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DIAGNOSIS AND MONITORING OF BONE METASTASES IN PROSTATE CANCER

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DIAGNOSIS AND MONITORING OF BONE METASTASES IN PROSTATE CANCER

by

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CV

I was born in Haderup in Central Jutland in 1987, lived in Aasiaat, Greenland from 1989-1993, and then moved to Fjerritslev in Northern Jutland where I grew up and graduated from high school.

In 2008 I began my studies for a bachelor's degree in Medicine with Industrial Specialisation. In 2013 I graduated from Aalborg University with a master's degree in Medicine with Industrial Specialisation, with specialisation in Translational Medicine. During the last two years of my master's education, I took part in a randomised controlled trial of vitamin D for the treatment of migraine. I was instrumental in planning the study, gaining approval from the Regional Research Ethics Committee, patient recruitment, and execution of all study-related procedures. The education in Medicine with Industrial Specialisation and its focus on gaining practical experience with the complexity of performing clinical trials sparked my interest in clinical research. When the opportunity then arose for me to conduct this PhD study, which is focused on bone imaging in prostate cancer I began as a PhD student at the department of Nuclear Medicine, Aalborg University Hospital, in September 2013.

PREFACE

This PhD thesis is based on clinical studies performed in the department of Nuclear Medicine, Aalborg University Hospital, in collaboration with the Department of Urology, Aalborg University Hospital, and the Department of Nuclear Medicine and the Department of Urology, Regional Hospital West Jutland Herning and Holstebro.

Over the course of this PhD study, some changes had to be implemented due to unforeseen challenges. First, this was intended to be a single, large, prospective, multicentre diagnostic test accuracy study of nuclear medicine bone imaging modalities in prostate cancer, with more than 100 patients included. Within the first year of the study, me and my supervisors realised that it was not possible to accomplish this within a realistic timeframe. Therefore, we planned two additional studies, which focused on observer agreement and monitoring of bone metastases in prostate cancer based on the same imaging modalities. This PhD thesis is thus based on three studies that focused on bone imaging in prostate cancer with different aims, outcomes and perspectives.

ACKNOWLEDGEMENTS

ENGLISH SUMMARY

Prostate cancer is one of the most common cancers in men worldwide. Prostate cancer often presents indolent tumours with little or no lethal potential, and patients may die from other causes. Some patients have aggressive prostate cancer that evolves quickly and is associated with increased morbidity and early death. A major complication in advanced prostate cancer is bone metastases, which can cause pain, pathological fractures, and compression of spinal nerves resulting in severe pain radiating to the extremities and possibly sensory and motor disturbances.

Treatment of prostate cancer can roughly be divided into treatment with curative intent and palliative, life-sustaining treatment. In patients with a high risk of metastases, treatment is limited to palliative, life-sustaining therapies. Therefore, accurate methods for the detection of bone metastases are essential. Clinical guidelines recommend using planar whole-body bone scan (BS) for the diagnosis and monitoring of bone metastases. This method uses a radioactive tracer to visualise the skeleton and possible changes. It is a sensitive, but not particularly specific method, as it also detects benign bone disorders.

Technical advances such as single-photon emission computed tomography/computed tomography (SPECT/CT), which allows for tomographic image acquisition and CT for attenuation correction and anatomical co-localisation have emerged since the introduction of BS. The use of positron emission tomography/CT (PET/CT) scanners has also increased in the past decade, including the use of bone PET/CT with ^{18}F-sodium-fluoride (NaF), which, like the BS, is able to visualise the skeleton and possible changes. NaF PET/CT is associated with higher tracer uptake, increased target-to-background ratio and the higher spatial resolution of PET. However, these newer technologies have not been adopted in clinical guidelines because of the lack of clear-cut evidence that these methods improve the diagnosis of bone metastases.

Study I of this PhD was a prospective study, which was in complete compliance with recommendations for diagnostic test accuracy studies. This study was conducted to compare the diagnostic performance of BS, SPECT/CT and NaF PET/CT in prostate cancer patients at high risk of bone metastases and the results showed that there was no statistically significant difference between the three modalities. SPECT/CT and NaF PET/CT demonstrated an apparent improved sensitivity, while the specificity was comparable across the three modalities. Thus, SPECT/CT and NaF PET/CT can be used for the detection of bone metastases and should be included in clinical guidelines.

Another important aspect of prostate cancer management is the monitoring of treatment responses; for bone metastases, this is also done using BS. Bone response monitoring is not uniform, and several methods and approaches are employed.

Furthermore, response classification might be associated with inter-observer variations. Therefore, Study II of the PhD investigated inter-observer agreement for evaluation of treatment responses in bone on BS for three different methods for classification of response. Considerable variation in observer agreement was observed depending on the method being used. Stringent criteria that distinguish only progression (appearance of two or more new bone metastases) vs non-progression demonstrated an almost perfect agreement (Prostate Cancer Working Group 2 – PCWG-2 criteria). Only moderate agreement was found when using more subjective methods that take into account the degree of response (MD Anderson criteria and standard clinical assessment). Therefore, the use of strict criteria such as PCWG for the evaluation of treatment responses in bone is recommended.

No studies have investigated the use of NaF PET/CT vs BS to assess treatment responses in bone. In Study III of the PhD, which was a prospective exploratory study, no significant difference between NaF PET/CT and BS was found when using the PCWG criteria for treatment response assessment. However, a trend was observed that with more advanced prostate cancer stages, agreement between these two modalities decreased. With evidence showing that progression on BS is correlated with impaired survival, our results indicate that further studies on the use of NaF PET/CT for treatment response monitoring are necessary before this can be recommended as equal to bone scan.

In conclusion, this PhD study demonstrated that SPECT/CT and NaF PET/CT can be considered as equal to BS for the diagnosis of bone metastases and that these modalities should be adopted in clinical guidelines for this purpose. When monitoring treatment responses in bone, the use of strict criteria, such as the PCWG criteria, in both clinical trials as well as in daily clinical situations, is recommended. NaF PET/CT for treatment response monitoring in bone should be investigated more fully, especially with a focus on whether the use of NaF PET/CT is associated with improved patient outcome.

DANSK RESUMÉ

Globalt er prostatakræft er en af de hyppigste kræftformer hos mænd. Prostatakræft er ofte et fredeligt forløb uden dødelig udgang. Dog har nogle patienter en aggressiv prostatakræft som vokser hurtigt, forårsager komplikationer og for tidlig død. Knoglemetastaser, som kan være svært invaliderende, er en af de største komplikationer ved prostatakræft og det kan lede til knoglesmerter og patologiske frakturer. Knoglemetastaser i rygsøjlen kan give rygsmerter og føre til afklemning af nerverne i rygmarven med svære smerter, der stråler ud i arme og ben, føleforstyrrelser og evt. lammelser til følge.

Behandling af prostatakræft kan overordnet inddeles i kurativt intenderet behandling og palliativ, livsforlængende behandling. Hos patienter med høj risiko for spredning af kræft gives i reglen kun palliativ, livsforlængende behandling. Derfor er gode og præcise metoder til at detektere spredning af prostatakræft essentielle. Rutinemæssigt anvendes knogleskintigrafi til påvisning og monitorering af knoglemetastaser. Her visualiseres skelettet og eventuelle forandringer vha. et radioaktivt sporstof. Undersøgelsen har en høj sensitivitet, men er relativt uspecifik da den også viser benigne knoglelidelser, gamle frakturer mm.

I de seneste årtier er der sket en udvikling af scannere, f.eks. SPECT/CT som giver mulighed for tomografiske billeder, og fusionering med CT til attenuationskorrektion og lokalisationsbestemmelse. Brugen af PET/CT scannere er desuden steget betydeligt, herunder også knogle-PET/CT, hvor sporstoffet ^{18}F-natrium fluorid (NaF) bruges til at visualisere forandringer i skelettet som ved knogleskintigrafien. I forhold til knogleskintigrafi har NaF PET/CT en højere billedopløsning, optaget af sporstoffet i knoglerne er større og der er et bedre signal-støj-forhold. Til trods for den teknologiske udvikling er det fortsat knogleskintigrafi der anbefales i kliniske vejledninger. Grundlaget for dette er, at der ikke foreligger klar evidens for, at de nye metoder forbedrer diagnosen af knoglemetastaser.

Studie I i denne PhD var et metodologisk velfunderet, prospektivt studie der fulgte retningslinjerne for diagnostiske akuratesse studier. Heri blev de diagnostiske egenskaber for knogleskintigrafi, SPECT/CT og NaF PET/CT sammenlignet hos en gruppe prostatekræftpatienter med høj risiko for knoglemetastaser. Der blev ikke fundet nogen signifikant forskel mellem de tre metoder. Tilsyneladende var sensitivitet højere for både SPECT/CT og NaF PET/CT end for knogleskintigrafi, mens specificiteten var sammenlignelig metoderne imellem. Disse nyere metoder kan dermed anvendes på lige fod med knogleskintigrafi og bør derfor inkluderes i kliniske vejledninger.

Et andet vigtigt element i behandling af prostatakræft er monitorering af behandlingseffekt. Traditionelt bruges også her knogleskintigrafi. Vurdering af

behandlingsrespons er ikke ensartet, og der anvendes forskellige metoder og tilgange. Desuden kan der være variation i klassifikation af respons mellem forskellige observatører. Studie II i denne PhD undersøgte observatørvariationen ved vurdering af behandlingsrespons på knogleskintigrafi for tre forskellige metoder til at klassificere respons. Der sås betydelig forskel i overensstemmelsen mellem observatørerne afhængigt af hvilken metode der blev anvendt til klassificering af respons. Ved brugen af meget stringente kriterier (Prostate Cancer Working Group 2, PCWG-2 kriterier), hvor der kun skelnes mellem progression (minimum to nye knoglemetastaser) eller ej, var overensstemmelsen meget god. Ved mere subjektive metoder hvor graden af respons angives (MD Anderson kriterier og rutinemæssig klinisk vurdering) var overensstemmelsen mellem observatørene kun moderat. Brugen af stringente kriterier, gerne PCWG, til vurdering af behandlingsrespons i knogler anbefales derfor både til klinisk brug og til brug i kliniske studier.

Ud over hvilke metoder der skal bruges til at vurdere behandlingsrespons ved knoglemetastaser, er der ingen studier der direkte har sammenlignet NaF PET/CT og knogleskintigrafi ved monitorering af behandlingseffekt om end begge undersøgelsesmetoder anvendes. I studie III i denne PhD blev overenstemmelsen mellem knogleskintigrafi og NaF PET/CT til klassificering af respons vha. PCWG-2 kriterierne undersøgt. Det var et prospektivt, eskplorativt studie der involverede prostatakræft patienter der var under forskellige behandlinger og sygdomsstadier. Der var ingen signifikante forskelle mellem de to metoder, men der var en tendens til, at man med knogleskintigrafi fandt progression hos flere patienter og/eller på et tidligere tidspunkt end med NaF PET/CT. Denne tendens blev mere udtalt ved sene sygdomsstadier. Man har set, at der ved progression på knogleskintigrafi er korrelation til dårligere overlevelse. Derfor indbyder resultaterne til, at NaF PET/CT undersøges nærmere til vurdering af behandlingsrespons ved prostatekræft patienter med knoglemetastaser, før denne metode kan anbefales på lige fod med knogleskintigrafi.

Afslutningsvist har resultaterne af denne PhD vist, at NaF PET/CT og SPECT/CT kan bruges, og bør anbefales, på lige fod med knogleskintigrafi, til detektering af knoglemetastaser ved prostatakræft. Ved evaluaering af behandlingseffekt bør der som udgangspunkt anvendes stringente kriterier, som PCWG, for at give de mest konsekvente besvarelser både i klinikken og i kliniske studier. Brugen af NaF PET/CT til vurdering af behandlingseffekt bør undersøges nærmere, særligt i forhold til om resultaterne af NaF PET/CT scanning bidrager til forbedret patientforløb.

ABBREVIATIONS

ADT	Androgen-Deprivation Therapy
BS	Planar whole-body Bone Scan
CI	Confidence Interval
CRPC	Castration-Resistant Prostate Cancer
nm-/mCRPC	non-metastatic/metastatic CRPC
CT	Computed Tomography
DTA	Diagnostic Test Accuracy
LH	Luteinising Hormone
LHRH	Luteinising Hormone-releasing Hormone
M0	Benign
Me	Equivocal
M1	Malignant
MRI	Magnetic Resonance Imaging
NaF	^{18}F-sodium fluoride
NPV	Negative Predictive Value
OS	Overall survival
PCa	Prostate Cancer
PCWG	Prostate Cancer Working Group
PD	Progressive Disease
PERCIST	Positron Emission Tomography Response Criteria in Solid Tumours
PET	Positron Emission Tomography
PFS	Progression-Free Survival
rPFS	radiographic PFS
PPV	Positive Predictive Value
PSA	Prostate-Specific Antigen
RECIST	Response Evaluation Criteria in Solid Tumours
SPECT	Single-Photon Emission Computed Tomography
STARD	Standards for Reporting of Diagnostic Accuracy
SUV	Standardised Uptake Values

LIST OF PUBLICATIONS

This PhD thesis is based on the following four papers

Paper 1   Fonager RF, Zacho HD, Langkilde NC, Petersen LJ. $^{(18)}$F-fluoride positron emission tomography/computed tomography and bone scintigraphy for diagnosis of bone metastases in newly diagnosed, high-risk prostate cancer patients: study protocol for a multicentre, diagnostic test accuracy study. *BMC Cancer. 2016;16:10.*

Paper 2   *Unpublished work:* Fonager RF, Zacho HD, Langkilde NC, Fledelius J, Ejlersen JA, Haarmark C, Hendel HW, Lange MB, Jochumsen MR, Mortensen JC, Petersen LJ. Diagnostic test accuracy study of ^{18}F-sodium fluoride PET/CT, ^{99m}Tc-labelled diphosphonate SPECT/CT, and planar bone scintigraphy for diagnosis of bone metastases in newly diagnosed, high risk prostate cancer

Paper 3   Fonager RF, Zacho HD, Albertsen S, Fledelius J, Ejlersen JA, Christensen MH, Aleksyniene R, Biurrun Manresa JA, Petersen LJ. Observer agreement of treatment responses on planar bone scintigraphy in prostate cancer patients: importance of the lesion assessment method. *Nuclear Medicine Communications. 2017 Mar;38(3):215-221.*

Paper 4   *Unpublished work:* Fonager RF, Zacho HD, Langkilde NC, Fledelius J, Ejlersen JA, Hendel HW, Haarmark C, Moe M, Petersen LJ.^{18}F-sodium fluoride PET/CT PET/CT and planar bone scintigraphy for bone response monitoring in prostate cancer.

An oral presentation was given at the European Association of Nuclear Medicine annual meeting in Barcelona 2016:

Fonager RF, Zacho HD, Albertsen S, Fledelius J, Ejlersen JA, Christensen MH, Aleksyniene R, Biurrun Manresa JA, Petersen LJ. Observer agreement of treatment responses on planar bone scintigraphy in prostate cancer patients: importance of the lesion assessment method *European Journal of Nuclear Medicine and Molecular Imaging. Conference: 29th Annual Congress of the European Association of Nuclear Medicine, EANM 2016. Spain. 43 (1 Supplement 1) (pp S108), 2016.*

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CHAPTER 1. INTRODUCTION

1.1. EPIDEMIOLOGY

Prostate cancer (PCa) is the second most frequent cancer in men worldwide (1, 2). During the past decade, the incidence of PCa has shifted substantially. An increase in regular testing of prostate-specific antigen (PSA) resulted in a dramatic increase in PCa incidence until approximately 2009, while the mortality remained stable. It was later recognised that regular PSA screening resulted in detection of a large proportion of latent and asymptomatic PCa that would never become clinically significant. Thus, regular PSA screening has since decreased and the incidence of PCa has consequently decreased or stabilised in most countries, including Denmark. This has not affected mortality (1, 3, 4).

1.2. STAGING

Prostate cancer is diagnosed either by opportunistic PSA testing or by PSA testing in the setting of lower urinary tract symptoms, e.g., urgency, frequency, incomplete bladder emptying. A definitive diagnosis is based on histopathological verification from transrectal ultrasound-guided biopsies from the prostate or from post-operative histopathology (5-7). The standard for grading of PCa is the Gleason grading system in which histopathological patterns of the tumour specimens are assessed and assigned a score. The Gleason score is the sum of the scores of the two most frequent patterns found in the tumour specimens, where a higher score is associated with a more aggressive cancer and worse prognosis (8).

Prostate cancer is classified and staged according to the TNM staging system for malignant tumours (9). T-staging is based on the primary tumour: T1) a non-palpable tumour that can be detected by biopsies; T2) the tumour is palpable, but confined in within the prostate; T3) the tumour has extended through the prostatic capsule; and T4) the tumour has invaded adjacent structures. N-staging determines the involvement of regional lymph nodes, and M-staging identifies the presence of distant metastases, distinguishing between non-regional lymph nodes, bone, and other sites (9).

Prostate cancer patients are risk-stratified according to their risk of biochemical recurrence following treatment with curative intent, i.e., radical prostatectomy or external beam radiation; see Table 1 for risk classifications according to clinical guidelines (5-7). The current PhD thesis studied only high-risk and advanced PCa patients who were not eligible for treatment with curative intent.

Table 1 Risk stratification according to clinical guidelines

	Low-risk	**Intermediate-risk**	**High-risk**
EAU (5)	PSA < 10 ng/mL and GS < 7 and cT1-2a	PSA 10-20 ng/mL or GS 7 or cT2b	PSA > 20 or GS > 7 or cT2c
NCCN (6)	PSA < 10 ng/mL GS ≤ 6 T1-T2a	PSA 10-20 ng/mL or GS 7 or T2b-T2c	PSA >20 ng/mL or GS 8-10 or T3a
AUA (7)	PSA ≤ 10 ng/mL and GS ≤ 6 and cT1c-T2a	PSA 10-20 ng/mL or GS 7 or cT2b	PSA > 20 ng/mL or GS 8-10 or cT2c

EAU, European Association of Urology; NCCN, National Comprehensive Cancer Network; AUA, American Association of Urology; PSA, prostate specific antigen; GS, Gleason Score

1.3. BONE METASTASES

In many cases, PCa is associated with clinically indolent tumours that have little or no lethal potential. However, some patients present with more aggressive PCa that grows quickly and spreads to other parts of the body, resulting in increased morbidity and early death. Bone metastases are common in advanced PCa and cause severe morbidity for the affected patients, including bone pain, vertebral collapse, pathological fractures, and spinal cord compression (10-12). A large proportion of patients show bone metastases post-mortem (13). It was previously shown that 7.7% of newly diagnosed PCa patients have or will develop bone metastases within the first year post-diagnosis (14). A recent Danish study showed that in a population of newly diagnosed PCa patients, approximately 13% had bone metastases at the time of diagnosis regardless of stage (15), and unexplained bone pain was found to be a predictor of bone metastases in this patient population (16).

Detection of bone metastases is essential in the management of PCa, as treatment with curative intent is only indicated in patients with local or locally advanced PCa, while patients with advanced PCa are treated with palliative, life-sustaining therapies only. Clinical guidelines recommend bone metastases staging in patients with intermediate- and high-risk PCa by planar whole-body bone scan (BS), and they agree that staging is unnecessary in low-risk PCa patients (Table 1) (5-7). This is supported by studies showing that BS is redundant in the majority of patients with low- to intermediate-risk PCa (15, 17, 18). However, despite the lack of evidence showing improved detection or survival, imaging-based staging of low-risk PCa patients is often routinely performed. For this reason, the American Society of Oncology

identified staging of bone metastases in PCa as number two of five major opportunities to reduce costs and improve care within oncology (19).

1.4. SYSTEMIC TREATMENT OF PROSTATE CANCER

Treatment of PCa depends on the clinical disease state, which can roughly be divided into treatment of localised disease with curative intent, or palliative, life-sustaining therapies. Treatment of incurable PCa depends on the clinical disease state of advanced PCa (Figure 1) i.e., non-metastatic clinically localised PCa, metastatic hormone-sensitive PCa, and nonmetastatic (nm) or metastatic (m) castration-resistant prostate cancer (CRPC). An overview of the most commonly used treatment options in Denmark is shown in Figure 1, and the options are briefly described below.

1.4.1. ANDROGEN-DEPRIVATION THERAPY

Androgens promote the growth of normal prostate cells, and initially, androgens are necessary for the growth of PCa by stimulating the proliferation of PCa cells. Therefore, androgen-deprivation therapy (ADT) remains the primary treatment for incurable patients with androgen-dependent PCa (20). Androgen-deprivation therapy involves a complete elimination or blockage of androgens. The most common therapies include surgical removal of the androgen-producing glands (the testes) by bilateral orchiectomy, inhibition of gonadotropin-secretion by luteinising hormone-releasing hormone (LHRH) agonists or antagonists, or by blocking androgen receptors with steroid or non-steroid anti-androgens. Most of these treatments affect libido.

Surgical castration is a simple but irreversible procedure. It is the fastest and easiest way to achieve castration levels of testosterone (< 50 ng/mL), and it is considered the "gold standard" of ADT (11).

Luteinising hormone-releasing hormone agonists initially interact with LHRH receptors and stimulate the production of luteinising hormone (LH), which causes an initial flare response with increased androgen production lasting for a few weeks. The LHRH receptors are then downregulated as the pituitary gland is desensitised, which leads to a decrease in androgen production in the testes. Blood levels of testosterone decrease to castration levels within 2-4 weeks (21, 22). A meta-analysis found that there is no significant difference in overall survival (OS) (p>0.2) and progression-free survival (PFS) between treatment with LHRH agonists and orchiectomy (23). Androgen blockade by LHRH agonists can be reversible and might therefore be preferred. Because of the initial flare response, treatment with LHRH agonists is often combined with anti-androgen therapy initially for complete androgen blockade (11).

Non-CRPC
CRPC

Clinically localised Pca
Watchfull waiting
Anti-androgen monotherapy
Orchiectomy
LHRH agonist or antagonist

Rising PSA
Watchfull waiting
Anti-androgen monotherapy
Orchiectomy
LHRH agonist or antagonist

Clinical metastases: non-CRPC
Asymptomatic patients:
Anti-androgen monotherapy
Orchiectomy
LHRH agonist or antagonist ± antiandrogen
Symptomatic patients :
Orchiectomy
LHRH agonist or antagonist ± antiandrogen

Non-metastatic CRPC
Continued LHRH agonist or antagonist

mCRPC 1st line
Abiraterone
Enzalutamide
Docetaxel
Radium-223

mCRPC 2nd line
Cabazitaxel

Figure 1 Clinical states of non-curable prostate cancer and management options most used in Denmark. PCa, prostate cancer; LHRH, luteinising hormone-releasing hormone; PSA, prostate-specific antigen; CRPC, castration resistant prostate cancer; mCRPC, metastatic CRPC. Inspired by (24).

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Luteinising hormone-releasing hormone antagonists block the LHRH receptors, thus blocking the release of LH. This causes an almost instant decrease in testosterone, and patients reach castration levels within a few days, i.e., there is no flare reaction. Studies have found that the most commonly used LHRH antagonist, Degarelix, is non-inferior in relation to OS and PSA PFS compared with LHRH agonists (25).

Steroid anti-androgens act by blocking the androgen receptors and by supressing androgen production. Non-steroidal anti-androgens act solely by blocking the androgen receptors. Most often, anti-androgens are used in combination with LHRH agonists. Anti-androgen monotherapy is associated with reduced OS and PFS and is rarely used. In many cases, the libido is preserved when using anti-androgens as monotherapy, which is the most common rationale behind anti-androgen monotherapy (26, 27).

1.4.2. NEXT-GENERATION HORMONAL THERAPY

Initial treatment with ADT leads to a decrease in PSA and clinical improvement. In the majority of patients, however, the cancer inevitably becomes castration-resistant, and it is estimated that 10-20% of PCa patients develop CRPC within five years (28). The definition of CRPC is serum castration levels of testosterone and confirmed PSA progression or progression of osseous or soft-tissue metastases (11). Treatment of CRPC has evolved significantly in recent years with the introduction of highly effective novel therapies.

Abiraterone acetate is an androgen synthesis inhibitor. It inhibits both testicular androgen synthesis and extra-gonadal androgen synthesis. Abiraterone has been shown to have a significant effect on OS in chemotherapy naïve men with mCRPC (34.7 vs 30.2 months for placebo, p=0.0033) (29) as well as in mCRPC patients in the post-chemotherapy setting (15.8 vs 11.2 months for placebo, p < 0.0001) (30). In the post-chemotherapy setting, Abiraterone was also found to have a significant effect on radiographic PFS (rPFS) (5.6 vs 3.6 months for placebo, p < 0.0001) (30).

Enzalutamide is a non-steroidal anti-androgen that inhibits androgen receptor signalling pathways. It competitively binds to androgen receptors, inhibits androgen receptor translocation to the cell nucleus, and inhibits binding of androgen receptors to DNA (31). In chemotherapy naïve PCa patients, Enzalutamide demonstrated a significant effect on rPFS and OS. At 12 months, the rate of rPFS was 65% vs 14% for placebo and there was a 29% decrease in the risk of death compared with placebo (p < 0.001) (31). Enzalutamide has also shown significantly improved OS in the post-chemotherapy setting (18.4 vs 13.6 months for placebo, p < 0.001) (32).

1.4.3. CHEMOTHERAPY

Docetaxel is an anti-mitotic chemotherapy agent that is used as first-line chemotherapy in PCa patients. Compared with Mitoxantrone, which is another chemotherapeutic agent that relieves pain and improves quality of life but does not improve OS, Docetaxel was found to improve OS (18.9 months vs 16.5 months, p = 0.009 and 17.5 vs 15.6 months, p = 0.002) (33, 34) as well as rPFS (16.5 vs 8.2 months, p < 0.001) (35). A recent meta-analysis demonstrated that Docetaxel in combination with primary ADT for patients with androgen-dependent metastatic and non-metastatic PCa is associated with improved survival (p = 0.003) (36).

Cabazitaxel is a microtubule inhibitor, which is used as a second-line chemotherapy option for patients who have previously received Docetaxel. Compared with Mitoxantrone, Cabazitaxel showed improved OS and PFS in the post-Docetaxel setting with a 30% decrease in the risk of death (37).

1.4.4. RADIUM-223

Radium-223 is an alpha-emitting radiopharmaceutical that is used to treat bone metastases in PCa. It is absorbed by bone, especially in bone metastases that exhibit increased bone turnover. When it has been absorbed, Radium-223 emits highly potent, short-range alpha particles and kills cancer cells. It is highly effective for pain relief in patients with painful bone metastases and CRPC (38, 39). Furthermore, Radium-223 has demonstrated improved OS compared with placebo, 14.9 vs 11.3 months for placebo (p < 0.001) (40). This PhD study did not involve any patients receiving Radium-223.

1.5. BONE IMAGING IN NUCLEAR MEDICINE

Reliable detection of bone metastases in PCa is an essential component of patient management. Several imaging modalities can be used for this purpose, including nuclear medicine and radiological imaging modalities. The most widely used and recommended modality for the detection and monitoring of bone metastases in PCa is BS (5-7). A brief introduction of nuclear medicine modalities for bone metastases imaging in PCa is provided below. Radiological imaging modalities are omitted as they are beyond the scope of this PhD thesis.

1.5.1. PLANAR WHOLE-BODY BONE SCAN

Bone scintigraphy is a highly sensitive imaging modality that visualises the distribution of active bone formation within the skeleton by use of a radioactive tracer, ^{99m}Tc-labelled diphosphonates. It is not a highly specific modality as it not only visualises cancerous bone metastases but also benign conditions including degenerative and inflammatory bone disease, fractures, and infections (41, 42).

1.5.2. SPECT/CT

Single photon emission computed tomography (SPECT) is a technical enhancement of the planar BS in which tomographic image acquisition allows for three-dimensional visualisation of tracer uptake. Most often, SPECT is combined with computed tomography (CT), thus allowing the opportunity to correlate SPECT findings with anatomical image data. Computed tomography is mainly used for attenuation correction and anatomical co-localisation (41, 42). Imaging with SPECT/CT is most often performed as an add-on to BS and is thus acquired immediately after the BS with no additional radiation exposure beyond the CT, which is most often a low-dose CT.

1.5.3. PET/CT

[18]F-sodium fluoride (NaF), which was initially introduced in the 1960s, is a bone-specific tracer that, like ^{99m}Tc-diphosphonates, visualises sites of increased bone turnover. Nevertheless, because of the immense technical requirement for using this tracer, the widespread availability of ^{99m}Tc-generators, and the low costs associated with BS imaging, BS was preferred (43-46). As a consequence of the increasing availability of positron emission tomography (PET)/CT scanners, interest in the clinical use of NaF for skeletal imaging has spiked in the past decades (47, 48). The uptake of NaF is higher compared to ^{99m}Tc-diphosphonates. Furthermore, it has a faster blood clearance and higher target-to-background ratio. Together with the improved spatial resolution of PET scanners, image quality is improved compared with BS imaging (43-46). Like with SPECT/CT, CT is often performed simultaneously with PET, allowing for attenuation correction and anatomical co-localisation.

Several other PET tracers are currently being used and investigated for the detection of bone metastases in PCa. Unlike NaF, these tracers primarily target malignant cancer cells. ^{18}F-labelled fluorodeoxyglucose is the most commonly applied radiopharmaceutical across many other cancer types . Bone metastases from PCa are mostly sclerotic and therefore have lower metabolic activity compared with lytic lesions. Thus, these lesions are not particularly avid for ^{18}F-labelled fluorodeoxyglucose, and the sensitivity when using this tracer for detection of bone metastases in PCa is lower than that of BS (49-51). ^{18}F-acetate, ^{18}F-choline, and ^{11}C-choline likewise target tumour cells, and have shown promising results with high sensitivity and specificity for the detection of bone metastases. However, these modalities have not currently been adopted for routine use (52, 53). In addition, ^{68}Ga-labelled prostate specific membrane antigen is currently under investigation for bone imaging in PCa and is showing promising results (54, 55). These tracers are, however, not within the scope of this PhD study and will not be discussed further.

1.5.4. COMPARISON OF BS, SPECT/CT AND NAF PET/CT

The diagnostic performance of BS versus SPECT and NaF PET (with or without CT) has been investigated in diagnostic test accuracy (DTA) studies on multiple occasions during the past decade. Table 2 shows the results of studies involving at least two of the imaging modalities of interest in this PhD study, i.e., BS, SPECT/CT and NaF PET/CT. The reference standards used in these studies are presented as well. Previous studies have included highly heterogeneous and mixed study populations, and the studies have had some methodological issues, but this will be addressed more thoroughly later.

The sensitivity of BS in previous studies has varied from as low as 57% to as high as 97% (50, 51, 56-59). For studies in which the reference standard was primarily based on other imaging, e.g., full-diagnostic CT or MRI, the sensitivity of BS was lowest (56, 59), while studies that used a combination of imaging, clinical follow-up, etc., found a higher sensitivity of BS (50, 51, 57, 58). The specificity of BS has been even more wide-ranging with reported values from 57-80% (50, 51, 56-59).

Independent of whether SPECT was used alone or in combination with CT, the sensitivity of SPECT ranged from 78-96% (56-58). When it came to the specificity of SPECT, the addition of a CT had a major impact on the results. The specificity for SPECT alone was in the range of 56-64% (57, 58), while the specificity for SPECT/CT ranged from 67-96% (56-58). The improved specificity is probably due to the attenuation correction and anatomical co-localisation gained from CT.

The sensitivity of NaF PET/CT studies has, in most studies, been 100% (50, 51, 56, 57, 59, 60). In a few studies in which NaF PET/CT was compared with ^{18}F-choline PET/CT, the sensitivity of NaF PET/CT was 81% (61, 62). The specificity of NaF PET/CT has shown greater variation with reported specificities ranging from 71-100% (50, 51, 56, 57, 59-62).

When comparing the results for BS, SPECT/CT and NaF PET/CT, the sensitivity of NaF PET/CT was higher than those of SPECT/CT and BS across all studies (50, 51, 56-59). The specificity of NaF PET/CT was outperformed by that of SPECT/CT in the study by Jambor et al. (57). The sensitivity of SPECT/CT was higher than or equal to BS in all studies, and the specificity was higher (56-58). In summary, the diagnostic performance of these three imaging modalities can be ranked with NaF PET/CT demonstrating the best diagnostic performance, followed by SPECT/CT and BS. However, even though studies continue to demonstrate an apparent advantage of NaF PET/CT and SPECT/CT over BS, current guidelines have refrained from including SPECT/CT, NaF PET/CT, or other PET tracers as standard imaging options for the detection of bone metastases in PCa (5-7). The rationale behind this is probably that there is a lack of clear-cut evidence and varying degrees of methodological issues with these studies.

1.5.5. CHALLENGES IN DIAGNOSTIC TEST ACCURACY STUDIES

Previous DTA studies within bone imaging in PCa have included highly heterogeneous and limited study populations with various cancer types and have included both newly diagnosed patients and those evaluated for re-staging purposes. In addition, the reference standard has often relied on clinical follow-up, which has not been clearly defined, and sometimes the reference standard was predominantly based on consensus evaluation of the index test, thus resulting in an artificially boosted performance due to circular reasoning (50, 51, 56-62). The methodological issues were summarised in a review by Wondergem et al., who also determined that the level of evidence in these DTA studies was quite low, Oxford Centre for Evidence-Based Medicine level 3b (53, 63).

The persistent presence of methodological issues within DTA studies has long been known, and some common issues include poorly described study populations and sampling procedures, and verification bias (64-67). A major issue is that for most diseases and conditions, it is practically impossible to obtain a single perfect "gold" reference standard, and in previous studies, the reference standard has varied and different solutions have been used to account for imperfect or missing values of the reference standard (68). Within bone imaging, the theoretical "gold" reference standard would be biopsies and histological verification of bone metastases, but this is neither practical nor ethically reasonable; in DTA studies with PCa and bone metastases consensus reviews or expert panels are commonly used (Table 2) (51, 57, 58). In recent years, the use of expert panels has increased, i.e., a consensus reading between a group of experts who determine the final diagnosis on the basis of all available relevant data for each patient (69). While not perfect, this might be one of the more ideal approaches, as it resembles clinical practice. Bertens et al. (69) investigated the use and reporting of expert panels in DTA studies and concluded that expert panels can be used in the absence of a single "gold standard", and they encouraged the development of formal methodology guidelines.

Table 2 Comparison of the diagnostic performance of bone imaging modalitiesin nuclear medicine

Study	n (ND/RS)	Index tests	Sensitivity	Specificity	PPV	NPV	Accuracy	Reference standard
Even-Sapir 2006 (56)	44 (25/19)	BS SPECT/CT NaF PET NaF PET/CT	57 78 100 100	57 67 62 100	59 72 74 100	55 74 100 100	- - - -	CT from NaF PET/CT
Withofs 2011 (59)	10 (10/0)	BS +SPECT NaF PET/CT	67 100	82 90	54 75	89 100	78 79	Full diagnostic CT or or MRI
Iagaru 2012 (51)	18 (0/18)	BS NaF PET/CT	88 100	80 80	- -	- -	90 94	Expert panel review of histological confirmation, clinical follow-up, and other imaging
Damle 2012 (50)	49 (25/24)	BS +SPECT NaF PET/CT	97 100	41 71	76 87	88 100	78 90	MRI, thin slice contrast-enhanced CT, or skeletal radiograph findings

Table 2 continued Comparison of the diagnostic performance of bone imaging modalitiesin nuclear medicine

Study	n (ND/RS)	Index tests	Sensitivity	Specificity	PPV	NPV	Accuracy	Reference standard
Palmedo 2013 (58)	97 (-/-)	BS	96	75	61	98	-	Expert panel review of clinical follow-up, including; clinical examination, medical reports, imaging, and tumour markers
		SPECT	96	64	52	98	-	
		SPECT/CT	96	94	87	99	-	
Jambor 2016 (57)	27 (0/27)	BS	85	59	-	-	67	Expert panel review of index test results, follow-up data (6-32 months) of clinical, imaging, and laboratory data
		SPECT	95	56	-	-	69	
		SPECT/CT	95	88	-	-	90	
		NaF PET/CT	100	82	-	-	89	

Values of sensitivity, specificity, PPV, and NPV are presented with equivocal results regarded as malignant.
ND, newly diagnosed; RS, re-staging; PPV, positive predictive value; NPV, negative predictive value; BS, planar whole-body bone scintigraphy; SPECT, single-photon emission tomography; CT, computed tomography; NaF, ^{18}F-sodium fluoride; PET, positron emission tomography; MRI, magnetic resonance imaging.

Standards for Reporting of Diagnostic Accuracy

In an attempt to improve the quality of reporting of all aspects of DTA studies, Bossuyt and colleagues (70) published the Standards for Reporting of Diagnostic Accuracy (STARD). The original STARD checklist contained 25 specific items to be included in the abstract, title, methods, results, and discussion that are needed for complete and accurate reporting in DTA studies. In 2015, Korevaar et al. (66) investigated the reporting of the items included in the STARD checklist and compared this to articles published before STARD and one and 10 years after STARD was first published. They found that reporting in DTA studies has improved since the initiation of STARD. However, there are still some shortcomings, especially regarding patient selection, details on the readers of index tests, and variations in the accuracy of the index test between subgroups of patients, centres, and/or readers. The STARD checklist was updated in 2015 with additional essential items to improve completeness and transparency in DTA studies (71). In summary, some attempts have been made to improve the design and reporting of DTA studies. While some progress has been seen in recent years, there is still room for improvement.

1.6. TREATMENT RESPONSE ASSESSMENT

1.6.1. RESPONSE ASSESSMENT METHODS

Disease monitoring is essential for optimal patient management, especially with the dramatic increase in the cost of cancer therapies that has occurred over the past years (72-74). Response assessment is standard when evaluating the efficacy of new therapeutic agents in cancer imaging. In PCa, it remains a challenge to determine response to therapy, as most patients with metastatic PCa have disease limited to bone, and it is well-known that assessment of treatment response in bone metastases is difficult (75).

RECIST and PERCIST

The most commonly used set of response criteria in cancer imaging is the Response Evaluation Criteria in Solid Tumours (RECIST) (76), which classifies sclerotic bone lesions as non-measurable. These criteria are therefore of little use when determining response of bone metastases and are hence of limited use in PCa (77). Current guidelines recommend BS for monitoring bone metastases (6, 7, 11). The RECIST criteria were adapted for use in PET in 2009 as the Positron Emission Tomography Response Criteria in Solid Tumours criteria (PERCIST) (78). As with RECIST, PERCIST has not gained footing within PCa as a large proportion of PCa patients remain non-evaluable by PERCIST (79). These criteria are, due to their limited applicability in PCa, beyond the scope of this PhD thesis and will not be described further.

MD Anderson criteria

Because of the lack of criteria for assessment of tumour response in bone, Hamaoka et al. (80) proposed a set of visual assessment criteria for evaluation of bone metastatic response, known as the MD Anderson criteria. These criteria included similar response categories as those used by RECIST, i.e., complete response, partial response, stable disease or progressive disease, but instead of quantifying response they focused on acknowledging the presence of a response. Besides BS, the MD Anderson criteria included plain radiographs, CT and MRI, but these are beyond the scope of this PhD thesis. It has been shown that the MD Anderson criteria are able to distinguish responders (complete and partial response) from non-responders (stable and progressive disease) with regard to PFS in bone-only metastatic breast cancer patients receiving systemic treatment (23.3 vs 5.5 months, respectively, p = 0.025) (81). Improved OS was likewise demonstrated for responders vs non-responders (61.9 vs 34.4 months, not significant p=0.13) (81). No studies have investigated this relationship in PCa patients.

Prostate Cancer Working Group Criteria

It has been a great challenge to determine the efficacy of new therapeutic agents in PCa studies without excluding patients with non-measurable disease. Therefore, the Prostate-Specific Antigen Working Group was established in an attempt to develop consensus criteria for response assessment in PCa studies (82); they were revised in 2008 with the Prostate Cancer Working Group (PCWG) 2 criteria (83), and in 2016 the PCWG-3 criteria were published (24). These response evaluation criteria addressed symptoms, biochemical response, response of measurable disease, and response of non-measurable bone lesions. Since their introduction, the PCWG criteria have been widely adopted in clinical trials for the assessment of treatment response in bone (30-32, 84, 85).

The focus of the PCWG criteria is to rule out or identify the presence of progression on BS. Unlike RECIST and the MD Anderson criteria, the PCWG criteria do not distinguish between stable disease and improvement (partial or complete response) and include only two response categories: 1) progressive disease (PD) and 2) non-progressive disease (non-PD).

Progressive disease according to the PCWG criteria was associated with OS in a large population of men with CRPC, where PD at three months was associated with a median OS of 9.2 months vs 17.8 months in patients showing non-PD (p < 0.0001) (86). At six months, median OS was 10.1 months for PD vs 19.3 months non-PD (p < 0.0001) (86).

1.6.2. TREATMENT RESPONSE ASSESSMENT IN BONE BY BS AND NAF PET/CT

Only very few studies have directly investigated the use of BS and other imaging modalities for bone response in PCa.

Bone scan response assessment

Sonpavde and colleagues (87) collected data from two large prospective clinical trials and showed that radiographic progression according to the PCWG-2 criteria was associated with poorer OS in patients taken off study due to radiographic progression vs patients who were taken off study for other reasons.

In a large clinical trial comparing abiraterone acetate vs placebo rPFS, according to the PCWG-2 criteria, was positively correlated with OS (Spearman correlation coefficient (R^2) = 0.72, 95% CI: 0.65-0.77) (88). The positive correlation was evident in both the treatment group and the placebo group. Furthermore, in the entire group of patients, OS was shorter for those who met the PCWG-2 criteria for confirmed PD on a subsequent scan compared with those who did not have confirmed PD (88).

In patients who had previously failed Docetaxel chemotherapy and were assigned to treatment with Radium-223, response on BS was mixed, showing the appearance of new lesions simultaneously with decreased tracer uptake in bone metastases that demonstrated a high pre-treatment uptake (89).

In recent years, studies have found a correlation between OS and bone response, defined as changes in the Bone Scan Index, a quantitative imaging biomarker developed for assessment of bone tumour load on BS (90-94). Kaboteh et al. (93) compared the correlation between OS and bone response by changes in the Bone Scan Index and response according to the PCWG-2 criteria. Although it was a small and retrospective study, they showed that changes in the Bone Scan Index correlated with OS, while progression by the PCWG-2 criteria did not.

In summary, the results of the above studies indicate that progression on BS, either according to the PCWG criteria or as changes in Bone Scan index, can be correlated with OS and BS is therefore useful in determining response to therapy.

Observer agreement for assessment of BS

An important aspect of treatment monitoring is the consistency of response classification among observers. When analysed by Cohen's kappa, inter-observer agreement for the diagnosis of bone metastases is reportedly moderate to almost perfect depending on the number of categories used for classification of the presence of bone metastases (95-97). Kaboteh et al. (93) assessed BS according to the PCWG-2 criteria and found an agreement of 87% (222/255) among three experienced readers for evaluation of PD vs non-PD. No kappa values were reported. In 173 PCa patients with bone metastases, evaluation of treatment response on BS showed substantial

agreement by Cohen's kappa when using the PCWG-2 criteria (Cohen's kappa: 0.66) and standard clinical assessment (Cohen's kappa: 0.70) (98). However, knowledge on observer agreement for assessment of treatment response on BS and has not been investigated at all for NaF PET/CT. A high level of agreement between observers is important as decisions to continue or discontinue treatments and investigational treatments are often based on the detection of progression on BS.

NaF PET/CT response assessment

A few minor studies have investigated changes on NaF PET/CT.

Cook et al. (99) showed that changes on NaF PET/CT, as measured by changes in standardised uptake values (SUV), closely followed changes in PSA in five patients after receiving two doses (six weeks apart) of Radium-223.

In a mixed population of bone metastases-positive and -negative PCa patients who were undergoing a wide range of treatments, Apolo and colleagues investigated changes on NaF PET/CT at 6 and 12 months and correlation with clinical assessment of bone response and PSA (100). Clinical assessment of bone response was categorised as regression (regression of existing lesions), stable disease (no new lesions) or progression (new lesions). Changes in SUV correlated with clinical assessment of bone response at 6 and 12 months when analysed by the Kruskal-Wallis rank test ($p = 0.0147$ and $p = 0.0053$, repectively). Likewise, there was a correlation between change in PSA and maximal percent change in SUV at 6 and 12 months ($R^2 = 0.39$, $p = 0.014$ and $R^2 = 0.58$, $p = 0.0005$, respectively) (100).

Kairemo et al. (101) investigated changes on NaF PET/CT in 10 mCRPC patients receiving Radium-223. They summed the two highest SUV from two skeletal regions and found that after six cycles of Radium-223 all patients responded on NaF PET/CT with $\geq 6\%$ change in SUV compared to baseline. This was accompanied by changes in PSA in some but not all patients.

A survey of the National Oncologic PET Registry in America showed that patient management was changed in up to 53% of PCa patients following a NaF PET/CT (16% when adjusted for patients who already had a pre-treatment plan involving imaging). However, this study did not investigate whether the change in management led to improved patient outcome (47).

Thus, previous studies on response assessment by NAF PET/CT are scarce, has included small study populations, have not compared the results with BS, and furthermore, no studies have investigated response on NaF PET/CT in relation to patient outcome.

1.7. RATIONALE FOR PHD STUDIES

Although there is a growing body of evidence showing an apparent superiority of NaF PET/CT and SPECT/CT over BS, the methodological issues in previous DTA studies, as outlined in section 1.5.5., discouraged clinical guidelines from including these newer modalities as standard for the diagnosis of bone metastases in PCa. Therefore, properly designed studies are needed to establish the improved diagnostic performance of these modalities.

Monitoring of treatment responses in bone is essential for patient management in PCa, both in clinical trials and in clinical practice. Clinical guidelines recommend using BS for monitoring of bone metastases in PCa and the PCWG advocate the use of BS for determination of bone progression in clinical trials. It is essential for patient management that there is a high level of agreement for response classification between readers. Different methods for response classification have been presented; however, observer agreement has not been adequately investigated. Delineation of such agreement is necessary to establish the best method for future use in treatment response monitoring in bone.

Finally, the use of NaF PET/CT in PCa is increasing both for diagnostic purposes as well as for treatment response monitoring. No studies have investigated the use of NaF PET/CT for treatment response assessment in comparison with conventional BS, for which response classification is correlated with OS. Therefore, studies are needed to investigate the concordance between BS and NaF PET/CT for treatment response assessment and how they might differ.

CHAPTER 2. AIMS

The overall aim of this PhD thesis was to evaluate BS, SPECT/CT and NaF PET/CT for diagnosis and monitoring of bone metastases in PCa. This was done in three sub-studies, for which the specific aims are listed below.

Study I (Papers 1 & 2)
To compare the diagnostic performances of BS, SPECT/CT and NaF PET/CT in newly diagnosed high-risk PCa patients in a fully STARD-compliant DTA study (102).

Study II (Paper 3)
To evaluate observer agreement in the assessment of treatment responses in bone on BS in PCa patients undergoing different anti-cancer treatments at varying stages of PCa, using three different methods for treatment response evaluation (103).

Study III (Paper 4)
To prospectively explore the concordance between BS and NaF PET/CT when evaluating bone metastases response in PCa patients receiving various anti-cancer treatments and to explore the relationships between imaging, clinical, and biochemical responses.

CHAPTER 3. MATERIALS AND METHODS

3.1. STUDY POPULATION

Study I

From February 2014 to December 2015, consecutive patients with newly diagnosed high-risk PCa from the Departments of Urology at Aalborg University Hospital, Regional Hospital West Jutland Holstebro, and Regional Hospital Viborg were invited to participate in this study. Eligibility criteria consisted of the following: 1) biopsy-proven PCa; 2) PSA blood levels $\geq$ 50 ng/mL; 3) eligible for ADT; 4) no other cancer within five years; 5) ability to comply with study procedures; and 6) have not received any investigational drugs.

The Regional Research Ethics committee (N-20130068) and the Danish Data Protection Agency approved the study. Written informed consent was obtained from 52 patients. Of these, 10 patients either withdrew consent or were excluded for incompatibility reasons. Furthermore, three patients died before completion of the study, resulting in 39 patients remaining. Two of these were excluded from the final analysis because a final diagnosis could not be determined.

Study II

In this retrospective study, all patients who, during the period from January 2009 to November 2014, had undergone two or more bone scans within one year at the Department of Nuclear Medicine, Aalborg University Hospital, were identified from the hospital records (103). Patients were then selected according to the following criteria: 1) patients were treated with either ADT, NGH, or chemotherapy; and 2) patients had two BS performed within the same treatment, a baseline BS and a follow-up BS. The baseline BS was performed within three months before initiation of therapy or a maximum 14 days within treatment. The follow-up BS was performed 12-52 weeks within treatment for patients receiving ADT and 12-30 weeks within treatment for patients receiving NGH or chemotherapy. Patients treated successively with different treatments and with more than one BS pair fulfilling the above criteria were allowed to enter the study twice (103).

A total of 105 patients were identified from the hospital records. Of these, 55 patients with 63 evaluable BS pairs fulfilled the above criteria and were included in the final analyses (103).

Study III

Patients from Study I who had completed all study-related procedures were included in Study III along with consecutive patients with confirmed bone metastases (by

clinical evaluation) scheduled to receive either primary ADT, NGH, or chemotherapy. The latter patients were included in a separate protocol approved by the Regional Research Ethics committee (N-20140057) and the Danish Data Protection Agency. Eligibility criteria for this protocol were as follows: 1) histologically confirmed PCa; 2) bone metastases on BS at inclusion; 3) clinical life expectancy > six months; 4) no other cancer within five years; and 5) ability to comply with study procedures.

A total of 64 patients were included in the final analysis in this study, 23 of which originated from Study I.

3.2. METHODS

3.2.1. SCANS

All scans were performed according to current institutional guidelines, which are consistent with European and International guidelines (41-43, 46). Scans were performed at Aalborg University Hospital or at Regional Hospital West Jutland Herning.

3.2.1.1 Planar Whole-Body Bone Scan

Aalborg

Bone scans were performed on Symbia dual-head gamma cameras with multi-purpose, low-energy, high-resolution collimators (Symbia T16, Siemens Medical Solutions, Erlangen, Germany). Data acquisition was performed two to three hours after intravenous administration of 750-1000 MBq ^{99m}Tc-labelled diphosphonate, with a scan speed of 24 cm/min. The use of an alpha blending technique allowed for an apparent increase in counts by a factor of two, thus accounting for the faster acquisition time in Aalborg.

Herning

Bone scans were performed on Symbia dual-head gamma cameras with multi-purpose, low-energy, high-resolution collimators (Symbia T2 and T16, Siemens Medical Solutions, Erlangen, Germany). Data acquisition was performed two to three hours after intravenous administration of 10 MBq/kg ^{99m}Tc-labelled diphosphonate, with a scan speed of 10 cm/min.

3.2.1.2 SPECT/CT

Aalborg

A three-bed SPECT/CT scan, from vertex to mid-thigh, was performed immediately following the planar imaging using the following parameters: matrix 128 x 128, zoom factor 1, 20 s per view, 32 views, and rotation of the detectors by 180 degrees in a non-circular orbit using step-and-shoot mode. A low-dose CT without intravenous contrast was acquired and used for attenuation correction and anatomical co-registration: 30 mA, 130 kV, slice thickness 3 mm.

Herning

A three-bed SPECT/CT scan, from vertex to mid-thigh, was performed immediately following the planar imaging using the following parameters: matrix 128 x 128, zoom factor 1, 10 s per view, 64 views, and rotation of the detectors by 180 degrees in a non-circular orbit in a continuous mode. The low-dose CT had the following parameters: reference mA 100 (CARE dose), 130 kV, and a slice thickness of 5 mm.

3.2.1.3 NaF PET/CT

Aalborg

Patients were scanned on a dedicated VCT discovery True 64 PET/CT, (GE Healthcare). Scans were performed after intravenous administration of 200 MBq NaF in 3D mode from vertex to mid-thigh, encompassing 7-9 bed position (150 s per bed position). The images were reconstructed by iterative construction, using low-dose CT images for attenuation correction and anatomical co-localisation. The CT parameters were 70-200 mA smart mA, 120 kV. The slice thickness was 0.625 mm.

Herning

Patients were scanned on a dedicated Biograph mCT 64, 4R PET/CT (Siemens Medical Solutions). All scans were performed 30 minutes after intravenous administration of approximately 200 MBq NaF in 3D mode from vertex to mid-thigh, encompassing 7-9 bed positions (120-180 s per bed position according to body mass index). Images were reconstructed as in Aalborg, using low-dose CT images for attenuation correction and anatomical co-localisation. The CT parameters were 30 mAs, 120 kV. The slice thickness was 0.625 mm.

3.2.2. IMAGING SCHEDULE

Study I

Patients were scanned at baseline and after 26 weeks of therapy. Patients were routinely referred for BS for staging purposes. As an add-on, the three-bed SPECT/CT was performed immediately after the BS. NaF PET/CT was then performed. All scans had to be performed before or a maximum of 14 days within treatment. After 26±4 weeks, all three scans were repeated, and these data were used to assist in the determination of a final diagnosis (102). Figure 2 shows the scan times and the number of patients scanned at each time-point.
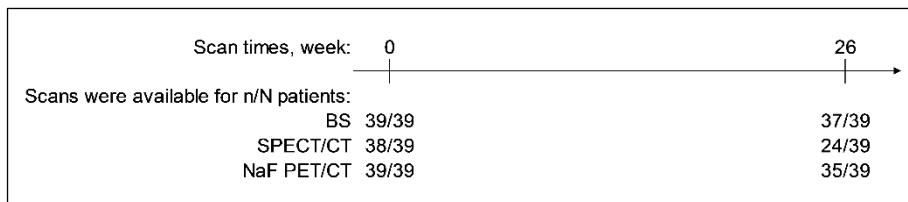
Figure 2 An overview of scan times in Study I, and the number of scans available for evaluation at each time-point. BS, bone scan; SPECT/CT, single-photon emission computed tomography / computed tomography; NaF PET/CT, ^{18}F-sodium fluoride positron emission tomography /CT.

3.2.2.1 Study II

See Study Population, section 3.1, Study II (103).

Study III

Before initiation of either ADT, NGH, or chemotherapy, patients were routinely referred for BS for assessment of bone metastases status. Additionally, a NaF PET/CT scan was performed no later than 14 days within treatment. These constituted the baseline scans. Including the baseline scans, imaging with BS and NaF PET/CT was performed 2-4 times within a 26-week time period for patients receiving ADT or NGH and 2-3 times within a 20-week time period for patients receiving chemotherapy. Figure 3 shows the scan times and the number of patients scanned at each time-point by treatment.
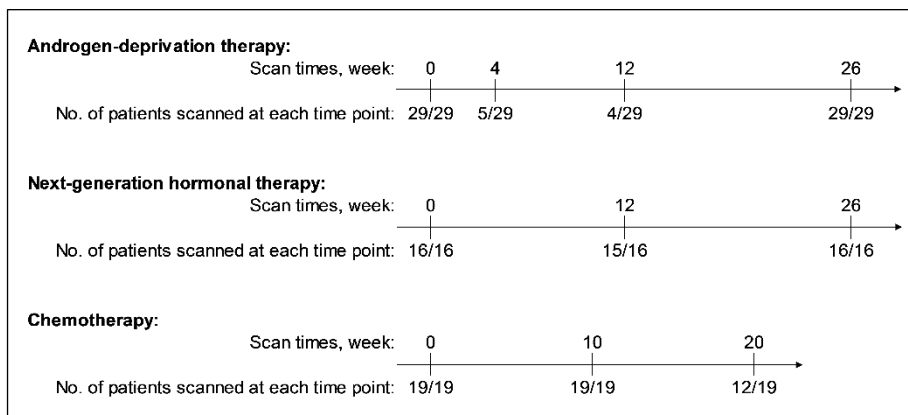
Figure 3 An overview of scan times for Study III, and the number of evaluable scans at each time point according to treatment. This includes patients who had both a bone scan and a ^{18}F-sodium fluoride positron emission tomography/computed tomography at each time point.

3.2.3. IMAGE ANALYSIS

For all three studies, specific forms and guides for completion of these were designed. These are presented in Appendices A-C.

Study I
Expert readings

Two nuclear medicine specialists with more than 10 years of experience with BS evaluated all BS images. Likewise, two nuclear medicine specialists with 5 and 10 years of experience with NaF PET/CT evaluated all NaF PET/CT images. Readers were blinded to any clinical and biochemical information regarding the patients, except for the diagnosis of high-risk PCa. Readers were first asked to rate the images on a three-point scale of benign (M0), equivocal (Me), or malignant (M1) and subsequently on a dichotomous scale of M0 or M1. The readers were then asked to indicate if the patient had more than 10 suspicious bone lesions or a scan compatible with superscan. Finally, the readers were asked to draw lesions on a schematic drawing of the skeleton if the patient had 10 or fewer suspicious bone lesions. The readers used the form included in Appendix A-1 and were guided by A-2. In cases of disagreement, the readers performed a consensus reading.

Reference standard

To determine the final diagnosis, a multidisciplinary committee consisting of experienced specialists, a urologist, a radiologist and a nuclear medicine physician reviewed all relevant and available information about each patient. The reference standard was thus a compilation of the following:

1) Results of the expert readings
2) All available baseline and follow-up imaging
3) All available biochemical information about the patient
4) A standard questionnaire filled out routinely with each BS including information about any bone-related disease or trauma, joint replacements, and any unexplained bone pain.
5) If necessary, any existing routine imaging was also made available if a final diagnosis could not be determined based on points 1-4.

The multidisciplinary committee used the form included in Appendix A-3.

Study II

Five experienced nuclear medicine physicians participated in the evaluation of images in Study II (103). Two readers evaluated each baseline and follow-up image individually (Appendix B-1). Images were evaluated for the presence of bone metastases (M0/M1) and the number of suspicious lesions within five skeletal regions (skull, thorax incl. sternum, columna, pelvis, and extremities incl. scapula). Readers were asked to count up to 20 lesions within each region (103), and these counts were subsequently reclassified according to the extent of disease classification

Soloway et al. (104). Each pair of baseline and follow-up images was then evaluated side-by-side for response using three different methods for response evaluation; readers classified patients according to specific response categories as shown in Table 3 and Appendix B-2, B-3, B-4 (103).

The image pairs were evaluated three times by three different methods. Therefore, to account for the bias that the readers could remember an image pair, the image pairs were evaluated by two different readers for each response evaluation method. For instance, for Patient 1, readers 1 and 2 evaluated the images by Standard Clinical Assessment, readers 3 and 4 evaluated them by MD Anderson criteria, and readers 5 and 1 evaluated them by the PCWG-2 criteria (103).

Table 3 Response assessment methods and categories

Response criteria	Response categories
Standard clinical assessment	Regressive disease *-Regression of lesions/disappearance of hot spots* Stable disease *-No change* Progressive disease *-Progression of lesions/new lesions*
MD Anderson (80)	Complete response *-Disappearance of hot spots or tumour signal* Partial response *-Regression of lesions* Stable disease *-No new lesions* Progressive disease *-New lesions or increased activity*
Prostate Cancer Working Group 2 (83)	Non-progressive disease *-No or maximum one new lesion* Progressive disease *-Two or more new lesions, confirmed on subsequent scan (if one existed)*

Study III

The same nuclear medicine specialists who performed the expert readings in Study I evaluated all BS and NaF PET/CT images in Study III. Readers received careful instructions on how to evaluate images (Appendix C-1).

As in Study II, readers first determined the presence of bone metastases (M0/M1) and the number of bone metastases in the following intervals: 0, 1, 2-4, 5-9, 10-20, or >20 (modified from Soloway et al (104)) (Appendix C-2). The readers were then asked to evaluate images for response using modified PCWG-2 criteria (Table 3). The baseline scan was evaluated side-by-side with the first follow-up scan (Appendix C-3). In the case of PD, the second follow-up scan (if one existed) was used to confirm the presence of PD (Appendix C-4). In the case of non-PD, the baseline and the second follow-up scan (if one existed) were evaluated side-by-side (Appendix C-5), and then the third follow-up scan (if present) was used to confirm any PD. Additionally, readers were asked to rate the images according to Standard Clinical Assessment as described in Table 3 and Appendix C-1 to C-5.

3.2.4. BIOCHEMICAL MEASUREMENTS (STUDIES I AND III)

Prostate specific antigen

In Study I, blood levels of PSA were measured at baseline and at each subsequent set of follow-up scans. The same applied for patients receiving ADT or NGH in Study III. For patients receiving chemotherapy in Study III, PSA was measured at several varying time points during the study according to clinical practice.

Changes in PSA were classified according to the PCWG criteria as non-PD or PD. Non-progressive disease included PSA response (a decrease in PSA of > 50%) and stable disease (decrease in PSA of $\leq$ 50% or increase < 25%). Progressive disease included drifters (initial PSA response followed by progression, with a $\geq$ 25% increase in PSA from nadir) and progressive disease (an increase in PSA of $\geq$ 25% from nadir).

Testosterone

In Study I, testosterone levels were measured at baseline and at each subsequent set of follow-up scans. This was done to ensure that levels fell below castration levels during treatment, thus confirming that the treatment was effective in performing a medical castration, even in cases of progressing PSA levels.

In Study III, the same as above applied for patients receiving ADT. For patients receiving NGH, the testosterone levels were measured to ensure that patients were correctly classified as having CRPC. As it had no clinical significance, testosterone levels were not measured in patients receiving chemotherapy.

3.2.5. CLINICAL RESPONSE ASSESSMENT (STUDY III)

Assessment of clinical response to therapy was performed retrospectively based on patient charts. The responsible urologist reviewed charts for all patients receiving ADT or NGH and the responsible oncologist reviewed charts for patients receiving chemotherapy. Clinical response was based on changes in performance status, pain and other cancer-related symptoms. Response was assessed on a three-point scale: regression, stable disease, or progressive disease.

3.2.6. STATISTICS

Data are presented only on a patient level, and no lesion-based analyses were performed for this PhD thesis. Statistical analysis was performed using StataIC version 13 (StataCorp LCC, TX, USA) and Microsoft Office Excel 2013.

Study I
Sample size was based on recommendations for sample size calculations in DTA studies (102, 105). Sensitivity, specificity, and positive and negative predictive values were calculated for all three imaging modalities, BS, SPECT/CT, and NaF PET/CT, and presented with 95% confidence intervals (CI). The diagnostic performances were compared using McNemar's test.

Study II
Agreement between assessments of the presence of bone metastases and for response evaluations was calculated using Cohen's kappa (106). The terminology by Landis and Koch was used to evaluate the extent of agreement according to kappa values, where 0.00-0.20: slight; 0.21-0.40: fair; 0.41 – 0.60: moderate; 0.61 – 0.80: substantial; and 0.81 – 1.00: almost perfect agreement (107). These are presented with 95% CIs as well. Bland-Altman plots (108) were constructed to assess the difference between readers when counting the number of bone lesions on BS within five skeletal regions (103).

Study III
The proportions of PD vs non-PD for BS and NaF PET/CT, biochemical and clinical response assessments were compared using the McNemar test with $p < 0.05$ considered statistically significant. Data are presented with 95% CIs. Agreement between BS and NaF PET/CT for response evaluation was evaluated by Cohen's kappa for the total study population. Crude agreement was presented for the individual treatment groups.

CHAPTER 4. RESULTS

A brief summary of the main results of each paper is presented below. Detailed description of the results are found in the individual papers.

4.1. PAPER 1

[18]F-fluoride positron emission tomography/computed tomography and bone scintigraphy for diagnosis of bone metastases in newly diagnosed, high-risk prostate cancer patients: study protocol for a multicentre, diagnostic test accuracy study.

Randi F. Fonager, Helle D. Zacho, Niels C. Langkilde and Lars J. Petersen

BMC Cancer (2016) 16:10. DOI 10.1186/s12885-016-2047-1 (102)

Summary
Study I was a fully STARD-compliant DTA study. Paper 1 presents the study protocol, which includes detailed descriptions of the study design, the study population and rationale for selection of patients. Furthermore, it includes descriptions of imaging procedures and a detailed plan for image analysis.

4.2. PAPER 2

Diagnostic test accuracy study of ^{18}F-sodium fluoride PET/CT, 99mTc-labelled diphosphonate SPECT/CT, and planar bone scintigraphy for diagnosis of bone metastases in newly diagnosed, high risk prostate cancer.

Randi F. Fonager, Helle D. Zacho, Niels C. Langkilde, Joan Fledelius, June A. Ejlersen, Christian Haarmark, Helle W. Hendel, Mine Benedicte Lange, Mads R. Jochumsen, Jesper C. Mortensen, and Lars J. Petersen.

Manuscript under revision.

Summary

In a completely STARD-compliant DTA study, the diagnostic performance of NaF PET/CT, SPECT/CT and BS was compared in 37 newly diagnosed high-risk PCa patients (PSA $\geq$ 50 ng/mL). The prevalence of bone metastases in this study was 73%. More than 10 bone metastases were found by at least one imaging modality in 74% of patients. NaF PET/CT and SPECT/CT numerically outperformed BS with regard to sensitivity, specificity, PPV and NPV. The sensitivities were 78% for BS, 89% for SPECT/CT, and 89% for NaF PET/CT, and the specificities were 90%, 100%, and 90%, respectively. The PPVs for BS, SPECT/CT and NaF PET/CT were 96%, 100%, and 96%, and the NPVs were 60%, 77% and 75%, respectively. No statistically significant difference between the three imaging modalities was observed. In addition to the dichotomous classification of images, the images were evaluated with an equivocal rating option. The proportion of equivocal results was low for all three imaging modalities but lowest for NaF PET/CT (5% vs 11% for SPECT/CT and BS). In conclusion, all three imaging modalities showed high sensitivity and specificity. NaF PET/CT and SPECT/CT showed numerically improved, but not statistically superior, sensitivity compared with BS in this limited and selected patient cohort. In conclusion, SPECT/CT and NaF PET/CT can be used for the diagnosis of bone metastases on an equal level as BS.

4.3. PAPER 3

Observer agreement of treatment responses on planar bone scintigraphy in prostate cancer patients: importance of the lesion assessment method.

Randi F. Fonager, Helle D. Zacho, Signe Albertsen, Joan Fledelius, June A. Ejlersen, Mette H. Christensen, Ramune Aleksyniene, José A. Biurrun Manresa, and Lars J. Petersen.

Summary

The observer agreement for treatment response assessment on BS was investigated in 63 paired BS from 55 patients. Treatment response was assessed by three different methods: 1) Standard clinical assessment; 2) MD Anderson criteria for bone response; and 3) PCWG-2 criteria. Furthermore, observer agreement for the presence of bone metastases and number of bone metastases at baseline was investigated. This study showed that the observer agreement for treatment response assessment was highest when using the PCWG-2 criteria, which showed substantial to almost perfect agreement (Cohen's kappa 0.84, 95% CI: 0.69–0.99). When using standard clinical assessment, observer agreement was moderate (Cohen's kappa 0.52, 95% CI: 0.36-0.69). Moderate agreement was also found for the MD Anderson criteria (Cohen's kappa 0.60, 95% CI: 0.44–0.77). Evaluation of baseline images for the presence of bone metastases showed almost perfect agreement (Cohen's kappa 0.94, 95% CI: 0.82-1.00). There was a large variation for lesion counting at the patient level. The difference in lesion count from one reader to another could be as high as ±15 lesions depending on the skeletal region. This variation seemed to increase with an increasing number of lesions. In conclusion, response evaluation by individual counting of lesions on baseline and follow-up images cannot be recommended. The use of strict criteria, such as the PCWG-2 criteria, for assessment of treatment response evaluation by BS is therefore recommended (103).

4.4. PAPER 4

Prospective, comparative study of ^{18}F-sodium fluoride PET/CT and planar bone scintigraphy for treatment response in prostate cancer.

Randi F. Fonager, Helle D. Zacho, Niels C. Langkilde, Joan Fledelius, June A. Ejlersen, Helle W. Hendel, Christian Haarmark, Mette Moe, Jesper C. Mortensen, Mads R. Jochumsen and Lars J. Petersen

Manuscript in preparation

Summary

In this study, the agreement between NaF PET/CT and BS for treatment response assessment by the PCWG criteria was investigated in PCa patients undergoing various palliative anti-cancer treatments at different stages of PCa. Furthermore, the concordance between imaging (NaF PET/CT and BS), biochemical (PSA) and clinical response was evaluated. There was no statistically significant difference in the proportion of patients showing PD on BS vs NaF PET/CT (p=0.18). Analysis by Cohen's kappa showed moderate agreement between BS and NaF PET/CT for classification of PD vs non-PD (Cohen's kappa: 0.53). Crude agreement between NaF PET/CT and BS for assessment of treatment response in bone from baseline to last follow-up scan was 86%. There was a trend that with more advancing PCa, crude agreement decreased, i.e., crude agreement was 89% for ADT, 88% for NGH, and 80% for chemotherapy. When considering all intermediate scans and hence the time point for detection of PD, crude agreement decreased even further for NGH and chemotherapy: 75% and 70%, respectively. Most often, BS detected PD when NaF PET/CT did not, or BS detected PD on an earlier scan compared with NaF PET/CT. There were no statistically significant differences between the proportions of patients showing PD on BS and NaF PET/CT compared with PSA and clinical progression. Further studies are needed to investigate the use of NaF PET/CT for response monitoring of bone metastases in PCa and validation of NaF PET/CT for response assessment is necessary before this modality can be recommend for this purpose.

CHAPTER 5. DISCUSSION

The overall aim of this PhD thesis was to evaluate BS, SPECT/CT and NaF PET/CT for diagnosis and monitoring of bone metastases in PCa. More specifically, the aim was to compare BS, SPECT/CT and NaF PET/CT for diagnosis of bone metastases in PCa (Study I), to evaluate observer agreement for evaluation of treatment responses on by three different methods for classification of response (Study II), and to compare BS and NaF PET/CT for monitoring of bone metastases in PCa (Study III).

Diagnostic performance

Diagnosis of bone metastases is crucial for PCa patient management. It is therefore extremely important that diagnostic tests have a sufficiently high sensitivity to detect even small bone metastases and hence a low number of false negative results. Similar to previous DTA studies (Table 2) (31, 32, 37-40), the results of Study I showed a high sensitivity for all three imaging modalities. On a patient level, the sensitivity of SPECT/CT and NaF PET/CT numerically outperformed the sensitivity of BS (89% and 89% vs 78%, respectively). This was expected due to the inherent improved image quality of the latter imaging modalities, i.e., three-dimensional images, CT for attenuation correction and anatomical co-localisation, the improved spatial resolution of PET/CT, and the higher target-to-background ratio gained with NaF PET/CT.

The specificity of a diagnostic test is likewise of great importance. The specificity reflects the proportion of patients who are correctly identified as not having the disease, i.e., a high specificity reflects a low number of false positive results. The results of Study I showed that the specificity of NaF PET/CT was equal to that of BS (90%). This was in contrast to other studies, which have mostly demonstrated improved specificities of NaF PET/CT over BS (Table 2) (50, 51, 56-59). An even higher specificity was demonstrated by SPECT/CT (100%). The high specificity of BS in Study I, compared with previous studies, can in part be ascribed to the low number of patients without bone metastases in this study. However, it can also be explained by the experience of the expert readers who had more than 10 years of experience with BS reading starting before SPECT/CT became available as an add-on to BS. Therefore, these readers are likely to provide confident and unequivocal answers to BS.

The rationale for conducting this DTA study was the lack of properly designed large studies that adequately demonstrate the diagnostic performance of SPECT/CT and NaF PET/CT. Such evidence is needed for clinical guidelines to include these imaging modalities as options for diagnosis of bone metastases in PCa. Even if Study I did not achieve the goal of 114 evaluable patients, this study was large among comparable studies, and it was conducted with stringent procedures in accordance with the STARD guideline for DTA studies. The major challenge with DTA studies in imaging has been the lack of a proper reference standard. It must be realised, though, that

without histological verification of all potential bone metastases, a single, unambiguous gold standard is utopian (68, 69). Thus, a reference standard based on the findings on the index test as a guide for determining the final diagnosis and a well-documented stringent procedure, as in Study I, can be considered sufficient to determine the final diagnosis.

The diagnostic performance of BS, SPECT/CT and NaF PET/CT would most likely be different in an unselected population of newly diagnosed PCa patients or patients with recurrent disease following radical prostatectomy. However, a metastasis-enriched population was selected in Study I to optimize the sample size and statistical power (102). Study I was planned to include a high number of patients, which in combination with a methodologically sound design should have been able to provide firm evidence of the equal or superior diagnostic performances of SPECT/CT and NaF PET/CT for the diagnosis of bone metastases. Study I was prematurely ceased due to the realisation that recruitment of 114 patients was unlikely to be achieved within a realistic timeframe. Although Study I was large among similar studies, the power was limited due to the small number of patients in the study (50, 51, 56-58, 60, 91). The impaired recruitment in Study I could in part be ascribed to the decrease in the proportion of newly diagnosed patients with high-risk PCa that has occurred during the past few decades (3, 109, 110). Furthermore, it is known that high-risk patients are likely to show symptoms of morbidity (10, 11, 111), which may make patients reluctant to participate in studies that require additional procedures.

SPECT/CT is generally associated with a long acquisition time, thus causing additional discomfort to the patient. Recently, it was demonstrated that when using SPECT/CT for assessment of inconclusive bone lesions on BS the acquisition time of SPECT/CT can be reduced to as little as three minutes without compromising the diagnostic confidence of the examination (112). Thus, the discomfort of add-on SPECT/CT is notably reduced. This supports the use of SPECT/CT as an add-on to BS to gain an increased specificity of the examination. NaF PET/CT might be more comfortable for patients because the waiting time from injection of the tracer to the scan is shorter compared with BS (30-60 min vs 2-4 h for BS) and additionally NaF PET/CT has a faster acquisition time.

As mentioned above, Study I included the results of the index tests in the determination of a final diagnosis, thus causing a slight risk of bias with circular reasoning in the final decision making. However, as mentioned, it can be argued that without the results of the index test as a guide for final decision making, a firm reference standard is difficult to obtain in imaging studies, even if guidelines for DTA studies, such as STARD, recommend otherwise (71). Aside from this, a major strength of Study I was the strict methodology, which was in complete compliance with the STARD recommendations. Therefore, even in the absence of a single, large DTA study with a high level of evidence that shows the improved diagnostic performance of SPECT/CT and NaF PET/CT over BS, it can be argued that the existing body of

evidence and the results of Study I provide sufficient evidence of this. SPECT/CT and NaF PET/CT can be considered as equal to BS for diagnostic purposes in PCa, and clinical guidelines should embed these imaging modalities for bone metastases staging in PCa with equal recommendations as those for BS.

Treatment response assessment

Assessment of treatment responses in bone is, as previously mentioned, an important aspect of patient management both in daily clinical practice and in clinical trials. Just as for the diagnosis of bone metastases, clinical guidelines and the PCWG recommend the use of BS for treatment response assessment in PCa. The methods for classifying responses have varied, and different response assessment methods have been presented. In addition, a high level of agreement between readers for response classification is extremely important, since progression on BS often is a determining factor for ceasing or continuing a treatment or investigational drug. However, observer agreement has not been investigated in the assessment of treatment responses in bone metastases from PCa.

The results of Study II showed that inter-observer agreement according to Cohen's kappa for bone response assessment was substantial/almost perfect when using the PCWG-2 criteria (Cohen's kappa: 0.84). Agreement was moderate when using standard clinical assessment, as per daily clinical routine (Cohen's kappa: 0.52), or the MD Anderson criteria (Cohen's kappa: 0.60) (103). Standard clinical assessment and the MD Anderson criteria both have more response categories than PCWG-2, which by definition is associated with lower kappa values. However, agreement did not change when reclassifying these response classifications into non-PD vs PD. Thus, it is obvious that agreement for classification of response to treatment benefitted from the application of stringent criteria like the PCWG-2 (103). The results of Study II were consistent with the few existing studies on observer agreement for treatment response assessment in bone (93, 98).

There is no general consensus on how to report treatment responses in clinical practice, but the results of Study II suggest that a uniform approach using stringent criteria will be beneficial for patient management by providing the most consistent results. Therefore, strict criteria should be used both in clinical trials and in clinical practice for treatment response assessment of bone metastases in PCa (103). The study population in Study II was mixed and included patients undergoing different anti-cancer treatments and the small study population did not allow for subgroup analysis of variations in inter-observer agreement depending on disease state or treatment (103). This could have been an interesting perspective, as it has the potential to influence the results of future studies and recommendations for the use of response classification methods. Nonetheless, the results of Study II did demonstrate a substantial to almost perfect inter-observer agreement when using the PCWG criteria, and the PCWG criteria are becoming widely accepted for the evaluation of bone metastases treatment response in clinical trials (103, 113). This is well supported by

the fact that progression on BS according to the PCWG-2 criteria is associated with impaired survival (87). Overall, this suggests, that the PCWG criteria might be the ideal choice for future application in clinical trials and daily clinical practice.

The results from Study II on observer agreement clearly demonstrated that the PCWG criteria provided the most consistent results for evaluation of treatment response on BS (103). Based on these results, it was decided that the PCWG criteria should be used in Study III and in an exploratory setting, Study III prospectively compared the concordance between BS and NaF PET/CT for treatment response assessment in PCa. As mentioned, NaF PET/CT is not currently included in the clinical guidelines for the diagnosis or monitoring of bone metastases. The 2010 guideline from the Society of Nuclear Medicine stated that the role of NaF PET/CT is to be determined (46), while the 2015 European Association of Nuclear Medicine procedure guideline for NaF PET/CT recommended the use of NaF PET/CT for both diagnoses of bone metastases and for evaluation of treatment responses in bone metastases (43). However, no studies have directly compared the use of BS and NaF PET/CT for treatment response assessment in bone metastases.

The results of Study III showed that there are some non-statistically significant variations in response classification between BS and NaF PET/CT and in the timing of progression occurrence. Agreement between BS and NaF PET/CT was moderate for the classification of PD/non-PD from baseline to last follow-up scan when using the PCWG criteria (Cohen's kappa 0.53). In most cases where BS and NaF PET/CT showed discordance, BS detected PD when NaF PET/CT did not, or BS detected PD at an earlier time-point than NaF PET/CT, e.g., BS showed PD on the first follow-up scan while NaF PET/CT did not detect PD until the second follow-up scan. There was a trend that crude agreement declined with more advanced stages of PCa, i.e., CRPC for which the PCWG criteria were developed. This trend was even more evident when all individual scans were taken into consideration i.e., first, second and sometimes third follow-up scan. It is commonly known that NaF PET/CT detects a higher number of bone metastases than BS (56, 59). The discordance between BS and NaF PET/CT might therefore, in some cases be due to the appearance of new lesions on follow-up BS that were already visible on baseline NaF PET/CT, thus accounting for the classification of PD on BS but not on NaF PET/CT.

When using standard clinical assessment to determine bone response, overall crude agreement between BS and NaF PET/CT from baseline to last follow-up scan was lower than when using the PCWG criteria, this was expected since standard clinical assessment has more response categories than the PCWG criteria (Table 3). Like for the PCWG criteria, standard clinical assessment also demonstrated decreased agreement with advancing PCa stages.

Previous studies that have investigated treatment response on NaF PET/CT have focused on post-treatment changes in SUV inspired by the PERCIST criteria (99-101).

However, there is no universally agreed-upon reference level for changes in SUV that is considered significant, and no studies have investigated the impact of SUV changes on patient management. Other methods for quantification of NaF PET/CT have recently been presented (114, 115). Quantitative methods for evaluation of treatment response on NaF PET/CT are interesting, especially if small and clinically significant changes can be detected early during treatment. However, quantitative evaluation of NaF PET/CT remains under investigation and this was beyond the scope of this PhD thesis.

Study III was limited by the small number of patients, and this precluded formal statistical subgroup analysis of the individual treatment groups. Sub-group analyses would have been interesting in light of the trend that crude agreement between BS and NaF PET/CT decreased with advancing PCa stages, i.e., CRPC patients, especially those receiving chemotherapy. Larger studies are encouraged to show variations for different anti-cancer treatments as this might be critical for the validation of NaF PET/CT for bone response assessment, especially when using the PCWG criteria.

Clinical guidelines (5, 6) and PCWG-3 (24) emphasize that NaF PET/CT should be validated for bone response assessment before it can be recommended along with BS. This is supported by the results of Study III, which showed that there were some variations in the classification of bone response between BS and NaF PET/CT. The results of Study II demonstrated a high level of agreement between readers for evaluation of bone response on BS by the PCWG criteria (103) and it has previously been demonstrated that PD on BS, when assessed by the PCWG criteria, is associated with impaired OS (87). Therefore, recent recommendations of BS for bone response evaluation in PCa by PCWG-3 (24) and clinical guidelines (5, 6) are well substantiated. Combined, this indicates a need for further investigation of bone response assessment by NaF PET/CT. This is relevant both when assessing images on a visual basis, like in Study III, as well as when using quantitative methods for assessment of changes, such as SUV. In addition, even though a change in management was reported in up to 53% of PCa patients following NaF PET/CT (47) , a proper investigation is necessary to determine whether bone response assessment by NaF PET/CT is associated with improved patient outcome.

In conclusion, larger studies on NaF PET/CT for response assessment with a focus on patient outcome are encouraged, and until the results of NaF PET/CT have been validated, BS should be retained as the primary modality for bone response assessment.

CHAPTER 6. CONCLUSIONS

SPECT/CT and NaF PET/CT show apparent improved diagnostic performance over BS. If feasible, both SPECT/CT and NaF PET/CT can be used as modalities equal to BS for the detection of bone metastases in PCa, and they should be adopted in future clinical guidelines.

Observer agreement on bone response shows the least variation when using stringent criteria that distinguish only non-PD from PD and the use of stringent criteria should be encouraged for treatment response evaluation in clinical trials as well as in clinical practice. The PCWG criteria will likely become the standard approach in the future.

Treatment response assessment by NaF PET/CT should be investigated further to determine the association with patient outcomes, e.g., OS and changes in patient management. The recommendations for the use of BS for bone response assessment are well substantiated, and until NaF PET/CT has been validated for bone response assessment, NaF PET/CT cannot be recommended for bone metastases monitoring in PCa.

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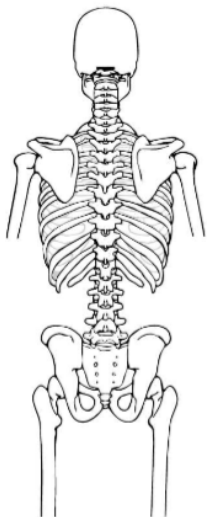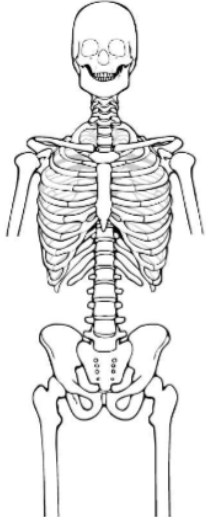
APPENDICES

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Appendix A. Study I assessment forms

A-1. Initial expert readings

Knoglevurderingsskema - Aalborg projekter

Patient ID (Aa-xxx)		Initialer vurderende læge:	

1. Afkryds venligst for begge skalaer: Ved udelukkende findes benigne fund, foretages ikke yderligere.

3-kategori skala:
Knoglemetastaser?
- ☐ M0 - Normal/Benign
- ☐ Me - Equivocal/tvetydig
- ☐ M1 - Knoglemetastaser

Dikotom skala:
Knoglemetastaser?
- ☐ M0 - Nej
- ☐ M1 - Ja

2. Er der flere end 10 sikre knoglemetastaser og/eller tvetydige læsioner?
   Nej ☐   Ja ☐   Superscan ☐
   Hvis Nej, udfyld punkt 3, 4 og 5. Hvis Ja eller Superscan, foretages intet yderligere!

3. Angiv venligst antal knoglemetastaser pr. område i skemaet herunder, inkl. tvetydige (benigne læsioner angives IKKE):

	Kranie inkl. ansigt	Thorax (Costae + sternum)	Columna	Pelvis Inkl. os sacrum	Ekstremiteter inkl. scapula
Me - Tvetydige læsioner					
M1 - Sikre knoglemetastaser					

4. Indtegn lokalisation af knoglemetastaser på skelettet (benigne læsioner angives IKKE):

NMA
Nuclear Medicine Aalborg

5. For hver enkelt indtegnet læsion; angiv om der er CT korrelat (se vejledning)

Knoglevurderingsskema – Aalborg v. 1.0 – 14. marts 2016

Vejledning til Knoglevurderingsskema – Aalborg projekter

SKEMAET UDFYLDES MED RØD TUSCH/PEN

Patient ID = koden der står listet under "Patient Name" og/eller "Patient ID" i scan-filerne.

Initialer vurderende læge: Skrives tydeligt med blokbogstaver.

1. **Afkrydsning venligst for begge skalaer:** Vurder først scanningen med 3-kategori skalaen.

   - Normal/benign = blank eller udelukkende benigne fund
   - Equivocal/tvetydig = det kan ikke afgøres om fund på scan er benigne eller maligne (ved equivocal/tvetydige fund – udfyldes pkt. 3-5 også).
   - Knoglemetastaser = det vurderes at fund på scan med al sandsynlighed er knoglemetastaser.

   Vurder herefter scanningen på den dikotome skala. Angiv om du vurderer, at der på scan er knoglemetastaser "Ja" eller der ikke er "Nej"

2. **Er der flere end 10 sikre knoglemetastaser?** Angiv "Ja", "Nej" eller "Superscan". Hvis der i pkt. 2 svares "Ja" eller "Superscan" er du færdig for denne patient. Hvis der svares "Nej", fortsættes der til pkt. 3 og 4.

3. **Angiv venligst antal maligne metastaser pr område i skemaet herunder (benigne læsioner angives ikke):** Tæl læsioner for hvert område og angiv antal i skemaet. Ses der udelukkende equivocal/tvetydige læsioner, skal disse angives disse i skemaet. Angiv også hvis der er nul knoglemetastaser.

4. **Indtegn lokalisation af maligne metastaser på skelettet (benigne læsioner undtages).** Indtegn alle malignitets-suspekte læsioner (IKKE benigne), men også equivocal/tvetydige.

5. **For hver enkelt indtegnet læsion; angiv om der er CT korrelat:** Gælder for alle læsioner indtegnet under pkt. 4. Dette gøres med en streg, ud fra hvilken der tydeligt angives CT+ eller CT÷. CT korrelatet (CT+) skal understøtte konklusionen om, at det er en knoglemetastase, fx. udgør læsioner nær led ikke en knoglemetastase, ligesom sammenfaldne hvirvler heller ikke gør.

   NB! Ved uenighed (både på patient og læsions-niveau) udføres konsensus-vurdering. Nyt skema udfyldes. Herpå angives initialer for begge vurderende læger og evt. "konsensus".

Eksempel; patient der har færre end ti sikre knoglemetastaser og/eller tvetydige læsioner.

Knoglevurderingsskema - Aalborg projekter

Patient ID (Aa-xxx)	Aa-001	Initialer vurderende læge:	RFF

1. Afkrydsning venligst for begge skalaer: Ved udelukkende findes benigne fund, foretages ikke yderligere.

3-kategori skala: Knoglemetastaser?	Dikotom skala: Knoglemetastaser?
☐ M0 - Normal/Benign	☐ M0 - Nej
☐ Me - Equivocal/tvetydig	☒ M1 - Ja
☒ M1 - Knoglemetastaser	

2. Er der flere end 10 sikre knoglemetastaser og/eller tvetydige læsioner?
   Nej ☒   Ja ☐   Superscan ☐
   Hvis Nej, udfyld punkt 3, 4 og 5. Hvis Ja eller Superscan, foretages intet yderligere!

3. Angiv venligst antal knoglemetastaser pr. område i skemaet herunder, inkl. tvetydige (benigne læsioner angives IKKE):

	Kranie inkl. ansigt	Thorax (Costae + sternum)	Columna	Pelvis inkl. os sacrum	Ekstremiteter inkl. scapula
Me - Tvetydige læsioner	0	0	0	0	0
M1 - Sikre knoglemetastaser	0	1	0	3	0

4. Indtegn lokalisation af knoglemetastaser på skelettet (benigne læsioner angives IKKE):

   (Me)CT +
   CT +
   CT +
   CT +
   CT +
   NMA

5. For hver enkelt indtegnet læsion; angiv om der er CT korrelat (se vejledning):

Vejledning til udfyldelse af Knoglevurderingsskema - Aalborg v. 1.0 - 14. marts 2016

A-3. Final diagnosis

Konsensuskomité vurdering - Aalborg projekter

Patient ID:

Mulighed for indtegning lokalisation af knoglemetastaser på skelettet:
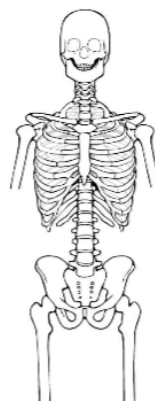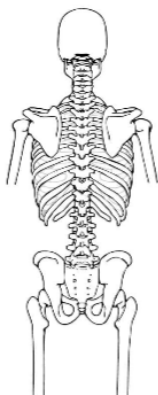
Noter til projektskanninger og klinisk information:

_____
_____
_____
_____
_____
_____

Kan der på baggrund af projektscanninger samt klinisk information afgives svar på om patienten har

knoglemetastaser eller ej?   Ja ☐   Nej ☐

Hvis Ja: har patienten knoglemetastaser?

Ja ☐   Nej ☐

Hvis Nej: Yderligere informationer findes.

Noter til yderligere information:
_____
_____

På baggrund af de yderligere informationer, har patienten knoglemetastaser?

Ja ☐   Nej ☐

Initialer   Urolog Niels Chr. Langkilde
konsensusgruppedeltagere   Radiolog Benedicte Lange
                                    Nuklearmediciner Helle D. Zacho

Konsensuskomité-vurdering – Aalborg v. 1.0 – 3. juni 2016

Appendix B. Study II assessment forms

B-1. Individual assessment of baseline and follow-up images

	Ja	Nej
Maligne knoglemetastaser Sæt kryds		

	Kranie inkl. ansigt	**Thorax (Costae + sternum)**	**Columna**	**Pelvis Inkl. os sacrum**	**Ekstremiteter inkl. scapula**
Antal maligne knoglemetastaser Angiv antal, også hvis nul "0"					

Initialer: Med blokbogstaver		**Patient nr:** Udfyldes af Randi

B-2. Standard Clinical Assessment

	Regression	Uændret	Progression
Almen klinisk Sæt kryds			

Initialer Med blokbogstaver		**Patient nr:** Udfyldes af Randi

B-3. MD Anderson criteria

	Komplet respons Alle hotspots og tumor signaler er forsvundet	Partielt respons Regression af læsioner (ekskluder hurtig regression)	Uændret Ingen nye læsioner (ekskluder flare)	Progression Nye læsioner (ekskluder flare) eller øget intensitet	
MDA Sæt kryds				Nye læsioner	
				Øget intensitet	

Initialer Med blokbogstaver		**Patient nr:** Udfyldes af Randi	

B-4. Prostate Cancer Working Group 2 criteria

	Non-progression	Progression 2 ≥ Nye læsioner
PCWG-2 Sæt kryds		

Initialer Med blokbogstaver		**Patient nr.** Udfyldes af Randi

Appendix C. Study III Assessment forms
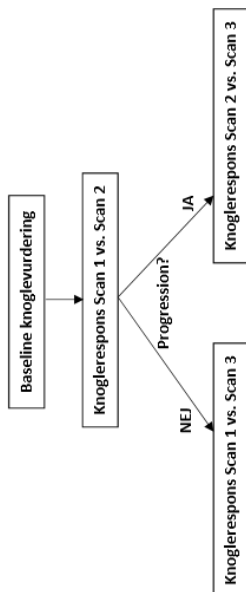
C-1. Guide for assessment of images in Study III

Vejledning til udfyldelse af Knoglerespons Vurderingsskemaer – Aalborg projekter

SKEMAET UDFYLDES MED RØD TUSCH/PEN

Patient ID = koden der står listet under "Patient Name" og/eller "Patient ID" i scan-filerne.

Initialer vurderende læge: Skrives tydeligt med blokbogstaver.

Udfyld skemaerne i følgende orden:

[Baseline knoglevurdering]

[Knoglerespons Scan 1 vs. Scan 2]

Progression?

NEJ → [Knoglerespons Scan 1 vs. Scan 3]

JA → [Knoglerespons Scan 2 vs. Scan 3]

Baseline knoglevurdering
1. Angiv ved afkrydsning om patienten på Scan 1 har knoglemetastaser eller ej (M0/M1). Hvis M1, optælles antallet af metastaser i de angivne intervaller, ved afkrydsning.

Knogle-respons Scan 1 versus Scan 2
1. Angiv ved afkrydsning om der er progression iht. PCWG-2 kriterierne.
2. Hvis der findes nye læsioner indtegnes op til 5 nye læsioner på skelet-tegningen. Dette skal være de 5 nye læsioner med størst intensitet/størrelse.
3. Angiv til sidst, ved afkrydsning, en subjektiv vurdering af om patienten viser regression, stabil sygdom eller progression.
4. Hvis der iht. PCWG-2 kriterierne vurderes at være progression bruges Scan 3 til at vurdere om denne progression kan verificeres. Hvis der ikke er progression sammenholdes scan 1 med scan 3, for da at vurdere om der er progression på dette tidspunkt.

Knoglerespons Scan 2 vs. Scan 3:
1. Angiv ved afkrydsning om fundet af progression på Scan 2 kan bekræftes ved gennemgang af Scan 3. Det vil sige, at mindst to af de nyopståede metastaser der blev lokaliseret på Scan 2 også er at finde på Scan 3.
2. Angiv ved afkrydsning, en subjektiv vurdering af om patienten viser regression, stabil sygdom, progression fra Scan 2 til Scan 3.

Knogle-respons Scan 1 vs. Scan 3:
1. Vurderes ligesom Scan 1 vs. Scan 2:
2. Angiv ved afkrydsning om der er progression iht. PCWG-2 kriterierne.
3. Hvis der findes nye læsioner indtegnes op til 5 nye læsioner på skelet-tegningen. Dette skal være de 5 nye læsioner med størst intensitet/størrelse.
4. Angiv til sidst, ved afkrydsning, en subjektiv vurdering af om patienten viser regression, stabil sygdom eller progression.

Patienter med fire scanninger
Scan 4 vurderes efter følgende principper:
1. Ved progression på Scan 2, som er bekræftet på Scan 3, vurderes Scan 4 ikke.
2. Ved progression på Scan 2, som ikke er bekræftet på Scan 3 sammenholdes Scan 2 med Scan 4 for at bekræfte fund på Scan 2.
3. Ved progression på Scan 3, sammenholdes Scan med Scan 4 for at bekræfte fund på Scan 3.
4. Hvis der ikke er fundet progression på Scan 2 og Scan 3 sammenholdes Scan 1 med Scan 4, for at identificere om der er her er nyopstået progression.

NB! Ved uenighed (både på patient og læsions-niveau) udføres konsensus-vurdering. Nye skemaer udfyldes. Herpå angives initialer for begge vurderende læger og evt. "konsensus".

Vejledning knoglerespons vurderingsskemaer - Aalborg v. 1.0 16. august 2016

C-2. Baseline images

Baseline knoglevurderingsskema - Aalborg projekter

Patient ID		Initialer vurderende læge:	

1. **Er fund på Scan 1 forenelig med knoglemetastaser?**

   ☐ M0 - Nej

   ☐ M1 - Ja

2. <u>Hvis Ja</u>, angiv venligst antallet af knoglemetastaser:

1	2-4	5-9	10-20	>20
☐	☐	☐	☐	☐

C-3. Baseline vs first follow-up scan

Vurderingsskema knoglerespons - Aalborg projekter
Scan 1 vs. Scan 2

Patient ID		Initialer vurderende læge:	

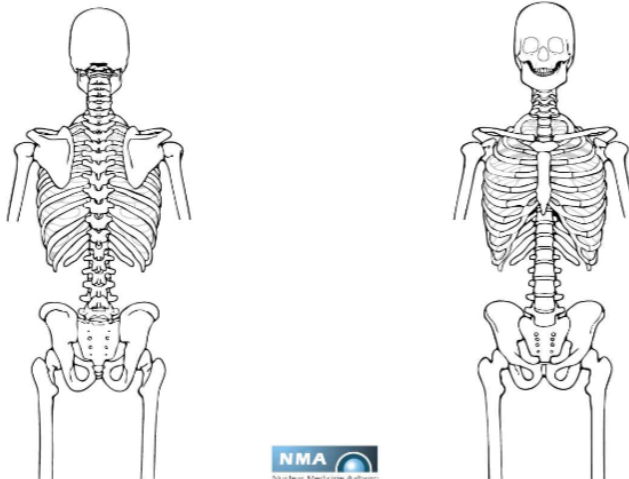1. **Iht. PCWG-2 kriterier, vurder venligst om der er progression**
   Non-progression: ingen eller maksimalt én nytilkommet knoglemetastaser
   Progression: to eller flere nytilkomne knoglemetastaser

   Afkryd iht. PCWG-2:
   ☐ Non-progression (Ingen eller maks. én nytilkommet metastase)
   ☐ Progression (≥2 nytilkomne knoglemetastaser)

2. **Hvis progression (≥2 ny knoglemetastaser): Angiv venligt lokalisation af op til 5 nye foci på nedenstående skelet:**

NMA
Nuclear Medicine Aalborg

3. **Klinisk vurdering**

Regression	Stabil Sygdom	Progression
☐	☐	☐

Knoglerespons scan 1 vs. scan 2 – Aalborg v. 1.0 – 12. august 2016

C-4. First follow-up scan vs second follow-up scan

Knoglerespons - vurderingsskema - Aalborg projekter
Scan 2 vs. Scan 3

Patient ID		Initialer vurderende læge:	

1. **Iht. PCWG-2 kriterier, bekræft venligst progression fundet på Scan 2.**
   Mindst to af de nytilkomne knoglemetastaser der blev identificeret på Scan 2 er tillige at finde på Scan 3.

Kan fund af to nye metastaser på Scan 2 bekræftes?
☐ **Nej**, ingen eller maks. én af de nytilkomne knoglemetastaser på Scan 2 kan identificeres på Scan 3
☐ **Ja**, mindst to af de nytilkomne knoglemetastaser identificeret på Scan 2 er til stede på Scan 3

1. **Klinisk vurdering**

Regression	Stabil Sygdom	Progression
☐	☐	☐

Knoglerespons scan 2 vs. scan 3 – Aalborg v. 1.0 – 12. august 2016

C-5. Baseline vs second follow-up scan

Vurderingsskema knoglerespons - Aalborg projekter
Scan 1 vs. Scan 3

Patient ID		Initialer vurderende læge:	

1. **Iht. PCWG-2 kriterier, vurder venligst om der er progression**
   <u>Non-progression:</u> ingen eller maksimalt én nytilkommet knoglemetastaser
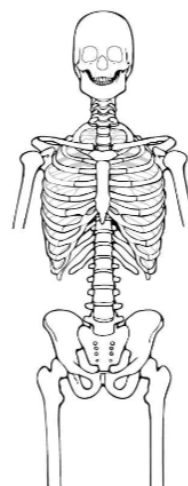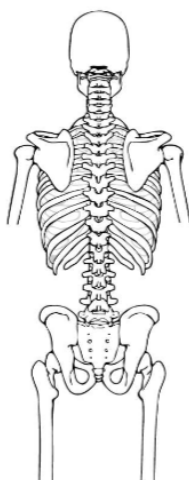   <u>Progression:</u> to eller flere nytilkomne knoglemetastaser

   Afkryd iht. PCWG-2:

   ☐   Non-progression (Ingen eller maks. én nytilkommet metastase)

   ☐   Progression (≥2 nytilkomne knoglemetastaser)

2. **Hvis progression (≥2 ny knoglemetastaser): Angiv venligst lokalisation af op til <u>5 nye</u> foci på nedenstående skelet:**

NMA
Nuclear Medicine Aalborg

3. **Klinisk vurdering**

Regression	Stabil Sygdom	Progression
☐	☐	☐

Knoglerespons scan 1 vs. scan 3 – Aalborg v. 1.0 – 12. august 2016