COMPARISON OF PROSTATE SPECIFIC ANTIGEN DENSITY IN PATIENTS WHO HAD UNDERGONE RADICAL RETROPUBIC PROSTATECTOMY WITH PSA LEVELS BETWEEN 4.0 TO 10.0 NG./ML. AND HISTOPATHOLOGICAL EXAMINATION

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ABSTRACT

Objective: We analyzed PSA density in patients who had undergone radical retropubic prostatectomy (RRP) with PSA levels between 4.0 to 10.0 ng/ml and compared these values to histopathological examination.

Methods: Between July 1992 and December 1997, we performed 117 radical retropubic prostatectomies for clinically localized prostatic carcinoma. Thirty patients whose serum PSA levels were between 4.0 to 10.0 ng/ml, were selected as the study group among all. No patients received neoadjuvant therapy, including androgen deprivation or radiation therapy. The age, preoperative PSA level (Hybritech Tandem assay), PSA density, transrectal ultrasound and Gleason pattern score of transrectal ultrasound guided biopsy and prostatectomy specimens were examined.

Results: The age of the patients ranged from 56 to 76 years and the mean age was 63.83 ± 5.01 years. Preoperative PSA levels ranged between 4.0 to 10.0 ng/ml. The mean value was 7.0 ± 1.60 ng/ml. The follow up period of the patients was between 21 and 78 months. The mean follow up was 49.8 ± 14.79 (median: 51) months. Prostate volume ranged from 18 to 110 cc and mean prostate volume was 44.81 ± 23.02 cc (median: 42.50 cc). PSA density ranged from 0.08 to 0.55 ng/ml/cc, mean PSA density was 0.19 ± 0.11 ng/ml/cc (median: 0.15 ng/ml/cc). Using 0.15 PSA density as the cut point, 12 (40%) patients had PSA density <0.15 ng/ml/cc. Of these, radical prostatectomy specimen pathological stage was pT2 in 4 (33%) cases, pT3a in 5 (42%), pT3c in 3 (25%). No patient had lymphatic invasion. PSA density was ≥ 0.15 ng/ml/cc in 18 (60%) patients. Of these, radical prostatectomy specimen pathological stage was pT2 in 7 (39%) cases, pT3a in 8 (44%), pT3c in 3 (17%) and 1 patient (6%) had lymph node positive. The follow up of PSA levels revealed recurrence in 6 (20%) patients. The period of these recurrences: mean time to recurrence was 17.3 ± 19.54 (median: 24.5 months) months with a range of 3 and 53 months. Five of 6 patients (83%) had PSA density ≥ 0.15 ng/ml/cc.

Conclusion: There is still some controversy regarding the treatment algorithm in cases with prostate cancer and PSA levels between 4.0 to 10.0 ng/ml. Recent studies, have underlined that free to total serum PSA ratio has a higher specificity than PSA density for cases with a PSA levels between 4.0 to 10.0 ng/ml in detecting and screening prostate cancer. But, PSA density has shown to be ≥ 0.15 ng/ml/cc in 60% cases who had undergone radical retropubic prostatectomy for localized prostate cancer and PSA levels between 4.0 to 10.0 ng/ml. Furthermore, 39% of them had organ confined disease while 6% had lymphatic invasion.

Key Words: Prostate carcinoma, Prostate specific antigen, Prostate specific antigen density, Pathological stage

INTRODUCTION

Serum prostate specific antigen (PSA) is an important tumor marker for adenocarcinoma of the prostate and serum PSA measurements are being widely used to screen for prostate cancer (1,2). However, the sensitivity and specificity of PSA are not yet sufficient to make it the perfect screening test for prostate cancer, particularly at moderately elevated concentrations (4.0 to 10.0 ng/ml) (3). Elevated PSA may be observed in benign diseases, such as prostatitis, benign prostatic hyperplasia (BPH), acute urinary retetion, and prostatic ischaemia, as well (4). Prostate cancer has been reported in about 37%

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patients with PSA levels between 4.0 to 10.0 ng/ml (3, 5-7). Therefore, the discrimination between prostatic cancer and benign diseases is more problematic among patients with intermediate PSA value between 4.0 to 10.0 ng/ml. Various attempts have been made to improve the specificity of PSA for detecting prostatic malignancies, including the use of PSA density, PSA velocity, age specific PSA ranges and PSA density of transition zone (8-12).

Prostate volume and age, which is correlated with volume, have been reported as important factors that contribute to PSA increase in the absence of adenocarcinoma of the prostate (12). PSA density was mainly studied to differentiate BPH from prostate cancer in the 4.0 to 10.0 ng/ml. PSA range, where the greatest overlap between the two pathological conditions exists. We analyzed PSA density in patients who had undergone radical retropubic prostatectomy (RRP) with PSA levels between 4.0 to 10.0 ng/ml and compared these values to histopathological examination.

METHODS

Between July 1992 and December 1997, we performed 117 radical retropubic prostatectomies for clinically localized prostatic carcinoma. Thirty patients, whose serum PSA levels were between 4.0 to 10.0 ng/ml, were selected as the study group among all. No patients received neoadjuvant therapy, including androgen deprivation or radiation therapy. The age, preoperative PSA level (Hybritech Tandem assay), PSA density, transrectal ultrasound and Gleason pattern score of both transrectal ultrasound guided biopsy and prostatectomy specimens were examined. Gleason scores determined both from transrectal ultrasound guided biopsy and prostatectomy specimens were calculated as described in the literature (13). Clinical and pathological staging were done according to TNM staging system. Patients with biochemical recurrence (PSA 0.4 ng/ml or greater, Hybritech Tandem assay) at follow up were identified.

Transrectal ultrasound of the prostate was performed using a scanner with a 7.5 MHz transducer. The prostate was scanned in the transverse and sagittal planes with the subject in the left lateral decubitus position. Prostate volume was determined with the formula for a prolate ellipsoid (width x length x height x 0.52). PSA density was calculated by dividing total serum PSA by prostate volume measured with the prolate ellipsoid formula during transrectal ultrasound.

The surgical specimen weighed, its entire external surface was inked and it was fixed in 10% formalin for 24 hours. After fixation the apical, basal, and urethral margins were removed for histopathological examination. The prostate gland and seminal vesicles were step-sectioned at 3 mm. intervals perpendicular to the long axis (apical-basal) of the gland and each section, which was stained with hematoxylin and eosine, was examined histopathologically.

RESULTS

Between July 1992 and December 1997, 30 patients, whose serum PSA levels were between 4.0 to 10.0 ng/ml, underwent radical retropubic prostatectomies for clinically localized prostatic carcinoma. The age of the patients ranged from 56 to 76 years and the mean age was 63.83 ± 5.01 years. Preoperative PSA levels ranged between 4.0 to 10.0 ng/ml. The mean value was 7.0 ± 1.60 ng/ml. The follow up period of the patients was between 21 and 78 months. The mean follow up was 49.8 ± 14.79 (median: 51) months.

Prostate volume ranged from 18 to 110 cc and mean prostate volume was 44.81 ± 23.02 cc (median: 42.50 cc.). PSA density ranged from 0.08 to 0.55 ng/ml/cc, mean PSA density was 0.19±0.11 ng/ml/cc. (median: 0.15 ng/ml/cc).

Using 0.15 PSA density as the cut point, 12 (40%) patients had PSA density < 0.15 ng/ml/cc. Of these, radical prostatectomy specimen pathological stage was pT2 in 4 (33%) cases, pT3a in 5 (42%), pT3c in 3 (25%). No patient had lymphatic invasion (Table I). PSA density was ≥ 0.15 ng/ml/cc in 18 (60%) patients. Of these, radical prostatectomy specimen pathological stage was pT2 in 7 (39%) cases, pT3a in 8 (44%), pT3c in 3 (17%) and 1 patient (6%) had lymph node positive (Table II).

Table I. Histopathological evaluation: PSA density <0.15 ng/ml/cc

	n (%)	Lymph Nodes (+)
pT2	5 (42)	-
pT3a	4 (33)	-
pT3c	3 (25)	-
Total	12	

Table II. Histopathological evaluation: PSA density ≥ 0.15 ng/ml/cc

	n (%)	Lymph Nodes (+)
pT2	8 (44)	-
pT3a	7 (39)	-
pT3c	3 (17)	1
Total	18	

Clinical and pathological staging were done according to TNM staging system. Clinical staging revealed predominantly T2b and T2c lesions. There were 1 (3.3%) patients with T1a, 3 (10%) with T1b, 1 (3.3%) with T1c, 6 (20%) with T2a, 9 (30%) with T2b, and 10 (33.3%) with T2c. Pathological staging revealed predominantly pT2 and pT3a lesions. Radical prostatectomy specimen pathological stage was pT2 in 11 (37%) cases, pT3a in 13 (43%), and pT3 in 6 (20%). One patient (3%) had lymphatic invasion (Table III).

The follow up of PSA levels revealed recurrence in 6 (20%) patients. The period of these recurrence mean time to recurrence was 17.3 ± 19.54 (median: 24.5 months) months with a range of 3 and 53 months. Five of 6 patients (83%) had PSA density ≥ 0.15 ng/ml/cc (Table IV).

DISCUSSION

Prostatic cancer is the most commonly diagnosed cancer in men and death rates are second only to those for lung neoplasm (14). A third of men older than 50 years have incidental carcinoma found at autopsy, yet clinical prostate cancer develops in only 10% of men during their lifetime (15). The treatment of localized prostate cancer is still a controversial topic. Many variables are involved in the long-term prognosis of prostate cancer (stage, grade, age, biological activity, and so on) and the spectrum of therapeutic options is considerably broad (watchful waiting, radical surgery, hormonal therapy, radiotherapy) (16). Radical prostatectomy is considered the gold standard treatment for localized prostate cancer and it is generally considered most effective when the disease is organ confined at surgery (17). Therefore, preoperative evaluation should aim at the most precise staging, ruling out extracapsular disease or nodal metastases. Serum PSA elevation correlates with tumor volume, grade, and pathological stage (18). According to previous studies PSA was elevated 3.5 ng per ml for every cc of cancer, a level at least 10 times that was observed for benign prostatic hyperplasia (19). Therefore, serum PSA level less than 4.0 ng/ml indicates lower cancer risk, whilst levels 4.0-10.0 ng/ml indicate medium cancer risk and level more than 10.0 ng/ml indicate high cancer risk (20). It has been reported that of patients with prostate cancer, about 23% patients with BPH and no clinical evidence of prostate cancer have PSA values of 4.0-10.0 ng/ml, and 5% are greater than 10.0 ng/ml (1).

In our series, we found that radical prostatectomy specimen pathological stage was pT2 in 11 (37%) cases, pT3a in 13 (43%), and pT3c in 6 (20%). One patient (3%) had lymphatic invasion (Table III). Several investigators reported that organ confined was between 9% to 82%, which was a wide range, whilst seminal vesicle invasion was between 0% to 4%, and lymphatic invasion was between 0% to 31% in patients who had undergone radical retropubic prostatectomy (RRP) with PSA levels between 4.0 to 10.0 ng/ml (16, 21-26). This shows that the biological behavior of prostate cancer is ever changing and tissue invasion outside the prostate gland is also possible with serum PSA levels of 4.0-10.0 ng/ml.

PSA density was first introduced by Benson et al to increase the predictive value of PSA (8). However, contradictory results have limited its usefulness. Factors limiting the accuracy of PSA density include the difficulty of accurate prostate volume measurement by transrectal ultrasound, demonstrated variability of PSA density with aging and variable distribution of glandular and stromal components in BPH (27-29). The role of this test in the staging of

Table III. Histopathological evaluation in 30 patients who had undergone RRP with PSA levels between 4.0 to 10.0 ng/ml

	n (%)	Lymph Nodes (+)
pT2	11 (37)	-
pT3a	13 (43)	-
pT3c	6 (20)	1
Total	30	

Table IV. Patients with biochemical recurrence (PSA 0.4 ng/ml or greater, Hybritech Tandem assay) at follow up

Patients no	Age (years)	PSA	PSA density	Clinical stage	Biopsy Gleason score	Specimen Gleason score	Pathological stage	Lymph invasion	Recurrence time (months)
1	63	5.5	0.21	T2c	6	6	pT3a	-	30
2	74	7.4	0.16	T2a	5	6	pT3c	+	3
3	59	9	0.25	T2c	6	6	pT3c	-	19
4	59	10	0.28	T2b	5	5	pT3a	-	53
5	64	5.4	0.27	T2a	6	7	pT3c	-	46
6	60	4	0.13	T2a	6	5	pT3a	-	12

prostate carcinoma has not been clarified. Bazinet et al evaluated 565 consecutive patients referred for prostatism, suspicious digital rectal examination or elevated PSA and concluded that use of PSA density at the best of cutoff value (0.15 ng./ml./cc.) could safely decrease the number of patients undergoing systematic biopsies without significantly compromising cancer detection (30). When using 0.15 PSA density as the cut point, we found that 18 (60%) patients had PSA density ≥ 0.15 ng/ml/cc. Of these, radical prostatectomy specimen pathological stage was pT2 in 7 (39%) cases, pT3a in 8 (44%), pT3c in 3 (17%) and 1 patient (6%) had positive lymph node (Table II). Akdaş et al, retrospectively analyzed 32 patients who underwent radical retropubic prostatectomy as the primary treatment for clinically localized disease and extracapsular extension was found in 21 patients. They found that an accuracy rate of 62.5% for a prostate specific antigen density of 0.15 ng/ml/cc (26). Zlotta et al retrospectively analyzed 198 patients who underwent radical retropubic prostatectomy with clinically localized prostate cancer and serum PSA less than 10.0 ng/ml. They found that prostate specific antigen density levels were significantly higher in extracapsular disease than organ confined cancer (0.17 versus 0.26 ng/ml/cc, $p < 0.0001$) (31).

There is still some controversy regarding the treatment algorithm in cases with prostate cancer and PSA levels between 4.0 to 10.0 ng/ml. Recent studies, have underlined that free to total serum PSA ratio has a higher specificity than PSA density for cases with PSA levels between 4.0 to 10.0 ng/ml in detecting and screening prostate cancer (32-36). Free to total PSA ratio has become a better marker (11). On the other hand, PSA density has shown to be ≥ 0.15 ng/ml/cc in 60% cases who had undergone radical retropubic prostatectomy for localized prostate cancer and had PSA levels between 4.0 to 10.0 ng./ml. Furthermore, 39% of them had organ confined disease while 6% had lymphatic invasion.

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