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No added value of ^{18}F-sodium fluoride PET/CT for the detection of bone metastases in patients with newly diagnosed prostate cancer with normal bone scintigraphy

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ABSTRACT

Aim: To determine if additional ^{18}F-sodium fluoride PET/CT (NaF-PET/CT) improves the prognostic accuracy in the initial staging of prostate cancer patients with normal bone scintigraphy undergoing prostatectomy.

Methods: A prospective cohort study examined NaF-PET/CT in intermediate- or high-risk prostate cancer with negative bone scintigraphy who were scheduled for prostatectomy. Biochemical response: PSA levels<0.2 ng/mL at six weeks and six months postoperatively, PSA level≥0.2 ng/mL was biochemical failure.

Results: Eighty-one patients were included in the study; seventy-five patients (93%) achieved biochemical responses, six patients had biochemical failure. NaF-PET/CT indicated bone metastasis in one patient (1.2%), was equivocal in seven patients (8.6%), without bone metastases in 73 patients (90.1%). Eight patients with bone metastases or equivocal results on NaF-PET/CT exhibited biochemical responses. All patients with biochemical failure had negative NaF-PET/CT and bone scintigraphy for bone metastases.

Conclusion: NaF-PET/CT has no added value for bone staging in intermediate- and high-risk prostate cancer patients with normal bone scintigraphy results undergoing prostatectomy.

Keywords: ^{18}F-sodium fluoride PET/CT, bone scintigraphy, prostate cancer, radical prostatectomy

INTRODUCTION

The European Association of Urology and National Cancer Comprehensive Network recommend bone scintigraphy for staging intermediate- and high-risk prostate cancer (PCa) patients (*1,2*). However, several studies have implied significantly improved diagnostic performance of ^{18}F-sodium fluoride PET/CT (NaF PET/CT) over bone scintigraphy for the detection of bone metastases in PCa patients (*3-5*). The use of NaF PET/CT has been shown to change patient management by 12% when applied during initial staging (*6*). However, it remains to be shown whether the increased diagnostic performance afforded by NaF PET/CT correctly changes patient management and improves patient outcomes. We prospectively investigated whether additional NaF PET/CT improves the prognostic accuracy of the initial staging of patients with newly diagnosed, intermediate- and high-risk PCa without bone metastases on standard bone scintigraphy.

MATERIALS AND METHODS

Patients

Consecutive patients from two sites were prospectively enrolled in this study. The recruitment period spanned from April 2015 to December 2016 (Regional Hospital West) and June 2015 to December 2016 (Aalborg University Hospital). During this time span, there were periods without patient screening due to limited scanner capacity and/or periods with scanner unavailability. The eligibility criteria were as follows: 1) intermediate- or high-risk PCa according to the European Association of Urology classification (*1*), 2) no bone metastases on standard bone scintigraphy reviewed by two readers according to institutional practices, 3) no prior treatment for PCa, 4) no history of malignancy other than PCa for five years prior to inclusion in the study, and 5) planned radical prostatectomy (Figure 1).

NaF PET/CT

NaF PET/CT was performed in accordance with The Society of Nuclear Medicine guidelines (*7*), in close conjunction with surgery (Figure 1); the results of NaF PET/CT scans were not available to the treating urologist and were not used for clinical decision making.

Procedure for Evaluating NaF PET/CT

Two physicians, who prior to the evaluation of the first batch of study-related scans had clinical experience with 2000+ and 2500+ NaF PET/CTs, evaluated the NaF PET/CT scans. The observers were blinded to all clinical information, including the results of bone scintigraphy, except for the diagnosis of PCa. A consensus diagnosis was reached on a patient level as either no bone metastases, equivocal for bone metastases, or bone metastases present.

Clinical Data and Follow-up

Clinical data were retrieved from medical charts, pathology reports, and routine blood samples, including prostate-specific antigen (PSA) levels six weeks and six months after radical prostatectomy for all patients. Patients who achieved a PSA level<0.2 ng/mL six weeks and six months after radical prostatectomy were defined as having a biochemical response and thus having no bone metastases (true M0) at the time of staging. Patients with a PSA level≥0.2 ng/mL at six weeks and/or at six months after radical prostatectomy were categorized as having biochemical failure. Biochemical failure was not used to categorize true bone metastasis since elevated PSA levels could be caused by remnant PCa in other sites, e.g., the prostatic bed or lymph nodes (*8*). Additional clinical and imaging follow-up focusing on bone metastases was conducted for 24 months in patients with biochemical failure and in patients in whom NaF PET/CT was equivocal or suggested bone metastases.

Statistics

All variables were summarized using descriptive statistics (mean and range), and the proportions are provided along with the 95% confidence intervals. For the statistical analysis, STATA®11 (StataCorp LP, College Station, TX, USA) was used. This study was of an exploratory nature, and no formal sample size calculation was performed.

Approvals

This study complied with the Helsinki II Declaration and was approved by the local ethics committee (N-20140042) and the Danish Data Protection Agency. All patients provided informed consent to participate.

RESULTS

Patient Characteristics

Eighty-one patients were included in the study, and the majority had intermediate-risk PCa (Table 1). All patients were included at the time of staging except for three patients who had previously been in active surveillance. No patients received any systemic treatment for PCa prior to inclusion in this study or 6 months after radical prostatectomy. A 6-month follow-up after radical prostatectomy was available for all patients.

NaF PET/CT Findings and Outcome

NaF PET/CT showed bone metastasis in one patient (1.2%; 95% confidence interval: 0-3.6%), equivocal findings in seven patients (8.6%, 95% confidence interval: 2.5-14.7%), and no pathological findings in 73 patients (90.1%). At follow-up six months after radical prostatectomy, 75 patients (93%) achieved a biochemical response, and six patients had biochemical failure. All eight patients classified as having bone metastasis or equivocal results on NaF PET/CT had a biochemical response. The six patients with biochemical failure were NaF PET/CT negative for bone metastases (Table 2).

Follow-up

At 24 months after radical prostatectomy, no bone metastases were identified in the group of patients with bone metastases or equivocal results on NaF PET/CT (Supplemental Table 1). Likewise, no bone metastases were identified within 24 months after radical prostatectomy in the group of patients with biochemical failure (Table 3).

DISCUSSION

NaF PET/CT has been introduced as a promising diagnostic method for assessing skeletal metastases, but studies of patient outcomes are scarce. In this study, NaF PET/CT did not improve outcomes in patients without metastases identified on standard bone scintigraphy.

The key findings, based on the concept of including NaF PET/CT findings in addition to negative bone scintigraphy findings, showed that NaF PET/CT did not show bone metastases in any patients with biochemical failure; this observation was correct in the present population because no bone metastases were detected after 24 months of follow-up. Moreover, NaF PET/CT showed definite (n=1) or unclear metastatic deposits in seven patients, who all had postoperative PSA levels <0.1 ng/mL that ruled out bone metastasis. Therefore, one patient could inappropriately have been deprived of curative treatment. , the proportion of equivocal findings was 8.6%, which might seem high for experienced observers. However, the findings are consistent with previous studies conducted by Even-Sapir et al (*4*), who reported that 7% of NaF PET/CTs were considered equivocal, and Löfgren et al, who reported 5% equivocal findings among experienced observers (*9*). In contrast, the proportion of equivocal findings (equivocal or probable) was 15% at the initial staging of PCa in the US National Oncology PET Registry study (*6*). Equivocal findings may lead to additional imaging and potentially lead to the improper withholding of treatment with a curative intent. In the present study, none of the equivocal findings were associated with biochemical failure. However, the present study also revealed that the likelihood of false positive NaF PET/CT findings was low, as emphasized by the narrow 95% confidence interval (0-3.6%). The study did not allow any conclusions regarding if bone scintigraphy findings were added in patients with negative NaF PET/CT findings.

Previous studies investigating NaF PET/CT have primarily been dedicated to diagnostic test accuracy. In 2006, Even-Sapir demonstrated significantly improved diagnostic accuracy of NaF PET/CT in a head-to-head comparison with bone scintigraphy (*4*), whereas more recent diagnostic test accuracy studies have not entirely confirmed these results (*9,10*); in particular, false positive findings have been reported (*5,11*). NaF PET/CT has a high patient acceptance rate (*12*), and this technique may have an advantage over bone scintigraphy in terms of high patient throughput, thereby increasing patient capacity and the possibility of performing simultaneous contrast-enhanced CT as a "one-stop-shop"(*13*). Nevertheless, NaF PET/CT may be less cost-effective than bone scintigraphy (with or without SPECT/CT) (*14*), and access to a cyclotron and PET/CT scanner may be limited for various reasons.

The major focus in the US National Oncology PET Registry study was to document the impact of NaF PET/CT on patient management. A change in patient management was found in 12% of the patients (*6*); however, no evaluation of the appropriateness of the treatment changes was performed. Recently, Gauthé presented data showing the potential of NaF PET/CT to change patient management in 7% (2/27) of patients at initial staging (*15*). The changes in patient management induced by NaF PET/CT were considered appropriate at follow-up; however, no comparison to a standard PCa workup was conducted. These data are not in line with our findings.

The strength of the present study lies in the prospective design including a homogenous and representative group of newly diagnosed PCa patients eligible for radical prostatectomy. The present study had a true reference standard for the absence of bone metastases at the time of staging based on postoperative PSA levels, whereas the majority of studies on NaF PET/CT either

focused on the detection rate without a proper reference or focused on the validation of bone metastases and not on the verification of a lack of bone metastases. The present design did not allow true verification of the localization of tumor cells in patients with biochemical failure (bone vs. nonbone); however, 24 months of clinical follow-up and imaging did not reveal any false negative bone metastases.

In the present study, 7% of the patients had biochemical failure within six months after radical prostatectomy. An investigation of biochemical recurrence at a later time point was not conducted. We retained this time frame to determine whether NaF PET/CT had potential to identify bone metastases not recognized on the initial bone scintigraphy prior to radical prostatectomy. This study did not allow for an evaluation of the false negative NaF PET/CT rate; thus, the lack of false negative NaF PET/CT in the present study cannot be generalized to other populations. Similarly, the present study represents a population with mainly intermediate-risk PCa suitable for surgery, and the findings cannot be extrapolated to high-risk or very high-risk populations.

In conclusion, NaF PET/CT did not provide any added prognostic value at the time of staging in patients with normal bone scintigraphy in terms of improved patient-related outcomes after radical prostatectomy.

DISCLOSURE

The authors have no potential conflicts of interest relevant to this study.

ACKNOWLEDGEMENTS

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Key Points

Questions: Does the use of ^{18}F-sodium fluoride PET/CT (NaF PET/CT) in the initial staging of prostate cancer (PCa) improve the prognostic accuracy after radical prostatectomy in patients with normal bone scintigraphy?

Pertinent Findings: A two-center, blinded, prospective cohort study of NaF PET/CT in 81 patients with intermediate- and high-risk PCa and negative bone scintigraphy who were scheduled for radical prostatectomy. Biochemical response was based on the postoperative PSA level. NaF PET/CT did not identify bone metastases in any patients with persistently elevated PSA levels after surgery but indicated bone metastases in one patient who had a PSA level <0.1 ng/mL 6 months after radical prostatectomy.

Implications for Patient Care: NaF PET/CT has no added value in terms of prognostic accuracy after radical prostatectomy in patients with normal bone scintigraphy.

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Legend to Figure 1

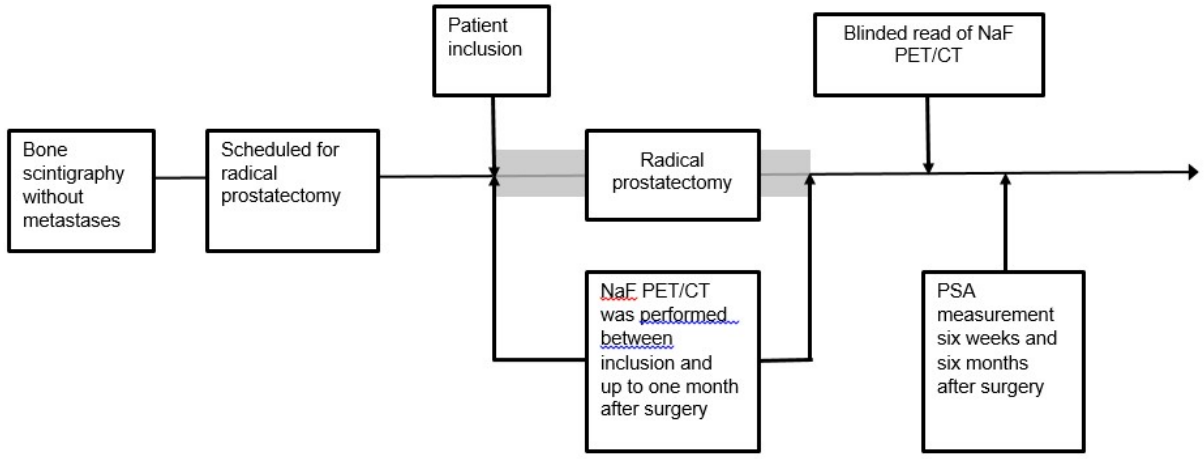

Figure 1 shows the outline of the study. Patients with negative standard imaging* who were undergoing radical prostatectomy were offered inclusion in the study. NaF PET/CT was performed between inclusion in the study and up to one month after radical prostatectomy within the timespan marked in grey. The results of the NaF PET/CT scan were unblinded six months after radical prostatectomy.

*Standard imaging consists of bone scintigraphy with/without SPECT/CT and diagnostic CT. RP: Radical prostatectomy

Table 1 Patient demographics and clinical characteristics

Patients, n	81
Age (y), mean (range)	65 (47-77)
PSA (ng/mL), mean (range)	10.2 (2.3-27)
Bone scan prior to inclusion	
Planar whole body	49
Planar whole body + SPECT/CT	32
Gleason	
< 7, *n*	5
7 (3+4), *n*	46
7 (4+3), *n*	18
>7, *n*	12
T-stage	
T1, n	41
T2, n	39
T3, *n*	1
EAU risk score	
Intermediate risk, n	60
High risk, n	21
PSA response six months after RP	
Biochemical response*, *n*	75
Biochemical failure†, n	6

EAU: European Association of Urology; SPECT/CT: Single photon emissions computed tomography; PSA: Prostate-specific antigen; RP: radical prostatectomy, *PSA<0.2 ng/mL at six weeks and at six months after radical prostatectomy; †PSA≥0.2 ng/mL at six weeks and/or at six months after radical prostatectomy.

Table 2, Diagnosis according to NaF PET/CT at staging compared to outcome after radical prostatectomy.

		Post-operative classification	
		Biochemical response* **n = 75**	**Biochemical failure†** **n = 6**
NaF PET/CT	**Bone metastases, n=1**	1	0
	Equivocal, n=7	7	0
	No bone metastases, n=73	67	6

*PSA<0.2 ng/mL six weeks and six months after radical prostatectomy, †PSA≥0.2 ng/mL at six weeks and/or at six months after radical prostatectomy.

Table 3: Patients with PSA ≥0.1 ng/ml six weeks and/or six months after radical prostatectomy.

Patient	**Bone metastases according to NaF PET/CT***	**PSA value at six weeks and six months after radical prostatectomy**	**Additional imaging during 24 months of follow up**	**Clinical follow up and PSA levels after radical prostatectomy – 24 months of follow up**
1	No bone metastases	0.2 ng/mL at six weeks, 0.1 ng/mL at six months	PSMA PET/CT and NaF PET/CT six months after radical prostatectomy revealed no bone metastases	PSA levels continuously 0.1 ng/mL at 24 months after radical prostatectomy
2	No bone metastases	0.1 ng/mL at six weeks, 0.2 ng/mL at six months	ceCT at 12 months after radical prostatectomy revealed no bone metastases	PSA levels 0.9 ng/mL at 24 months after radical prostatectomy. Have started ADT. No skeletal related symptoms
3	No bone metastases	1.2 ng/mL at six weeks 1.4 ng/mL at six months	PSMA PET/CT at six months after radical prostatectomy revealed no bone metastases	Have started ADT. No skeletal related symptoms
4	No bone metastases	0.6 ng/mL at six weeks 0.8 ng/mL at six months	PSMA PET/CT at six months after radical prostatectomy and ceCT 18 months after radical prostatectomy revealed no bone metastases	Have started ADT. No skeletal related symptoms
5	No bone metastases	0.1 ng/mL at six weeks, 0.2 ng/mL at six months	PSMA PET/CT at six and 15 months after radical prostatectomy and ceCT 18 months after radical prostatectomy revealed no bone metastases	Positive surgical margins. No skeletal related symptoms
6	No bone metastases	0.3 ng/mL at six weeks	PSMA PET/CT two months after radical prostatectomy revealed no bone metastases	Salvage radiotherapy of the prostatic bed 4 months post-surgery without concomitant systematic therapy, thereafter PSA<0.1 ng/mL

* Consensus diagnosis of two blinded observers (three point scale).

ceCT: contrast enhanced CT; PSMA prostate specific membrane antigen; ADT: Androgen deprivation therapy.

Supplemental Table 1: Patients with definite or unclear metastatic deposits according to NaF PET/CT.

Patient	Bone metastases according to NaF PET/CT*	PSA value at six weeks and six months after radical prostatectomy	Additional imaging during 24 months of follow up	Clinical follow up and PSA levels after radical prostatectomy – 24 months of follow up
1	Bone metastases present	<0.1 ng/mL	ceCT at 24 months without bone metastases	PSA levels < 0.1 ng/mL at 12 and 24 months after radical prostatectomy. No skeletal related symptoms
2	Equivocal	<0.1 ng/mL	No additional imaging during follow up	PSA levels < 0.1 ng/mL at 12 and 24 months after radical prostatectomy. No skeletal related symptoms
3	Equivocal	<0.1 ng/mL	No additional imaging during follow up	PSA levels < 0.1 ng/mL at 12 and 24 months after radical prostatectomy. No skeletal related symptoms
4	Equivocal	<0.1 ng/mL	No additional imaging during follow up	PSA levels < 0.1 ng/mL at 12 and 24 months after radical prostatectomy. No skeletal related symptoms
5	Equivocal	<0.1 ng/mL	No additional imaging during follow up	PSA levels < 0.1 ng/mL at 12 and 24 months after radical prostatectomy. No skeletal related symptoms
6	Equivocal	<0.1 ng/mL	ceCT at 24 months without bone metastases	PSA levels < 0.1 ng/mL at 12 and 24 months after radical prostatectomy. No skeletal related symptoms
7	Equivocal	<0.1 ng/mL	ceCT at 15 months without bone metastases	PSA levels < 0.1 ng/mL at 12 and 24 months after radical prostatectomy. No skeletal related symptoms
8	Equivocal	<0.1 ng/mL	No additional imaging during follow up	PSA levels < 0.1 ng/mL at 12 and 24 months after radical prostatectomy. No skeletal related symptoms

* Consensus diagnosis of blinded observers (three point scale).
ceCT: contrast enhanced CT