KJU
Korean Journal of Urology

www.kjurology.org
http://dx.doi.org/10.4111/kju.2012.53.2.82

Urological Oncology

Is Prostate Biopsy Essential to Diagnose Prostate Cancer in the Older Patient with Extremely High Prostate-Specific Antigen?

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Purpose: The results of all prostate biopsies may be positive and suggestive of adenocarcinoma in patients with prostate-specific antigen (PSA) values higher than 100 ng/ml. We considered that the prostate cancer in patients with high PSA might be advanced disease and therefore that the treatment strategy should not be changed according to pathological reports. Thus, we assessed the role of prostate biopsy when diagnosing prostate cancer in patients with extremely high PSA levels.

Materials and Methods: We reviewed the records of 1,150 cases undergoing prostate biopsies. Patients with urinary tract infection and acute urinary retention were excluded. According to the pre-biopsy PSA level, patients were divided into 6 groups (group A, 4 to 20 ng/ml; B, 20 to 40 ng/ml; C, 40 to 60 ng/ml; D, 60 to 80 ng/ml; E: 80 to 100 ng/ml; and F, above 100 ng/ml).

Results: The calculated positive predictive value (PPV) for prostate cancer was 22% in group A, 54% in group B, 73% in group C, 75% in group D, 89% in group E, and 100% in group F, respectively. Pathological diagnosis was adenocarcinoma in all patients in group F (n=56). Among them, 38 patients (67.9%) had lymph node metastasis or extra-prostatic disease or both and 43 patients (76.8%) had bony metastasis. In group F, all cases were advanced prostate cancer (stage III or IV). All of them received hormonal therapy following diagnosis.

Conclusions: We suggest the possibility for biopsy-free diagnosis of prostate cancer in patients with extremely high levels of serum PSA and evidence of advanced disease in imaging studies, especially in older patients with comorbid medical problems.

Key Words: *Adenocarcinoma; Biopsy-free diagnosis; Prostate; PSA*

Article History:
received 8 August, 2011
accepted 16 October, 2011

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INTRODUCTION

The incidence of prostate cancer has been gradually increasing in Korea. The increase in the aged population, a westernized lifestyle, the development of diagnostic tools, and national surveillance programs for early prostate cancer detection may all have contributed to the increased detection rate of prostate cancer.

Checking the serum prostate-specific antigen (PSA) level and a digital rectal examination (DRE) are the gold standards for prostate cancer screening. If repeated PSA levels exceed 4 ng/ml or prostate nodule or asymmetry are found by DRE, transrectal ultrasonography (TRUS)-guided needle biopsy is performed to pathologically confirm the diagnosis [1,2].

A higher PSA value is more frequently associated either with prostate cancer or with advanced disease, even though the opposite opinions have been reported in some cases (e.g., prostate cancer prediction with low PSA in the case of elderly patients with abnormal DRE and TRUS findings) [3]. More than 50% of men with a PSA value higher than 10 ng/ml have extra-prostatic disease. Twenty percent of men with a PSA higher than 20 ng/ml and 75% of those with a PSA higher than 50 ng/ml are found to have

pelvic lymph node involvement [4].

Common complications of prostate biopsy include post-biopsy infections and bleeding. Coagulopathy and immunosuppression can be problematic, and severe conditions are contraindications to prostate biopsy. After TRUS-guided needle biopsy, most infectious complications are limited to symptomatic urinary tract infection and low-grade febrile illness; however, recent studies showed that 1.4% of patients will go on to develop a febrile urinary tract infection, bacteremia, or acute prostatitis and require hospitalization for treatment with intravenous antibiotics [5].

Bleeding is the most common complication seen after prostate biopsy, even with normal coagulation parameters. It can present as hematuria, rectal bleeding, or hematospermia. Other complications include acute urinary retention (AUR), which may require temporary catheterization, the chance of which is increased with a prior history of benign prostatic hyperplasia and older age [6,7].

Therefore, particularly in patients with extremely elevated serum PSA levels and old age, prostate biopsy to confirm the diagnosis of prostate cancer should be carefully considered owing to possibly fatal complications. To prove the necessity for prostate biopsy in this group, we reviewed the outcomes of TRUS-guided prostate needle biopsy in patients with elevated PSA levels. We grouped the patients according to their PSA levels and calculated the positive predictive value (PPV).

MATERIALS AND METHODS

We retrospectively reviewed the medical records of 1,150 patients who underwent TRUS-guided prostate needle biopsy for the evaluation of prostate cancer from January 2000 to December 2010. Patients with a pre-biopsy PSA level less than 4 ng/ml were excluded from the study. We also excluded patients with acute prostatitis and acute urinary retention. In total, 1,121 patients were reviewed in this study.

All patients took antibiotic prophylaxis (either PO quinolones or third-generation cephalosporins) for 7 days, starting from the day before the biopsy. If any signs or symptoms suggesting urinary tract infection occurred, the procedure was canceled. Patients taking anticoagulation agents stopped the medication for at least 5 days before the biopsy. For most of the patients, 12-core or double sextant biopsy (i.e., right peripheral 3 core, right medial 3 core, left peripheral 3 core, and left medial 3 core) was performed. One or more cores were added if suspicious hypoechoic lesions or palpable nodules were present on ultrasound or DRE. Some patients in poor general condition underwent standard sextant biopsy or 8-core biopsy.

According to the pre-biopsy PSA level, patients were divided into 6 groups (group A, 4 to 20 ng/ml; B, 20 to 40 ng/ml; C, 40 to 60 ng/ml; D, 60 to 80 ng/ml; E, 80 to 100 ng/ml; and F, above 100 ng/ml). The patients' age, pre-biopsy PSA level, the result of biopsy (i.e., cancer cell type and the Gleason score), and clinical or pathologic TNM stage were compared. The cancer detection rate was analyzed for each group.

RESULTS

Overall, 356 (31.8%) of the 1,121 patients had prostate carcinoma. The mean age of the patients with reported prostate cancer at biopsy was 65.8 years (range, 34 to 88 years) and that of the patients with a negative biopsy result was 70.1 years (range, 38 to 91 years). The mean PSA level of the patients with a positive biopsy result was 16.12 ng/ml (range, 4.82 to 7,176 ng/ml). The mean PSA level of patients with a negative result was 10.39 ng/ml (range, 4.12 to 85.5 ng/ml). The detection rate was gradually increased as the pre-biopsy PSA level increased. For example, only 21.8% of group A (i.e., PSA 4 to 20 ng/ml) had prostate cancer, whereas all 65 patients of group F (PSA $>$100 ng/ml) had cancer (positive predictive value=100.0%), as presented in Fig. 1.

All 356 patients had prostate adenocarcinoma. Among them, 107 had high-grade cancer (Gleason score $\geq$8). The percentage of high-grade cancer was 30% in total, which increased to 71% in group F (Fig. 2).

Magnetic resonance imaging (MRI) was used to evaluate the local extent of disease and the possibility of lymph node involvement, and radionuclide bone scans were also per-

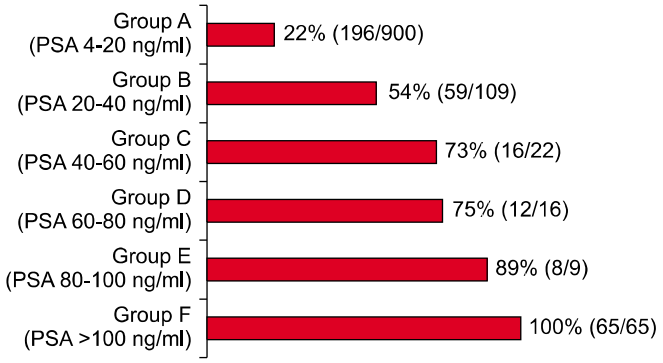

FIG. 1. Positive predictive values according to prostate-specific antigen (PSA) range.

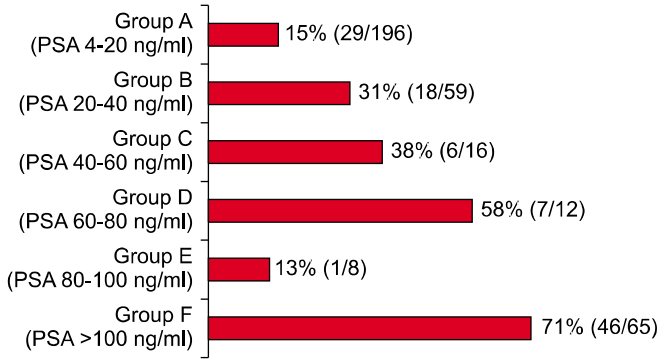

FIG. 2. The percentage of high-grade cancers (Gleason score $\geq$8). PSA, prostate-specific antigen.

formed to detect skeletal metastasis. If prostatectomy was performed, the radiologic findings and pathologic results were used to determine the TNM stage. Staging was possible for 311 of the 356 patients, whereas 45 patients had no record due to follow-up loss. A total of 156 patients (50%) had organ-confined cancer (Table 1). Of the 56 patients who underwent workup for TNM stage in group F (PSA >100 ng/ml), 38 patients had either extra-prostatic diseases (cT3-4) or lymph node metastasis (N1), and 43 patients had positive bone scan metastasis (M1). Combining the results in group F, all patients had advanced prostate cancer (i.e., 4 patients [7%] had stage III and the remaining 52 patients [93%] had stage IV cancer). No patient who underwent workup for TNM staging in group F had organ-confined cancer.

DISCUSSION

An elevated serum PSA level is one of the most important features suggestive of prostate cancer [8,9]. In most cases, the PSA cutoff of 4 ng/ml is a threshold for performing prostate biopsy. However, the test is painful and invasive, and various complications have been reported in the literature, albeit not common. Most of the complications were minor and did not require hospitalization, but serious life-threatening complications, such as sepsis, also occurred [10-13].

In general, the risk of prostate cancer is directly related to the PSA level. Our analysis demonstrated that a serum PSA level higher than 100 ng/ml was 100.0% accurate in predicting the presence of prostate cancer on tissue biopsy. Heyns et al. [14] reported similar results in a large unscreened population. Using a subset of 716 patients with a PSA value higher than 4 ng/ml, they found a positive predictive value of 98% for PSA over 60 ng/ml. Gerstenbluth et al. [4] reported that, when increased to over 50 ng/ml, the serum PSA level was 98.5% accurate in predicting cancer. Thus, they suggested that some highly selected patients may not need to undergo prostate biopsy before androgen deprivation therapy. There may be a disparity between these reports and ours, possibly resulting from racial differences. In our results, the PPV for PSA over 50 ng/ml was merely 81.2%, which was lower than the value in the other Western studies. In other words, the negative predictive value for PSA over 50 ng/ml was higher. It is well known that incidence and disease characteristics vary with race [1,15]. Also, the number of patients who had PSA over 50 ng/ml was comparatively smaller, resulting in a difference in PPV from other Western studies.

In the study by Egawa et al. [1], prostate cancer was present in 59.5% of patients with a PSA of 10 ng/ml or higher. Shim et al. [16] also reported that the risk of positive biopsy for PSA levels more than 100 ng/ml was 100%, which was quite similar to our results. Studies of Korean populations have also documented a positive predictive value of 93.8% with a PSA higher than 100 ng/ml and of 94.7% with a PSA higher than 50 ng/ml, which increased to 100.0% in conjunction with an abnormal DRE [17]. In the present study, the detection rate was 100.0% in the subgroup of patients with a PSA of 100 ng/ml or higher.

In group E (PSA, 80 to 100 ng/ml), one patient with a negative biopsy result was followed up for 6 months and a second prostate biopsy was performed, which confirmed prostate cancer. We did not include this patient in group F but rather in group E. This is because this study was conducted to verify the necessity for prostate biopsy in diagnosing prostate cancer; thus, we considered the result of the initial biopsy, not the repeated. Thus, patients with carcinoma reported at their repeated biopsy and not at their initial biopsy were classified as having a negative prostate cancer result. Gerstenbluth et al. [4] have suggested that a negative biopsy in patients with a PSA value of higher than 20 ng/ml is often a false-negative. The likelihood of cancer is significantly increased if the PSA level is persistently high at a subsequent measurement.

The most important role of prostate biopsy is to confirm the diagnosis pathologically, but it also helps to obtain the histologic subtype and to estimate the extent of disease (e.g., the number of positive cores and percentage of positive cores). Therefore, if cancer is expected to be present in almost 100% of a specific patient group, then the value of biopsy is reduced merely to histologic grading and estimation of disease extent [18].

In our review, all 65 patients in group F (PSA >100 ng/ml) had adenocarcinoma. Ninety percent of the patients had a Gleason grade of 4 or higher (i.e., Gleason score of 7 or higher), and radiologic studies showed that all the can-

TABLE 1. TNM stages of prostate cancer

Stage	I or II	III	IV	Total
Group A (PSA 4 to 20 ng/ml)	110 (63)	18 (11)	46 (26)	174
Group B (PSA 20 to 40 ng/ml)	36 (71)	0 (0)	15 (29)	51
Group C (PSA 40 to 60 ng/ml)	4 (27)	2 (13)	9 (60)	15
Group D (PSA 60 to 80 ng/ml)	3 (30)	1 (10)	6 (60)	10
Group E (PSA 80 to 100 ng/ml)	3 (60)	0 (0)	2 (40)	5
Group F (PSA >100 ng/ml)	0 (0)	4 (7)	52 (93)	56
Total	156 (50)	25 (8)	130 (42)	311

Values are presented as number of patients (%).
PSA, prostate-specific antigen.

TABLE 2. Characteristics of patients with a PSA level over 100 ng/ml

Stage	I-II	III	IV
Age (yr)			
≤65	0	1	7
>65	0	3	45
BMI (kg/m^2)			
<25	0	2	33
≥25	0	2	19
Gleason score			
<6	0	0	5
6 or 7	0	0	14
≥8	0	4	33
Positive core percentage (no. of positive cores/no. of biopsy cores) (%)			
<50	0	0	5
<75	0	0	5
<100	0	2	6
100	0	2	36

Values are presented as number of patients (%).
BMI, body mass index.

cers were stage III or IV (Table 1). In addition, the characteristics of the patients in group F are presented in Table 2. The patient's age, body mass index, Gleason score, and percentage of positive cores was investigated, but the results showed all patients to have high stages. Therefore, the information from the prostate biopsy (e.g., Gleason score and the number of positive cores) does not affect the treatment strategy. If advanced disease is suspected by a super-high PSA level and the results of imaging studies, definitive surgical treatment will not be an option. In our study, all 56 patients received androgen deprivation therapy. Thus, if cancer is suspected in 100% of the patient group, and both disease extent and histologic subtype can be expected to be in a narrow range, undergoing a needle biopsy would be of little value for this specific group (i.e., patients with extremely high levels of serum PSA).

Many other prostate diseases affect the PSA level. Inflammation due to infection has been found to produce significant PSA elevation, and up to 6 to 8 weeks might be needed for the PSA value to return to baseline. PSA elevations can also occur as the result of urethral procedures with instrumentation, or following prostatic manipulation, such as the DRE. Therefore, in a patient with an increased PSA level and any recent history of either acute infection, urinary retention, or urinary tract manipulation, prostate biopsy is not mandatory, and a period of time is required to obtain an accurate PSA level [19-21]. Accordingly, urinary tract infection and urinary retention were exclusion criteria in our study.

The limits of our study are the relatively small number of patients and the retrospective design. To validate this cutoff value, a prospective study is needed to compare patients who underwent prostate biopsy with those who did not.

CONCLUSIONS

Our results suggest the possibility for a biopsy-free diagnosis of prostate cancer, with the criterion of a PSA level >100 ng/ml and evidence of advanced disease in imaging studies. We still recommend that any patient who is considered a candidate for surgery or radiation, despite a high PSA level, should undergo biopsy. Nevertheless, because prostate needle biopsy can be associated with several adverse effects, if elderly patients with poor general medical condition present with an extremely elevated serum PSA level, a tissue diagnosis of prostate cancer may not be required for starting androgen deprivation therapy.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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