Histopathological Findings in Extended Prostate Biopsy with PSA ≤ 4 ng/mL

Katia R. Leite, Miguel Srougi, Marcos F. Dall'Oglio, Adriana Sanudo, Luiz H. Camara-Lopes

Laboratory of Medical Investigation - LIM55 (KRL, MS, MFD, AS), Division of Urology, University of Sao Paulo, USP, and Laboratory of Surgical and Molecular Pathology (KRL, LHCL), Sirio Lebanese Hospital, Sao Paulo, SP, Brazil

ABSTRACT

Objective: Cancer detection has been reported in up to 27% of patients when lowering the PSA cutoff to 2.5 ng/mL. Although this practice could increase the number of biopsies performed, it also could lead to more frequent detection of significant prostate cancers at an organ-confined stage and/or a less aggressive state. This study describes the incidence of malignancy and tumor characteristics in extended prostate biopsies with PSA ≤ 4 ng/mL.

Materials and Methods: Prostate biopsies from 1081 patients where examined, 275 (25.4%) patients had PSA level ≤ 4 ng/mL.

Results: Cancer was diagnosed in 32.0% and 35.7% of patients with PSA ≤ 4 ng/mL and > 4 ng/mL, respectively ($p = 0.906$). The median Gleason score was 7 independent of PSA > or ≤ 4 ng/mL ($p = 0.078$). The median number of cores positive for tumor was 4 and 3, respectively, for PSA > 4 ng/mL and PSA ≤ 4 ng/mL ($p = 0.627$). There was a difference in the total percent of tumors involving all cores, 11% and 7% for PSA > or ≤ 4 ng/mL ($p = 0.042$). Fifty-six patients underwent radical prostatectomy, 12 had PSA ≤ 4 ng/mL. In both groups, a diagnosis of cancer was accurate with no differences in Gleason score, tumor volume or staging for both groups.

Conclusion: When PSA is below 4 ng/mL, cancer is detected in a proportion equal to the proportion diagnosed with a PSA > 4 ng/mL, and tumor characteristics are similar between the two groups. Only clinically significant tumors were diagnosed following radical prostatectomy.

Key words: PSA; prostate cancer; biopsy; diagnosis; Gleason score; tumor volume
Int Braz J Urol. 2008; 34: 283-92

INTRODUCTION

Numerous investigators have demonstrated the detection of an increasing proportion of early-stage prostate cancer (CaP) and improvement in biochemical outcome after treatment in the Prostate-specific antigen (PSA) era (1-4). It is also believed to be at least partially responsible for the recent decline in prostate cancer mortality rates in the US and in some European countries (5,6).

Traditionally, a PSA cutoff of 4.0 ng/mL has been used to recommend prostate biopsy (7). However, one third of men with PSA level between 4 and 10 ng/mL and more than one half with PSA greater than 10 ng/mL are found to have cancer that has extended to the surgical margins or to the extraprostatic tissue (8).

When the PSA cutoff level is lowered to 2.5 ng/mL, the cancer detection rate has been reported to be up to 27%. Although a PSA threshold of less

than 4.0 ng/mL may increase the number of biopsies performed, studies have shown that it also leads to more frequent detection of significant CaP at an organ-confined stage and/or a less aggressive state with no excessive increase in the detection of clinically insignificant cancers (9-12).

Another matter of debate is the contemporary strategy of extended prostate biopsy, which increases the number of needle cores from 8 to 13, which is a practice that could lead to a greater detection of clinically insignificant cancers. Conversely studies have shown that this practice is responsible for an increase of more than 30% in cancer detection not related to clinically insignificant cancer (13).

Histopathological findings and tumor characteristics have not been well characterized when the PSA cut-off is below 4 ng/mL in the extended prostate biopsy era. To our knowledge complete data including tumor volume have not been previously reported. The aim of this study was to compare the histopathological findings of extended prostate biopsy and radical prostatectomy in men with PSA levels lower or higher than 4 ng/mL.

MATERIALS AND METHODS

From January 1st 2005 to October 31st 2006, 1587 biopsies were examined in our laboratory. All information was available for 1081 patients. The mean age was 61.7 years, median 61 (range 31-93). The mean PSA was 7.43 ng/mL, median 5.5 ng/mL (range 0.3-146.0 ng/mL). The mean size of the prostate was 57.6 cm^3, median 48 cm^3 ranging from 15 to 275 cm^3, and the mean number of cores taken in each biopsy section was 15.5, median 14, ranging from 6 to 47.

Of the 1081 patients, 275 (25.4%) had PSA levels ≤ 4 ng/mL. The median age was 59 years (range 31-78), the mean size of the prostate was 40.6 cm^3 (SD 21.5) and the median number of cores taken in each biopsy section was 14, ranging from 6 to 27. The characteristics of the patients according the PSA levels are in Table-1.

The reason for the biopsy in the men with PSA under 4 ng/mL was available for only 71 (25.8%) patients. Abnormalities in the digital rectal examination was the primary cause, described in 33 (46.5%)

patients, followed by suspicious or pre-malignant (prostate intraepithelial neoplasia (PIN) and atypical small acinar proliferation (ASAP)) lesion in previous biopsies in 27 (38.0%), persistent elevation of PSA in 5 (7.1%), family history of prostate cancer in 4 (5.6%) and cancer previously diagnosed in transurethral resection in 2 (2.8%).

Transrectal ultrasound guided prostate biopsies were routinely processed and examined by only one pathologist (KRL). Diagnosis was classified as: 1) benign; 2) suspicious but not conclusive for cancer, also known as ASAP; 3) PIN, and 4) cancer. When the diagnosis was adenocarcinoma, the Gleason score was used for histological differentiation and the tumor extension was shown by the number of cores positive for tumor and total percent of tumor in all cores seen.

A subset of 56 patients, from the 376 who were found to have cancer, underwent radical prostatectomy at our institution. The pathologic analyses of the prostatectomy specimens were completely sampled as described previously in detail (14). Organ-confined disease was defined as tumor that did not extend through the capsule, invade seminal vesicles, or metastasize to lymph nodes. Gleason score was used for grading. The tumor volume was determined as a percentage of the prostate gland involved by carcinoma, as estimated using the grid as described by Humphrey and Vollmer (15) and extrapolated to cm^3 for analysis. Staging followed the TNM 2002 recommendations (16).

The differences between the pathologic features were compared between patients whose cancers were detected at a PSA level between 0 and 4.0 ng/mL and those whose cancers were detected after the PSA level rose to greater than 4.0 ng/mL. Standard statistics, chi-square or Fisher's exact test, and Mann-Whitney test analysis were used to compare the data.

RESULTS

PSA was ≤ 4.0 ng/mL in 275 (25.4%) patients, with a mean of 2.85 ng/mL, (SD 0.94) and median of 3.04 ng/mL (range 0.3 to 4.0 ng/mL). The levels of PSA were between 0 to 1 ng/mL in 21 (7.6%),

Table 1 – *Characteristics of 1081 patients submitted to prostate biopsy between January 2005 and October 2006 considering the PSA level.*

	PSA		p Value
	> 4 ng/mL (n = 806)	≤ 4 ng/mL (n = 275)	
Age (years)	62.5 ± 8.7	59.3 ± 8.9	< 0.001
Number of cores	15 (6 – 47)	14 (6 – 27)	< 0.001
Prostate weight (g)	51.5 (16-275)	35.0 (15-120)	< 0.001

1.1 to 2 ng/mL in 34 (12.4%), 2.1 to 3 ng/mL in 82 (29.8%) and 3.1 to 4 ng/mL in 138 (50.2%) patients. The remaining 806 (74.6%) had a PSA higher than 4.0 ng/mL, with a mean of 8.99 ng/mL (SD 9.5 ng/mL), and a median of 6.6 ng/mL, ranging from 4.01 to 146.0 ng/mL.

Patients with PSA ≤ 4 ng/mL were significantly younger, with a mean age of 59.3 years (p < 0.001), and had lighter prostate glands 35.0g compared with 51.5g when PSA > 4 ng/mL (p < 0.001) (Table-1).

Considering the diagnosis, except for PIN, that was more frequently diagnosed in men with PSA ≤ 4 ng/mL, there was no statistical difference between the diagnosis of benign, ASAP and adenocarcinoma (p = 0.906) (Table-2).

Stratifying PSA levels for men with PSA ≤ 4.0 ng/mL, cancer was diagnosed in 1/21 (4.8%)

patients with PSA level ≤ 1.0 ng/mL, 10/34 (29.4%) with PSA 1.1 to 2 ng/mL, 23/82 (28.0%) with PSA 2.1 to 3 ng/mL and 54/138 (39.1%) with PSA 3.1 to 4 ng/mL.

The cancer characteristics were similar for both groups (Table-3). The median Gleason score was 7 for both (p = 0.078), the median of number of cores positive for tumor was 4 and 3, respectively, for PSA > 4 ng/mL and PSA ≤ 4 ng/mL (p = 0.627). Considering the total percent of tumor involving all cores, patients with PSA > 4 ng/mL had a median of 11% versus 7% for patients with PSA ≤ 4 ng/mL (p = 0.042).

Considering the 71 patients who had information about the reason of the biopsy, we studied the characteristics of those 33 who were clinical staged T2 comparing with the 38 where digital rectal

Table 2 – *Diagnosis of prostate biopsy in 1081 patients with PSA ≤ 4 ng/mL and PSA > 4 ng/mL.*

	PSA		
Diagnosis	> 4 ng/mL	≤ 4 ng/mL	Total
Benign	357 (44.3%)	112 (40.7%)	469 (43.4%)
PIN	120 (14.9%)	64 (23.3%)	184 (17.0%)
ASAP	41 (5.1%)	11 (4.0%)	52 (4.8%)
Adenocarcinoma	288 (35.7%)	88 (32.0%)	376 (34.8%)
Total	806 (74.6%)	275 (25.4%)	1081 (100.0%)

ASAP = atypical small acinar proliferation; PIN = prostatic intraepithelial neoplasia.

Table 3 – Tumor characteristics in prostate biopsies of 376 patients with PSA ≤ 4 ng/mL and PSA> 4 ng/mL.

	PSA		p Value
	> 4 ng/mL (n = 288)	≤ 4 ng/mL (n = 88)	
Gleason score	7 (4 - 10)	7 (5 - 9)	0.078
Number of cores positive for tumor	4 (1 - 18)	3 (1 - 14)	0.627
Total percent of tumor	11 (0.1 - 100)	7 (0.1 - 90)	0.042

examination was normal. Among patients that had abnormalities in the digital rectal examination, cancer was diagnosed in 13 (39.4%), comparing with only 8 (21.1%) in 38 without abnormalities in the digital rectal examination (p < 0.0001). PSA levels were similar for both groups, 2.54 ng/mL for T2 patients and 2.73 ng/mL for T1, as was the Gleason score, mean 6.7 for the T2 and 6.1 for T1. Tumors were larger for T2 lesions, with mean number of cores positive for tumor 3.9 and mean total percentage 13.0%, versus 2.3 cores and 2.7% for T1 lesions.

Fifty-six patients underwent radical prostatectomy and the findings are shown in Table-4. Twelve had PSA ≤ 4 ng/mL. There was no statistical difference between Gleason score and tumor volume for both groups of patients. The median Gleason score was 7 for both groups (p = 0.068), and tumor volume was 10% or 3.1 cm^3 and 11% or 4.05 cm^3 for ≤ 4 ng/mL and PSA > 4 ng/mL, respectively (p = 0.689 for percentage and p = 0.639 for cm^3). There were no differences between the groups regarding extra-prostatic extension (p = 0.424), seminal vesicles infiltration (p > 0.999), lymph node metastasis (p > 0.999) and positive surgical margins (p = 0.427). One (8.3%) patient was stage pT3 with PSA ≤ 4 ng/mL and 10 were staged at this level (22.7%) with PSA > 4 ng/mL (p = 0.424).

In the group of patients with PSA ≤ 4 ng/mL there was no insignificant cancer as defined by Epstein et al. (17) as a tumor volume of less than 0.5 cm^3, Gleason score less than 7, and organ-confined. Additionally, one patient was stage pT3a, showing extra-prostatic extension and positive surgical margin.

COMMENTS

In order to minimize economic impact in the health system and maximize the effectiveness of detecting and treating CaP, various studies have aimed to find the best levels of PSA and its variations, especially PSA density and PSA kinetics (18). CaP screening programs have shown that using 4.0 ng/mL as a cutoff results in only clinically significant tumors being detected, and one third of the men treated for radical prostatectomy disease that had progressed beyond the prostate (8). Lowering PSA levels to 2.5 ng/mL seems to better detect organ-confined tumors, enhancing chances of disease-free and overall survival, particularly in younger men (19,20). In association with lowering PSA levels, the current practice of more intensive biopsy regimens could lead to the detection of non-significant tumors. It was the aim of our study to describe histopathological findings in extended prostate biopsy in patients with PSA levels lower than 4 ng/mL.

We have shown that cancer was diagnosed in 32% of patients, which is the same proportion of patients diagnosed with cancer with a PSA > 4 ng/mL, which is the traditional cutoff for prostate biopsy. We also observed that cancer was diagnosed even in patients with a very low level of PSA, below 1 ng/mL, and there was significantly worse disease as PSA levels rose. Malignancy was observed in 29.4%, 28.0% and 39.1% of patients with PSA levels from 1.1 to 2 ng/mL, 2.1 to 3 ng/mL, and 3.1 to 4 ng/mL, respectively. Our numbers were even higher than those reported by the Prostate Cancer Prevention Trial, which

Table 4 – Patient age and tumor characteristics in radical prostatectomy specimens when PSA was ≤ 4 ng/mL or > 4 ng/mL.

	PSA		p Value
	> 4 ng/mL (n = 44)	**≤ 4 ng/mL** (n = 12)	
Age (years) mean ± SD	61.2 ± 7.8	61.5 ± 8.5	0.910
Gleason score Median (min - max)	7 (5 - 9)	7 (6 - 8)	0.068
Tumor volume (cm^3) Median (min - max)	4.05 (0.5 - 29.0)	3.10 (0.5 - 10.0)	0.639
%Gleason 4 Median (min - max)	34.3 (0 - 100)	24.0 (0 - 100)	0.079
Extra prostatic (+)	10 (22.7%)	1 (8.3%)	0.424
Seminal vesicles (+)	2 (4.5%)	-	> 0.999
Lymph node metastasis	2 (4.5%)	-	> 0.999
Margin (+)	11 (25.0%)	1 (9.3%)	0.427
Stage			0.424
pT3	10 (22.7%)	1 (8.3%)	
pT2	34 (77.3%)	11 (91.7%)	

indicated that the overall cancer detection was 15.2%. They found cancer in 6.6% of patients when PSA was less than 0.5 ng/mL, 10.1% when it was between 0.6 to 1.0 ng/mL, 17.0% from 1.1 to 2 ng/mL, 23.9%, from 2.1 to 3.0 ng/mL, and 26.9% when PSA was 3.1 to 4 ng/mL (21). The median PSA value for men in their 40s and 50s is approximately 0.7 ng/mL and 0.9 ng/mL, respectively, and a baseline PSA level greater than the median for each age group was related to a 12 to 22-fold greater risk of having CaP (22). Although the American Cancer Society Guidelines recommend screening for CaP before age 50 only in men with risk factors for CaP, including African-American descent or a strong family history of CaP, authors have recommended the measurement of baseline PSA at age 40, which could allow the determination of PSA kinetics, and is a sensitive marker for prostate cancer diagnosis and prognostic prediction (22). This knowledge may be changing the standard practice of urology since in this present study patients with PSA ≤ 4 ng/mL were significantly younger. Bill-Axelson et al. (23) have claimed that initiating screening before age 50 and detecting cancer earlier should prevent death, especially because patients undergoing radical prostatectomy younger than 65 years-old have reduced CaP-specific mortality. Sun et al. (18) have previously shown that in patients younger than 50, PSA levels of 2.5 ng/mL have specificity of 94% for detecting cancer, and strongly recommend measuring PSA in younger men. Together with the number of patients we have just found, biopsy should be recommended when PSA is higher than the median for that specific age, since almost one third of men will be diagnosed CaP.

Gleason score is the most important isolated prognostic factor, and we observed no difference in the Gleason score between the groups with PSA lower or higher than 4 ng/mL, which both had a median Gleason score of 7. Furthermore, tumor volume in prostate biopsy has been addressed as a very important predictor of cancer extension and outcome. Multiple measurements have been used, including number of positive cores, total millimeters of cancer amongst all cores, percentage of each core occupied by cancer and total percent of cancer in the entire specimen. The best method for determining tumor burden is not yet clear, but estimating a percentage is easy and has been demonstrated to be a useful predictor of tumor extension and cancer-free survival rate (24,25). In the current study we showed no difference considering the number of cores compromised by tumor, but tumors were smaller when PSA ≤ 4 ng/mL, with a total percentage of 7% against 11% when PSA > 4 ng/mL. Smaller tumors are also more likely to be organ-confined. This was not confirmed for patients undergoing radical prostatectomy where tumor characteristics, including volume were very similar to those with PSA higher than 4 ng/mL. One explanation for this fact is a bias considering the choice of treatment. Urologists could have preferred surgery for those patients with other associated adverse characteristics leading to similar results, mostly taking into account tumor volume. This data needs to be clarified in further series.

The detection of organ-confined cancer when PSA is lower than 4 ng/mL could cause some apprehension in treating "harmless" or insignificant cancer. Insignificant cancer is defined as tumor with Gleason pattern less than 4 or 5, organ-confined and volume less than 0.5 cm³ (17). Reports of fewer than 10% of insignificant cancers have been published, and our series is in agreement with the literature since we did not find any clinically insignificant cancer. In addition to the low number of patients who underwent radical prostatectomy with PSA ≤ 4 ng/mL, our data show tumors that can not be considered insignificant, with mean Gleason score 6.6, median 7, ranging from 6 to 8. In addition it is known that presence of tertiary Gleason 4 or 5, and the percent of a higher Gleason pattern impact the prognosis of prostate cancer. The mean percent of Gleason pattern 4 for this group of patients was 32%, which means a 30% reduction in disease free survival in 10 years (26). Considering tumor volume, McNeal (27) had found good prognosis for tumors with volume less than 4 cm³. The mean tumor volume of our surgical specimens was 3.9 cm³, but 33% were higher than 5 cm³, with one 10 cm³, which could be considered a huge tumor, with a 33% probability of recurrence in 10 years (26).

One limitation of our study was the lack of data of PSA velocity (PSAV). PSAV measurement has been shown to be very helpful, as clinically significant prostate cancer is more likely to be found in men with a rapidly rising PSA. Studies suggest that for men with a total PSA higher than 4 ng/mL, a PSA velocity of 0.75 ng/mL/year is an indication for biopsy. However, in men whose total PSA level is lower than 4 ng/mL, an ideal cutoff has not yet been determined and should range from 0.1 to 0.5 ng/mL/year (28-30). It has been demonstrated that for each 0.1 ng/mL per year increase in PSA, the likelihood of death from prostate cancer increases 15%. For men with a consistent increase in PSA of 0.35 ng/mL per year or higher, the relative risk of dying of prostate cancer is 5 times higher in the next 2 to 3 decades than for men with lower PSA increases(31). Nevertheless, this weak point may be overcome by the findings recently published by Yu X et al. (32). These authors have shown a correlation between total PSA and PSAV, describing a PSAV of more than 2 ng/mL per year in only 1% and 14% of patients whose PSA total levels were lower than 2.5 ng/mL or between 2.5 ng/mL and 4 ng/mL, respectively, indicating a less aggressive and more curable disease.

In conclusion, our findings show that in the extended biopsy era cancer will be detected in 32% of patients when biopsy is performed with PSA below 4 ng/mL. Gleason score and number of cores positive for cancer are similar to those with PSA > 4 ng/mL. Although cancer characteristics in radical prostatectomy were comparable for both groups as Gleason score, percentage of Gleason pattern 4, tumor volume and staging, patients that undergo biopsy with PSA lower than 4 ng/mL are younger and have smaller tumors in biopsies as measured by the total percent of tumor, and, consequently have better chances of having less aggressive tumors. Because of the small number of patients submitted to radical prostatectomy with PSA ≤ 4 ng/mL, other studies, with larger series are warranted to confirm our findings.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Amling CL, Blute ML, Lerner SE, Bergstralh EJ, Bostwick DG, Zincke H: Influence of prostate-specific antigen testing on the spectrum of patients with prostate cancer undergoing radical prostatectomy at a large referral practice. Mayo Clin Proc. 1998; 73: 401-6.

2. D'Amico AV, Whittington R, Malkowicz SB, Fondurulia J, Chen MH, Tomaszewski JE, et al.: The combination of preoperative prostate specific antigen and postoperative pathological findings to predict prostate specific antigen outcome in clinically localized prostate cancer. J Urol. 1998; 160: 2096-101.

3. Stephenson RA: Population-based prostate cancer trends in the PSA era data from the Surveillance, Epidemiology, and End Results (SEER) Program. Monogr Urol. 1998; 19: 3-19.

4. Newcomer LM, Stanford JL, Blumenstein BA, Brawer MK: Temporal trends in rates of prostate cancer: declining incidence of advanced stage disease, 1974 to 1994. J Urol. 1997; 158: 1427-30.

5. Catalona WJ, Loeb S: The PSA era is not over for prostate cancer. Eur Urol. 2005; 48: 541-5.

6. Han M, Partin AW, Piantadosi S, Epstein JI, Walsh PC: Era specific biochemical recurrence-free survival following radical prostatectomy for clinically localized prostate cancer. J Urol. 2001; 166: 416-9.

7. Catalona WJ, Smith DS, Ratliff TL, Dodds KM, Coplen DE, Yuan JJ, et al.: Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. N Engl J Med. 1991; 324: 1156-61. Erratum in: N Engl J Med 1991; 325: 1324.

8. Catalona WJ, Smith DS, Ratliff TL, Basler JW: Detection of organ-confined prostate cancer is increased through prostate-specific antigen-based screening. JAMA. 1993; 270: 948-54.

9. Catalona WJ, Ramos CG, Carvalhal GF, Yan Y: Lowering PSA cutoffs to enhance detection of curable prostate cancer. Urology. 2000; 55: 791-5.

10. Krumholtz JS, Carvalhal GF, Ramos CG, Smith DS, Thorson P, Yan Y, et al.: Prostate-specific antigen cutoff of 2.6 ng/mL for prostate cancer screening is associated with favorable pathologic tumor features. Urology. 2002; 60: 469-73; discussion 473-4.

11. Schröder FH, van der Cruijsen-Koeter I, de Koning HJ, Vis AN, Hoedemaeker RF, Kranse R: Prostate cancer detection at low prostate specific antigen. J Urol. 2000; 163: 806-12.

12. Zhu H, Roehl KA, Antenor JA, Catalona WJ: Biopsy of men with PSA level of 2.6 to 4.0 ng/mL associated with favorable pathologic features and PSA progression rate: a preliminary analysis. Urology. 2005; 66: 547-51.

13. Siu W, Dunn RL, Shah RB, Wei JT: Use of extended pattern technique for initial prostate biopsy. J Urol. 2005; 174: 505-9.

14. Epstein JI, Amin M, Boccon-Gibod L, Egevad L, Humphrey PA, Mikuz G, et al.: Prognostic factors and reporting of prostate carcinoma in radical prostatectomy and pelvic lymphadenectomy specimens. Scand J Urol Nephrol Suppl. 2005; 216: 34-63.

15. Humphrey PA, Vollmer RT: Intraglandular tumor extent and prognosis in prostatic carcinoma: application of a grid method to prostatectomy specimens. Hum Pathol. 1990; 21: 799-804.

16. Greene FL, Page DL, Fleming ID: AJCC Cancer Staging Manual. 6th edition. New York, Springer; 2002.

17. Epstein JI, Walsh PC, Carmichael M, Brendler CB: Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. JAMA. 1994; 271: 368-74.

18. Sun L, Moul JW, Hotaling JM, Rampersaud E, Dahm P, Robertson C, et al.: Prostate-specific antigen (PSA) and PSA velocity for prostate cancer detection in men aged <50 years. BJU Int. 2007; 99: 753-7.

19. Dall'Oglio MF, Crippa A, Passerotti CC, Nesrallah LJ, Leite KR, Srougi M: Serum PSA and cure perspective for prostate cancer in males with nonpalpable tumor. Int Braz J Urol. 2005; 31: 437-44.

20. Catalona WJ, Ramos CG, Carvalhal GF, Yan Y: Lowering PSA cutoffs to enhance detection of curable prostate cancer. Urology. 2000; 55: 791-5.

21. Thompson IM, Pauler DK, Goodman PJ, Tangen CM, Lucia MS, Parnes HL, et al.: Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng per milliliter. N Engl J Med. 2004; 350: 2239-46. Erratum in: N Engl J Med. 2004; 351: 1470.

22. Loeb S, Roehl KA, Antenor JA, Catalona WJ, Suarez BK, Nadler RB: Baseline prostate-specific antigen compared with median prostate-specific antigen for age group as predictor of prostate cancer risk in men younger than 60 years old. Urology. 2006; 67: 316-20.

23. Bill-Axelson A, Holmberg L, Ruutu M, Häggman M, Andersson SO, Bratell S, et al.: Radical prostatectomy

versus watchful waiting in early prostate cancer. N Engl J Med. 2005; 352: 1977-84.

24. Rubin MA, Bassily N, Sanda M, Montie J, Strawderman MS, Wojno K: Relationship and significance of greatest percentage of tumor and perineural invasion on needle biopsy in prostatic adenocarcinoma. Am J Surg Pathol. 2000; 24: 183-9.

25. Freedland SJ, Csathy GS, Dorey F, Aronson WJ: Clinical utility of percent prostate needle biopsy tissue with cancer cutpoints to risk stratify patients before radical prostatectomy. Urology. 2002; 60: 84-8.

26. Stamey TA, McNeal JE, Yemoto CM, Sigal BM, Johnstone IM: Biological determinants of cancer progression in men with prostate cancer. JAMA. 1999; 281: 1395-400.

27. McNeal JE: Prostate cancer volume. Am J Surg Pathol. 1997; 21: 1392-3.

28. Fang J, Metter EJ, Landis P, Carter HB: PSA velocity for assessing prostate cancer risk in men with PSA levels between 2.0 and 4.0 ng/ml. Urology. 2002; 59: 889-93; discussion 893-4.

29. Berger AP, Diebl M, Steiner H, Bektic J, Pelzer A, Leonhartsberger N et al., Longitudinal PSA changes in men with and without prostate cancer: assessment of prostate cancer risk. J Urol. 2005; 173 (Suppl. 4): 402.

30. Catalona WJ, Loeb S: The PSA era is not over for prostate cancer. Eur Urol. 2005; 48: 541-5.

31. Carter HB, Ferrucci L, Kettermann A, Landis P, Wright EJ, Epstein JI, et al.: Detection of life-threatening prostate cancer with prostate-specific antigen velocity during a window of curability. J Natl Cancer Inst. 2006; 98: 1521-7.

32. Yu X, Loeb S, Roehl KA, Han M, Catalona WJ: The association between total prostate specific antigen concentration and prostate specific antigen velocity. J Urol. 2007; 177: 1298-302; discussion 1301-2.

Correspondence address:
Dr. Katia R. M. Leite
Rua Adma Jafet, 91
Sao Paulo, SP, 01308-050, Brazil
Fax: +55 11 3231-2249
E-mail: katiaramos@uol.com.br

EDITORIAL COMMENT

This is a well conducted study concluding that when PSA is below 4 ng/mL, cancer is detected in a proportion equal to the proportion diagnosed with a PSA > 4 ng/mL, and tumor characteristics are similar between the two groups. These findings are supported by other studies. Krumholtz et al. (1) evaluated the pathologic characteristics of clinical stage T1c prostate cancers detected in the 2.6 to 4.0 ng/mL PSA range and compared them with cancers concurrently detected in the 4.1 to 10.0 ng/mL. The authors found that men detected at the 2.6 to 4.0 ng/mL PSA range had significantly smaller cancer volumes however, no difference was found in the proportion of tumors that met previously published criteria of "clinically insignificant" (organ confined, less than 0.2 cm³ tumor volume, and Gleason sum 6 or less) or "clinically unimportant" (organ confined, less than 0.5 cm³ tumor volume, and Gleason sum 6 or less) tumors. Using the lower PSA cutoff point resulted in the detection of a significantly higher percentage of organ-confined tumors. The authors conclude that the use of a 2.6

ng/mL PSA threshold for screening resulted in the more frequent detection of small, organ-confined tumors without over detecting possibly clinically insignificant ones. Obviously, additional studies in larger populations with longer follow-up are needed to confirm these findings.

REFERENCE

1. Krumholtz JS, Carvalhal GF, Ramos CG, Smith DS, Thorson P, Yan Y, et al.: Prostate-specific antigen cutoff of 2.6 ng/mL for prostate cancer screening is associated with favorable pathologic tumor features. Urology. 2002; 60: 469-73; discussion 473-4.

Dr. Athanase Billis
Full-Professor of Pathology
State University of Campinas, Unicamp
Campinas, Sao Paulo, Brazil
E-mail: athanase@fcm.unicamp.br

EDITORIAL COMMENT

Early in the PSA era patients with a serum prostate-specific antigen (PSA) level > 4.0 ng/mL and a normal digital rectal examination (DRE) were recommended to undergo prostate biopsy because of a 20-30% risk of prostate cancer at a pre-specified sensitivity of 95%. The majority of such patients have clinically important cancers and the rate of indolent disease, defined as specimen Gleason score 2-6, no extra-prostatic extension, and no Gleason pattern 4/5 is generally < 20%. Many have argued that a PSA threshold for biopsy of 4.0 is more frequently associated with under- rather than over-diagnosis as rates of non-organ-confined cancer (25-35%) are 2 to 4 times higher than indolent cancers, whereas cancers detected in the 2.6-4.0 PSA range are more likely to be organ-confined without substantial differences in the rate of low-grade or indolent cancer. In a longitudinal screening study, a decreased risk of PSA-defined biochemical recurrence was observed for patients treated by radical prostatectomy after lowering the PSA threshold for biopsy from 4.0 to 2.5 (1). As such, a lowering of the PSA level for biopsy to 2.5 has been advocated to increase the detection of clinically significant cancers at a more curable stage, and this had been adopted in the guidelines of some professional societies (2).

The Prostate Cancer Prevention Trial (PCPT) has challenged the validity of any PSA threshold for biopsy as no specific PSA value had sufficient sensitivity and specificity for the detection of prostate cancer to be clinically useful (3). Based on the results of patients who had an end-of-study biopsy without usual clinical implications, there was a continuum of cancer risk at all PSA values. Among patients with a PSA < 1.0, 1.1-2.0, and 2.1-3.0, the cancer detection rate was 9%, 17%, and 24%, respectively and the corresponding proportion of cancers graded as Gleason 7-10 was 11%, 12% and 19% (4). These results indicate that there is no PSA below which the risk of having cancer is zero.

In the current study, Leite et al. report on the biopsy and pathological characteristics of a cohort of patients biopsied with a PSA < 4. Reasons for biopsy included abnormal DRE, prior biopsies showing atypical small acinar proliferation or prostatic intraepithelial neoplasia, persistently elevated PSA and negative prior biopsy, or a positive family history, so that the population studied is not fully representative of the general population usually subjected to opportunistic screening. Nonetheless the findings are illuminating, demonstrating similar rates of prostate cancer in those with a PSA < 4 vs. > 4 (32 vs. 36%), no difference

in tumor grade (median score 7 in both groups), and slightly fewer positive cores in the PSA < 4 group. In the small subset of patients who underwent radical prostatectomy, there was no difference in tumor volume, grade, or pathological stage. Surprisingly, and unlike our own experience with similar patients where the incidence of indolent cancers is higher in men with PSA < 4, the authors found no indolent cancers as defined by Epstein's criteria of organ-confined tumors of volume < 0.5 cc and grade < 7. This likely reflects the indications for biopsy in this population and less widespread and repeated screening than in the United States.

What then is the optimal PSA cutoff for recommending biopsy in 2008? The theoretical answer is that the optimal threshold is one that maximizes detection of biologically significant but curable cancers, reduces prostate-cancer-specific mortality, and minimizes over-diagnosis of indolent disease. The practical answer is one that recognizes that PSA represents a continuum of risk that is also impacted by many other factors, and that the best way decides whom to biopsy includes a consideration of all of the relevant factors. At the Cleveland Clinic, we have stopped reporting a "normal" cutoff for PSA on our lab reports and substituted the following: "Published data from the Prostate Cancer Prevention Trial demonstrated that there is no PSA level below which the risk of having prostate cancer is zero. For an individual patient, the significance of a PSA level should be interpreted in a broad clinical context, including age, race, family history, digital rectal exam, prostate size, results of prior prostate biopsy, and use of 5 alpha reductase inhibitors. Considering the high incidence of asymptomatic cancer in the general population that may not pose an ultimate risk to the patient, the decision to recommend urological evaluation or prostate biopsy should be individualized after considering all of these factors." We have encouraged the use of the PCPT risk calculator (available at www.compass. fhcrc.org/edrnnci/bin/calculator/main.asp) as one tool (validated published nomograms for this purpose also exist) to achieve the goal of defining individual risk prior to recommending biopsy. Using this calculator, a 55 year old Caucasian male with a negative DRE, a PSA of 1.5, and no family history of prostate cancer has a 19% risk of having prostate cancer but only a 2% risk of having high grade (Gleason 7 or greater) disease, information that can give the patient a more precise estimate of the risks and benefits of undergoing biopsy before deciding whether to have it done. For a 55 year old African American man with a normal DRE, a positive family history, and PSA of 2.4, the calculator estimates a risk of any cancer at 31% and of high grade cancer at 8%; here the risk: benefit ratio probably justifies biopsy even though his PSA is generally considered below the current threshold. Adoption of this approach outside of the U.S. requires construction and validation of similar models on local populations; ultimately, proof of the utility of PSA screening at all awaits the reporting of large screening trials (the ERSPC and PLCO) currently nearing completion.

REFERENCES

1. Jang TL, Han M, Roil KA, Hawkins SA, Catalona WJ: More favorable tumor features and progression-free survival rates in a longitudinal prostate cancer screening study: PSA era and threshold-specific effects. Urology. 2006; 67: 343-8.
2. Smith RA, Cokkinides V, Eyre HJ: American Cancer Society guidelines for the early detection of cancer, 2006. CA Cancer J Clin. 2006; 56: 11-25; quiz 49-50.
3. Thompson IM, Ankerst DP, Chi C, Lucia MS, Goodman PJ, Crowley JJ, et al.: Operating characteristics of prostate-specific antigen in men with an initial PSA level of 3.0 ng/ml or lower. JAMA. 2005; 294: 66-70.
4. Thompson IM, Pauler DK, Goodman PJ, Tangen CM, Lucia MS, Parnes HL, et al.: Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng per milliliter. N Engl J Med. 2004; 350: 2239-46. Erratum in: N Engl J Med. 2004; 351: 1470.

Dr. Andrew J. Stephenson
Dr. J. Stephen Jones
Dr. Eric A. Klein
Section of Urologic Oncology
Glickman Urologic and Kidney Institute
Cleveland Clinic, Ohio, USA
E-mail: kleine@ccf.org