Prostate Specific Antigen Nadir After Radical Cystoprostatectomy in Patients with Benign Prostatic Tissue: A Benchmark to Define Biochemical Recurrence After Radical Prostatectomy

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Purpose: Biochemical failure after radical prostatectomy has been defined based on retrospective studies in men who underwent RP for localized prostate cancer. Nevertheless, retrospective strategy and possibility of extra-prostatic extension overshadowed the accurateness of the aforementioned cut-off value. To define a more precise PSA nadir value, we estimated serum PSA after cystoprostatectomy in cases with bladder urothelial cancer and no evidence of prostate cancer.

Materials and Methods: Study population consists of 52 subsequent patients who underwent radical cystoprostatectomy for muscle-invasive bladder cancer between December 2010 and December 2013. Patients with prostate adenocarcinoma and/or high grade prostate intraepithelial neoplasia were excluded from enrollment. Other exclusion criteria were prostate involvement with urothelial carcinoma, neoadjuvant or adjuvant chemotherapy and radiation therapy. Between all cases, 41 were enrolled for study. Serum PSA level was measured using immunochemiluminescence method from 6 months to 3 years after operation in study participants.

Results: Forty-one patients with mean age of 66.4 ± 8.9 years were assessed in this study. Average serum PSA level after radical cysto-prostatectomy was: 037 ± .031 ng/mL (from .002 to .1). Serum PSA level was not impressed with type of diversion or interval between operation and PSA measurement. Average serum PSA level in this study was meaningfully lesser than .2 ng/mL which is contemplated as PSA nadir value after RP.

Conclusion: Serum PSA level of 0.2 ng/mL as the definition for biochemical recurrence after RP may delay salvage treatment. Our results showed that cut off value of □0.1 ng/mL may be more precise in the era of early salvage treatment.

Keywords: biochemical recurrence; nadir; prostate specific antigen; radical cystectomy; radical prostatectomy.

INTRODUCTION

With the advent of prostate specific antigen (PSA) in 1980, clinicians were able to recognize prostate cancer at an early stage when the disease is amenable to definitive treatments.[1] PSA is also a valuable biomarker for early detection of disease recurrence after initial definitive treatment i.e. radical prostatectomy and radiation therapy. PSA increase to a certain threshold after radical prostatectomy, biochemical recurrence, may predict local or distant recurrence in future. The natural history after biochemical recurrence is variable and biochemical recurrence does not translate to metastatic disease and death in all patients.[2] The median time from biochemical recurrence to metastatic disease has been reported to be 8 years.[3] Definition of biochemical recurrence may be of utmost importance in the diagnosis of treatment failure and timely use of salvage treatments. Some investigators have proposed a cut-off value of .4 ng/mL for definition of biochemical recurrence.[4,5] According to American Urological Association and American Society of Clinical Oncology guidelines an initial and confirmatory PSA value of ≥ .2 ng/mL after radical prostatectomy is considered as biochemical recurrence.[6] National Comprehensive Cancer Network has defined biochemical failure as a detectable PSA (while it was undetectable after surgery) and 2 subsequent rises. However there is no definition of detectable PSA.[7] Therefore, there is no consensus on the definition of biochemical recurrence after radical prostatectomy in the literature; in addition, the presence of benign prostatic tissue after radical prostatectomy, and extra-prostatic sources of PSA may interfere with postoperative PSA measurements and precise definition of biochemical recurrence. We conducted this study to assess postoperative PSA in men who underwent radical cystoprostatectomy for urothelial bladder cancer and no pathological evidence of prostate cancer. The distribution of PSA values in this population can be used as a benchmark for determining the optimal nadir value as well as defining detection threshold in the era of ultrasensitive PSA.

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Table 1. Association between post-cystectomy serum PSA level and patient characteristics

Patient Characteristics		No. (%)	Mean Serum PSA Level (ng/mL)	*P*-value
Age	≤ 65	18 (43.9)	.042 ± .040	.703[a]
	> 65	23 (56.1)	.034 ± .027	
Type of urinary diversion	Ileal conduit	18 (43.9)	.033 ± .027	.906[b]
	Orthotopic neobladder	17 (41.5)	.040 ± .038	
	Continent cutaneous pouch	6 (14.6)	.042 ± .040	
Pathologic stage	T1	14 (34.1)	.037 ± .042	.566[b]
	T2	18 (43.9)	.042 ± .029	
	T3	9 (22.0)	.030 ± .027	

Abbreviations: PSA, Prostate Specific Antigen.
[a] Mann Whitney test
[b] Kruskal Wallis Test

MATERIALS AND METHODS

All consecutive patients who underwent radical cystoprostatectomy with curative intent between December 2010 and December 2013 were considered for enrollment in this prospective cohort. Patients with prostate adenocarcinoma or high grade intraepithelial neoplasia in the final cystoprostatectomy specimen were excluded from enrollment. Additional exclusion criteria were prostate involvement with urothelial carcinoma, neoadjuvant or adjuvant chemotherapy and radiation therapy. It should be noted that all surgeries were performed by or under supervision of one urologist (SYH). Histopathological evaluation of prostatic tissue in cystoprostatectomy specimens was performed in slices with 3 micrometers in thickness. Any evidence of prostatic adenocarcinoma and/or high grade prostatic intraepithelial neoplasia were considered as exclusion criteria. A total of 41 patients were eligible for the study. The serum PSA level was measured by ECLIA (Electro chemi luminesence immunoassay) between 6 months and 3 years after surgery. Institutional review board approved the study and written informed consent was obtained from all participants.

Statistical analysis

Statistical Analysis was performed using SPSS version 16 (SPSS Inc., Chicago, IL, USA). Frequency of patients with undetectable PSA was determined. Different cut-off values were used to define undetectable PSA. Using t-test, mean value of serum PSA after cystoprostatectomy was compared to 0.2 as the threshold of biochemical recurrence. In addition, the effect of age, disease stage, and time elapsed from surgery as well as type of urinary diversion on postoperative serum PSA was evaluated. P value of less than 0.05 was considered as statistically significant.

RESULTS

A total of 41 patients with mean age of 65.1 ± 8.7 (range from 48 to 83) were evaluated in this study. Mean serum PSA after radical cystoprostatectomy was .037 ± .031 ng/mL ranging from .002 to .1. When compared to cut off values .1 and .2 (current definition of biochemical recurrence after radical prostatectomy), the mean value of serum PSA after cystoprostatectomy was significantly lower ($p < .001$, one sample *T*-test). Neither of patients had serum PSA above .1 and 30 of 41 patients (73.2%) had serum PSA less than .05. We also noted that 20 (48.8%) and 13 (31.7%) patients had PSA ≤ .03 and ≤ .01 respectively. No correlation was found between postoperative PSA value and interval between surgery and PSA measurement (r = .036, $p = .821$; Pearson correlation). To assess the effect of age on postoperative serum PSA level, patients were dichotomized into 2 groups (younger and older than 65). Mean serum PSA was comparable between different age groups (**Table 1**). Similarly, we did not find any association between either pathologic stage of urothelial cancer or type of urinary diversion and serum PSA level (**Table 1**).

DISCUSSION

According to our findings the majority of patients after cystoprostatectomy have undetectable serum PSA level and applying ultrasensitive PSA assay showed that more than 70% of patients had PSA less than .05 and neither of patients had PSA greater than .1 ng/mL. Based on these findings we expect similar PSA nadir values in patients with localized prostate cancer who undergo radical prostatectomy. Therefore, applying ultrasensitive PSA to detect biochemical recurrences after radical prostatectomy provides an opportunity to initiate early salvage treatment in eligible patients. Despite improvements in surgical methods and case selection, about 25% to 41% of patients will show prostate specific antigen (PSA) relapse 10 years after operation.[8-10] The likelihood of recurrence is even higher when radical prostatectomy is performed in patient with high risk advanced prostate cancer. Therefore, a significant proportion of patients after radical prostatectomy require adjuvant treatment and determining proper cut off values for initiation of salvage treatment is of utmost importance. A measureable PSA level after operation may be secondary to residual benign tissue rather than residual malignancy or existence of micrometastatic disease.[4,11] Measuring PSA after cystoprostatectomy in patients with benign prostatic tissue provides an opportunity to assess the role of benign residual tissue and/or extra-prostatic sources of PSA in post radical prostatectomy nadir value. According to our findings remaining benign tissue and/or extraprostatic sources of PSA is not associated with values greater than .1 and remains below .05 in majority of patients. Several studies have investigated the importance of PSA nadir value after radical prostatectomy. Sokoll et al. in a study assessing 754 men who underwent radical prostatectomy showed that a lower PSA nadir value (i.e .01 vs. .1 ng/mL) is an independent predictor of biochemical recurrence.[12] Other studies also showed that in the range of .01 and .1, higher PSA nadir is associated with increased risk of biochemical relapse.[13,14] PSA nadir value has also been shown to be an independent predictor of biochemical recurrence in the range of .001 and .01 ng/mL. In another study Kang et al. using ultrasensitive PSA as-

say, proposed that cut-off value of .03 is an independent predictor of biochemical recurrence. This ultrasensitive PSA relapse criterion of ≥ .03 ng/mL predicted all eventual relapses with high sensitivity (100%) and specificity (96%) and provided a median 18 months lead time advantage over the standard definitions of PSA relapse.[15] Lowering the threshold and applying advanced ultrasensitive PSA assays that detect concentrations as low as .001 ng/mL are associated with a high rate of false positive findings. In addition, it is not necessary to measure extremely low values as residual benign and malignant cells produce higher amounts of PSA. Some investigators have questioned the accuracy of ultrasensitive PSA at cut-off values in the .01 - .1 ng/mL range as overlap of PSA values was found in recurrent and non-recurrent patient groups.[16] Despite all limitations associated with the use of ultrasensitive PSA, current definition of PSA failure may be flawed. In the era of early salvage treatment values less than .2 ng/mL should not be considered undetectable.

Using ultrasensitive assays and lowering the cut-off value for the definition of biochemical recurrence provide an opportunity to detect the biochemical recurrence sooner when salvage treatment might be more effective. Mir et al. evaluating different cut off values for defining biochemical recurrence, proposed PSA ≥ .05 ng/mL as a criteria for therapy[14]. Our findings also showed that majority of patients had PSA less than 0.05 after cystoprostatectomy. One limitation in the present study was the absent of re-review of pathology slides to confirm the absence of prostate cancer in the specimens; however, all specimens were assessed by a limited number of uropathologists who are expert in the field of urologic oncology. More recently there has been interest in using salvage radiation therapy instead of adjuvant treatments in patients with adverse pathologic features after radical prostatectomy. Although 3 different randomized trials showed improved outcomes in patients with adverse pathologic features who receive adjuvant radiation therapy compared to "wait and see" approach[17-19], recent evidence questions the benefit of adjuvant compared to salvage radiation therapy in a subset of patients. One study showed that only 17% of men with adverse pathologic features after radical prostatectomy progressed to biochemical recurrence.[20] Therefore, applying salvage radiation instead of adjuvant treatment has the potential to prevent overtreatment in a significant proportion of patients. Applying ultrasensitive PSA has also the potential to safely prevent unnecessary adjuvant treatments. The definition of biochemical recurrence also should be refined to prevent delays in salvage treatment.

CONCLUSIONS

By determining the serum level of PSA in patients whose prostate tissue is completely removed and have no malignancy, we can achieve an accurate definition for PSA nadir value, which is comparable to a successful curative radical prostatectomy without micrometastasis. PSA nadir in the present study was less than 0.1 ng/mL in all patients indicating that a lower cut-off value might be more accurate compared to the current definition of biochemical recurrence and prevents delays in salvage therapy.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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