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REVIEW ARTICLE

Association of Prostate-Specific Antigen Density and Gleason score of Positive Surgical Margin with Biochemical Recurrence in Prostate Cancer

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Abstract: **Objective:** We aimed to investigate the association between prostate specific antigen (PSA) density and Gleason score of the positive surgical (PSM) margin after radical prostatectomy with biochemical recurrence in patients with prostate cancer. **Methods:** In this retrospective cohort study, patients with prostate cancer referred to Hasheminejad Hospital in Tehran, Iran, during 2009-2019, who underwent radical prostatectomy were enrolled through the convenience sampling method. The follow-up period was determined as at least one year after radical prostatectomy to determine biochemical recurrence. Prostate-specific antigen density (PSAD) and the Gleason score of surgical specimen and positive surgical margins (PSM) were evaluated and their association with biochemical recurrences was investigated. **Results:** One hundred and three patients were assessed. The overall biochemical recurrence rate was 48.5% with a mean follow-up of 24 months (12-42 months) and an average time to biochemical recurrence of 18 months (16-20 months). BCR-free (Biochemical recurrence-free) survival rates of patients divided based on the PSAD cut-off point (0.205 ng/ml/cc) were significantly different using the log-rank test (P= 0.008) (85.7%, 57.1%, and 14.3% for values ≤ 0.205 ng/ml/c versus 55.8%, 20.9%, and 0% for values 0.205 ng/ml/cc, respectively for 1-, 2- and 3-year survival). Moreover, Cox regression showed that the Gleason score of PSM, the Gleason score of the surgical specimen, and the PSAD predicted biochemical recurrence more, respectively. **Conclusions:** PSAD and PSM Gleason scores were strong predictors of biochemical recurrence after radical prostatectomy and their use along with other common indicators including tumor grade and stage and PSA level can increase the accuracy of risk assessment in patients with prostate cancer.

Keywords: Prostate cancer, Biochemical recurrence, Positive surgical margin, PSA density, Gleason score

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1. Introduction

Prostate cancer is the most common cancer and the second leading cause of cancer-related mortality in men (1, 2). In the United States, more than 230,000 new cases and 44,000 deaths are annually attributed to prostate cancer (3). Prostate cancer incidence has almost doubled in recent years which is a great concern. Therefore, periodic screening, as early detection can reduce the disease burden and the treatment expenses (4, 5). Moreover, the relatively long doubling time of cancer cells in patients with prostate cancer (3 to 4 years) emphasizes early screening (6). Early detection of prostate cancer also decreases the probability of distant metastases and greatly improves the patients' quality of life (7, 8).

Biochemical recurrence is defined as a rise in serum Prostate-Specific Antigen (PSA) to 0.2 ng/mL and a confirmatory value of 0.2 ng/mL or greater following radical prostatectomy usually without clinical signs of disease progression (9). This is the most common type of recurrence after prostate cancer surgical treatment and is observed in 30% of the patients. Patients with biochemical recurrence have a poorer prognosis and are more likely to experience metastasis and lower survival. Therefore, identifying the predictors of biochemical recurrence after radical prostatectomy is necessary to decide which patients would benefit more from multimodal adju-

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vant treatment (10-12).

Based on previous studies, various indicators such as the Gleason score, preoperative serum PSA level, seminal vesicle invasion, tumor stage in pathology, and lymphatic invasion have been linked with biochemical recurrence (13, 14). However, research has mainly examined the role of each of these factors separately and the interaction between them is not very clear. Moreover, the role of PSA Density and Gleason score of the positive surgical margins has been less investigated. The positive surgical margin (PSM) has a prevalence 6% to 41% in various studies (15), but its prognostic role is controversial. Accordingly, in this study, we aimed to investigate the association between PSA Density and the Gleason score of the PSM of radical prostatectomy with biochemical recurrence in patients with prostate cancer.

2. Method

This retrospective cohort was done on all patients with prostate cancer referred to Hasheminejad Hospital, Tehran, Iran, during 2009-2019, who underwent radical prostatectomy. Of the 817 patients who underwent surgery, 103 (12.6 %) with a PSM during the post-operation follow-up period were included. Inclusion criteria were patients with prostate cancer who underwent radical prostatectomy and had a PSM, willingness to participate and complete document information, who did not receive adjuvant radiation or hormonal therapy prior to biochemical recurrence. Exclusion criteria were mesenchymal and urothelial prostate cancer and follow-up period less than one year.

All Gleason grading was done by one uropathologist. The PSA Density is the PSA level (ng/mL) divided by the volume of the prostate gland (mL) and using transrectal ultrasonography and serum PSA level before surgery. Also, serum PSA level was extracted from medical records in the postoperative phase and biochemical recurrence was identified. The follow-up period was determined as at least one year after radical prostatectomy to determine biochemical recurrence. The PSA density and the Gleason score of the positive margins were extracted and their association with biochemical recurrences was investigated.

2.1. Data analysis

Mean and standard deviation, frequency and percentage were used to describe quantitative and qualitative data. Kolmogorov-Smirnov test was used to evaluate the normality of quantitative data. Independent t-test and Chi-square or their non-parametric counterparts such as Mann-Whitney and Fisher's exact tests were used where appropriate. However, ROC, log-rank test, and Cox regression were used to find the predictive factors for biochemical recurrence. P-value below 0.05 was considered as statistically significant. All data analysis steps were done using SPSS software version 16 (SPSS Inc. Chicago, Il, The USA).

2.2. Ethical issues

All the steps were performed according to the Helsinki Declaration. Patients' information was used without disclosing their identities. Moreover, the study protocol was approved by the Ethics Committee of Iran University of Medical Sciences, Tehran, Iran (IR.IUMS.FMD.REC.1399.360).

3. Results

One hundred and three patients entered the study. The mean±SD age of the patients was 64.88±5.91 years (range: 45-76 years). The mean±SD PSA density was 0.22± 0.06 ng/ml/cc. The mean size of the PSM was 2 ± 1.32 mm. Table 1 presents the baseline demographic and pathological characteristics of the study participants.

There was no significant statistical difference between age and biochemical recurrence (P=0.43). On the other hand, there was a statistically significant association between PSA density and biochemical recurrence(P<0.001). However, there was a significant correlation between the Gleason score of the surgical specimen or the Gleason score of the PSM with biochemical recurrence (P =0.003, 0.013, Table 2).

Moreover, ROC showed that the length of PSM, the Gleason score of PSM, or the surgical specimen could predict biochemical recurrence to some extent, despite the fact, PSAD could strongly predict biochemical recurrence. As PSA density at the cut-off point of 0.205 ng/ml/cc had a sensitivity of 86% and a specificity of 83% in the prediction of biochemical recurrence. Figure 1 shows the ROC curve results.

Besides, 1-, 2- and 3-years BCR-free(Biochemical recurrence-free) survival rates were 60%, 26% and 2%, respectively. Nonetheless, BCR-free survival rates of patients divided according to the PSAD cut-off point (0.205 ng/ml/cc) were significantly different using the log rank test (p = 0.008) (85.7%, 57.1% and 14.3% for values ≤ 0.205 ng/ml/c versus 55.8%, 20.9% and 0% for values 0.205 ng/ml/cc, respectively for 1-, 2- and 3-year survival).

In addition, Cox regression showed that the Gleason score of the PSM, the Gleason score of the surgical specimen, and PSA density predicted biochemical recurrence most, respectively (Table 3).

4. Discussion

Radical prostatectomy is the gold standard treatment for patients with clinically localized prostate cancer (16-18). Some patients with prostate cancer may present with lymph node invasion (LNI), seminal vesicle invasion (SVI), and extra-prostate extension (EPE) after radical prostatectomy, which may affect the prognosis of cancer, recurrence rate, and sur-

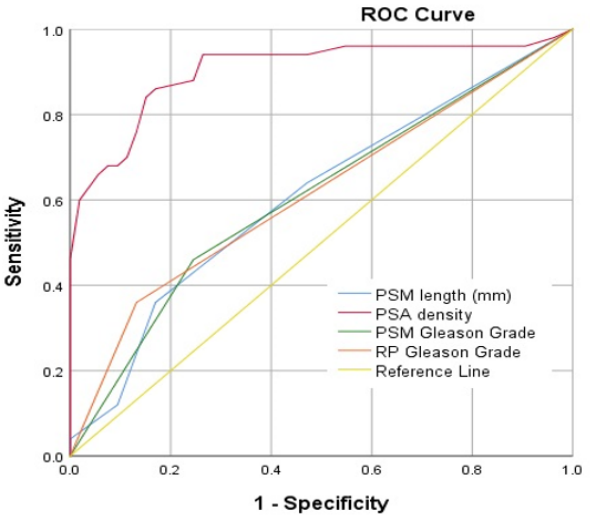

Figure 1: ROC results of prognostic factors for biochemical recurrence.

vival (19, 20). Patients with undesirable pathological features after radical prostatectomy require adjuvant therapy such as radiation or hormonal therapy (21, 22). The Gleason score, PSA density, and PSA velocity are parameters used to predict poor pathological features. However, the results are controversial regarding the role of PSA density. The difference in results is multifactorial. Multivariate analysis has not been used in many studies, and in others, the sample size was small (23, 24). However, few studies examined the association between PSM Gleason score and biochemical recurrence. Song and colleagues showed that the Gleason score and percent tumor volume (PTV) were two independent prognostic factors for biochemical recurrence (25).

In our study, the overall biochemical recurrence rate was 48.5% with a mean follow-up of 24 months (12 to 42 months) and an average time to biochemical recurrence of 18 months (16-20 months). The mean time to biochemical recurrence was 20 to 38 months in the literature (26, 27), which was lower in our study. Although biochemical recurrence often occurs in the first 3 years after radical prostatectomy, longer follow-up is necessary, as some patients may recur even after 15 years (28). There was no difference in the mean age of the patients in terms of biochemical recurrence. However, the mean PSA density and length of positive surgical margin were significantly higher in patients with biochemical recurrence. Adverse Gleason patterns, both in the surgical specimen and in the PSM, were also more prevalent in patients with biochemical recurrence.

Evaluation of the power of each variable in predicting the incidence of biochemical recurrence in our study showed that PSA density with an AUC (area under the curve) of 0.903 and sensitivity and specificity of 86 and 83 at the cut-off point of 0.205 ng/ml/cc was the strongest indicator predicting biochemical recurrence after radical prostatectomy. Moreover, the length of the positive margin with a sensitivity and specificity of 94% and 52.8% at a cut-off point of 1.5 mm, had a weak power to predict biochemical recurrence. On the other hand, the Gleason score (low grades including 3 + 3 and 3 + 4 patterns, vs. higher grades of 3 + 4, 4 + 4, and 5 + 4 patterns), in both surgical specimen and PSM, had a high specificity and a low sensitivity to predict biochemical recurrence. In one study., the mean PSAD was 0.27 (standard deviation 0.17) and there was a significant association between PSAD and pathological features. They concluded that PSA, PSA density, and the Gleason score should be considered together to more accurately predict poor pathologic features of prostate cancer (29). Moreover, Radwan and co-workers concluded that PSA density was a strong predictor of advanced pathological features and biochemical recurrence after radical prostatectomy (30). In contrast, another investigation indicated that the use of preoperative PSAD, compared to PSA, had only a small role in predicting poor pathological findings and biochemical recurrence after radical prostatectomy, which is contrary to our results (23). They used three cut-off points for PSA density, which is different from our study. Such inconsistent results might be due to different study designs and statistical modeling.

However, more studies are required with larger sample sizes to elucidate the role of PSA density versus serum PSA level in determining the risk of biochemical recurrence.

Furthermore, in another study, both PSA and PSA density levels were found to be independent predictors of biochemical recurrence. They claimed that since the PSA level is as effective as PSA density in predicting chemical recurrence, additional efforts to calculate PSA density may not be rational (31). In this study, we found PSA density as an independent predictor of biochemical recurrence, but the degree of agreement between PSA density and PSA measurements in diagnosing this outcome was not calculated, which could be evaluated in further trials. Nevertheless, some other studies such as Kang (32), Koie (33), and Sfoungaristos (34) and their colleagues PSA density was also introduced as a valuable parameter in estimating the risk of biochemical recurrence. According to Evren and co-workers the Gleason score before surgery in the group with recurrence was significantly higher than in those without recurrence. Besides, the length of positive surgical margin in the group with biochemical recurrence was 7.4±4.4 mm, which was significantly higher than those without recurrence (4.7±3.8 mm) (35). This is in line with our study, showing the importance of surgical margins at radical prostatectomy.

Some other studies also indicated that the Gleason score should be recorded in the surgical margin (36). In our study, Cox regression showed that the Gleason score of PSM was

an important predictor of biochemical recurrence, which should be considered in clinical risk assessments. Consistent with our findings, researchers indicated that high Gleason scores in PSM have a poor prognosis and are associated with biochemical recurrence (37).

Noteworthy, the binary regression odds ratio for biochemical recurrence was 30 comparing values less and greater than 0.205 ng/ml/cc for PSA density, while in the Cox regression this risk ratio was 2.55. This indicates a non-linear relationship between PSA density and biochemical recurrence so that with the addition of the time factor, the predictive power of PSA density was decreased. Therefore, it seems that PSA density measurement in the early months and years after radical prostatectomy can adequately predict biochemical recurrence and is not suitable for long-term follow-ups. We suggest performing larger clinical trials with more sample size trying to design a predictive model including clinical and pathological tumor features for better prediction of biochemical recurrence.

The main strength of this study was the large size of the cohort of patients participating in the study. The other strength is its easy applicability and its reproducibility in a completely independent external cohort; however, since this study is done in a retrospective fashion, it has all the disadvantages of this type of study. Hence, there is a need for prospective models for further validation, taking care to include patients from multiple ethnic backgrounds. In addition, it is expected that more quantitative measures of bone metastasis and novel clinical parameters such as the bone scan index are considered for a more comprehensive evaluation and follow-up of patients with prostate cancer.

5. Conclusion

PSA density and PSM Gleason score are strong predictors of biochemical recurrence after radical prostatectomy and their use along with other common indicators including tumor grade and stage and PSA level can increase the accuracy of risk assessment in patients with prostate cancer.

6. Appendix

6.1. Acknowledgment

None.

6.2. Conflict of interest

The authors declare that they have no competing interests.

6.3. Funding support

None.

6.4. Author's contributions

All the authors have the same contribution.

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Table 1: Baseline characteristics of the study participants.

Variable		Mean	Standard deviation
Age, year		64.88	5.91
Positive surgical margin length, mm		2	1.32
PSA density (ng/ml/cc)		0.22	0.06
		Frequency	**Percentage**
Biochemical recurrence		50	48.5%
Gleason score of the surgical specimen	3 + 3	3	2.9%
	3 + 4	75	72.8%
	4 + 3	19	18.4%
	4 + 5	6	5.8%
Gleason score of the PSM*	3 + 4	67	65%
	4 + 3	21	20.4%
	4 + 4	8	7.8%
	4 + 5	7	6.8%

***PSM**: positive surgical margin.

Table 2: Comparing clinical and pathological features based on biochemical recurrence.

Variable		Without BCR (53 patients)	With BCR (50 patients)	P-value
Age, (Mean ± SD), year		64.43 ± 6	65.36 ± 5.84	0.43
PSM length, (Mean ± SD), mm		1.74 ± 0.96	2.28 ± 1.57	0.41
PSA density (ng/ml/cc)		0.17 ± 0.03	0.26 ± 0.05	< 0.001
Gleason score of the surgical specimen	3 + 3	3 (5.7%)	0	
	3 + 4	43 (81.1%)	32 (64%)	
	4 + 3	7 (13.2%)	12 (24%)	0.003*
	4 + 5	0	6 (12%)	
Gleason score of the PSM	3 + 4	40 (75.5%)	27 (54%)	
	4 + 3	10 (18.9%)	11 (22%)	0.013*
	4 + 4	3 (5.7%)	5 (10%)	
	4 + 5	0	7 (14%)	

***Fisher's Exact Test, BCR;**: Biochemical Recurrence, **PSM**; Positive Surgical Margin

Table 3: Cox regression analysis for risk factors of biochemical recurrence.

Variable	Hazard ratio (HR)	95% confidence interval (CI)	P-value
PSA density level (less than 0.205 vs. more than 0.205 ng/ml/cc)	2.555	6.138 – 1.064	0.036
PSM length (less than 1.5 vs. more than 1.5 mm)	1.348	2.416 – 0.752	0.315
PSM Gleason degree (low vs. high)	3.107	5.662 – 1.705	0.001
Surgical specimen Gleason degree (low vs. high grade)	2.584	4.719 – 1.414	0.002