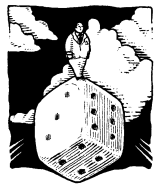
Clinical basics

Prostate cancer: 5. Diagnostic tools for early detection



Education

Éducation

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This article has been peer reviewed.

The members of the Prostate Cancer Alliance of Canada, an umbrella group formed to carry out the recommendations of the 1997 National Prostate Cancer Forum, are pleased to support the intent to inform both health care professionals and lay people about the detection, diagnosis and treatment of prostate cancer through this 13-part series. The list of members of the Alliance appears at the end of this article.

Series editors: *Dr. Neill A. Iscoe, Medical Oncologist, Toronto–Sunnybrook Regional Cancer Centre, and Dr. Michael Jewett, Professor and Chairman, Division of Urology, University of Toronto, Toronto, Ont.*

CMAJ 1998;159:1139-46

The case

A 65-year-old otherwise healthy man is referred for a urologic assessment by his family physician. He has a 1-year history of mildly decreased urinary stream and occasional urgency. The results of a digital rectal examination performed by the referring physician are reported as "unremarkable." Urinalysis demonstrates no abnormal findings. The serum prostate-specific antigen level is 4.6 ng/mL, but 1 year ago it was only 3.8 ng/mL. Transrectal ultrasonography reveals a prostate of normal ultrasonic appearance. No hypoechoic lesion is seen in the peripheral zone. The volume is estimated at 38 cm^3. According to the ultrasound report, biopsy was not performed because of the normal appearance of the prostate.

Diagnosis of prostate cancer at an early stage, when the lesion is localized and curable, followed by effective, definitive therapy, is essential to reduce the number of deaths from this disease.[1] Definitive studies to prove that early detection and treatment lower the mortality rate have been initiated;[2,3] however, only indirect evidence suggesting the effectiveness of treatment is available.[4] Those in favour of screening for prostate cancer, irrespective of symptoms, recommend an annual serum prostate-specific antigen (PSA) test and digital rectal examination (DRE) for men between the ages of 50 and 70 years.[5] Because of the natural history of the disease, detection is not recommended for men with a life expectancy less than 10 years. For men at high risk for prostate cancer, such as black North Americans and those with a family history of prostatic carcinoma, the age range during which testing is recommended is extended to 40 to 70 years.[6]

Our goal here is to take a critical look at the available diagnostic tools that allow detection of prostate cancer in its localized, curable form. We will demonstrate and discuss the following points:

- PSA and DRE represent the most widely used initial evaluation methods.
- Transrectal ultrasonography (TRUS) of the prostate allows visualization of the gland and is required for adequate needle positioning if biopsy is performed.
- TRUS-guided core biopsy of the prostate has become the most widely used and the most definitive means of tissue diagnosis.
- Although classified as prostate cancer staging tools, CT[7] and MRI[8] of the prostate have not compared favourably with TRUS for early diagnosis.

This 13-part series was made possible in part by an unrestricted educational grant from ZENECA Pharma

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Digital rectal examination

DRE is the simplest, least expensive and most widely used method for detecting prostate cancer. However, it is highly subjective.[9] Because of this and the differing levels of skill of examiners, many men may be excluded from further assessment because of DRE findings that mimic benign, age-related changes. DRE may also fail to detect cancers of the anterior prostate, which are inaccessible to palpation but contribute to 25% of prostatic malignancy.[10] In addition, 50% of clinically palpable prostatic cancers will either not be amenable to complete surgical excision or will demonstrate local extension before such an attempt.[11] Thus, although DRE constitutes an important diagnostic tool, it may fail to identify a substantial proportion of clinically significant cancers at an organ-confined, curable stage. Further investigation is recommended for any man with DRE findings that raise suspicions of cancer.

Teaching points

- Early detection of prostate cancer is of utmost importance, given that localized disease represents the only curable stage. Men with serum levels of prostate-specific antigen (PSA) between 4 and 10 ng/mL constitute the prime target population for effective early detection.
- PSA screening should be limited to men at risk of harbouring clinically significant prostate cancer, i.e., men aged 50–70 years (40–70 years in black men and those with a family history of prostate cancer). In selected cases, PSA testing may be performed in men older than 70 years of age if they have longer-than-average life expectancy.
- Although digital rectal examination is the least expensive and most widely used method for detecting prostate cancer, it depends on the skill and subjective assessment of the physician.

Serum prostate-specific antigen test

Testing for serum PSA, a normal serine protease produced by the prostate epithelium, has replaced the relatively insensitive prostatic acid phosphatase test. The function of PSA is to lyse proteins derived from the seminal vesicle; it thus causes semen liquefaction. Under normal conditions, only a small fraction of the PSA produced leaks back from the prostatic acini and ducts to become detectable in the serum.[11]

Conditions that disrupt the junctions thought to prevent leakage of PSA into the serum[12] include prostate cancer, benign prostatic hyperplasia and prostatitis. Urinary retention, prolonged urethral catheterization, recent cystoscopy or prostatic biopsy may also increase circulating PSA levels temporarily.[13] DRE and ejaculation have not been associated with clinically significant elevation of PSA. Drugs that affect the conversion of testosterone to dihydrotestosterone, such as finasteride, reduce circulating serum PSA by about 50%.[14]

When DRE does not raise a suspicion of cancer, serum PSA testing becomes pivotal in establishing the need for TRUS and TRUS-guided core biopsy (Table 1). Serum PSA levels can be determined with either a polyclonal or a monoclonal assay. (The antibodies used in the polyclonal assay react with several epitopes on the PSA molecule, whereas a monoclonal assay is directed against one specific epitope.) At present monoclonal PSA assays are most common. The normal range of PSA determined from the polyclonal assay is 0 to 2.5 ng/mL,[15] whereas the normal range determined by a monoclonal assay is 0 to 4.0 ng/mL. The polyclonal assay is currently performed in only a few laboratories, and its use will likely be further restricted with the advent of newer forms of PSA testing that rely on monoclonal measurement of the concentration of free and complexed serum PSA. Consequently only the monoclonal immunoassay will be further discussed here.

Although serum PSA is currently the best clinically available tumour marker, it is not specific to prostate cancer.[16] For example, elevation of PSA occurs in 20% to 50% of men with benign prostatic hyperplasia. The test's limitations in sensitivity also account for the discovery of cancer on TRUS-guided core biopsy in as many as 10% of men with PSA values between 0 and 4.0 ng/mL. However, as many as 2 out of 3 men with PSA values greater than 10 ng/mL will be found to have cancer regardless of

Table 1: Recommended diagnostic tests for various digital rectal examination (DRE) findings and levels of serum prostate-specific antigen (PSA)

Test; findings		
DRE	Serum PSA level, ng/mL	Recommended diagnostic test
Normal	≤ 4.0	Observation, including annual DRE and PSA test
Normal	> 4.0	TRUS and TRUS-guided systematically distributed sector biopsy, as well as biopsy of ultrasonically suspicious areas
Suspicious	Any level	TRUS and TRUS-guided biopsy, including biopsy of palpably or ultrasonically abnormal areas, as well as systematically distributed sector biopsy

Note: TRUS = transrectal ultrasonography.

DRE findings.[17] The current recommendation is that men with serum PSA levels above 4 ng/mL be referred for further evaluation by a urologist. In general, the next diagnostic test consists of TRUS-guided needle biopsy of the prostate.

The limitations in sensitivity and specificity of serum PSA testing have led to attempts to improve its clinical usefulness. New concepts include PSA density, age-specific PSA ranges and PSA velocity, as well as measurements of the proportions of free and bound PSA (Table 2).

PSA density

PSA density, the initial refinement of the PSA test, is an index calculated by dividing total serum PSA by the volume of the prostate, measured ultrasonically by TRUS. In the absence of cancer, prostatic volume is directly proportional to circulating serum PSA.[18] Benign prostatic hyperplasia is associated with, on average, only 0.26 ng/mL PSA per gram of tissue, whereas cancer results in a density 10-fold higher.[19] Any PSA value greater than that predicted by gland volume should raise a suspicion of prostate cancer.

The optimal cut-off value for PSA density is a trade-off between sensitivity and biopsy rate. A low cut-off value yields high sensitivity and better detection but corresponds to a higher rate of potentially unnecessary biopsies. The opposite is true with a higher cut-off value. Because 2 out of 3 men with a PSA level between 4 and 10 ng/mL are found by prostate biopsy not to have cancer, PSA density is used to identify those who should not undergo unnecessary biopsy. Because a PSA density of less than 0.15 ng/mL per cubic centimetre of prostatic tissue is associated with a low likelihood of cancer, this the most widely used cut-off point.[20]

The suggested benefit of PSA density derives from the fact that a significant number of men are spared biopsy even though they have PSA levels above 4.0 ng/mL. Although this was initially reported not to result in lack of detection of clinically significant cancers,[20] more recent

Table 3: Reference ranges for age-specific PSA levels

Age range, yr	Upper limit of PSA, ng/mL
40–49	2.5
50–59	3.5
60–69	4.5
70–79	6.5

Table 2: Summary of currently available types of PSA tests

Diagnostic test	Sensitivity, %	Specificity, %	Comments
Traditional PSA	72–90	59–90	Based on cut-off level of 4.0 ng/mL. Remains standard with which modified forms of PSA testing are compared, although percentage of free PSA appears to offer significant advantages
PSA density	91*	63*	Because of the variability in its performance, which depends on prostate size, this method has fallen out of favour
PSA velocity	61–67†	71–99†	Low sensitivity compared with traditional PSA testing and PSA density. Specificity is superior and increases with increasing follow-up time. However, PSA velocity is often impractical because of long follow-up time required (at least 1.5 to 2 years to maintain adequate specificity)
Age-specific PSA ranges	Improvement of 11% over traditional PSA test	Reduction of 9% compared with traditional PSA test	Because of lower cut-off for men aged 40–49 years, this method offers superior sensitivity than traditional PSA testing. Although its overall specificity is lower than that of traditional PSA testing, age-specific PSA also offers better specificity in men aged 70–79 years
% free PSA	90% or greater	Up to 80%	Still an investigational tool. Can increase the specificity of traditional PSA testing, especially in the diagnostic "grey zone," between 4 and 10 ng/mL. No consensus on cut-off value

*Based on the suggested cut-off value of 0.15 ng/mL PSA per cubic centimetre of prostate tissue.
†Based on a cut-off value of 0.75 ng/mL annually.

analyses have demonstrated that the diagnostic accuracy of PSA density is limited because of the inherent limitations of TRUS in determining prostate volume.[21,22] In addition, inadequate sampling in men with prostates larger than 50 to 60 cm^3 may have led to false-negative biopsy results, which may have further undermined the validity of initial PSA density results.[17,23,24] On the basis of these findings, the use of PSA density in clinical practice has declined substantially. Finally, given the minimal morbidity associated with biopsy, the excellent level of patient tolerance associated with this procedure and the requirement to perform TRUS gland volumetry in order to calculate PSA density, performing an ultrasonic assessment without concomitant biopsy is of questionable benefit.

Teaching point

- The level of PSA in blood serum is currently the best test for prostate cancer, but limitations in its sensitivity and specificity have led to attempts to improve its clinical usefulness.
- The PSA density test factors in prostate volume to avoid unnecessary biopsy in men whose prostate is enlarged.
- Age-specific PSA ranges are based on the assumption that older men have larger prostates and may therefore have higher serum PSA levels not associated with carcinoma.
- A further refinement of the PSA test — PSA velocity testing — measures the rate of change of serum PSA levels over time.
- The measurement of free and bound forms of PSA in the serum distinguishes between men with prostate cancer and those with benign prostatic hyperplasia and is the most promising method of increasing the specificity of PSA testing.
- PSA testing and each of its modifications still necessitate a trade-off between specificity and sensitivity.

Age-specific PSA ranges

Age-specific PSA ranges, which rely on age instead of TRUS volumetry, are based on the assumption that older men have larger prostates and, therefore, may have higher serum PSA levels not associated with carcinoma. More specifically, the introduction of age-specific PSA ranges was aimed at increasing the sensitivity of PSA testing in younger men and increasing the specificity of such testing in older men.[25] The reference ranges are given in Table 3.

The adoption of these age-specific maximum PSA values has increased the number of biopsies performed in younger men and decreased the number performed in older men. The rationale was to detect more early cancers in the men who could benefit most from definitive therapy, while limiting detection of cancers of questionable clinical significance in men with shorter life expectancy. An additional advantage of age-specific PSA over PSA density is the fact that ultrasonic gland measurement and the associated cost can be avoided. At present, because of the limited data regarding age-specific PSA and the lack of precise guidelines for its clinical use, its role in the early detection of prostate cancer remains unclear.

PSA velocity

A further refinement of the single PSA measurement is serial measurements and trend analysis.[26] The term "PSA velocity" refers to the rate of change of serum PSA level over time. Early investigators of this concept demonstrated significant differences in PSA velocity between men with benign prostatic hyperplasia and those with prostate cancer. These differences were detectable as early as 9 years before prostate cancer was diagnosed. Others have confirmed the benefit of PSA velocity over a single PSA measurement.[27] However, at least 3 consecutive measurements are required for reliable calculation of PSA velocity. The optimal interval between these measurements has not yet been determined, but 6 months is currently recommended. Therefore, a follow-up of at least 18 months is necessary to achieve the maximum benefit of PSA velocity in prostate cancer detection.

Problems with PSA velocity include important physiologic and intra-individual variability, reportedly as high as 23.5%.[28] Therefore, if 2 samples are obtained from the same person 2 to 3 weeks apart, the serum PSA level may be 3.5 ng/mL for the first test and 4.3 ng/mL for the subsequent analysis, without any change in the condition of the prostate itself. Similarly, methodological variation in PSA tests may range from 10% to 45%.[29] Thus, if the same serum sample is subjected to analysis by 2 different assays, the PSA level may be 4.0 ng/mL with one assay and between 4.4 and 5.8 ng/mL with the other. These variations may preclude effective use of PSA velocity in large-scale screening.

A potential benefit can be derived from PSA velocity in men with serum PSA values below 4 ng/mL who harbour prostate cancer. In men with normal PSA values, an annual increase in excess of 20%[30] or PSA velocity exceeding 0.75 ng/mL annually[31] is suggestive of prostate cancer and indicates the need for urological evaluation. Determining PSA velocity in men with traditional serum

PSA values above the normal upper limit of 4 ng/mL is of little additional benefit, given that a urological assessment is warranted regardless of the rate of increase in PSA level.

Percentage of free PSA

In further efforts to enhance the sensitivity and specificity of PSA testing, the measurement of free and bound forms of PSA in the serum has been proposed. In the serum, PSA complexes predominantly with the alpha-1 subunit of antichymotrypsin and the alpha-2 subunit of macroglobulin (Fig. 1). Most commercially available complexed-PSA assays determine the concentration of the PSA–antichymotrypsin complex. Nearly all of the remaining circulating PSA is in its free form. The proportion of free PSA is known to be lower in those with prostate cancer than in those with benign prostatic hyperplasia; thus, the likelihood of prostate cancer increases with decreasing free PSA. In contrast, the proportion of free PSA increases with advancing age and increasing prostate volume.

Recent studies have identified the proportion of free PSA as an independent predictor of prostate cancer, superior to both DRE and total PSA level. Likewise, the proportion of free PSA has a superior diagnostic accuracy relative to PSA density.[32] In a recently published large-scale study, determination of the proportion of free PSA would have maintained a specificity of 90% and would have eliminated the need for biopsy in 31.3% of men with benign DRE findings and serum PSA levels between 4 and 10 ng/mL.[33] At present, only free PSA offers high specificity and adequate sensitivity. Consequently, it is the most clinically valuable and most promising modification of the PSA test.

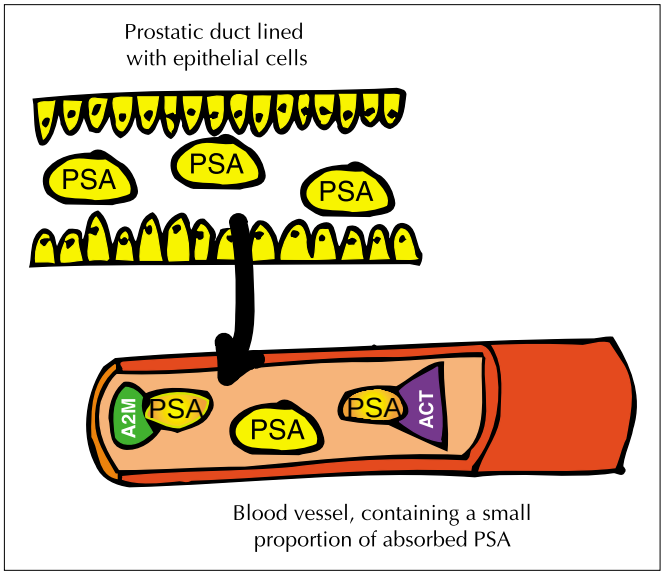

Fig. 1: Measurement of the percentage of free prostate-specific antigen (PSA) is now gaining credence as an enhancement of PSA testing. A small proportion of the PSA secreted from the epithelial cells lining the prostatic ducts is absorbed into the systemic circulation. In the blood stream, PSA exists predominantly in the bound form, complexed with either the alpha-1 subunit of antichymotrypsin (ACT) or the alpha-2 subunit of macroglobulin (A2M). A small proportion is detectable as free, uncomplexed PSA. The level of this free form is inversely correlated with the likelihood of prostate cancer.

Several recommendations for cut-off levels have emerged. As with all other forms of PSA tests, there is a trade-off between sensitivity and specificity. A cut-off of 23.4% free PSA eliminated 31% of biopsies while maintaining 90% sensitivity.[34] In men with serum PSA values between 2.6 and 4.0 ng/mL, a cut-off point of 27% eliminated 18% of biopsies with a sensitivity greater than 90%. Therefore, proportion of free PSA appears capable of enhancing the sensitivity and specificity of traditional PSA testing, even in men with normal serum PSA levels.[34]

Diagnostic limitations of PSA testing and its enhanced forms

Although results obtained by measuring serum PSA levels are superior in terms of prostate cancer detection to those obtained with any other clinically available tumour marker, the traditional total PSA value and each of its enhanced forms share several limitations. The principal concern is that although diagnostic accuracy has improved with each of the modifications to total serum PSA measurement, none of the forms is specific for prostate cancer. Each requires a trade-off in specificity for increased sensitivity and vice versa. This trade-off appears to be most advantageous with proportion of free PSA. Currently, proportion of free PSA appears to be the best detection tool for men with serum PSA levels below 10 ng/mL and is rapidly approaching routine clinical practice. However, definitive large-scale studies aimed at defining the optimal cut-off value are continuing.[33] Thus, this test remains an investigational tool.

Transrectal ultrasonography

TRUS plays an invaluable role in directing and positioning biopsy needles; however, its direct contribution to detection of prostate cancer is limited. Cancerous lesions are associated with decreased echogenicity if situated within the periphery of the prostate or the posterior aspect of the gland closest to the rectal wall. Malignant lesions can be associated with mixed echogenicity, as well as hypoechoic appearance, if situated within the anterior prostate.[10] Recently, colour-flow Doppler imaging has been introduced in an attempt to detect increased vascularity associated with prostate cancer. Although this method is not specific, it allowed the detection of approxi-

mately 7% more cancers than were detected by DRE and TRUS.[35] It has been suggested that the detection of vascular cancers in particular is important as they may be more likely to spread.[36]

Biopsy of suspicious lesions anywhere in the prostate is mandatory, and positive biopsy results in as many as 30% of cases have been reported.[16,17] However, because of the heterogeneity of ultrasonically visible prostatic findings, their interpretation is highly subjective. Consequently, the sensitivity and specificity of TRUS alone in prostate cancer detection is unacceptably low. Therefore, the importance of adequate histologic sampling of the prostate by obtaining multiple core biopsy specimens of both suspicious and visually normal tissue cannot be overemphasized. In the presence of elevated PSA levels, prostatic biopsy is recommended, even if DRE and TRUS findings indicate benignity, because nonpalpable, nonvisible prostate cancer may be found in 40% of such cases.[17]

Teaching points

- Transrectal ultrasonography of the prostate allows visualization of the gland and is required for adequate needle positioning if biopsy is performed.
- Transrectal ultrasound-guided core biopsy of the prostate has become the most widely used and the best means of determining the grade, volume and localization of a tumour, as well as its distribution within the prostate.

CT is not useful for early detection of prostate cancer. MRI is about as accurate in detecting early cancer as TRUS but cannot be used to direct biopsy. Its current inaccessibility for timely clinical applications and its high cost preclude its use for early detection. Both CT and MRI can be helpful in staging cancer, because they can indicate periprostatic tumour spread, lymph node abnormality and bone involvement, but their sensitivity for revealing tumour extension has limitations.

Prostatic biopsy

Prostatic biopsy represents the cornerstone of prostate cancer diagnosis.[17] It provides valuable information about grade, volume and localization, as well as the distribution of tumour within the prostate.[37] Digitally guided transrectal and transperineal biopsy, although still used occasionally, are associated with dismally low positive biopsy rates compared with TRUS-guided core biopsy.[38] TRUS-guided core biopsy of 6 cores of tissue in addition to cores directed toward palpable or ultrasonically visible abnormalities is the current standard for prostate biopsy. Although associated with some discomfort, TRUS-guided biopsy is performed without anesthesia or sedation and is a well-tolerated procedure with minimal morbidity.[39] Quinolone antibiotic prophylaxis — consisting of 1 dose before biopsy and 4 doses afterward — is usually administered. A study assessing biopsy-related complications reported temperature elevation above 38°C, consistent with infection, in 1.4% of patients who underwent peripheral zone biopsies.[39] The most commonly reported complications consist of traces of blood in the urine, semen or feces. Although reported by most patients, these complications are limited and subside within 2–3 weeks after the procedure. Pain at the time of biopsy is universally reported. However, only in exceptional cases is analgesia or sedation required. As many as 50% of men report significant pain after biopsy, but this usually subsides within 4 days.

Table 4: Recommended number of cores for prostate biopsy according to prostate size[43]

Prostate size, cm^3	No. of cores
≤ 30	6
30.1–40	8
40.1–50	10
50.1–60	12
60.1–70	14
70.1–80	16
> 80	18

Recent reports suggest the need for additional systematic biopsy of glands that seem normal (by both palpation and visualization), which results in denser sampling.[17,23,24,40,41] These reports are based on the observation of suboptimal sampling with sextant biopsy. Lack of detection of clinically significant cancers may occur predominantly in men with prostates in excess of 50 or 60 cm^3. An algorithm incorporating prostate size has been advocated to maintain a steady positive biopsy rate throughout the wide range of gland sizes. It has been suggested that as many as one core for each 5 cm^3 of prostate tissue may be required for effective detection of clinically localized disease.[42,43] In a rationale similar to that for age-specific PSA levels, patient age may be used to determine the appropriate sampling density.[40] Although sextant biopsy with additional biopsy of palpable or ultrasonically visible lesions is still the most widely used approach, several centres employ a denser biopsy template.[24]

In men with normal biopsy results despite elevated serum PSA, we suggest follow-up with serial PSA mea-

surements. Although such repeat PSA measurements are usually obtained at 3- to 6-month intervals, there is no consensus regarding the optimal interval. Should the serial PSA measurements demonstrate rising PSA, repeat biopsy is indicated. Repeat biopsy is also recommended if high-grade prostatic intra-epithelial neoplasia is found in the initial biopsy specimen. The repeat procedure should be performed within 3 months of the initial biopsy. We suggest a denser pattern of sampling, in which the number of cores is determined according to the gland volume (Table 4).[43]

Conclusion

Localized prostate cancer represents the only curable stage of this disease. Therefore, effective detection implies diagnosis at this stage. In view of the elevated rate of locally advanced disease associated with serum PSA levels above 10 ng/mL, men with PSA between 4 and 10 ng/mL constitute the prime target population for effective early detection. However, because of the high prevalence of benign prostatic hyperplasia, which may contribute to intermediate serum PSA elevation (between 4.1 and 10 ng/mL), and normal-appearing DRE results, many physicians delay the required biopsy. Failure to perform biopsy at this time may result in lack of detection of clinically significant disease while it is still at a curable stage.

We have reiterated here the subjectivity of DRE and stress its poor performance when used alone for the early detection of prostate cancer. We have also highlighted the need for PSA testing, especially in the face of normal DRE results. The current recommendations for prostate cancer detection suggest the use of both DRE and serum PSA testing instead of one or the other alone. The usefulness of the traditional PSA cut-off value of 4 ng/mL may be further enhanced: PSA velocity and proportion of free PSA may prove highly beneficial in young, otherwise healthy men. In this patient subgroup, early and effective diagnosis maximizes the long-term benefits of curative therapy. Finally, we have completed this review by restating the central role of prostatic biopsy under TRUS guidance. We have re-emphasized the need for adequate histologic sampling of the prostate once the suspicion of cancer has been entertained. To obtain such valuable diagnostic information as tumour grade, volume, localization and distribution, a minimum of 6 core biopsy samples should be obtained, and several additional biopsy samples are required in patients with large prostate glands, where localization of the malignancy within abundant prostatic tissue is more difficult.

On the basis of the information given in the case presented at the beginning of this article and our discussion of diagnostic methods, the presence of nonpalpable, ultrasonically nonvisible cancer cannot be excluded in this patient. As many as 20% of men fitting this description may harbour prostatic malignancy. Consequently, ultrasonically guided sector biopsies are clearly indicated.

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The following organizations are members of the Prostate Cancer Alliance of Canada: Canadian Association for Nurses in Oncology, Canadian Association of Radiation Oncologists, Canadian Cancer Society (National), Canadian Prostate Cancer Network, Canadian Prostate Cancer Research Foundation, Canadian Urology Association, Canadian Uro-Oncology Group and National Cancer Institute of Canada.