^{18}F-fluoride positron emission tomography imaging of Penile Arteries and Erectile Dysfunction

A brief title; Penile Fluoride uptake & Erectile Dysfunction.

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Abstract

Background Fluorine-18 sodium fluoride (NaF)- a bone-seeking radiopharmaceutical employed to detect osseous metastases, localizes in regions of microcalcification in atherosclerosis.

Objectives To determine if atherosclerosis of penile arteries plays a role in erectile dysfunction (ED), we analyzed NaF images in prostate cancer patients.

Methods (NaF) PET-CT bone scans were evaluated in 437 prostate cancer patients (age 66.6±8.7 years). Their urologic histories were reviewed for Prevalent ED (diagnosed before the scan date), or Incident ED (no ED at first scan, but developed during 1-year follow-up); patients with No ED (neither before the scan nor during follow-up) were included as control group. A semicircular ROI was set on the dorsal half of the penis (to avoid residual excreted activity in the urethra) on 5 contiguous slices at the base of penis on PET-CT coronal reconstructions, and the average SUV_{max} was described as NaF uptake.

Results Of 437 patients, 336 (76.9%) had Prevalent ED, 60 Incident ED (13.7%), and 41 had No ED (9.4%). SUV_{max} in patients with Prevalent (median 1.88; IQR 1.67-2.16) or Incident (1.86; 1.72-2.08) ED was significantly higher than No ED (1.42; 1.25-1.54) patients ($p < 0.001$). After adjustment for other risk factors, the Odds Ratio of Prevalent or Incident ED was 25.2 (95% CI: 9.5-67.0) for every 0.5 unit increment in SUV_{max} with ROC area of 0.91 (0.88-0.94).

Conclusions NaF uptake in penile vessels is associated with ED in prostate cancer patients. The importance of NaF uptake needs to be tested in non-cancer subjects and cause-effect relationship needs to be established.

Condensed Abstract To determine if atherosclerosis of penile arteries plays a role in erectile dysfunction (ED), we analyzed Fluorine-18 sodium fluoride (NaF) images in prostate cancer patients. Of 437 patients, SUV_{max} of penile vessels in patients with Prevalent (median 1.88; IQR 1.67-2.16) or Incident (1.86; IQR 1.72-2.08) ED was significantly higher than No ED (1.42; IQR 1.25-1.54) patients ($p < 0.001$). After adjustment for other risk factors, the odds of Prevalent or Incident ED was 23.5 (95% CI: 9.0-61.3) for 0.5 unit increment in SUV_{max} with ROC area of 0.91 (95%CI: 0.88-0.94) for ED. NaF uptake in penile vessels is associated with ED.

Key words Atherosclerosis, Calcification, Erectile Dysfunction, NaF, Sodium Fluoride

Abbreviations list NaF: Fluorine-18 sodium fluoride, ED: erectile dysfunction, EBRT: external beam radiotherapy, ROC: receptor operating characteristic, AUC: areas under curve

Introduction:

Erectile dysfunction (ED) shares multiple risk factors with atherosclerosis (1). Previous studies have demonstrated the relationship of ED to increasing age, obesity, smoking, hypertension (HTN), metabolic syndrome, diabetes mellitus (DM) and dyslipidemia (2-4). Endothelial dysfunction, which is commonly linked to all risk factors, is considered to play a major role in ED (5,6), and may be the precursor of early atherosclerotic processes. To determine if atherosclerotic involvement of penile vasculature contributes to ED, we analyzed Fluorine-18 sodium fluoride (NaF) PET-CT images in prostate cancer patients. NaF, which is a bone-seeking radiopharmaceutical and is used to detect osseous metastases, is also known to localize in the focal areas of active microcalcification in atheromatous plaques (7-10).

We hypothesized that NaF uptake in penile vessels could serve as a marker of vasculogenic ED. We had, during our review of bone scans, frequently noted NaF uptake in penile arteries which led to the current hypothesis. The present study investigates the relationship of penile vascular NaF uptake in patients with and without ED.

Methods:

Study population

The institutional review board approved this retrospective study and waived the necessity for a written informed consent. Prostate cancer patients (n= 442) who had NaF bone scans for detection of osseous metastases were enrolled in this study. The urologic histories were reviewed to determine the presence of ED at the time of initial and 1-year follow-up scans. ED was present when a diagnosis had been established by an experienced urologist or the International Index of Erectile Function (IIEF-5) score was $\leq$21 in the absence of any drugs known to cause ED. Five patients with penile implants were excluded from analysis reducing the study cohort to 437 patients. Patients were divided into 3 groups; (I) Prevalent ED, i.e. ED diagnosed before the date of scan, (II) Incident ED, i.e. no ED at the time of the first scan, but ED developed during 1-year follow-up, (III) No ED, i.e. ED neither at the first date nor during follow-up; this group was treated as the control group. Coronary risk factors on the scan dates were also obtained.

PET-CT Protocols and Image Reconstruction

Approximately 70 min after intravenous injection of 5-6 mCi ^{18}F-NaF, whole body

PET-CT images were acquired on integrated PET-CT systems (Discovery 690 or 710; GE Healthcare, Milwaukee, USA). A low dose CT (120 kVp, 40-100 mA based on the body weight, 0.8 second per rotation, and 3.75mm slice thickness) was performed for attenuation correction and anatomic registration. No iodinated contrast material was administered. PET images were acquired from the vertex to the feet in 3-dimensional mode for 3 minutes per bed position. PET-CT images were transferred to an offline workstation and reconstructed into coronal, axial and sagittal planes with dedicated software (Hermes hybrid viewer software; Hermes Medical Solutions, Stockholm, Sweden).

To evaluate NaF uptake in penile arteries at the base of the penis five consecutive coronal PET-CT images and the corresponding CT were analyzed. The first slice was at the anterior-inferior margin of the symphysis pubis, and incremented anteriorly by one PET slice (with corresponding CT) for each of the remaining 4 slices. The images were evaluated for both calcifications on CT and fluoride PET uptake in the dorsal artery and cavernosal vessels (PET). To exclude residual excreted activity in urine within the penile urethra, a semi-circle ROI was set on the upper half of the penis (Central Illustration A, B, C, D). The average SUV_{max}(11) of 5 ROIs was defined as the NaF uptake. The comparable slices on CT were evaluated for CT calcification (>130

Hounsfield units) using an OsiriX workstation (Osirix version 32 bit; OsiriX Imaging Software, Geneva, Switzeland). This software was also used to measure CT calcification in the common carotid (CCA) and common/internal iliac (CIA/IIA) arteries. For measurement of coronary calcification, we used the 0-12 scoring method developed for non-gated scans (12,13).

Statistical Analysis

Intraobserver and interobserer variability in NaF measurements was assessed using Bland-Altman analysis and Spearman's rank correlation coefficients. Data are presented as median (interquartile range, IQR; i.e. 25th to 75th percentile, or Q1, Q3) or as Mean±1SD. Continuous data were compared using Mann-Whitney U test between 2 the groups or Kruskal-Wallis test with post ad -hoc Dwass, Steel, Critchlow-Fligner (DSCF) multiple comparison analysis. Proportions were compared with Fisher's exact probability test. We examined differences in SUV_{max} in various groups including in patients with extra-capsular extension of their prostate cancer or evidence of neuronal involvement of histopathology (See below). The Spearman Rank Correction coefficient test was used for the assessment of linear correlation of two parameters. We used multivariable logistic regression model to study the relationship between ED and NaF

SUV_{max} after adjusting for potential confounders. The areas under curve (AUC) of receptor operating characteristic (ROC) curve were used to compare incremental diagnostic utility of NaF for diagnosis of Prevalent ED or Incident ED. A two-sided p <0.05 was considered statistically significant. Statistical analyses were performed with SAS software, version 9.4., SAS Institute Inc., Cary, NC, USA.

Results

Patient characteristics

Of the 437 patients with prostate cancer (age 66.6±8.7 years, BMI 28.9±4.4), 244 patients had hypertension (HTN, 56%), 247 dyslipidemia (57%), 70 type 2 diabetes mellitus (DM, 16%), and 204 reported a smoking history (47%; 26 currently smokers); 52 (12%) patients had a history of coronary artery disease (Table 1). Based on histopathology, ED patients with (n=165) or without (n=31) extracapsular extension of prostate cancer and with (n=173) or without (n=7) evidence of neuronal involvement were also separately evaluated and compared with no ED group. As presented in Figure 1, 220 patients had radical prostatectomy prior to the NaF scan (4.1±4.4 years) and 45 patients had radical prostatectomy within one year after the (NaF) PET-CT. 145 patients

were treated with radiation (25 seed implant and 131 external beam radiotherapy (EBRT)); interval from initial EBRT to NaF scan was 7.7±5.0 years, salvage EBRT to NaF scan was 4.6±3.7 years, brachytherapy to NaF scan was 8.1±4.1 years, and total 6.2±4.6 years. 139 patients received androgen deprivation therapy (ADT) with or without other radiation therapy and surgical intervention within 6 months. Finally, 92 patients were monitored for follow-up without any active surgical, radiation or hormonal therapy.

NaF uptake and ED

Penile NaF uptake was commonly observed in the ED patients (Figure 2); the uptake was observed distinctly from the urethral activity in the cavernous and dorsal penile arteries. Former vessels are considered important for cavernous filling and erectile competence. Quantitative penile NaF uptake in Prevalent ED (SUV_{max}1.88; IQR 1.67-2.16) and Incident ED (SUV_{max} 1.86; IQR 1.72-2.08) was significantly higher than in No ED (SUV_{max} 1.42; IQR 1.25-1.54) patients ($p<0.001$) (Figure 3). Quantification of penile NaF uptake demonstrated excellent inter- and intra- observer reproducibility (Supplemental Figure 1). The age adjusted mean difference in SUV_{max} was higher by 0.53 (0.37-0.60) among Prevalent ED and by 0.56 (0.44-0.61) among Incident ED

patients compared to No ED. In our study cohort, IIEF scores were available for 176 patients at baseline and 1-year follow-up IIEF score for 90 patients. NaF uptake was negatively correlated with IIEF score ($R = -0.26$, $p < 0.001$, n = 144 Prevalent ED, 13 No ED) at baseline and at 1-year follow-up ($R = -0.32$, $p < 0.001$, n = 69 Prevalent ED, 11 Incident ED, 10 No ED patients). On the other hand, even though higher, there was no statistically significant difference in CT-verified calcium score in the carotid, internal iliac, common iliac and penile arteries among Prevalent and Incident ED compared with No ED. In the coronary arteries (on the ungated scale of 0-12 score), the calcium score showed significant difference in three groups, it was higher in Prevalent ED patients than in No ED patients albeit statistically non-significant (p=0.07) in multiple comparisons (Table 1). Penile NaF uptake was not significantly different in ED patients with [1.86 (1.64-2.10); n=165] or without extracapsular extension [1.83 (1.61-2.01); n=31], nor in ED patients with [183 (1.63–2.10); n=173] or without perineural invasion [1.91 (1.66–2.29); n=7].

Although Prevalent ED patients were older (67.5±8.3 years) than No ED (64.0±9.4 years) or Incident ED (63.5±9.6 years), there was only a modest correlation between age and SUV_{max} ($R = 0.22$, $p < 0.001$). The BMI was not significantly different between No ED (28.1±3.8 kg/m^2), Incident ED (29.4±5.0 kg/m^2), and Prevalent ED (29.0±4.3

kg/m^2) groups but showed a significant correlation with the SUV_{max} (R =0.37, p <0.001). The eGFR (MDRD) was not significantly different between the No-ED (84.4±23.9 ml/min/1.73m^2), Incident ED (85.2±19.4 ml/min/1.73m^2), and Prevalent ED (82.9±20.5 ml/min/1.73m^2) and showed no correlation with the SUV_{max} (R =-0.08, p =0.12) (Table 1). SUV_{max} was significantly higher in patients with hypertension, diabetes and prior radiation therapy. SUV_{max} was not different in patients with a history of smoking, CAD and/or radical prostatectomy. Dyslipidemia did not affect SUV_{max} and, in the subgroup with dyslipidemia, statin did not affect SUV_{max} (Supplemental Table 1).

After adjustment for age, BMI, eGFR, hypertension, hyperlipidemia, diabetes mellitus, smoking status, prevalent CAD, prior radiation therapy, prior prostate surgery and ADT, the Odds Ratio of any ED (Prevalent or Incident versus NO ED) was 25.2 (95% C.I.: 9.5–67.0) for each 0.5 unit increment in SUV_{max} (Supplemental Table 2). Only a negligible change occurred after adding all other clinical variables, including CT calcification in the coronary, carotid, common/internal iliac arteries, and penile arteries to this model. The strong relationship between SUV_{max} and ED was also reflected in area under ROC of 0.91 (95% C.I.: 0.88 –0.94) in a model with SUV_{max} alone as predictor (Figure 4).

Effect of therapeutic strategy on NaF uptake

Because ED may also result as a consequence of the treatment, such as nerve injury, we reviewed the results separately in groups of patients treated by surgical, radiation or hormonal protocols (14). In all subgroups SUV_{max} was higher for the Prevalent and Incident ED including only radiation [2.01 (1.83–2.40); n =36], only prostatectomy [1.81 (1.59–2.10); n =111], only androgen deprivation therapy [1.94 (1.69–2.16); n=40] and those only under surveillance without any surgical, radiation or hormonal intervention[1.84 (1.63–2.16); n =79] compared to the No ED patients ($p < 0.05$) (Figure 3). Within one year after the (NaF) PET-CT, 45 patients underwent radical prostatectomy, 46 patients received radiation therapy and 153 patients were treated with ADT. However, these therapies within one year after the NaF imaging did not influence Incident ED. Although medications, especially beta-blockers and anxiolytics, and anti-depressant agents including selective serotonin-inhibitors, which could potentially cause ED did not influence the Prevalent or Incident ED (p NS) (Supplemental table 3).

Discussion

NaF Imaging in Erectile Dysfunction

This study showed that penile NaF uptake was associated with the presence of ED and the likelihood of future ED. It is possible that penile NaF uptake is an indicator of penile vascular pathology and hence vasculogenic ED. Using SUV_{max} of 1.56 as the cut-off value based on the ROC analysis, NaF uptake showed sensitivity of 85%, specificity 80%, positive predictive value of 98% and negative predictive value 35%, with diagnostic accuracy of 84%. The low negative predictive value is due in part to the small number of No ED patients or could represent the patients with non-vasculogenic ED, such as that could result from psychologic, neurologic, or hormonal causes (1-3,14). A sub-analysis of MESA study showed coronary calcium score to be an important predictor of endothelial and erectile dysfunction (15). Although our study population was smaller (n= 437, CAD 52) compared to 1862 men (age 45-84 years, free of CAD) in the MESA study, our results of calcium scores were compatible with the MESA study. The ROC analysis and Odds Ratio showed NaF ED was superior to coronary calcium score to predict ED.

Pathogenetic basis of NaF uptake in Erectile Dysfunction

NaF has been used for more than 50 years (16) as a tracer to detect osseous metastasis.

It has also been proposed that NaF uptake could identify the active process of microcalicifiaction in atheromatous plaques (7,17,18). The initial step of microcalcification in atheroma involves extracellular vesicles, including matrix vesicles and apoptotic bodies in the necrotic core (19), which serve as nucleation sites for calcium phosphate deposition. As microcalcification increases, it coalesces into large masses or triggers a calcification cascade (as seen in bone formation) and results in macrocalcification (10,20).

There are no reports describing the use of NaF to evaluate possible atherosclereosis in erectile dysfunction. The artery size hypothesis, suggests that a relatively small decrease in penile aretery diameter, such as due to plaque, could cause ED (21). In an autopsy study of 31 subjects, the prevalence of atherosclerotic lesions in penile arteries (12.9%) was lower that of the coronary arteries (87.1%) and internal iliac arteries (77.4%) (22). AHA type Vb atherosclerosis was observed in penile arteries, wherein the mineral deposition is expected to have replaced the contents of the atheromatous necrotic core. From these observations, it is conceivable that NaF should localize in early microcalcific foci in penile vessels. The fluoride uptake provides information that differs from late calcification seen on CT (10).

Due to the limited spatial resolution (3-5mm) of PET imaging, it is not certain if the

penile NaF uptake is localized to cavenous arteries. Since there was no significant correlation between iliac calcification and penile fluoride uptake, it is also possible that calcification could be associated with the venous compartment or smooth muscle cell damage leading to possible venous insufficiency and ED.

Inflammation as the basis of vascular involvement and NaF uptake

Inflammation, which is the obligatory component of atherosclerosis, has been proposed as the precursor of microcalcification and NaF uptake (10). Although nerve injury from prostatectomy has been widely implicated as an etiology of ED, Mulhall and colleagues have emphasized that ED is associated with arterial insufficiency and venous leakage especially when the cavernous nerve remained unaffected during radical prostatectomy (23). The result of the current study with high prevalence of NaF uptake in the penile vasculature in ED patients is consistent with their data. Further, the relationship between ED and external beam radiation was reported in the 1970s, with impotence occurring several months to several years after therapy (24,25), possibly an inflammatory consequence of irradiation. Our study demonstrated that patients who received radiation therapy more than 3 years before NaF scan showed a high odds ratio in univariate analysis [Odds Ratio: 12.3 (95%CI: 1.7-90.5)], but did not achieve statistical

significance in multivariable analysis (Supplemental Table 2). It is possible that vascular risk factors act synergistically with radiation to result in ED (25). Animal studies have demonstrated that radiation induced inflammation could accelerate development of atherosclerotic lesions in $ApoE^{-/-}$ mice (26,27).

To evaluate if inflammation was a necessary accompaniment of NaF uptake in ED patients, we reviewed a subset of 63 patients who had undergone both (FDG) PET-CT and (NaF) PET-CT scans within 6 months of each other (Supplemental Figure 2); FDG uptake is an established marker of vascular inflammation. There was, however, no significant difference of penile FDG uptake in the No ED [1.52 (1.09-2.29); n= 7], Incident ED [1.64 (1.33-2.07); n= 11], or Prevalent ED [1.95 (1.63-2.40); n= 45] groups (p= 0.08). Also, there was no significant correlation between NaF uptake and FDG uptake (r=0.15, p=0.24). However, SUV_{max} of FDG was significantly higher in patients treated with irradiation [2.29 (1.85-2.42); n=19] compared to those without radiation therapy [1.77 (1.51-2.05); n=44, $p<0.05$]; NaF imaging also demonstrated a trend (albeit statistically insignificantly) towards higher uptake in the radiation group supporting an inflammatory basis. In all other patients, ED correlated with increased penile fluoride uptake, but not with FDG uptake, suggesting that the calcification may not necessarily

be associated with the inflammatory stage of the atherosclerotic process. Medial and intimal calcification is commonly seen in peripheral artery disease regardless of inflammation (28), and may also contribute to penile NaF uptake.

Management strategy, ED and NaF uptake

In our series of unselected prostatic malignancy patients, variable degrees of Prevalent ED were reported in 77% of patients, which might seem high. A plausible approach to evaluate the true prevalence of ED in the prostate cancer patients is to compare No ED patients with Incident ED patients, because all patients in these 2 groups should not have erectile dysfunction at the time of initial scan, the Incident ED patients developed erectile dysfunction during follow up. Whereas 41 patients belonged to No ED group, 60 patients had Incident ED; approximately 60% of patients with no evidence of ED at baseline developed ED within the ensuing year. The impotency rates have been reported to range from 54-90% in the 12 months of follow up after radical prostatectomy with or without robot-assistance (29) and approximately 50% of patients at 5 years after radiation theraphy (30). The prevalence of ED in a normal population (mean age :62.3 years old) has been reported as 52% (31). Considering our patients were older than 66 years, the prevalence of ED in our study is not an overestimate. In the subgroup of No

ED vs Incident ED (n=101) patients, ROC curve analysis showed a high diagonstic accuracy of NaF SUV_{max} for Incident ED, with the area under the curve of 0.91 (95%CI: 0.86-0.97) (Supplemental Figure 3) .

Limitations of the study.

Although the results are intriguing and provocative, there are several limitations of this study. It is a retrospective study of prostate cancer patients from a single tertiary care referral center and the inherent bias of inclusion of only severe and complicated cases cannot be excluded. In addition, the number of No ED patients is small. However; considering published rates of ED in patients with prostate cancer as discussed above, it appears that we have sampled a representative group of patients with a high prevalence of ED. Regardless, the lower number of No ED patients reduces the confidence in our findings. Unfortunately, most of our patients did not have lipid profiles, so we could not calculate Framingham Risk Scores to evaluate relationship between risk factors and possible penile artey atherosclerosis. Therefore, this study still leaves open the possibility that the NaF uptake is a consequence of or a co-occurrence from ED causing mechanisms i.e. risk factors and endothelial dysfunction rather than a causative etiology

of ED. Finally, even though there is a higher likelihood of active penile arterial calcification in erectile dysfunction, the study does not prove causality nor reveals clues that may help manage Prevalent ED or prevent occurrence of Incident ED.

Conclusions.

Fluoride uptake in penile vessels is significantly higher in patients with Prevalent or Incident ED. NaF uptake occurs both in patients undergoing surgical or radiation therapy. The study only demonstrates a correlation and causative association needs to be established. Therefore, future studies would examine the role of penile vascular fluoride uptake as a contributor to ED especially in a general patient population.

Contributors:

TN, HWS and JN designed the study and wrote the protocol. JM collected the patient characteristics data. MC, MD, PAC, JR, MJ, JN helped draft and edit the manuscript, and discuss the intricacies of calcification imaging. TN and HWS performed image analysis. SA and JGPT performed statistical analysis. TN, HWS and JN interpreted results and finalized the manuscript, which was shared with all authors for their editing.

All authors contributed substantially to the study and approved the report for publication.

Declaration of interests

None

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Clinical Perspectives

Altough the association of NaF uptake with ED is very strong, it is reasonable to accept that the NaF uptake will not influence clinical management in a significant way. However, this study suggests that vascular abnormality may be a more important mechanism of ED regardless of the management strategy.

Clinical Competencies

The study refutes the higher likelihood of ED in patients undergoing prostatectomy and relative sparing of ED in irradiated cancer patients. Even though not much preventive practice can be proposed, higher uptake of NaF is a forewarning of ED.

Translational Outlook 1

Lack of relationship of penile NaF uptake with atherosclerosis in other arterial beds, standard coronary risk factors, and preceeding inflammation prompts us to explore other mechanisms and solutions of vascular impairment.

Translational Outlook 2

This study also paves the way for a systematic prospective study of NaF imaging in general, non cancer patients to explore underlying causes of ED.

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Figure legends

Central Illustration: The assessment of penile NaF uptake, definition of ROI, and calculation of SUV_{max}.

(A) Schematic presentation of origin of penile arteries from common iliac, internal iliac and internal pudendal arteries. (B) Schematic representation of the distribution of penile arteries in coronal images. Main arteries (dorsal penile arteries and cavernous arteries in red) are located in the upper half of the penis. A semi-circle ROI is set on the upper half of the penis, red dots on panel B far right, avoiding urethra. Blue vessels correspond to veins and yellow circles correspond to the nerves. (C) (NaF) PET-CT coronal image of the penis (SUV Upper level is set as 2.8). High uptake is observed in the cavernous area. The NaF in the bottom half of the penile cross-section corresponds to the urethra. (D) Semi-circle ROI is set on 5 contiguous slices on PET images near the inferior margin of the symphysis pubis on PET-CT image (red arrows). The average of SUV_{max} on the 5 ROI was presented as the NaF uptake.

Figure 1: Prostate cancer patients included in the present study grouped by various therapeutic interventions.

Prostate cancer patients (n= 442) who had NaF bone scans for detection of osseous metastases were enrolled in this study. Five patients with penile implants were excluded from analysis reducing the study cohort to 437 patients. Patients were treated with radical prostatectomy, radiation and/or androgen deprivation therapy (ADT). Ninety-two patients were monitored for follow-up without any active surgical, radiation or hormonal therapy (Active Surveillance).

Figure 2: Representative (NaF) PET-CT images in Prevalent ED and No ED.
(A) 55 year- old patient with Prevalent ED shows high NaF uptake (SUV_{max} 1.61) is observed in the area of the penile arteries (arrows). (B) 51 years old patient with No ED shows no evidence of NaF uptake (SUV_{max}: 1.21) (arrows). SUV upper level is set as 2.0 for both scans.

Figure 3: NaF uptake in Prevalent, Incident and No ED patients by therapeutic intervention strategy.
NaF uptake in Prevalent and Incident ED patients is significantly higher than No ED patients, regardless of radiation (n=36), prostatectomy (n=111), androgen deprivation therapy (ADT, n=40) or surveillance (n=79) strategy. A trend of higher uptake in

irradiated patients is not statistically significant.

Figure 4: ROC analysis to diagnose Prevalence ED or Incident ED.

ROC analysis showed that SUV_{max} showed high diagnostic accuracy for Incident ED or Prevalent ED, with the area under ROC curve of NaF being 0.91 (95% C.I.: 0.88-0.94).

Table 1: Patient characteristics

	No ED	Incident ED	Prevalent ED	P value
N	**41**	**60**	**336**	
Age	64.0± 9.4	63.5±9.6	67.5 ±8.3‡	0.001†
BMI	28.1±3.8	29.4±5.0	29.0±4.3	0.754
eGFR (MDRD)	84.4± 23.9	85.2±19.4	82.9±20.5	0.601
Hypertension	23 (56%)	29 (48%)	192 (57%)	0.450
Dyslipidemia	18 (44%)	36 (60%)	193 (57%)	0.158
Diabetes Mellitus	3 (7%)	8 (13%)	59 (18%)	0.200
CAD	2 (5%)	4 (7%)	46 (14%)	0.105
Smoking	15 (37%)	22 (37%)	167 (50%)	0.070
Surgery	10 (24%)	15(25%)	195 (58%)	<0.001†
Radiation	8 (20%)	7(12%)	130 (39%)	< 0.001†
EBRT	8	7	116	
Brachy	0	0	25	
ADT	18 (44%)	16 (27%)	105 (31%)	0.171

NaF SuV_{max}	1.42 (1.25-1.54)	1.86 (1.72-2.08) §	1.88(1.67-2.16) §	<0.001 †
Ca 12 score	2.0 (0.0-3.0)	2.0 (0.0-4.0)	2.5 (1.0-5.0)	0.042*
CCA CS	0.0 (0.0-17.5)	5.0 (0.0-82.0)	5.0 (0.0-84.0)	0.131
CIA CS	165.0 (28.0-834.0)	228.5 (16.3-731.3)	338.5 (26.3-1374.3)	0.260
IIA CS	40.0 (12.0-247.0)	92.0 (18.8-342.5)	133.0 (18.0-471.8)	0.135
PA CS	18.0 (2.0-36.0)	13.0 (0.0-42.8)	9.0 (0.0-27.0)	0.137

BMI: Body Mass Index, CAD: Coronary Artery Disease, EBRT: External Beam Radiation Therapy, ADT: Androgen Deprivation Therapy, , Ca 12 score: Coronary artery calcification 12 score, CCA CS: Common Carotid Artery Calcium Score, CIA CS: Common Iliac Artery Calcium Score: CIA, IIA CS: Internal Iliac Artery Calcium Score, PA CS: Penile artery Calcium Score.

*: P<0.05, †: P<0.01 from Kruskal-Wallis's test for 3 groups.

With post ad –hoc Dwass, Steel, Critchlow-Fligner (DSCF) multiple comparison analysis, ‡ Age was higher in Prevalent ED group as compared to Incident ED and No ED group. § NaF was higher in Incident ED and Prevalent ED group as compared to the No ED group. Ca 12 score showed significant difference in Kruskal-Wallis's test,

however; it do not showed the difference in DSCF analysis.

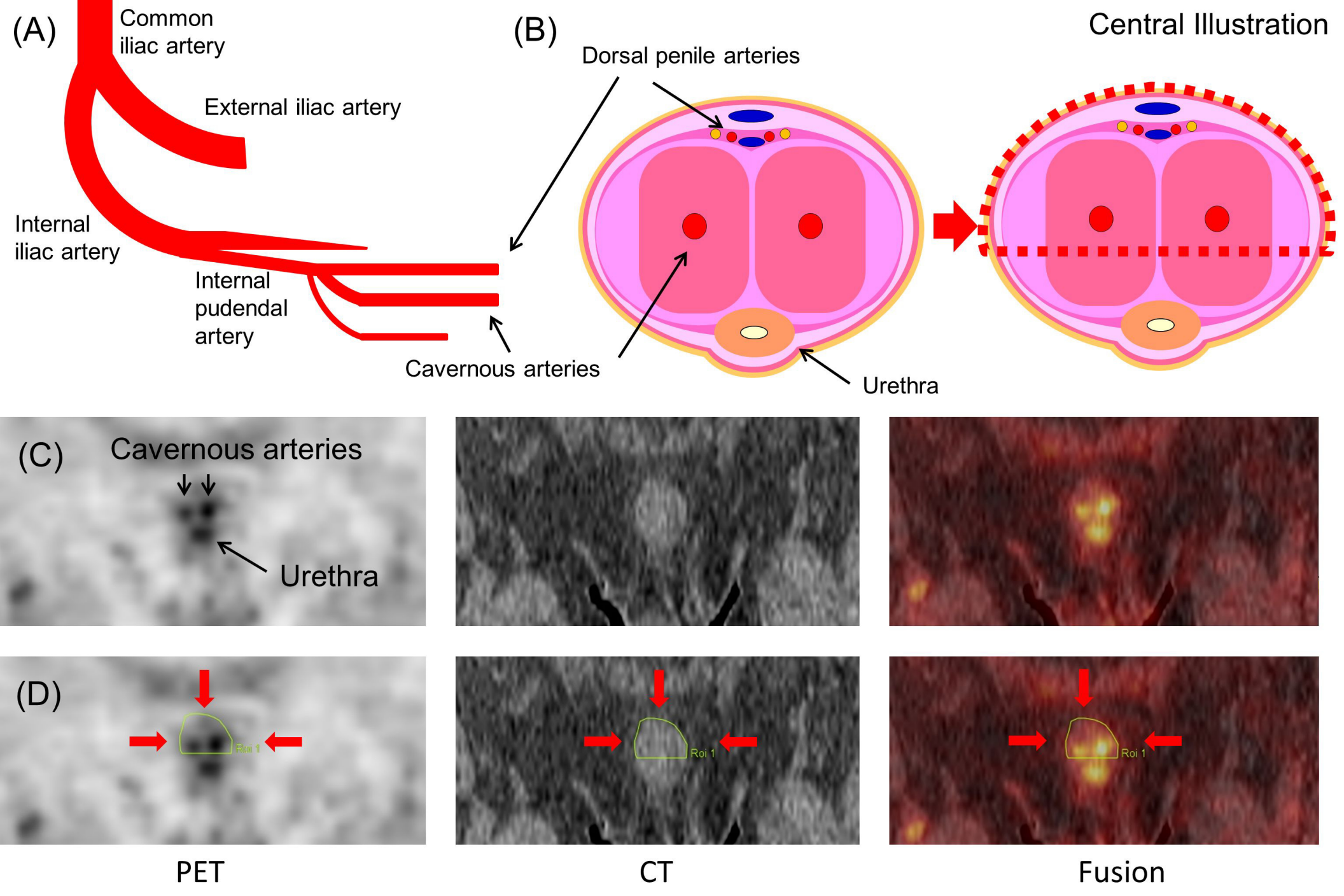
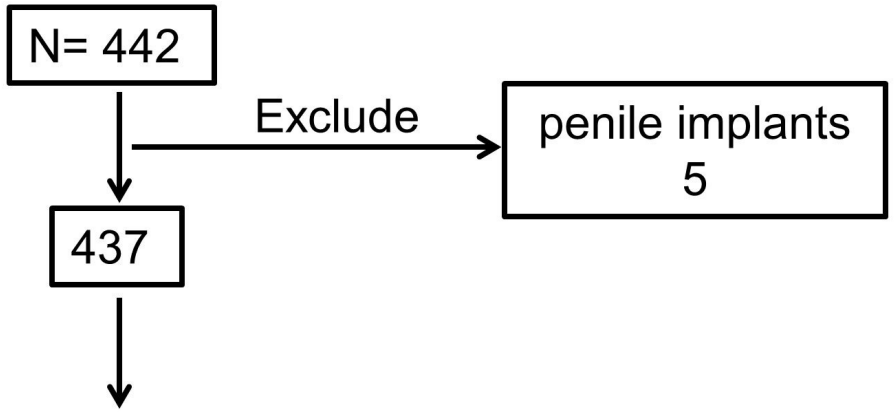

(A)
Common iliac artery
External iliac artery
Internal iliac artery
Internal pudendal artery
Cavernous arteries
(B)
Dorsal penile arteries
Urethra
Central Illustration
(C)
Cavernous arteries
Urethra
(D)
Roi 1
Roi 1
Roi 1
PET
CT
Fusion

Figure 1



Radiation	Prostatectomy	ADT	Surveillance	Number of patients
+	-	-	-	38
-	+	-	-	116
-	-	+	-	55
-	-	-	+	92
+	+	-	-	52
+	-	+	-	32
-	+	+	-	29
+	+	+	-	23

Figure 2

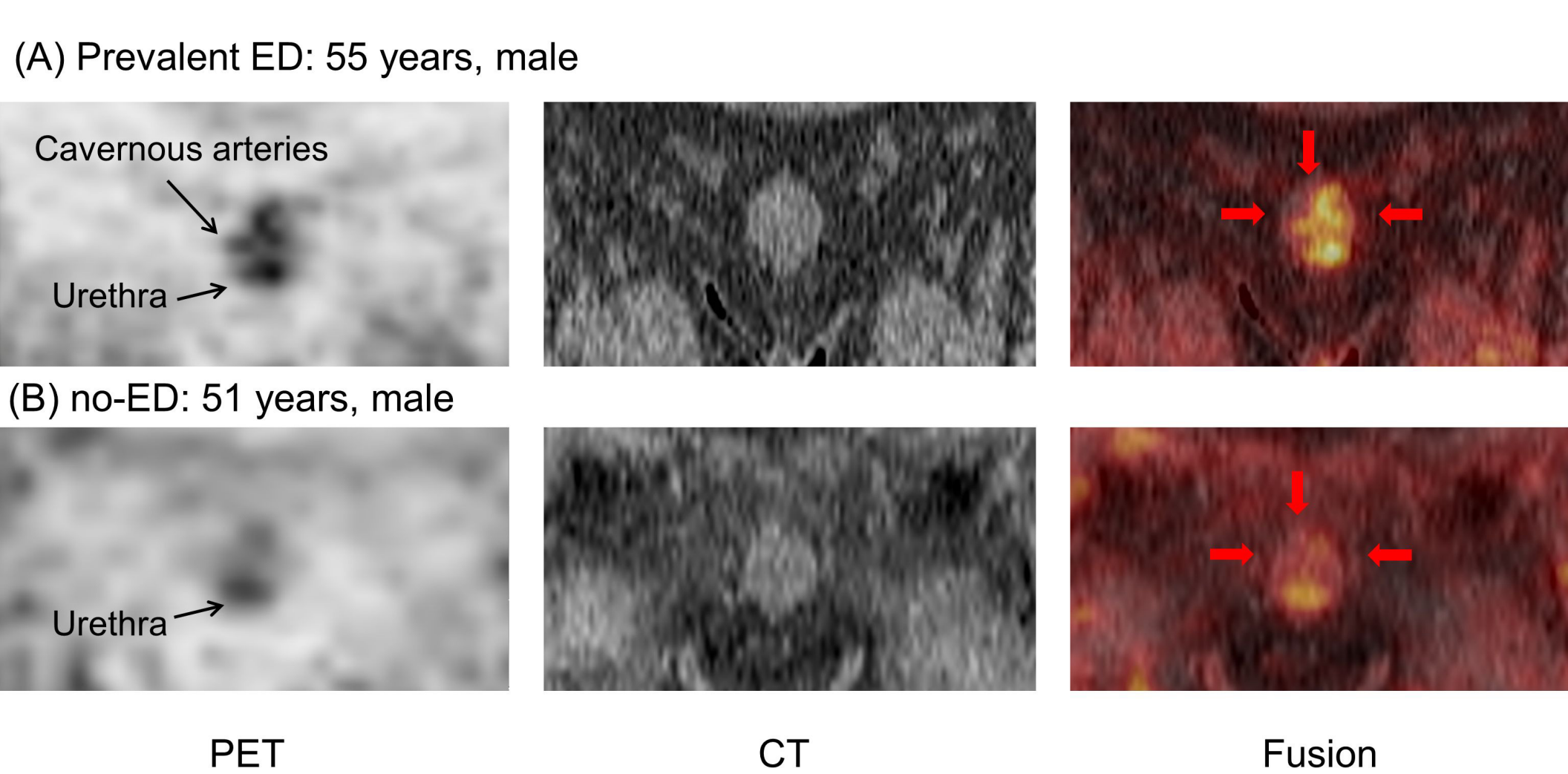

(A) Prevalent ED: 55 years, male
Cavernous arteries
Urethra
(B) no-ED: 51 years, male
Urethra
PET
CT
Fusion

Figure 3

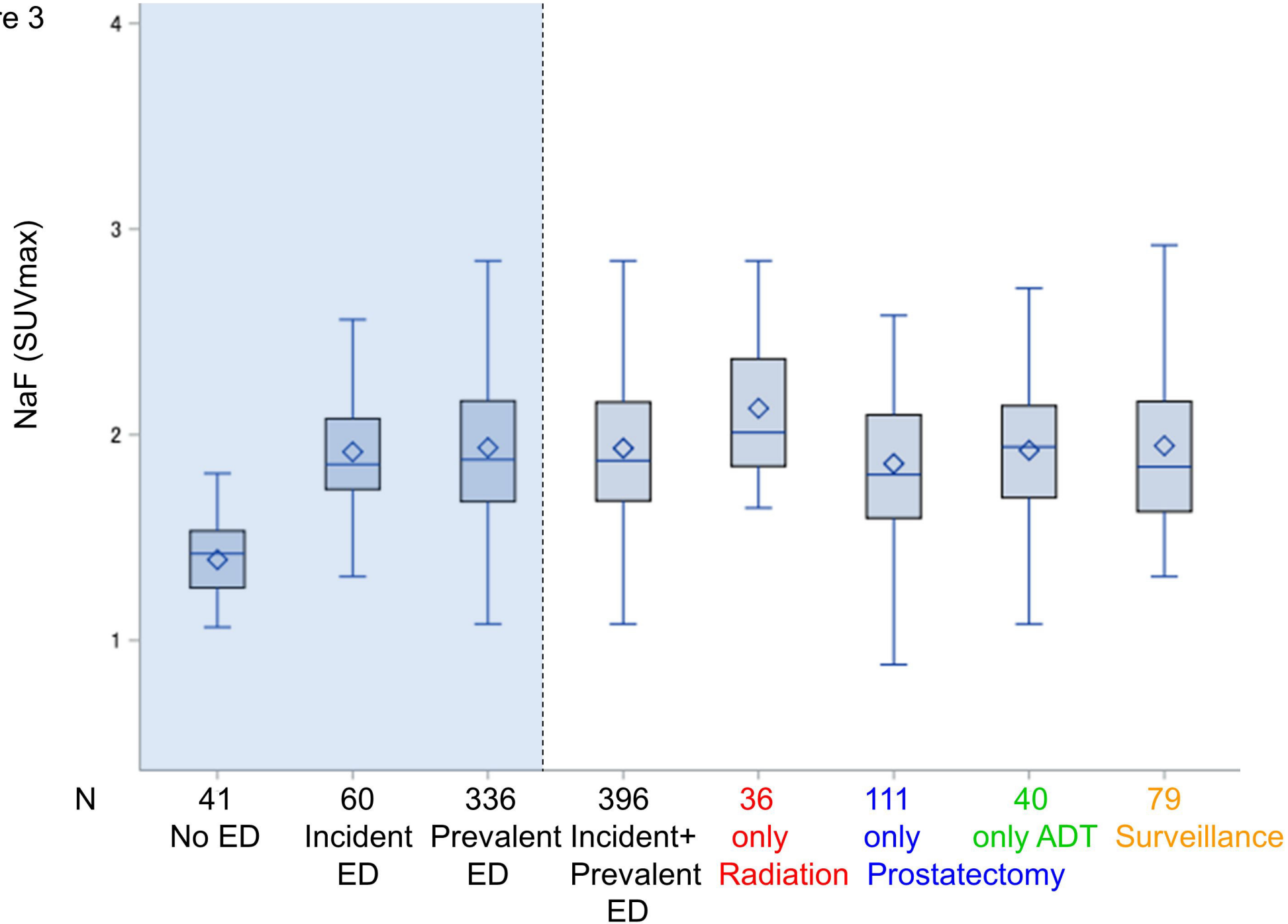
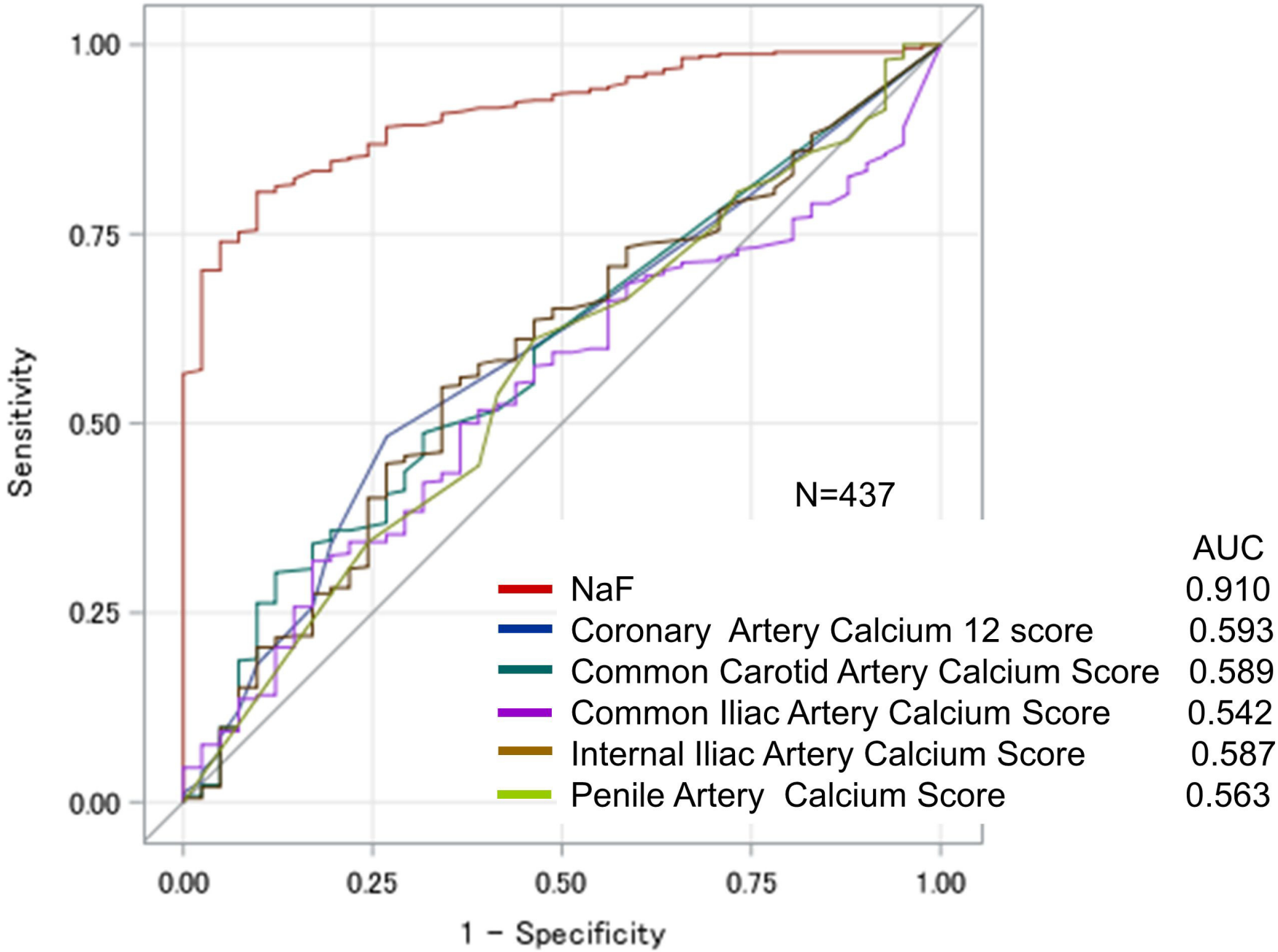

NaF (SUVmax)
4
3
2
1
N
41
No ED
60
Incident ED
336
Prevalent ED
396
Incident+ Prevalent ED
36
only Radiation
111
only Prostatectomy
40
only ADT
79
Surveillance

Figure 4


1.00
0.75
0.50
0.25
0.00
Sensitivity
0.00
0.25
0.50
0.75
1.00
1 − Specificity
N=437
AUC
NaF 0.910
Coronary Artery Calcium 12 score 0.593
Common Carotid Artery Calcium Score 0.589
Common Iliac Artery Calcium Score 0.542
Internal Iliac Artery Calcium Score 0.587
Penile Artery Calcium Score 0.563