

ORIGINAL ARTICLE: A COMPREHENSIVE STUDY OF PROSTATIC LESIONS AND ITS PROSTATE-SPECIFIC ANTIGEN LEVELS IN ANATOMICAL PATHOLOGY INSTALLATION OF RSUD DR. SOETOMO, SURABAYA FROM YEAR 2014 TO 2016

¹Izzan Khalidah Binti Muhamad, ²Anny Setijo Rahaju, ³Lukman Hakim

¹Faculty of Medicine Universitas Airlangga, Jl. Mayjen. Prof. Dr. Moestopo no. 47, Surabaya

²Department of Anatomical Pathology, RSUD Dr. Soetomo, Jl. Mayjen., Prof. Dr. Moestopo no. 47, Surabaya

³Department of Urology, RSUD Dr. Soetomo, Jl. Mayjen., Prof. Dr. Moestopo no. 47, Surabaya

*telephone +6287853906865, e-mail: ezann02@gmail.com

Abstract. Background: Diseases primarily affects prostate gland are inflammation, hyperplasia, and malignant tumour. Gleason score (GS) is an essential facet and together with PSA are substantial in diagnosing, managing, and determining the prognosis of CaP. **Purpose:** The aims of this study is to investigate the prevalence of prostatic lesions and its PSA level among patients in anatomical pathology installation in RSUD Dr. Soetomo from year 2014 to 2016. **Method:** This research is a retrospective study of prostatic lesions that were conducted from year 2014 to 2016 (3 years) with emphasis on GS and PSA levels. **Result:** The distribution of histopathological lesion found are benign lesion, benign prostate hyperplasia, adenocarcinoma, prostatitis, benign prostate hyperplasia with prostatitis, prostatic intraepithelial neoplasia, non-Hodgkin lymphoma, sarcoma, transitional cell carcinoma, and squamous cell carcinoma. The most common findings in this cohort is benign lesion (34.6%) with age group of 61-70 years old (51.94%) and adenocarcinoma with high GS of 9 (60%). Meanwhile, patients with GS ≥ 8 (high risk patient) contributed for 84.8%. Most of the cases (69.2%) have elevated PSA level of > 20 ng/ml. **Conclusion:** The prevalence of prostatic lesions were able to be determined in different age groups. High GS indicates a more aggressive type of adenocarcinoma suffered, high risk for CaP. The results show that the possibility to detect malignancy with rising PSA level are higher, although PSA is not considered as a specific marker.

Keywords: prostate, histopathology, benign lesion, PSA.

Summary

Prostatic lesion can occur due to the processes that take place inside the prostate such as hyperplasia, inflammation, or tumour. Histopathology examination can be conducted to find out the histopathological type of the prostatic lesion as well as determining the Gleason score that is used in grading CaP. While prostate-specific antigen (PSA) test is commonly used in the diagnosis and management of CaP. It is used as a marker for the presence and progression of the disease. 4 ng/mL as the cut-off between normal and abnormal. Knowing the prevalence of prostate lesions in a specific area is useful for assessing and explaining the progression of the disease, prevention programs, clinical interventions, and health services on disease. This study is a retrospective study which aims to investigate the prevalence of prostatic lesions and its PSA levels among patients in anatomical pathology installation in RSUD Dr. Soetomo from year 2014 to 2016. In this study, total sampling with a population of all patients with the diagnosis of prostatic lesions with histopathology

examination in pathology anatomy installation in RSUD Dr. Soetomo Surabaya, Indonesia for the period of three years from year 2014 to 2016. A total of 593 samples were received and studied. In this study, the distribution of histopathological lesion found are benign prostate hyperplasia (BPH), adenocarcinoma, prostatitis, benign prostate hyperplasia with prostatitis, prostatic intraepithelial neoplasia (PIN), non-Hodgkin lymphoma (NHL), sarcoma, transitional cell carcinoma (TCC), and squamous cell carcinoma (SCC). From the result, the most common type of histopathological lesion in this cohort is benign lesion. The highest incidence of prostatic lesion is seen in the age group of 61-70 years old (51.94%). Patient with mean age 64 ± 9 standard deviation mostly diagnosed with adenocarcinoma. While patient in the age ranging from 51 to 70 most commonly have benign lesion. Patient over 71 years old mostly diagnosed with benign prostate hyperplasia. Patient diagnosed with adenocarcinoma mostly has Gleason score 9 (60%). This shows that most adenocarcinoma cases were poorly differentiated

and indicates a more aggressive type of cancer. PSA estimation was done in 13 cases. 69.2% of the cases have elevated PSA level of >20 ng/ml.

Introduction

Prostatic diseases constitute a sententious portion of the cases seen by urologists in males.¹ It is a significant source of morbidity and mortality among adult male population globally.² The pathologic processes that have major effects on the prostate gland are: benign prostatic hyperplasia, infectious of inflammatory, and neoplastic disorder, of which prostatic carcinoma is by far has the utmost importance clinically.²

Among the three pathologic processes, benign prostatic hyperplasia (BPH) have the highest prevalence especially to men in their late age that it sometimes considered as a “normal” aging process.² The histologic evidence of BPH found in 40 year-old men is approximately 20%, this number escalate to 70% in 60 year-old men and to 90% in 90 year-old men.²

CaP is second most often diagnosed cancer and the sixth most common cause of cancer death in male worldwide.³ The incidence rate of CaP increased by more than 25-fold worldwide may be due to intensified effort in early detection and screening with the widespread use of prostate-specific antigen (PSA) testing and the practice of prostate biopsy. Adenocarcinoma is its most common histological variant.⁴ Tumor grading using the Gleason score greatly affects the decisions regarding treatment plans.⁵

Prostatitis accounts for an estimation of two million visits to health care provider in the United States every year.⁶ Inflammation of prostate gland characterized by urinary frequency,

The possibility of malignancy increases with elevated level of PSA.

dysuria, body aches, and sometime fever. Prostatitis can be further classified into infective and non-infective.⁴ Prostatitis refer to a combination of infectious diseases (acute and chronic bacterial prostatitis), a chronic pelvic pain syndrome and asymptomatic inflammation.

Materials and Methods

This research is a retrospective study which aims to investigate the prevalence of prostatic lesions and its PSA level among all patients with the diagnosis of prostatic lesions found in anatomical pathology installation of RSUD Dr. Soetomo Surabaya, Indonesia from year 2014 to 2016.

Results

A total of 593 cases of prostate lesions during the 3 year period from 2014 to 2016 were analysed age ranged from 35 to 91 years (mean 64 years). 68.7% (n = 407) of the cases were benign that comprised of benign lesion, BPH, BPH with prostatitis, and prostatitis. The most common prostate lesion in this cohort was benign lesion (n = 205; 34.6%).

Malignant lesions were seen in 186 (31.3%) patients with 138 adenocarcinoma, 36 transitional cell carcinoma (TCC), 8 prostatic intraepithelial neoplasia (PIN), 2 non-hodgkin lymphoma (NHL), 1 sarcoma, and 1 squamous cell carcinoma (SCC).

The age distribution of histopathology diagnosis of prostate lesions is shown in Table 1.

Table 1: Age distribution of histopathology diagnosis of prostatic lesions.

Histopathology Diagnosis of Prostatic Lesions											
Age Group	BPH	Adeno Ca	Prostatitis	BL	PIN	TCC	Sarcoma	SCC	NHL	BPH + Prostatitis	Total
≤ 50	2	10	1	4	0	4	0	0	1	1	23 (3.88%)
51-60	37	31	2	45	1	5	1	1	1	4	128 (21.59%)
61-70	96	57	1	122	3	23	0	0	0	6	308 (51.94%)
71-80	41	36	2	29	4	4	0	0	0	2	118 (19.90%)
> 80	7	4	0	5	0	0	0	0	0	0	16 (2.70%)
Total	183	138	6	205	8	36	1	1	2	13	593 (100%)

Maximum number of cases (n = 308; 51.94%) were in the age group of 61-70 years followed by 51-60 years age group (n = 128; 21.59%). 23 cases (3.88%) were observed younger than 50 years of age.

Gleason score (GS) among adenocarcinoma patients was used for grading. Out of 138 adenocarcinoma patients, there were a total of 125 cases with available GS. 1 was well differentiated (GS 2), 7 were moderately differentiated (GS 5 and 6), 117 were poorly differentiated (GS 7 to 10). GS 9 (n = 75, 60%)

has the highest prevalence. Most patients (n = 106, 84.4%) were high risk patients (GS 8 to 10).

The PSA values were available in 13 cases. Most of the cases (69.2%) have PSA level of > 20 ng/ml followed by 23.1% of cases with PSA level ranged 8.1-12.0 ng/ml. Lastly, PSA level ranged 16.1-20.0 comprised of 7.7% of the cases. Adenocarcinoma cases (80%) mostly has a high PSA level (> 20 ng/ml). While, both prostatitis and PIN have PSA level ranged 8.1-12.0 ng/ml and TCC has PSA level of > 20 ng/ml.

Table 2: Histopathology diagnosis based on range of PSA level.

PSA Level (ng/ml)	PROSTATITIS	ADENOCARCINOMA	PIN	TCC	Total
0-4.0	0	0	0	0	0
4.1-8.0	0	0	0	0	0
8.1-12.0	1 (100%)	1 (10%)	1 (100%)	0	3 (23.1%)
12.1-16.0	0	0	0	0	0
16.1-20.0	0	1 (10%)	0	0	1 (7.7%)
>20	0	8 (80%)	0	1 (100%)	9 (69.2%)
Total	1 (100%)	10 (100%)	1 (100%)	1 (100%)	13 (100%)

Discussion

According to the data obtained, there are a total of 593 patients diagnosed with prostatic lesions. Two most important histopathological prostatic lesions are benign prostatic hyperplasia and Prostatic carcinoma.⁴ In this study, 68.7% (407) of cases are benign that constitutes of benign lesion, benign prostatic hyperplasia (BPH), BPH and prostatitis, and prostatitis. While the other 31.3% (186) of the cases were malignant that made up of prostatic adenocarcinoma, transitional cell carcinoma (TCC), prostatic intraepithelial neoplasia (PIN), non-Hodgkin lymphoma (NHL), squamous cell carcinoma

(SCC) and sarcoma. The most common malignancy of the prostate is adenocarcinoma, comprising more than 90% of malignant lesion.⁷ However, in this study it is found that although adenocarcinoma is the most common malignancy of the prostate but it only consist of 74.10% of the malignant lesions. The incidence of rare prostate malignancy such as transitional cell carcinoma (19.35%), prostatic intraepithelial neoplasia (4.30%), non-Hodgkin lymphoma (1.08%), squamous cell carcinoma (0.54%) and sarcoma (0.54%) were found in this study. These other malignant prostate lesions that are not

adenocarcinoma are exceedingly rare in prostate pathology.⁷

In general, cancer of prostate affects men over the age of 50 years and it is the commonest type of cancer in males, accounting for 25% of cancer in male in the United States in 2009.² In this study, age afflicted with prostatic pathology was 35 to 91 years with mean age of 64 years. A Saudi Arabia study showed similar mean age. However, the youngest case reported in their study was 20 year-old.⁸ It is found that the highest prevalence of prostatic lesions occur in 61-70 years with more than half (51.94%) of the patients are in this age group. The second highest prevalence is the age group of 51-60 years, followed by 71-80 years with 21.59% and 19.90% respectively. Fewer incidence occurred in the age group of ≤ 50 and > 80 years with only 3.88% and 2.70%. Therefore, the incidence of prostatic lesions can be found commonly in the age of 51-80 years old similar to a Saudi Arabia study.⁸

In this three-year study period, a total of 205 cases (34.6%) out of all 593 cases are diagnosed as benign lesion, making it the most common type of prostatic lesion found in this study. The age ranges between 40 to 89 years old with mean age of 64.92 years. The peak age group for benign lesion is in the 6th decade. Most cases diagnosed with benign lesion are from biopsy specimens. It is found that these benign lesions to be unspecific. This may be due to the limitations of pathologic staging. It could be because of the sample that only represents one part of the organ studied or because of a series of factors that make it hard to be categorically certain of the pathology study. The quality of prostatic needle biopsy tissue processing to get an optimal processing procedure, leading to a maximum amount of tissue being examined by the pathologist has an important role in increasing the sensitivity for detection of prostatic carcinoma.⁹ Other than that, we must be aware with the limitation of pathologic staging itself in the interests of improving the evaluation and being able to make more solidly based decisions. In fact, there are several limitations in biopsy specimens such as determining staging via needle biopsy includes the many possible carcinoma foci and the tiny proportion of prostatic tissues that can be obtain in this method.¹⁰ Another aspect that can influence that pathologic features is the quality of the biopsy such as the fixation technique and

length of the biopsy and the fact that biopsies mostly done at random without having as suspicious area but following some guidelines determined by the age of the patient, prostate volume and PSA level.¹⁰ Hence, a close relationship between pathologist and urologist may leads to better handling of specimens and improvement of morphologic criteria.

BPH accounted for 30.86% of all prostatic lesions, and most cases were in 6th and 7th decade. The age range was 41 to 91 years. According to the recent literature, the youngest patient to be diagnosed with BPH was 20 years old and the oldest patient at the time of diagnosis was 100 years old.^{8, 11} In this study however, the youngest patient at the time of diagnosis of BPH is 41 years old. BPH in association with prostatitis made up only 2.2% of prostatic lesions, and most cases were in 6th and 5th decade. Prostatitis accounted for the most of the histological changes associated with BPH in the index study, similar to findings from Saudi Arabian study.⁸ From this study, it is found that the age range for BPH with prostatitis is 43 to 75 years with mean age 62.15 years. There were 6 cases (1%) having only prostatitis. The age ranges between 44 to 71 years old with mean age of 61.5 years. The highest incidence can be found in 6th decades.

Of all 593 cases, 1.3% of PIN lesions is found in this study. Other studies mostly have higher incidence of PIN lesions.^{12, 13} This may be due to the fact that most of their diagnosed lesions were in TURP specimens where they sampled and examined whole part of the gland under microscope hence the higher chance of diagnosing PIN as it may occur in small foci within a gland, which might go unnoticed in a biopsy, which is the most used procedure in this study.¹² The age range for PIN is 53 to 78 years old with mean age 69 years and the highest incidence can be found in 7th decade.

In this study, the earliest age at diagnosis of CaP was 35 years and the oldest was 86 years, similar to a study with more than 200 cases of CaP by Nigerian scientists, the youngest age at diagnosis reported to be 40 years.¹⁴ Of all the malignant lesions diagnosed, adenocarcinoma was the commonest histological subtypes and seen in 74.19% cases. The earliest age at diagnosing adenocarcinoma was 35 years and the oldest was 86 years with mean age 64.93 years.

Adenocarcinoma is peaked at the 6th decade. The rest 25.81% is comprising of PIN and other rare malignant prostate lesions. 36 cases (19.35%) of transitional cell carcinoma (TCC), two cases (1.08%) of Non-Hodgkin lymphoma (NHL) and 1 case (0.54%) for both squamous cell carcinoma (SCC) and sarcoma were diagnosed in this study. All the prostate disease studies in the recent literatures mentioned adenocarcinoma of prostate as the highest prevalence tumor. None of the study recently mentioned any other malignancy of prostate in their series except the study from Saudi Arabia, report two cases of SCC and a case of TCC in their 417 patients' series and a study from Oman, reported two cases of NHL in their 1163 patients' series.^{8, 15}

Among the rare malignant prostate lesions found in this study, TCC is the second most common type of malignancy after adenocarcinoma. The age range is 37 to 79 years old with mean age of 61.72 years. It occurred mostly in the 6th decade. Prostatic involvement by TCC is not unusual because its occurrence can be as primary TCC with foci of carcinoma in-situ or as extension from Bladder TCC.¹⁶ Next, lymphoma presenting in the prostate is rare and accounts for 0.1% of all newly diagnosed lymphoma.¹⁷ 2 cases of large cell type Non-Hodgkin lymphoma (NHL) is recorded with patient 47 and 54 years of age in this study. Both cases are using biopsy specimens. Meanwhile, SCC is a rare tumor of prostate with aggressive behaviour found in less than 1% of men worldwide.¹⁸ One case with age of 53 years old is found in this study. This case is diagnosed using biopsy specimen. Lastly, sarcoma is a rare malignant tumor comprising 1% of all cancers and only 0.7% of primary malignancy of the prostate.¹⁹ In this study, high grade sarcoma is diagnosed using prostatectomy specimen. Sarcoma is comprised of only one case (0.2%) of all the malignant cases found. The age of the patient is 59 years. For these rare malignant prostate lesions, the recent literature search reveals only some occasional case reviews or case reports.

According to this study, Gleason score (GS) 9 was the most frequent score (60%). It is found that poorly differentiated carcinoma (GS of 7 to 10) was the most frequently diagnosed carcinoma comprising of 93.6% (117 cases) of all carcinoma cases. GS correlates closely to clinical behaviour and provides a crucial index of prognosis. It is one

of the key determinants in deciding the treatment, together with stage, age, and PSA.¹ The classification of high risk disease includes GS of ≥ 8 . In this study, it is found that most cases can be categorized as high risk cases with 84.8% have GS ≥ 8 . This problem with high GS need to be addressed probably by commencing screening protocols as an analysis of 451 patients revealed that death from prostate cancer increases with GS.¹⁵ There is 29-43% risk of death by prostate cancer in men with GS of 7 and above.¹

Measurement of PSA is substantial in diagnosing and managing prostatic carcinoma (CaP). However, when used alone, it has many limitations. This is due to the fact that PSA is organ-specific but not cancer-specific. Hence, PSA alone is non-effective in CaP screening due to its low sensitivity and specificity.² Elevated PSA level can be caused by any process that interrupt the normal state of prostate hence permitting the diffusion of PSA into the stroma, conveying its entry into the blood through the microvasculature. One of the main reason for the rising PSA level in BPH cases is due to the increase glandular volume. Therefore, in conditions like prostatitis, prostatic infarcts and BPH, an elevated PSA level can be observed. However, the most clinically significant elevations are seen in prostatic adenocarcinoma.²¹

In this study, the total number of PSA level recorded is 13 cases. Most of the cases (69.2%) have PSA level of > 20 ng/ml followed by 23.1% of cases with PSA level ranged 8.1-12.0 ng/ml. Lastly, PSA level ranged 16.1-20.0 comprised of 7.7% of the cases. Hence, most patients have an abnormal and elevated PSA level since the threshold used is 4.0 ng/ml. However, the chance of getting adenocarcinoma is possible even with a low PSA level. A study reported that using 4.0 ng/ml as threshold for biopsy results in a large proportion of cancers already spread to the prostate gland during the time of detection.²²

PSA level from 4 to 10 ng/ml suggest risk of carcinoma for 25% while level more than 10 ng/ml suggest a risk higher than 67%.²³ Therefore, the higher levels of PSA, the higher the risk of prostatic carcinoma. The classification of high risk disease includes PSA > 20 ng/mL.²⁰ Meanwhile in this study, most of adenocarcinoma cases (80%) has a high PSA level (> 20 ng/ml), hence classified as high risk cases. This findings

could imply that as PSA rose, the probability of getting carcinoma among patient is higher. In this case, rising PSA level suggests underlying malignancy. Study in India shows a similar results.²⁴ However, the other 40% of adenocarcinoma cases indicates that it can also occur in a lower PSA level. From the data, it is shown that 10% of adenocarcinoma case has PSA level of 8.1-12.0 and the remaining 10% has PSA level of 16.1-20.0 ng/ml. Adenocarcinoma cases can have a wide range of PSA levels proven with mean = 75.56 ± 40.91 standard deviation from this study.

This varieties of PSA levels are dependent to the glandular volume. The bigger the glandular volume, the higher the level of PSA.²¹ The type of histopathology examination also influence the PSA level. In TURP specimens, the entire part of the gland is sampled, compared to biopsy specimens with higher chances of missing a small focus of adenocarcinoma is high as only a small portion of the gland is sampled.¹³ It is found that prostatitis and PIN have PSA level ranged 8.1-12.0 ng/ml. Elevated PSA occurs naturally in infection and may need up to a month post-infection to resolve.⁷ Transitional cell carcinoma has an elevated PSA level with > 20 ng/ml.

Conclusion

In conclusion benign lesions is the commonest pathology encountered is prostatic specimens. PSA is specific for prostatic tissue and the possibility of malignancy increases with its elevation.

References

1. Nwafor, C., Keshinro, O. and Abudu, E. (2015). A histopathological study of prostate lesions in Lagos, Nigeria: A private practice experience. *Nigerian Medical Journal*, 56(5), p.338.
2. Kumar, V., Abbas, A., Aster, J. and Perkins, J. (2007). *Robbins basic pathology*. 7th ed. Philadelphia: Elsevier.
3. Aslam H, Shahid N, Shaikh N, Shaikh H, Saleem S, Mughal A. Spectrum of prostatic lesions. *International Archives of Medicine* [Internet]. 2013 [cited 8 September 2017];6(1):36. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/?term=10.1186%2F1755-7682-6-36>
4. Dabir P, Ottosen P, Høyer S, Hamilton-Dutoit S. Comparative analysis of three- and two-antibody cocktails to AMACR and basal cell markers for the immunohistochemical diagnosis of prostate carcinoma. *Diagnostic Pathology*. 2012;7(1):81.
5. Al-Samawi, A.S., M.Phill, and Aulaqi, S.M., (2014). The histopathological pattern of prostatic disease and prostatic cancer in Yemeni patients. *Sana'a University Journal of Medical Sciences*. [online] 6(1) [Accessed 24 Sept. 2017].
6. Dickinson, S. (2010). Premalignant and Malignant Prostate Lesions: Pathologic Review. *Cancer Control*, [online] 17(4), pp.214-222. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20861809> [Accessed 10 Oct. 2017].
7. Albasri A, El-Siddig A, Hussainy A, Mahrous M, Alhosaini A, Alhujaily A. Histopathologic Characterization of Prostate Diseases in Madinah, Saudi Arabia. *Asian Pacific Journal of Cancer Prevention*. 2014;15(10):4175-4179.
8. Algaba F. Pitfalls of Pathologic Staging in Prostate Cancer. *European Urology Supplements*. 2008;7(1):6-14.
9. George, E. and Thomas, S., (2005) A Histopathologic Survey Of Prostate Disease In The Sultanate Of Oman. *The Internet Journal of Pathology*, 3(2).
10. Chang, A.J., Autio, K.A., Roach, M., Scher, H.I. (2014). "High-Risk" Prostate Cancer: Classification and Therapy [online] 11(6), p. 308-323. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4508854/> [Accessed on 12 Dec. 2017]
11. Ross M, Pawlina W. *Histology*. 6th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins Health; 2011.
12. Ross, M. and Pawlina, W. (2011). *Histology*. 6th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins Health, pp.808-812.
13. Ross, M. and Pawlina, W. (2011). *Histology*. 6th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins Health, pp.808-812.