PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	USE OF 18F-NaF-PET IN THE STAGING OF SKELETAL METASTASES OF NEWLY DIAGNOSED, HIGH-RISK PROSTATE CANCER PATIENTS - A NATIONWIDE COHORT STUDY.
AUTHORS	Mogensen, Anna Winther; Petersen, Lars J; Torp-Pedersen, Christian; Nørgaard, Mette; Pank, Marie T; Zacho, Helle

VERSION 1 – REVIEW

REVIEWER	Emberton, Mark University College London, Division of Surgery and Interventional Sciences
REVIEW RETURNED	22-Dec-2021

GENERAL COMMENTS	The Danish cancer registry is an extraordinary resource and in this paper, many of its unique attributes have been exploited well.

REVIEWER	Kairemo, Kalevi Docrates Cancer Hospital, Nuclear Medicine & Molecular Radiotherapy
REVIEW RETURNED	26-Jan-2022

GENERAL COMMENTS	The set-up of this registry-derived nationwide study is very odd. The question is, if two methods for detecting skeletal metastases differ from each other when they are used to predict the outcome in prostatectomized patients. It is obvious that these two methods act in the same manner; Na18F-PET is more sensitive, but more expensive and less used and rather new in this perspective, whereas bone scintigraphy (BS, diphosphonate compound SPECT) has been used for decades. Therefore it is difficult to find the scientific soundness in this, because these agents used for imaging do not target prostate cancer cells. Both methods depict unspecific structural changes in skeletal tissue that occur late in the development of skeletal metastases and may remain unchanged for a long time after the cancer may have disappeared, as a result of treatments. There is no close or no association at all between biochemical failure and abnormal 18F-NaF PET/CT findings. An increase in prostate-specific antigen (PSA), although unspecific, is usually a reaction to cancer cells that are still present and growing after prostatectomy. However, this may have little to do with what is seen by 18F-NaF PET/CT or BS. The imaging modalities demonstrating structural bone changes are not reliable indicators of skeletal metastases and should be avoided in favor of PET/CT with PSMA analogs. The issue is, what is happening in the bone marrow and in the cortical bone. Prostate targetor PET studies and

	NaF show different different distributions, and both PET tracers are good in the follow-up (maybe even BS), but NaF nor BS are no predictors of the outome at the time of initial staging, before prostatectomy. As a matter of fact, both NaF and BS should be negative, i.e. no cancer suspision. Now, the authors do not find any difference between these tracers when they act as prognostic factors. Still, they conlude that bone scintigraphy should be used, eventhough their findings do not support this statement. Now, this study has major concerns and lack of clinical relevance, which is often the problem with registry studies. I do not know, if the authors looked at the real patient data, besides their own. In this study, imagings were performed up to six (6) months before the surgery, meaning that the staging by imaging differed definitely from that of the surgery, if the disease is a high risk cancer. It would be interesting to know e.g. the biomarker behavior during this period. This is cumbersome registry study with no biological nor clinical uro-oncological relevance. The agents could be compared with each other in a prospective randomized study (less biased) or in a double-tracer study in the same patients. The outcome of this requires much less patients. And the interval between imaging and operation should be much shorter. This cumbersome study is not scientifically sound, but methodology is relevant and this a large nationwide registry study. Thus, it may be published in a national journal with a list of real shortcomings, but not in this international forum.

REVIEWER	Aben, Katja Netherlands Comprehensive Cancer Organisation
REVIEW RETURNED	07-Feb-2022

GENERAL COMMENTS	The authors conducted a population based cohort study to determine whether preoperative staging with 18-F-NaF PET in patients with high-risk prostate cancer is superior in terms of SREs and OS compared to bone scintigraphy. For this purpose multiple Danish population-based registries were used (which was adequately described). The research question is relevant as it is unknown whether newly introduced imaging modalities improve patient relevant outcomes. Several analysis were conducted including multivariable cox proportional hazards regression and IPTW to address confounding by indication. Comments: 1. The authors state that hospitals generally only perform bone scintigraphy or 18-F-NaF PET. However, higher PSA-values, Gleason score and T-stage are observed in the 18-F-NaF PET group. Can the authors explain this difference? 2. In recent years, mpMRI has been introduced in the diagnostic work-up of prostate cancer. Targeted biopsy of suspicious lesions can potentially affect Gleason grading. Is information available on whether mpMRI and targeted biopsies were performed? If this information is available I recommend including it in the analyses, otherwise a brief discussion is warranted. 3. In the discussion section the authors state that the risk of SREs was primarily driven by a high percentage of radiotherapy of bone (53.7%) or bone fracture cases (30.7%). Therefore, the influence of the use of 18F-NaF PET in the BCR setting would be limited. But what was the reason to treat patients with radiotherapy?

	Minor comments: 1. The authors state that death was treated as competing risk. However for the main analysis cox proportional hazards regression was used. 2. Little information is provided regarding the multiple imputation method used, I recommend adding this information. 3. In 28.5% of the population other/no imaging was performed. I recommend reporting these separately. 4. What was the rationale for performing a sensitivity analysis restricted to patients from the capital region? 5. I recommend adding a citation supporting the statement at line 28-31 (page 12) of the discussion section.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1
Prof. Mark Emberton, University College London, University College London Hospital Comments to the Author:
1. The Danish cancer registry is an extraordinary resource and in this paper, many of its unique attributes have been exploited well.
REPLY: We thank you for your comment.

Reviewer #2
Dr. Kalevi Kairemo, Docrates Cancer Hospital Comments to the Author:
The set-up of this registry-derived nationwide study is very odd. The question is, if two methods for detecting skeletal metastases differ from each other when they are used to predict the outcome in prostatectomized patients.It is obvious that these two methods act in the same manner; Na18F-PET is more sensitive, but more expensive and less used and rather new in this perspective, whereas bone scintigraphy (BS, diphosphonate compound SPECT) has been used for decades. Therefore it is difficult to find the scientific soundness in this, because these agents used for imaging do not target prostate cancer cells. Both methods depict unspecific structural changes in skeletal tissue that occur late in the development of skeletal metastases and may remain unchanged for a long time after the cancer may have disappeared, as a result of treatment. There is no close or no association at all between biochemical failure and abnormal 18F-NaF PET/CT findings. An increase in prostate-specific antigen (PSA), although unspecific, is usually a reaction to cancer cells that are still present and growing after prostatectomy. However, this may have little to do with what is seen by 18F-NaF PET/CT or BS. The imaging modalities demonstrating structural bone changes are not reliable indicators of skeletal metastases and should be avoided in favor of PET/CT with PSMA analogs. The issue is, what is happening in the bone marrow and in the cortical bone. Prostate targetor PET studies and NaF show different distributions, and both PET tracers are good in the follow-up (maybe even BS), but NaF nor BS are no predictors of the outome at the time of initial staging, before prostatectomy. As a matter of fact, both NaF and BS should be negative, i.e. no cancer suspision. Now, the authors do not find any difference between these tracers when they act as prognostic factors. Still, they conlude that bone scintigraphy should be used, eventhough their findings do not support this statement. Now, this study has major concerns and lack of clinical relevance, which is often the problem with registry studies. I do not know, if the authors looked at the real patient data, besides their own. In this study, imagings were performed up to six (6) months before the surgery, meaning that the staging by imaging differed definitely from that of the surgery, if the disease is a high risk cancer. It would be interesting to know e.g. the biomarker behavior during this period. This is a cumbersome registry study with no biological nor clinical uro-oncological relevance. The agents could be compared with each other in a prospective randomized study (less biased) or in a double-tracer

study in the same patients. The outcome of this requires much less patients. And the interval between imaging and operation should be much shorter. This cumbersome study is not scientifically sound, but methodology is relevant and this a large nationwide registry study. Thus, it may be published in a national journal with a list of real shortcomings, but not in this international forum.

REPLY:
1. Thank you for your comments regarding the use of NaF PET/CT. We completely agree with the fact that NaF PET and BS act in the same manner by indirectly detecting skeletal metastases through the activation of osteoblasts, with NaF PET being the more sensitive method. With NaF PET being more sensitive than BS, we would expect a better selection of patients for radical prostatectomy resulting in fewer skeletal related events during the follow up period for this group. We have made this point clearer in the discussion (p 12, line 11-13)
Consequently, the outcome of this study is skeletal related events as a proxy for skeletal metastases, and not biochemical recurrence measured by PSA values. Skeletal related events include bone fractures, radiation to the bone (bone pain), spinal cord compression, surgery to the bone and bone metastasis coding in the registries.
2. We are aware that direct cancer targeting agents such as PSMA, FDG and Choline possess an inherent advantage of depicting the tumor cells directly, compared to the indirect methods of NaF and BS. However, none of the direct-targeting agents are recommended for primary bone staging in prostate cancer according to urological guidelines. PSMA stands as the only emerging imaging method in this setting. Also, all public available comparisons of NaF and PSMA, have consistently shown that NaF is non-inferior to PSMA in terms of diagnostic accuracy for the detection of skeletal metastases in prostate cancer.1-6 This includes studies with comparisons of a lesion types (ostesclerotic- osteolytic- and bone marrow metastases without morphological changes).7 8 We therefore believe that our evaluation of the added value of NaF before radical prostatectomy compared to BS is of clinical relevance.
3. We acknowledge in agreement with the reviewer that imaging performed 0-6 months before radical prostatectomy is a wide interval. The interval was chosen due to administrative reasons for reporting imaging to the registries by clinicians. The median time of imaging (both modalities combined) before radical prostatectomy is much closer to the actual date of surgery than 6 months (45 days, IQR (30, 63)). We have added the median and interquartile range for both imaging modalities to table 1 (p 20, line 3, table 1, row 7)
4. Furthermore, we agree with the reviewer that our conclusion in the abstract can be interpreted as contradictory to our main finding. We have deleted the statement in question (p 3, line 20-22)

Reviewer #3
Dr. Katja Aben, Netherlands Comprehensive Cancer Organisation Comments to the Author:
The authors conducted a population based cohort study to determine whether preoperative staging with 18-F-NaF PET in patients with high-risk prostate cancer is superior in terms of SREs and OS compared to bone scintigraphy. For this purpose multiple Danish population-based registries were used (which was adequately described). The research question is relevant as it is unknown whether newly introduced imaging modalities improve patient relevant outcomes. Several analysis were conducted including multivariable cox proportional hazards regression and IPTW to address confounding by indication.

1. The authors state that hospitals generally only perform bone scintigraphy or 18-F-NaF PET. However, higher PSA-values, Gleason score and T-stage are observed in the 18-F-NaF PET group. Can the authors explain this difference?
REPLY: This is an interesting observation that is caused by the fact, that most of the NaF PET scans were performed in the Capitol region. We observed that patients from this region had higher PSA-values, Gleason score and T-stage, this was also the case for patients undergoing bone scintigraphy in the Capitol region, and the reason why we performed a sensitivity analysis restricted to patients

from the Capitol region. However, we do not have an explanation to why this pattern exists. We have added the reason for the sensitivity analysis in the methods section (p 8, line 16-19).

2. In recent years, mpMRI has been introduced in the diagnostic work-up of prostate cancer. Targeted biopsy of suspicious lesions can potentially affect Gleason grading. Is information available on whether mpMRI and targeted biopsies were performed? If this information is available I recommend including it in the analyses, otherwise a brief discussion is warranted.
REPLY: mpMRI targeted biopsy was made widespread in Denmark during 2018-2021, therefore these data are not yet available by registries. Before 2018 only few institutions made systematically use of the method. In agreement with the reviewer, we have added a section regarding the topic in the discussion (p 13, line 21-25)

3. In the discussion section the authors state that the risk of SREs was primarily driven by a high percentage of radiotherapy of bone (53.7%) or bone fracture cases (30.7%). Therefore, the influence of the use of 18F-NaF PET in the BCR setting would be limited. But what was the reason to treat patients with radiotherapy?
REPLY: We might have been unclear the original manuscript. We are only evaluating NaF for primary staging of prostate cancer, not biochemical recurrence. This has been clarified in the discussion (p 12, line 4-5). PSMA have been available nationally in Denmark since approximately 2016 where it has been used in patients with BCR when deemed clinically relevant. We have added a section in the discussion regarding the use of PSMA in BCR (p 13, line 31-33). The use of radiotherapy in our study refers to the treatment of bone pain related to skeletal metastases. This has been added to the method section (p 7, line 16). The way this type of radiotherapy is coded in the registries ensures that we only include patients with radiotherapy of the bone, and not patients undergoing radiotherapy to the prostate bed.

Minor comments:
1. The authors state that death was treated as competing risk. However for the main analysis cox proportional hazards regression was used.
REPLY: It is correct that we regarded death as a competing risk when computing the cumulative incidence since Kaplan-Meier estimates would potentially provide biased results due to the competing risk of death. In the cox regression we simply censored patients who died.

2. Little information is provided regarding the multiple imputation method used, I recommend adding this information.
REPLY: We appreciate the recommendation of describing the multiple imputation method a bit more thoroughly. We have added: To account for missing data and enable adjustment for PSA, Gleason score, and T-stage we used multiple imputation using splines with all the main analysis variables and the outcome variable in the model. We produced and combined 200 sets of imputations. (p 8, line 19-23)

3. In 28.5% of the population other/no imaging was performed. I recommend reporting these separately.
REPLY: We combined the two categories since there were no difference in frequency of no/other imaging between sites performing NaF or BS. Moreover, we experienced inconsistencies in the way CT and MR scans where coded in the registries, making it difficult to distinguish between imaging of the prostate and other sites. We have added this response to the text for figure 1 (p 19, line 7-9)

4. What was the rationale for performing a sensitivity analysis restricted to patients from the capital region?

REPLY: As explained in major comment #1 from this reviewer, most of the patients who received a NaF PET stemmed from the Capitol region, which is why this was chosen as a sensitivity analysis. This has been added to the method section (p 8, line 18).

5. I recommend adding a citation supporting the statement at line 28-31 (page 12) of the discussion section.
REPLY: We thank you for noticing the missing citation. We have added two citations supporting the statement in question (p 12, line 18).

Reference List

1. Regula N, Kostaras V, Johansson S, et al. Comparison of (68)Ga-PSMA PET/CT with fluoride PET/CT for detection of bone metastatic disease in prostate cancer. European journal of hybrid imaging 2022;6(1):5. doi: 10.1186/s41824-022-00127-4 [published Online First: 2022/03/02]
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3. Harmon SA, Mena E, Shih JH, et al. A comparison of prostate cancer bone metastases on (18)F-Sodium Fluoride and Prostate Specific Membrane Antigen ((18)F-PSMA) PET/CT: Discordant uptake in the same lesion. Oncotarget 2018;9(102):37676-88. doi: 10.18632/oncotarget.26481 [published Online First: 2019/02/01]
4. Dyrberg E, Hendel HW, Huynh THV, et al. (68)Ga-PSMA-PET/CT in comparison with (18)F-fluoride-PET/CT and whole-body MRI for the detection of bone metastases in patients with prostate cancer: a prospective diagnostic accuracy study. European radiology 2019;29(3):1221-30. doi: 10.1007/s00330-018-5682-x [published Online First: 2018/08/23]
5. Zacho HD, Nielsen JB, Afshar-Oromieh A, et al. Prospective comparison of (68)Ga-PSMA PET/CT, (18)F-sodium fluoride PET/CT and diffusion weighted-MRI at for the detection of bone metastases in biochemically recurrent prostate cancer. European journal of nuclear medicine and molecular imaging 2018;45(11):1884-97. doi: 10.1007/s00259-018-4058-4 [published Online First: 2018/06/08]
6. Harmon SA, Bergvall E, Mena E, et al. A Prospective Comparison of (18)F-Sodium Fluoride PET/CT and PSMA-Targeted (18)F-DCFBC PET/CT in Metastatic Prostate Cancer. Journal of nuclear medicine : official publication, Society of Nuclear Medicine 2018;59(11):1665-71. doi: 10.2967/jnumed.117.207373 [published Online First: 2018/04/01]
7. Uprimny C, Svirydenka A, Fritz J, et al. Comparison of [(68)Ga]Ga-PSMA-11 PET/CT with [(18)F]NaF PET/CT in the evaluation of bone metastases in metastatic prostate cancer patients prior to radionuclide therapy. European journal of nuclear medicine and molecular imaging 2018;45(11):1873-83. doi: 10.1007/s00259-018-4048-6 [published Online First: 2018/05/17]
8. Rowe SP, Li X, Trock BJ, et al. Prospective Comparison of PET Imaging with PSMA-Targeted (18)F-DCFPyL Versus Na(18)F for Bone Lesion Detection in Patients with Metastatic Prostate Cancer. Journal of nuclear medicine : official publication, Society of Nuclear Medicine 2020;61(2):183-88. doi: 10.2967/jnumed.119.227793 [published Online First: 2019/08/28]

VERSION 2 – REVIEW

REVIEWER	Aben, Katja Netherlands Comprehensive Cancer Organisation
REVIEW RETURNED	30-May-2022

GENERAL COMMENTS	I have no further comments