PREDICTION OF HYPOECHOIC LESIONS ON ULTRASOUND OF PROSTATE CANCER BASED ON PSA INTERVAL AND GLEASON GROUP

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ABSTRACT

Objective: *To evaluate hypoechoic lesion in transrectal ultrasonography of prostate (TRUS-P) predictive value on prostate cancer based on PSA Interval and Gleason Group.* ***Material & Methods:*** *An observational analytic study with a cross-sectional design take place from January 2015 to December 2018 analyzing patients who had undergone TRUS-P Biopsy at Hasan Sadikin Hospital. Patients are divided into several subgroups according to different PSA levels. A p-value < 0.05 was considered statistically significant. PPV, NPV, and Youden's index were all indexes reflecting the performance of a diagnostic test.* ***Results:*** *There were 35 cases (49.3%) with a visible hypoechoic lesion in TRUS and 36 cases (41.7%) without a visible hypoechoic lesion. In our study, 23.9% of the patients with hypoechoic lesions were diagnosed with prostate cancer on TRUSP-Biopsy. The results of the analysis with Youden's index show that PSA at intervals of 10-20 is the best predictor of diagnostic values. Then we analyzed the overall detection rate based on PSA interval. Patients with PSA > 20 ng/ml, hypoechoic lesions were significantly associated with Gleason Group.* ***Conclusion:*** *We concluded in our study that the hypoechoic lesion in transurethral ultrasonography of prostate could improve the predictive efficacy for diagnosing prostate cancer.*

Keywords: *Prostate cancer, ultrasonography, hypoechoic lesion.*

ABSTRAK

Tujuan: *Mengevaluasi nilai prediksi dari lesi hipoekoik pada ultrasonografi transrektal prostat (TRUS-P) pada pasien kanker prostat berdasarkan Interval PSA dan Gleason Group.* ***Bahan & Cara:*** *Penelitian analitik observasional dengan desain cross-sectional, yang dilakukan pada bulan Januari 2015 sampai dengan Desember 2018, dengan menganalisis pasien yang telah menjalani Biopsi TRUS-P di RS Hasan Sadikin. Pasien dibagi menjadi beberapa sub kelompok sesuai dengan tingkat PSA yang berbeda. Nilai p < 0.05 dianggap signifikan secara statistik. PPV, NPV, dan indeks Youden semuanya adalah indeks yang mencerminkan performa uji diagnostik.* ***Hasil:*** *Terdapat 35 kasus (49.3%) dengan lesi hipoekoik yang dapat terlihat saat TRUS, dan 36 kasus (41.7%) dengan lesi hipoekoik yang tidak terlihat. Dalam penelitian ini, 23.9% dari pasien dengan lesi hipoekoik didiagnosis sebagai kanker prostat pada Biopsi TRUS-P. Hasil analisis dengan indeks Youden menunjukkan bahwa PSA pada interval 10-20, merupakan prediktor terbaik sebagai nilai diagnostik. Kemudian kami menganalisis tingkat deteksi keseluruhan berdasarkan interval PSA. Kami temukan bahwa lesi hipoekoik secara signifikan berhubungan dengan Gleason Group pada pasien dengan PSA > 20 ng/ml.* ***Simpulan:*** *Bahwa lesi hypoechoic pada ultrasonografi transurethral prostat (TRUS-P) dapat meningkatkan keefektifan dari nilai prediktif dalam mendiagnosis kanker prostat.*

Kata Kunci: *Kanker prostat, ultrasonografi, lesi hipoekoik.*

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INTRODUCTION

Prostate cancer (PCa) is one of the most frequently diagnosed malignant tumors and the second leading cause of cancer deaths among men worldwide.[1] Based on the 2018 Globocan statistics, the incidence of prostate cancer in Indonesia ranks 12th. Prostate cancer estimates at 11.3 per 100.000 men in Indonesia.[2] Early detection of prostate cancer, especially cases of clinical significance, is the key to disease control.

A prostate biopsy is the only confirmation diagnostic tool for prostate cancer. Since the introduction of multiparametric prostate magnetic

resonance imaging (mpMRI) to detect and stratify PCa, much research has been done to explain the benefits of using mpMRI to increase PCa detection rates.[3] However, this procedure requires sophisticated technology and costs much higher.[4] Detection of the hypoechoic lesion by TRUS has reported controversial results. Although TRUS has a lack of abnormal specificity abnormalities and difficulties in tumor and tissue differentiation.[5] It improves the visualization of prostate lesions and is routinely used by most urologists for diagnosis and staging of local prostate cancer. At present, it is accepted that 60-70% of prostate cancer is hypoechoic, and about 30-40% is isoechoic or invisible. Prostate cancer originating from hyperechoic lesions is sporadic, with 1% to 1.5% incidence.[2]

A breakthrough in diagnostics occurred when Transrectal Ultrasonography (TRUS) was used to visualize prostate and guide biopsy. Biopsy with TRUS guidance is not without obstacles, but this technique is a substantial advance compared to the previous method. Levin and colleagues showed that an additional 12-core biopsy succeeded in detecting 30% more cancers than 6-core, leading to a 12-point systematic biopsy scheme that included anterior and lateral zones.[6]

OBJECTIVE

This study aims to investigate the hypoechoic lesion on ultrasound to see their predictive ability, as evidenced by the results of prostate biopsy examination.

MATERIAL & METHODS

The subjects included in this study were patients diagnosed with prostate cancer, which had been proven by histopathological examination based on transrectal prostate biopsy and results of prostatic transrectal ultrasound in men who came for treatment at the Urology Outpatient Unit of the Hasan Sadikin General Hospital Bandung, in January 2015 to December 2018. Patients who had elevated levels of PSA above four ng/ml or susceptible nodules of the prostate gland in DRE received the transrectal ultrasound and prostate biopsy. Patients with negative PA results of Prostate Cancer were excluded from this study. Prostate biopsy was performed by both surgeon and resident.

Clinical parameters involving age, DRE, PSA, prostate volume, pathological diagnosis, and Gleason group documented for each patient. Patients are divided into several subgroups according to different PSA levels and transrectal ultrasound findings. Statistical analysis was performed by applying a Chi-square test. A p-value < 0.05 was considered statistically significant. Statistics analysis was conducted with the software of SPSS v21.0. PPV, NPV, and Youden's index were all indexes reflecting the performance of a diagnostic test. The higher the value of these indexes, the better the predictive efficacy.

RESULTS

Table 1. explains the comparison between Age, Grading, and histopathological results. In the TRUSP group with hypoechoic lesions, the mean age was 65.54 ± 7.624 years. The average PSA had 242.12 ± 424.620. Patients with nodules were 11 (31.4%), and patients without nodules were 24 (68.6%). The average volume of the Prostate is 54.80 ± 35.636. Patients with PA results in the Adenocarcinoma Prostate category were 17 (48.6%) and patients with Benign Prostatic Hyperplasia were 18 (52.9%).

Of 71 patients, there were 35 patients without hypoechoic lesions and 36 patients who had hypoechoic lesions on transrectal ultrasound prostate examination. The presence of palpable nodules during the digital rectum and the higher Gleason score is statistically related to the presence of hypoechoic lesions on transrectal prostatic ultrasound.

Table 2. describes the compilation of PSA with concentrations of 0-4 ng/ml, sensitivity, specificity, PPV, NPV are 0%, 100%, 0%, and 100%, respectively. At 4-10 ng/ml, sensitivity, specificity, PPV, NPV are 0%, 71.4%, 0%, and 100%, respectively. In groups with PSA 10-20 ng/ml, the four values were 100%, 62.5%, 40%, and 100%. In the group with PSA > 20 ng/ml, the four values were 52%, 44.4%, 56.5%, and 40%.

Then an analysis is performed to assess and evaluate this diagnostic test with a combined index. The combined index used in this analysis was Youden's Index, where this index is the amount of sensitivity plus specificity minus 1. The formula is as follows: $J = s + f - 1$. Youden's indexes of the four PSA intervals are 1.000, 1.000, 0.087, and 0.818, respectively.

Table 1. Characteristic of the study population

Variable	TRUSP		P-value
	Hypoechoic Lesion N = 35	No lesion N = 36	
Age			
Mean±Std	65.54 ± 7.624	66.72 ± 5.406	0.454
Range (min-max)	51.00 - 84.00	54.00 - 75.00	
PSA (ng/mL)			
Mean ± SD	242.12 ± 424.420	49.23 ± 77.342	0.064
Range (min max)	8.83 1634.00	0.18 375.72	
DRE			
Nodul	11 (31.4%)	0 (0.0%)	0.0001*
Without Nodule	24 (68.6%)	36 (100.0%)	
Volume Prostat (mL)			
Mean ± SD	54.80 ± 35.636	47.02 ± 18.007	0.913
Range (min-max)	15.40 - 172.00	16.20 - 89.40	
Pathologic Diagnostic			
Adenocarcinoma Prostat	17 (48.6%)	12 (33.3%)	0.804
Benign Prostatic Hyperplasia	18 (52.9%)	24 (66.7%)	
Gleason Group			
I	2 (5.7%)	6 (16.6%)	0.058
II	-	-	
III	2 (5.7%)	4 (11.1%)	
IV	2 (5.7%)	6 (16.7%)	
V	13 (37.1%)	2 (5.6%)	

Notes: For numerical data, the p-value was tested by an unpaired T-test. We used an unpaired T-test when the data normally distributed, and we used Mann -Whitney when the data not normally distributed. Categorical data on the p-value is calculated based on the Chi-Square test with an alternative of the Kolmogorov Smirnov and Exact Fisher test if the terms of Chi-Square are not met. Value of significance based on p-value < 0.05. Sign * shows a p-value < 0.05, meaning significant or statistically significant.

Table 2. The ability to predict hypoechoic lesions in prostate cancer from several PSA intervals.

Interval PSA (ng/mL)	Hipoechoic	Cancer	No Cancer	Sensitivity (%)	Spesifisity (%)	PPV	NPV	Youden Index	Detection rate	P-value
0-4	+	0 (0.0%)	0 (0.0%)	0%	100%	0%	100%	0	0	1.000
	-	0 (0.0%)	1(100.0%)							
4-10	+	0 (0.0%)	2 (28.6%)	0%	71.4%	0	100%	-0.286	0	1.000
	-	0 (0.0%)	5 (71.4%)							
10-20	+	4 (100.0%)	6 (37.5%)	100%	62.5%	40%	100%	0.625	40.0	0.087
	-	0 (0.0%)	10 (62.5%)							
> 20	+	13 (52.0%)	10 (55.6%)	52%	44.4%	56.5%	40%	-0.04	56.6	0.818
	-	12 (48.0%)	8 (44.4%)							

Notes: Categorical data of p-value are calculated based on the Chi-Square test with an alternative Kolmogorov Smirnov test and Exact Fisher. If the requirements of Chi-Square don't fulfill, then the significance value is based on a p-value < 0.05. Sign * indicates p-value < 0.05 means significant or statistically meaningful.

Table 3. PSA Level on Cancer and non-Cancer Subjects.

Variable	Group		P-value*
	Cancer N = 29	Non-Cancer N =4 2	
PSA			
Mean±Std	297.32 ± 451.515	38.67 ± 59.277	0.0001**
Median	44.14	18.05	
Range (min-max)	11.00 - 1634.00	0.18 - 347.00	

Note: Considered significant if P < 0.05.

Table 4. Difference and Proportion Regard to Cut off PSA in Cancer and non-Cancer Patient.

Variable	Group		P-value
	Cancer N=29	Non-Cancer N=42	
PSA			
> 26.99	21 (72.4%)	14 (33.3%)	0.001**
< 26.99	8 (27.6%)	28 (66.7%)	

Sensitivity = a/(a+c) = 21/29 100% = 72.4%
Specificity = d/(b+d) = 28/42 x 100% = 66.7%
PPV = a/(a+b) = 21/35x100% = 60.0%
NPV = d/(c+d) = 28/36 x 100% = 77.7%
Accuracy = (a+d)/N = 49/71x 100% = 69.0%

Table 3. describes the patient in the cancer group who has an average PSA of 297.32 ± 451.515. Meanwhile, in the non-cancerous group was 38.67 ± 59.277. P-value was less than 0.05, means there was a significant difference PSA between cancer non-cancerous group.

Table 4. showed the difference PSA in cancer and non-cancer group. PSA > 26.99 was found in 21 (72.4%) patients with cancer and PSA < 26.99 was found in 8(27.6%) patients. Meanwhile, PSA > 26.99 was found in 14 (33.3%) Non-cancerous patients and PSA < 26.99 in 28 non-cancerous patients. P-value was found less than 0.05, which means there was a significant difference in PSA cut-off between the cancer group and the non-cancer group.

The sensitivity result was 72.4% (moderator), and specificity was 66.7% (Weak). PPV was also weak. But NPV was found at a moderate level. From those results, we could conclude there was a relationship between PSA level cutoff and cancer. Although our current result showed a relatively low result in PPV, sensitivity, and specificity, it was the first to analyze this finding. Furthermore, the AUC on the ROC curve (77.4%, closer to 80%) showed moderate strength of PSA to discriminate cancer group, with significant P value, therefore it indicates a tendency towards a proper clinical value, with a larger population needed to validate this result, with higher PPV, specificity, and sensitivity should be expected then.

Figure 1. describes the ROC (receiver operating characteristic) curve. As the curve near 100%, the PSA level had a strong diagnostic value. AUC (area under the curve) was 77.4%,with p-value 0.000. It means significant.

Based on calculations, the PSA cut-off point in this study was 26.99 with a sensitivity value of 72.4% and a specificity value of 66.7%. Based on the above calculation, sensitivity has a value almost the same as specificity, so it concludes that sensitivity and specificity produce positive accuracy values that are different from negative accuracy values.

Table 5. shows the relationship between hypoechoic lesions, the Gleason group based on the PSA interval. For the analysis of categorical data in table 4.6, it was tested using the Kolmogorov-Smirnov statistical test, Hypoechoic at the PSA interval 0-4, Hypoechoic at the PSA 4-10 interval, Hypoechoic at the PSA interval 10-20 and Hypoechoic at PSA interval > 20. As we can see from the table, hypoechoic lesions tend to detect in patients with higher Gleason scores. In patients with PSA > 20 ng/ml, hypoechoic lesions were significantly associate with Gleason Group with a p-value < 0.05

In our study, patients who had hypoechoic lesions had a higher Gleason Grade group than those who did not, especially for patients with PSA > 20 ng/ml.

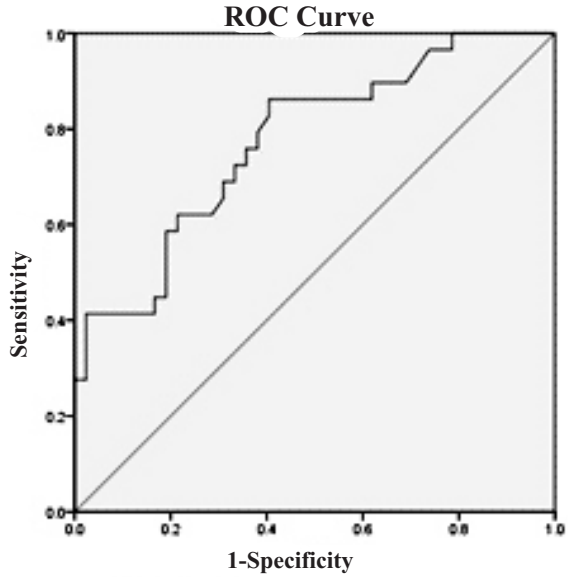

Figure 1. PSA in the cancer group.

Table 5. Relationship between hypoechoic lesions and Gleason groups from PSA intervals.

Interval PSA (ng/mL)	Hypoechoic	Gleason Group I	Gleason Group II	Gleason Group III	Gleason Group IV	Gleason Group V	P-value
0-4	+	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.000
	-	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
4-10	+	2 (28.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.000
	-	5 (71.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
10-20	+	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (100.0%)	2 (100.0%)	0.789
	-	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
>20	+	0 (0.0%)	0 (0.0%)	1 (20.0%)	1 (14.3%)	11(84.6%)	0.001**
	-	0 (0.0%)	0 (0.0%)	4 (80.0%)	6 (86.7%)	2 (15.4%)	

Notes: The value of p from categorical data is calculated based on a Chi-Square test with an alternative test of Kolmogorov Smirnov and Exact Fisher if the condition of Chi-Square is not fulfilled. p-value based on $p < 0.05$. Note * indicates the value of $p < 0.05$, meaning significant or statistically significant.

DISCUSSION

The incidence of prostate cancer is increasing in Indonesia, although it is still lower than in Western and other Asian countries.[1] TRUS-guided biopsy is still the only accurate preoperative method for the early diagnosis of prostate cancer. Besides having great importance in guiding the needle direction for prostate biopsy, TRUS allows the visualization of suspected focal lesions of prostate cancer. Biopsy samples taken from the prostate by a TRUS-guided biopsy when the hypoechoic lesion is present are more likely to show cancer. Hypoechoic lesions can also be detected in other diseases including granulomatous prostatitis, prostate infarction, and lymphoma.

Literature reviews from several Asian countries found that the detection rate of prostate cancer in patients with raised PSA levels lay within the range of 14.4% to 26.5%. The detection rate of prostate cancer by serum PSA levels is different in Indonesian men as compared to other populations. In our study, there were 17 patients with prostate cancer with hypoechoic. The detection rate from this study

was 24 %. In their study, Yuri et al. observed a prostate cancer diagnosis rate of 40.1%. This value was much higher than we observed.

The proportion of PSA Interval in all patients with prostate cancer was shown in table 2. PPV (Positive predictive value), NPV (negative predictive value), and Youden's index were used to evaluate the predictive efficacy of a hypoechoic lesion in predicting prostate cancer. PPV reflected the possibility of prostate cancer in patients who had a hypoechoic lesion in ultrasound and NPV reflected the possibility of non-prostate cancer in patients who did not have a hypoechoic lesion.

The results of our study show that the Youden's index at PSA intervals of 10-20 was 0.625 which is the highest and closest to 1. This means that PSA 10-20 is the best predictor or diagnostic value because it has the most substantial Youden index value.

To further investigate the relationship between prostate cancer and hypoechoic lesions, we classified patients according to different PSA intervals and the Gleason group. According to the novel prostate cancer grading system, we reclassified the patients by the new five grades based on the revised original Gleason score: group 1 (Gleason score ≤ 6), group 2 (Gleason score 3 + 4 = 7), group 3 (Gleason score 4 + 3 = 7), group 4 (Gleason score 8), and group 5 (Gleason score 9 –10).

We found that hypoechoic lesions were significantly associated with a prostate cancer diagnosis at all PSA intervals and had the highest predictive ability in patients with PSA > 20 ng/ml, as expected, followed by PSA 10-20, PSA 4-10, and PSA < 4. The p-value on the hypoechoic variable at the PSA interval > 20 is 0.001, which smaller than 0.05 (value < 0.05), which means that it is a statistically significant proportion of the difference between the hypoechoic variable at the PSA interval > 20 in the Gleason score group.

Several studies have examined the use of hypoechoic lesions, an indicator related to TRUS with potential prostate cancer, as a risk factor in different PSA intervals. Our research can give a new dimension to the diagnostic value of hypoechoic lesions in prostate cancer. More confirmation studies were necessary to do in the future.

Shahab et al. estimate that PSA levels of around 6.95 ng/ml were an appropriate cut-off point in their study for prostate cancer detection in Indonesia (97.8% sensitivity and 19.6% specificity). The PSA cut-off point in our study was 26.99, with a sensitivity value of 72.4% and a specificity value of 66.7%. This value was much higher in our study than in the previous research.

The limitation of this study was the sample size. There were only 71 patients were recruited in this study. More subjects would help further analysis.

CONCLUSION

Hypoechoic lesion predicting carcinoma prostate shows a correlation in PSA interval and high Gleason score. We concluded in our study that the hypoechoic lesions in TRUS could improve the predictive efficacy for diagnosing prostate cancer in the respective PSA Interval and higher Gleason Score. Further investigation is needed in a larger sample size.

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