RESEARCH ARTICLE

Correlation between Low Gleason Score and Prostate Specific Antigen Levels with Incidence of Bone Metastases in Prostate Cancer Patients: When to Omit Bone Scans?

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Abstract

Background: To identify correlation and incidence of bone metastases in prostate cancer patient with low Gleason scores (GS) and prostate specific antigen (PSA) levels. Materials and Methods: This descriptive restrospective study covered patients with prostate cancer in Cipto Mangunkusumo Hospital in 2006-2011. Of a total of 478, those who had PSA values, histological examination, and bone scan were included, resulting in 358 eligible cases. PSA values were measured using the sandwich electrochemiluminescent immunoassay. Histological examination was graded according to Gleason's grading system and divided into 3 categories: well differentiated (GS≤6), moderately differentiated (GS 7) and poorly differentiated (GS 8-10). Bone scans were performed using a radiopharmaceutical agent (Tc 99m methylenen diphosphonate) with images captured by gamma camera. Results: The mean age was 67.5±7.8, mean GS was 7.7±1.3 and median PSA was 56.9 (range: 0.48-17000 ng/mL). There were 11 patients (3.0%) with positive bone scan with PSA<20 ng/mL and GS<8. Furthermore, there were 2 patients (0.6%) with GS≤6 and PSA<10 ng/mL showing bone metastasis. Conclusions: In our study, there were still small percentage of patients with bone metastasis even when low values of PSA (PSA<10 ng/mL) and GS (GS≤6) were applied.

Keywords: Prostate cancer - low PSA - low GS - bone metastases - bone scans

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Introduction

Cancer is the leading cause disease and death worldwide. Among all cancers, prostate cancer is second most frequently diagnosed cancer of men after lung cancer. (Quinn and Babb, 2002; Ferlay et al., 2010; Jemal et al., 2010). Almost 75%, of registered prostate cancer cases occurred in developed countries, the highest incidence rates occurred in Northern America and Europe region, meanwhile the lowest rate was in South-East Asia Region (8.3 per 100,000) (Ferlay et al., 2010; Center et al., 2012). Despite the low incidence of prostate cancer, there is rapid increasing of prostate cancer's incidence and mortality in Asian countries due to more westernized lifestyle and high proportion of advanced stage prostate cancer's patients. (Matsuda and Saika, 2009; Ferlay et al., 2010; Namiki et al., 2010).

Bone Metastasis (BM) is the commonest metastasis site of prostate cancer (90%) and the first site to be metastasized by the cancers' cells, preceding the lung and liver (Bubendorf et al., 2000; Nguyen et al., 2009). Bone metastasis occurred up to 14% cases at presentation and around 80-85% in advanced stage (Pal et al., 2008; Sadik et al., 2008; Zaman et al., 2011). Planar Bone Scan (BS) is the most sensitive method (72-77%) to detect BM and currently is the investigation of choice (Sadik et al., 2008; Zaman et al., 2011). Many studies had confirmed that incidence of BM correlated positively with staging of the tumor, PSA and Gleason Score (GS) (Pal et al., 2008; Briganti et al., 2010; Lai et al., 2011; Zaman et al., 2011; Mateen et al., 2012). However, there was still a lack of consensus, of the selection of criteria for bone scan in low risk patients, and PSA and GS cut-off value. Though, European Association of Urology (EAU), American Urological Urological Association (AUA) and American Joint Committee on Cancer (AJCC) had recommended similar indication for BS, which were: GS>7, PSA level>20 ng/mL and presence of bony symptoms, based on studies in western countries (Axel et al., 2007; Sadik et al., 2008). Interestingly, there were several studies in Asian countries that revealed incidence of BM in prostate cancer's patients, despite of low PSA and GS. Ito et al. (2000) in Japan Screening Program had reported 36% incidence of BM in patients with PSA≤10ng/mL, Yang et al. (2009) in China reported 19% incidence of BM in patients with PSA <20ng/mL, and the most recent study form Pakistan by Zaman et al. (2011) reported 14% incidence of BM in PSA≤10ng/mL.

The purpose of the current study was to identify and correlate the incidence of BM in low PSA and GS in prostate

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cancer patients in Indonesian population. Furthermore, evaluating the recommendation of international urology consensus of prostate cancer's patient selection to undergone BS.

Materials and Methods

This study was a retrospective study of patients diagnosed with prostate cancer in Cipto Mangunkusumo hospital in 2006-2011. Data were collected from the medical records of the patients. Recorded data were PSA value, histopathological examination of prostate's tissue, and bone scan result.

PSA value was measured using the sandwich electrochemiluminescent immunoassay technique. The PSA value in the study was divided into 5 categories: <10 ng/mL, 10 to ≤20 ng/mL, 20 to ≤50 ng/mL, 50 to ≤100 ng/mL, and >100 ng/mL. Prostate tissue for histopathological examination were obtained from various ways: Trans-Rectal Ultrasound (TRUS) Prostate biopsy, Trans-Urethral Resection of Prostate (TURP) and surgery (Open or Laparascopic Prostate Enucleation). Histological examination was graded according to the Gleason's grading system [International Society of Urological Pathology (ISUP) consensus, 2005] (Epstein et al., 2005). The histopathologic findings based on GS were divided into 3 categories, based on ISUP 2005 consensus: GS≤6, GS=7 and GS 8-10. Bone scans were done using radiopharmaceuticals agent (Tc 99m methylenen diphosphonate) and then the image was captured using gamma camera. The bone scan result was divided into patients with BM and patients without BM.

The data were analyzed using descriptive study in SPSS 17.0. Prostate Specific Antigen subgroups and GS subgroups to the incidence of BM were compared using Chi-Square test, $p<0.05$ was considered significant.

Results

There were 478 patients with prostate cancer in 2006-2011, and 358 patients with the complete data. The mean age of the patients was 67.52±7.8 years, median PSA was 56.9 (range: 0.48-17000 ng/mL), and mean GS were 7.7±1.3

Patients divided according to PSA value into 5 subcategories: <10 ng/mL, 10 to ≤20 ng/mL, 20 to ≤50 ng/mL, 50 to ≤100 ng/mL and >100 ng/mL. Meanwhile, GS were divided into 3 subcategories: GS≤6 (62/358; 17.3%), GS=7 (104/358; 29.0%) and GS≥8 (192/358; 53.6%).

The correlation between incidence of BM and PSA and GS value was shown in Table 1. Table 1 showed that PSA and GS had significant positive correlation with the incidence of BM ($p<0.001$) with highest incidence of BM occurred in PSA>100 ng/mL and GS≥8 group.

Bone scan result was also analyzed per subgroup of PSA value and GS combined. This, resulting in higher incidence of BM in subgroup of higher value of PSA and GS (Table 2).

Table 2 showed that higher PSA value was associated with higher GS. Patients with high PSA more likely to have high GS. In subgroup PSA<10 ng/mL, only 4 patients (2.1%) had GS≥8, compared to subgroup PSA>100 ng/mL, 79 patients (41.1%) had GS≥8. Patients with high PSA and high GS, had more percentage of having BM, and this percentage increased when subgroup of high PSA and high GS combined.

Low GS and low PSA value were also combined to see the incidence of BM when these 2 values were combined. The combination were PSA<20 ng/mL +GS<8 and PSA<10 ng/mL +GS≤6. There were 11 patients (3.1%) with positive BM (Negative Predictive Value of 96.9%) in first combination group and 2 patients (0.56%) with positive BM (Negative Predictive Value of 99.4%) in the second combination group.

In our study, 2 patients had BM, both of them were in

Table 1. Correlation between PSA Value and BM and between GS and BM

		BM+	BM-	Total
PSA value (ng/mL)	<10	10 (2.8%)	32 (8.9%)	42 (11.7%)
	10 to ≤20	15 (4.2%)	33 (9.2%)	48 (13.4%)
	20 to ≤50	24 (6.7%)	55 (15.4%)	79 (22.1%)
	50 to ≤100	32 (8.9%)	19 (5.3%)	51 (14.2%)
	>100	111 (31%)	27 (7.5%)	138 (38.5%)
Total		192 (53.6%)	166 (46.4%)	358 (100%)
GS	≤6	22 (6.1%)	40 (11.2%)	62 (17.3%)
	=7	46 (12.8%)	58 (16.2%)	104 (29.1%)
	≥8	124 (34.6%)	68 (19.0%)	192 (53.6%)
Total		192 (53.6%)	166 (46.4%)	358 (100%)

*p<0.001; PSA: Prostate Specific Antigen; BM: Bone Metastasis; GS: Gleason Score

Table 2. Bone Scan Results for Each PSA and GS Subgroup Combined

PSA (ng/mL)	GS≤6		GS=7		GS≥8		Total	
	+	-	+	-	+	-	+	-
<10	2 (0.5)	13 (3.9)	4 (1.0)	11 (3.3)	4 (1.0)	8 (2.4)	10 (2.6)	32 (9.6)
10 to ≤20	6 (1.5)	12 (3.6)	1 (0.3)	12 (3.6)	8 (2.1)	9 (2.7)	15 (3.9)	33 (9.9)
20 to ≤50	5 (1.3)	11 (3.3)	7 (1.8)	21 (6.3)	12 (3.2)	23 (6.9)	24 (6.2)	55 (15.0)
50 to ≤100	2 (0.5)	2 (0.5)	9 (2.3)	6 (1.8)	21 (5.4)	11 (3.3)	32 (8.3)	19 (5.7)
>100	7 (1.8)	2 (0.6)	25 (6.5)	8 (2.4)	79 (20.5)	17 (5.1)	111 (28.9)	27 (8.2)

PSA: Prostate Specific Antigen; GS: Gleason Score

Table 3. Incidence of BM in Low PSA Patients in Asian Countries

Country	(Study)	No of patients	PSA (ng/mL)	BM+ No. (%)
Pakistan	(Zaman et al., 2011)	204	≤20	15/119 (12.6%)
Japan	(Ito et al., 2000)	303	≤10	13/36 (36.1%)
China	(Yang et al., 2009)	77	<20	5/26 (19.2%)
Indonesia	(Current study)	358	≤20	25/90 (27.7%)
			<10	10/42 (23.8%)

*PSA: Prostate Specific Antigen; BM: Bone Metastasis

Table 4. Studies Recommending Lower Value of PSA and GS of Omitting BS

Country	(Study)	No. of Patients	BM+, No. (%)	Recommendation for performing BS (ng/mL)
USA	(Oesterling et al., 1993)	852	7 (0.8)	PSA>10
Turkey	(Ataus et al., 1999)	160	51 (24)	PSA>10
Italy	(Rudoni et al., 1995)	118	54 (45.8)	PSA>10
Germany	(Wolff et al., 1998)	359	40 (11.2)	PSA>10
Norway	(Haukaas et al., 1997)	287	128 (44.6)	PSA>10

*BM: Bone Metastasis; BS: Bone Scan; PSA: Prostate Specific Antigen

their 60's, prostate's nodules were palpated in digital rectal examination, had PSA value of 9.20 ng/mL and 8.82 ng/mL, and both had GS 6.

Discussion

The incidence of BM of this study was high (53.6%), compared to other studies (0.8-50%) (Briganti et al., 2010). Even it was still higher compared to the other developing Asian nations, such as Pakistan (33%) (Zaman et al., 2011). This high number of BM could be due to several causes: most of patients come with advance stages [in Jakarta, 62% prostate cancer patients came with metastatic disease (Akaza et al., 2012)], majority of the patients came with high PSA and GS at diagnosis, and BS was performed to all of PC patients regardless of the PSA and GS value (McArthur et al., 2012). The other studies that had high percentage of BM in western countries were conducted in Italy in 1995 (45.8%) and in Norway in 1997 (44.6%) (Rudoni et al., 1995; Haukaas et al., 1997).

The EAU recommended that PC patients with PSA<20ng/mL, GS<8, and absence of bony symptoms could be omitted from BS, and this recommendation had been validated by Briganti et al. (2010) in Italy with 853 PC patients. They found that the recommendation had 99% negative predictive value, 70.8% sensitivity and 88.7% specificity. Moreover, recent study by McArthur et al. (2012) with 672 PC patients found negative predictive value of 100% by applying EAU guidelines. These recent studies were conducted in Europe, which had different PC patients' characteristics than PC patients in Asia, including Indonesia.

When applying the EAU/AUA recommendation, there will be 11 patients missed the diagnostic of BM. Several studies in Asia also found similar findings. Somehow there were higher incidence of BM in low PSA and GS in Asian population, even though there were lower incidence of prostate cancer. This phenomenon was still not well understood. The studies reported incidence of BM in low PSA were shown in Table 3.

Those findings were contrary to the EAU recommendation. Even when lower PSA and GS was applied in our study (PSA<10 ng/mL and GS≤6) there were still 2 patients (0.56%) had BM. By lowering the value of GS and PSA (PSA<10 ng/mL and GS≤6) we had similar negative predictive value with the validation study by Briganti et al (PSA<20 ng/mL and GS<8) which were 99.4% vs 99%. There were also several studies recommended lower PSA value as a cutoff point of having BS (Table 4).

Lin et al. (1999) also found patients with BM in PSA<10 ng/mL (1.6%) and GS≤6 (2.5%). Due to this findings, they couldn't find any exclusions criteria for BS. Therefore, recommended BS to be performed in all PC patients (Lin et al., 1999). Similar to our study, was by Kosuda et al. (2002) that stated BS could be safely omitted in PSA<10 ng/mL and GS≤6, though there were still 1.33% patients with BM in the exclusion criteria group (meanwhile our study was 0.56%). Those 2 studies showed that there were still incidence of BM in low PSA and GS (similar low cutoff PSA and GS as in our study) in Asian population, and those findings were contrary to the application of EAU recommendation in Asian population.

Limitation of the study was no adequate follow up to the patients with metastatic bone disease in prostate cancer patients with low PSA and GS and this study did not investigate other variables that could predict BM such as: alkaline phosphatase and bony symptoms.

In conclusion, there was high incidence of BM in newly diagnosed PC in our study (53.6%) compared to other studies; PSA and GS positively related to the incidence of BM; and there were still small number of patients had BM with low GS and PSA.

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