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Prostate Cancer

IGF-II Serum Levels Increase Discrimination Between Benign Prostatic Hyperplasia and Prostate Cancer and Improve the Predictive Value of PSA in Clinical Staging

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Abstract

Purpose: IGF-I serum levels have been demonstrated as being associated with prostate cancer (PCa) and can serve as a predictive factor for the risk of PCa development. However, the role of IGF-II in PCa and its importance as a predictive marker is still unclear. Our aim was to determine PSA and IGF-II serum levels in patients with PCa and benign prostatic hyperplasia (BPH) and to analyse the value of IGF-II as an additional predictive factor in the diagnostics of PCa.
Methods: 112 patients who underwent surgery for BPH or PCa (no hormonal treatment, no further malignancies) were included in this study ((I) 38 PCa, PSA $\leq$ 15 ng/ml; (II) 34 PCa, PSA $>$ 15 ng/ml; (III) 40 BPH). Preoperative serum levels of total PSA and total IGF-II were determined by ELFA and ELISA, respectively.
Results: PSA levels were (I) 5.7 $\pm$ 1.9 ng/ml; (II) 25.0 $\pm$ 11.5 ng/ml and (III) 4.0 $\pm$ 2.8 ng/ml. (II) was statistically associated with a high grading (2b/3; $p = 0.0182$), a high Gleason sum score (7–10; $p = 0.0049$) and a non-organ confined tumor (T3/4; $p = 0.0009$) compared to (I), all Chi^2 test. IGF-II levels were significantly higher in PCa (I + II) compared to BPH (833.8 $\pm$ 238.9 ng/ml vs. 633.3 $\pm$ 141.4 ng/ml, $p < 0.0001$, *t*-test). Both PSA and IGF-II were associated with tumor staging ($p = 0.0097$, $p = 0.0308$; *t*-test). No significant correlation was observed between PSA and IGF-II levels. Logistic regression analysis revealed that the combination of PSA and IGF-II improves the prediction of tumor staging

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in PCa ($p = 0.0175$ and $p = 0.0459$, Wald test). Additionally, the combination of PSA and IGF-II can significantly increase discrimination between BPH and PCa; each $p < 0.0001$, Wald test.

Conclusions: This study provides evidence that IGF-II serum levels may serve as an additional parameter for (a) improved determination of tumor staging and (b) better discrimination between BPH and PCa.

1. Introduction

Prostate cancer (PCa) is the most common cancer in men in Western Europe and in the United States, with incidence increasing over the last 20 years [1]. 85.200 deaths related to PCa in 2004 in the European Union [2] document a definitive demand for prevention, diagnosis and the appropriate individual and stage-related therapeutic strategy. Since its discovery in 1979 [3], prostate specific antigen (PSA) has changed the diagnostics of prostate cancer and is responsible for the rising number of diagnosed PCas that had previously remained undetected by digital-rectal examination and transrectal ultrasound.

Two problems in the diagnostics of PCa remain unsolved to date. Even though PSA exists as a powerful marker and indicator for prostate cancer, the discrimination between BPH, which can also cause PSA elevation, and PCa is still difficult. PCa is usually diagnosed by needle biopsy with a 30% rate of false negative biopsies. To assure an appropriate treatment strategy, exact staging is required. To date, preoperative staging by biopsy, CT scan or MRI and additional parameters such as the PSA serum level remains unsatisfactory. PCa is often understaged preoperatively. Thus, there is a need for additional markers to resolve these two issues.

The IGF axis is a multicomponent network of polypeptides including insulin-like growth factors-I and -II, which function both as endocrine hormones and tissue growth factors [4]. It is therefore not surprising that the insulin-like growth factor (IGF) system has been associated with prostate cancer in a number of studies, e.g. high IGF-I serum levels have been shown to be associated with the risk of developing prostate cancer, independent of PSA baseline levels, or improving PCa detection in combination with PSA [5–8]. Recent controlled prospective studies did not find a correlation between IGF-I serum levels and PCa risk but suggested an association between IGF-I serum levels and pathogenesis and progression of the disease [9–11].

IGF-II has been shown to be expressed in more than 50% of prostate cancer specimens, with the mRNA and protein being mainly localized in the malignant cells, whereas expression in the stroma is minimal [12]. IGF-II mRNA in specimens of radical prostatectomies has been demonstrated as being significantly increased (by 30%) in adenocarcinoma compared to benign epithelium [13]. There is also a significant correlation with the pathologic stage, lymph node metastasis, histological differentiation and serum PSA levels [14], although specimens were collected from hormone-treated cases. Other findings are somewhat contradictory: IGF-II serum levels were lower in patients with PCa compared to BPH, but higher compared to healthy controls [15]. Additionally, low IGF-II serum levels were shown to be independently associated with an increased risk of PCa [16]. Other data (analysis of serum levels of IGF-II by RIA or ELISA, respectively) revealed no differences among subjects with cancer and normal controls [17,18]. However, the significance of IGF-II as a serum marker for the preoperative estimation of definitive tumor characteristics and its relevance for the discrimination of PCa and BPH is unclear as yet.

The aim of the study was therefore to determine the serum levels of IGF-II and PSA in patients with PCa and BPH and to analyse the value of IGF-II as an additional predictive factor in the diagnostics of the prostatic malignancy as well as its value for preoperative staging and grading in the case of prostate cancer.

2. Materials and methods

2.1. Sample population

112 male patients were included in this study. Patients underwent surgery for prostatic pathologies for BPH (40 males aged 53–83, median age 66) or PC (72 males aged 47–75; median age 63) in the University Hospital Mannheim between 03/1998 and 05/2003. Patients with prostate cancer were diagnosed because of an elevated serum PSA. Patients with additional cancer or consuming diseases and a hormone treatment were excluded. Pathological staging of cancer specimens was done in accordance with the 5th edition of the UICC TNM classification (1997), grading according to the histopathological grading of Helpap [19] and the Gleason method [20]. The sample population was divided into three groups. Group I