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Diagnosis value of prostate specific antigen density (PSAD) and prostate specific antigen (PSA) in bone metastases of prostate cancer among Indonesian population

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ABSTRACT

Cancer prostate (PCa) is currently reported as the most diagnosed cancer in males. Bone metastases in PCa indicate poor prognosis and the major cause of pain and death. Early diagnosis of metastases is important in PCa management. Prostate specific antigen (PSA) velocity was used to predict overall survival and metastasis-free survival. However, this test should be conducted 2 times, for at least 4 weeks apart. Therefore, a cross-sectional test with higher positive probability value is needed. This study aimed to compare PSA density (PSAD) and PSA level to evaluate patients at risk of bone metastases in Yogyakarta, Indonesia. Aretrospective study with a total subject of 106 patients with (n = 31) and without (n = 75) bone metastases were analyzed. The initial PSA measurement, as well as bone scan and prostate volume, were evaluated in all patients. Bone survey found to be positive in 31/106 (29.2%) patients. The total of 50(47.2%), 10(9.4%) and 46(43.4%) patients had PSA level <50, 50-100 and >100ng/mL, respectively. Furthermore, receiver operating characteristic (ROC) area under the curve of PSAD (0.75) was higher that that ofPSA (0.65).PSAD more than 0.15 indicated sensitivity of 93% and specificity of 38%, while PSA more than 20 ng/mL shown sensitivity 82% and specificity 21%. In conclusion, PSAD level more than 0.15 shows high sensitivity and specificity in causing potential skeletal metastases. Using this PSAD cut-off value, unnecessary investigation canbe avoided.

ABSTRAK

Kanker prostat (PCa) saat ini dilaporkan sebagai kanker yang paling banyak didiagnosis pada pria. Metastasis tulang pada PCa menunjukkan prognosis yang buruk dan penyebab utama nyeri dan kematian. Diagnosis dini metastasis penting dalam manajemen PCa. Kecepatan antigen spesifk prostat (PSA) telah digunakan untuk memprediksi kelangsungan hidup secara keseluruhan dan kelangsungan hidup bebas metastasis. Namun demikian, tes ini harus dilakukan 2 kali, setidaknya selama 4 minggu. Oleh karena itu, tes potong lintang dengan nilai probabilitas positif yang lebih tinggi diperlukan. Penelitian ini bertujuan untuk membandingkan tingkat PSA *density* (PSAD) dan PSA untuk mengevaluasi pasien yang berisiko metastasis tulang di Yogyakarta, Indonesia. Ini merupakan penelitian retrospektif dengan subjek total 106 pasien dengan (n = 31) dan tanpa (n = 75) metastasis tulang dianalisis. Pengukuran PSA awal, serta pemindaian tulang dan volume prostat, dievaluasi pada semua pasien. Survei tulang ditemukan positif pada 31/106 (29,2%) pasien. Total 50(47,2%), 10(9,4%) dan 46(43,4%) pasienberturut-turutmemilikikadar PSA <50, 50-100, dan >100 ng/mL. Selanjutnya, area di bawah kurva ROC menunjukkan kurva PSAD (0,75) lebih tinggi dibandingkan PSA (0,65). Nilai PSAD lebih dari 0,15 mempunyai sensitivitas 93% dan spesifisitas 38%, sementara PSA lebih dari 20 ng/mL mempunyai sensitivitas 82% dan spesifisitas 21%. Level PSAD lebih dari 0,15 menunjukkan sensitivitas tinggi dan spesifisitas dalam memperkirakan potensi metastasis tulang. Dengan menggunakan nilai ambang batas PSAD ini, pemeriksaan yang tidak perlu bias dihindari.

Keywords:
prostate cancer;
metastatic prostate cancer;
PSAD;
PSA;
bone metastases;

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INTRODUCTION

Prostate cancer (PCa) is well known as the most common cancer among men. Various biomarkers was introduced over the last decades for the early screening and surveillance of PCa. Currently, prostate specific antigen (PSA) is one of the indicators of the bone investigation in several guidelines.[1,2] The appearance of PSA as biomarker screening for early diagnosis has shown effectiveness and is noted to have reduced more than half the morbidity and mortality due to early detection. However, the use of PSA as indication of bone investigation wasassociated with relatively high false positive, especially in grey area (PSA <20ng/mL) and it has resulted in over-diagnosis and therapy and affected the quality of management of patients.

On current the European Association of Urology (EAU) Guidelines, the bone investigation is performed in symptomatic patients and high PSA level. Despite PSA used on monitoring progress prostate cancer, the positive finding among patients with PSA level between 20.0 – 49.9 ng/mL is just 16.2%.[1]This indicates that overuse of this modality is an issue in bone investigation. The overuse remains an issue both in term of financial burden and lower quality of life patient. Medicare reported the bone investigation and downstream procedures used at a cost of $ USD 11,300,000.00- annually and only found 14% were positive.[2] In contrast, late staging or under staging resulted in standards that caused poor outcomes in PCa.

Several options beside PSA have been developed such as PSA density (PSAD), PSA velocity (PSAV), and PSA body mass index (PSABMI) as the surveillance indicator in both screening and evaluation of PCa. The use of PSA as indicator bone metastatic investigation may lead to overtreatment and overused bone survey. A study reported that PSAD is a more powerful predictor of clinical stage and prognosis compared to PSA. However, its role in predicting the bone metastatic needs to be evaluated.[3] Thus, this study as aimed to determine the role of PSAD compared to PSA in predicting bone metastatic in PCa.

METERIALS AND METHODS

Subjects and data collection

This study was conducted in Dr. Sardjito General Hospital, Yogyakarta, Indonesia. Patients were selected from the database and medical records. The data in this study were collected from the medical records with patient's criteriashowing clinical signs and symptoms of PCa and confirmed histological diagnosis of PCa, bone survey, routine PSA measurement. Prostate volume measurement by USG wereenrolled on this study.The data was collected from July 2015to January 2019. Patients who underwent previous related surgery, hormonal treatment prior to PSA check in Dr.Sardjito General Hospital, radiation therapy prior to PSA measurement were excluded from this study.

Prostate examination

Prostate volume was calculated with a TAUS examination. The patient was examined with a 3.5 MHz convex probe in the supine position. The prostate was examined in the sagittal and transverse plane; the largest dimensions of the prostate in the mid-transverse and mid-sagittal plane were recorded. Prostate measurement was calculated according to the ellipsoid shape formula:(Height x Length x Width τ/6). PSAD was calculated by divided PSA with Prostate volume that estimated on the TAUS examination. This study received approval from the Medical and Health Research Ethic Committee, Faculty of Medicine, Public

Health and Nursing, Universitas Gadjah Mada, Yogyakarta (Ref. KE/0644/05/2019).

Statistical analysis

The cut of value of PSAD determined sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV). Statistical analysis was performed using SPSS version SPSS 17.00.

RESULTS

A total of 112 eligible patients were enrolled in this study. Only 6 patients were excluded due to incomplete data. The mean of ages for metastases group was 67.62 ± 7.7 years and the non-metastases group was 69.80± **8.7 years.** There wasno statistical difference among ages between groups. The demographic data of this study is shown in TABLE 1.

TABLE 1. Demographic data

Parameters	n	p
PSA (%)		
• <50	65	
• 50-100	22	>0.05
• >100	19	
Ages (mean ± SD years)	69.11 9.2	
PSA (mean ±SD ng/mL)	50.80±150	
TAUS (mean± SD cm^3)	80.4 36.1	
Site of bone metastasis		
• Multiple	7	
• Pelvis	6	
• Vertebra thoracic	7	
• Cranium	1	
• Pelvis	3	
• Upper extremities	2	
• Lower Extremities	4	

The mean of non-metastases PSA was 43.34± 41.54 ng/mL and metastases group was 122.3 ± 122.32 ng/mL.T here was statistical difference between two groups (p=0.001). The size of prostate was56.220.16 cm^3 in both groups.

The majority of prostate values in this study were less than 50 ng/mL (47.2%), with more than 100 ng/mL(43.4%),and the between 50-100 ng/mL. The mean of ages for metastases was 67.62 7.7 years, and none metastasis was 69.80 8.7 years. The mean of PSA non-metastases was 70.94±45.08 ng/mL and prostate size was 56.2 20.16 cm^3.

Bone metastases were the most common site of metastases. Bone survey was found to be positive in 31 patients (29.2%). The mean of patient's age was 69 9 years, from the 31 29.2%. In the ROC, area under the curve (AUC) of PSAD (0.75) showed higher compared to PSA (0.65). PSAD more than 0.15 ng/mL/cm^3 shown sensitivity 93% and specificity 38% compared to PSA more than 20 g/mL which shown sensitivity 82 % and specificity 21% (FIGURE 1).

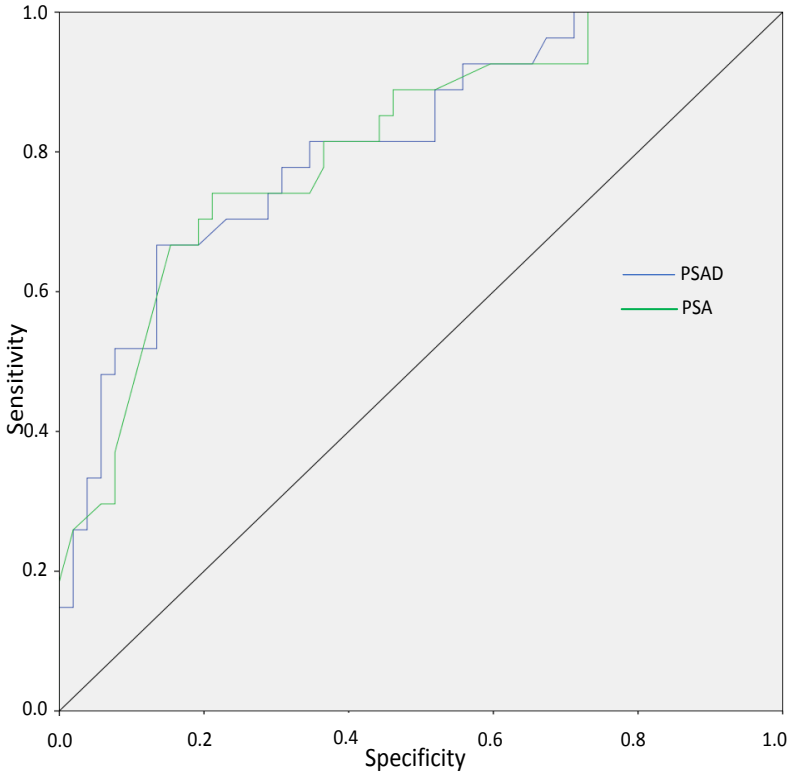

FIGURE 1. Receiver operating characteristic (ROC) curve showing sensitivity and specificity of PSA (blue line) and PSAD (green line) as diagnosed bone-metastasis. PSA: prostate specific antigen, PSAD: prostate specific antigen density.

Positive predictive value (PPV) of PSA in predictive bone metastases in this study was 93.33 (78.02-98.22%) and negative predictive value (NPV) was 34.15 (30.16-38.37%). Compared to PPV of PSAD, more than 0.15 ng/mL/cm^3 was found as much as 91.67 (78.56 - 97.08) and NPV as much as 35.53 (30.79 - 40.56). Although PSAD showed a wider AUC than PSA in the prediction of bone metastasis, PPV and NPV were observed to be comparable.

DISCUSSION

Early detection of metastases can reduce harm while maintaining the benefits of specific therapy. Bone metastases are recorded as the main problem in advanced stages of PCa, with the most common morbidities were caused by severe pain that required high doses of anti-analgesia, and pathological fractures that resulted in spinal compression of spinal problem.[4–7] Bone problems not only resulted from metastases itself, but also prostate cancer treatment such as androgen deprivation therapy (ADT). Pinpoint indication of bone investigation is needed to provide optimal clinical benefit to patients, and cost-effective management of PCa.

Various ways have been sought to correlate potential biomarkers of skeletal involvement with Gleason score >8, PSA >20 ng/mL, and PSAD > 0.15 ng/mL/cm^3.However, many studies showed contradictory results that make the debate unresolved. The American Urological Association (AUA) and European Society of Medical Oncology (ESMO) recommended to perform bone survey or bone scan if PSA valued over 20 ng/mL[8,9] and otherwise guidelines recommend that bone investigation remain independent from PSA levels.[10,11]

Thus, the role of PSA remains uncertainty due lack of sensitivity and specific as indicator bone metastases.

With the lack of supporting data, PSA remains arbitrary as an indication for bone investigation. However, PSA remains an irreplaceable biomarker for PCa. The current cut-off widely used as indication of bone survey was PSA level of 20 ng/mL, while PSAD has been reported better specificity and sensitivity on PCa evaluation.[12–16] Our study confirms similar results, and the data shown PSAD has better area under the curve (0.75) compared to PSA (0.65).

Our study confirmed that using cut off point 0.15 ng/mL/cm^3 was better compared to 20 ng/mL of PSA. On the other hand, when the reference point of PSA 20 ng/mL was adopted, PSA showed better results on positive predictive for the bone metastases compared to PSAD. However, PSAD shown better on excluding bone metastases compared to PSA itself. These results indicated that PSA is superior as a surveillance tool but can cause over diagnoses and unnecessary treatment. Both PSA and PSAD may play important roles as indication of bone investigation, with aforementioned pros and cons these modalities still need further study on their role. More focused studies on patients with PSA less than 20 ng/mL are needed to establish its role as an indication of bone investigation.

The limitation of this study was the level of PSA that enrolled in relatively considered high risks.Further study on patients with PSA lower than 20 ng/mL is needed to establish clear protocols for usage of PSAD. In addition, in this study we used bone survey on evaluating bone metastatic, this method may results higher false-negative compared the standard 99mTc-Bone scan. Even though it is too early to conclude that the predictive value of PSAD in bone metastases, this study indicated that PSAD may has potential to minimize the overuse of bone survey. The future direction of this study is to confirm the use of PSAD as indicator of bone evaluation and more focusing on lower PSA levels.

CONCLUSION

The study shows that using cut off point 0.15 ng/mL/cm^{3}of PSAD is better compared to 20 ng/mL of PSA.PSA shows better results on positive predictive for the bone metastases compared to PSAD. However, PSAD shows better on excluding bone metastases compared to PSA itself.

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