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Use of ^{18}F-NaF PET in the staging of skeletal metastases of newly diagnosed, high-risk prostate cancer patients: a nationwide cohort study

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ABSTRACT

Objective To determine whether preoperative staging of high-risk prostate cancer with ^{18}F-sodium-fluoride (^{18}F-NaF) positron emission tomography (PET) reduces the risk of skeletal metastases.

Design Nationwide, population-based cohort study using real-world data.

Setting The study used national health registries, including all sites in Denmark from 2011 to 2018.

Participants Newly diagnosed high-risk prostate cancer patients who underwent radical prostatectomy from 2011 to 2018. Patients were stratified into two groups according to the preoperative imaging modality of either ^{18}F-NaF PET or bone scintigraphy.

Main outcome measures The risk of skeletal-related events (SREs) as a proxy for skeletal metastases following radical prostatectomy. The secondary endpoint was overall survival.

Results Between 1 January 2011 and 31 December 2018, 4183 high-risk patients underwent radical prostatectomy. Of these patients, 807 (19.3%) underwent ^{18}F-NaF PET and 2161 (51.7%) underwent bone scintigraphy. The remaining 30% were examined by a different imaging method or did not undergo imaging. Using the inverse probability of treatment weighting to control potential confounding, the HR of experiencing an SRE for patients in the ^{18}F-NaF PET group versus the bone scintigraphy group was 1.15 (95% CI 0.86 to 1.54). The 3-year survival rates were 97.4% (95% CI 96.1 to 98.7) and 97.1% (95% CI 96.4 to 97.9) for patients receiving ^{18}F-NaF PET and bone scintigraphy, respectively.

Conclusion Patients with high-risk prostate cancer undergoing preoperative staging with ^{18}F-NaF PET did not display a lower risk of developing SREs after prostatectomy compared with patients undergoing bone scintigraphy. The survival rates were similar between the two groups.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Registry data provides real-world data on the clinical impact of clinical practices.
⇒ This study identified a large cohort from all institutions in Denmark using high-quality registry data.
⇒ The routinely collected health data are not specifically registered for the purposes of this research, resulting in a minor degree of missing data.
⇒ Regression analysis weighted by the inverse probability of treatment ensured consideration of all measured confounders and addressed confounding by indication.

INTRODUCTION

Prostate cancer is one of the most common malignancies in the Western world, with over 1.4 million new cases reported in 2020.[1] Prostate cancer frequently metastasizes to the bone, which is associated with significant morbidity and mortality.[2 3] Accurate detection of bone metastases at primary staging is essential for decision-making regarding subsequent management. At the time of diagnosis, the risk of recurrence is determined based on the prostate specific antigen (PSA) level, Gleason score and clinical tumour stage (T-stage).[4] Patients classified as unfavourable—intermediate risk or high risk will often receive preoperative staging by imaging. International urology and oncology guidelines recommend bone scintigraphy with 99mTechnetium-labelled phosphonate (99mTc) for the assessment of bone metastases at primary staging.[4 5]

However, several studies have shown that the bone-specific positron emission tomography (PET) tracer ^{18}F-sodium-fluoride (^{18}F-NaF) is superior to bone scintigraphy in terms of its diagnostic accuracy for detecting bone metastases including fewer equivocal findings.[6–8] In previous studies, the sensitivity of bone scintigraphy for the detection of bone metastases varied from 57% to 97%, and the specificity varied from 57% to 80%.[6–9] In contrast, the sensitivity of ^{18}F-NaF PET for the diagnosis of bone metastases has ranged from 81% to 100% in the majority of studies, with a specificity ranging from 71% to 100%.[6–8 10 11] With the purported lower accuracy of bone scintigraphy, the risk of misdiagnosing patients

is high, possibly resulting in suboptimal treatment strategies. Among patients referred for suspected metastases, the use of ^{18}F-NaF PET instead of bone scintigraphy in patients with prostate cancer has been shown to affect the patient management strategy in 6%–12% of cases.[12 13] However, no studies have documented that the subsequent change in patient management strategies induced by ^{18}F-NaF PET and its improved diagnostic accuracy confer any patient benefit in terms of mortality, morbidity and quality of life. Thus, we performed a cohort study with real-world data of men diagnosed with prostate cancer in Denmark who underwent either bone scintigraphy or ^{18}F-NaF PET as part of primary staging before curative intent prostatectomy to examine whether the type of preoperative imaging modality was associated with overall survival and skeletal-related events (SREs) after radical prostatectomy.

METHODS

Study population and data sources

This nationwide register-based cohort study was conducted in Denmark, which has approximately 5.8 million residents. In Denmark, all residents are provided with free, tax-supported healthcare by the National Health Service. A unique 10-digit civil registration number is assigned to all residents at birth by the Central Office of Civil Registration. This number allows unambiguous linkage across all Danish population-based registries.[14] Reporting to the registries by clinicians is mandatory, which ensures high completeness of medical information. The applied data included nationwide information from the Danish Cancer Registry,[15] the Civil Registration System,[16] the Danish National Patient Registry,[17] the Register of Laboratory Results for Research,[18] the Danish Prostate Cancer Database,[19] the Danish National Pathology Register[20] and the Register of Causes of Death.[21] Online supplemental appendix 1, p1 provides a detailed description of the codes found in the registries for prostate cancer characteristics, treatment, outcomes and covariates. Furthermore, the study is reported in accordance with Strengthening the Reporting of Observational Studies in Epidemiology guidelines, and a checklist is provided in online supplemental files.

Identifying men with prostate cancer

No formal screening programme for prostate cancer existed during the study period. Therefore, men were referred to the urology department on suspicion of prostate cancer. We used the Danish National Patient Registry to identify a cohort consisting of men with a first-time prostate cancer diagnosis from 2011 through 2018 who had undergone radical prostatectomy. This registry was established in 1977 for hospitalised patients; outpatient visits at hospitals have been included since 1995.[17] The registry includes dates of admission and discharge, diagnosis (ICD-10 codes), surgical procedures and treatment information. The validity of a prostate cancer diagnosis in this register has previously been evaluated and found to be high, with a positive predictive value of nearly 90%.[22]

Risk classification

We restricted the cohort to patients we could classify as having a preoperative high risk of cancer recurrence according to the European Association of Urology (EAU) risk classification of prostate cancer. The EAU defines high-risk patients as those with a PSA of more than 20 ng/mL OR a Gleason score >7 OR a T-stage of T2c as the minimum.[4] PSA values were retrieved from the Danish Register of Laboratory Results, which includes laboratory data from four of the five regions of Denmark.[18] Data from the last region were obtained directly from the relevant regional database. The Gleason score was obtained from the Pathology Register, which contains information on all pathological examinations conducted in Denmark since 1997. T-stage was obtained from the Danish Cancer Registry, which has prospectively recorded all cancers diagnosed in Denmark since 1943, classified according to ICD-10, and ICD Oncology codes (ICD-0-3) for topography and morphology.[15] For all three variables, we included the latest recorded value within 6 months prior to surgery. If PSA, Gleason score or T-stage were missing, we used the Danish Prostate Cancer Database to fill in the missing variables. This register is a nationwide clinical cancer database established in 2010 that records data on all incident, historically verified prostate cancer cases.

Imaging modality

We retrieved information on imaging modalities from the Danish National Patient Registry. We identified the preoperative use of bone scintigraphy and ^{18}F-NaF PET, recorded up to 6 months before surgery, combined with CT or MRI. Single-photon emission/CT was conducted according to institutional practices. Patients were categorised according to their preoperative imaging into two groups: those who underwent bone scintigraphy only (bone scintigraphy group) and those who underwent ^{18}F-NaF PET scan with or without bone scintigraphy (^{18}F-NaF PET group). In general, each site performed only one of the two scans; thus, physicians did not stratify patients according to a specific imaging modality. Patients with an ^{18}F-NaF PET scan performed as a part of a clinical research project were excluded from the cohort because the results of these scans were not made available to the referring physician.

SREs and bone metastases

We obtained information on SREs through the Danish National Patient Registry. SREs comprised the following events occurring after the date of radical prostatectomy: radiation to the bone defined as 1–4 treatments with external radiation therapy (standard practice in Denmark for the treatment of bone pain), pathological and osteoporotic fractures, spinal cord compression, surgery to the bone or a first-time bone metastasis diagnosis code.

Mortality

Mortality and migration updates were obtained from the Civil Registration System, which is updated daily.[14] The register contains information on the vital status (dead or alive), date of death and migration status of all Danish citizens.

Comorbidity

We used the Charlson comorbidity index to describe preexisting comorbidities in the prostate cancer cohort[23] (online supplemental appendix 1, p2). We calculated the index based on diagnoses recorded in the Danish National Patient Registry up to 10 years before the date of surgery. For analysis, we categorised the index into three comorbidity levels, including (1) those without comorbidity, (2) those with a comorbidity index equal to 1 and (3) those with a comorbidity index above 1.

Statistical analysis

Baseline characteristics are reported as frequencies with percentages and medians with IQRs. We estimated the cumulative risk of SREs according to the type of imaging modality and plotted the cumulative risk as a function of time since radical prostatectomy; death was treated as a competing risk event. Patients contributed time at risk from the date of radical prostatectomy until the date of first-time registered SRE, migration, death or 31 December 2018, whichever came first. Finally, we similarly estimated the cumulative incidence of death.

For the main analysis, we used Cox proportional hazards regression analysis to estimate the age-adjusted and multivariate-adjusted HRs of SREs with 95% CIs, comparing those who underwent ^{18}F-NaF PET scans with those who underwent bone scintigraphy. Additionally, to better control potential confounding by indication, analysis of the inverse probability of treatment weighting (IPTW) was performed based on the propensity score for ^{18}F-NaF PET. Propensity scores were calculated using logistic regression with the inclusion of the same variables as in the adjusted Cox analysis. We adjusted for age, Charlson comorbidity index, PSA (categorical variable:<10, 10–20, >20 ng/mL), Gleason score (categorical variable: <7, 7, >7) and T-stage (categorical variable: T1, T2, T3+T4). Adjusting with categorical variables was deemed necessary due to outliers and the limited number of records available on the outer areas of the scales. Furthermore, we stratified the analysis by PSA, Gleason score, T-stage and year of radical prostatectomy. In the stratified analysis, we only adjusted for age and Charlson comorbidity index. An adjusted HR of death was also calculated. No further analyses were performed for patients with other types of imaging or no imaging before surgery.

Several sensitivity analyses were performed to test the robustness of our findings. First, due to potential site-related differences in risk factors among the included patients, we conducted an analysis restricted to the capital region of Denmark, which performed most of the ^{18}F-NaF PET scans. Second, we executed the analysis with a reclassification of the exposure group to include patients with both scans. To account for missing data and enable adjustment for PSA, Gleason score and T-stage we used multiple imputation using splines[24] with all the main analysis variables and the outcome variable in the model. We produced and combined 200 sets of imputations.

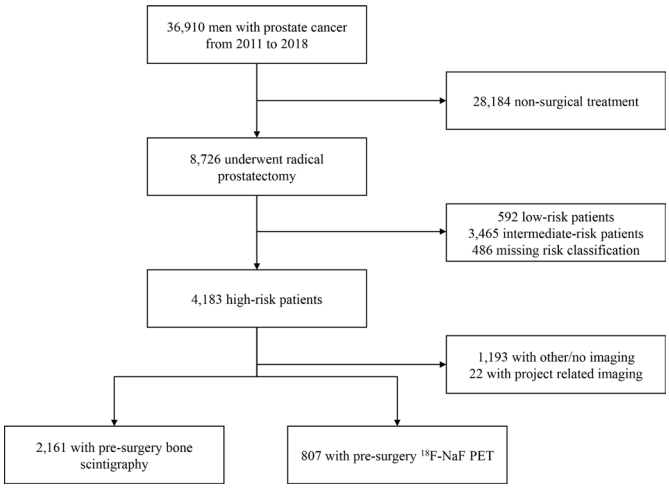

Figure 1 Study profile study cohort of 2161 men undergoing presurgical imaging with bone scintigraphy and 807 men undergoing ^{18}F-sodium-fluoride (^{18}F-NaF) positron emission tomography (PET). Patients with no or other imaging were combined since there were no differences between sites performing ^{18}F-NaF PET or bone scintigraphy. Moreover, we experienced inconsistencies in the way CT and MRI scans where coded in the registries, making it difficult to distinguish between imaging of the prostate and other sites.

Statistical software

Data management and analyses were conducted in R V.4.0.3 using RStudio 2020 (RStudio, PBC, Boston, Massachusetts, USA) with the following packages: heaven, data.table, Publish, survival, stringr, mitools, smcfcs and ipw.

Patient and public involvement

This study was observational and based on data from routine healthcare records. No patients were directly involved in the study.

RESULTS

Between 1 January 2011 and 31 December 2018, 36 910 men were diagnosed with prostate cancer in Denmark, of whom 8726 (23.6%) underwent radical prostatectomy (figure 1). Among those who underwent radical prostatectomy, 4183 patients (47.9%) were classified as high risk according to the EAU preoperative staging criteria. A total of 2161 (51.7%) high-risk patients undergoing surgery were evaluated for skeletal metastasis with bone scintigraphy only, and 807 (19.3%) men were evaluated with ^{18}F-NaF PET. Information on the PSA values, Gleason score and T-stage from the registries ensured nearly 90% completeness of the high-risk classification, resulting in a large study population for our analysis. A notable

Table 1 Baseline patient characteristics by imaging modality

	Bone scintigraphy (n=2161)	^{18}F-NaF PET (n=807)	All (n=2968)
Age (years, median (IQR))	66.3 (61.7, 69.7)	67.9 (62.9, 71.2)	66.7 (62.0, 70.1)
Year of surgery			
2011–2013	852 (39.4)	212 (26.3)	1064 (35.8)
2014–2015	602 (27.9)	235 (29.1)	837 (28.2)
2016–2018	707 (32.7)	360 (44.6)	1067 (36.0)
Imaging date before prostatectomy (days, median (IQR))	46 (32, 65)	42 (28, 56)	45 (30, 63)
PSA (ng/mL)			
<10	955 (45.0)	263 (33.1)	1218 (41.8)
10–20	642 (30.2)	292 (36.8)	934 (32.0)
>20	526 (24.8)	239 (30.1)	765 (26.2)
Gleason biopsy score			
<7	345 (16.2)	70 (8.8)	415 (14.2)
7	1225 (57.5)	469 (58.6)	1694 (57.8)
>7	560 (26.3)	261 (32.6)	821 (28.0)
Clinical T-stage			
T1	259 (12.6)	50 (7.5)	309 (11.4)
T2	1260 (61.5)	241 (36.0)	1501 (55.2)
T3-T4	529 (25.8)	378 (56.5)	907 (33.4)
Comorbidity*			
Cardiovascular diseases	118 (5.5)	52 (6.4)	170 (5.8)
Other malignancies	102 (4.7)	64 (7.9)	166 (5.6)
Diabetes	62 (2.9)	48 (6.0)	110 (3.7)
Charlson comorbidity index			
1	267 (12.4)	115 (14.3)	382 (12.9)
>1	203 (9.4)	107 (13.3)	310 (10.4)

Characteristics on the day of surgery for men with high-risk prostate cancer from 2011 to 2018. Percentages may not add up to 100 due to rounding or missing data.
*Top three comorbidities.
^{18}F-NaF, ^{18}F-sodium- fluoride; PET, positron emission tomography; PSA, prostate specific antigen; T-stage, tumour stage.

proportion of high-risk patients (28.5%) underwent different imaging modalities or no imaging to evaluate bone metastasis, and a small portion of patients (0.5%) were excluded because they underwent project-related imaging. The median age at the date of radical prostatectomy was 67 years (IQR, 62–70.1), and the median follow-up from surgery was 4.1 years (IQR, 2.4–6.0 years). In general, patients receiving ^{18}F-NaF PET had a higher PSA level, Gleason score, and T-stage at primary staging (table 1).

SREs and bone metastases

The unadjusted 1-year cumulative risk of SREs was 2.4% (95% CI 1.8 to 3.1) for men who underwent bone scintigraphy and 4.3% (95% CI 2.8 to 5.7) for those who underwent ^{18}F-NaF PET (figure 2). The unadjusted 3-year cumulative risk of SREs was 7.2% (95% CI 6.0 to 8.3) for men undergoing bone scintigraphy and 11.9% (95% CI 9.4 to 14.4) for those undergoing ^{18}F-NaF PET. Of the 300 men with at least one SRE recorded during follow-up, 53.7% had radiation to bone recorded as their first event, 30.7% had a pathological or osteoporotic fracture, 6.3% had spinal cord compression, 6.3% had a code for bone metastases and 3.0% had bone surgery. In the main analysis, we did not find that ^{18}F-NaF PET decreased the HR of experiencing SREs after surgery; in contrast, we observed a slightly increased HR, which was reduced when adjusting the model (adjusted HR, 1.22; 95% CI 0.93 to 1.61; figure 3). When we used IPTW to control for potential confounding factors, the risk of experiencing an SRE was attenuated (IPTW adjusted HR, 1.15: 95% CI 0.86 to 1.54; figure 3). Stratified analyses similarly demonstrated increased HRs for SREs in patients undergoing ^{18}F-NaF PET compared with those undergoing bone scintigraphy, except for patients with stage 2 disease and those with a Gleason score <7 (figure 3).

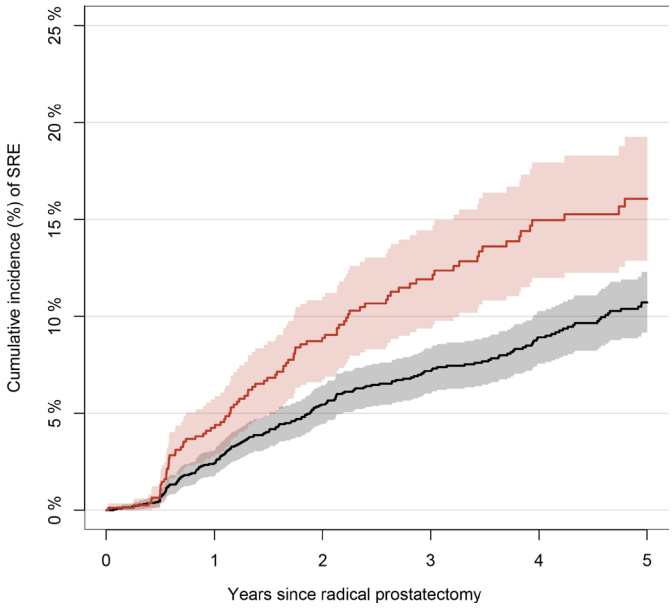

Figure 2 Unadjusted cumulative incidence of skeletal-related events (SREs). The unadjusted cumulative incidence with 95% CIs of SREs in men after undergoing radical prostatectomy. Death was treated as a competing event. The red curve represents ^{18}F-sodium-fluoride positron emission tomography and the black curve represents bone scintigraphy.

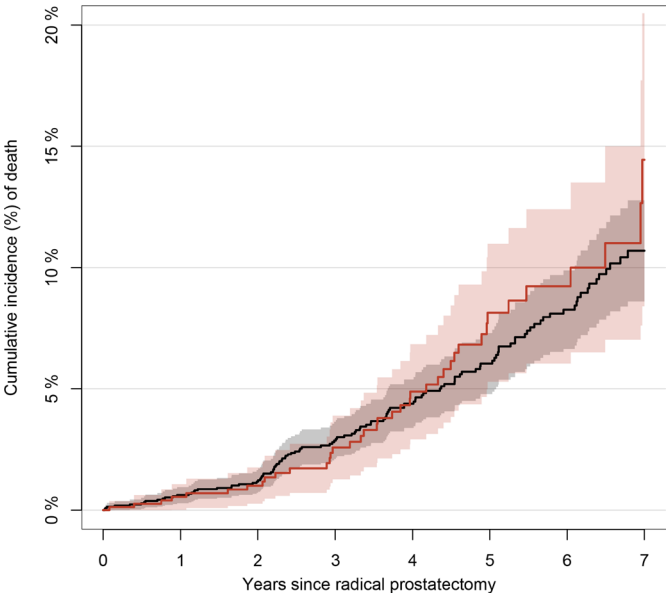

Figure 4 Unadjusted cumulative incidence of death. Unadjusted cumulative incidence of death with 95% CIs for men with prostate cancer after undergoing radical prostatectomy, stratified by type of imaging modality. The red curve represents ^{18}F-sodium-fluoride positron emission tomography and the black curve represents bone scintigraphy.

Survival

Figure 4 shows the cumulative survival curves of the cohorts for up to 7 years of follow-up. The 1-year survival was 99.4% (95% CI 99.0 to 99.7) in men who underwent bone scintigraphy and 99.5% (95% CI 98.9 to 100) in men who underwent ^{18}F-NaF PET, and the corresponding 3-year survival rates in the cohorts were 97.1% (95% CI 96.4 to 97.9) and 97.4% (95% CI 96.1 to 98.7), respectively. Adjusted analyses showed a modest reduction in mortality for patients who underwent ^{18}F-NaF PET (adjusted HR, 0.89; 95% CI 0.61 to 1.30).

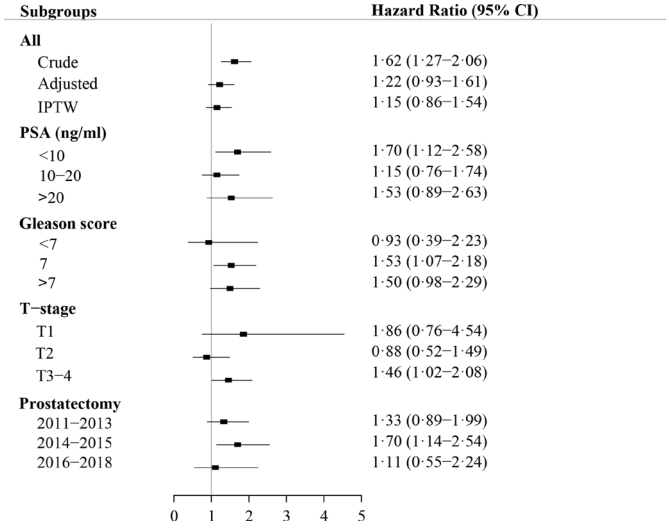

Figure 3 Main analysis results HRs for skeletal-related events following radical prostatectomy among patients undergoing ^{18}F-sodium-fluoride positron emission tomography before surgery versus patients undergoing bone scintigraphy. IPTW, inverse probability of treatment weighting; PSA, prostate specific antigen; T-stage, tumour stage.

Sensitivity analysis

Restricting to patients from the capital region yielded cumulative SRE risk estimates consistent with those of the main analysis (online supplemental appendix 1, p3). Similar to the main analysis, the cumulative risk of SREs was higher for men evaluated with ^{18}F-NaF PET than for those evaluated with bone scintigraphy. Adjusted analysis for the capital region was also comparable to the main analysis (online supplemental appendix 1, p4) and did not suggest any added value of using ^{18}F-NaF PET.

Including patients with both bone scintigraphy and ^{18}F-NaF PET in the bone scintigraphy group or excluding them entirely yielded HRs similar to those of the main analysis. A final analysis with imputed values for PSA, Gleason score and T-stage yielded HRs similar to those of the analysis without imputation.

DISCUSSION

Principal findings

In this nationwide cohort study of Danish patients with high-risk prostate cancer undergoing prostatectomy, we found that primary staging with ^{18}F-NaF PET did not reduce the risk of SREs compared with primary staging with bone scintigraphy, whereas a slight tendency towards a reduction in all-cause mortality was observed in the group undergoing ^{18}F-NaF PET. To the best of our knowledge, this is the first study to evaluate patient-relevant

outcomes of using a PET-based method for primary staging.

Comparison with other studies

Prior studies on ^{18}F-NaF PET in prostate cancer have focused on its improvements in diagnostic accuracy compared with bone scintigraphy[6–8] or its impact on patient management.[12 13] The superior diagnostic performance of ^{18}F-NaF PET when detecting bone metastases, should presumably result in improved patient selection for curative and life-prolonging treatment, resulting in fewer SREs the first few years after surgery. However, in this study, we did not observe any superiority over bone scintigraphy in terms of patient benefit among newly diagnosed, high-risk prostate cancer patients.

Evidence of patient-relevant outcomes is often reported from randomised controlled trials. Randomised trials are, however, not commonly conducted within the field of imaging, and it has previously been debated whether randomised trials are necessary to evaluate diagnostic procedures.[25 26] In prostate cancer, only two randomised controlled trials have been published, employing PET in one arm and standard imaging in the other arm. One such trial confirmed the diagnostic superiority of prostate specific membrane antigen (PSMA) PET/CT during primary staging,[27] whereas the other trial focused on the changes in patient management based on fluciclovine PET/CT at the time of biochemical recurrence;[28] none of these trials were linked to patient-relevant outcomes.

Randomised trials have demonstrated the clinical benefit of PET within other types of cancers, such as haematological and lung cancers.[29] Fischer *et al* compared preoperative staging with FDG PET/CT to conventional staging by CT in patients with lung cancer and found that patients in the PET/CT group showed a reduction in both the total number of thoracotomies and the number of futile thoracotomies; however, they did not observe a decrease in overall mortality.[30] Similar results were reported for colorectal liver metastases, with one study finding that FDG PET led to a reduction in futile laparotomies in one of six patients.[31] It could be expected that the use of ^{18}F-NaF PET would reduce the number of 'futile' prostatectomies in patients harbouring bone metastases at the time of diagnosis, thereby reducing the incidence of SREs postoperatively. With recent trials demonstrating superior diagnostic properties of PSMA PET for primary staging in high-risk prostate cancer, its impact on treatment choice—and perhaps outcome—is likely to be greater than that of ^{18}F-NaF PET.

Strengths and limitations

The major strengths of our study are its national scale, large cohort, high-quality registry data and complete follow-up. The registration of information related to prostate cancer diagnosis and radical prostatectomy, as well as variables defining the high-risk population, is thought to be practically complete because of a uniformly organised healthcare system where healthcare is free (tax-supported) and available to all residents.[32] Furthermore, a median follow-up time of 4.1 years is adequate for the purpose of evaluating bone metastases not captured by the imaging modality at primary staging; hence, only patients with a negative scan will undergo radical prostatectomy with curative intend in Denmark.

Nevertheless, our study has several limitations worth considering. The potential of confounding by indication was particularly concerning because of the observed higher values for PSA, Gleason score and T-stage in the ^{18}F-NaF PET group; however, the indication of usage was the same for both scans. Moreover, the demographics of the groups might have been more alike if the International Society of Urological Pathology (ISUP) grading system was used for the Gleason score, which distinguishes between normal high-risk prostate cancer and very high-risk (ISUP grade 5) cancer cases. It was not possible to use the ISUP grading due to unavailability in some of the registers. Furthermore, confounding by indication is only an issue in hospitals that offer both bone scintigraphy and ^{18}F-NaF PET, which is highly uncommon in Denmark. Since sites only used one of the imaging modalities, physicians did not have to choose between the two, resulting in minimal selection bias. We attempted to control for confounding by using a propensity score-based IPTW, but we cannot rule out residual confounding due to misclassified or unmeasured prognostic factors. Multi-parametric MRI (mpMRI) is also a factor worth considering in relation to targeted biopsies in the diagnostic work-up of prostate cancer. This method has been gradually implemented nationally in Denmark and prior to 2018 only very few sites had access to mpMRI for all patients; hence, we do not have data available yet. The introduction of mpMRI targeted biopsy is likely to affect the selection of patients for radical prostatectomy in the future.

In the present study, we defined SREs as either external radiation therapy, pathological or osteoporotic fractures, spinal cord compression, surgery to the bone or a bone metastases code. It can be speculated that patients treated at a site using ^{18}F-NaF PET would undergo ^{18}F-NaF PET rather than bone scintigraphy in case of biochemical recurrence, thereby increasing the detection of bone metastases during follow-up. However, the risk of SREs was primarily driven by a high percentage of radiotherapy of bone or fracture cases, which are not related to ^{18}F-NaF PET. Moreover, with the widespread introduction of prostate specific membrane antigen (PSMA) PET/CT in Denmark from 2015 and onwards, patients with biochemical recurrence would undergo PSMA PET/CT rather than ^{18}F-NaF PET/CT. Information regarding bone metastases was noted in only 6.3% of SREs across the groups.

CONCLUSIONS

In conclusion, we found that the use of ^{18}F-NaF PET at primary staging did not improve patient-relevant outcomes in terms of a reduction in SREs compared with that with bone scintigraphy.

Contributors AWM, LJP and HDZ conceived the study and contributed to the literature search. AWM and CT-P had access to the data and carried out the data management and analysis. AWM, CT-P and MN designed the graphs. AWM, LJP, HDZ, CT-P, MN and MTP aided in the interpretation of results. AWM prepared the first draft of the paper. AWM, CT-P and HDZ acts as guarantors for the overall content. All authors contributed to critical revision and approval of the final draft of the paper.

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Competing interests One author received grants from Bayer and Novo Nordisk for the submitted work.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The Danish Data Protection Agency approved the use of data for this study (reference number 2008-58-0028). Furthermore, the study was granted approval by the Danish Patient Safety Authority to collect laboratory data (reference numbers 3-3013-3183/1 and 31-1522-37). Ethics approval is not required for historical register-based studies in Denmark.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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APPENDIX 1

Table 1. Registry data used in the analysis.

Registry	Code
The Danish Cancer Registry	
ICD-10 diagnosis and morphologic codes	
Prostate cancer	DC61.9
Tumor stage	TNM
The Danish National Registry of Patients	
Imaging modality	
Danish Health Care Classification System, sks-codes	
Bone scintigraphy	WKBxx
^{18}F-NaF PET	WDTPSFCXX
The Danish National Registry of Patients	
Primary prostate cancer treatment	
NCSP codes	
Radical prostatectomy	KKECxx
The Danish National Registry of Patients	
Skeletal-related events	
NCSP codes	
Radiation to bone	BWGxx
Surgery to bone	KNAGxx
ICD-10 codes	
Bone metastases	DC79.5
Spinal cord compression	DG952
Pathological fractures	
Osteoporotic fractures	
The Danish Register of Laboratory Results	
NPU codes	
PSA	NPU0866
The Danish National Pathology Registry	
SNOMED codes	
Gleason score	ÆF0xx

NCSP: Nomesco Classification of Surgical Procedures; NPU: Nomenclature for Properties and Units; SNOMED: Systematized Nomenclature of Medicine

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Table 2. Comorbidity codes from The Danish National Patient Registry used to calculate the Charlson Comorbidity Index. All codes are ICD-10 codes.

Comorbidity	Code
Myocardial infarction	DI21, DI22
Heart failure	DI099, DI110, DI130, DI132, DI255, DI425, DI426, DI427, DI429, DI428A, DP290, DI43, DI50, DE105, DE115, DE125, DE135, DE145
Peripheral vascular disease	DI70, DI71, DI72, DI731, DI738, DI739, DI77, DI790, DI792, DK551, DK558, DK559, DZ958, DZ959
Cerebrovascular disease	DI60, DI61, DI62, DI63, DI64, DI65, DI66, DI67, DI68, DI69, DG45, DG46, DH340
Dementia	DF00, DF01, DF02, DF03, DG30, DF051, DG311
Chronic pulmonary disease	DJ40, DJ41, DJ42, DJ43, DJ44, DJ45, DJ46, DJ47, DJ60, DJ61, DJ62, DJ63, DJ64, DJ65, DJ66, DJ67, DJ684, DI278, DI279, DJ84, DJ701, DJ703, DJ920, DJ953, DJ961, DJ982, DJ983
Rheumatic disease	DM05, DM06, DM08, DM09, DM30, DM31, DM32, DM33, DM34, DM35, DM35, DM36, D86
Peptic ulcer disease	DK25, DK26, DK27, DK28, DK221
Mild liver disease	DB18, DK700, DK701, DK702, DK709, DK703, DK713, DK714, DK715, DK717, DK73, DK74, DK760, DK762, DK763, DK764, DK769, DZ944
Severe liver disease	DB150, DB160, DB162, DB190, DI850, DI859, DI864, DI982, DK704, DK711, DK721, DK729, DK765, DK766, DK767
Diabetes without complications	DE100, DE101, DE108, DE109, DE110, DE111, DE119, DE120, DE121, DE129, DE130, DE131, DE139, DE140, DE141, DE149
Diabetes with complications	DE102, DE103, DE104, DE105, DE106, DE107, DE112, DE113, DE114, DE115, DE116, DE117, DE118, DE122, DE123, DE124, DE125, DE126, DE127, DE128, DE132, DE133, DE134, DE135, DE136, DE137, DE138, DE142, DE143, DE144, DE145, DE146, DE147, DE148
Hemiplegia paraplegia	DG830, DG831, DG832, DG833, DG834, DG81, DG82, DG041, DG114, DG801, DG802, DG839
Renal disease	DN032, DN033, DN034, DN035, DN036, DN037, DN052, DN053, DN054, DN055, DN056, DN057, DZ490, DZ491, DZ492, DN18, DN19, DI120, DI131, DI132, DN250, DZ940, DZ992, DN26
Any malignancy	DC0, DC1, DC2, DC3, DC40, DC41, DC42, DC43, DC44, DC45, DC46, DC47, DC48, DC49, DC5, DC6, DC70, DC71, DC72, DC73, DC74, DC75, DC76, DC86, DC97
Metastatic solidtumor	DC77, DC78, DC79, DC80
AIDS/HIV	DB20, DB21, DB22, DB23, DB24
Leukemia	DC91, DC92, DC93, DC94, DC95
Lymphoma	DC81, DC82, DC83, DC84, DC85, DC88, DC90, DC96

Figure 1. Unadjusted cumulative incidence with 95% confidence interval of skeletal-related events (SRE) in men after undergoing radical prostatectomy, restricted to men from the Capitol region of Denmark. Death was treated as a competing event. Red curve represents ^{18}F-NaF PET, black curve bone scintigraphy.

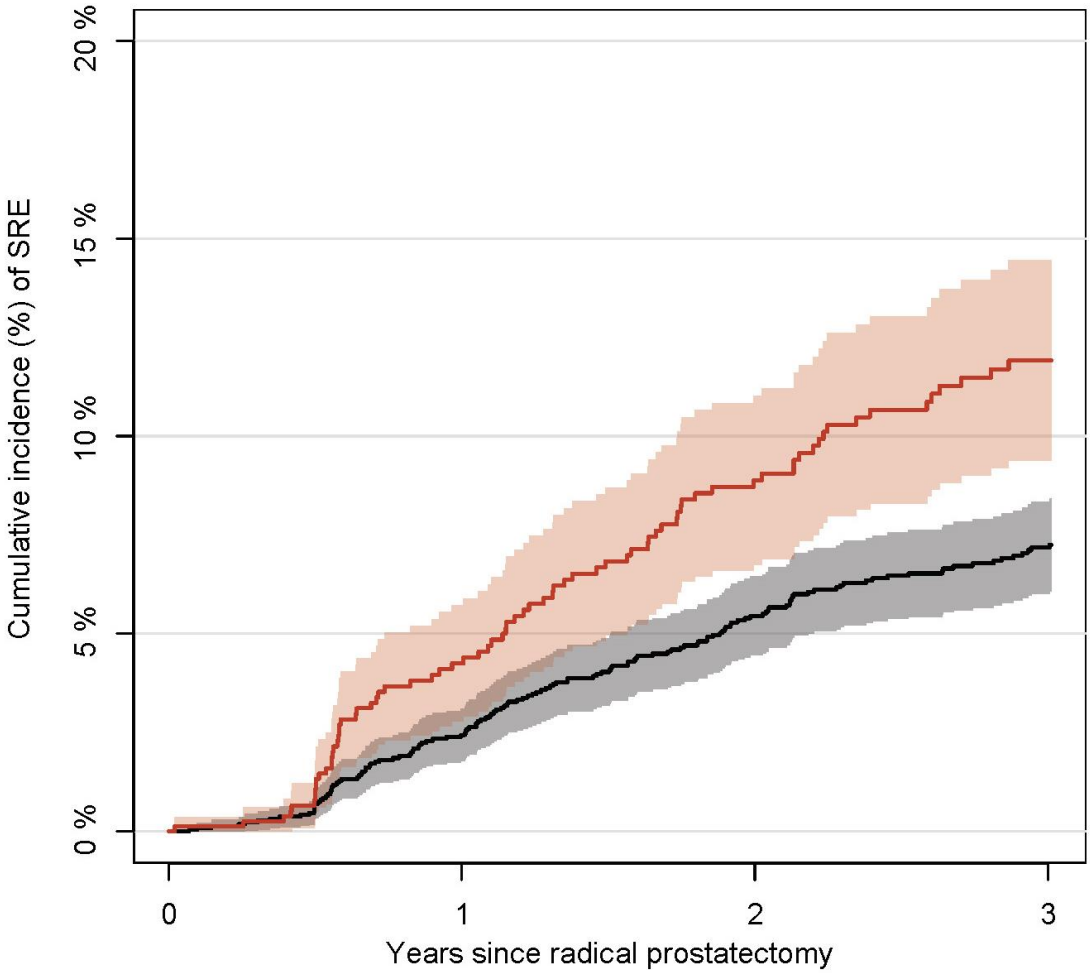

Figure 2. Hazard ratios for skeletal-related events following radical prostatectomy among patients receiving a ^{18}F-NaF PET before surgery compared with patients receiving a bone scintigraphy. Restricted to the Capitol region of Denmark.

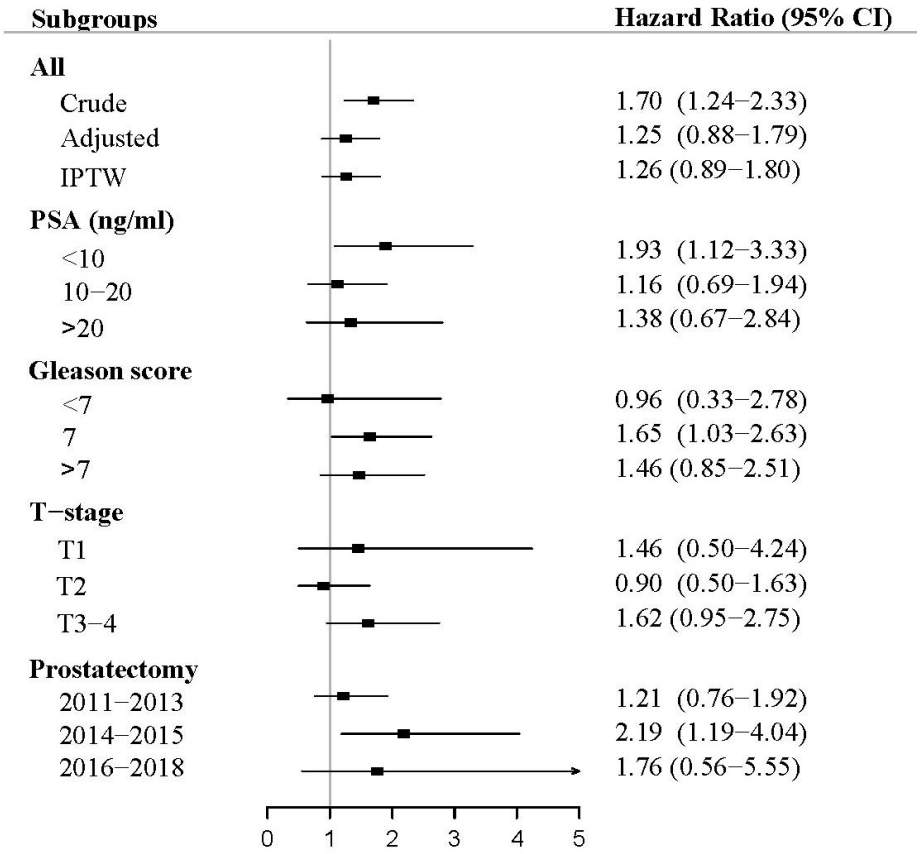

Table 3. Demographics for the Capitol region of Denmark. Baseline characteristics on the day of surgery for men with high-risk prostate cancer from 2011-2018* Stratified by pre-surgery imaging.

	Bone scintigraphy (n=690)	**^{18}F-NaF PET (n=740)**	**All (n=1,430)**
Age (year, median (IQR))	66.2 (60.8, 69.3)	67.9 (62.9, 71.1)	66.9 (61.9, 70.1)
Year of surgery			
2011-2013	331 (48.0)	212 (28.6)	543 (38.0)
2014-2015	185 (26.8)	231 (31.2)	416 (29.1)
2016-2018	174 (25.2)	297 (40.1)	471 (32.9)
PSA (ng/mL)			
<10	300 (44.1)	250 (34.4)	550 (39.1)
10-20	229 (33.6)	271 (37.3)	500 (35.5)
>20	152 (22.3)	206 (28.3)	358 (25.4)
Gleason score			
<7	81 (12.0)	61 (8.3)	142 (10.1)
7	401 (59.6)	432 (58.9)	833 (59.2)
>7	191 (28.4)	240 (32.7)	431 (30.7)
Clinical T-stage			
T1	58 (9.0)	39 (6.3)	97 (7.7)
T2	435 (67.3)	220 (35.8)	655 (51.9)
T3-T4	153 (23.7)	356 (57.9)	509 (40.4)
Comorbidity			
Cardiovascular diseases	35 (5.1)	46 (6.2)	81 (5.7)
Other malignancies	29 (4.2)	59 (8.0)	88 (6.2)
Diabetes	21 (3.0)	44 (6.0)	65 (4.6)
Charlson comorbidity index			
1	84 (12.2)	103 (13.9)	187 (13.1)
>1	59 (8.6)	97 (13.1)	156 (10.9)

*Percentages may not sum to 100 due to rounding or missing data
IQR: Interquartile range; PSA: Prostate specific antigen; T-stage: Tumor stage.