Contrast-enhanced transrectal ultrasound can reduce unnecessary biopsy during prostate cancer screening and predict biochemical recurrence after radical prostatectomy in patients with localized prostate cancer

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Abstract

Background: To investigate the value of contrast-enhanced transrectal ultrasound (CETRUS) in reducing unnecessary biopsy during prostate cancer screening and predicting biochemical recurrence in patients with localized prostate cancer. Methods:This was a prospective study of patients suspected of prostate cancer who were evaluated with CETRUS followed by prostate biopsy. Prostate blood flow on CETRUS was graded using a 5-point scale. The relationship between CETRUS score and biopsy outcomes was analyzed; Univariate and multi-variate analyses were used to determine the probable prognostic factors with biochemical recurrence in patients with localized prostate cancer underwent radical prostatectomy. Results:A total of 347 patients were enrolled. Prostate cancer was found in 164 patients. A significant positive correlation ($r = 0.69$, $p < 0.001$) was found between CETRUS scores and prostate cancer. Using CETRUS score ≥ 2 as the threshold for biopsy could have reduced the number of biopsies by 12.1% (42/347) without missing cancer and spared 23.0% (42/183) of patients from unnecessary biopsy. 77 patients with localized prostate cancer underwent radical prostatectomy and followed up. 17 of 77 patients exhibited biochemical recurrence. The 3-year biochemical recurrence-free survival rates were 86% for patients with CETRUS low scores (≤ 3) and 59% for patients with high scores (> 3; $p = 0.015$). Multivariate Cox regression analysis showed that CETRUS score was an independent predictor of biochemical recurrence (HR: 7.02; 95% CI: 2.00-24.69; $p = 0.002$). Conclusions:CETRUS score may be a useful tool to reduce unnecessary biopsy during prostate cancer screening and predict biochemical recurrence of localized prostate cancer after radical prostatectomy.

Background

Prostate cancer is the most common solid neoplasm and the second leading cause of cancer death in men in the U.S. [1]. With increasing incidence and mortality, an estimated 60,300 new cases were diagnosed and 26,600 deaths were attributed to this disease in China in 2015 [2]. Approximately one million prostate biopsies are conducted per year in the U.S.. However, prostate-specific antigen (PSA) testing, the most widely used screening tests for prostate cancer, leads to 750,000 unnecessary biopsies—and attendant pain, inconvenience, financial burden, and risk of infection [3]. Therefore, one way to reduce the harm of PSA testing and thus shift the ratio between benefit and harm would be to improve its moderate predictive value and thereby reduce unnecessary biopsy [4].

About 15%-40% of patients with localized prostate cancer will develop recurrence after radical prostatectomy [5]. Traditional clinicopathologic risk factors, such as serum PSA level, pathological grade (Gleason score), and TNM stage, are used to predict the probability of recurrence, but they are not accurate for every patient [6]. Therefore, new tools are needed to complement the prognostic value of traditional risk factors. Such tools may help guide individual therapeutic management, improve patient counseling, and optimize clinical trial design.

Previous studies have shown that contrast-enhanced transrectal ultrasound (CETRUS)-based blood flow grade is a reliable tool to predict the pathological outcome of prostate diseases [7-11]. The diagnostic

accuracy of contrast-enhanced ultrasound has improved with the development of new ultrasound contrast agents and equipment [12]. Although a very promising imaging tool, CETRUS is still not widely used to evaluate prostate cancer. In this study, we investigated whether CETRUS can reduce unnecessary biopsy during prostate cancer screening. Furthermore, to investigate whether CETRUS can predict biochemical recurrence after radical prostatectomy in patients with localized prostate cancer.

Methods

Patients selection

Patients referred for prostate biopsy for elevated serum total PSA levels (> 4 ng/mL) or abnormal digital rectal examination (DRE) between Feb 2014 and Sep 2018 in our collaborate institutions (Yantai Yuhuangding Hospital, First Affiliated Hospital of Sun Yat-sen University and Cancer Center of Sun Yat-sen University) were included. The exclusion criteria were as follows: (1) age > 80 years; (2) refuse CETRUS; (3) patients received prostate biopsy previously; (4) with severe cardiopulmonary diseases. The study was approved by the ethics committee of the institutions. Written informed consent to participate and for the publication of their individual data was obtained from each participant.

Procedures

CETRUS was performed for each patient before prostate biopsy. The ultrasound equipment used for CETRUS was the IU 22 system, and the contrast agent used was SonoVue (Bracco, Milan, Italy). Conventional and contrast-enhanced transrectal ultrasound examinations were performed by sonologists with more than 5 years of experience in contrast-enhanced ultrasound and who were not involved in the analysis of ultrasound images. All patients were examined in the left lateral position. The contrast agent was prepared and administered in a standard fashion. To obtain comparable images from the precontrast and postcontrast portions of the examination, multiple identical series of angled axial sweeps through the gland were obtained from base to apex, each sweep extending over a period of 20-30 seconds [13]. The process was observed continuously for at least 3 minutes. All sonologists were blinded to the patients' clinical presentations and other imaging results.

The diagnostic confidence was scored on a five-point scale based on blood flow, according to previously published reports: [8,13] score 1, definitely benign, minimal enhancement (capsular and periurethral flow only); score 2, probably benign, mild enhancement (symmetric radial flow from capsular branches); score 3, indeterminate, mildly increased enhancement (asymmetric/increased flow in the prostate); score 4, probably malignant, moderately increased enhancement (asymmetric/increased flow in the prostate); score 5, definitely malignant, substantially increased enhancement (asymmetric/increased flow in the prostate) (Additional Fig. 1).

After CETRUS examination, a 12-core prostate systematic biopsy was performed. The systematic biopsy strategy was obtained by 6 standard cores and an additional 3 cores positioned more laterally on each side. Each biopsy sample was reviewed by a urological pathologist and reported individually. Tumors were classified according to the 2002 TNM staging system and graded according to the Gleason grading system. High-grade cancer was defined as Gleason score 7 or higher.

Surgical management and follow-up

Patients with clinical stage T1 and T2 prostate cancer underwent laproscopic radical prostatectomy. Patients with pathologically proven localized prostate cancer (T1/T2N0M0) were enrolled and followed up prospectively. Data collected from each patient included age at diagnosis, CETRUS score, tumor stage, Gleason score, body-mass index (BMI), Eastern Cooperative Oncology Group performance status (ECOG PS), and biochemical recurrence-free survival time. Postoperatively, patients were examined to obtain serum PSA measurements every 3 months for the first year and semi-annually from the second through the fifth years. Biochemical recurrence was defined as PSA level $\geq$ 0.2 ng/mL and rising, and recurrence date was assigned to the first instance of a PSA value $\geq$ 0.2 ng/mL [6]. No patient received adjuvant therapy before biochemical recurrence. Biochemical recurrence-free survival was calculated from the date of surgery to the date of biochemical recurrence, and was censored at the date of death from other causes or the date of the last follow-up visit for survivors.

Statistical analysis

The correlation between CETRUS blood flow grade and biopsy outcomes were analyzed by Spearman correlation test. Two groups were compared by using the chi-square test for categorical variables. Receiver operating characteristic (ROC) curves and area under the curves (AUCs) were employed to assess the diagnostic accuracy of CETRUS. Survival curves were estimated using the Kaplan-Meier method. Univariate Cox proportional regression hazard model was used to analyze the correlation between variables and clinical outcomes. Multivariate survival analysis was performed on all parameters that were significant on univariate analysis using the Cox regression model. The predictive accuracy of prognostic factors was determined using time-dependent ROC analysis, and the AUCs at 3 years were used to measure predictive accuracy. R software version 2.7.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for time-dependent ROC analysis. SPSS software (SPSS Standard version 16.0; SPSS Inc., Chicago, IL, USA) was used for all the other calculations. Statistical significance was indicated by $p < 0.05$.

Results

Patient characteristics

A total of 379 consecutive patients suspected of prostate cancer were referred for prostate biopsy. 32 patients were excluded. Finally, 347 patients were enrolled into the study and evaluated with CETRUS followed by prostate biopsy. No adverse events related to the contrast agent were observed in any of the 347 patients. The mean patient age was 68.5 years (range: 53-79), mean prostate volume was 52.8 mL^3 (range: 18-136), and mean PSA was 10.3 ng/mL (range: 1.9-382). Prostate cancer was found in a total of 164 of 347 (47.3%) patients. Among the 164 patients, 91 patients underwent laproscopic radical prostatectomy. 17 patients were excluded. Finally, 74 patients with localized prostate cancer were enrolled and followed up as shown in Figure 1.

The performance of CETRUS in reducing unnecessary biopsy

The proportions of prostate cancer in CETRUS score groups 1-5 were 0% (0/42), 11.5% (6/52), 32.5% (40/123), 87.1% (61/70), and 95.0% (57/60), respectively. A significant positive correlation ($r = 0.69$, $p < 0.001$) was found between CETRUS scores and prostate cancer. When cut off at 4 (≤ 3 as BPH and ≥ 4 as prostate cancer), CETRUS score had the highest accuracy of 83.3% (289/347) in the diagnosis of prostate cancer, with a sensitivity and specificity of 90.8% (118/130) and 78.8% (171/217), respectively. ROC analysis showed the AUC of the CETRUS score was 0.89 (95% CI: 0.85-0.92), indicating that CETRUS score can be used to differentiate prostate cancer from benign prostatic hyperplasia (BPH) (Additional Table 1, Fig. 2). Moreover, when cut off at 2 (1 = BPH and ≥ 2 as prostate cancer), CETRUS score had the highest specificity of 100% for differentiating prostate cancer from BPH, indicating that CETRUS with a cut-off score of 2 might be an effective tool for reducing unnecessary prostate biopsy. In this study, performing biopsy when CETRUS score ≥ 2 could have reduced the number of biopsies by 12.1% (42/347) without missing cancer diagnosis and spared 23.0% (42/183) of men from unnecessary biopsy (Table 1).

CETRUS can predict biochemical recurrence after radical prostatectomy in patients with localized prostate cancer

The clinicopathologic characteristics of the 77 patients with localized prostate cancer treated with radical prostatectomy were summarized in Table 2. CETRUS score results were dichotomized into low score (≤ 3) and high score (> 3) groups. No significant correlation was found between CETRUS score and patient age, tumor stage, Gleason score, PSA, BMI, or ECOG PS ($p > 0.05$, Table 2).

The median age of the 77 patients was 65.1 years (range: 49-74 years), and the median follow-up time was 30 months (range: 8-56 months). Biochemical recurrence was observed in 22% (17/77) of patients during follow-up. The 3-year biochemical recurrence-free survival rates were 86% (95% CI: 73%-93%) for patients with low CETRUS scores and 59% (95% CI: 53%-67%) for patients with high CETRUS scores (Fig. 3). Univariate Cox regression analysis revealed that CETRUS score, clinical stage, Gleason score, PSA

level, and ECOG PS had a significant impact on biochemical recurrence-free survival (p = 0.015, 0.042, 0.011, 0.037 and 0.047, respectively, Table 3), while other clinicopathologic variables, including age and BMI, did not (p = 0.618, 0.205, respectively, Table 3). Using multivariate analysis to further examine the parameters that were significant in univariate analysis, we determined that CETRUS score was an independent predictor of biochemical recurrence (HR: 7.02; 95% CI: 2.00-24.69; p = 0.002; Table 3).

To develop a more accurate prognostic tool, we used Cox proportional hazards regression to construct a prognostic model combining CETRUS score and clinicopathologic risk factors. Time-dependent ROC curve was used to compare the predictive accuracy of the combined model with models of CETRUS score alone or individual clinicopathologic factors alone. As shown in Figure 4, the model combining CETRUS score, Gleason score, tumor stage, and PSA (AUC at 3 years: 0.886; 95% CI: 0.754-1.000) had a better prognostic value than the model of CETRUS score alone (AUC at 3 years: 0.696; 95% CI: 0.520-0.890; p=0.006), Gleason score alone (AUC at 3 years: 0.679; 95% CI: 0.554-0.811; p=0.018), tumor stage alone (AUC at 3 years: 0.620; 95% CI: 0.500-0.748; p<0.001), or PSA alone (AUC at 3 years: 0.611; 95% CI: 0.500-0.792; p=0.004). Therefore, CETRUS score may add prognostic value to clinicopathologic risk factors of localized prostate cancer.

Discussion

Our study shows, for the first time, that using CETRUS as a supplement to PSA screening can reduce unnecessary prostate biopsy, and CETRUS score can independently predict biochemical recurrence of localized prostate cancer after radical prostatectomy.

PSA testing is not specific to prostate cancer. Other conditions, such as benign prostatic hyperplasia and prostatitis, also increase PSA levels. Therefore, the challenge is to design screening programs that maximize benefits and minimize morbidity and costs [14]. Angiogenesis, or the process of new blood vessel formation, is necessary during cancer progression. Compared with healthy tissue, prostate cancer is generally characterized by an increased number of newly created blood vessels [15,16]. However, most of these vessels have small diameters and may not have sufficient native flow to be detected by conventional Doppler transrectal ultrasound. The development of ultrasound contrast agents and contrast-specific imaging techniques have facilitated CETRUS, a novel imaging modality for continuous visualization of neovascularity associated with prostate cancer [17]. Prostate cancer tissue is associated with increased microvessel density due to the proliferation of neovessels. Additionally, the microvascular blood supply to prostate tissue is more uniform in malignant than in benign tissue [18].

Microbubble ultrasound contrast agents provide one approach to detect microvessels below the resolution of conventional transrectal ultrasound. Sedelaar et al. concluded in 2001 that CETRUS has the potential to reveal malignant prostate lesions with increased microvessel density, after finding that enhanced areas on CETRUS had a microvessel density 1.93 times higher than non-enhanced areas [19]. Ultrasound is a real-time, easily accessible, cost-effective, and non-invasive imaging modality. In addition, because ultrasound contrast agents have a low incidence of side effects and are not nephrotoxic,

CETRUS can be used in patients with iodine allergies, impaired renal function, or other contraindications that may make them unsuitable for contrast-enhanced computed tomography or magnetic resonance imaging [20]. Several studies have shown that the CETRUS-based blood flow grade significantly correlated with the histopathological outcome of biopsy. Thus, CETRUS can improve prostate cancer diagnosis, and prostate biopsy based on CETRUS represents an innovative approach to detecting significant disease with fewer biopsy cores [8,9,21,22]. With the development of new ultrasound contrast agents and equipment, the diagnostic accuracy of CETRUS is increasing, and the ultimate hope is to eliminate biopsy in patients without cancer [23]. However, at present, there is limited knowledge of the impact of CETRUS in reducing unnecessary biopsy in patients without prostate cancer. In the present study, a second generation contrast agent and low mechanical index were used to improve the survival of microbubbles in the circulation and facilitate real-time depiction of both the macrocirculation and microcirculation. In addition, a low mechanical index was used to prolong the time of parenchymal enhancement [24]. The present study showed a strong correlation between the CETRUS blood flow grade score and histopathological findings. Asymmetrical, substantially increased enhancement of the prostate during CETRUS was more likely to be malignant. On the contrary, minimal enhancement with only capsular and periurethral flow was more likely to be benign. We found that adding information on the CETRUS other than PSA can help predict the result of biopsy in men with elevated PSA. Biopsy on the basis of CETRUS score ≥ 2 could have reduced the number of biopsies by 12% without missing cancer and spared 23% of men from unnecessary biopsy.

Traditional clinicopathologic risk factors are inadequate for accurately predicting the prognosis of patients with localized prostate cancer after radical prostatectomy, additional tools for predicting prostate cancer recurrence may help to identify high-risk patients who might benefit from early intervention. Previous studies have shown that angiogenesis correlate with tumor recurrence after radical prostatectomy [25-27]. Contrast-enhanced ultrasonography, which is useful in assessing microvessel density, has also been reported to have potential value in predicting the outcome of patients with prostate cancer [28,29]. Our study firstly demonstrated that CETRUS score may be a reliable predictor of biochemical recurrence after radical prostatectomy in patients with localized prostate cancer. CETRUS score successfully categorized patients into high-risk and low-risk subgroups with a significant difference in 3-year biochemical recurrence-free survival. Furthermore, the combination of CETRUS score and clinicopathologic risk factors had a better prognostic value than CETRUS score alone or any of the clinicopathologic risk factors alone, suggesting that CETRUS score complemented the prognostic ability of traditional clinicopathologic features. Ultimately, patients with the same stage or grade of localized prostate cancer could potentially be stratified into different CETRUS-score-defined risk groups for disease recurrence, and such stratification may lead to more effective personalized management.

This study has noteworthy limitation. Our study was conducted in only three institutions, the results may not be universally generalizable. We acknowledge that prospective, large-scale, multicenter studies are necessary to confirm our results.

Conclusions

In summary, the CETRUS-based blood flow grade is a reliable tool to reduce unnecessary prostate biopsy during prostate cancer screening and may be considered a new independent predictor for biochemical recurrence after radical prostatectomy in patients with localized prostate cancer. Using CETRUS might add prognostic value to the current staging system.

Abbreviations

CETRUS: contrast-enhanced transrectal ultrasound; PSA: prostate-specific antigen; DRE: digital rectal examination; BMI: body-mass index; ECOG PS: Eastern Cooperative Oncology Group performance status; ROC: Receiver operating characteristic; AUCs: area under the curves; BPH :benign prostatic hyperplasia

Declarations

Acknowledgments

None.

Authors' contribution

Hong-wei Zhao and Yong Fang: Project development, Data Collection, Study design, Manuscript editing; Jian Li, Jia-Zheng Cao and Juan Lin: Manuscript writing, Study design, Data Collection, Statistical analysis; Zhu Wang, Jian-yao Lv,and Jin-huan We:Manuscript editing, Data Collection; Jin-huan Wei and Zhen-hua Chen: Data Collection,Statistical analysis; Hao-hua Yao, Yi-hui Pan, Zhen-li Gao, Jun-hang Luo, Wei Chen,and Lei Shi: Data Collection, Datainterpretation. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study has been approved by the Institutional Ethical Committee of Yantai Yuhuangding Hospital, First Affiliated Hospital of Sun Yat-sen University and Cancer Center of Sun Yat-sen University. Written

informed consent was obtained from each patient before the experiments.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Additional Material

Additional Table 1.

Diagnostic efficacy of CETRUS score in differentiating prostate cancer from benign disease at different cut-off points.

Additional Fig. 1

Baseline and CETRUS scores 1-5 are depicted in images a-e, respectively.

Figures

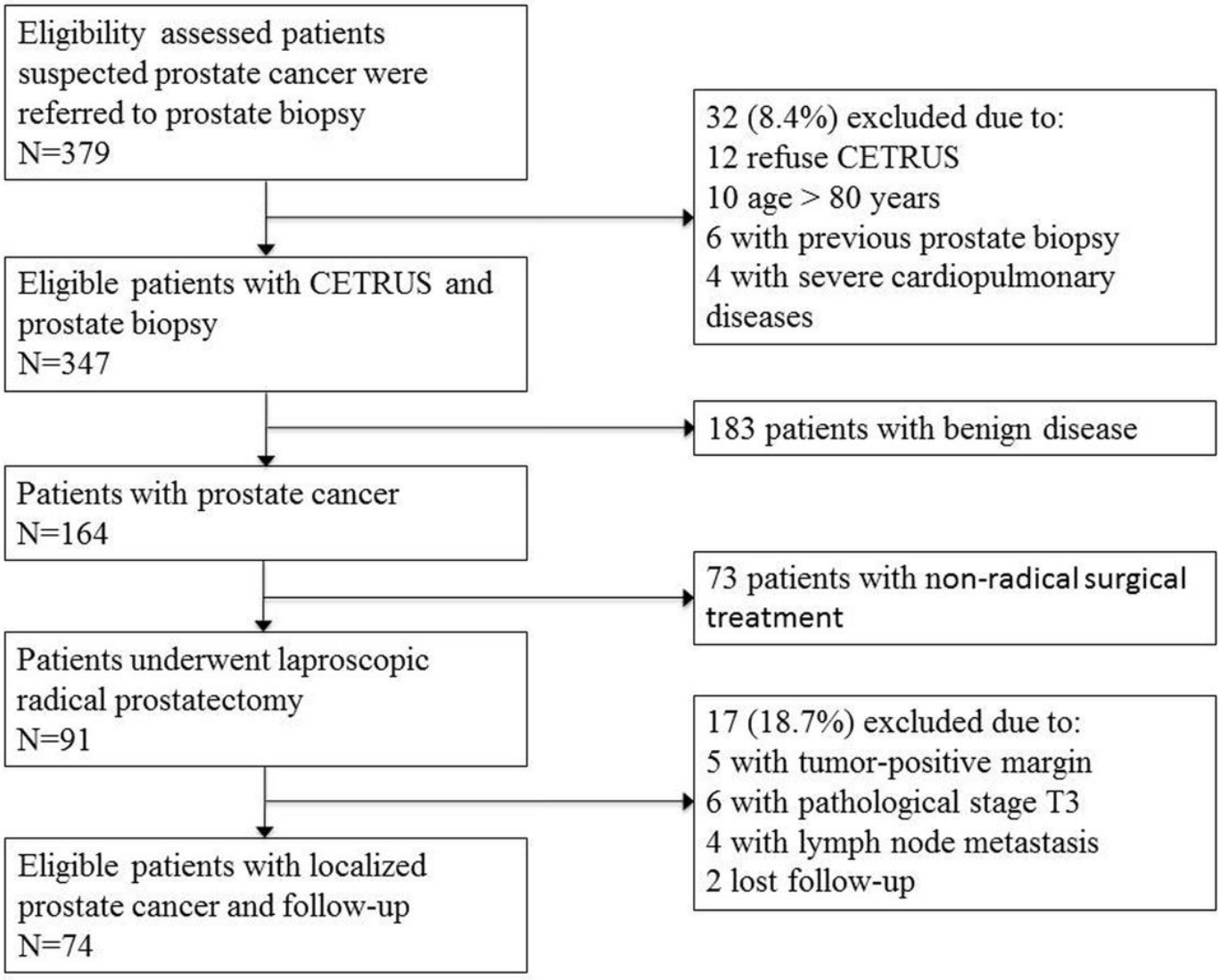


Figure 1

Flowchart of selecting patients for CETRUS examination and follow up.

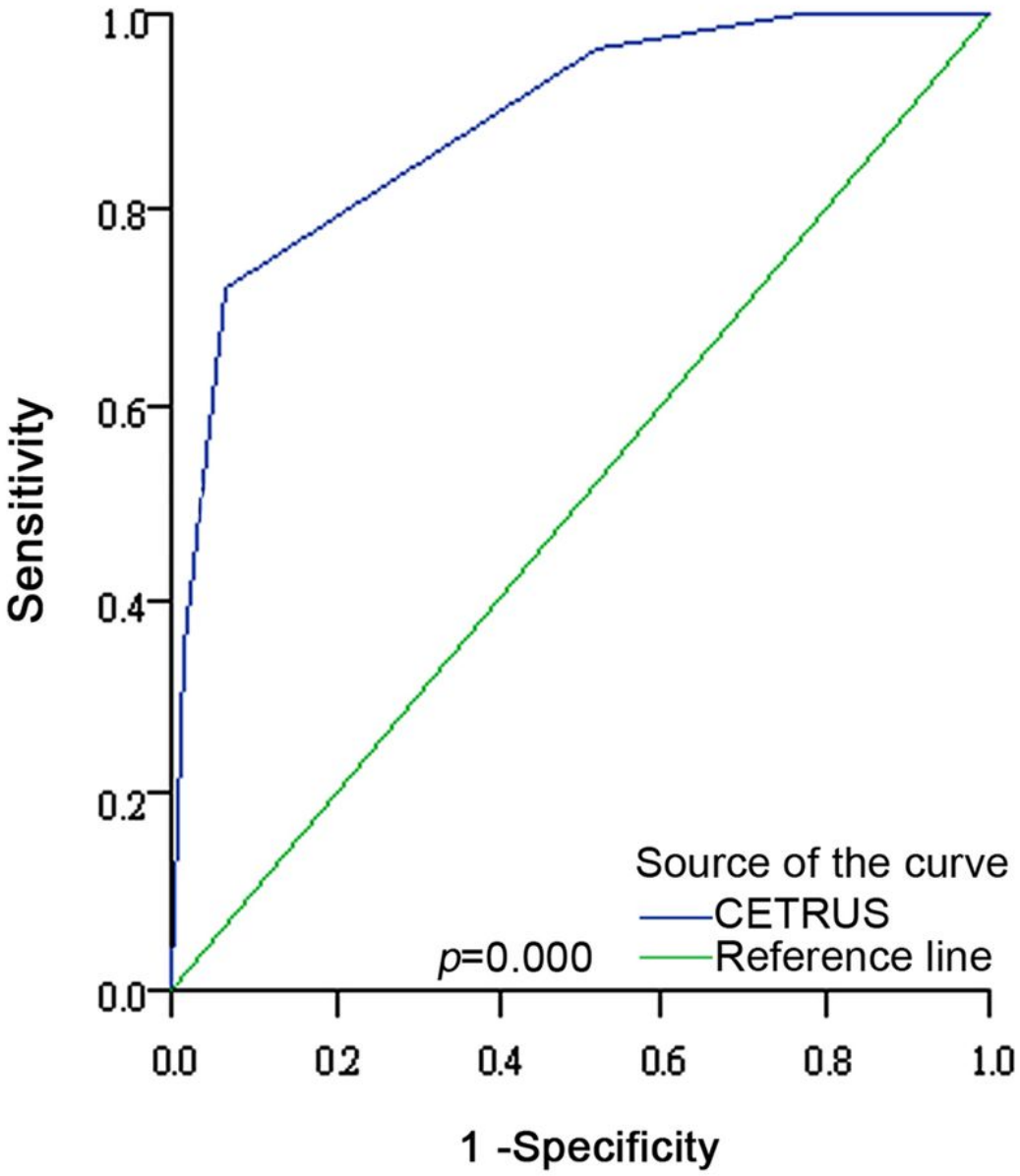


Figure 2

ROC curve of the CETRUS scores in differentiating prostate cancer from benign disease. The AUC of the CETRUS scores was 0.89 (95% CI: 0.85-0.92, p<0.0001).

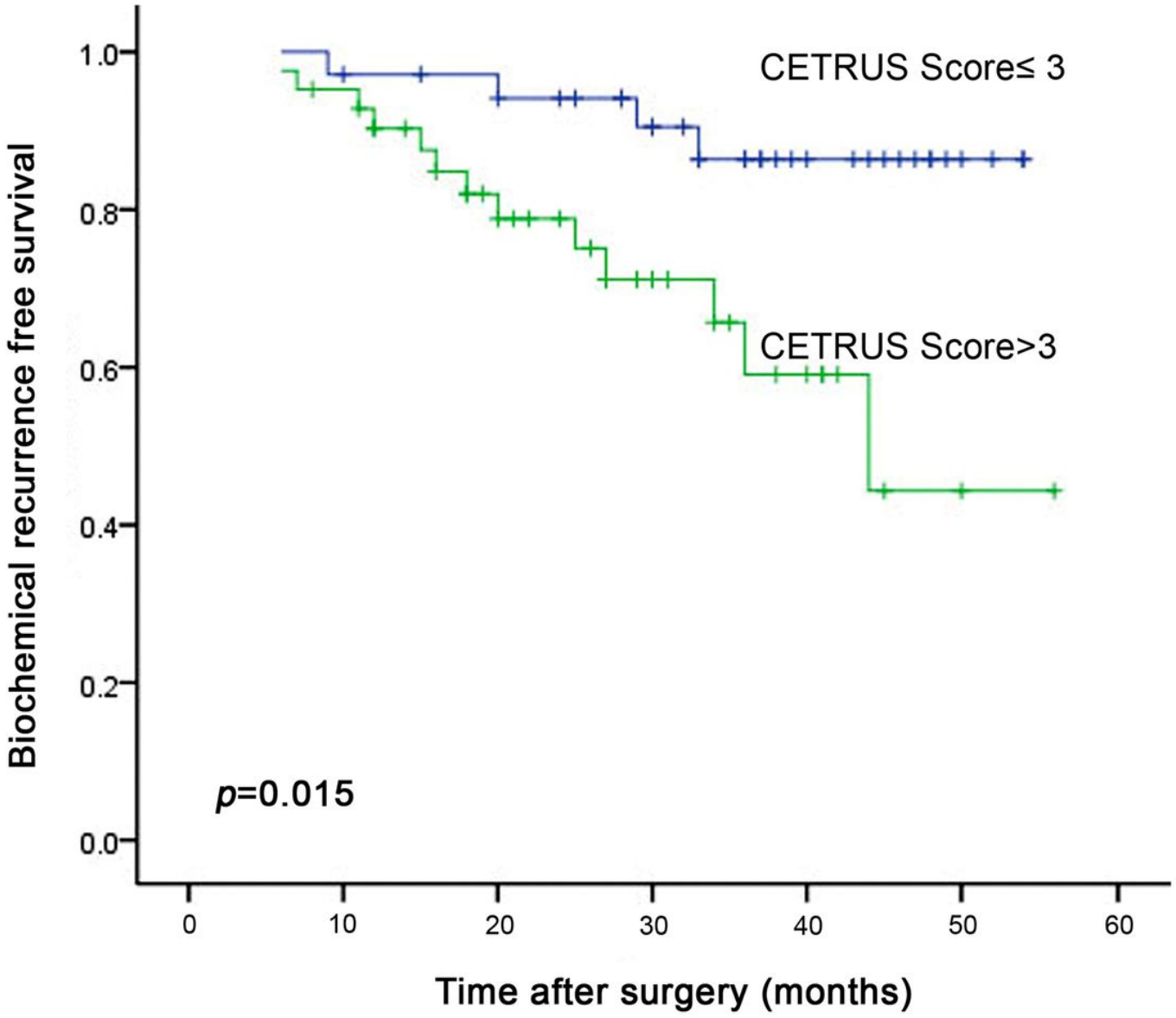
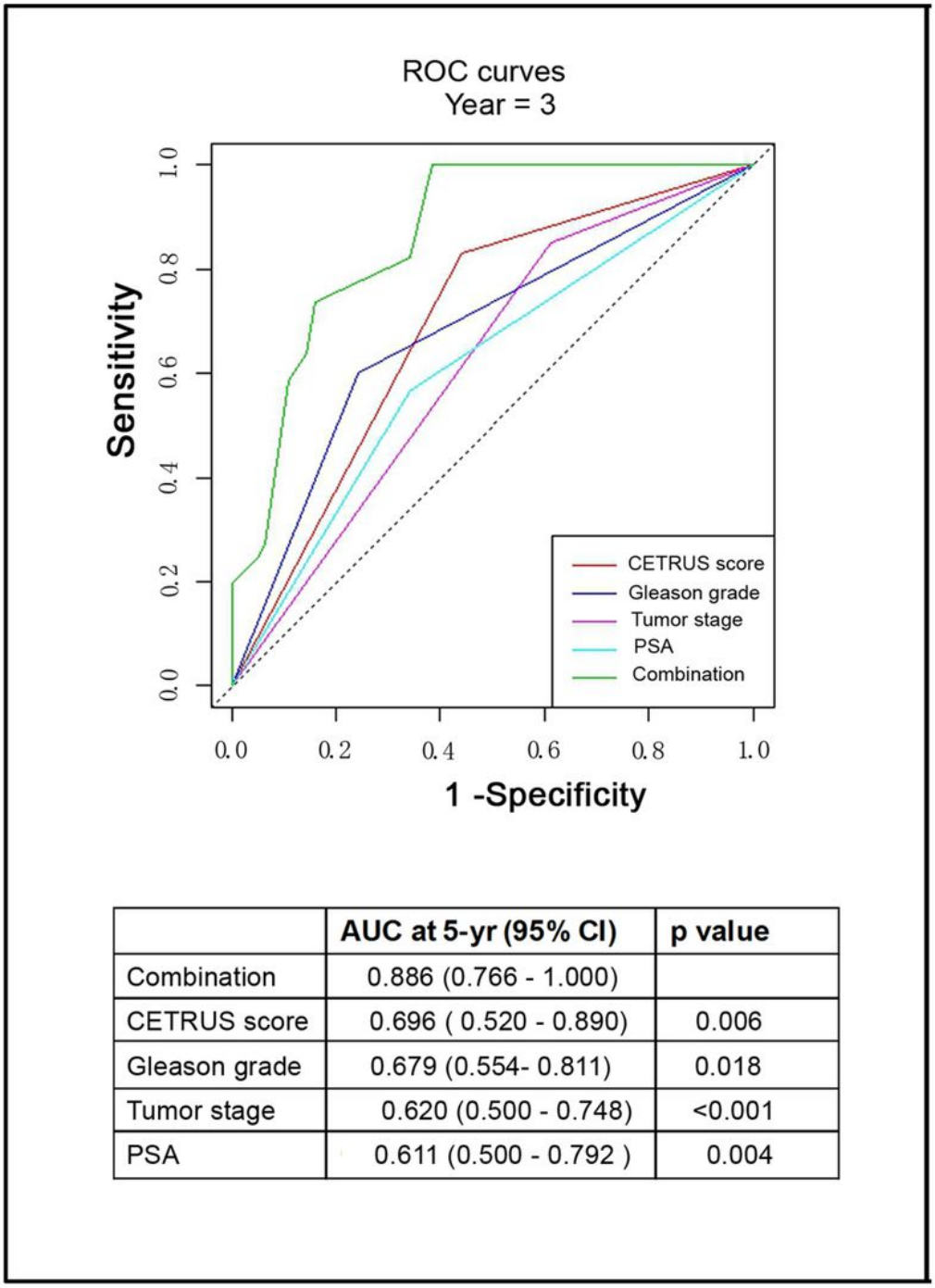


Figure 3

Kaplan-Meier biochemical recurrence-free survival analysis according to the CETRUS score in 77 patients with localized prostate cancer who underwent radical prostatectomy (p=0.015).



	AUC at 5-yr (95% CI)	p value
Combination	0.886 (0.766 - 1.000)	
CETRUS score	0.696 (0.520 - 0.890)	0.006
Gleason grade	0.679 (0.554- 0.811)	0.018
Tumor stage	0.620 (0.500 - 0.748)	<0.001
PSA	0.611 (0.500 - 0.792)	0.004

Figure 4

Comparisons of the predictive accuracy by different models. P values showed the AUC at 3-year for the combined CETRUS score, Gleason grade, tumor stage, and PSA model versus the AUC at 3-year for the CETRUS score alone model, the Gleason score alone model, the tumor stage alone model, or the PSA alone model.

Supplementary Files

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