Is bone scintigraphy necessary in initial staging of prostate cancer patients?

Abstract

Our aim was to determine whether serum prostate specific antigen (PSA) and total Gleason score (GS) on biopsy in newly diagnosed prostate cancer (PCa) can predict osseous metastases and eliminate the need for a bone scan as a routine procedure in initial staging. *We studied* retrospectively 155 patients with previously untreated PCa who underwent bone scintigraphy. Relationship between PSA, GS and bone metastases was examined. Sensitivity, specificity, likelihood ratio (LR) and odds ratio (OR) were calculated with corresponding 95% confidence interval. *Results showed* that thirty of all bone scans (19.35%) were positive for metastases. This proportion was significantly higher in patients with PSA>20ng/mL (31.66%, P=0.002) vs. PSA<10ng/mL (10.52%). For PSA<10ng/mL as well as 10ng/mL≤PSA≤20ng/mL the test was not a predictor for bone metastases (OR=0.36; OR=0.55). For PSA>20 ng/mL (OR=3.53) the likelihood of bone metastases was increased by 13%. The proportion of positive scintigraphy findings was significantly lower in patients with GS≤7 (11.47%) vs. GS≥8 (48.48%, P<0.0001). The GS≥8 was highly predictive for bone metastases (OR=7.260). The analysis showed that GS≥8 increases the risk of bone metastases by 29%. *In conclusion,* bone scintigraphy is not necessary in asymptomatic patients with localized disease, GS≤6 and PSA<10ng/mL, because of the negligible risk of bone metastases in that stage. Higher levels of GS and PSA may predict bone metastases.

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Introduction

Prostate cancer (PCa) is the most common malignant tumour in men with estimate incidence of 11% in Europe and mortality of 9% of the male population [1, 2]. The main diagnostic tools used for diagnosing PCa are digital rectal examination, serum concentrations of prostate specific antigen (PSA) and transrectal prostate biopsy [3]. The TNM system is most commonly used to prostate cancer staging. Another scheme often used by clinicians is the Whitmore-Jewett stage: patients are categorized as those with low and high risk who are much more likely to have skeletal metastases. Bone scintigraphy (BS) has been routinely performed in patients with initial staging of prostate cancer and considered as optimal method for evaluating bone metastases. The extent of osseous metastatic disease from PCa is an independent prognostic factor [4]. The threshold level of serum PSA which can be connected with increased risk of PCa is still not clearly defined. Many doctors are now using the following ranges: low level PSA: 0-2.5ng/mL, slightly to moderately elevated PSA: 2.6-10ng/mL, moderately elevated PSA: 10-19.9ng/mL and significantly elevated PSA: 20ng/mL or more [5, 6]. This approach reflects that PCa may also be associated with low levels of PSA. According to the recommendations of the American Urological Association BS is not required in the initial staging of asymptomatic patients with clinically localized disease and PSA values lower than 20ng/mL [7].

The European Urological Association also does not recommend BS in asymptomatic patients with highly and medium developed tumour and PSA values lower than 20ng/mL [8]. The Japanese Association recommends BS in patients who have PSA value of 10ng/mL and greater in the same group of patients [9], indicating that BS may be useful in the initial diagnosis of patients from this group. The controversy on which patients, the BS should be performed still exists. The number of patients with PCa is constantly rising and a more critical consideration of diagnostic algorithms in these patients is welcomed.

The aim of this study was to evaluate serum PSA levels and Gleason score (GS) on biopsy in predicting skeletal metastatic spread detected by BS in patients with newly diagnosed prostate cancer.

Patients and methods

We retrospectively studied assessment of 155 patients (range 51-87 years, median age of 72 years) with newly diagnosed untreated PCa who underwent bone scintigraphy between 2006 and 2008. Serum PSA measurement was performed prior of the biopsy using fluoroimmunoassay technique (ProStatus™ PSA Free/Total kit). Prostate cancer was diagnosed by histology examination of specimens obtained by core needle biopsy and evaluated according to the Gleason grading system. Patients were stratified on the basis of PSA level, GS, histological grade of PCa, clinical stage (Whitmore-Jewett) and TNM classification according to the current American Joint Commission on Cancer (AJCC) staging category [10]. Planar images of the entire skeleton were acquired three hours after intravenous injection of 740MBq technetium- 99m-medronate (MDP) or dicarboxypropandiphosphate (DPD) using a dual-head camera (ADAC-Vertex V60). Scintigraphic findings were interpreted by two nuclear medicine specialists (LJ, BA) and were evaluated as positive or negative for bone metastases under proclaimed criteria [11]. BS findings with lesions due to trauma, rheumatic or degenerative skeletal diseases or suspected of bone metastases were considered negative.

Comparison of the detection rate of bone metastases in the different groups of PCa patients was performed using Chi- square test and Fisher's test with P<0.01 being statistically significant. Diagnostic tests analysis was performed according to the 2x2 tables. Likelihood ratio (LR) and diagnostic odds ratio (OR) were calculated and analyzed in the interval of confidence of 95%. The concept of LR has been suggested as an alternative method to assess the predictive properties of a test, having the direct relationship to sensitivity and specificity. The LR for a positive test result (LH+) could be calculated as sensitivity divided by 1 minus the specificity value. The LR for a negative test result (LH-) is obtained as (1-sensitivity) divided by specificity. A likelihood ratio of 1 implies that the test result is equally likely to occur among patients with the disease as in patients without the disease. The diagnostic odds ratio (OR) is calculated as LH+ divided by LH- therefore the OR provides a robust measure for dichotomous outcomes and test results [12, 13].

On the basis of these data the evaluation of posttest probability for bone metastases was made with different PSA values and total GS as separate and as associated variables.

Results

All the subjects had histologically confirmed cancer. Clinical stage of the disease was available in 114/155 patients**.** Sixty six (57.8%) of the patients had a tumour with no spread outside the prostatic capsule (Stage A-B). Locally advanced (Stage C) and metastatic disease (Stage D) were diagnosed in 28 (24.6%) and 20 (17.6%) patients, respectively. The number of patients with disease in each clinical stage (stage A-D) and histological grade (G1-G4) of PCa is given in Table 1. The median PSA serum level was 14.2ng/mL (range 1.1 -2200).

Scintigraphy findings were interpreted as negative for metastases in 113 patients. Equivocal findings (up to two hot spots) were obtained in 12/155 patients (7.7%), requiring computed tomography (CT). In statistical analysis equivocal findings were considered as negative for metastases.

Table 1. *Relationship between bone metastases, clinical stage at diagnosis and pathological grade of PCa*

Variables	Bone metastases		Total
	Negative n	Positive n	
Number of patients	125	30	155
Clinical stage			
A	5	0	5
B, B1, B2	54	7	61
C, C+	25	3	28
D2	5	15	20
Unknown	36	5	41
Grade			
G1	1	0	1
G2	81	10	91
G3	42	20	62
G4	1	0	1

The relationships between bone metastases and a) clinical-pathology stage, b) serum PSA and c) GS are found in tables 1,2 and 3 respectively.

Thirty of all bone scans (19.35%) were positive for metastases. Serum PSA<10ng/mL as well as 10ng/mL ≤PSA≤ 20ng/mL was not a predictor of bone metastases (OR= 0.36; OR =0.55). The PSA> 20ng/mL (OR=3.53) changes the likelihood for bone metastases due to PCa by 13%. Unlike the serum PSA level, our results showed that GS was predictive for bone metastases. The proportion of positive scintigraphy finding was significantly lower in patients with GS≤7 (11.47%) vs. GS≥8 (48.48%, P<0.0001). Gleason score≥8 was highly predictive for bone metastases in PCa (OR=7.260, 2.733 to 19.157). At the same time, calculated post testing probability indicates that the GS≥8 increases the risk for bone metastasis for 29 %.

In the analysis using the combination of GS and PSA level, highly significant difference of positive bone scan between the group of patients with GS≤7 and PSA<10ng/mL and the group with GS≥8 and PSA≥10ng/mL, was obtained (P<0.0001). Diagnostic test analysis showed the likelihood ratio of 4.666 (2.478 to 8.923), indicating that PCa in patient with GS≤7 at biopsy and serum PSA≤10ng/mL is almost 9 times less likely to harbor bone metastases.

We tested the frequency of bone metastasis in patients with GS≤7 and different cut off value of serum PSA. Four of 47 (8.5%) men with PSA<10ng/mL, 3/30 (10%) men with 10ng/mL≤PSA≤20ng/mL and 7/45 (15.5%) men with PSA>20ng/mL had bone metastases. Patients with GS≤7 and bone metastases had significantly more frequent serum PSA>20 ng/mL.

Table 2. *Relationship between bone metastases and serum PSA level as the clinical variable*

Variables	Total	Bone metastases								
		Negative n (%)	Positive n (%)	P value	sensitivity (%)	95% CI	Specificity (%)	95% CI	OR	95%CI
Number of patients	155	125 (80.70)	30 (19.30)							
Serum PSA										
< 10	57	51(89.48)	6 (10.52)	0.034	20.00	7.71–38.57	59.2	50.05–67.90	0.36	0.11–1.00
10–20	38	33(86.85)	5 (13.15)	0.266	16.67	5.64–34.72	73.6	64.90–81.08	0.55	0.15–1.65
> 20	60	41(68.34)	19 (31.66)	0.002	63.33	43.85–80.07	67.2	58.23–75.33	3.53	1.43–8.98

Table 3. *Relationship between bone metastases and GS as the pathological variable*

Variables	Total	Bone scintigraphy								
		Negative n (%)	Positive n (%)	P value	Sensitivity (%)	95% CI	Specificity (%)	95% CI	OR	95% CI
Number of patients	155	125 (80.70)	30 (19.30)							
Gleason score										
≤5	7	6 (85.80)	1 (14.20)							
6	40	34 (85.00)	6 (15.00)	< 0.0001	46.67	28.34-65.67	13.6	8.13-20.88	0.13	0.052-0.365
7	75	68 (81.67)	7 (9.33)							
8	17	8 (47.06)	9 (52.94)							
9–10	16	9 (56.25)	7 (43.75)	< 0.0001	53.33	34.33–71.66	86.4	79.12-91.87	7.26	2.733-19.157

Bone metastases were found in 6/57 patients with serum PSA<10ng/mL with 20% sensitivity and 59.2% specificity. Four of these 6 patients had GS ≥7, G2 and G3 grade of the disease and B and D2 clinical stage of the disease. Two patients had GS 6 and B clinical stage of disease. In the group of patients with 10ng/mL≤PSA≤20ng/mL, bone metastases were found in 5 patients (sensitivity 16.67% and specificity 73.6%) with D2 clinical stage (3 patients) and one in the C2 clinical stage, while one patient's clinical stage was unknown. Total GS≥7 and the G3 grade was in all patients except for one. Table 2 and Table 3 summarize the sensitivity, specificity and odds ratio along 95% confidence interval of serum PSA and GS in 155 patients with PCa.

Discussion

Most patients with newly diagnosed prostate cancer have clinically localized disease at presentation. Despite the widespread PSA testing and the use of extended-pattern prostate biopsy techniques over the last fifteen years, there are still patients who already have bone metastases at the time of diagnosis of PCa [14]. Early detection or exclusion of bone metastases in PCa patients is of high clinical importance for initial treatment and the later course of disease.

Among 155 patients included in our study, bone metastases were detected in 30 patients (19.35%). Because of correlation between the incidence of bone metastases and var-

iables such as serum PSA, histological grade, clinical stage and Gleason score at biopsy, BS may not be necessary for patients who are at low risk for bone metastases. Numerous studies evaluated PSA as a predictor of the presence of bone metastasis. Data from study on randomly chosen 521 patients with newly diagnosed, untreated PCa showed that PSA value was the best predictor compared to other clinical variables. Metastases were found in only one of 307 patients with total serum PSA values <20ng/mL, reaching negative predictive value of 99.7% [15]. In another study, bone deposits were found in only 7 of 852 patients (0.8%) with PSA≤20ng/mL [16].

The results of other studies studies question whether a staging bone scan could be omitted in newly diagnosed prostate cancer patients with PSA of 20ng/mL and less, as bone deposits were found in even 17.5% of patients with PSA values <10ng/mL [17]. Analyzing the 23 studies that dealt with bone scintigraphy in the initial staging in patients with PCa, bone metastases were detected in 2.3%, 5.3% and 16.2% of patients with PSA<10ng/mL, 10ng/mL≤PSA≤20ng/mL and PSA>20ng/mL, respectively [18]. In our study bone metastases have been found in 10.52%, 13.15% and 31.66% of patients with PSA<10ng/mL, 10ng/ml≤PSA≤20ng/mL and PSA>20ng/mL, which is more frequent when compared with literature data [18-21]. It must be noted that these studies had higher proportion of patients with localized disease**,** as compared to our study. The prevalence of bone metastases increased with the elevation of serum PSA, clinical stage and histological grade of prostate tumour. However, bone metastases were found in 11 patients with PSA values ≤20ng/mL (6 patients with PSA<10ng/mL, and 5 patients with 10ng/mL≤PSA≤20ng/mL). Gleason grading of prostate cancer was available for all patients. As expected, patients with bone metastases had significantly more frequent GS≥ 8 at biopsy (P<0.0001), which is consistent with published results [22].

The combination of prognostic factors in PCa patients was studied by others [23, 24]. They concluded that in patients with PSA≤20, incorporation of clinical stage of disease and GS into prediction of bone metastases may reduce the number of BS in initial staging, without making a misdiagnosis [23]. Unlike used alone, combining the prognostic value of serum PSA level, GS, TNM staging and BS leads to a better prognosis in PCa patients [24].

According to the protocol of the European Urologic Association the bone scan in initial staging may not be indicated in asymptomatic patients if the serum PSA level is <20ng/mL in the presence of well or moderately differentiated tumors [25]. Based on our results with previously defined criteria–omission of scintigraphy in the initial staging, bone deposits would be "missed" in 3 out of 155 patients (1.9%).

If we assume the cut-off value of serum PSA at 10ng/mL, and GS on biopsy ≥6 as criteria for the bone scan, deposits would have not been diagnosed in only 2 out of 155 patients (1.3%). In our opinion this percentage is of no importance for treatment modality. Our determination of avoiding the bone scan in those patients is in concordance to the recommendations of the Japanese Urological Society [9], as well as the guidelines supported by recent studies [26].

In conclusion, bone scintigraphy is not necessary in initial staging of asymptomatic PCa patients with localized disease, Gleason score at biopsy ≤6, and PSA values <10ng/mL, because of the negligible risk of bone metastatic spread. The combination of GS and PSA level enhance predictability of bone scan findings in initial staging of prostate cancer patients.

All authors declare that they have no conflicts of interest.

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