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ORIGINAL ARTICLE

Prostate cancer volume associates with preoperative plasma levels of testosterone that independently predicts high grade tumours which show low densities (quotient testosterone/tumour volume)

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Abstract *Objective:* To investigate potential associations of preoperative total testosterone (TT) with tumor volume (TV) and grade of prostate cancer (PCa).
Methods: Patients who were under medications impacting on the hypothalamic-pituitary-adrenal-testis-prostate axis were excluded. TT was measured preoperatively at least 1 month after biopsies and TV was calculated on the removed prostate specimen. Other continuous variables included total prostate specific antigen (PSA), percentage of positive cores (P+) and weight (W) of the removed prostate. Patients were categorized according to the pathologic Gleason score (pGS) in 3 groups (pGS 6, 7 and > 7). Invasion of the seminal vesicles was coded as seminal vesicle invasion (SVI).
Results: The median levels of TT were significantly and increasingly higher from pGS 6

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(14.7 nmol/L) to pGS 7 (15.0 nmol/L) and pGS > 7 (18.8 nmol/L). The median values of TV were also detected significantly and increasingly higher from pGS 6 (5.6 mL) to pGS 7 (8.1 mL) and pGS > 7 (14.8 mL). The median preoperative levels of PSA were also increasing from pGS 6 (5.9 μg/L) to pGS 7 (6.2 μg/L) and pGS > 7 (7.7 μg/L). There was a significant and positive correlation of TV to PSA, TT and P+. Multiple linear regression analysis showed that TV was significantly and independently predicted by TT, PSA and P+. High grade PCa (pGS > 7) independently associated with TV, TT, P+ and SVI. The median density values of TT relative to TV (quotient TT/TV) significantly decreased from pGS 6 (2.6 nmol/L/mL) to pGS 7 (1.9 nmol/L/mL) and pGS > 7 (1.4 nmol/L/mL). The median density values of PSA relative to TV (quotient PSA/TV) also significantly decreased from pGS (1.1 μg/L/mL) to pGS 7 (0.7 μg/L/mL) and pGS > 7 (0.6 μg/L/mL).

Conclusion: The investigation shows that TT relates to volume and grade of PCa; moreover, the density of TT relative to TV inversely associates with rate of increase of cancer that depends on the grade of the tumour.

1. Introduction

Biology of the prostate depends on the endocrine system which includes the hypothalamus, the pituitary gland, the adrenals and testes in which Leydig's interstitial cells are responsible for the production of 95% of all circulating androgen in the form of testosterone. Androgens, estrogens and pituitary hormones regulate prostate physiology.

Actually, prostate cancer (PCa) is the most studied endocrine tumour which needs further clinical research in order to explore etiology and physiopathology factors relating to its natural history. The disease depends on the androgens [1] and increases the levels of prostate-specific antigen (PSA) [2,3]. Since the pioneering work of Higgins and Hodges [1], androgens have been universally considered pivotal in the regulation of normal function and malignant growth of the prostate. Moreover, pretreatment total testosterone (TT) serum levels have been detected abnormal in the PCa population [4–7]. It has also been hypothesized that PCa might produce a substance that alters the normal function of the pituitary–testicular–prostate axis which responds by abnormal luteinizing hormone (LH) and follicle-stimulating hormone (FSH) serum levels [4–11]. It has also been suggested that the impact of the disease on the hypothalamic–pituitary–testis–prostate axis may be more profound in high-grade tumours [11]; however, the hypothesis has not been confirmed [12]. The association of pretreatment TT levels with pathological Gleason score (pGS), which represents the most effective factor for predicting the natural history of the disease (biochemical recurrence, development of metastases and PCa specific mortality) [13–16], is still a controversial and unsettled subject area [4–7,10–12,17–29] which requires further research [30].

In PCa patients, the volume of the tumour (TV) has been related to metastasis, seminal vesicle invasion and loss of histological differentiation [31]; moreover, high grade tumours (Gleason pattern 4 or 5) showed the highest rate to metastasize [31]. As a consequence, the association of high grade PCa with TV might express the highest potential of aggressive disease. Actually, the potential association of preoperative TT with both TV and high grade PCa remains an unexplored area of clinical research which is subject of the present investigation.

2. Materials and methods

2.1. Patients

The present analysis was part of a study aimed at evaluating a potential link between PCa and the hypothalamic–pituitary–testis–prostate axis. The data of 220 operated patients were retrospectively reviewed. Standard retro-pubic radical prostatectomy (RRP) was the surgical procedure performed with or without limited local lymph node dissection (LND). All patients had not previously received 5α-reductase inhibitors, LH-releasing hormone analogues or testosterone replacement treatment. The 14-core transrectal ultrasound scan (TRUS) guided prostate biopsy technique was routinely used and additional cores were taken when a lesion on either TRUS or digital rectal examination was evident. The biopsy Gleason score (bGS) of positive cores was assessed and percentage of positive cores (P+) was computed. After informed signed consent, pretreatment simultaneous serum samples of TT and PSA were obtained from a cubital vein, at least 1 month after TRUS biopsy, between 8:00–8:30 a.m. The samples were analyzed at our laboratory. TT (normal range, 9–29 nmol/L) and PSA (normal range, 2–4 μg/L) were measured by immunochemiluminescent test performed by ADVIA Centaur XP Immunoassay System (Siemens Company, Munich, Germany). The study obtained Institutional Review Board approval.

2.2. Data collection

The prostatectomy specimens were fixed *in toto* overnight (10% neutral buffered formhaldeyde), coated with India ink and then weighted (W). Tissue sections of 4 μm were