

# Prostate-specific antigen cutoff value for ordering sodium fluoride positron emission tomography/computed tomography bone scan in patients with prostate cancer

## ABSTRACT

The use of F-18 sodium fluoride (NaF) positron emission tomography/computed tomography (PET/CT) bone scan is increasing because of its higher sensitivity and specificity over standard bone scintigraphy (BS). Studies previously reported a prostate-specific antigen (PSA) cutoff value for ordering standard BS. However, this has not been determined for NaF PET yet. In this study, our goal was to determine a PSA cutoff level for ordering NaF PET/CT bone scan. Newly diagnosed and previously treated prostate cancer patients who had NaF PET/CT scan and PSA measurements within 2 mos of PET study were selected for analysis. When available, other parameters, such as Gleason score (GS), clinical stage, alkaline phosphatase levels, skeletal symptoms, and correlative image findings, were recorded. Receiver operating characteristic (ROC) analysis was performed to determine PSA cutoff values. Sixty-two patients (32 newly diagnosed and 30 previously treated) met the inclusion criteria. Near half of previously treated patients were on hormone therapy. NaF PET/CT was positive in 9 newly diagnosed (PSA mean: 91.6 ng/ml, range: 6.2–226 ng/ml) and in 6 previously treated patients (PSA mean: 146.4 ng/ml, range: 6.6–675 ng/ml). ROC analysis indicated that PSA cutoff value for NaF PET/CT positivity was >20 ng/ml in newly diagnosed and >6 ng/ml in previously treated patients. PSA cutoff value for ordering NaF PET/CT in newly diagnosed patients does not seem significantly different than the previous results for BS (>20 ng/ml). However, we found a lower PSA cutoff value of >6 ng/ml in previously treated patients.

**Keywords:** Cutoff, F-18 sodium fluoride, positron emission tomography/computed tomography, prostate cancer, prostate-specific antigen, sodium fluoride

## INTRODUCTION


Bone scintigraphy (BS) is the standard imaging technique for searching bone metastasis in prostate cancer patients. The presence of bone metastasis is important as it changes the stage and the treatment approach in prostate cancer. To reduce the unnecessary use and cost, various guidelines recommend ordering BS only in high-risk patients or patients with bone symptoms.<sup>[1-4]</sup> There are slight differences in the definition of high-risk prostate cancer by various sources.<sup>[1-5]</sup> Definition of high-risk prostate cancer by D'Amico *et al.* is prostate-specific antigen (PSA)  $\geq 20$ , Gleason score (GS)  $\geq 8$ , or clinical stage  $\geq T2c$ .<sup>[5]</sup> The National Comprehensive Cancer criteria for high risk is clinical stage T3a, Gleason score 8 to 10/Gleason grade group 4-5, or PSA level greater than 20 ng/ml.<sup>[1]</sup>

In the past 10 years, there has been increasing use of F-18 sodium fluoride (NaF) positron emission tomography/computed tomography (PET/CT) bone scan in

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the detection of metastatic diseases in various cancers. NaF PET/CT has mostly replaced BS in many hospitals and diagnostic centers equipped with PET/CT camera. The main advantages of NaF PET/CT bone scan over BS are improved image resolution and contrast with high bone-to-background uptake ratio. The low-dose CT component of the study is not only used for soft-tissue attenuation correction of the photons emitted by PET radiotracers but also utilized for anatomic localization of PET uptake and correlation of PET with CT findings (lytic or sclerotic lesion, osteophyte, etc.) which improves the specificity of this study. In addition to high technologic features of PET/CT cameras, bone PET radiotracer, F-18 NaF, is an excellent bone imaging agent. Its extraction by the bone tissues is proportional with the blood flow and osteoblastic activity. F-18 NaF has faster blood clearance and approximately 2-fold higher uptake in bone than the Tc-99m-based BS radiotracers.<sup>[6]</sup>

Studies have demonstrated higher sensitivity of NaF PET/CT over standard BS in patients with osteoblastic metastases.<sup>[7-10]</sup> PET can detect small lesions, particularly sclerotic lesions, and early metastatic disease.<sup>[10-12]</sup> The sensitivity/specificity of BS and NaF PET were determined as 70%/57% and 100%/100%, respectively, by Even-Sapir *et al.* and 51%/82% and 93%/54%, respectively, by Poulsen *et al.*<sup>[7,13]</sup> Low specificity of PET in the Poulsen's study was assumed to be due to false-positive lesions due to degenerative changes in the elder population. However, careful evaluation of the PET, CT, and PET/CT fusion images usually helps to differentiate degenerative from metastatic disease. In cases with coexisting degenerative and metastatic disease in the same vertebra, careful evaluation of the images with reducing PET image intensity and comparing with CT findings usually helps not missing metastatic disease adjacent to the degenerative changes.

PSA cutoff value for ordering BS in patients with prostate cancer has been previously published by various studies, mainly in newly diagnosed patients.<sup>[14-17]</sup> However, a PSA cutoff value for ordering NaF PET scan has not been reported yet. Given its higher sensitivity in detecting small and early bone metastasis, PSA cutoff value for positive NaF PET/CT may be less than that with BS. In this study, our goal was to determine PSA cutoff values for NaF PET/CT scan in newly diagnosed and previously treated prostate cancer patients.

## MATERIALS AND METHODS

Prostate cancer patients either newly diagnosed or previously treated who had NaF PET/CT bone scan and PSA measurements available within 2 months of PET study were selected for this study. When available, other parameters (GS, clinical stage, alkaline phosphatase levels,

skeletal symptoms, and correlative imaging findings) were recorded.

NaF PET/CT bone images were provided from two institutes (Mubarak Al-Kabeer and Trakya University Hospitals). This retrospective study was approved by Kuwait Ministry of Health and Ethics Committee at Trakya University Faculty of Medicine.

NaF PET/CT bone images were obtained at Philips Gemini Time-of-Flight 64 PET/CT and GE discovery 8 PET/CT cameras. Sixty minutes following intravenous injection of 222 MBq (6 mCi) of F-18 NaF, first, a low-dose CT and then PET images (3 min/bed) were obtained from top of the head to toes. Iterative reconstruction was used for image processing. Images were evaluated by two readers using attenuation corrected and uncorrected PET, CT, and PET/CT fusion slices in transaxial, sagittal, and coronal planes and maximum intensity projection image. PET/CT findings were reported as positive, negative, or indeterminate for bone metastasis.

Serum total PSA concentrations were determined based on enzyme immunoassay. Normal PSA range in our laboratories is 0.0–3.0 ng/ml.

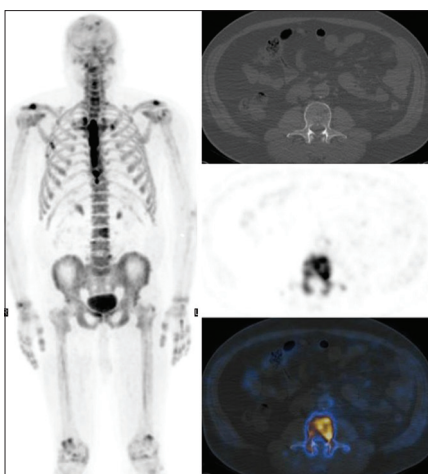
Receiver operating characteristic (ROC) analysis was performed to determine PSA cutoff values for NaF PET/CT imaging in newly diagnosed and previously treated patients.

## RESULTS

Sixty-two patients with prostate cancer met the inclusion criteria. Thirty-two patients were newly diagnosed (Group 1, mean age: 67.2 years, range: 52–90 years) and 30 patients were previously treated (Group 2, mean age: 73.9 years, range: 61–95 years).

In Group 1 (32 newly diagnosed patients), 10 patients were symptomatic showing bone pain and rest were asymptomatic. Table 1 shows the PET results of this group. PET was positive in 9 patients (PSA mean: 91.6 ng/ml, range: 6.2–226 ng/ml). Majority of PET-positive patients (7/9) had PSA value of >20 ng/ml. In a PET-positive patient with GS of 8, PSA was 6.2 ng/ml [Figure 1]. In PET-positive cases, 7 patients were asymptomatic and 2 were symptomatic. In symptomatic patients, PSA was >100 ng/ml. Figure 2 demonstrates a PET-positive study (multiple metastasis) in a patient with PSA of 77.5 ng/ml and GS of 7. PET was negative in 10 patients (PSA mean: 6.55 ng/ml, range: 0.01–15.7 ng/ml) and indeterminate in 13 (PSA mean: 14 ng/ml, range: 0.87–31.3 ng/ml).

Radiological correlation (RC) was available only in 9 patients in this group. RC was negative in 2 PET-positive and 2



**Figure 1:** Sodium fluoride maximum intensity projection and selected transaxial computed tomography, positron emission tomography, and positron emission tomography/computed tomography fusion images demonstrate increased uptake in the left part of the L3 vertebral body with small lytic lesions on computed tomography. There is also increased uptake in the right superior pubic ramus, ribs, and skull, which are suspicious for metastasis, particularly pubic bone. Also note the degenerative changes in extremity joints as well as lower lumbar spine. Increased uptake along the sternum is due to sternectomy for cardiac surgery

PET-negative patients. RC was positive in 1 PET-positive and 1 PET indeterminate patient. In 3 other patients (2 PET-positive and 1 PET indeterminate), RC was limited to pelvis only which was negative. GSs were available only in 13 patients in this group. GS were 9, 9, and 8 in 3 PET-positive, 7 and 6 in 2 PET-negative, and 6, 6, 6, 7, 7, and 8 in 6 PET indeterminate patients. ROC analysis indicated that PSA cutoff value for PET positivity was >20 ng/ml in this group with newly diagnosed prostate cancer patients.

In Group 2 (30 previously treated patients), 17 patients were currently on hormone therapy, and patients had rising PSA and/or bone pain. Table 2 shows the PET results of this group. PET was positive in 6 patients (PSA mean: 146.4 ng/ml, range: 6.6–675 ng/ml). In 2 PET-positive patients (GS: 9 and 8), PSA values were <10 ng/ml (6.6 and 7.35 ng/ml). In another PET-positive patient, PSA value was <20 ng/ml (17.4 ng/ml). In 3 PET-positive patients, PSA was >20 ng/ml. Five of 6 PET-positive patients were on hormone therapy. In this group, PET was negative in 14 patients (PSA mean: 3.4 ng/ml, range: 0.01–13 ng/ml) and indeterminate in 10 (PSA mean: 4 ng/ml, range: 0.01–35 ng/ml).

RC was available only in 9 patients in this group. RC was positive in 2 PET-positive, 1 PET-negative, and 2 PET indeterminate cases. RC was negative in 1 PET-negative and 3 PET indeterminate cases. GSs were available in 18 patients in this group. GSs were 9, 7, 6, and 6 in PET-positive, 10, 9, 7, 7, 6, and 5 in PET-negative, and 9, 9, 8, 8, 7, 6, 6, and 5



**Figure 2:** Sodium fluoride positron emission tomography maximum intensity projection image from the limited area shows multiple bone metastases in the spine, ribs, pelvis, and proximal femora

**Table 1: Sodium fluoride positron emission tomography/computed tomography results of newly diagnosed prostate cancer patients (Group 1)**

PSA (ng/ml)	NaF PET/CT		
	Positive	Negative	Indeterminate
≤10	1	8	7
>10-≤20	1	2	3
>20	7		3
Total	9	10	13

PSA: Prostate-specific antigen; NaF: Sodium fluoride; PET/CT: Positron emission tomography/computed tomography

**Table 2: Sodium fluoride positron emission tomography/computed tomography results of previously treated patients (Group 2)**

PSA (ng/ml)	NaF PET/CT		
	Positive	Negative	Indeterminate
≤10	2	12	9
>10-≤20	1	2	
>20	3		1
Total	6	14	10

PSA: Prostate-specific antigen; NaF: Sodium fluoride; PET/CT: Positron emission tomography/computed tomography

in PET indeterminate cases. ROC analysis indicated that PSA cutoff value for PET positivity was >6 ng/ml in this group with previously treated prostate cancer patients.

## DISCUSSION

Bone metastases are associated with high morbidity and mortality. The presence of bone metastasis changes the stage and the treatment approach. BS is a routine procedure for detecting bone metastases and initial staging of high-risk prostate cancer.

In newly diagnosed high-risk prostate cancer, near one-fifth of the patients will have a positive BS on initial evaluation.<sup>[18]</sup>

In the current study, NaF PET was positive in 28% of the newly diagnosed prostate cancer patients. Abuzallouf *et al.* reported positive BS in 2.3% of men with PSA levels <10 ng/ml, in 5.3% of men with PSA levels 10.1–19.9 ng/ml, and in 16.2% of men with PSA levels 20.0–49.9 ng/ml in newly diagnosed prostate cancer patients.<sup>[19]</sup> PSA was >20 ng/ml in 77.7% of PET-positive newly diagnosed patients in our study. In the other 2 PET-positive patients, PSA was below 10 ng/ml in one patient and below 20 ng/ml in the other.

In various studies, a PSA cutoff value of  $\geq 10$  or  $> 10$  ng/ml has been recommended for ordering BS in newly diagnosed and untreated asymptomatic prostate cancer patients.<sup>[14-17,20,21]</sup> Other studies have reported a higher PSA cutoff value of  $\geq 20$  or  $> 20$  ng/ml for ordering BS.<sup>[22-24]</sup> In our study, we found a PSA cutoff value of  $> 20$  ng/ml for ordering NaF PET scan in newly diagnosed patients. However, in high risk or symptomatic patients, NaF PET can be ordered at lower levels of PSA.

Although PSA is less reliable following radiotherapy than radical prostatectomy (RP), a rising PSA in treated prostate cancer patients usually indicates local recurrence or metastatic disease. Early detection of recurrent and metastatic disease in patients with biochemical failure after definitive therapy for localized primary prostate cancer is important for appropriate treatment. In patients with rising serum PSA after RP, current serum PSA is accepted as the best predictor of the BS result. Cher *et al.* suggested that there is limited usefulness of BS until PSA increases above 30–40 ng/ml.<sup>[25]</sup> In a study by Dotan *et al.*, patients with an increasing PSA after RP, for the PSA levels of 0–10, 10.1–20, 20.1–50, and above 50 ng/ml, BS was positive in 4%, 36%, 50%, and 79%, respectively.<sup>[26]</sup> Gomez *et al.* suggested that a BS is unlikely to be positive in patients with a serum PSA of <7 ng/ml on biochemical recurrence after RP, whereas it is likely to be positive when a PSA of  $\geq 20$  ng/ml.<sup>[27]</sup> They suggested that the presence of skeletal symptoms or a PSA level of >7 ng/ml should prompt the clinician to obtain a BS.<sup>[27]</sup> In our study, PET was positive in 20% of the previously treated patients and PSA was <10 ng/ml in 2 of them. Jadvar *et al.* reported that in 16.2% of men with biochemical failure only, NaF PET/CT may reveal sites of occult osseous metastases.<sup>[28]</sup> In the same study in 8 of 10 patients with positive NaF PET/CT, the PSA level was relatively low (range: 1.9–5.83 ng/ml) at levels where conventional BS is often negative. Cook *et al.* reported that in 11% of high-risk localized prostate cancer with normal pretreatment baseline BS, scan became positive following initial hormone therapy (flare phenomenon).<sup>[29]</sup> Majority of our PET-positive patients (83.3%) were on hormone therapy during PET scan.

The main limitations of our study are the relatively small number of patients as well as lack of uniform follow-up or correlative/confirmatory data in some of our patients. However, the importance of this article is to be the first study determining a PSA cutoff value for ordering NaF PET scan in patients with prostate cancer.

## CONCLUSION

In our study, we did not find a major difference in PSA cutoff value for NaF PET and BS in patients with newly diagnosed prostate cancer. However, we found a lower PSA cutoff value in previously treated patients. A study with larger number of patients with follow-up NaF PET scan, correlative radiological imaging, or histopathological confirmation may determine a more accurate PSA cutoff level for ordering NaF PET/CT in patients with prostate cancer.

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## Conflicts of interest

There are no conflicts of interest.

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