important – outcomes from a contemporary cohort of men undergoing an initial 12-18 core prostate needle biopsy

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Introduction: *Indications for prostate needle biopsy (PNB) include elevated serum prostate-specific antigen (PSA) and/or abnormal digital rectal examination (DRE). We evaluated a contemporary cohort of men undergoing PNB to determine cancer detection rates when stratified by DRE status.*

Materials and methods: *The charts of 806 men who underwent a PNB were reviewed. Serum PSA was categorized as normal or abnormal according to age-specific criteria. A normal DRE was defined as a smooth, age-appropriate, asymmetric, or uniformly enlarged prostate. An abnormal DRE was defined by either a nodule or induration. Sensitivity, specificity, and predictive values were determined for an abnormal DRE and the diagnosis of prostate cancer.*

Results: *Within the cohort, 516 patients (64%) had a normal and 290 (36%) an abnormal DRE. Three hundred six (38%) men were diagnosed with prostate cancer of which 136 (44%) had an abnormal DRE. Fourteen percent of patients with prostate cancer had an isolated DRE abnormality. Furthermore, when specifically considering these 136 men with an abnormal DRE and prostate cancer, 43 (31%) had a normal age-specific PSA value. No differences in cancer detection rate were noted when stratifying by type of DRE abnormality. In this select cohort of patients undergoing prostate biopsy, an abnormal DRE had a sensitivity of 44%, specificity of 68%, positive predictive value (PPV) of 46%, and a negative predictive value (NPV) of 67% for detecting prostate cancer on biopsy.*

Conclusion: *Almost 50% of men in our cohort diagnosed with prostate cancer had an abnormal DRE. While only 14% of all patients with prostate cancer had an isolated DRE abnormality, 31% of these men had normal age-specific PSA values. Such observations underscore the importance of the DRE for prostate cancer screening.*

Key Words: prostate cancer, digital rectal examination, prostate-specific antigen, prostate needle biopsy

Introduction

Prostate cancer is the most common visceral cancer in men accounting for 29% of incident cancer cases and over 28,000 deaths yearly.[1] Improvements in screening methodology and refinements in cancer care have contributed in part to a reduction in contemporary mortality rates.[2] At present, evaluation of the serum prostate-specific antigen (PSA) level and digital rectal examination (DRE) comprise the mainstay modalities for prostate cancer screening.[3] Abnormalities in these parameters, in turn, prompt recommendation of a prostate needle biopsy (PNB), which is the most accurate diagnostic technique to characterize prostate pathology.

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A recent Canadian population based study has implicated that hospital admission rates due to complications of PNB have increased dramatically over the past 10 years.[4] Therefore, it is increasingly important to define appropriate indications for this procedure.[5,6] Elevated PSA values are associated with an increased likelihood of detecting prostate cancer at the time of biopsy. For example, men older than 50 years of age with a normal DRE have a 10% likelihood of detecting prostate cancer at biopsy if the PSA level is 0.0 to 2.0 ng/mL; 15% to 25% if the PSA level is 2.0 to 4.0 ng/mL; 17% to 32% if the PSA level is 4.0 to 10.0 ng/mL; and 43% to 65% if the PSA is greater than 10 ng/mL.[7-10] Thus, assessment of PSA levels has continued to assume a central role in the screening for prostate cancer.

Limitations of accurately assigning DRE status include inter-observer variability, dependence on examiner experience, and the confounding impact of concurrent benign pathologies (i.e. prostatitis or BPH).[11] Nonetheless, older studies have implicated that the DRE plays an important role in prostate cancer detection. In particular, a 1993 study by Richie and colleagues noted that 18% of cancers in their series were detected by DRE alone.[12] A subsequent study by Crawford et al further highlighted that 24% of tumors were missed by PSA and detected solely by DRE.[10] Many of these older studies, however, are limited in that cancer detection is based on older sextant biopsy schemes. Furthermore, most of these studies use absolute PSA values (≤ 4 ng/mL) as opposed to age-specific thresholds when categorizing men according to PSA and DRE status.

Therefore, in this contemporary cohort of patients undergoing an initial 12-18 core biopsy, we investigate the diagnostic yield of PNB when patients are stratified by age-specific PSA values and DRE status. In particular, we seek to define the prostate cancer detection rate of PNB for men with an abnormal DRE and a normal age-specific PSA value.

Materials and methods

Study population

Institutional review board (IRB) approval was obtained to review the medical charts of patients who underwent an ultrasound guided PNB between September 2001 and December 2008. The study population was composed of all male patients over the age of 18. We specifically considered only those men who were undergoing their initial PNB using a 12-18 core biopsy scheme. Therefore, patients with a prior PNB as well as those who had either fewer than 12 or greater than 18 cores obtained at the time of biopsy were excluded from the study. With such criteria, we identified 814 patients who met the biopsy criteria for inclusion. Eight of these patients did not have serum PSA information leaving a final evaluable cohort of 806 men.

Clinical variables

The database created included demographic variables (ie. age, race), serum PSA level, and DRE status. The serum PSA was categorized as normal or abnormal according to age-specific reference.[3] Specifically, age-specific thresholds utilized were age < 50 (PSA < 2.5 ng/mL), age 51-60 (PSA < 3.5 ng/mL), age 61-70 (PSA < 4.5 ng/mL), and age > 70 (PSA < 6.5 ng/mL). Increasing data has implicated that use of age-specific PSA values can increase PSA specificity thereby reducing the number of unnecessary biopsies.[3] Therefore, in contrast to other studies using absolute PSA thresholds,[11,16,17] our analysis restricts to a biopsy cohort that reflects contemporary screening cut offs and biopsy indications.

DRE status was classified based on the initial office evaluation and was considered abnormal if the indicated the gland had a discrete prostate nodule or had focal or diffuse induration. Conversely, the DRE was considered normal if the prostate was noted to be smooth, age-appropriate, benignly asymmetric, or uniformly enlarged. All clinical data including laterality of DRE abnormality was reviewed by two authors to achieve a consensus of recorded DRE status.

Biopsy and pathologic data

All ultrasound guided needle biopsy specimens were performed by one of five attending urologists at our institution. Variables of interest included ultrasound measurement of prostate volume, number of core biopsies taken, number of cores positive for cancer, clinical stage and Gleason sum score (if cancer was detected), as well as benign pathological findings (calcification, prostatic intraepithelial neoplasia, and atypical small acinar proliferation). The total number of biopsies taken from each patient was determined by the individual urologist. However, we restricted the maximum number of cores to 18 to limit the impact of sampling bias increasing our cancer detection rate.

Statistical analysis

Statistical analysis was done using SAS version 9.2 statistical software. Descriptive statistics for the study cohort determined the number and percent of subjects in different groups. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of an abnormal DRE and elevated PSA value for detecting prostate cancer in this select cohort of patients undergoing biopsy were calculated. The chi-square test determined the association between categorical variables and outcomes of interest.

TABLE 1. **Clinical and biopsy data for the 806 men in our study cohort who underwent prostate needle biopsy**

Variable	No. patients (%)
Mean age (range)	63 (39-84)
Race	
White non-hispanic	705 (87)
Black non-hispanic	53 (7)
Hispanic	31 (4)
Asian	17 (2)
Mean PSA (range)	9.1 ng/mL (0.8-265.0)
Age-specific PSA threshold	
Normal	225 (28)
Elevated	581 (72)
DRE status	
Normal	516 (64)
Abnormal	290 (36)
Nodule	134 (46)[1]
Induration	156 (54)[2]
Indication for biopsy	
Elevated PSA only	429 (53)
Elevated PSA and Abnormal DRE	152 (19)
Abnormal DRE only	139 (17)
Other[3]	86 (11)
Year of biopsy	
2001-2004	68 (9)
2005-2006	308 (38)
2007-2008	430 (53)
Mean prostate volume (range)	47 cc (13-175)
Mean number of cores (range)	14.2 (12-18)
Patients with biopsy positive prostate cancer	306 (38)

[1,2]percentage of abnormal DRE cases
[3]increased PSA velocity or low free PSA fraction
PSA = prostate-specific antigen; DRE = digital rectal examination

Results

Clinical and biopsy information

Table 1 highlights the clinical and biopsy data for our study cohort. The mean patient age was 63 years and almost 90% of men were of white non-hispanic race. The mean pre-biopsy PSA was 9.1 ng/mL with 72% of our biopsy cohort having elevated age-specific PSA values. Almost two-thirds of patients were classified as having a normal DRE, while 36% had an abnormal exam with a relatively equal distribution of focal nodules (n = 134 pts) or induration (n = 156 pts). When stratifying patients by PSA and DRE status, 53% had isolated PSA elevations, 19% had an elevated PSA and abnormal DRE, 17% were biopsied solely for DRE abnormalities, and 11% had a normal age-specific PSA and rectal exam. Indications for biopsy in this latter group included increased PSA velocity or low free PSA fraction. We observed an increase in the number of inclusive cases when stratifying by year of biopsy, although a function of this may be that earlier time periods (2001-2004) were more likely to use sextant biopsies and thus were excluded in analysis. Nonetheless, there was no difference observed in the number of digital rectal examinations considered abnormal from 2001-2008 when stratifying into three groups ($\chi^2 = 2.9$, $p = 0.23$).

PNB diagnosis of cancer stratified by PSA level and DRE status

Overall, 306 of 806 men (38%) had prostate cancer detected on needle biopsy. Table 2 highlights the distribution of these 306 patients as stratified by age-specific PSA level and DRE status. Eighty percent (245 of 306) of men diagnosed with prostate cancer had an elevated PSA, while 44% (136 of 306) had an abnormality on rectal examination. Forty-three of 306 (14%) of patients diagnosed with prostate cancer on biopsy had an isolated DRE abnormality. However, when specifically considering the 136 men with DRE

TABLE 2. **Biopsy positive prostate cancer cases (n = 306) stratified by age-specific PSA level and DRE status**

	DRE status		
Age-specific PSA level	Normal	Abnormal	Total
Normal	18 (6)	43 (14)	61 (20)
Elevated	152 (50)	93 (30)	245 (80)
Total	170 (56)	136 (44)	306 (100)

Percentages in parenthesis reflect fraction of the entire cohort of 306 patients. Patients with normal age-specific PSA and normal DRE were biopsied due to increased velocity or low percentage free PSA.
PSA = prostate-specific antigen; DRE = digital rectal examination

TABLE 3. **Biopsy Gleason score stratified by DRE status in 306 patients with prostate cancer**

	DRE status		
Gleason score	**Normal (%)[1]**	**Abnormal (%)[1]**	**Total**
6	101 (61)	64 (39)	165 (54)
7	50 (61)	32 (39)	82 (27)
8	13 (45)	16 (55)	29 (9)
9	6 (23)	20 (77)	26 (8)
10	0 (0)	4 (100)	4 (1)
Total	170	136	306 (100)

[1]percentage distribution of each Gleason score
DRE = digital rectal examination

abnormalities, 43 (31%) had a normal age-specific PSA level while 93 (69%) had an elevated PSA. Additionally, of the 136 men with an abnormal DRE and prostate cancer, 64 (47%) had a positive biopsy ipsilateral to DRE abnormality, 57 (42%) had a positive biopsy both ipsilateral and contralateral to DRE abnormality, and 15 (11%) had DRE abnormality contralateral to positive biopsy. No significant difference was observed between the subgroups of DRE abnormalities studied (nodule versus induration) and presence of cancer ($\chi^2 = 0.08$, $p = 0.79$). These observations persisted even when stratifying by PSA levels ($\chi^2 = 0.45$, $p = 0.50$ for normal PSA and $\chi^2 = 3.1$, $p = 0.07$ for elevated PSA).

Table 3 summarizes the biopsy Gleason grade information for the 306 men diagnosed with prostate cancer stratified by DRE status. We observed that higher Gleason sum scores were associated with a greater percentage of patients with abnormal DREs. Specifically, while 39% of men with Gleason 6 and 7 cancers had an abnormal DRE, this increased to 81% for Gleason 8-10 cancers ($p < 0.0001$).

Diagnostic accuracy of elevated PSA and abnormal DRE for prostate cancer detection

Within our cohort of 806 men, 581 (72%) had an elevated age-specific PSA level, while 225 (28%) had normal serum values. In this select cohort population of patients undergoing a prostate biopsy, an elevated PSA level had a sensitivity of 80%, specificity of 33%, PPV of 42%, and NPV of 73% for cancer detection on prostate biopsy. When considering DRE status, 516 (64%) had a normal and 290 (36%) had an abnormal DRE. An abnormal DRE had a sensitivity of 44%, specificity of 68%, PPV of 46%, and NPV of 67% for detecting prostate cancer at the time of biopsy. Table 4 further stratifies the predictive accuracy of DRE when stratified by serum PSA levels. For patients with an elevated PSA, the sensitivity of a DRE decreased to 38%, specificity increased to 82%, PPV increased to 61%, and NPV decreased to 64%. In men with a normal PSA level, the sensitivity of a DRE increased to 70%, the specificity decreased to 41%, the PPV decreased to 31% and the NPV increased to 79%.

TABLE 4. **Sensitivity, specificity, and predictive values of an abnormal DRE for prostate cancer detection stratified by age-specific PSA thresholds**

	All patients (n = 806)	**Normal PSA (n = 225)**	**Elevated PSA (n = 581)**
Sensitivity	44%	71%	38%
Specificity	69%	41%	82%
PPV	46%	31%	61%
NPV	67%	79%	65%

DRE = digital rectal examination; PSA = prostate-specific antigen; PPV = positive predictive value; NPV = negative predictive value

Discussion

The extensive use of PSA testing and digital rectal exam in screening for prostate cancer has contributed to an increase in the number of men undergoing PNB. PNB is currently the best method to characterize prostate pathology and provides significant information on management. The goal of PNB is to detect clinically significant prostate cancer at an early stage so that treatment can be most effective.[1,13] A physician's recommendation to undergo PNB is influenced by many factors, but most commonly from PSA and DRE findings. This recommendation is also based on knowledge of the potential risks, benefits, and costs of the succeeding interventions. The diagnostic yield of PSA and DRE remains a critical area of investigation in order to appropriately counsel patients and to prevent unnecessary biopsies.

Several population based studies have investigated the utility of PSA in a screening setting. In particular, the European Randomized Study of Screening for Prostate Cancer (ERSPC) noted a 20% decline in prostate cancer specific mortality using PSA as a screening tool.[14] When compared to large studies using DRE as a screening modality, PSA appears to be a more sensitive and specific test particularly at low serum levels.[15] To our knowledge, the utility of DRE has not been investigated in patients when being evaluated using age-specific cutoffs for PSA. Such considerations are increasingly paramount as the updated AUA best practice guidelines underscore the importance of age-adjusted as opposed to absolute PSA thresholds for prostate cancer screening.[3] Therefore, in this study, we were most interested in the diagnostic yield of an abnormal DRE particularly in the era of using age-specific PSA thresholds and contemporary spectrum (12-18 core) biopsies.

We noted that over 50% of patients biopsied in our series had isolated elevations in their serum PSA value, while 36% had an abnormal DRE (with or without PSA elevation), Table 1. Amongst our cohort, 306 (38%) men were diagnosed with prostate cancer. Of these men, 136 (44%) had an abnormal DRE finding. An isolated DRE abnormality occurred in 14% of patients diagnosed with prostate cancer. Of particular note, however, 43 (31%) of these men with abnormal rectal examinations and biopsy-proven prostate cancer had a normal age-specific PSA value, Table 2.

While only 14% of all patients with prostate cancer had an isolated DRE abnormality, 31% of these men had normal age-specific PSA value. This latter value is somewhat higher than that reported in older series.[10,12,16,17] This may be explained in large part by the biopsy schemes used. Our cohort all had 12 to 18 core biopsies thereby resulting in 2-3 cores from the apex, mid, and base of the gland on both the left and right sides. Conversely, most of these earlier studies describe quadrant or sextant biopsies that yield a significantly lower percentage of sampled prostate. Additionally, our study differs from the previously mentioned historical series in that age-specific PSA cutoffs are used to stratify men. Therefore, men with serum PSA values as low as 2.6 ng/mL were biopsied within our series. Increasing data now implicates that a percentage of men with PSA values lower than 4 ng/mL will have cancers (even high grade cancers) detected at these lower thresholds.[7]

Nonetheless, it is important to acknowledge that age-specific PSA cutoffs contribute some limitations in prostate cancer screening. In particular, while age-specific thresholds increase the sensitivity in younger men, these same cutoff values lower the sensitivity in older patients. By increasing the PSA threshold for older men, it is possible that clinically significant prostate cancers are missed by solely using PSA. Our study confirms that DRE still remains an important part of screening such patients because 31% of cancers would have been missed by solely using age-specific PSA cutoffs. Furthermore, our results indicated that abnormal DRE status correlated with increasing Gleason scores (and more aggressive cancers), Table 3. Collectively, these findings underscore the clinical significance of an abnormal DRE, and therefore it should continue to factor in the algorithm for prostate cancer screening.

In isolation, the digital rectal exam has been known to be a fairly insensitive test for the detection of prostate cancer.[11,18] Overall, the cancer detection rate is lower for DRE than it is for PSA, and DRE misses more localized cancers.[19] Observations from our study further support these findings. Specifically, we noted that an abnormal DRE had a sensitivity of 44%, specificity of 68%, PPV of 46%, and a NPV of 67% for detecting prostate cancer on needle biopsy. However, when incorporating PSA data, we noted that the PPV increased to 61% for patients with an elevated age-specific PSA level. Both Schroder and colleagues and Bozeman et al have both similarly reported that the PPV of DRE improves when restricting analysis to patients with an elevated PSA.[15,17] It has also been well documented in multiple large studies that the utility of the DRE exam as a predicting tool is poorer in lower PSA values, and steadily improves with higher PSA.[15] Clinically, these findings underscore the collective benefit of both diagnostic modalities whereby the predictive power for cancer detection improves.[12,16] Finally, an important consideration is recognizing that predictive accuracy of DRE and PSA

reported in this study are extrapolated from a relatively small cohort population undergoing prostate needle biopsy. Therefore, reported outcomes may vary when considering a larger screening population.

Our study also investigated the subgroups of abnormal DRE findings with the goal of elucidating whether certain DRE abnormalities were more diagnostic for cancer. When reviewing our cohort 290 men with abnormal DREs, we found no difference in cancer detection rate if the exam noted a nodule (n = 134) or induration (n = 156). Finally, we observed that abnormal DREs were associated with higher grade cancers. In particular, while 39% of men with Gleason 6 and 7 cancers had an abnormal DRE, this increased to 81% for Gleason 8-10 cancers ($p < 0.0001$). Therefore, clinically both of these entities (nodularity and/or induration) should prompt concern for potentially higher grade malignancy and therefore encourage urologists to recommend prostate needle biopsy.

We would like to acknowledge several limitations. Firstly, the study design is a retrospective series which is therefore susceptible to the inherent limitations of such an analysis. Secondly, evaluation of DRE status was limited by inter-observer variability as the examinations were performed by 1 of 5 urologists at our academic center. Thirdly, we elected to include in our cancer detection analysis, patients with a DRE abnormality and a contralateral positive prostate needle biopsy (11% of cases). This decision was made in part based on several studies including that by Wu and colleagues which highlights that laterality of positive biopsy for clinical T2 prostate cancer does not impact oncologic outcomes.[20] Finally, our sample is restricted in that it originates from a single institution which is limited by case numbers. Thus, it is unclear if these observations can be generalized to a larger cohort of patients. Nonetheless, many of these limitations are similar to those from earlier published series and thus, we believe that our observations remain significant.

Conclusion

With an increasing number of patients undergoing PNB, it is important to evaluate the diagnostic yield of screening methods for detection of prostate cancer. In the cohort of men undergoing PNB, the cancer detection rate was 38%. A DRE abnormality was detected in 44% of the men diagnosed with prostate cancer. While only 14% of all patients with prostate cancer had an isolated DRE abnormality, 31% of these men had normal age-specific PSA value. These observations underscore the importance of digital rectal examination when screening men for prostate cancer. □

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