Original Article

A Ten-Year Study of Prostate Cancer: A Southern Iranian Experience

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Received: 01 March 2017
Revised: 11 March 2017
Accepted: 17 May 2017

Abstract

Background: Prostate cancer is the most common malignancy among the male population in the United States and the 3rd most common non-skin cancer among men in Iran. Its prevalence has shown a rising trend in recent decades. The aim of this study was to report the epidemiological features of prostate cancer in patients referred for prostate biopsy in the south of Iran and to evaluate the accuracy of the levels of the prostate-specific antigen (PSA) and the PSA-density (PSAD) as well as the extension of the disease in the prediction of the biological behavior of prostate cancer.

Methods: This is a retrospective study on the medical records of 1982 consecutive patients who underwent transrectal ultrasound-guided biopsy due to an abnormal digital rectal examination and/or an elevated PSA level following referral from the Urology Ward to the Radiology Department of Shahid Faghihi Hospital in Shiraz, southern Iran, between December 2003 and July 2014.

Results: The overall cancer detection rate was 33.1%. Although the cancer was more prevalent among the elderly patients, a significant fraction (7%) of the patients were aged < 55 years. The sensitivity and specificity of the PSA were 97.4% and 8.7% and those of the PSAD were 82.9% and 52%, respectively. Of the 637 patients with prostate cancer, 250 (39.2%) had unilateral disease, 378 (59.4%) had bilateral disease, and 9 (1.4%) had inner-gland involvement. Most of the patients with bilateral involvement had high-grade Gleason scores.

Conclusion: Our study underlines the relationship between age and the frequency of cancer; the levels of the PSA and the PSAD and the Gleason score; and the extent of tumor involvement and the grade of prostate cancer and also highlights the significance of screening, especially in younger patients.

Please cite this article as: Lotfi M, Beheshti R, Rouhezamin MR, Rezaianzadeh A, Farhadi P, Daneshi Z. A Ten-Year Study of Prostate Cancer: A Southern Iranian Experience. Iran J Med Sci. 2018;43(4):372-379.

Keywords ● Prostate cancer ● Screening ● Neoplasm grading ● Prostate-specific antigen

What's Known

- Prostate cancer is most common malignancy among male population in the United States and third common non-skin cancer among men in Iran. The prevalence of this disease is following a rising trend in recent decades
- Biopsy is gold standard for diagnosis of prostate cancer in men with elevated PSA level

What's New

- Our study showed a notable percent (7%) of patients suffer from prostate cancer are diagnosed at age of 55 or younger, which can lead further studies about epidemiologic behavior of prostate cancer and may change the beginning age of screening
- Most patients with bilateral involvement had high grade Gleason scores

Introduction

Prostate cancer is the most common malignancy and the 2nd leading cause of cancer-associated death among the male population in the United States.[1] It is the 3rd most common non-skin cancer among men in Iran.[2] The value of lives lost due to prostate cancer is estimated to be about 30 billion U.S. dollars per year.[3] The prevalence of this disease has demonstrated a rising trend in recent decades.[4]

The epidemiological behavior of cancers, specifically prostate cancer, is not the same worldwide.[2,5] The early incidence of some cases of breast cancer has been implied in the Iranian population when compared with the Western pattern of the disease in several epidemiological studies.[6] These studies have reported new regional screening approaches toward breast cancer. In our experience, the same pattern vis-à-vis prostate cancer seems to be present. Moreover, despite the recent advances in the diagnosis and treatment of prostate cancer, some controversial issues are still present. The most important issue is an incremental debate over the role of screening. Although screening is augmenting the detection rate of prostate cancer, the mortality rate does not seem to be affected,[5] which is due to lower life expectancy at the age of diagnosis. Consequently, more dedicated epidemiological studies are necessary for regional policy-making.

The aim of our study was to report the epidemiological features of prostate cancer in patients referred for prostate biopsy in the southern Iranian city of Shiraz and to evaluate the accuracy of the levels of the prostate-specific antigen (PSA) and the PSA-density (PSAD) as well as the extension of the disease in the prediction of the biological behavior of prostate cancer.

Patients and Methods

Ethics

The present study was approved by the Ethics Committee of Shiraz University of Medical Sciences (ref. code: ec-p-9388-8108).

Study Population

This is a retrospective study on the medical records (including the pathology reports) of 1982 consecutive patients (age range=32–101 years old) suspected of prostate cancer who underwent transrectal ultrasound (TRUS)-guided biopsy due to an abnormal digital rectal examination (DRE) and/or an elevated PSA level (>4 ng/mL). All the patients were referred from the Urology Ward to the Radiology Department of Shahid Faghihi Hospital, a referral center in the south of Iran, affiliated to Shiraz University of Medical Sciences, between December 2003 and July 2014. DRE was performed after obtaining informed consent from the patients. Patients with incomplete medical records were excluded from the study. Tissue samples were taken; they consisted of 12 cores in 4 zone biopsies: 3 cores (i.e., apex, middle, and base) from each of the 4 zones (i.e., left lateral, left far lateral, right lateral, and right far lateral) with 2 additional transition zone biopsies. All the biopsies were performed using an 18-gauge biopsy gun and a Tru-Cut biopsy needle under ultrasound guidance, with a GE ultrasound scanner (GE LOGIQ 500, U.S.A.) and a 6.0–8.0 MHz endorectal probe. All the biopsies were taken by a single radiologist, who had considerable experience in TRUS-guided biopsy. The total prostate volume was measured using TRUS and the following formula: height×length×width×0.523. The PSAD was calculated as the PSA divided by the total prostate volume.

Data Collection

Medical records and pathological reports were reviewed regarding age, the levels of the PSA and PSAD, the prostate volume, histopathological findings, the Gleason score (the most common histopathological grading system for prostate cancer) of the 14 core biopsies, and the extension of the disease (defined as unilateral or bilateral involvement). Then, the PSA and PSAD levels were compared with respect to tumor involvement. Moreover, the effects of the PSA and PSAD levels on the Gleason scores were evaluated. The histopathological findings of the biopsy specimens were classified as negative or positive for prostate cancer. The pathological evaluations were performed by experienced pathologists.

Statistical Analysis

All the statistical analyses were performed using SPSS software, version 24.0 (SPSS Inc., Chicago, IL, U.S.A.), Stata 13.0, and Winpepi 11.65. The Pearson χ^2 or the Fisher exact test was employed to compare the differences in proportions. Other statistical tests such as the Student *t*-test, Mann–Whitney *U*-test, receiver operating characteristic (ROC) curve, and trend test were utilized for the analyses. A $P \leq 0.05$ was considered statistically significant.

Results

The histological results obtained from TRUS-guided prostate biopsy showed that of the 1982 patients, 657 (33.1%) patients had positive biopsy results for prostate cancer and the negative rate of prostate cancer was 62.6% (n=1240). Also, the reports were not available in 85 (4.3%) patients, who were subsequently excluded from the study. The PSA and PSAD levels in the patients diagnosed as having prostate cancer were significantly higher than those in the patients without prostate cancer (Mann–Whitney *U*-test, P<0.001) (table 1).

The mean age of the study population was 65.8±9.5 (range=32–101) years. The mean

Table 1: Association between the PSA and PSAD levels and the pathological reports of the specimens

Variables	Biopsy Positive for Cancer (n=657)	Biopsy Negative for Cancer (n=1240)	P value
PSA (ng/mL)	23.8±30.8	10.8±10.3	<0.001
PSAD (ng/mL/cc)	0.57±0.74	0.23±0.31	<0.001

PSA: Prostate-specific antigen; PSAD: Prostate-specific antigen density

age of the patients with prostate cancer was 69.1±8.5 (range=36–101) years. Of the total positive cases, 7% (46/657) of the cases were seen among the men <55 years old, 28.6% (188/657) among those aged between 55 and 65 years, 39.9% (262/657) among those aged between 66 and 75 years, and 24.5% (161/657) among those aged >75 years. The statistical analyses showed that there were significant differences between the age groups as regards prostate cancer (P<0.001). The χ^2 test for trend demonstrated that the rate of cancer rose with an increase in the age of the patients (P<0.0001).

In the present study, the study population was also stratified based on age groups. The results revealed that 7% of the patients with prostate cancer were <55 years of age (table 2). The mean age of this group was 51.06±4.07 (range=32–55) years.

The biopsy samples of the patients with prostate cancer were classified based on the Gleason score. There were 43 (6.5%) patients with low-grade, 347 (52.8%) with intermediate-grade, and 247 (37.6%) with high-grade Gleason scores. Moreover, in 20 (3.1%) patients with prostate cancer, the pathological Gleason scores were not available (table 2). Also, we found that 12 (26.1%) out of the 46 patients with prostate cancer who were <55 years of age had high-grade Gleason scores.

The sensitivity, specificity, positive predictive value, and negative predictive value of the PSA (cutoff>4) and the PSAD (cutoff>0.15) in the diagnosis of prostate cancer (for the whole study population as well as for the patients aged<55 years) are listed in table 3. Regarding the confidence intervals, there was no significant difference in terms of the sensitivity and specificity of the PSA and the PSAD between the patients aged<55 years and the rest of the study population. Figure 1 depicts the ROC curve and the area under the curve of the PSA for the whole study population (AUC=0.705, P<0.001 [95%CI 0.681-0.730]) as well as for the patients<55 years of age (AUC=0.680, P<0.001 [95%CI 0.587-0.773]). Figure 2 illustrates the ROC curve and the area under the curve of the PSAD for the entire patient population (AUC=0.761, P<0.001

Table 2: Distribution of the positive cases of prostate cancer in the age groups and the different grades of the Gleason scores

	Number (657)	Percentage
Age groups		
<55 y	46	7%
56–65 y	188	28.6%
66–75 y	262	39.9%
>75 y	161	24.5%
Gleason score		
Low grade (2–4)	43	6.5%
Intermediate grade (5–7)	347	52.8%
High grade (8–10)	247	37.6%
Unknown grade*	20	3.1%

*Only the overall result (positive prostate cancer) was available, and no Gleason score was evident.

Table 3: Accuracy of PSA >4 ng/mL and PSAD > 0.15 mL/ng/cc in the diagnosis of prostate cancer

		PSA >4 ng/mL		PSAD >0.15 mL/ng/cc	
		Value %	95% CI	Value %	95% CI
All cases	Sensitivity	97.4	95.9-98.5	82.9	79.8-85.8
	Specificity	8.8	7.2-10.4	52	49.1-54.8
	PPV	36.1	33.9-38.4	47.8	44.9-50.8
	NPV	86.4	79.1-91.9	85.2	82.4-87.7
Cases<55 years old	Sensitivity	95.45	84.5-99.4	76.19	60.5-87.9
	Specificity	13.08	9.1-18.0	46.52	39.9-53.2
	PPV	16.82	12.3-22.0	20.64	14.5-27.8
	NPV	93.98	79.9-99.2	91.45	84.8-95.8

PSA: Prostate-specific antigen; PSAD: Prostate-specific antigen density; PPV: Positive predictive value; NPV: Negative predictive value

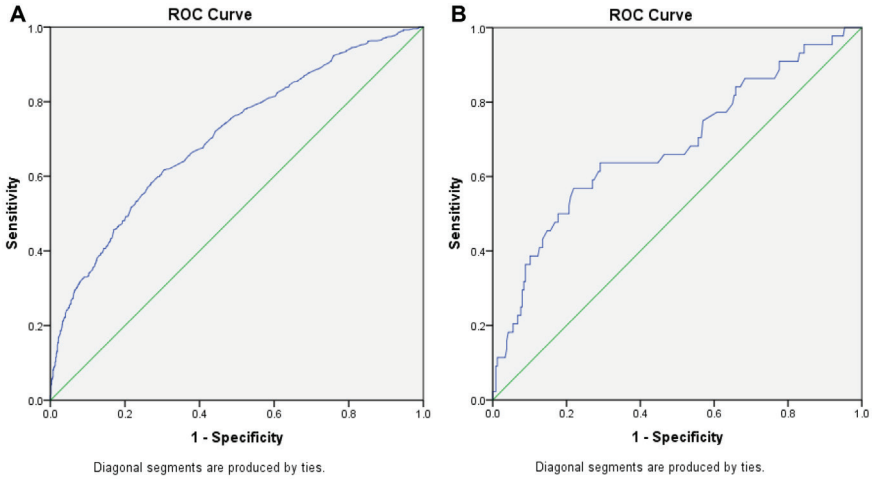

Figure 1: Receiver operating characteristic (ROC) curve and the area under the curve (AUC) of the prostate-specific antigen for the whole study population (A) as well as for the cases aged<55 years (B).

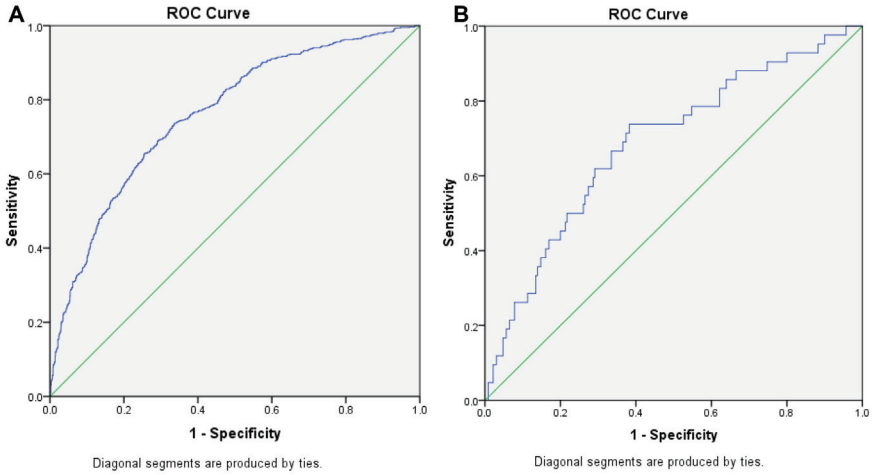

Figure 2: Receiver operating characteristic (ROC) curve and the area under the curve (AUC) of the prostate-specific antigen density for the entire study population (A) as well as for the cases aged<55 years (B).

[95%CI 0.738-0.784]) as well as the patients aged<55 years (AUC=0.686, P<0.001 [95%CI 0.597-0.775]).

Moreover, we evaluated the relationship between disease involvement and the Gleason score. Of the 637 patients with prostate cancer, 250 (39.2%) had unilateral disease, 378 (59.4%) had bilateral disease, and only 9 (1.4%) patients had transition zone involvement (table 4). Stratifying the involvements of the patients based on their Gleason scores revealed that there was a significant relationship between the disease involvements and the Gleason scores (P=0.001), and most of the patients with bilateral involvement had high-grade Gleason scores.

Discussion

Prostate cancer is the most common malignant tumor among the male population in the United States.[1] Recent studies have shown rapid growths in the incidence and mortality of prostate cancer in some Asian countries.[7] It is also the 3rd most common non-skin cancer among men in Iran.[2] A large number of studies have been conducted on the various aspects of this disease, but a small fraction of such literature is on the epidemiological aspects of prostate cancer diagnosed by core needle biopsy sampling.

Currently, prostate biopsy and the Gleason score, which was firstly introduced by Donald F. Gleason in 1966, are the gold standard for the diagnosis of prostate cancer.[8] Since 1966, the Gleason score as well as the technique of biopsy taking has been modified. Sextant needle biopsy had been used worldwide until the 1990s, when a study emphasized the high false negative results of that method.[9] Since 1998, there has been a rise in the number of core needle samples;[10,11] however, the number of specimens has remained controversial. Fourteen core needle samples were taken for every patient in our series.

One of our goals was to identify the

Table 4: Classification of the extent of the involvement based on the Gleason scores

Gleason scores	Involvement		
	Unilateral (n=250)	Bilateral (n=378)	Transition zone (n=9)
Low grade (2–4)	25 (58.1%)	15 (34.9%)	3 (7%)
Intermediate grade (5–7)	159 (45.8%)	182 (52.4%)	6 (1.7%)
High grade (8–10)	65 (26.4%)	181 (73.6%)	0

cancer detection rate of prostate biopsy. We retrospectively evaluated the correlation between the levels of the PSA and the PSAD and the results of prostate biopsy.

Several studies have been done regarding the pathological results of prostate biopsies performed because of high PSA levels and/or abnormal DRE findings. According to the report of Ojewola and colleagues,[12] the total average cancer detection rate was 44%. The reviews of the pathological results of the biopsies performed due to both high PSA levels and abnormal DRE findings showed a cancer detection rate of 33% in the study done by Catalona et al.,[13] 31% in the study by Eskicorapci et al.,[14] and 32% in the study by Emiliozzia et al.[15] In our study, the overall cancer detection rate with the PSA level>4 ng/mL and/or abnormal DRE findings was 33.1%. Our finding regarding the rate for cancer detection is overall consistent with previous studies.

Traditionally, prostate cancer has been assumed as the disease of the elderly. Similarly, more than 60% of our patients were aged ≥65 years. Consequently, given the lower life expectancy in older people, there is a significant controversy in the screening of prostate cancer in this population.[16] While some studies have shown the role of PSA-based screening in the reduction of prostate cancer mortality,[17] others have suggested that screening programs for these patients are not effective in reducing the mortality rate despite high rates of diagnosis.[18,19] Moreover, our results revealed that 46 (7%) patients with prostate cancer were diagnosed aged≤55 years. This finding is inconsistent with the findings of Quinn and Babb,[20] who reported that the cancer rate was very low in their male patients aged<50 years, whereas it is consistent with a study done by Daniel et al.,[21] who reported that the proportion of men aged≤55 years at diagnosis increased over the study period, from 2.3% between the years 1988 and 1991 to 9.0% between the years 2000 and 2003. Unfortunately, our findings showed that most of the patients in this age group were affected by the moderately or severely aggressive form of the disease. Obviously, the delay in the diagnosis of malignancy in the mentioned group would result in the presentation of a more extended form of the cancer. The above findings underscore the need for urgent studies into the epidemiological behavior of prostate cancer in younger age groups, which may revolutionize the screening programs in our region.

Interestingly, a similar chronological pattern was detected previously in studies on breast cancer in our region. Alipour et al.[6] showed that 1.7% of breast cancers occurred in younger patients in our country. Furthermore, a recent study showed a higher risk among women of developing breast cancer among the 1st-degree family members of patients with prostate cancer.[22] These findings may indicate the same behavioral and environmental risk factors for these cancers in our region, which may call for further intervention.

An important controversial issue in the management of prostate cancer is the prediction of the biological behavior of the cancer. In other words, a clearer distinction of patients who suffer from an indolent low-grade disease from those who suffer from an aggressive one is of value for the conservative management of more patients.[6] Some factors have been introduced to achieve this goal such as the PSA and PSAD levels as well as the Gleason score. Our study showed that higher PSA and PSAD levels were compatible with a more aggressive disease, which chimes in with other studies.[23] However, in the current study, we also sought to determine whether the cancer was unilateral or bilateral. We found that most of the patients with bilateral involvement had high-grade Gleason scores. Therefore, this factor can be included in further guidelines as a new predictor of cancer behavior.

Our study demonstrated a higher risk of cancer in those with higher PSA levels. The same findings were implied by Thompson et al.[24] who studied 2950 patients and reported cancer detection rates of 6.6% for those with PSA levels<0.5 ng/mL, 10.1% for those with PSA levels between 0.6 and 1 ng/mL, 17% for those with PSA levels between 1.1 and 2.0 ng/mL, 23.9% for those with PSA levels between 2.1 and 3.0 ng/mL, and 26.9% for those with PSA levels between 3.1 and 4 ng/mL.

In our study, the sensitivity and specificity of the PSA were 97.4% and 8.7%, respectively. Our results are well in line with those of Djavan and coworkers,[25] who reported that the sensitivity and specificity of the PSA level at a cutoff point of 4 ng/mL were 95% and 8.3%, correspondingly.

According to our results, the PSA was not specific enough. Similar to the report by Thompson et al.,[24] our series revealed that prostate cancer could be detected as well at lower PSA levels. Besides, as has been mentioned in the literature, using only a serum PSA test might not be sufficient for the further follow-up and evaluation of the possibility of prostate cancer if the initial prostate biopsy shows benign prostatic hyperplasia.[26] The PSAD has been introduced to overcome these shortcomings.

For more specific results, we considered a PSAD level>0.15 mL/ng/cc as the cutoff point. In our study, the sensitivity and specificity of the PSAD were observed to be 82.9% and 52%, respectively. Nevertheless, the sensitivity and specificity of the PSAD at a cutoff point of 0.13 ng/mL were 74% and 44%, correspondingly, in a study by Djavan et al.[25]

The most important limitation in our study is that the prevalence was calculated in patients referred for biopsy, not in the normal population. We, nonetheless, think that the results are completely relevant in spite of this limitation. On the other hand, although prostatectomy was not done for our patients as the most reliable method for the evaluation of prostate cancer, core needle tissue sampling is acceptable because of its comparable results and fewer complications. However, an important strong point of our study is that all the biopsies were done by a single, experienced radiologist, which can minimize the operator variability.

Finally, it should be emphasized that more dedicated, well-designed epidemiological studies are necessary to not only evaluate the prevalence of prostate cancer, but also to detect the actual rate of prostate cancer in younger men, especially in developing countries.

Conclusion

Our study underlines the relationship between age and the frequency of cancer; the PSA and PSAD levels and the Gleason score; and the extent of tumor involvement and the grade of prostate cancer and also underscores the importance of screening, not least in younger patients. The overall cancer detection rate was 33.1% in our study. Higher PSA and PSAD levels were compatible with a more aggressive disease. Although prostate cancer was seen more frequently in our older patients, a notable percentage (7%) of the patients with prostate cancer was seen in our younger patients as well (<55 years old). We, accordingly, suggest that more studies be undertaken into the epidemiological behavior of prostate cancer in younger age groups with a view to altering the screening programs in our region. In our study, most of the patients with bilateral involvement by the tumor had high-grade Gleason scores, suggesting that this factor can be a predictor of cancer behavior.

Acknowledgement

This article was extracted from a thesis written by Reza Beheshti for the degree of specialty in radiology and was sponsored and supported by Vice-Chancellery for Research, Shiraz University of Medical Sciences (grant #8108).

Conflict of Interest: None declared.

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