

Preliminary study on ultrasound-guided prostate biopsy specimen scores

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Abstract. Prostate cancer (PCa) is the second most frequently diagnosed cancer in males worldwide and resulted in ~258,000 cases of cancer-associated mortality in 2008. The present study visually determined the pathology scores of PCa specimens by taking into account five characteristics, including the hardness, color, plumpness, transparency and uniformity of specimens. The current study also aimed to identify the association between pathology scores and prostate specific antigen (PSA) levels, in order to reduce the complications caused by punctures and elevate the specimen positive rates. A total of 1,608 specimens from 268 patients were analyzed by one sonographer, one urologist and one pathologist. A standard pathological examination was performed on the PCa biopsy specimens and specimen scores were recorded under double-blinded conditions. A receiver operator characteristic curve identified a linear correlation between the visually determined score and PSA levels ($r=0.255$; $P<0.001$). Furthermore, logistic regression analysis indicated that the visually determined score and PSA were correlated with the diagnosis of PCa. Additionally, the authenticity of the visually determined score was higher than PSA in the diagnosis of PCa, with the best sensitivity and specificity of the visually determined scores used to predict PCa being 0.817 and 0.931, respectively.

Introduction

Prostate cancer (PCa) is the second most frequent type of cancer diagnosed in males worldwide. The cancer can invade bones and lymph nodes and it is the second leading cause of cancer-related mortality in men (1-4). There are no obvious

symptoms when PCa first occurs, however in the later stages the patient will experience difficulty urinating, blood in the urine, or pain in the pelvis or back when urinating. There were ~910,000 new cases of PCa and 258,000 cases of PCa-associated mortality in 2008 and it is estimated that the incidence of PCa may double by 2030 (5). Prostate specific antigen (PSA; clone ER-PR8, cytoplasmic staining) was initially identified ~30 years ago and is currently the most useful biomarker for cancer detection. Furthermore, serum PSA levels are widely applied to distinguish between PCa and benign prostatic hyperplasia (6,7). Additionally, in patients with PCa, it is crucial to accurately assess tumor aggressiveness to guide treatment decisions, as well as determine patient prognosis. Transrectal ultrasound (TRUS)-guided biopsy, typically performed with blind finger-guided intervention under general anesthesia to a directed lesion, is the standard procedure used for PCa diagnosis (8).

Diverse sampling devices and biopsy techniques, including X-ray examination, ultrasonic testing, computed tomography and magnetic resonance imaging, have been utilized to reach an optimum performance-hazard ratio. The dilemma between higher sensitivity and higher morbidity has been ongoing since the first description of the sextant biopsy scheme, which is an accurate and basic method for diagnosing PCa using a fine needle inserted into the prostate, by Hodge *et al* (9). Techniques that are more sensitive increase the likelihood of morbidity in patients (10). Although the sextant biopsy scheme is applied in multiple centers, it has been recommended that a minimum of 10-12 core biopsies should be taken and this method is currently adopted by the majority of urologists (11). The optimal number of core biopsies remains unknown, however, it has been confirmed that increasing the number of cores notably improves cancer detection. The use of 12-21 cores markedly increases cancer detection rates compared with sextant biopsies (12,13). However, this also increases the incidence of complications, and may even cause some serious complications (14).

The aim of the current study was to achieve the highest cancer detection rate using the minimal number of cores. Therefore, pathology standard examination scoring was used to analyze five different aspects of the specimens, including hardness, color, plumpness, transparency and uniformity. Additionally, the association between pathology scores and PSA levels was investigated.

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Patients and methods

Patients. A total of 268 patients aged 71 ± 8 years old and suspected of having PCa were admitted and treated at Ruijin Hospital (Shanghai, China) between January 2013 and December 2013. Indications for prostate biopsy were as follows: Serum PSA >4 ng/ml, or ultrasound or MRI found suspicious nodules, or clinical anus examination identified hard nodules. All patients were hospitalized, underwent routine hospitalization tests and coagulation index detection. A total of 6 prostate biopsy specimens were obtained from each patient and all specimens possessed pathological results. Prior written and informed consent was obtained from each participant and the present study was approved by the Ethics Committee of Ruijin Hospital Affiliated to Shanghai Jiaotong University, School of Medicine (Shanghai, China).

Serum PSA evaluation. Patients should have not ejaculated within 24 h, conducted bladder microscopy or catheterization within 48 h, accepted prostate massage within 1 week or performed prostate puncture within 1 month prior to serum PSA evaluation. This was to limit the presence of confounding factors that may have affected PSA levels. Following overnight fasting, patients had 3 ml forearm venous blood drawn in the morning and were inspected using a PSA ELISA kit (cat. no. KA0208; Abnova, Taipei, Taiwan R.O.C.) and analyzed using an automated immunochemistry analyzer (Abbott Laboratories, Abbott Park, IL, USA).

Puncture method. A MyLab™ 60 diasonograph (Esaote, Genova, Italy), rectal biplanar probe (Esaote), automated biopsy gun (Bard Biopsy Systems, Tempe, AZ, USA) and 16-gauge (G) Tru-cut biopsy needle (Bard Biopsy Systems) were used in the present study. The length of the specimen slot was set to 2.2 cm. Patients were asked to lift up the scrotum to fully expose the perineum, then transverse scanning was performed using a convex array probe to measure the prostate anteroposterior and transverse diameters. Axial scanning was performed by linear array probe to measure prostate axial diameter. This allowed for the detection of nodules, cysts or calcification, and the selection of an appropriate puncture site.

Following perineum disinfection, infiltration anesthesia was administered with 5 ml 1% lidocaine (Century Pharmaceutical Co., Ltd., Tianjin, China) on each side of the midcourt line, which was at the middle of the urethral bulb and ischial tuberosity, and 1.5-2.0 cm away from the anus. The sextant biopsy scheme was subsequently utilized to obtain prostate biopsy specimens. Puncture points were on the tip of the prostate near the midline sagittal section, as well as the middle and bottom of the prostate, for a total of six puncture points per patient.

Visual scoring method. One sonographer, one urologist and one physician pathologist evaluated all the specimens. Specimens were scored based on five aspects: Hardness, color, plumpness, transparency and uniformity, and were given a score of either 0 or 1 (Table I). Specimen scores were recorded under double-blinded conditions and thereafter, the averages of six specimen ratings were calculated.

Hematoxylin and eosin (H&E) staining. Prostate tissues were fixed with 4% paraformaldehyde at room temperature for 24 h, embedded in paraffin and then sliced into sections ($6\ \mu\text{m}$). Briefly, slices were dewaxed with xylene and rehydrated using graded alcohols. Following rinsing with tap water and distilled water, slices were stained with hematoxylin for 3-5 min. Slices were washed with tap water and stained with eosin for 1-4 min and subsequently underwent dehydration and differentiation with HCl in 70% alcohol. Slices were then studied using a light microscope.

Statistical analysis. Quantitative data were expressed as the mean \pm standard error of the mean. Statistical comparisons between the PCa and non-PCa groups were performed using a Student's t-test. Logistic regression and receiver operator characteristic curve (ROC) analysis were used to analyze the sensitivity and specificity of the visually determined score and PSA level. Finally, Spearman correlation was applied to determine the correlation between the visually determined scores and PSA levels. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Demographic and clinical characteristics of patients. The average age of the 268 patients with suspected PCa patients was 71 ± 8 years old. The indications for prostate biopsy were serum PSA >4 ng/ml, a suspicious nodule identified by heterogeneous echo that was confirmed by ultrasound/magnetic resonance imaging examination or hard nodules revealed following clinical rectal examination. The demographic and clinical characteristics of all patients are presented in Table II.

H&E staining. The corresponding H&E staining of the PCa puncture specimen is presented in Fig. 1. The following features were observed: Irregular glands, glandular fibrous hyperplasia, tumor invasive growth, basal cell disappearance, tumor cell nucleolus appearance, mostly single cell morphology.

Extirpated prostate tumor. A representative extirpated tumor from a PCa patient is presented in Fig. 2. The tumor can be seen with the naked eye. The tumor had many ashen hard nodules from 0.3-1.3 cm in diameter with some red patches spreading out.

PSA and visually determined score. PSA levels in the PCa group (99.35 ± 1.40) were significantly higher than those of the control group (17.12 ± 0.10 ; Fig. 3A; $P<0.01$). However, the visually determined score (3.44 ± 0.01) of the PCa group was also significantly increased compared with the control group (0.99 ± 0.01 ; Fig. 3B; $P<0.01$). Correlation analysis was carried out on the biopsy specimen visual grading score and PSA. The correlation coefficient was 0.255 ($P<0.001$), which indicated a linear relationship between the two characteristics.

Logistic regression analysis. Logistic regression analysis verified that upregulated PSA and visually determined scores were two independent determining factors in the diagnosis of PCa (Table III). From the data it was identified that PAS and prostate biopsy specimen visual grading have

Table I. Specimen score principles.

Aspects	Specimen score	
	1	0
Hardness	Hard	Soft, naturally bends, naturally deformed by gently pressing with fingers
Color	White	Other colors
Plumpness	Plump and mellow	Slender or filamentous
Transparency	Pattern of the white mat behind specimens could be recognized clearly	Not transparent
Uniformity	Undoped with other tissues	Impure

Table II. Demographic and clinical characteristics of patients.

Characteristics	Number (%)
Age, years	71±8
PSA	
<4 ng/ml	0
Hard nodules examined by ultrasound	5 (1.9)
Hard nodules examined by MRI	8 (3.0)
Hard nodules revealed by rectal examination	8 (3.0)
4-10 ng/ml	61 (22.8)
10-20 ng/ml	89 (33.2)
>20 ng/ml	97 (36.2)
Pathology result of puncture	
Prostate cancer	93 (34.7)
Prostatic hyperplasia	109 (40.7)
PIN	21 (7.8)
Atypical hyperplasia	45 (16.8)

PSA, prostate specific antigen; MRI, magnetic resonance imaging; PIN, prostatic intraepithelial neoplasm.

statistical significance to distinguish between prostate cancer and non-prostate cancer patients. Higher PSA (OR=1.045, 95% CI=1.021-1.069, P<0.001) or higher visual grading score (OR=14.096, 95% CI=6.326-31.409, P<0.001) was correlated with a higher risk of PCa.

ROC curve of PSA and visually determined score. An ROC curve analysis was performed to further investigate the clinical value of PSA and visually determined score in the diagnosis of PCa. As shown in Fig. 4 and Table IV, the area under ROC curve of visual grading biopsy specimens was 0.929 (P<0.001). The area under ROC curve of PSA was 0.817 (P<0.001). The area under ROC curve for visual grading was significantly higher compared with PSA (P<0.05). Overall, this indicates that the visually determined score is more accurate than PSA in the clinical diagnosis of PCa.

Sensitivity and specificity of the visually determined score. In the current study, if visually determined score was greater

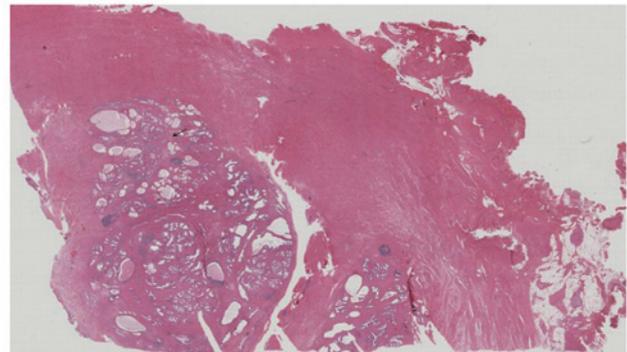


Figure 1. H&E staining of a prostate cancer specimen. The tumor was taken from a representative PCa patient in the current study and stained with H&E. The glands have become irregular, and glandular fibrous hyperplasia, tumor invasive growth, basal cell disappearance and tumor cell nucleolus appearance are visible. The tumor cell morphology is mostly single. The arrow indicates acinar adenocarcinoma area of PCa. H&E, hematoxylin and eosin.

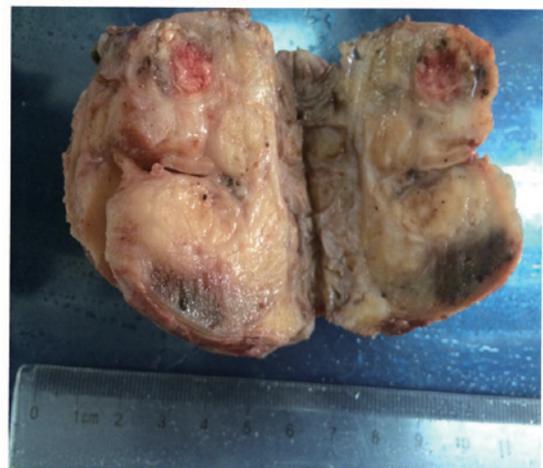


Figure 2. Extirpated prostate tumor. The prostate cancer specimen was taken from a representative PCa patient and has typical characteristics of PCa. The tumor had many ash hard nodules from 0.3-1.3 cm in diameter with some red patches spreading out. The specimen size is 8.3x7.2x5 cm.

than 1, 2 or 3 scores, it was considered to be positive. The sensitivity and specificity of the visually determined score in the diagnosis of PCa is presented in Table V. Taking sensitivity and specificity into consideration, diagnosis of PCa using the

Table III. Logistic regression analysis.

Indicators	B	S.E.	Wald	P-value	Exp (B)	95.0% CI for Exp (B)	
						Lower	Upper
PSA	0.044	0.012	13.592	<0.001	1.045	1.021	1.069
Visually determined score	2.646	0.409	41.894	<0.001	14.096	6.326	31.409

PSA, prostate specific antigen; S.E., standard error; CI, confidence interval; Exp (B), B coefficient index.

Table IV. Area under the ROC curve of visually determined score and PSA.

Test result variable(s)	AUC	S.E.	P-value	95% CI of area	
				Lower bound	Upper bound
PSA	0.817	0.028	<0.001	0.762	0.873
Visually determined score	0.929	0.019	<0.001	0.892	0.967

PSA, prostate specific antigen; ROC, receiver operator characteristic curve; AUC, area under curve; S.E.; CI, confidence interval.

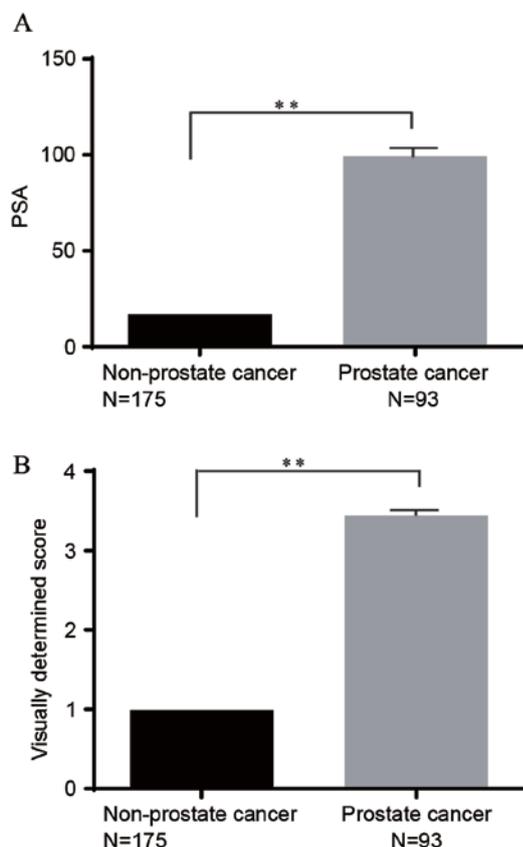


Figure 3. (A) PSA and (B) visually determined score in non-prostate cancer and prostate cancer groups. PSA, prostate specific antigen. **P<0.01 as indicated.

visual method should take into account 2 scores (the sensitivity is 0.817 and the specificity is 0.931), as this has the highest sensitivity and specificity compared with other numbers of scores.

Table V. Sensitivity and specificity of the visually determined score in the diagnosis of prostate cancer.

Diagnostic point of visually determined score	Sensitivity	Specificity
1	0.957	0.686
2	0.817	0.931
3	0.548	1.000

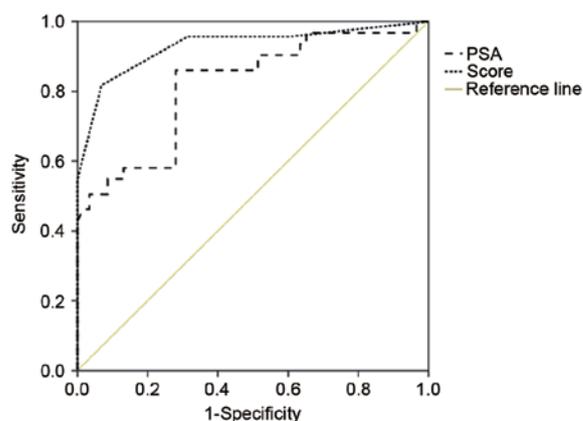


Figure 4. ROC curve of PSA and visually determined score. ROC identified a linear correlation between the visually determined score and PSA level ($r=0.255$, $P<0.001$). PSA, prostate specific antigen; ROC, receiving operator characteristic.

According to the visual method of two scores, patients were divided into two groups as shown in Table VI. The table showed that when the cutoff for diagnosis used as the visually determined score was set to ≥ 2 points, the positive predictive

Table VI. Pathological diagnosis results when 2 points are set as the cutoff.

Visually determined score	Pathological diagnosis		Total
	Non-prostate cancer	Prostate cancer	
<2 (negative)	120	4	124
≥2 (positive)	55	89	144
Total	175	93	268

$\kappa=0.570$, $P<0.01$ between the <2 scores group and ≥2 scores group.

value of the diagnosis was 61.8% whereas the negative predictive value of the diagnosis was 96.8%.

Discussion

Pathological examinations indicated that PCa specimens were solid and hard with a homogeneous texture and mostly gray-white or orange-yellow in color. Additionally, according to the PCa specimens in the current study, there were few hemorrhages and necrosis observed whereas normal prostate tissue is usually brown and porous (9,11-13,15-18).

A TRUS-guided biopsy is the primary method for clinically diagnosing PCa (8). The sextant biopsy scheme was initially proposed by Hodge *et al* (9) in 1989 and since then, this technique has been widely applied by clinicians. However, studies have since determined that the detection rate of the sextant biopsy scheme is only 20-30%, due to the smaller number of needle punctures performed (19,20). Subsequently, a 12-core biopsy was created on the basis of the sextant biopsy scheme by adding one puncture point on each side of the bottom, middle and apex of the peripheral zone in the prostate of patients, and the positive detection rate subsequently increased to 44% (21). Furthermore, a 12-pointed puncture biopsy based prospective study conducted by Takenaka *et al* (22) demonstrated that the cancer detection rate was 47%; significantly higher than that of the sextant biopsy scheme. Pepe and Aragona (23) performed a saturation prostate needle biopsy, utilizing 24-37 puncture needles, which had a detection rate twice that of the 12-pointed puncture. Therefore it seems that using more needles increases the detection rate (24).

PCa commonly occurs in older men (25), who often have other accompanying illnesses including hypertension, coronary disease and diabetes. In such patients, complications may occur following puncture biopsy. Mild complications can be resolved without treatment; however, serious ones may require surgical intervention (26). Common complications that occur during puncture are the vasovagal reflex, urethral hemorrhage, dysuria, acute urinary retention, hemospermia and infection (27). The vasovagal reflex manifests as palpitations, cold sweats and a drop in blood pressure, and a longer operation time increases the probability of developing this complication (28). A urethral hemorrhage (even heavy hemorrhage) occurs due to the damage of the cavernous body of the urethra and urinary mucosa, and requires surgical intervention (29). The incidence of severe complications, such as perineal

rectofistula, is highly associated with the number of punctures performed. Increasing the number of punctures increases the positive diagnostic rate but also increases the risk of serious complications occurring (30-32).

In the present study, prostate specimens were visually inspected and scored, and the correlation between the visually determined scores and pathological results was determined. ROC identified a linear correlation between the visually determined score and PSA level. Furthermore, logistic regression analysis indicated that PAS and prostate biopsy specimen visual grading have statistical significance to distinguish between prostate cancer and non-prostate cancer patients. Furthermore, the accuracy of the visually determined score was higher than PSA in the diagnosis of PCa. When the visually determined score was set to 2 points, the sensitivity (81.7%) and specificity (93.1%) were relatively higher compared with when the score was set to 1 or 3 points. Among the 268 participants, the visually determined score of at least one specimen in 144 patients was ≥2, of which 89 patients (61.8%) were diagnosed with PCa. Therefore, the sextant biopsy scheme was used. For specimen scores that were <2, while PSA or imaging suggested PCa, a 12-pointed puncture method or saturation prostate needle biopsy was applied in order to obtain more samples to elevate the positive rate. For the scores of specimens >2 identified using the sextant biopsy scheme, it was deemed unnecessary to increase the number of puncture needles and thus the risk of complications and time of biopsy were reduced.

After applying this method in our hospital for the PCa biopsy, the positive rate was as high as 53.2%, which is higher than 34.8% as previously reported (33). Furthermore, the incidence of postoperative hematuria was 21.3%, which is lower than the 30% previous reported in the statistical analysis (34).

In conclusion, the current study demonstrated that the positive biopsy rate of PCa could be significantly improved. Additionally, under the sextant biopsy scheme rate of PCa, the postoperative complications and repetition rate of puncture were significantly reduced. Future studies investigating the current method should include a greater number of participants.

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