ORIGINAL RESEARCH

Examining the value PSA=10ng/ml as a cutoff for predicting metastatic bone disease in NaF18 PET/CT bone scans, a pilot study

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Received: April 12, 2012 **Accepted:** May 8, 2012 **Published:** June 1, 2012
DOI: 10.5430/jbgc.v2n1p57 **URL:** http://dx.doi.org/10.5430/jbgc.v2n1p57

Abstract

Objectives: NaF18 PET/CT is considered to be more sensitive than Tc99m-MDP bone scan in detecting osseous metastasis. Some studies have suggested that for newly diagnosed prostate cancer patients with PSA<10ng/ml, a Tc99m-MDP bone scan is unnecessary. The main goal of this study is to assess if PSA= 10ng/ml is a good cutoff value to predict metastatic bone disease in newly diagnosed prostate cancer patients imaged with NaF18 PET/CT.

Methods: From the NaF18 PET/CT ordered to evaluate for prostate cancer metastasis between January 2010 and April 2011 (n=91), newly diagnosed biopsy proven prostate cancer cases before treatment were chosen (n=28). The sample was divided into two groups: group I (bone metastasis) and group II (no bone metastasis). PSA values were also reviewed.

Results: Group I (n=4) had mean PSA 121.29ng/ml, range 8.9-297.55ng/ml, mean age 74.5 years) and group II (n=24) had (mean PSA 27.43ng/ml, range 0.05- 348.68ng/ml, mean age 69.6 years). In our sample, 1 patient (25%) from group I with PSA<10ng/ml had bone metastasis. PSA cutoff value of 10ng/ml has a negative predictive value of 92.86% (odds ratio=3.55, 95% confidence interval 0.32 to 39.14, *P*=0.596).

Conclusions: For our study with veterans, there appears to be no significant relationship between PSA of < 10ng/ml and negative bone metastasis in newly diagnosed prostate cancer cases. 1 in 4 patients with PSA<10ng/ml from group I had bone metastasis. With the new introduction of NaF18 PET/CT as a more sensitive technique than MDP-99m whole body bone scans, we question the strict use of PSA=10ng/ml as a cutoff value. Age, race and region specific guidelines for bone scan use need to be developed. Both retrospective and prospective studies involving multiple institutions and larger sample sizes are needed to further confirm the association between PSA value alone and positive NaF18 PET/CT bone scans.

Key words

PSA, Prostate specific antigen, Prostate cancer, NaF18 PET/CT bone scan, Bone metastasis

1 Introduction

Prostate cancer is very common among men in America. It is the second most leading cause of cancer deaths in men. In 2010, 217,730 men were diagnosed with prostate cancer and 1545 men died from the disease [1]. Bone is the second most common site of metastasis in prostate cancer and bone metastasis is present in 80-85% of patients who die from prostate cancer [2]. There is an increasing risk of prostate cancer with increasing age in men. As men age, there is a general increase in PSA. Different age groups have different normal PSA values and it is important to recognize that. There is a rise in the diagnosis of prostate cancer due to a growing population of elderly men in this country and due to widespread use of prostate specific antigen (PSA) screening. We must acknowledge that since the advent of PSA testing for prostate cancer detection in 1994, the mortality rate of prostate cancer has gone down [3]. There may be other factors involved such as advances in treatment regimens. In general, PSA is used in combination with other parameters such as prostatic acid phosphatase levels, serum alkaline phosphatase levels, digital rectal exam (DRE) findings, clinical symptoms such as bone pain, pathologic fractures, and spinal cord compression and Gleason score. Chybowski et al. found that PSA is the most reliable and accurate predictor of abnormal bone scan compared to clinical stage, tumor grade and acid phosphatase level [4]. Still, Zaman et al. found that PSA and Gleason score are independent predictors of bone metastasis while age is not [5]. The combination of abnormal MRI and PSA value can also predict aggressive prostate cancers [2].

It is important to look at the type of treatment received by the patients when looking at PSA levels. The abnormal PSA value after hormonal therapy will be different from that of post-radical prostatectomy or radiation therapy. In this study, we examine the relationship between PSA value and positive NaF18 PET/CT bone scan in newly diagnosed prostate cancer patients prior to starting any type of treatment. For recurrent prostate cancer cases and for prostate cancer restaging, the PSA guidelines are different. PSA of 2ng/ml may be significant in post hormonal therapy cases. The normal PSA range of 0-4ng/ml is mainly for PSA screening and for making an initial diagnosis. Ando et al. found that there is an inverse relationship between obesity and PSA level, independent of race [6]. Moreover, not all cases of prostate cancer increases the PSA level [7]. Some studies report that even aggressive prostate cancers are not uncommon in patients with PSA< 4ng/ml [8, 9]. Carroll et al. reported that about 20% of aggressive prostate cancers are found in men with PSA<4ng/ml [10]. Also, various herbal medications can lower PSA levels [10]. In this sense, the normal value of PSA can be used only as a reference and other factors such as family history and free to total PSA ratio must also be looked at.

It is reported in the literature that NaF18 PET/CT bone scan is more sensitive than Tc99m bone scan [3]. CT, MRI, X ray have also been used in the prostate cancer work up. Since the beginning of the acceptance of PSA by the FDA, guidelines have been developed by different countries. It must be noted that the incidence and the mortality rate of prostate cancer is not the same in different countries and among different races [5, 11, 12]. So, PSA testing guideline must be tailored to each individual region. People of African descent have higher prevalences of prostate cancer compared to Asian and Caucasians [11]. Studies have reported that normal PSA values differ in different races. Mavropoulos et al. found that after adjusting for demographics and cancer-specific characteristics, including prostate size, black men have higher PSA levels than white men [13]. Likewise, Oesterling et al. reported that Japanese men have lower serum PSA levels than whites [14]. The population of United States is becoming very diverse with people from many countries around the world.

There is a need to investigate whether the current guideline regarding Tc99m-MDP bone scan use are applicable to all racial groups. According to the National Institute for Clinical Excellence (NICE), Tc99m-MDP bone scans are not required for staging purposes in patients with a PSA level of <10 ng/ml, a Gleason score of <8 and absence of bone pain. This agrees with the Japanese Urological Association guidelines (2006) and American College of Radiology (ACR) of omitting Tc99m-MDP bone scans in patients with PSA<10ng/ml [15]. However, other professional societies such as American Society of Clinical Oncology, American Society for Therapeutic Radiology and Oncology, and American Cancer Society do not have such guidelines [1]. Yet, Zaman et al. found that there is a rise in the incidence of bone metastasis in newly diagnosed prostate cancer patients with PSA <20ng/ml and Gleason Score <8. So, they conclude that the Western guidelines are questionable, even contradictory, to apply to local Pakistani (Asian) population [5].

The aim of this study is to see if the PSA value of 10 ng/ml can be used as a cutoff value to screen for bone metastasis in newly diagnosed prostate cancer patients. Previous studies have looked the PSA cutoff value to for bone scan using Tc99m bone scan and this is the first study to look at the PSA value and positive bone scan using NaF18 PET/CT bone scan. There is a concern over over-using the bone scan in the initial diagnosis of prostate cancer [1]. Lastly, we will try to address if the guidelines for Tc99m scan is applicable to NaF18 PET/CT bone scan as well.

2 Methods

We did a retrospective study on all patients who were referred to the Nuclear Medicine Section of the San Francisco Veterans Affairs Medical Center (SFVAMC) for evaluation of prostate cancer between January 2010 and April 2011 (n=91). All the NaF18 PET/CT bone scans for the study were done at the SFVAMC. From the 91 patients, we further selected newly diagnosed prostate cancer cases (n=28). Our inclusion criterion was newly diagnosed prostate cancer patients with no prior treatment and with PSA values tested within 2 months of the NaF18 PET/CT bone scan. We excluded recurrent cases, restaging cases and cases where any type of treatment has started. The 28 patients were divided into two groups: group I (bone metastasis, n=4) and group II (no bone metastasis, n=24). PSA values at the time of the bone scans are collected. The bone scans were independently reviewed by two nuclear medicine physicians to confirm the findings.

60min after intravenous administration of NaF18, CT transmission images without intravenous contrast was acquired from the vertex to the toes for attenuation correction and anatomic localization. This was followed by the PET emission scan over the same anatomical regions. A rotation 3D MPI, as well as axial, coronal and sagittal PET images with and without attenuation correction was interpreted. Acquired CT and fused PET/CT images were reviewed alongside the PET images in a dedicated work station.

Statistical analysis

We used the MedCalc and IBM SPSS 20 for statistical analysis. Fischer's exact method is used to calculate for statistical significance and a p value of <0.05 is considered significant for our study.

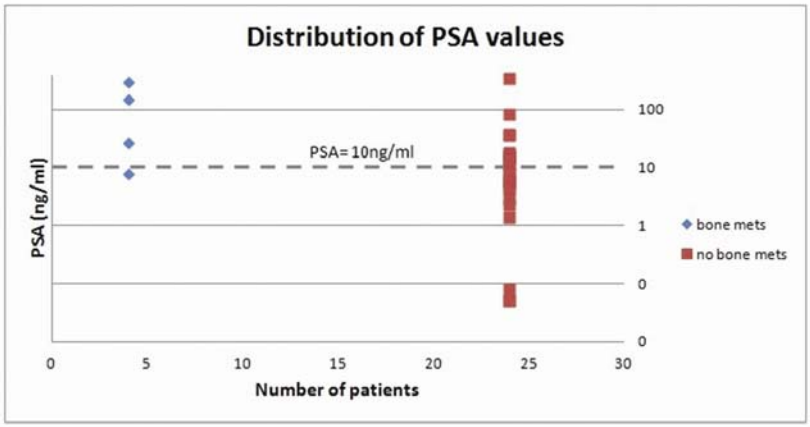

Figure 1. Distribution of PSA values in bone metastasis group and no bone metastasis group

3 Results

Table 1 shows the characteristics of the patients in the final study population. In the final sample of 28 newly diagnosed prostate cancer patients at the SFVAMC, 4 out of 28 (incidence rate of 14.3%) has bone metastasis. Group I had (mean

PSA 121.29ng/ml, range 8.9-297.55ng/ml, mean age 74.5 years) and group II had (mean PSA 27.43ng/ml, range 0.05-348.68ng/ml, mean age 69.6 years). In our small sample, 25% of patients from group I with PSA<10ng/ml had bone metastasis and 46% of patients from group II with PSA>10ng/ml had no bone metastasis. Figure 1 shows the distribution of PSA values in group I (bone metastasis) and group II (no bone metastasis).

Table 1. Characteristics of the patients in group I and group II

Group	Mean PSA (ng/ml)	PSA values (ng/ml)	Mean Age (years)
I (bone metastasis) (n=4)	121.29	297.55 151.56 27.15 8.9	74.5
II (no bone metastasis) (n=24)	27.43	348.68 81.22 37.3 35.66 18.29 16.55 16.5 15.07 14.2 13.77 11.11 8.7 7.86 5.94 5.87 5.86 4.77 4.25 2.91 2.26 1.41 0.08 0.05 0.05	69.6

PSA <10ng/ml has a negative predictive value of 92.86%. However, the calculated two tailed *p* value was 0.596. There is an odds ratio of 3.55 (95% confidence interval 0.32 to 39.14) associated with PSA greater than 10 ng/ml. We found no significant association between PSA > 10ng/ml and bone scan positivity.

4 Discussion

According to our study, 1 patient (25%) from group I with metastasis to the bone has PSA <10 ng/ml. This patient presented to Nuclear Medicine in November 2010, during the study period. If we refuse to screen such patients, we will miss the cancer metastasis and it will affect the staging, treatment plan and prognosis. Likewise, 46% of the patients from group II with PSA > 10ng/ml have no bone metastasis. This agrees with our statistical analysis result of finding no correlation between PSA >10ng/ml and NaF 18 PET/CT bone scan positivity. The results of our study agree with the studies by Lai et al [16], Janane et al. [11], Lee et al. [17], and Huang et al. [18] from Table 2. On the other hand, our findings do not agree with the studies by Jaukovic et al [19], Hirobe et al [20], Kosuda et al. [21], Gleave et al. [22] and Oesterling et al. [23]. Incidence rates of bone metastasis in Table 2 range from 0.8-34.2%. In the initial diagnosis of prostate cancer, if the biopsy reports or physical symptoms arouse suspicion of bone metastasis regardless of the low PSA level, NaF 18 PET/CT bone

scan should be ordered, despite a concern for overuse of the bone scan. We must always put the safety of the patient first before any financial costs.

Table 2. Comparison of incidence rates and findings of different studies. Note: Except for our study, all other studies in this table used Tc99m-MDP bone scan

Author(s), Year	Incidence	Findings
Our study With NaF18 PET/CT	14.3%	No association between PSA>10ng/ml and bone scan positivity
Janane et al., 2012 [11]	29.3%	No significant relationship between PSA and bone scan
Lee et al, 2011[17]	14.3%	New guidelines for eliminating bone scans in newly diagnosed prostate cancer cases are needed, especially for Asians
Jaukovic et al, 2011 [19]	19.35%	Bone scans are not needed in Gleason Score ≤6, and PSA<10ng/mL
Lai et al, 2011 [16]	29.3%	No statistically significant relationship between Gleason score, PSA and bone scan results
Hirobe et al, 2007 [20]	7.7%	Bone scans may be eliminated in patients with PSA≤10ng/ml
Huang et al, 2006 [18]	34.2%	Bone metastases cannot be ruled out in patients with PSA<10ng/ml
Kosuda et al, 2002 [21]	22.2%	Bone scans can be eliminated in newly diagnosed prostate cancer patients with PSA ≤10ng/ml, Gleason Grade ≤2 or Gleason score≤6
Gleave et al, 1996 [22]	6%	Bone scans can be eliminated in newly diagnosed prostate cancer cases with PSA below 10 micrograms/liter
Oesterling et al, 1993 [23]	0.8%	A bone scan is not necessary in patients with PSA ≤10ng/ml and no skeletal symptoms

The patient from group I with PSA<10ng/ml is a 67 year old male who presented with a PSA of 8.9 ng/ml at the time of the prostate cancer diagnosis and subsequent NaF18 PET/CT scan. The tumor had a Gleason score of (4+4). He did not have any bone pain and he was referred to us for evaluation of metastatic disease. The patient was started on androgen deprivation therapy (ADT) with casodex/zoledex 1 month after the diagnosis. 3 gold seeds were also placed near the tumor by transrectal ultrasound. His PSA level went down from 8.9ng/ml to 0.23 ng/ml in 4 months. After that, the patient was treated with external beam radiation therapy (EBRT) and brachytherapy. His latest PSA was less than 0.05. Figure 2 shows the images of this patient. If we use the cutoff PSA value of 10ng/ml for bone scan use, we will miss this patient.

This is a retrospective single institution study. Veterans are a unique population, where the majority of men are over 50, and findings from this study may not be generalized to other populations [24]. Even within the Veterans Affairs (VA) health system, there are regional differences in the incidence, mortality and bone metastasis rates of prostate cancer. Cooperberg et al reported that the use of bone scans have actually been decreasing and the use of imaging in prostate cancer depends on race, insurance type, demographic region and type of hospital (community hospital vs. institution) [25]. Therefore, physician preference and institutional guidelines are not the only factors in deciding the use of Tc99m-MDP bone scans. According to Cooperberg et al., the VA system has lower utilization rates than other insurance types and Latinos have lower rates than other racial groups [25]. In terms of geographic region, Tc99m-MDP bone scan use goes in the decreasing order of East, South, West and Midwest. In a manage care setting such as the VA, there is no extra incentive for referring for any type of bone scans. In the VA system, referrals can be made by the primary care doctors in small clinics. It is common in the VA system to see pre-referral bone scans before patients present to the Urologists. This pattern is also observed at the SFVA and this can contribute to the rate of bone scan use for the VA system [26].

Potential biases include referral bias and lead time bias. There can also be statistical bias due to our small sample size and due to the outliers in PSA values which can affect the final analysis. Different doctors have different referral preferences. Lead time bias is where patients diagnosed with prostate cancer in the early stages seem to live longer than patients

diagnosed in the late stages of prostate cancer. There is also an issue of practicing defensive medicine in this country. It is possible to eliminate the psychological stress of the patient with the negative bone scan and better quality of life can result because of the right treatment plan. Patients must be well informed so that they can make better decisions and preparations for their lives. Quality of life of patients outweighs the economic burden of bone scans. The practice guidelines have to be continually updated, and this study has shown that bone metastases are not uncommon in newly diagnosed prostate cancer patients with PSA<10ng/ml.

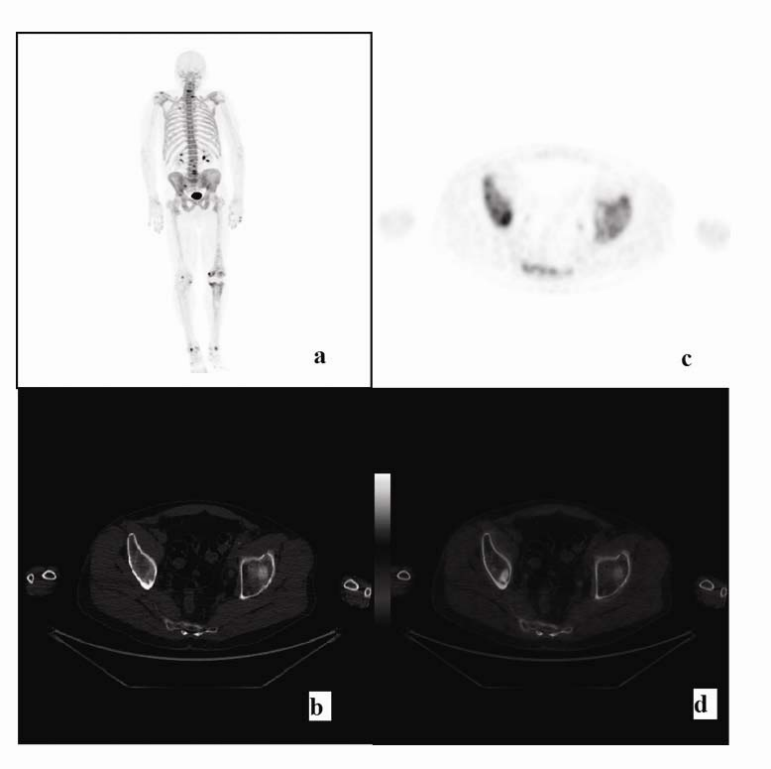

Figure 2. (a) Whole body MIP of the NaF18 PET/CT image shows multilevel osteoblastic degenerative changes, left knee prosthesis and abnormal focal NaF activity in the right iliac bone. (b) CT image at the level of the iliac spine showing sclerotic activity at the right ilium. (c) NaF 18 image showing increased activity at the right ilium correlating with the sclerotic lesion. (d) NaF 18 PET/CT fusion image showing increased NaF18 uptake with sclerosis along the medial superior aspect of the iliac bone.

5 Conclusion

For our study with veterans, there is no significant direct relationship between PSA value of less than 10ng/ml and negative bone metastasis in newly diagnosed prostate cancer cases. This is evidenced by the fact that 1 in 4 patients with PSA<10ng/ml from group I had bone metastasis. There is a need for age and race specific PSA guidelines to be developed, for ordering NaF 18 PET/CT bone scans. It is also important to note that there are regional differences in incidence and mortality of prostate cancer and guidelines for the use of any type of bone scans must also reflect that. From our experience with the small sample, we recommend against the routine use of bone scans in every newly diagnosed prostate cancer cases, but if there are indications such as bone pain or Gleason score >6, then an NaF 18 PET/CT bone scan must be used even if PSA is <10ng/ml. Bone metastases can occur in newly diagnosed patients with PSA < 10ng/ml, and this cutoff value should not be strictly observed. Besides the major factors such as PSA, Gleason score and clinical stage, other information such as age, race, family history and clinical symptoms need to be considered before ordering a NaF 18 PET/CT bone scan. Overall, we cannot entirely eliminate the use of NaF18 PET/CT bone scans in all patients with PSA

less than 10ng/ml. Patient safety and quality of life must come first before economic costs. Both retrospective and prospective studies involving multiple institutions and larger sample sizes are needed to further confirm the association between PSA value alone and finding bone metastasis on NaF18 PET/CT bone scans.

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