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ORIGINAL ARTICLE

Predictive values of vascular endothelial growth factor and microvessel-density levels in initial biopsy for prostate cancer

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Abstract Angiogenesis is an important factor in the development and progression of prostate cancer (PCA). We aimed to investigate the values of vascular-endothelial-growth-factor (VEGF) expression level and microvessel density (MVD) in the prediction of PCA diagnosis at repeated prostate biopsy (re-PBx). We retrospectively evaluated 167 patients with re-PBx according to elevated prostate-specific antigen levels, suspicious digital rectal examination, and the presence of premalignant lesions. Patients with PCA on re-PBx were included in the cancer group ($n = 17$). Patients with benign prostatic hyperplasia or normal tissues on re-PBx were included in the control group ($n = 21$). The groups were compared according to the expression level of VEGF and MVD in initial prostate biopsy. There was no statistically significant difference between groups according to age and serum prostate-specific-antigen values. The mean VEGF scores of the cancer and control groups were 232.64 ± 11.14 and 183.09 ± 14.56, respectively ($p < 0.05$). The mean MVD of the biopsy samples in the cancer and control groups were 246.47 ± 17.59 n/mm^2 and 197.33 ± 16.26 n/mm^2, respectively ($p < 0.05$). The cutoff values of VEGF scores and MVD were set as 200 and 215, respectively, for PCA detection in our study. Our results showed that the expression level of VEGF and MVD significantly increased in the initial prostate-biopsy samples of patients with PCA diagnosed with re-PBx. The evaluation of VEGF expression level and MVD might have an important value in the prediction of PCA at re-PBx. The expression level of VEGF and MVD should be kept in

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mind as PCA-related histopathological changes that indicate the increased angiogenesis in prostatic tissue.

Introduction

Prostate cancer (PCA) accounts for 10% of all cancers in men, and causes 9% of cancer-specific deaths in men in developed countries [1]. The incidence of PCA has increased with the development of new diagnostic tools. The measurement of prostate-specific antigen (PSA) and its derivatives, the increased frequency of prostate biopsy (PBx), and the specific diagnosis of premalignancy by biopsy in pathological investigations are the main factors resulting in repeat PBx (re-PBx). Histopathological signs on first PBx and PSA levels at follow-up are mainly used for the prediction of PCA diagnosis on re-PBx [2].

Angiogenesis is an important factor in the development and progression of PCA and other tumors. PCA cells secrete proangiogenic factors, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor, interleukin-8, and platelet-derived growth factor [3].

Microvessel density (MVD) is the quantitative indicator of tumoral angiogenesis. Endothelium-specific antibodies, such as CD24, CD31, CD34, CD105, and von Willebrand factor (factor VIII), are used for the immunohistochemical staining of vessels, and MVD is calculated by counting the small and meandering vessels of the tumor. Recent investigations have suggested that increased MVD is related to high histological grade and poor prognosis in breast, lung, colon, stomach, malign melanoma, prostate, and bladder cancer [4,5].

Differences in VEGF expression level and MVD between PCA, premalignant lesions, and benign prostatic hyperplasia (BPH) have been reported. A pathological investigation of radical-prostatectomy materials showed an increased VEGF expression and MVD in PCA tissue in comparison to benign prostatic glands [6–8].

Here, we compared the VEGF expression level and MVD at re-PBx between patients initially diagnosed with BPH and PCA. We also investigated the values of VEGF expression level and MVD in the prediction of PCA diagnosis at re-PBx.

Methods

We retrospectively evaluated 1055 patients who underwent transrectal ultrasound (TRUS)-guided PBx between January 2000 and June 2013 at our department. A total of 167 patients underwent re-PBx during the study period due to an increased PSA level, suspicious digital rectal examination (DRE), or premalignant lesions, such as atypical small acinar proliferation (ASAP) and high-grade prostatic intraepithelial neoplasm (HGPIN). A total of 129 patients with ASAP, HGPIN, or prostatic inflammation were excluded. The remaining 38 patients were evaluated according to age, family history of PCA, laboratory findings, serum total PSA values, physical-examination findings, DRE findings, and radiological findings. The interval between the initial PBx and re-PBx was 6–12 months.

The patients were divided into the cancer and control groups. All patients in both groups were diagnosed with BPH on initial PBx. Seventeen patients with a PCA diagnosis at rebiopsy were included in the cancer group. The remaining 21 patients with a BPH diagnosis at re-PBx were included in the control group. These groups were compared according to VEGF score and MVD at initial PBx.

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Technique of TRUS-guided PBx

All patients were orally administered 500-mg ciprofloxacin twice daily for 2 days before undergoing PBx. The patient was placed in the left lateral decubitus position under local anesthesia for all TRUS evaluations and PBx procedures. A Logiq C2 ultrasound device with a transrectal probe (GE Healthcare, Milwaukee, WI, USA) was used to evaluate the prostate, and 5 mL of 2% prilocaine (2.5 mL for each side) was used as the local anesthetic agent and was injected bilaterally with a 22-gauge, 20-cm Chiba aspiration biopsy needle (GEOTEK Medical Corporation, Ankara, Turkey) just lateral to the junction between the prostate base and the seminal vesicle for periprostatic nerve blockade. The prostate was morphologically examined in transverse and sagittal planes after prilocaine infiltration. The ellipsoid formula was used to calculate the prostate volume. Five minutes after prilocaine injection, the PBx was performed in a transverse plane using the 10- to 12-core technique with a biopsy gun containing an 18-gauge, 25-cm Maxicore automatic biopsy gun needle (GEOTEK Medical Corporation).

Immunohistochemical staining and evaluation of VEGF expression and MVD levels

For all groups, hematoxylin/eosin-stained slides were reevaluated before immunohistochemical staining by the same pathologist. One core-biopsy sample of approximately 2 cm in diameter from each patient was used for immunohistochemical staining. Four-micrometer-wide paraffin blocks in polylysine-coated lam were deparaffinized in xylene and dehydrated in a series of baths containing decreasing concentrations of ethanol; then, the blocks were stained using the streptavidin–biotin–peroxidase method. Briefly, the sections were heated in citrate buffer (10mM, pH 6.0) at 120°C for 20–255 minutes (pressure cooker) for antigen retrieval, and were rinsed three times