EANM
European Association of Nuclear Medicine

BIOMEDICAL IMAGING AND THERAPY FOR PERSONALIZED HEALTHCARE

PROSTATE CANCER IMAGING AND THERAPY

A TECHNOLOGIST'S GUIDE

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SNMMI SOCIETY OF NUCLEAR MEDICINE AND MOLECULAR IMAGING TECHNOLOGIST SECTION

Foreword

Individualised medicine and tailored treatment solutions are nowadays unimaginable without diagnostic imaging. The development and implementation of disease-specific tracers within nuclear medicine has impacted on patient clinical management and positively affected the lives of thousands of patients all over the globe.

Nuclear medicine technologists are specialised professionals who perform or are involved in a number of procedures, including radiopharmaceutical labelling, patient management, image reconstruction and radiation safety.

The multidisciplinary effort in nuclear medicine to discover new molecules with a significant clinical impact is well known through the recent research and developments with respect to diagnostic and therapeutic radiopharmaceuticals for use in prostate cancer.

As a reference scientific body in Europe, the European Association of Nuclear Medicine (EANM), and its Technologist Committee (EANMTC), has had the privilege of gathering top quality clinical scientists, technologists, physicians, physicists, radiochemists, radiopharmacists and dosimetrists whose coordinated effort has culminated in this guide. Such an ongoing joint effort is the reason behind the acknowledged wide readership for past editions of *A Technologist's Guide* (TG) and the extremely positive response that EANM receives every year concerning this publication.

This year's edition of the TG celebrates a return to clinical applications, being totally focussed on one pathology in which nuclear medicine is deeply involved. The motivation for the content design of this TG was the desire to explore the multidisciplinary approach to prostate cancer, from preclinical studies with animal models through to established diagnostic and therapeutic methodologies. The guide accordingly provides a complete overview

of the nuclear medicine vision regarding prostate cancer, from anatomy to clinical tracers, with consideration of both conventional nuclear medicine and PET/CT and both fluorine-18 and non-fluorine-18 tracers. The role of nuclear medicine with respect to external radiotherapy is also discussed in this TG, as are a range of therapeutic and theranostic applications. Likewise, patient-focussed practice and translational medicine chapters are presented.

I would like to express my gratitude for the collective effort of all authors who participated in this publication. Special thanks are due to the EANM Technologist, Oncology, Radiopharmacy, Dosimetry and Translational Molecular Imaging & Therapy Committees involved in this venture, without whom the truly multidisciplinary nature of this book could not have been realised. From overseas my gratitude extends to the Society of Nuclear Medicine and Molecular Imaging Technologist Section (SNMMI-TS) and I would also like to thank the European Society of Radiotherapy & Oncology (ESTRO) Radiation Therapist (RTT) Committee for their valuable contribution.

Lastly, I am very much indebted to the EANM-TC editorial group, to Rick Mills for copyediting assistance and to the EANM Board and Executive Office for their continuous support on one of the most significant and well-received projects to originate from our committee.

Pedro Fragoso Costa
Chair of the EANM Technologist Committee

Introduction

Prostate cancer is the second most common cancer in men worldwide. Due to increasing life expectancy and the introduction of more sensitive diagnostic screening techniques, prostate cancer is being diagnosed more frequently, with rapidly increasing incidence and prevalence. It has a wide spectrum of biological behaviour, ranging from indolent low-risk disease to highly aggressive castration-resistant prostate cancer.

Nuclear medicine imaging plays a key role in this heterogeneous disease as it can answer key clinical questions at various phases of the disease, the imaging being tailored to each phase. Nuclear medicine has demonstrated efficacy for cancer detection, with an increasing number of potential targets for imaging and treatment.

The first chapter of this book describes the prostate's anatomy, physiology and pathology. The radiopharmaceuticals that allow study or treatment of prostate cancer are discussed in the subsequent chapter. Conventional nuclear medicine represents a cost-effective resource in the management of prostatic disease, and the third chapter documents the specific imaging procedures for diagnostic planar imaging and hybrid SPECT/CT. The following two chapters provide an overview on protocols and the diagnostic value of PET/CT imaging using fluorine-18 and other non-fluorine-18 radioisotopes labelled with different molecules. PET/CT is a useful tool for guided radiotherapy planning; consequently the sixth chapter describes the acquisition and reconstruction protocol for the purpose of radiotherapy. One of the most recent developments in nuclear medicine is theranostics: the seventh chapter reviews the state of the art, describing the use of theranostic pairs and quantitative analysis of tissue and tumour uptake in optimisation of patient treatment. The eighth chapter broadens the vision of the field of therapy, adding treatment based

on alpha-emitting radionuclides. Nuclear medicine technologists play an important part in the multi-professional management of the prostate cancer patient. In addition to being directly involved in therapy through the performance of various roles, they are responsible for other tasks such as patient preparation and imaging processing. The ninth chapter describes the clinical pathway of the patient in order to improve understanding of the technologist's tasks.

The recent advances in prostate cancer specific tracers were significantly supported by the advent of translational medicine. With this in mind, the final chapter explains how molecular and non-invasive preclinical imaging become rapidly emerging fields in preclinical cancer drug research and development.

We hope that this overview of the state of the art of nuclear medicine imaging and therapy in prostate cancer will provide a valuable resource for all technologists and clinical staff involved in this field.

The EANM Technologist Committee would like to thank all the authors who have kindly offered their time and expertise, which have been fundamental to the creation of this book.

Luca Camoni
on behalf of the editors

1

ANATOMY, PHYSIOLOGY AND PATHOLOGY OF THE PROSTATE

by Lucia Zanoni, Cristina Nanni and Stefano Fanti

INTRODUCTION

The prostate is a glandular and muscular structure positioned immediately below the neck of the bladder and around the commencement of the urethra. It is located within the pelvic cavity, below the inferior margin of the symphysis pubis and above the triangular ligament, anterior to the rectum. Its base is below the neck of the bladder and is directed upwards, whereas the apex touches the ligament and is directed downwards. Its posterior surface is close to the second part of the rectum, whereas its anterior surface is connected to the pubis by puboprostatic ligaments. The lateral surfaces are in contact with the levator ani muscles[1].

The prostate consists of two lateral lobes, equal in dimension, and a third middle lobe, which lies in the central posterior region. It is surrounded by a thin, fibrous capsule separated by a plexus of veins from the rectovesical fascia. Immediately below the capsule, there is muscular tissue, which is also seen around the urethra. The prostate derives its arterial supply from the internal pudic, vesical and haemorrhoidal arteries, while the venous drainage starts from the dorsal vein of the penis and terminates into the internal iliac vein. The nerve supply of the prostate is from the pelvic plexus (inferior hypogastric plexus). The intraprostatic portion of the urethra is the most dilatable part of the canal[2].

DEVELOPMENT AND PHYSIOLOGY

Prostate development occurs through a series of sequential steps dependent on systemic steroid hormone signals, local paracrine signalling pathways and cell autonomous factors. The prostate is an exocrine gland whose role is part of the male reproductive function in mammals. The mouse has emerged as the most important model system for investigation of prostate organogenesis. The first steps in prostate development are the male-specific molecular and morphological changes in the urogenital sinus, the embryonic precursor of the prostate in males and precursor of part of the vagina in females. Organ determination is mediated by male-specific gene expression changes in the urogenital sinus in response to androgen signalling. Epithelial budding is the first morphological step in prostate development, in which cords of undifferentiated epithelial cells from the urogenital sinus epithelium invade the surrounding urogenital sinus mesenchyme. Following budding, the developing prostatic buds elongate via proliferation at the distal

bud tips. Lumen formation also occurs in proximal (adjacent to the urethra) to distal fashion to form prostatic ducts. Prostatic ducts then undergo multiple rounds of branching morphogenesis during the development process.

Unlike the prostate in mice, the human prostate is not organised into discrete lobes; it also has a different tissue organisation, with epithelial ducts surrounded by a dense and continuous fibromuscular stroma. Early molecular studies identified several paracrine signalling pathways as playing key roles in prostatic development, including components of the transforming growth factor beta, fibroblast growth factor, bone morphogenetic protein, insulin-like growth factor and sonic hedgehog pathways. Further early studies involved transcription factors, including the androgen receptor, homeobox genes and Nkx3.1. Various differentiated epithelial cell types are present within the adult prostate (i.e. luminal, basal and relatively rare neuroendocrine cells). Androgens and androgen receptors are critical for normal prostate development, and they function in the normal adult prostate to maintain organ integrity and the expression of prostate-specific secretory proteins[3–5].

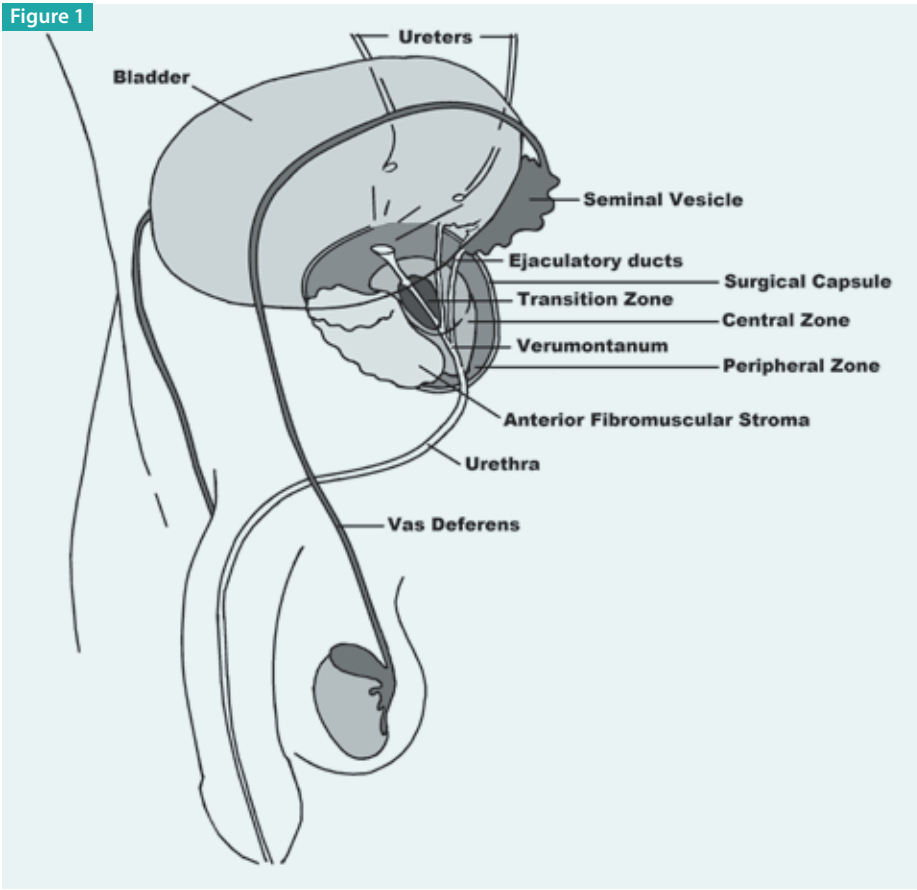
A crucial role in the hormonal regulation of the prostate is played by the hypothalamus, which produces releasing factors (luteinising hormone releasing factor, follicle stimulating hormone-releasing factor and prolactin inhibiting factor) and thus controls the synthesis and release by the pituitary of various gonadotropins (luteinising hormone, follicle stimulating hormone) that influence the production of testosterone by the testes. The majority of testosterone production in adult human males derives from the testes and it plays a crucial role in prostatic growth and physiology. A further, though minor role is played by the adrenal cortex through its steroid production. Moreover, prolactin produced by the adenohypophysis has a direct effect on the prostate[6].

ANATOMY

McNeal divided the prostate into three major areas that are histologically distinct and anatomically separate: the non-glandular fibromuscular stroma and two glandular regions called the peripheral and central zones that contain a complex and histologically distinct ductal system (Fig. 1).

The *anterior fibromuscular stroma* is a band of fibromuscular tissue anterior to the transition zone, contiguous with the bladder smooth muscle and the skeletal muscle of the sphincter and continuous with the pseudocapsule. It covers the anterior and anterolateral surfaces of the gland and comprises dense irregular connective tissue with a large amount of smooth mus-

Figure 1



cle fibres interposed with adjacent skeletal muscle fibres of the urethra.

The central zone is a layer of tissue that surrounds the ejaculatory ducts from the level of the prostatic base down to the verumontanum. The central zone ducts run predominantly proximally, closely following the ejaculatory ducts. It is most prominent at the base of the prostate and has a conical shape. Embryologically, it originates from the wolffian duct. It accounts for 25% of the total prostate volume but almost 40% of the epithelium owing to its high epithelial-to-stromal ratio; how-

ever, after the age of 35 years its volume decreases gradually. Compared with the peripheral zone, the glands of the central zone are larger and more complex, with much denser and more compact stroma. Central zone cancers are rare, accounting for 0.5%–2.5% of all prostate cancers and 3%–8% of index tumours, but are usually associated with a higher risk.

The *peripheral zone* constitutes the remainder of the gland, surrounding most of the central zone and extending inferiorly to partially surround the distal tract of the urethra. It is a derivative of the urogenital sinus. Its ducts exit directly laterally from the posterolateral recesses of the urethral wall. The system consists of ducts and acini that are lined with simple columnar epithelium. This area represents the main site of origin of prostatitis and prostate cancer, although not of benign prostatic hyperplasia (BPH). It includes the proximal urethral segment of the prostate, between the base of the urinary bladder and the verumontanum (the area where the ejaculatory ducts feed into the urethra). This small region also includes the preprostatic sphincter, a cylindrical sleeve of smooth muscle which extends from the base of the bladder to the verumontanum.

The *surgical capsule (pseudocapsule)* is a layer of compressed tissue between the hyperplastic transition zone and the surrounding peripheral zone, whereas the *true prostate capsule* surrounds the peripheral zone.

The *neurovascular bundles* are located posterolateral to the prostate bilaterally and penetrate into the prostate at the apex and base. They consist of cavernous nerves for erectile function, arterial branches of the inferior vesicle artery and veins. In the setting of cancer, they provide a route for extraprostatic spread of malignancy[7].

The *periprostatic venous plexus* (also known as the Santorini venous plexus) is contiguous to the pseudocapsule of the prostate and lies mainly anterior and lateral to the gland. The calibre of the veins varies and is usually larger in younger patients and smaller glands.

The *periprostatic lymph nodes* are not common, being detected in 4.4% of radical prostatectomy specimens. Most commonly they are located at the base of the prostate laterally or posterolaterally. Malignant involvement of the periprostatic lymph nodes has been documented in 15% of patients who undergo radical prostatectomy[8].

PRACTICAL INTEGRATED APPROACH TO PROSTATE ANATOMY

On imaging studies of the prostate, there is a lack of correlation between the images seen routinely and the lobar or zonal

descriptions of prostatic anatomy. From a radiological viewpoint, there are two important subdivisions of the prostate, the peripheral zone and the central gland. Using this terminology, the central gland contains both the central and transition zones, which are present in varying proportions depending on the degree of BPH. In young men, the central gland is composed mainly of the central zone, whereas in older men with BPH it is composed mainly of the transition zone. The definition of the central gland as the combination of the peri-urethral, central and transition zones is somewhat arbitrary but has the clear advantage of corresponding to findings on imaging and therefore is the most useful radiologically.

MAIN PATHOLOGIES AFFECTING THE PROSTATE

A significant overlap can exist in the clinical history and imaging findings associated with prostate disorders; therefore biopsy is often warranted for final diagnostic confirmation. However, many diseases also have distinct imaging features which can be recognised.

Neoplasms

A wide variety of neoplasms occur in the prostate, both benign and malignant. The World Health Organisation's histological classification of tumours[9] categorises them by cellular origin: epithelial, neuroendocrine, prostatic stromal, mesenchymal, miscellaneous and haematolymphoid[7, 10].

Prostate cancer. Currently prostate cancer (PCa) is the second most commonly diagnosed cancer in men, accounting for 15% of all cancers diagnosed. The highest incidence of PCa diagnosis is in Australia/New Zealand and Northern America and in Western and Northern Europe. A family history of the disease is associated with an increased incidence of PCa, and incidence is also related to racial/ethnic background. This suggests a genetic predisposition; however, less than 10% of PCa patients have true hereditary disease (defined as three or more affected relatives, or at least two relatives who have developed early-onset PCa). Genetic studies have identified 100 common susceptibility loci and germline mutations in genes such as *BRCA1/2 and HOXB13* that are associated with a higher risk of PCa. Furthermore, while a wide variety of dietary and environmental factors have also been discussed, no effective preventive dietary or pharmacological interventions are currently available. The 2009 TNM classification for staging of PCa, the EAU risk group classification and the International Society of Urological Pathology (ISUP) 2005 modified Gleason score are the recommended

grading systems for PCa and all three are widely used[11]. The key histological features of PCa are increased cellular density, decreased luminal volume, reduced extracellular space and neoangiogenesis.

Cystadenoma. Most patients with this rare benign tumour initially present with urinary obstruction or a palpable abdominal mass. Aspiration usually yields haemorrhagic fluid and histiocytes but no malignant cells.

Stromal tumour of uncertain malignant potential (STUMP). STUMPs are rare proliferative lesions of the prostatic stroma. There are several subtypes with a wide range of biological behaviours and an unpredictable clinical course. The lesions are large, well circumscribed and heterogeneous and may arise from any prostatic zone. It is difficult to differentiate a STUMP from a prostate sarcoma, and less aggressive forms of STUMP may even mimic BPH nodules. Patients usually undergo surgical resection because of the potential aggressiveness.

Sarcoma. Only 0.1%–0.2% of all primary prostatic neoplasms are accounted for by sarcomas. Most are of mesenchymal origin but in rare cases they arise from the prostatic stroma. Patients often present with rapid onset of urinary obstruction or a palpable mass and the prognosis is poor. Sarcomas generally appear as well-circumscribed masses of large size and heterogeneous appearance, with areas of central necrosis due to the rapid growth. Many sarcomas demonstrate a partial or complete pseudocapsule which separates the tumour from the adjacent compressed periprostatic fat. A rim of fibrosis due to an inflammatory reaction may also be detected. Rhabdomyosarcoma is the most common type (42%), especially in children and adolescents. Embryonal rhabdomyosarcomas are typically large lobulated masses that often protrude into the bladder, whereas the more aggressive alveolar form appears more infiltrative and less well defined. Leiomyosarcoma accounts for 25% of sarcomas, mainly in adults, with early pulmonary and hepatic metastases. Prostate sarcomas are rarely confused with adenocarcinoma, given their large size and heterogeneous appearance and, in the case of rhabdomyosarcoma, their manifestation in a different age group.

Urothelial carcinoma (or transitional cell carcinoma). Urothelial carcinoma originates from the prostatic ducts or acini and accounts for 2%–4% of all prostate cancers. It usually presents as a synchronous or metachronous tumour associated with urothelial carcinoma of the bladder or urethra.

Prostatic carcinoid. Along with small cell carcinoma, large cell neuroendocrine carcinoma and focal neuroendocrine differentiation in prostate adenocarcinoma,

prostatic carcinoid is one of the four rare manifestations of neuroendocrine malignancy of the prostate. It demonstrates true neuroendocrine differentiation with classic chromogranin A and synaptophysin immunoreactivity. Patients do not present with an elevated prostate-specific antigen (PSA) level and the clinical history is fairly indolent.

Paraganglioma. Paragangliomas are extremely rare extra-adrenal phaeochromocytomas that develop from extra-adrenal chromaffin cells, from the parasympathetic tissue adjacent to and behind the prostate. They are associated with several familial syndromes (i.e. multiple endocrine neoplasia IIA and IIB, neurofibromatosis 1, von Hippel-Lindau syndrome, Carney complex and familial paraganglioma). Patients with functional tumours often present the classic triad of headache, tachycardia and sweating associated with catecholamine production.

Sarcomatoid carcinoma and carcinosarcoma. These are rare biphasic tumours (accounting for less than 0.1% of prostate cancers) that show a mixture of sarcomatous and carcinomatous features, the latter usually in the form of a high-grade adenocarcinoma. Differential diagnosis can be critical but sarcomatoid carcinoma may be supposed on the basis of a lobulated tumour with areas of cystic degeneration. Carcinosarcoma is considered one of the most aggressive prostate malignancies, the mean survival after diagnosis being only 7 months regardless of the form of therapy.

Ductal or endometrioid adenocarcinoma. Despite the postulated müllerian origins of the tumour, patients often present with an elevated PSA level. Ductal carcinoma is the most common histological variant of prostate carcinoma. In most studies, the prognosis of ductal adenocarcinoma has been observed to be worse than that of typical acinar adenocarcinoma, a finding probably related to the higher stage and grade of the ductal subtype.

Mucinous adenocarcinoma. Mucinous adenocarcinomas account for approximately 0.4% of prostatic cancers. Unlike typical acinar adenocarcinomas, mucinous tumours characteristically present a proteinaceous fluid content. Originally, such tumours were thought to be more aggressive than typical acinar adenocarcinoma but this hypothesis was finally excluded.

Metastatic involvement of the prostate by primary carcinomas of other organs. Involvement of the prostate occurs rarely as a result of direct extension of tumours in adjacent organs or dissemination of disease involving multiple organs. Bladder urothelial carcinoma is most commonly responsible owing to the proximity of the

bladder; colorectal cancer is the next most frequent source, but such cases are much less frequent.

Benign disorders

Benign entities affecting the prostate are associated with variable clinical manifestations and in some cases are indistinguishable from prostate cancer at standard imaging. They may even present extraprostatic extension and lymphadenopathy, mimicking locally advanced prostate cancer[7, 10].

Benign prostatic hyperplasia (BPH). BPH is a benign proliferation of prostatic epithelial and stromal cells of the transition zone, which form large hyperplastic nodules. These nodules are most commonly seen in the transition zone but occasionally can protrude into the peripheral zone or even beyond the prostate as an exophytic pelvic/bladder mass. BPH is exclusively a disease of the non-peripheral prostate and therefore does not involve the prostate distal to the verumontanum [12].

Bacterial prostatitis. Both acute and chronic cases of bacterial prostatitis are possible. Acute bacterial prostatitis is uncommon and more likely to occur in young men. It is characterised by an influx of neutrophils and originates from intraprostatic reflux of urine infected by *Escherichia coli, Enterococcus* or *Proteus* or from instrumentation (i.e. prostatic biopsy). Undertreated acute prostatitis and recurrent infection may cause chronic bacterial prostatitis, which can also occur in older men without a prior history but presenting with lower urinary tract obstruction. Lymphocytes are usually detected in chronic prostatitis, often accompanied by glandular atrophy. The chronic form tends to be more indolent, with lower urinary tract symptoms and no systemic symptoms, unlike in the acute form. It is important to be aware that (a) bacterial prostatitis is most commonly visualised in the peripheral zone but can also occur in the transition zone, (b) enlarged reactive lymph nodes may be present and (c) a clinical history of urinary and/or sexual symptoms, a fluctuating PSA level or PSA response to antibiotics can alert the practitioner to the fact that the origin is bacterial and not carcinomatous.

Granulomatous prostatitis. The following types of granulomatous prostatitis may occur: idiopathic (the most common type, divided into non-specific and non-necrotic), infective (specific, non-necrotic or necrotic), iatrogenic (postsurgical), malacoplakia and associated with systemic granulomatous disease. Its hallmark is histiocytoid granulomas with central necrotising or fibrinoid necrosis, surrounded by infiltrative eosinophils. Infective granulomatous prostatitis can be caused by *Mycobacterium tuberculosis* or develop after intravesical bacillus Calmette-Guérin therapy

for bladder cancer. It is characterised by well-formed granulomas with epithelioid cell and multinucleated giant cell infiltration with or without central necrosis (caseation). Rarer causative organisms are *Treponema pallidum*, viruses (herpes zoster) and fungi *(Cryptococcus, Candida, Aspergillus)*. Non-necrotic granulomatous prostatitis is highly cellular and may simulate prostate cancer at standard imaging. Malacoplakia is a rare granulomatous inflammatory condition associated with recurrent infection. It predominantly affects the genitourinary tract, particularly the renal collecting system.

Pyogenic abscess. This is the most common complication of bacterial prostatitis. Patients usually present with fever, dysuria, pain and fluctuation at digital rectal examination. A complex collection may be seen, with increased peripheral vascularity.

Fungal abscess. Prostatic fungal infections are commonly seen only in immunocompromised patients, and in particular in the setting of concomitant renal abscesses. These abscesses are indistinguishable from pyogenic abscesses on the basis of imaging alone and a confirmatory diagnosis is often made on the basis of the results of a urine or aspirate culture. Prolonged multi-agent systemic antifungal therapy is necessary.

Prostatic amyloidosis. This is a disease of uncertain cause that is characterized by extracellular deposition of amyloid. Prostatic amyloidosis can be interpreted as a secondary sign of prostate inflammation. The identification of localized disease prompts the need for a systemic disease workup.

Prostatic cyst. Various cystic entities may be seen within the prostate, all with different embryological origins and clinical implications. When a cyst is pear shaped and is detected in the midline of the prostate, it may be either a prostatic utricle cyst or a müllerian duct cyst (as an embryological remnant of the müllerian duct or urogenital sinus), which are virtually indistinguishable at imaging. Paramedian cysts are usually ejaculatory duct cysts (that arise congenitally or secondary to duct obstruction), while most lateral cysts are retention cysts (from dilatation of glandular acini secondary to small duct obstruction) or cystic degeneration of BPH (more common and usually multiple). In the setting of a cystic lesion in the prostate, it is important to exclude an abscess, cystic degeneration of a neoplasm and pseudocyst secondary to a neoplasm. If there is haemorrhage, internal complexity or a solid component within the cyst, further workup for malignancy is warranted.

Atrophy. Histological subtypes of atrophy include simple, sclerotic with cyst formation and post-atrophic hyperplastic. Focal atrophy, more frequently occurring

in the peripheral zone, may mimic prostate malignancy owing to its complex glandular architecture. It may be caused by inflammation, radiation, anti-androgens or chronic ischaemia due to local arteriosclerosis.

Necrosis. Necrosis can occur secondary to treated infective prostatitis or focal therapy of prostate cancer (radiofrequency ablation, cryoablation, high-intensity focused ultrasound, irreversible electroporation, laser ablation). It is characterised by central well-defined coagulative necrosis of glands and stroma, with peripheral chronic inflammatory cellular infiltrate and atrophy.

Calcification. Prostatic calcification may arise due to precipitation of prostatic secretions or calcification of the corpora amylacea. Extraprostatic cases are due to a phlebolith in the periprostatic venous plexus. In the context of BPH calcification is more frequent at the junction between the transitional and the peripheral zone.

Haemorrhage. Areas of haemorrhage may occur after biopsy, especially in the peripheral zone. Tumours display a lower rate of biopsy haemorrhage (2%–10.5%) than normal tissue owing to the reduction in the anticoagulant effect of citrate, which is produced within the prostate.

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2

CLINICAL RADIOPHARMACEUTICALS FOR PROSTATE CANCER

by Martin Behe

INTRODUCTION

This chapter describes the radiopharmaceuticals used for the diagnosis and treatment of prostate cancers, covering logistics, biochemical characteristics and mechanism of action. One may distinguish two major types of radiopharmaceutical according to their mechanism of action: metabolic radiopharmaceuticals, the accumulation of which reflects the metabolism at the site of interest, and targeted radiopharmaceuticals, which target specific proteins overexpressed on prostate cancer cells.

Prostate cancer is one of the most common cancers. After early detection, prostatectomy and/or radiation is the most promising therapeutic approach, with 80% of patients remaining free of recurrence for 7 years. However, at the time of diagnosis 12% of patients already have metastatic spread to the lymph nodes or to other organs, and such patients have a shorter survival time[1]. It is therefore important to have a tool available that can detect metastatic and recurrent lesions at an early time point and in addition offer these patients an effective therapeutic option. Radiotracers play an important role in this situation: they both permit the stratification of prostate cancers and may be applied therapeutically. Radiotherapeutic tracers have long played an important role in the palliative treatment of painful bone metastases, but in recent years targeted radiotherapy via proteins overexpressed on the cell membrane has also been used successfully in various clinical trials. In the case of prostate cancer, the main targets are prostate-specific membrane antigen (PSMA) and gastrin-releasing peptide receptor.

During the preparation and application of radiopharmaceuticals, the relevant national regulations always have to be followed and it is recommended that the rules of current good radiopharmaceutical practice are taken into consideration[2].

PET AND SPECT IMAGING RADIOPHARMACEUTICALS

Sodium [^{18}F]fluoride

Sodium [^{18}F]fluoride (Na[^{18}F]F) is a bone-seeking positron-emitting tracer which has been used for skeletal imaging since the early 1970s[3]. Although technical issues limited its use for a long time, more routine use has been established for some years, a trend that has occurred in conjunction with greater availability of medical cyclotrons and positron emission tomography (PET) scanners[3].

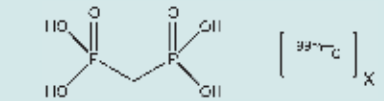
As regards the mechanism of uptake, following chemisorption of fluoride ions

onto the surface of hydroxyapatite, they exchange with the hydroxyl (OH–) ions in the crystal, forming fluoroapatite[3]:

$$Ca_5(PO_4)_3OH + F^- \rightarrow Ca_5(PO_4)_3F + OH^-$$

The uptake of Na[^{18}F]F, which has a half-life ($T_{1/2}$) of 110 min, reflects the blood flow and the bone metabolism. The tracer can be directly produced using a medical cyclotron by purification after irradiation of oxygen-18 labelled water. The maximum recommended adult dose, delivered by intravenous injection, is 1.5–3.7 MBq/kg, with a maximum injected dose of 370 MBq for obese patients. In children, 2.2 MBq/kg is administered, with a minimum activity of 18.5 MBq and a maximum of 185 MBq[3]. The EANM guideline "^{18}F-NaF PET/CT: EANM procedure guidelines for bone imaging" gives a very good general overview[3].

Figure 1

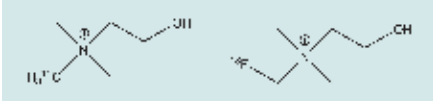


Formula of technetium (^{99m}Tc) medronic acid; exact formula is unknown

[^{99m}Tc]Tc-diphosphonates

[^{99m}Tc]Tc-diphosphonates ($T_{1/2}$=6 h) are the most widely used radiotracers for seeking bone metastases with SPECT imaging. ^{99m}Tc labelling of hydroxymethylene diphosphonate (HMDP, HDP), 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) and medronic acid (Fig. 1) can be performed using a kit preparation. These tracers show a high stability after preparation and may be applied for up to 8 h afterwards[4]. The recommended injected dose in adults is 300–740 MBq[5]. In the first phase of a bone scan, [^{99m}Tc]Tc-diphosphonates show the perfusion status of a lesion, in the second phase, the blood pool and in the third (static) phase, the bone metabolism. They appear to be actively taken up during bone mineralisation, and consequently most metabolically active lesions in bone are visualised, along with bone metastases of various tumours or inflammation[6].

Figure 2

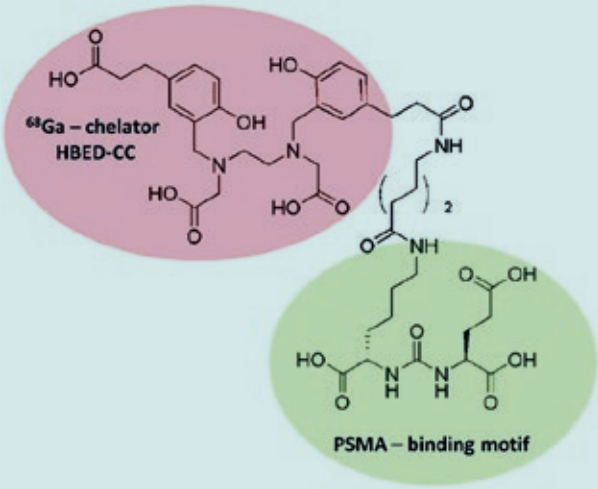


^{11}C[C]-choline and ^{18}F[F]-fluorcholine

^{18}F[F] and ^{11}C[C] labelled choline

Studies in the 1990s showed that choline kinase expression is associated with immortality and transformation in cancer cells[7]. Further studies with phosphorus-31 magnetic resonance spectroscopy

Figure 3



PSMA-11, a compound for ^{68}Ga[Ga] labelling[16]. With copyright permission from ACS Publications

verified this by revealing a high phosphatidylcholine concentration in tumours[8]. This led to the development first of ^{11}C[C] labelled choline[9] and later of ^{18}F[F] derivatives[10] (Fig. 2). The ^{11}C[C] compounds suffer from the fact that ^{11}C has a short half-life of 20 min, whereas the half-life of ^{18}F is 110 min. On the other hand, the ^{18}F[F] labelled compounds have the disadvantage of higher and faster urinary secretion, which has to be overcome by means of early dynamic PET images[11]. Both ^{11}C[C] and ^{18}F[F] compounds can be produced in specialised centres with a medical cyclotron and a radiopharmaceutical GMP infrastructure on a dedicated module. The ^{11}C[C] compounds can only be applied in a nearby PET centre owing to the short half-life of ^{11}C, whereas ^{18}F-fluorocholine can be delivered to PET centres without a dedicated radiopharmaceutical infrastructure.

PSMA targeting compounds

Prostate-specific membrane antigen, or PSMA, is a type II transmembrane protein which is expressed in different normal tissues, including prostate epithelium, the small intestine, renal tubules and salivary glands[12,13]. The protein is 100 to 1000

times overexpressed in prostate cancer and is associated with tumour aggressiveness[14].

The tracers in this field are still under development and the situation is quite confusing. Several clinical studies are underway. The initial tracers were based on antibodies radiolabelled with different radionuclides for PET and SPECT imaging[15]. The antibody tracers have in the meantime been replaced by small-molecule inhibitors of the enzymatic domain. One of the most popular is [^{68}Ga]Ga-PSMA-11[16,17] (Fig. 3), but other compounds based on the same structural features and radiolabelled with ^{18}F or 99mTc are under clinical investigation for use with PET and SPECT imaging. These compounds are discussed in the review by Virgolini et al.[15].

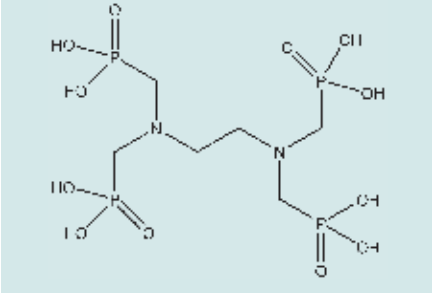
The [^{68}Ga]Ga compounds are radiolabelled in a dedicated module. [^{68}Ga]$GaCl_3$ can be eluted from commercially available generators. The recommended injected dose of [^{68}Ga]Ga labelled PSMA derivatives is 1.8–2.2 MBq/kg[18]. Efforts are underway to establish a kit-based preparation. [^{18}F]F labelled derivatives have to be synthesised in a dedicated radiopharmaceutical centre with a medical cyclotron for production of the [^{18}F]F and modules. The radiolabelling of ^{99m}Tc tracers is performed using a kit-based procedure.

RADIOPHARMACEUTICALS FOR THERAPEUTIC APPLICATION

[^{153}Sm]Sm-EDTMP

Ethylenediamine tetra(methylene phosphonic acid) (EDTMP) (Fig. 4) chelated with [^{153}Sm]Sm is a bone-seeking compound which can be used for the treatment of bone metastases in prostate and other cancers[19]. The mechanism of uptake in bone is the same as with the diagnostic biphosphonate and is mainly driven by the blood delivery and bone metabolism. [^{153}Sm]Sm is a weak beta emitter with a maximum energy of 0.81 MeV, a mean energy of 0.23 MeV and a tissue range of 0.6 mm. The gamma emission with an energy of 103 keV in 30% of the decays allows in vivo scintigraphy and/or SPECT control of the distribution of the compound. The half-life is 46.3 h.

Figure 4



Structure of EDTMP, an EDTA derivative

Bone is the most common site of metastases in patients with advanced prostate cancer. Such metastases result in bone pain, bone fracture and spinal cord compression and are associated with a higher morbidity and mortality. This necessitates treatment[20]. The treatment of bone metastases with [^{153}Sm]Sm-EDTMP is basically a palliative treatment for pain relief; it allows reduction or elimination of the use of powerful painkillers like opiates, which have a major adverse effect on quality of life.

The radiopharmaceutical is delivered as a ready-to-use compound to nuclear medicine departments. For palliative treatment of bone metastases, the injected dose of [^{153}Sm]Sm-EDTMP should be 37 MBq/kg.

[^{223}Ra]RaCl$_2$

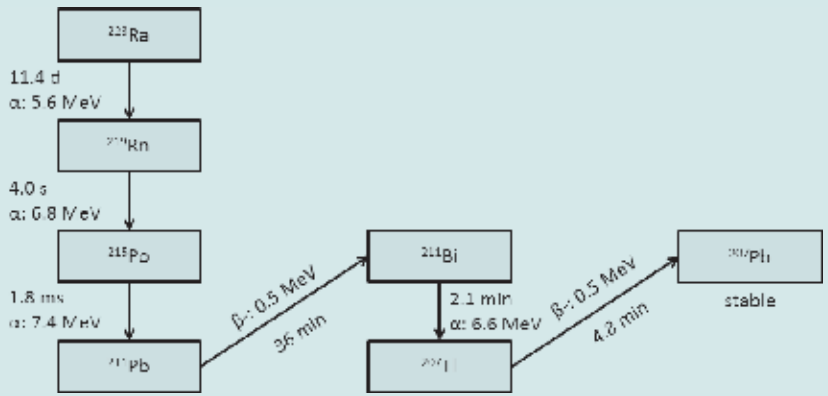
[^{223}Ra]radium chloride is a one of the first alpha-emitting compounds to have been approved for clinical use. Radium is a calcium antagonist and replaces the Ca in hydroxyapatite in bone (see section "Sodium [^{18}F]fluoride")[20, 21]. Therefore the highest uptake of [^{223}Ra]radium chloride occurs in locations with a high bone metabolism caused by metastasis. [^{223}Ra]radium chloride was tested in comparison with a placebo in a phase III study in 921 patients[22]. The alpha targeted radionuclide therapy showed a clear benefit over the placebo arm in relation not only to overall survival but also to all other secondary efficacy end points. Therefore the study was terminated prior to the predefined endpoint and authorisation of the compound was placed in a fast track process by the competent authorities in Europe (EMA) and USA (FDA). The compound achieved market authorisation in Europe in 2013.

[^{223}Ra]Ra is a radionuclide with an alpha decay (E=6.64 MeV) and a half-life of 11.4 days. The first alpha decay is followed by three other alpha decays and two beta minus decays, ending in stable [^{207}Pb]Pb (Fig. 5). [^{223}Ra]RaCl2 is delivered as a ready-for-use solution. Patients receive six cycles every 4 weeks[22].

PSMA targeting compounds

The same considerations that apply for the imaging compounds hold true for therapeutic radiopharmaceuticals targeting PSMA. Various clinical trials are underway with different radionuclides and small-molecule PSMA inhibitors[23]. The most widely used radionuclide is [^{177}Lu]Lu in combination with PSMA-617 or PSMA I&T. [^{177}Lu]Lu is a weak beta minus emitter with an energy of 0.5 MeV, a mean tissue range of 0.5 mm and a maximum tissue range of 2 mm[24]. The studies to date have shown very promising results, with some sustained responses[23]. The most common adverse effects are damage to the salivary

Figure 5



Decay scheme of [^{223}Ra]Ra

glands, which also express the target, mild haematological toxicology and fatigue. This is still a method under investigation but it is expected that it will enter routine clinical application in the near future.

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3

CONVENTIONAL NUCLEAR MEDICINE IN PROSTATE CANCER IMAGING

by Wolfgang Römer

INTRODUCTION

In about 30% of patients with prostate cancer, bone metastases are seen. These are predominantly osteoblastic. Bone scintigraphy with technetium-99m labelled diphosphonates is cost-effective and widely available and provides high sensitivity for the detection of bone metastases[1]. For this reason, bone scintigraphy is recommended by most national and international guidelines to exclude or confirm such metastases.

However, only patients with advanced tumour stages should be examined by this means nowadays. The most recent EAU-ESTRO-SIOG guidelines on prostate cancer recommend metastatic screening only for patients with high-risk localised prostate cancer (PSA >20 ng/ml or Gleason score >7 or cT2c) or high-risk locally advanced prostate cancer (any PSA, any Gleason score, cT3-4 or cN+)[2]. These recommendations are based on a meta-analysis by Abuzallouf et al., who showed that in patients with PSA <10 ng/ml the prevalence of bone metastases was only 2.3%[3].

After the treatment of prostate cancer, the probability of a positive bone scan is low (<5%) if the PSA level is <7 ng/ml[4]. Consequently, following treatment, bone scan is recommended only in patients with biochemical recurrence (rising PSA values without evidence of tumour relapse) who have a high PSA (>10 ng/ml) or high PSA kinetics (PSA doubling time <6 months) and in patients with new-onset bone pain[5]. Guidelines explicitly advise against routinely performing bone scintigraphy after treatment of prostate cancer.

Several studies have proven the high sensitivity of planar whole-body bone scintigraphy especially in prostate cancer, since its metastases are typically osteoblastic, resulting in increased bone metabolism. However, its specificity is limited since it is not only bone metastases that show enhanced tracer uptake. Rather, various benign lesions of the bone, e.g. degenerative, inflammatory and traumatic, are also visualised by bone scan on the basis of focal tracer enhancement. In the majority of cases, the vertebral column and pelvis are affected. Especially the differentiation of deforming spondylosis and spondylarthrosis from metastases is difficult. On planar scintigraphy, superimposition hampers the exact anatomical localisation of lesions. The addition of single-photon emission computed tomography (SPECT) allows better distinction of benign from malignant changes due to more exact localisation of increased diphosphonate uptake. However, the specificity of SPECT is also insufficient for reliable diagnosis[6].

Up to now, planar radiography has been the next step in the diagnostic workup in cases of focally enhanced diphosphonate uptake. It represents the least expensive and most widely available morphological imaging modality. If planar radiography shows clear-cut signs of arthrosis or fracture, it is concluded that the scintigraphic abnormalities are benign. However, the drawbacks of planar radiography in the identification of lesions, especially in the spine, are well known. There is clear evidence that destruction of more than 50% of trabecular bone is a prerequisite for the visibility of metastases on planar x-ray studies. Thus, if the radiographs are unremarkable, further tests, in particular, magnetic resonance imaging (MRI), are necessary. This may be time consuming and may delay therapeutic procedures. Furthermore, waiting for the diagnosis causes considerable stress to patients.

More than 15 years ago, a hybrid camera combining a dual-headed SPECT camera with a low-dose non-diagnostic CT scanner became commercially available. However, more recently, hybrid cameras combining SPECT and spiral CT offer the opportunity to perform a diagnostically sufficient CT of scintigraphically suspicious lesions in one session. Two clinical examples are shown in Figures 1 and 2.

SCIENTIFIC STUDIES ON THE BENEFIT OF SPECT/CT IN BONE SCINTIGRAPHY

The first report on the value of SPECT/spiral CT in bone scintigraphy was presented in 2006 by the Erlangen study group[8]. In a population of 44 patients with different tumour entities, a total of 52 lesions detected on SPECT images were judged as indeterminate. Of these, 33 (63%) could be correlated with benign findings on CT. These findings mostly involved osteochondrosis, spondylosis and spondylarthrosis of the spine. Fifteen (29%) lesions could be correlated with osteolysis on CT. Only four lesions (8%) remained indeterminate; these lesions were located in the ribs and the scapula. In summary, SPECT/CT allowed for a definite diagnosis in 92% of lesions located and thus considerably shortened the diagnostic process.

Helyar et al. examined 40 patients with prostate cancer[9]. They detected 50 suspicious lesions on planar scans, of which 72% were classified as indeterminate, 18% as benign and 10% as malignant. When reporting the SPECT scans, 50% of the lesions were rated as equivocal, 33% as benign and 17% as malignant. The addition of SPECT/CT resulted in a significant reduction in the percentage of equivocal reports, to only 8%; 68% of the lesions were classified as benign and 24% as malignant.

Figure 1A

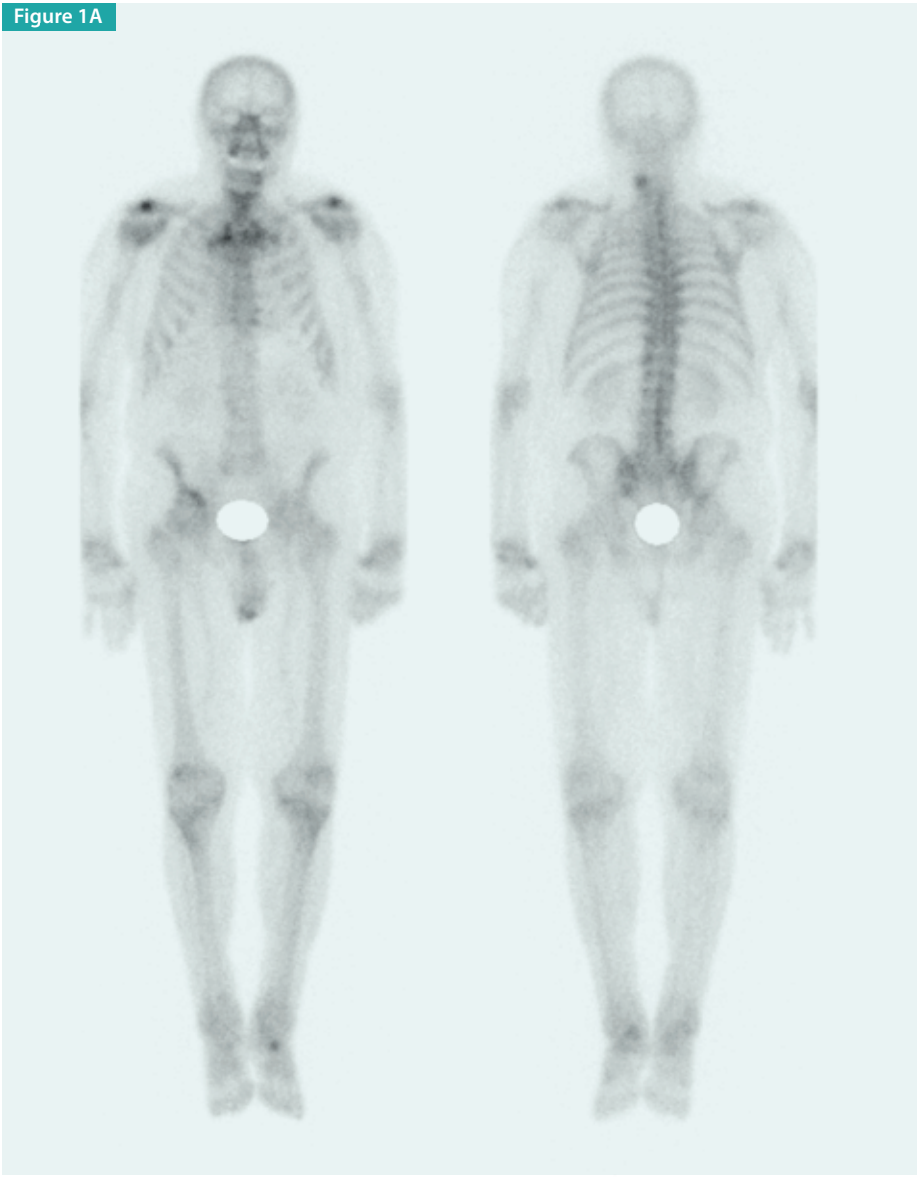


Figure 1B

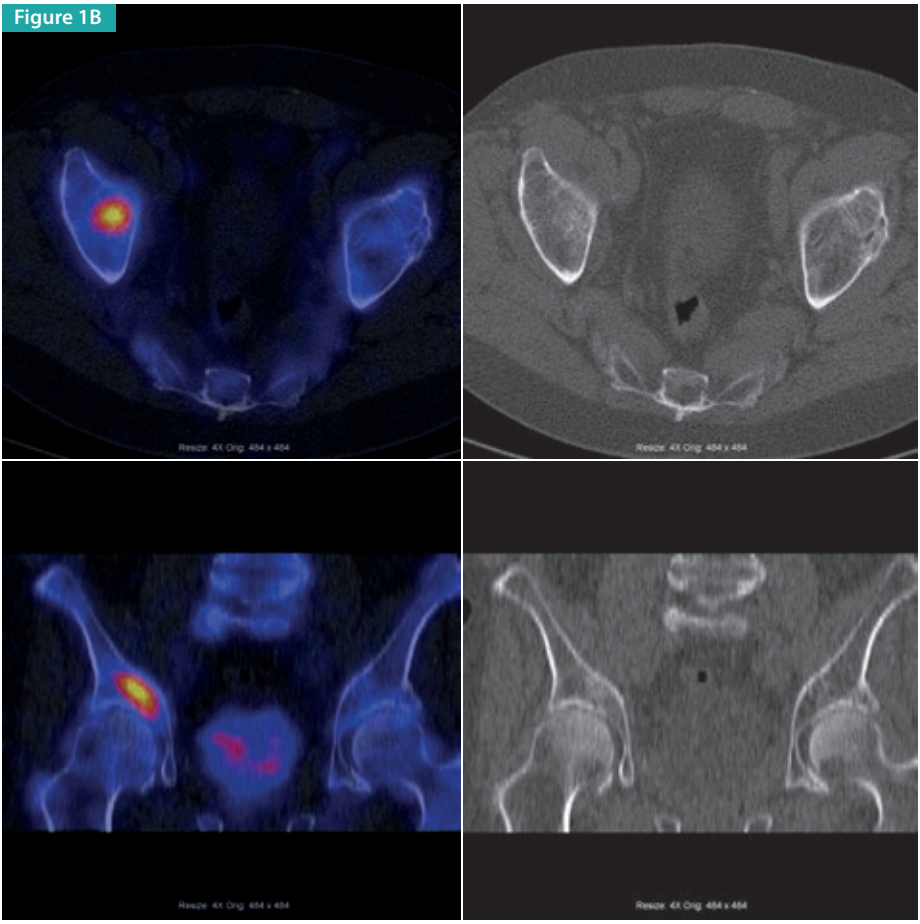


Figure 1a,b: *Bone scintigraphy and SPECT/CT using 99mTc-DPD in a patient with prostate cancer.* ***a)*** *Planar whole-body bone scan shows enhanced tracer uptake in the left acetabulum.* ***b)*** *On CT, the focally enhanced bone metabolism correlates with focal sclerosis in the acetabulum, typical for osteoblastic metastasis in prostate cancer*

Figure 2A

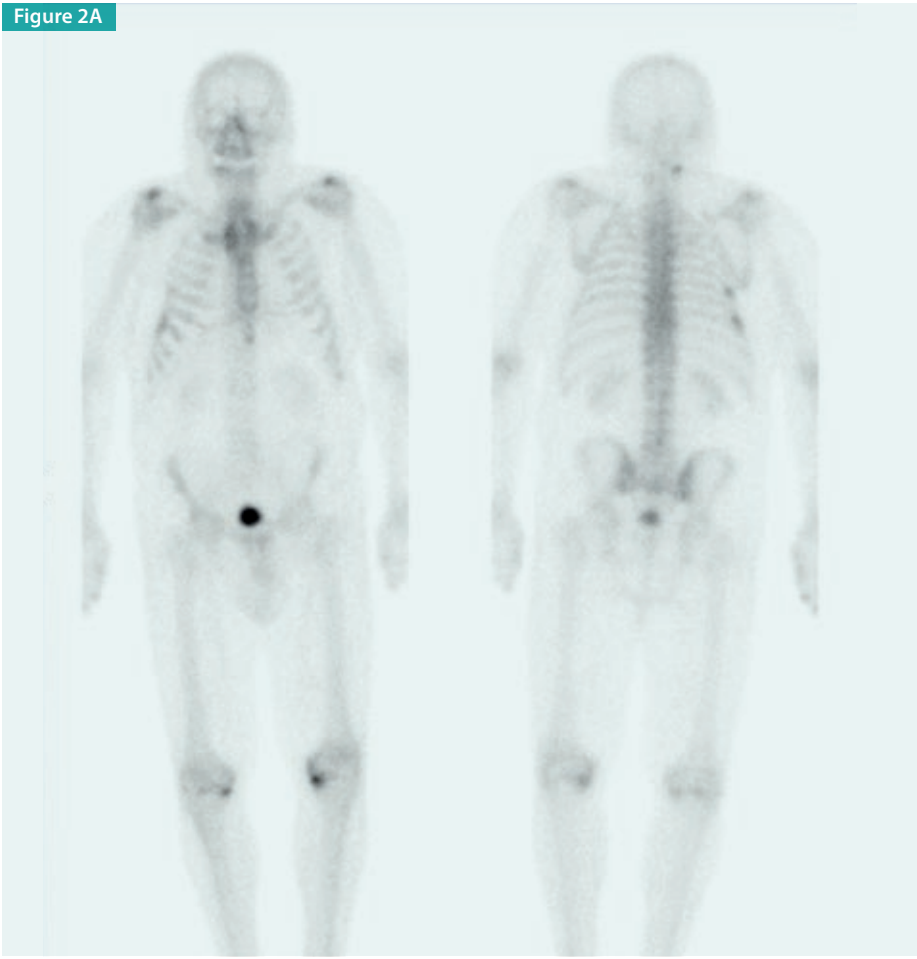


Figure 2a–c: *Bone scintigraphy and SPECT/CT using 99mTc-DPD in a patient with prostate cancer.* ***a)*** *Planar whole-body bone scan shows two lesions in the seventh and ninth ribs with increased tracer uptake. Lesions with enhanced bone metabolism in both knees and in the right cervical spine are typical for osteoarthritis.* ***b)*** *On CT, the focally enhanced bone metabolism correlates with focal sclerosis in the rib, typical for osteoblastic metastasis in prostate cancer.* ***c)*** *The findings on low-dose CT from SPECT/CT are confirmed by a diagnostic CT scan*

Figure 2B

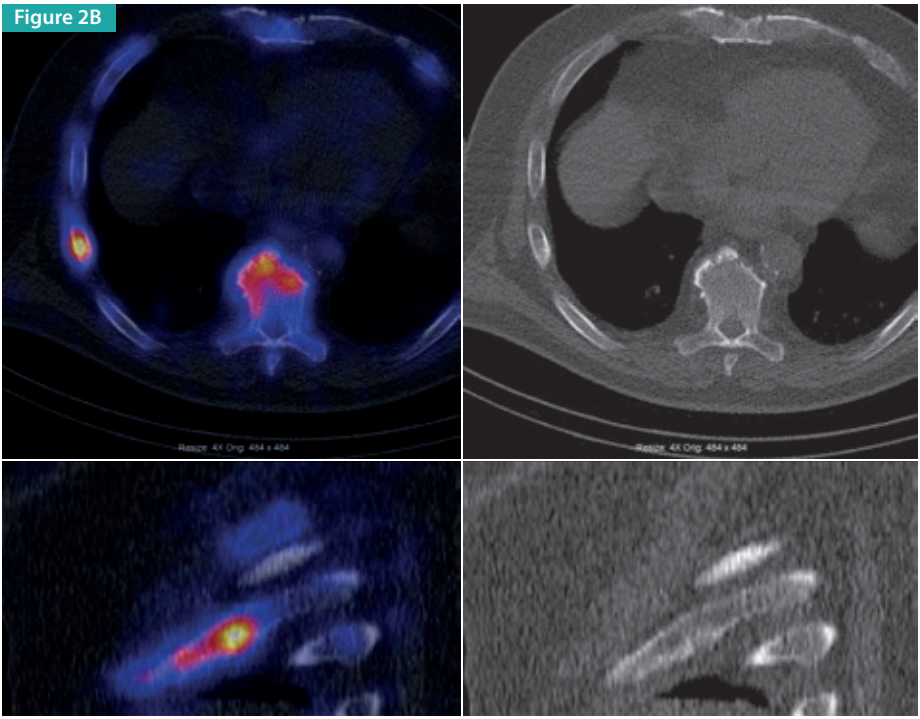
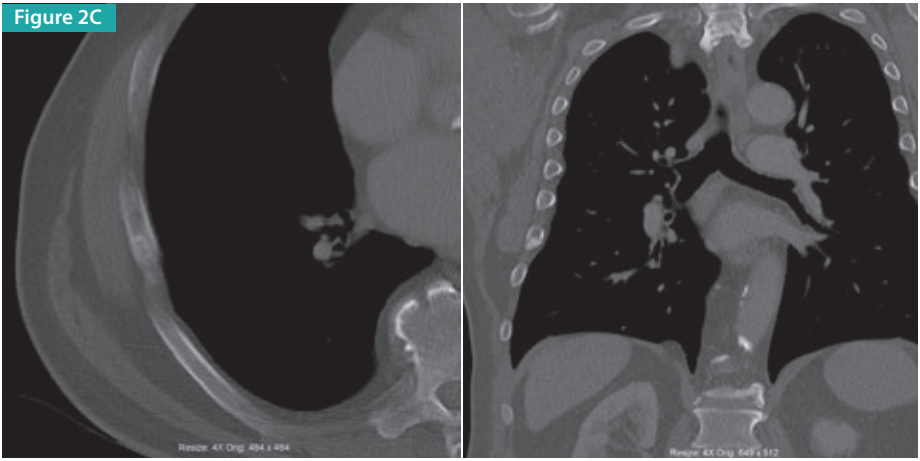


Figure 2C



In 2010 the value of SPECT/CT was studied by Ndlovu et al.[10] In this study, 48% of patients had indeterminate findings when only SPECT images were analysed, compared with 14% when using hybrid imaging. This study included 42 patients, most of whom were suffering from breast cancer (n=22) or prostate cancer (n=8). The additional analysis on a lesion-by-lesion basis of 189 suspicious lesions found that indeterminate findings could be reduced from 31% with SPECT alone to 9% with SPECT/CT. All findings were statistically significant.

Zhao et al. reported the results of SPECT/CT in 141 bone lesions in 125 tumour patients[11]. The sensitivity of SPECT and SPECT/CT was 83% and 98%, respectively, and the specificity was 67% and 94%, respectively. The number of indeterminate findings was reduced from 37 with SPECT to five with SPECT/CT.

Sharma et al. evaluated 99 patients who received a bone scan including SPECT/CT owing to different malignant and non-malignant diagnoses[12]**.** A total of 108 vertebral lesions were detected on planar scans. On planar scintigraphy 49 lesions were interpreted as indeterminate, compared with 16 on SPECT. However, on SPECT/CT scan, only one remained indeterminate. The calculated sensitivity and specificity were 100% and 36% for planar scintigraphy, 82% and 88% for SPECT and 93% and 100% for SPECT/CT. The authors reported that SPECT/CT characterised 96% of the equivocal lesions on conventional planar bone scan and showed that SPECT/CT had a significant influence on the clinical management of 60.6% of patients compared with planar scintigraphy and 18% compared with SPECT.

Palmedo et al. studied the incremental value of SPECT/CT compared with planar scintigraphy and SPECT alone in 308 oncological patients with different tumour entities, 33% of whom had prostate cancer[13]. At interpretation of the planar scans, 19% of lesions were classified as equivocal, 29% as benign and 34% as malignant (in remaining cases no lesions were detected). When reporting SPECT scans, the corresponding values were 20%, 33% and 43%. The addition of SPECT/CT resulted in a significant reduction in equivocal reports to only 3.5% of the lesions; 52% of lesions were classified as benign and 36% as malignant. The authors found that the specificity and positive predictive value were significantly ($p<0.01$) higher for SPECT/CT compared with planar whole-body scans and SPECT alone. On a per-patient basis, the sensitivity, specificity, positive predictive value and negative predictive value were, respectively, 97%, 94%, 88% and 97% for

SPECT/CT compared with 93%, 78%, 59% and 95% for whole-body bone scan. Furthermore, SPECT/CT caused downstaging in 29.5% of patients with prostate cancer. The authors concluded that SPECT/CT had a significant effect on clinical management because of correct downstaging or upstaging, better definition of the extent of metastases and a reduction in further diagnostic procedures.

Table 1 provides an overview of studies discussed in this section.

COMPARISON OF ^{99M}TC-DPD SPECT/CT AND PET/CT WITH DIFFERENT TRACERS

It is well known that the resolution of positron emission tomography (PET) is significantly higher than that of SPECT. In the last decade, several PET radiotracers have been developed that specifically target cells from prostate cancer. Since prostate cancer in most cases exhibits only low metabolic activity, imaging with the widely available glucose analogue fluoro-

Author, year [ref.]	No. of patients	No. of lesions	Scanner	No. of CT slices	Tube current in CT (mA)	Indeterminate findings after SPECT/CT
Horger, 2004 [17]	47	104	GE Millennium VG Hawkeye	1	2.5	15%
Römer, 2006 [8]	44	52	Siemens Symbia T2	2	40	8%
Helyar, 2010 [9]	40	50	Philips Precedence 16	16	100	8%
Ndlovu, 2010 [10]	42	189	GE Infinia Hawkeye	1	2.5	9%
Zhao, 2010 [11]	125	141	Philips Precedence 6	6	140	4%
Sharma, 2013 [12]	99	108	Siemens Symbia T6	6	100	4%
Palmedo, 2014 [13]	308	839	GE Hawkeye 4 Infinia/ Siemens Symbia T2	4	2.5–20	3.5%

Table 1: *Overview of literature concerning the use of SPECT/CT in tumour patients with indeterminate findings on planar bone scintigraphy*

deoxyglucose (FDG) is not useful. Therefore, several PET studies on prostate cancer imaging have been published using ^{11}C-acetate and ^{18}F- or ^{11}C-choline. Since both tracers do not seek lesions with enhanced bone metabolism but rather bind specifically to the tumour cells, soft tissue metastases can also be detected.

More recently, another tumour-specific tracer has been introduced. Ligands binding to the prostate-specific membrane antigen (PSMA) have shown high clinical value for detection of local recurrence of prostate cancer as well as for lymph node staging. In addition, several studies have shown its great value in the detection of bone metastases. Pyka et al. investigated the diagnostic accuracy of bone scanning including SPECT and ^{68}Ga-PSMA-PET for detection of bone metastases in prostate cancer[14]. The sensitivity and specificity of PET were 99% and 100% compared with 86% and 98% for bone scintigraphy. In another study combining PET and SPECT with CT in hybrid scanners, 68Ga-PSMA PET/CT outperformed 99mTc-2,3-dicarboxypropane-1,1-diphosphonate (DPD) SPECT/CT, with a sensitivity of 97.7% vs 69.4% and a specificity of 100% vs 98.3%. As when comparing SPECT and SPECT/CT, in the case of ^{68}Ga-PSMA PET the proportion of equivocal findings was significantly reduced by CT fusion in PET/CT[15]. In summary, despite higher sensitivity and specificity, PET and PET/CT are of limited use due to their restricted availability and higher costs. In some countries, PET/CT studies will not be reimbursed by the insurance provider. Therefore, bone scanning remains the imaging modality of first choice to confirm or exclude bone metastases.

ACQUISITION PROTOCOL

In order to confirm or exclude bone metastases, primarily anterior and posterior planar whole-body scans are acquired between 2 and 4 h after tracer injection. If any remarkable findings are observed on these scans, SPECT imaging of the indeterminate areas should be performed. Using modern iterative reconstruction algorithms, a detailed anatomical correlation of focally enhanced tracer uptake is possible. This is especially helpful in the axial skeleton, where differentiation is hampered by superimposition of different anatomical structures. Following the development of efficient reconstruction algorithms and fast computer processors, reconstruction of three-dimensional images can be performed within less than 60 s. However, as already discussed above, SPECT images alone will often not help to clarify indeterminate findings with certitude.

Following the implementation of CT scanners in SPECT cameras, the combination of functional and morphological

information regarding a lesion enables the definite clarification of indeterminate findings in one examination. Since the density of bone differs extremely from that of the surrounding soft tissue, even low-dose CT using a tube current of around 20 mAs enables sufficient imaging of the areas of interest. Thus, the additional radiation exposure due to CT can be limited. Another approach in order to limit the radiation exposure from additional CT in SPECT/CT is so-called SPECT-guided CT. If there is only a single lesion in the field of view of the SPECT scan, the field of view of the CT can be restricted to this area. Modern SPECT/CT software should be able to limit the examined area by drawing the boundaries of the CT scan on the SPECT images.

In a recent study, Zacho et al. revealed that in order to establish the status of equivocal lesions on planar bone scintigraphy, a 3-min SPECT/CT is sufficient[16]. There was no difference in diagnostic accuracy between standard SPECT/CT lasting 11 min and ultra-fast SPECT/CT lasting 3 min. This may be because the SPECT data indicate the anatomical localisation of the lesion with enhanced bone metabolism and the final diagnosis is primarily derived from the CT information.

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4

PET/CT PROCEDURES WITH FLUORINE-18 RADIOPHARMACEUTICALS IN PROSTATE CANCER

by Daniel Tempesta and David Gilmore

PET/CT IMAGING

Positron emission tomography (PET) makes use of gamma ray pairs emitted by specific radiopharmaceuticals in order to observe physiological processes in the body. Most PET scanners today are hybrid systems with computed tomography (CT) scanners built into the same gantry to create a PET/CT scanner. The PET data provide information on the physiology of the body while the CT serves several purposes, including attenuation correction of the PET data as well as improved anatomical correlation.

All PET radionuclides have in common that they emit positrons from their nuclei. The positron emitted will pair with an electron through an annihilation event. The annihilation will then cause a pair of 511-keV photons to be emitted in opposite directions at nearly 180°. PET scanner design takes advantage of this by using a ring of detectors, only registering events when both photons are detected, thereby improving resolution compared with traditional planar and SPECT imaging. Multiple rings of detectors are arranged longitudinally along the patient's body so that sections of anatomy may be imaged simultaneously, in what are called "bed positions". The number of beds per scan depends on the scanner design and the amount of anatomy imaged.

The majority of positron-emitting radionuclides used in medical imaging (fluorine-18, carbon-11, nitrogen-13 and oxygen-15) are accelerator produced and have relatively short half-lives compared with the radionuclides used in planar and SPECT imaging (technetium-99m, indium-111 and iodine-123). Due to the short half-lives, PET imaging facilities either have their own cyclotron onsite or must be relatively close to a central radiopharmacy with a cyclotron. While most PET radionuclides are produced in a cyclotron, two exceptions exist: rubidium-82 and gallium-68. These two radionuclides are produced by generators.

Fluorine-18 (^{18}F) is the most commonly used radionuclide in PET imaging today, partly due to its desirable properties. 18F can be substituted for a hydroxyl group and therefore synthesise many radiopharmaceuticals. With a physical half-life of 110 min, ^{18}F can not only be synthesised using on-site cyclotrons but also be produced at central nuclear pharmacies and be transported to local imaging facilities. While ^{18}F can be used to synthesise a variety of radiopharmaceuticals, one in particular, known as fluorodeoxyglucose (FDG), has drastically changed the way in which most cancers are diagnosed, staged and restaged.

PROSTATE CANCER IMAGING WITH PET/CT

Traditional methods of imaging with PET/CT have proven difficult for patients with

prostate cancer. ^{18}F-FDG, the most commonly used radiopharmaceutical in nuclear medicine, is not particularly helpful for imaging patients with prostate cancer. ^{18}F-FDG has proven to be a very useful tool in other oncology applications such as lymphoma, breast cancer, lung cancer and melanoma. In these instances, ^{18}F-FDG will show increased accumulation in tumour cells because these types of cancer exhibit increased glucose metabolism. In contrast, prostate cancer usually demonstrates low metabolic activity, making ^{18}F-FDG much less useful. Since the development and widespread use of ^{18}F-FDG in oncology, researchers have been looking to develop new radiopharmaceuticals to evaluate prostate cancer.

^{18}F-FDG

Fluorodeoxyglucose is a glucose analogue that diffuses into the cell using glucose transporters in the cell membrane. Many forms of cancer are characterised by rapidly dividing cells with increased metabolic demands and an increased number of glucose membrane transporters. Because FDG is not metabolised in the same way as glucose, FDG remains trapped in the cytosol of the cell long enough to allow for imaging.

Patient preparation for the exam involves depriving the body's cells of glucose. Patients should have nothing to eat or drink, other than plain water, for at least 4 h before the exam and should attempt to avoid carbohydrates and sugar in their last meal. Certain medications, especially those used for the management of diabetes (metformin, insulin, etc.), may alter the biodistribution of the radiopharmaceutical. The physician of diabetic patients and the radiologist should discuss the best way to manage each patient's blood glucose levels in order to optimise the scan.

The patient's blood glucose should be taken and a peripheral intravenous line should be placed. Patients with blood glucose levels exceeding 200 mg/dL should be rescheduled because excess circulating glucose will compete with the injected ^{18}F-FDG and uptake in tumour cells will be reduced. The institutional and manufacturer based activity[1] of ^{18}F-FDG (MBq/kg) should be injected intravenously and the patient asked to relax quietly in a chair or stretcher for 1 h while the tracer circulates and is taken up into the cells. While not normally employed for oncology patients, diuretics and bladder catheters may be used to help reduce bladder activity of the radiopharmaceutical in order to better visualise the prostate. These techniques should be utilised at the discretion of the physician.

Imaging should begin at 60 min post-injection. It is imperative that the patient

voids immediately before imaging if a bladder catheter is not being used in order to reduce activity from urine in close proximity to the prostate. The ideal patient position is supine with the arms raised above the head to reduce attenuation and prevent artefacts over the chest and abdomen. The scout and CT scans can be performed first, before the PET emission scan. For the emission scan, the patient should be scanned in the caudo-cranial direction, beginning at the pelvis and continuing through the skull base. Data acquisition should be for 2–5 min at each bed position, depending on factors such as the age of the scanner and the manufacturer's recommendations. Sample acquisition parameters for both the CT and the emission PET scan are shown in Tables 1 and 2, respectively.

Many areas of the body will normally accumulate ^{18}F-FDG, with the most intense activity noted in the brain, kidneys and bladder. Other organs normally accumulate ^{18}F-FDG to a lesser extent, including the liver, spleen, salivary glands, thyroid gland, stomach, bowel, bone marrow and muscles. Myocardial uptake is quite variable, and usually depends on the fasting state of the patient.

As previously mentioned, ^{18}F-FDG PET has traditionally not been used routinely in prostate cancer patients due to the low-metabolic properties of the disease. While some studies have shown that PET/CT using 18F-FDG can influence the management of patients with prostate cancer, the influence is not as great as in other types of cancer[2]. 18F-FDG PET is typically least useful early on in the diagnosis and

Table 1	
Topogram	35 mA 120 kVp 1024 mm
Slide	5 mm
Rotation time	0.55 s
Pitch	0.85
Reconstruction for AC	B30s, medium smooth FOV 780 mm
Reconstruction for Images	B30f, medium smooth, 5×5 mm, 500 mm FOV

Sample CT scan parameters [8]

Table 2	
Matrix	256
Zoom	1
Energy peak	511 keV
Acquisition mode	3-dimensional
Scan duration	2–5 min/bed position
Reconstruction	Iterations 2, subsets 21
Attenuation correction	CT
FWHM	5 mm
Filter	Gaussian

Sample PET scan parameters [8]

initial staging of prostate cancer. One area where 18F-FDG PET may be a valuable tool is for the staging of advanced prostate cancer in patients with a high Gleason score. Limited studies have shown ^{18}F-FDG PET to be appropriate for detection of prostate cancer, but only in patients at more than an intermediate risk[3]. Because of the previously mentioned limitations, researchers have been seeking to develop new radiopharmaceuticals that focus on physiological properties other than glucose metabolism in order to image prostate cancer.

^{18}F-FLUCICLOVINE (AXUMIN®)

^{18}F-fluciclovine, produced under the commercial name Axumin® by Blue Earth Diagnostics Ltd., has recently emerged as a promising PET radiopharmaceutical for the detection of recurrent prostate cancer in patients with a rising prostate-specific antigen (PSA) level. ^{18}F-fluciclovine, a synthetic amino acid, is transported into the cell membrane by amino acid transporters. Because prostate cancer cells are upregulated, tumour cells will exhibit greater tracer accumulation than the normal tissues of the body. ^{18}F-fluciclovine may offer an alternative to carbon-11 choline, which requires close proximity to a cyclotron for imaging owing to the relatively short physical half-life of ^{11}C.

Patient preparation includes refraining from any strenuous exercise for at least 24h before the exam. Other than plain water, the patient should not eat or drink anything for 4 h prior to the scan.

The prescribed dose is 370 MBq, injected intravenously as a bolus, usually while the patient is on the imaging table owing to the quick turnaround time between injection and scan. When possible, the patient should be injected in the right arm in an attempt to prevent a left axillary lymph node artefact from occurring. Imaging should begin 3–5 min after radiopharmaceutical injection, the time when tumour uptake is highest. When possible, the patient's arms should be placed above the head and imaging should start at the midthigh. Five-minute bed positions are acquired over the pelvis, followed by 3-min bed positions through the abdomen and chest. The scan should continue through the skull base and takes about 20–30 min to complete, depending on the height of the patient.

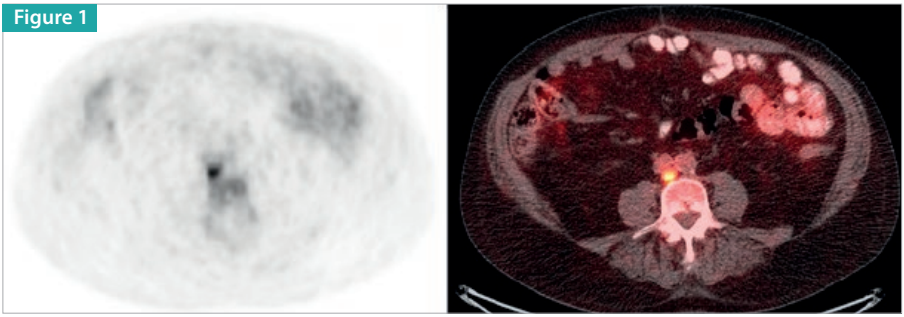
Normal physiological uptake of ^{18}F-fluciclovine includes the pancreas, liver, spleen and kidneys. The pancreas and liver exhibit the highest uptake, with the pancreas receiving the highest radiation dose, at 38 mGy. Mild salivary gland, pituitary gland and muscle uptake is normal while the brain and lungs are generally not visualised. A major benefit of ^{18}F-fluciclovine is

that urine excretion and bladder activity are minimal at the time of imaging, allowing for better visualisation of the nearby prostate or prostate bed in prostatectomy patients.

As a general rule, during image interpretation large lesions with visual activity equal to or greater than that of the bone marrow should be considered suspicious for prostate cancer (Fig. 1). Smaller lesions should be of concern when their visual activity exceeds that of the blood pool activity. Similar to the rules for large lesion malignancy, lymph nodes demonstrating activity equal to or greater than the activity of the bone marrow should raise concern regarding prostate cancer involvement[4].

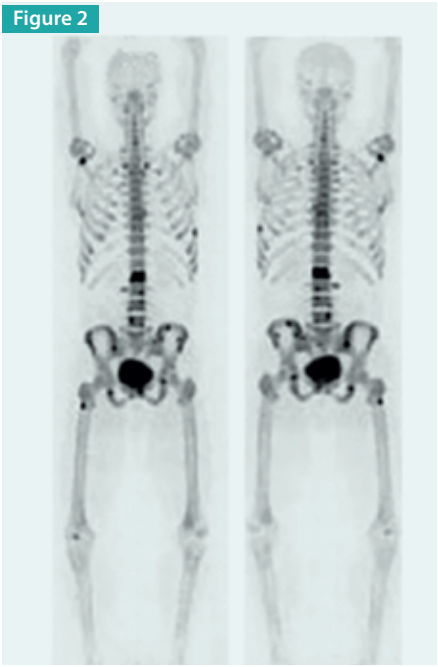
Image interpretation requires attention to detail and a full medical history, as some situations can cause false positive results. For example, benign inflammation may show areas of increased uptake because amino acid transporters are over-expressed in some types of inflammation. Some caution should be exercised when interpreting images as other types of cancer, in addition to prostate cancer, can accumulate ^{18}F-fluciclovine. Furthermore, benign prostate hypertrophy in patients with primary prostate cancer can also show increased areas of uptake, potentially leading to false positive results. It may be difficult to differentiate between benign prostate pathology and prostate cancer. Therefore, it is recommended that the patient's full medical history is reviewed when interpreting imaging and in some cases the findings should be confirmed histologically[4].

Figure 1



Transaxial PET (left) and PET/CT (right) F-18 fluciclovine images demonstrating metastatic disease to a lymph node

Figure 2



Anterior and posterior MIP views using F-18 sodium fluoride

^{18}F-SODIUM FLUORIDE

^{18}F-sodium fluoride is a PET radiopharmaceutical that identifies areas of altered osteogenic activity, including those affected by metastatic disease of prostate cancer and other types of cancer[5]. Bone scintigraphy using technetium-99m labelled radiopharmaceuticals, such as ^{99m}Tc-medronate (MDP), has long been a useful tool for identification of metastatic prostate cancer in the bones. However, with the development of PET technology and the great improvement in resolution from gamma cameras to PET scanners, ^{18}F-sodium fluoride may become a better choice for imaging of skeletal metastases.

The patient should be well hydrated before the exam to promote soft tissue tracer clearance, reduce radiation dose to the patient and reduce bladder activity that may obscure surrounding bony structures. The typical adult dose of ^{18}F-sodium fluoride is 185–370 MBq injected intravenously. The radiopharmaceutical accumulates in the skeleton based on blood flow and bone remodelling. Since ^{18}F-sodium fluoride localises in the bones and clears from the soft tissue faster than ^{99m}Tc-based skeletal agents, imaging may begin 30–45 min after injection when imaging the axial skeleton. Imaging should begin 90–120 min after injection when imaging the extremities, but such imaging is not usually performed when looking for prostate cancer metastases. The patient should void immediately before the scan. If only imaging of the axial skeleton is requested, the patient should be positioned supine with the arms raised above the head. It may be useful to begin the scan at the pelvis, before the bladder fills, and continue through the skull base. If head-to-toe skeletal imaging is requested, the arms should be placed down by the side of the body.

Fluorine-18 incorporates into the hydroxyapatite of bones in place of hydroxyl groups and therefore will accumulate in the entire skeleton during normal bone turnover. In areas of new bone formation, such as in the case of bones attempting to repair themselves from prostate cancer metastases, more binding sites are available for ^{18}F, causing increased radiopharmaceutical accumulation. In addition, bone tumours tend to exhibit increased perfusion, allowing more of the radiopharmaceutical to be transported to the tumour. For both these reasons, prostate cancer metastases should exhibit increased activity on imaging compared with normal tissue around the tumours. While ^{18}F-sodium fluoride imaging is sensitive for the detection of bone metastases, caution should be exercised as benign processes may also exhibit increased accumulation of ^{18}F-sodium fluoride, and differentiation between malignant and benign processes may be difficult in certain situations.

Beyond radiopharmaceutical accumulation in the skeleton, ^{18}F-sodium fluoride is normally visible in the kidneys, ureters and bladder due to urinary excretion (Fig. 2). This can pose challenges when imaging the bony anatomy around the bladder and every effort should be made to keep the patient hydrated and to ensure that they empty their bladder before imaging. Prostate cancer that has spread to the bones should be identifiable as focal areas of increased tracer accumulation. Correlation with the CT scan can improve specificity and improve confidence in the anatomical localisation of lesions. Determination of the presence or absence of skeletal metastases in patients with known prostate cancer can be useful in the staging or restaging of disease and in management planning.The results of a recent study suggested that up to 77% of referring physicians would not have formulated a treatment plan in the absence of availability of ^{18}F-sodium fluoride PET (and conventional bone scintigraphy), instead opting for further advanced imaging[6].

PSMA RADIOPHARMACEUTICALS

Prostate-specific membrane antigens (PSMA) are transmembrane proteins found in normal prostate tissues as well as other normal tissues in the body. PSMA is also found in malignant prostate tissue, and PSMA expression correlates with disease progression, including metastatic disease. Targeting of PSMA is one of the alternatives to ^{18}F-FDG explored by researchers for detection of prostate cancer. Also, while ^{18}F-fluciclovine has shown much promise, researchers are looking for a PSMAligand for theranostic purposes, to be

coupled with the prostate radiotherapy agent lutetium-177 PSMA. The theory is that a PSMA imaging agent will perform better than ^{18}F-fluciclovine in predicting the distribution of ^{177}Lu. To date, the most successful PSMA agent has been gallium-68 PSMA. However, since the development of ^{68}Ga-PSMA there has been a desire to develop an ^{18}F-based PSMA radiopharmaceutical owing to the more favourable imaging characteristics of ^{18}F[7].

In comparison with ^{18}F, ^{68}Ga has a shorter physical half-life of 68 min, which can cause logistical problems when attempting to ship the material from central radiopharmacies to imaging facilities. In addition, ^{68}Ga is produced by a generator and can only be eluted a few times per day, with each elution only producing enough activity for a single patient dose. Because of these elution limitations, the number of doses that can be produced per day is drastically limited in comparison with the number of doses that can be produced with ^{18}F, which is produced in large amounts by a cyclotron.

Recently, multiple PSMA ligands have been developed for labelling with ^{18}F, all of which are still being researched. The benefit of these radiopharmaceuticals is their specificity for prostate cancer, and normal distributions have demonstrated very low urine and bladder activity, something that is key in prostate cancer imaging. In total, only a few hundred patients have to date been scanned using ^{18}F-PSMA tracers, compared with the thousands of patients scanned with ^{68}Ga-PSMA[7]. Despite the additional research that needs to be done, it appears that PSMA radiopharmaceuticals may successfully fill a long-term void in prostate cancer imaging with PET/CT.

CONCLUSION

PET/CT imaging has become standard of care in most oncology cases, especially for breast cancer, lung cancer and lymphoma. While ^{18}F-FDG PET has proven successful in many oncology applications, the biology of prostate cancer has prevented it from being standard of care for prostate patients. Researchers have developed new prostate cancer radiopharmaceuticals, some labelled with ^{18}F and some with other radionuclides, the most promising being ^{18}F-fluciclovine. ^{18}F-sodium fluoride also remains a useful tool for imaging skeletal metastases from prostate cancer. While only a few ^{18}F-based radiopharmaceuticals are currently being used, researchers are investigating a variety of other options for prostate cancer imaging with PET/CT.

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AVAILABLE AS WEBINAR

5

PROSTATE CANCER PET/CT IMAGING BEYOND FLUORINE-18 TRACERS

by Giorgio Testanera and Giovanna Pepe

INTRODUCTION

Prostate cancer is one of the most commonly diagnosed tumour types. United States data show that in that country (a) around 160,000 new cases are identified annually, (b) nearly 30,000 men die of the disease each year and (c) about one in nine men will be diagnosed with prostate cancer during their lifetime[1]. In the management of prostate cancer, the methods currently applied for risk stratification, treatment selection and response prediction, as well as for estimation of prognosis, are considered suboptimal. Screening for prostate-specific antigen (PSA) is controversial owing to its low specificity and the risk of overtreatment of cancers that are not clinically significant. Tissue biopsy samples, on the other hand, can provide only a small window on the biological characteristics of a cancer, particularly in cases of widespread disease.

Diagnostic imaging is crucial in the evaluation of patients with suspected metastatic or biochemically recurrent prostate cancer[2]. The identification and localisation of metastatic disease may significantly alter the treatment options available to the patient, particularly in the oligometastatic setting, as different authors have demonstrated oncological benefit of salvage lymph node dissection or radiotherapy in the setting of low-burden metastatic disease. Furthermore, stereotactic radiotherapy or metastasectomy in limited/isolated metastatic disease has been proven to be of benefit, with an improvement in progression-free survival in patients with oligometastatic prostate cancer recurrence who are treated with high-dose stereotactic body radiotherapy (3-year progression-free survival 99% vs 79% with low dose)[3].

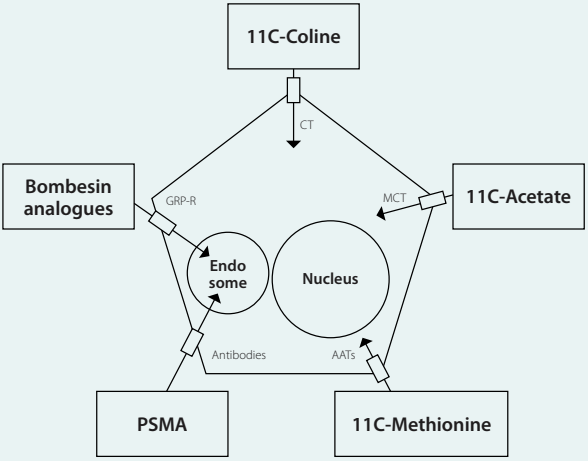
Molecular imaging techniques are used to generate maps of functional and biochemical activity in target tissues in vivo and may provide non-invasive insights into tumour biology and diversity on a whole-body scale (Fig. 1).

Currently, positron emission tomography (PET) is one of the most successful techniques in the diagnostic work-up of prostate cancer, playing an important role by addressing several metabolic features.

In this chapter, in the spirit of continuity with EANM and international guidelines on the topic[4, 5], we will cover major clinical applications of PET/CT techniques with non-^{18}F-based tracers, together with acquisition methods, patient preparation and quality criteria. The aims are to:

- Identify the non-^{18}F tracers used in prostate cancer
- Describe patient preparation for each tracer

Figure 1



Overview of molecular imaging strategies currently applied for prostate cancer. AATs, amino acid transporters; CT, choline transporter; GRP-R, gastrin-releasing peptide receptor; MCT, monocarboxylate transporter, PSMA, prostate-specific membrane antigen

- Describe PET/CT protocols
- Identify the challenges posed by the non-^{18}F tracers
- Describe the advantages of the non-^{18}F tracers

PET/CT TRACERS

Cancer cells and healthy tissues show significant differences in the uptake and use of nutrients and constitutional elements. It is well known that selected radiolabelled metabolites are capable of being incorporated into cancer cells in a dramatically different fashion compared with normal tissues, and this understanding forms the background for the development of novel biomarkers that can be used for imaging purposes.

The most commonly used oncological radiopharmaceutical, ^{18}F-fluorodeoxyglucose (FDG), which detects increased glucose metabolism within malignant tumours, has a low sensitivity in detecting prostate cancer, severely limiting its use

except, possibly, in aggressive, poorly differentiated tumours. Therefore, different PET probes have been developed with the aim of enabling better investigation of this neoplastic disease. These tracers can target the metabolic changes characteristic of prostate cancer cells (phospholipids with ^{11}C- or ^{18}F-choline, fatty acids with ^{11}C-acetate and amino acids with ^{18}F-fluciclovine) or bone remodelling from osteoblastic osseous metastases (^{18}F-sodium fluoride) or overexpressed cell surface

	Scanner A	Scanner B
CT protocol		
Topogram	50 mA 110 kV >1000 mm	10 mA 120 kV >1000 mm
Dose modulation parameters	95 mA 130 kV	400 mA, maximum value 140 kV
Slice	3 mm	3.75 mm
CT collimation	6×3 mm	64×3.75 mm
Rotation time	1.0 s	0.5 s
Pitch	1.0	0.984
Reconstruction for attenuation correction	B10s very smooth 4 mm, DFOV 70 cm	AC wide view – DFOV 70 cm 2.5 mm
Reconstruction for imaging	B31s medium smooth +3 mm	Standard wide view 2.5 mm
PET protocol		
Scan duration per bed position	>2.0 min	>1.5 min
Matrix	128	256
Reconstruction	Iterations 2; subset 8; OSEM	Iterations 3, cut-off 5, subset 24, TOF+PSF correction
Filter	Gaussian	Standard axis Z
FWHM	4 mm	/

Table 1: *Practical example of different parameters used with two different scanners for ^{11}C-choline imaging (data courtesy of Humanitas Research Hospital, Milan, Italy)*

proteins [labelled prostate-specific membrane antigen (PSMA) ligand][6].

Here we provide an overview of the tracers routinely available for prostate cancer PET/CT imaging, with the exception of ^{18}F-labelled radiopharmaceuticals.

PET AND CT PROTOCOLS WITH NON-^{18}F TRACERS

There are some general aspects that must be considered when carrying out PET/CT imaging with tracers other than ^{18}F:

- National and local rules on radiopharmaceutical preparation and use must be respected by all single centres that perform PET studies for clinical or research purposes.
- Patient preparation should be as homogeneous as possible, to avoid misleading findings caused by modifications of physiological radiopharmaceutical biodistribution.
- With short half-life tracers, a strict protocol, which includes timing and instrument cross-calibration, is advisable for radiopharmaceutical administration.
- Administered activity must be adjusted to the clinical question addressed by the PET/CT study. In Europe, Directive 97/43/EURATOM must be taken into account and recommended national activities for radiopharmaceuticals should not be exceeded for standard procedures.
- Particular attention must be paid to image quality, by calculating radiopharmaceutical activity as a function of patient characteristics, scanner type, scanning mode and time of acquisition (Table 1).
- PET and CT parameters for whole-body acquisition, and reconstruction, must be set according to the manufacturer's recommendations and national and international guidelines. These parameters usually need to be set according to patient characteristics and clinical needs. However, in order to guarantee a quality scan for all patients scheduled in each session, it is also important not to forget operational challenges due to the short half-life of the tracer.
- The justification principle of radiation protection ought always to be considered before using any radiation-emitting device or radiopharmaceutical for medical purposes.
- Acquisition protocols should be standardised to allow direct comparison of PET/CT images acquired in different centres and correct participation in multicentre clinical research protocols.
- Physicians and technologists/radiographers must be aware of the physiological tracer distribution and its variants in order to recognise pitfalls that could lead to misinterpretation.
- Reporting should be as homogeneous as possible, stressing the most relevant

clinical findings and specifying conclusions in order to help guide further clinical decisions.

» When previous PET/CT examinations have been performed, images and reports must be available for comparison.
» In pregnant or breast-feeding patients, specific guidelines must be followed.
» The patient should be positioned with both arms elevated above the head, as tolerated by the patient. If PET/CT data are used for radiation therapy planning, the examination should be performed in exactly the same position and employing the same positioning devices as in the radiation therapy department.
» CT scans should be performed from the skull base to the mid-thigh followed by the PET acquisition. CT acquisition parameters (such as kV, mAs, pitch in helical CT and dose modulation) should be in accordance with institutional protocols.
» If there are focal symptoms or disseminated disease, coverage may be extended to include the entire lower extremity and/or the skull.
» When diagnostic contrast-enhanced CT (with intravenous contrast media) needs to be performed after the PET/CT examination, indications and contraindications must be evaluated by qualified personnel[7].
» If intravenous CT contrast is used, the suggested protocol consists in a contrast-enhanced CT in the portal venous phase 80 s after intravenous injection of contrast agent (1.5 mL per kilogram body weight, maximum 120 mL).
» PET acquisition should start from the mid-thigh and extend to the base of the skull.
» When using ^{68}Ga-PSMA, acquisition should proceed from the lower end of the axial field of view cranially in order to minimise misalignment for the urinary bladder, which tends to fill up during the course of the examination. PET scans are acquired in three-dimensional mode with an acquisition time of usually 2–4 min per bed position.
» Overall, PET coverage should be identical to the anatomical CT scan range.

CHALLENGES OF WORKING WITH ^{11}C-LABELLED TRACERS

The main challenge of working with ^{11}C tracers is the reduced half-life of the isotope, only 20.4 min (^{18}F: 110 min). As stated above, these tracers are available only in centres with availability of an on-site cyclotron.

The operational challenges associated with this situation mean that:

» All steps in the imaging process must be performed without delays.
» All professional staff involved in the process must be adequately instructed.

Problems	Advantages
» Shortage of synthesis product » Quality control not "clearly positive" » Patient delay in turning up at the imaging site » Difficulties in injecting the patient » Poor physical, mental and psychological condition of the patient » Insufficient scanners available (e.g. due to a technical problem) » Staff shortage » Bad patient scheduling	» Easy rescheduling of the synthesis process » Possibility of staff intervention in the process » Easy rescheduling of patients » Rapid tracer decay means that only a short interval is needed between two syntheses within the same hot cell » Departmental internal coordination without external agents » Internal agreement on protocols and time scheduling

Table 2: *Problems and advantages of working with ^{11}C tracers with a cyclotron on site*

» Patients MUST be adequately instructed by PET centre staff.
» Each exam is performed within a short time, which is sometimes critical for good quality imaging.

Table 2 summarises the problems and advantages of working with ^{11}C tracers with a cyclotron on site. The table shows that problems that are easy to solve with long-lived tracers may cause poor quality imaging when using rapidly decaying tracers in a complex procedure such as a PET/CT scan. Solutions require extra efforts in terms of internal cooperation and standardisation of protocols.

QUALITY CRITERIA AND ARTEFACTS

Various potential sources of errors in interpretation must be considered when deciding whether a scan meets the quality criteria. The sources of artefact on PET/CT are very similar to those described in the EANM guidelines for ^{18}F-FDG[8], but the different biodistribution needs to be considered. These sources include:

» Patient movement
» Scanner-related factors
» Inappropriate processing
» Insufficient attenuation correction
» CT artefacts (e.g. respiration)
» Recent radiotherapy or chemotherapy

^{11}C-CHOLINE

Prostate cancer cells show increased phosphocholine levels and elevated turnover of the cell membrane phospholipid, namely phosphatidylcholine[9]. A high-affinity transporter system imports choline into the cell, where it is phosphorylated

by choline kinase in the first step of the Kennedy cycle. Key enzymes in choline metabolism, such as choline kinase, are up-regulated in prostate cancers, and this is likely the primary reason why prostate cancers concentrate ^{11}C-choline[10].

Both ^{11}C-choline and ^{18}F-fluorocholine have received much attention over the past several years, particularly in Europe and Japan, for imaging of men with prostate cancer. 11C-choline has recently been approved by the Food and Drug Administration for production and use to detect recurrent prostate cancer at the Mayo Clinic in Rochester, Minnesota[11].

A major advantage of ^{11}C-choline is its rapid blood clearance (5 min) and rapid uptake within prostate tissue (3–5 min), allowing for early imaging before excretion of the tracer into the urine. Thus, the pelvis can be viewed before significant excretory activity becomes a potential confounder. Unfortunately, the 20-min half-life of ^{11}C restricts the use of 11C-choline to centres with an on-site cyclotron. In contrast, the longer half-life of ^{18}F (110 min) allows transportation of ^{18}F-fluorocholine to centres without a cyclotron, although ^{18}F-choline has a higher urinary excretion than ^{11}C-choline[12].

Specific patient preparation

» The indication for use of choline imaging should be evaluated before scheduling the examination to confirm that the procedure is appropriate.
» On the day of the examination, the patient should be asked to fast for at least 4 h before injection.
» The physician in charge of the patient may request the withdrawal of specific drugs during prior clinical evaluations.
» Patient height and body weight and the principal clinical details are recorded, in particular:
  - Tumour type
  - PSA value
  - Known tumour localisations
  - Previous therapies (type and time of surgery, chemotherapy, radiation therapy, mono-therapy or others)
» Patients should be well hydrated

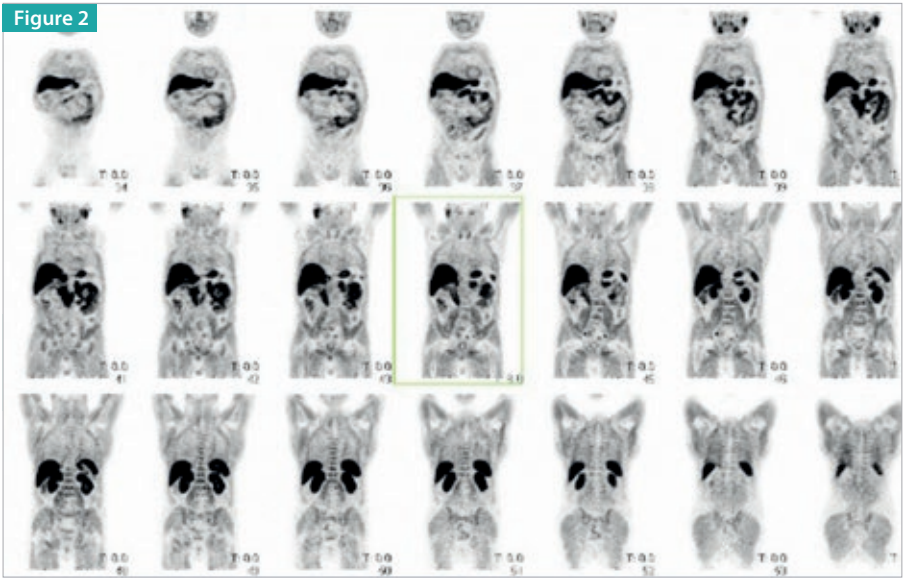
Administered activity

The radiopharmaceutical is administered as a bolus by intravenous injection, followed by flushing of physiological saline solution. After the administration, the patient needs to wait 10 min before the scan starts. Activities of around 350 MBq are recommended.

Image interpretation

Physiologically increased uptake of choline is noted in the salivary glands, liver, kidney parenchyma and pancreas, with faint uptake in the spleen, bone marrow and muscles; bowel activity is variable (Figs. 2, 3).

Figure 2



Physiological distribution of ^{11}C-choline

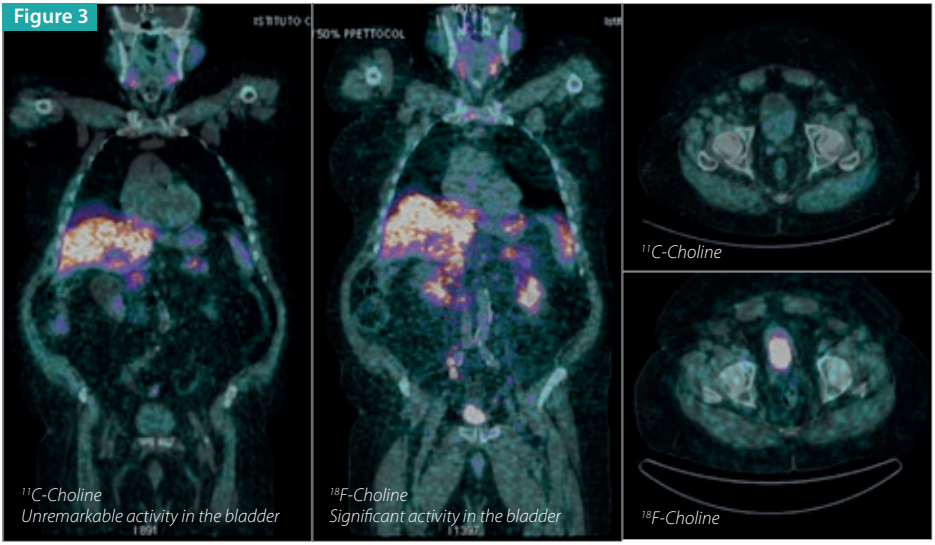
Clinical indications

The principal indication for ^{11}C-choline PET/CT is local disease evaluation. The high uptake of choline in prostate cancer seems to be caused by its active incorporation in tumour cells for production of phosphatidylcholine, a cell membrane constituent, to facilitate rapid cell duplication.

Uptake of ^{11}C-choline is similar in patients with benign prostatic diseases and proven prostate cancer; this is the major limitation to use of this tracer for identification of the primary tumour. In addition, the limited spatial resolution of PET/CT needs to be borne in mind.

Most groups have not found a significant correlation between ^{11}C-choline maximum standardised uptake value (SUV_{max}) and PSA levels, Gleason score and disease stage. SUV is affected by many factors, such as patient size and time between tracer injection and PET/CT scan. It is also possible to calculate the ratio between SUV_{max} of the prostate lesion (P) and of the pelvic muscles (M), (SUVmax P/M). This may be a promising approach, as evidenced by a recent study in which Chen and colleagues found SUVmax P/M ratio to be significantly associated with clinical tumour stage and Gleason score[13].

Figure 3

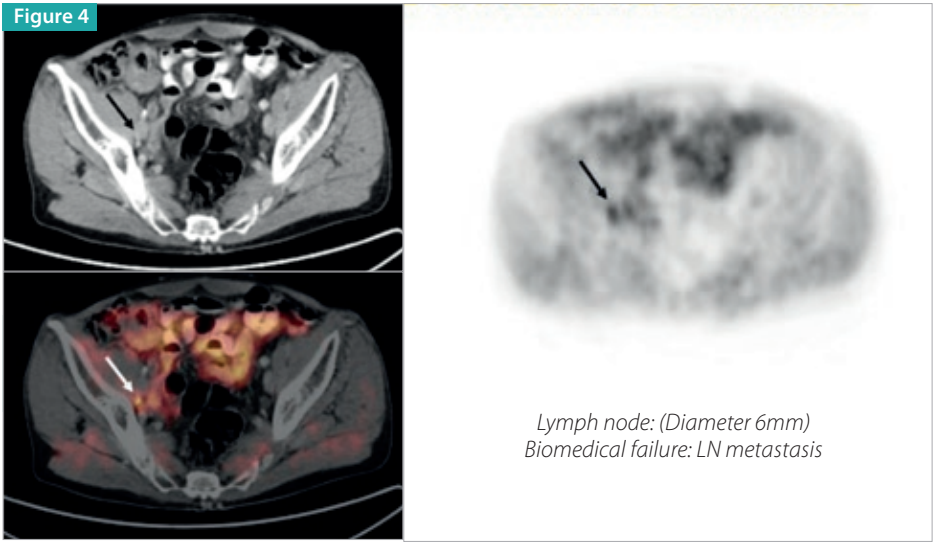


Comparison between ^{18}F-choline and ^{11}C-choline PET/CT imaging in the same patient. ^{18}F-choline shows higher activity in the urinary bladder than ^{11C}-choline, limiting evaluation of the prostatic bed

^{11}C-Choline PET/CT appears to be a powerful tool for the restaging of biochemically recurrent prostate cancer, particularly for those patients in whom standard imaging (CT, MR imaging and bone scan) has failed to identify the site of recurrence. This subgroup of patients frequently has one or more lymph node metastases in the pelvis that are normal in size on anatomical imaging but show increased tracer uptake on functional imaging (Fig. 4).

^{11}C-Choline PET/CT is an optimal imaging modality for the assessment of viable prostate cancer burden in the skeleton; non-sclerotic skeletal metastases can be identified as foci of high uptake, not rarely outside the routine field of view of pelvic MR imaging. It has been clearly demonstrated that ^{11}C-choline PET/CT has better sensitivity than bone scan. This is attributable to the fact that choline accumulates directly in the tumour cells in the bone marrow, ensuring earlier detection of lesions, whereas bone-seeking radiopharmaceuticals accumulate in the osteoblastic cells, giving an indirect sign of metastatic disease[14, 15].

Figure 4



^{11}C-Choline PET/CT in biochemical recurrence. Images show pathological uptake in an iliac lymph node

^{11}C-ACETATE

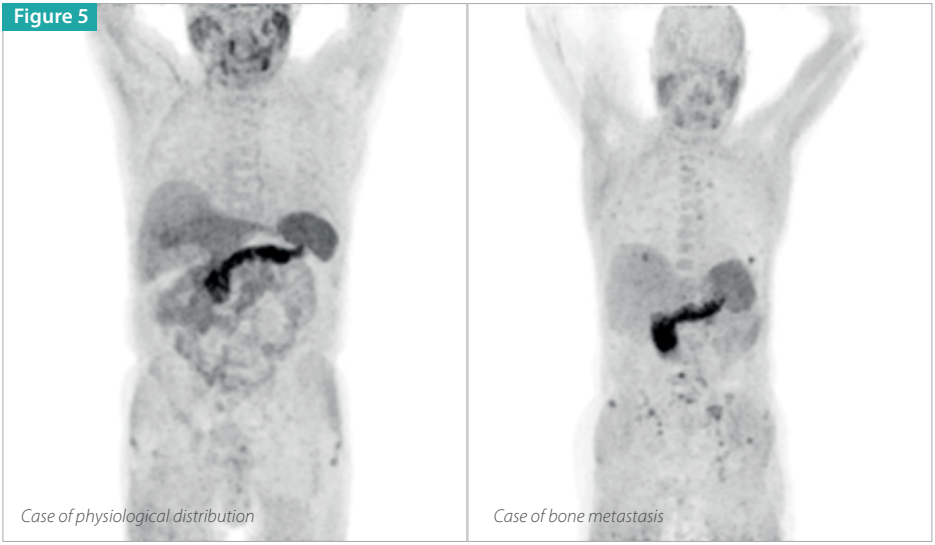
^{11}C-Acetate is transported across the cellular membrane via the monocarboxylate transporter and participates in the de novo synthesis of fatty acids from acetyl-CoA and malonyl-CoA through the action of fatty acid synthase, which is upregulated in prostate cancer[16].

The normal prostate usually shows only minor uptake of the tracer while focal inflammation of the prostate can cause increased focal tracer accumulation. Automated synthesis of ^{11}C-acetate has been implemented by carboxylation reaction of MeMgBr on a polyethylene Teflon loop ring with $^{11}C-CO_2$, followed by acidic hydrolysis with acid and SCX cartridge and purification on SCX, AG11A8 and C18 SPE cartridges using a commercially available ^{11}C-tracer synthesiser[17].

Specific patient preparation

Currently there are no agreed guidelines for ^{11}C-acetate, and a protocol similar to that described for generic ^{11}C tracers and ^{11}C-choline is routinely used. There is no evidence in the literature regarding specific patient preparation.

Figure 5



^{11}C-Acetate PET/CT: physiological and pathological findings. Courtesy of G. Karanikas and M. Beheshti

Administered activity

The radiopharmaceutical is administered as a bolus by intravenous injection, followed by flushing with physiological saline solution. After the administration, the patient needs to wait 10–15 min before the scan starts. Activities of 740 MBq are recommended[22].

Clinical indications

^{11}C-Acetate PET has been applied to measure myocardial oxygen consumption and to study several different cancers, including hepatocellular carcinoma, renal cell carcinoma, bladder carcinoma and brain tumours; it has also been extensively used to evaluate prostate cancer (Fig. 5).

With regard to prostate cancer, ^{11}C-acetate PET has been tested in the detection of the primary tumour and staging (particularly in the evaluation of nodal involvement and distant metastasis), as well as in the evaluation of disease relapse. Oyama and co-workers demonstrated a sensitivity of 100% in the detection of the primary tumour in a series of 22 patients with histologically proven prostate cancer[18]. However, Kato et al. found that ^{11}C-acetate PET

cannot reliably distinguish benign prostatic hyperplasia from prostate cancer[19]. In contrast, Mena et al. demonstrated that ^{11}C-acetate uptake in tumour is higher than that in normal prostate tissue[20]. Although ^{11}C-acetate PET/CT does not seem to be an accurate diagnostic modality for assessment of primary gland-confined prostate cancer, it has the potential to guide biopsy in individual clinically suspicious cases with negative biopsy results[21].

There are few data in the literature on the sensitivity of ^{11}C-acetate in assessing the initial nodal stage in prostate cancer, with a range of results. It has been found that ^{11}C-acetate may be useful for pelvic nodal staging and treatment planning in men with intermediate-risk (T2b–T2c or Gleason score 7 or PSA 10–20 ng/mL) to high-risk (T3a or Gleason score 8–10 or PSA >20 ng/mL) prostate cancer[22, 23].

Spick et al. retrospectively compared conventional bone scan and ^{11}C-acetate PET with respect to the detection of bone metastases. They found the two imaging techniques to be comparable in a patient-based analysis, suggesting that ^{11}C-acetate PET can reliably survey bone involvement[24].

^{11}C-Acetate also appears to be useful in the localisation of tumour recurrences in men with biochemical failure, with a detection rate that tends to be positively associated with increasing serum PSA level.

Information on the prognostic value of ^{11}C-acetate PET imaging is still limited. Moreover, studies that have systematically evaluated ^{11}C-acetate as an intermediate endpoint biomarker are lacking in the literature, even if anecdotal evidence suggests that ^{11}C-acetate imaging may provide such information in the context of prostate cancer treatment[25].

^{68}GA-PSMA

Prostate-specific membrane antigen is a transmembrane protein primarily present in all prostatic tissues. Increased PSMA expression is seen in a variety of malignancies, but most notably in prostate cancer[26]. Nearly all adenocarcinomas of the prostate – both primary tumours and metastatic lesions – demonstrate PSMA expression. Immunohistochemical studies have shown that PSMA expression increases in de-differentiated, metastatic or hormone-refractory disease and its expression level is a significant prognosticator for disease outcome[27]. Investigators have developed and evaluated, in preclinical animal and pilot human studies, several radiolabelled ligands using various platforms that include antibodies or antibody fragments targeting the intracellular (binding to apoptotic or necrotic cells) or extracellular (binding to viable cells) motifs of the antigen. These PSMA-based

tracers include ^{89}Zr-desferrioxamine B (DFO)-7E11; ^{64}Cu-labelled aptamers; and ^{11}C, ^{18}F, ^{68}Ga-, ^{64}Cu- and ^{86}Y-labelled low-molecular-weight inhibitors of PSMA, including ^{18}F-labelled N-[N-[(S)-1,3-dicarboxypropyl] carbamoyl]-4-[^{18}F]fluorobenzyl-L-cysteine and ^{18}F-labelled phosphoramidate peptidomimetics, with some formulations that can also be labelled with radionuclides such as ^{177}Lu or ^{90}Y for targeted radioimmunotherapy[28].

^{68}Ga-PSMA is currently one of the most successful PET tracers in prostate cancer due to its clinical specificity and also its availability, given that ^{68}Ga is easily obtained from a ^{68}Ge/^{68}Ga generator system. ^{68}Ga decays with 89% yield by positron emission and has a half-life of 67.63 min. Several low-molecular-weight ligands for human PSMA, linked with a chelator for ^{68}Ga complexation, are clinically available for PET/CT imaging. ^{68}Ga-labelled PSMA ligands were first radiosynthesised and validated in preclinical models at Johns Hopkins University[29].

Specific patient preparation

The indication for use of 68Ga-PSMA imaging should be evaluated before scheduling the examination to confirm that the procedure is appropriate. The physician in charge of the patient may request the withdrawal of specific drugs during prior clinical evaluations.

Patient height and body weight and the principal clinical details are recorded, in particular:

- Tumour type
- PSA value and Gleason score
- Known tumour localisations
- Previous therapies (type and time of surgery, chemotherapy, radiation therapy, monotherapy or others)
- Relevant symptoms (bone pain, frequent urination, nocturia, haematuria, dysuria, impotence, erectile dysfunction or painful ejaculation)
- Previous imaging findings
- Relevant co-morbidities
- Allergies
- Renal failure

Patients should be well hydrated before the injection and during the uptake period. Voiding immediately before imaging acquisition is recommended. Despite this, in some circumstances, high residual activity in the urinary system may lead to so-called halo artefacts on PET. Activity in the ureters may lead to false positive findings. Furosemide administration (20 mg i.v., shortly before or after administration of ^{68}Ga-PSMA) may be especially useful in these situations. Furosemide should not be administered in patients with medical contraindications to furosemide administration, including allergies (e.g. sulfa allergies).

	^{11}C-Acetate	^{11}C-Choline	^{68}Ga-PSMA
Patient preparation	Hydration with, for example, oral intake of 500 mL of water 2 h prior to acquisition	Hydration with for example, oral intake of 500 mL of water 2 h prior to acquisition	Hydration with for example, oral intake of 500 mL of water 2 h prior to acquisition
Activity	~ 740 MBq	~ 350 MBq	1.8–2.2 MBq per kilogram body weight
Administration	Intravenous; flushing with at least the same volume of saline	Intravenous; flushing with at least the same volume of saline	Intravenous; flushing with at least the same volume of saline
Concomitant medication	None	None	Possibly furosemide (20 mg i.v.)
Uptake time	10–15 min	10 min	60 min (50–100 min)
Patient position	Supine with arms elevated above the head	Supine with arms elevated above the head	Supine with arms elevated above the head.
CT protocol FOV	Base of the skull to mid-thigh	Base of the skull to mid-thigh	Base of the skull to mid-thigh
PET protocol	From mid-thigh to base of the skull; 1.5–2.5 min per bed position	From mid-thigh to base of the skull; 1.5–2.5 min per bed position	From mid-thigh to base of the skull; 3–4 min per bed position
PET reconstruction	Attenuation correction from CT data	Attenuation correction from CT data	Attenuation correction from CT data

Table 3: *Comparison of possible protocols for ^{11}C-acetate, ^{11}C-choline and ^{68}Ga-PSMA*

Table 3 provides a comparative overview of possible protocols for ^{68}Ga-PSMA, ^{11}C-acetate and ^{11}C-choline.

Administered activity

^{68}Ga-PSMA is injected as an intravenous bolus. Currently, the optimal injected activity is still under debate. The majority of published data are based on an injected activity of approximately 1.8–2.2 MBq per kilogram of body weight.

Clinical applications of ^{68}Ga-PSMA PET/CT

As stated in the recently issued EANM/SNMMI guidelines on ^{68}Ga-PSMA PET/CT,

data from prospective multicentre trials are not yet available; therefore the criteria for appropriate use of this imaging technique mainly derive from the clinical evidence available at present. The physiological distribution of ^{68}Ga-PSMA is illustrated in Fig. 6.

The current fields of application of this imaging technique are:

» Staging in primary cancer and in intraprostatic tumour
» Restaging in biochemically recurrent prostate cancer

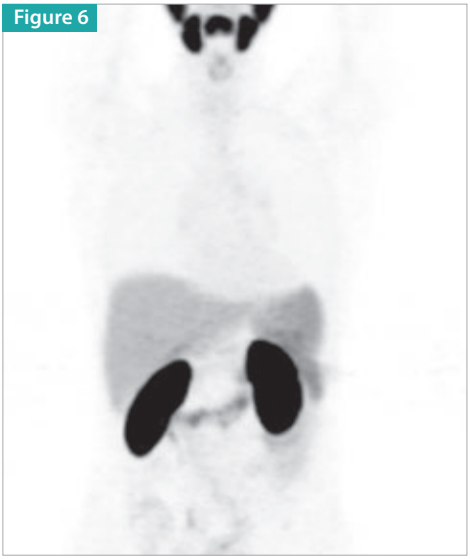
Interest is increasing in targeted biopsy in patients with a high suspicion of prostate cancer and previous negative biopsy and in PSMA-directed radiotherapy.

The use of ^{68}Ga-PSMA PET/CT in the primary staging of high-risk prostate cancer is increasingly being reported, though it has also been performed in patients with intermediate-risk disease. In a recent retrospective analysis by Budaus et al.[30] the sensitivity and specificity were found to be 33.3% and 100%, respectively. Maurer et al.[31] compared the detection rate of metastatic lymph nodes on ^{68}Ga-PSMA PET/CT and conventional imaging (CT and MRI) in patients prior to radical prostatectomy and pelvic nodal dissection. Sensitivity and specificity were 65.9% and 98.9% respectively on a per-patient level for ^{68}Ga-PSMA-PET/CT, as compared with 44.9% and 85.4% for conventional imaging.

While its role in primary staging has yet to be definitively determined, the benefit of ^{68}Ga-PSMA PET/CT in this context seems to lie especially in the possibility of early identification of metastatic disease, particularly in uncommon locations such as the mesorectum, and as a consequence it can lead to sensible modification of the treatment algorithm.

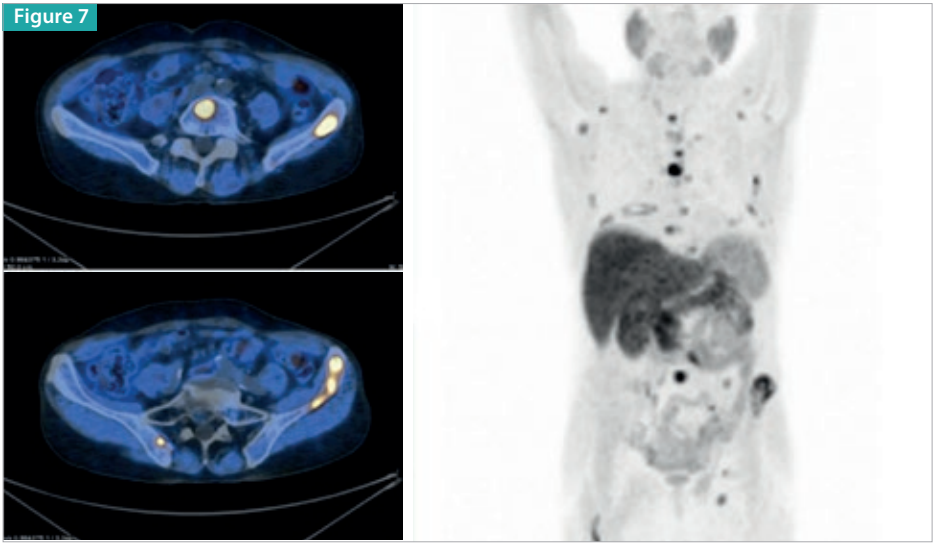
It is to be noted that multiparametric MRI represents a promising imaging modality in the diagnosis of primary intraprostatic prostate cancers and current data suggest that ^{68}Ga-PSMA PET/MRI may

Figure 6



^{68}Ga-PSMA PET/CT: physiological distributio

Figure 7



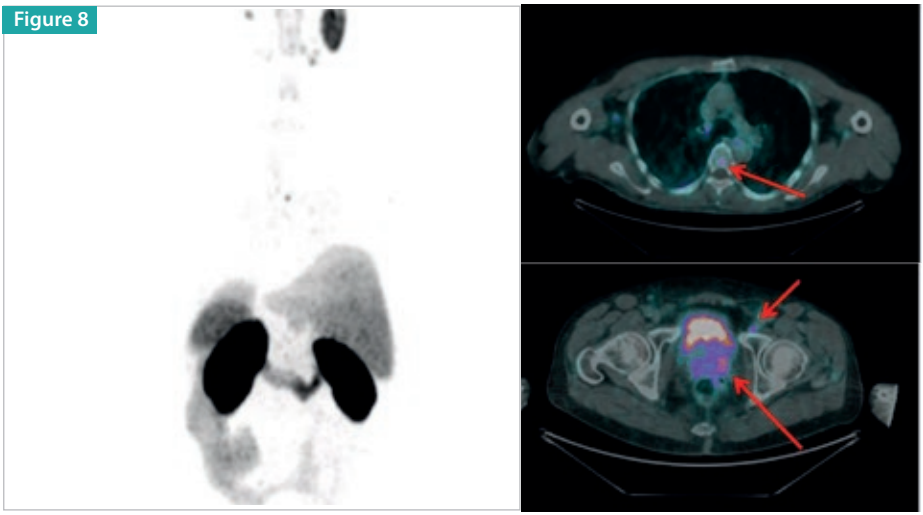
^{68}Ga-PSMA PET/CT in biochemical recurrence. Images show foci of pathological uptake in bones with no morphological lesions seen on CT, indicating rapidly growing disease

improve diagnostic yield and localisation in this setting[32].

A large majority of the evidence supporting the use of ^{68}Ga-PSMA PET/CT has been reported in the setting of biochemically recurrent prostate cancer (Figs. 7–9). In this scenario the evaluation of sensitivity and specificity is not easily accomplished as a comparative gold standard measure does not exist. Histopathology is not always feasible and sampling errors may arise due to the small volume of disease detectable on ^{68}Ga-PSMA-PET/CT. However, comparative data on ^{68}Ga-PSMA PET/CT and choline PET/CT are available in the literature. For example, in a retrospective analysis by Schwenck and co-workers of 103 patients with biochemical recurrence after primary treatment, ^{68}Ga-PSMA PET/CT showed a higher detection rate than ^{11}C-choline PET[33]. It is notable that the superiority of ^{68}Ga-PSMA PET/CT compared with current imaging modalities appears to be most significant at low PSA levels.

Apart from the EANM/SNMMI guidelines, it appears that only the European Association of Urology makes reference to ^{68}Ga-PSMA PET/CT. This not only highlights

Figure 8



^{68}Ga-PSMA PET/CT in biochemical recurrence. Images show nodal and bone involvement.

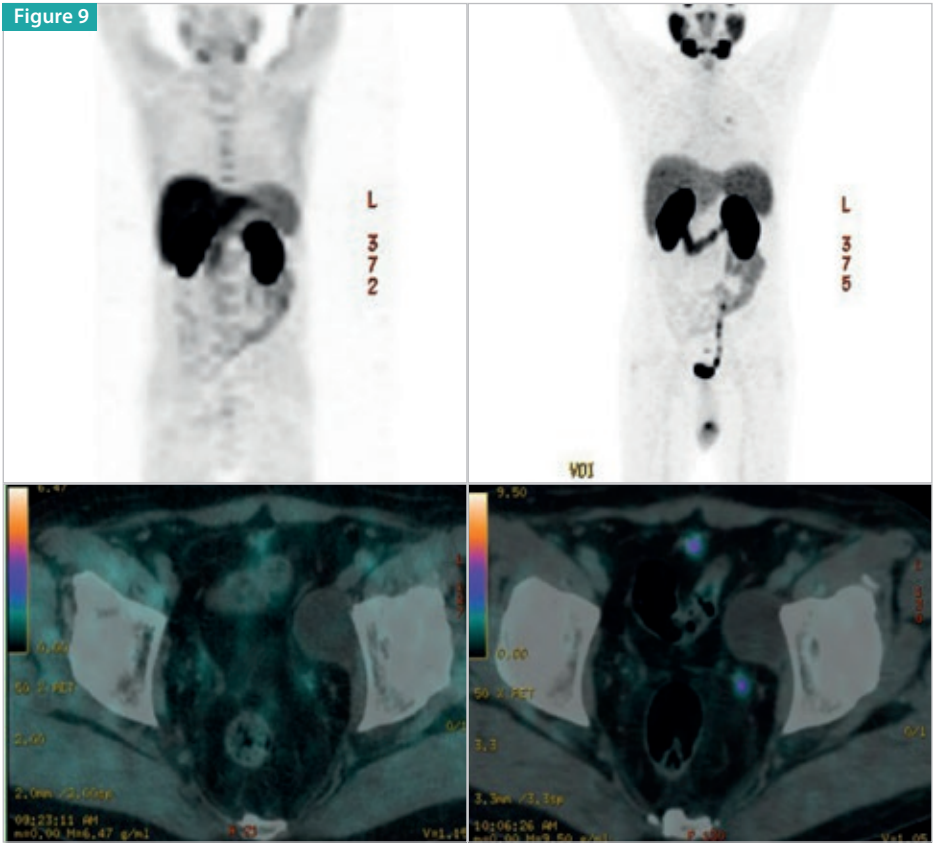
again the need for more extensive validation of the technique but also reflects the regional variation in availability of ^{68}Ga-PSMA PET/CT due to varying regulation with respect to the administration of novel radiopharmaceuticals. Nonetheless, use of ^{68}Ga-PSMA PET/CT has been increasingly reported in routine clinical practice in countries where scanning is available[34].

RADIOMICS AND FUTURE PERSPECTIVES

Recently radiomics has attracted growing interest in the field of imaging. It is a concept based on the idea that biomedical images contain more information than it is possible to capture by visual analysis only. Therefore sophisticated computerised algorithms have been developed to accomplish such "high-level" quantitative studies. Medical images suitable for radiomics include CT, MR imaging and, of course, PET/CT.

One example is provided by an article presenting a quantitative radiomics feature model for performing prostate cancer detection using multiparametric MRI (mpMRI). In this study a radiomics feature model was constructed to detect tumour regions within the prostate. The interesting point is that the high-level data derived from this computerised analysis were designed to fit categories already used by

Figure 9



Comparison between ^{11}C-choline and ^{68}Ga-PSMA PET/CT imaging in the same patient. A suspicious node seen in the supravesical area on ^{11}C-choline is confirmed on ^{68}Ga-PSMA PET/CT in a patient with biochemical recurrence and no other pathological findings

radiologists to diagnose prostate cancer – Morphology, Asymmetry, Physiology and Size (MAPS) – using biomarkers inspired by the PI-RADS guidelines for performing structured reporting on prostate MRI[35]. Further validation of the proposed algorithm is needed using a larger dataset, but this represents an interesting application of the radiomics concept that could also be applied to other imaging techniques.

In a study by Giesel et al. a correlation between SUVmax and CT radiomic analysis on lymph node density was performed in several different tumours, including prostate cancer. CT density measurements of lymph nodes correlated with tracer uptake on PET/CT (the radiopharmaceutical used for prostate cancer was ^{68}Ga-PSMA, while for other tumours different tracers were applied). The data suggested that this analysis could serve as an additional surrogate parameter for differentiation between malignant and benign nodes[36].

While few studies are currently available on the application of radiomics in PET/CT for prostate cancer, this is of course a brand new horizon that may disclose relevant diagnostic information and potentially also assist in the development of tailored treatments. For example, in the future radiomics data might be integrated into the radiotherapy workflow for the purposes of improved risk stratification, radiogenomics, treatment-related toxicity prediction, target volume definition, and follow-up.

Disclaimer: if not stated differently all images are property of Humanitas Research Hospital.

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PET/CT-GUIDED RADIOTHERAPY PLANNING IN PROSTATE CANCER

by Yat Man Tsang and Michelle Leech

INTRODUCTION

Prostate cancer is one of the most common cancers in men globally and the incidence across Europe is amongst the highest in the world, with 420,000 new cases reported in 2012[1,2]. The diagnostic assessment and management of prostate cancer remains challenging and controversial owing to the disease's wide spectrum of histopathological behaviours[3].

In the past decade, therapies for prostate cancer have undergone rapid change and development. In order to fully optimise the clinical management of patients with various stages of prostate cancer, improved diagnostic tools are required to allow accurate characterisation and localisation of the disease.

In general, positron emission tomography (PET) based staging has proven to be more accurate than non-PET staging owing to the sensitive and quantifiable molecular information that it provides on the biology and extent of the cancers[4]. The additional metabolic information on the primary tumour and lymph nodes has been suggested to be useful in radiotherapy planning. Fluorine-18 fluorodeoxyglucose (^{18}F-FDG) is the most commonly used radionuclide in clinical PET imaging, its uptake being assessed by means of the semi-quantitative standardised uptake value (SUV). ^{18}F-FDG accumulates in most cancers because of the expression of both glucose transporters and hexokinase in tumour cells. Hence, it may be used to identify regions of metabolically active disease within the tumour volume. However, experience in the use of 18F-FDG in prostate cancer for the purpose of staging has been discouraging owing to the low glucose metabolism in most prostate cancers. Carbon-11/fluorine-18 choline, which contains markers of cell membrane and metabolism, and prostate-specific membrane antigen (PSMA), a cell surface membrane glycoprotein, have been suggested to be promising targets for the diagnosis and treatment of prostate cancer[5, 6].

PROSTATE CANCER MANAGEMENT

Several treatment options are available for early prostate cancer, including active surveillance, radical prostatectomy, fractionated external beam radiotherapy and brachytherapy. As yet, no single one of these treatment modalities has been proven to be superior to the others. In optimal practice, all suitable options are discussed with the patient to facilitate individualised treatment based on the patient's clinical scenario and personal preferences.

Radiotherapy is an extremely effective treatment for prostate cancer and is one of the most important components in the prostate cancer management chain. Radiotherapy administered with curative intent, termed radical radiotherapy, involves the delivery of small doses of radiation once a day for several weeks. Each radiotherapy exposure is termed a fraction. Historically, prostate external beam radiotherapy has been given over 7–9 weeks with a daily fraction size of 1.8–2 Gy.

There is a compelling case for treating prostate cancer using hypofractionation. Hypofractionation is the delivery of a course of radiotherapy using a smaller number of fractions with a higher dose of radiation at each fraction compared with the conventional 1.8–2 Gy. The hypothesis that this approach improves the therapeutic ratio in prostate cancer was tested in the conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer (CHHIP) trial in a sample of 3216 patients[7]. The trial compared schedules of 60 Gy in 20 daily fractions and 57 Gy in 19 daily fractions over 4 weeks with a standard treatment schedule of 74 Gy in 37 daily fractions over 7.5 weeks. Early data from the trial suggested that hypofractionated prostate radiotherapy is safe and well tolerated.

EXTERNAL BEAM RADIOTHERAPY PROCESS

Radiotherapy volume delineation and planning

There has been exponential development in radiation delivery techniques, especially using external beam radiotherapy. The use of intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) allow individualised, highly conformal dose delivery to tumours while sparing surrounding normal tissues. These advanced techniques enable the delivery of the dose in more than one target volume and have realised the potential of dose escalation to the tumour. To exploit the advantage of IMRT/VMAT in creating a steep dose gradient between target volumes and normal tissues, it is essential to obtain precise target volume delineations and to achieve accurate daily treatment delivery with image-guided radiotherapy.

A successful course of radiotherapy for prostate cancer begins with the treatment planning process. With its excellent spatial reproducibility, kilovoltage x-ray computed tomography (CT) imaging is the current standard modality for radiotherapy planning. CT images can provide electron density information to radiotherapy treatment planning systems (RTPS) for heterogeneity-based dose calculations. However, sole use of CT for tumour volume delin-

eation is sometimes inadequate owing to its limited soft tissue contrast, which has the potential to give rise to significant inter-observer variability when contouring the target volumes. An increased risk of local relapse due to inaccurate target volume delineation with inadequate imaging cannot be compensated for by the use of advanced delivery techniques or dose escalation. Multi-parametric magnetic resonance imaging (MRI) is consequently often used in combination with CT for prostate target delineation for radiotherapy.

As recommended by the International Atomic Energy Agency (IAEA), PET can also be incorporated into the planning process with CT for more accurate target volume definition[8]. A radiotherapy plan can be designed for an individual patient to meet various treatment goals using a detailed computer algorithm describing how the radiation dose can be deposited within the patient's anatomy.

With the aim of standardising the practice of prescribing radiotherapy and designing treatment plans, the International Commission on Radiation Units and Measurements (ICRU) have produced reports 50, 62 and 83. These reports guide radiotherapy centres on how they can deliver an adequate and reliable dose to the tumour when treating with fractionated radiotherapy[9–11].

ICRU report 50 was published in 1993 and contained recommendations on how to report a treatment using external beam radiotherapy[9]. ICRU report 62 (a supplement to ICRU 50) was developed in 1999 to accommodate the rapid changes in radiotherapy technologies that had occurred with the increased use of multimodality imaging, computerised treatment planning, delivery and verification[10].

These two reports introduced common terminologies for radiotherapy reporting and prescribing with the intention of standardising radiotherapy prescribing practice internationally. The volumes described in the reports are outlined in Table 1.

In addition to the target volumes, the reports recommended that treatment plans should be prescribed to a stable point; this was termed the ICRU reference point. Often the isocentre of the treatment is used as the appropriate ICRU reference point. The treatment plan should be designed so as to fulfil the dose homogeneity criteria, such that the dose within the planning target volume (PTV) should vary by no more than −5% and +7% in relation to the prescribed dose at the ICRU reference point.

ICRU report 83 was produced in 2010 and referred specifically to the prescribing, recording and reporting of advanced radiotherapy techniques such as IMRT and VMAT[11]. The general principles of the previous ICRU reports were maintained with-

Volume name	Description
Gross tumour volume (GTV)	The gross palpable or visible/demonstrable extent and location of the malignant growth. For prostate radiotherapy, the GTV can be interpreted as the actual tumor(s) in the prostate gland. The PET/CT information is useful to aid in the volume delineation.
Clinical target volume (CTV)	The tissue volume that contains a GTV and/or subclinical microscopic malignant disease, which has to be eliminated. For radiotherapy to early stage prostate cancer, the CTV often refers to the whole prostate gland.
Planning target volume (PTV)	A geometrical concept, defined to select appropriate beam sizes and beam arrangements, taking into consideration the net effect of all the possible geometrical variations and inaccuracies in order to ensure that the prescribed dose is delivered to the CTV.
Organs at risk (OARs)	Normal tissues whose radiation sensitivity may significantly influence treatment planning and/or prescribed dose. For prostate radiotherapy, the OARs often refer to the bladder, rectum and femoral heads.

Table 1: *The various volumes described by ICRU 50/62* [9,10]

in the report, which highlighted the need for consistent dose reporting of PTVs by reporting of the median absorbed dose, the near maximum D2% (the highest dose received by at least 2% of the volume) and the near minimum absorbed doses D98% (the lowest dose received by at least 98% of the volume). In terms of dose prescribing, it recommended volumetric prescribing of the required treatment dose rather than just a single point (e.g. D95, D98 or median PTV dose).

For organs at risk (OARs), the report recommended the reporting of the mean absorbed dose, the near maximum dose and the VD, which, if exceeded, has a known probability of causing complications, e.g. V70Gy for rectum means the volume of rectum receiving 70 Gy. More consistent reporting may be achieved by the reporting of the highest dose or lowest dose received by at least 1 cc of an OAR, as this is independent of the volume of the region of interest.

With radiotherapy planning, it is clear that the initial images used to develop the treatment plan yield a single snapshot of the patient concerned, whereas the resulting treatment plan has to be designed

in a way that allows adequate delivery of radiation dose to the tumour in multiple fractions over a period of several weeks. In order to fulfill this requirement, treatment margins are added to the initial target at the treatment planning stage. Different margin recipes have been developed to allow determination of the margin size required in order to ensure that the clinical target volume (CTV) is covered by a certain radiation dose. Van Herk presented the most commonly used margin recipe from a Monte Carlo study of prostate radiotherapy treatments[12]. The margin size to ensure that the CTV receives at least 95% dose in 90% of patients is given as:

$$M_{ptv} = 2.5\,\Sigma + 1.64\,(\sigma - \sigma_p)$$

where Σ refers to the systematic variation, σ to the random variation and σp to the penumbra margin.

Radiotherapy treatment delivery

To account for the geometrical uncertainties, safety margins are applied. Geometrical uncertainties may be reduced by the implementation of image-guided radiotherapy (IGRT). Clinically, IGRT often refers to the ability to:

a) quantify the variation in position of the anatomical target between the planned and initial setup treatment images;
b) correct any patient misalignment by changing the relative geometry of the treatment machine (couch position) before the treatment is delivered.

There is a technical component that involves the acquisition and registration of images and a professional component that involves image review and decision-making on the extent of patient repositioning required. A multidisciplinary approach, particularly with significant involvement of radiation therapists, is considered essential in the development of an effective IGRT protocol.

Incorporating PET/CT into radiotherapy planning

With a view to incorporating the information from molecular or functional images into radiotherapy treatment planning, Ling et al. introduced the concept of dose painting[13]. This approach entails the prescription of a non-uniform radiation dose distribution to the target volume based on the acquired images, with the aim of achieving biological instead of physical conformity of radiation dose delivery to the tumour[13]. Subsequently, several investigators proposed further promising new ways to design radiotherapy treatment in accordance with the radiobiology of tumour cells and illustrated the techni-

cal feasibility of these approaches, which provide the foundation for PET/CT-based dose escalation[14–16].

In view of the limited temporal and spatial resolution of PET, technical issues such as hardware calibration, quality assurance, data post-processing and reconstruction techniques are of major importance when aiming for reliable assessment of a biologically active area[17]. Accurate patient positioning and immobilisation are crucial in radiotherapy treatment. Very often, patient positioning for routine diagnostic PET/CT image acquisition differs from that for the planning CT scan. Hence, it is recommended that PET/CT data to be used as a basis for radiotherapy planning should be acquired in the treatment position[18]. Standardisation of these technical requirements can ensure a more reliable target volume delineation using PET/CT images, leading to a solid basis for PET/CT-based dose escalation treatments.

When fusing the biological PET data with the dedicated planning CT, it is necessary to carry out image registration, which is a process of determining the optimal spatial transformation for mapping of one image to another. In general, the accuracy of image registration depends on the quality of images to be registered. The PET images are usually noisy and contain little anatomical information for registration with CT images. With the use of a hybrid PET/CT scanner, the PET is assumed to be automatically registered with the attenuation CT acquired during the same imaging session. First, automatic methods are used to register the attenuation correction CT to the treatment planning CT. The derived CT-to-CT transformation is then applied to the PET, and the registration accuracy of PET to treatment planning CT is thereby improved[18]. Several steps are involved in the process of image registration, including image set transfer, storage, coordination transformation and voxel interpretation. The process is prone to errors, which can cause serious adverse effects on target volume delineation. In accordance with the recommendations of the American Association of Physicists in Medicine (AAPM) Task Group 53 Report, it is essential to implement a quality assurance program to review general commissioning tests and to ensure that routine procedural checks are undertaken for verification of post-transfer image data integrity, image spatial integrity, image orientation and image registration accuracy[19].

With the high spatial resolution of IMRT/VMAT, it is feasible to deliver highly conformal radiotherapy to highly complex biological target volumes based on PET information. Accurate verification of patient positioning can lead to successful PET-based dose escalation treatment. Due to the delivery of an extremely high dose

to very small sub-regions of the tumour, very small (in the order of millimetres) systematic errors in patient positioning could cause severe penalties in terms of tumour control probability and normal tissue toxicities [20]. It is important to maintain a high quality of geometric accuracy in radiotherapy treatment with use of the latest daily IGRT techniques.

Efficient and successful IGRT implementation refines the delivery of radiotherapy by using imaging techniques to visualise and localise the target volume precisely, in order to allow proper patient repositioning that will ensure accurate treatment and minimisation of the volume of normal tissue irradiated. The rapid evolution of radiotherapy technology demands that radiation therapists continuously advance their practices to keep up to date with new developments, ensuring that these new techniques are implemented safely and accurately to the benefit of prostate cancer patients.

CONCLUSION

The use of PET/CT with advanced radiotherapy delivery techniques and IGRT approaches has the potential to improve radiotherapy treatment outcomes in prostate cancer patients. The introduction of molecular information from PET/CT imaging into the radiotherapy process is paving the way for personalised medicine for prostate cancer management.

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7

THERANOSTICS IN PROSTATE CANCER

by Sarah M. Schwarzenböck, Bernd Joachim Krause and Jens Kurth

INTRODUCTION

The prostate-specific membrane antigen (PSMA) is a transmembrane protein which is expressed on the surface of most prostate cancer cells (expression is 100- to 1000-fold higher compared with normal cells)[1].

PSMA ligands are increasingly being used for molecular imaging and therapy of prostate cancer in the sense of a theranostic approach. ^{68}Ga-PSMA-11 (^{68}Ga-PSMA HBED-CC), ^{68}Ga-PSMA-617 and ^{68}Ga-PSMA-I&T (being theranostic agents)[2–4] are the most widely used PSMA ligands for PET/CT imaging for staging of high-risk PC and restaging of recurrent PC (for an overview see[5]); besides ^{68}Ga-labelled PSMA ligands, ^{18}F-DCFBC, ^{18}F-DCFPyL and ^{18}F-PSMA-1007 have been introduced for PSMA PET/CT imaging[6–8]. In a meta-analysis including 1309 patients, PSMA PET positivity was demonstrated in 76% [95% confidence interval (CI) 66%–85%] and 40% (95%CI 19%–64%) of patients in the detection of recurrence and initial staging, respectively. In patients with biochemical recurrence and PSA values of 0.2–1, 1–2 and >2 ng/mL, detection rates were 58%, 76% and 95%, respectively[9]. These data are in line with the results of another recently published meta-analysis which reported detection rates of 50% for patients with a PSA value of 0.2–0.49 ng/mL and 53% for those with a PSA of 0.5–0.99 ng/mL[10]. These data were confirmed by the results of a retrospective analysis of 1007 patients with recurrent prostate cancer which demonstrated PSMA PET positivity in 46%, 46%, 73% and 80% at PSA levels of below 0.2, 0.21–0.5, 0.51–1 and 1.1–2 ng/mL, respectively[11].

Besides its diagnostic use, PSMA ligand PET/CT is increasingly being used before and during PSMA-based radioligand therapy (RLT) of metastasised and castration-refractory PC (mCRPC), a stage which will be reached after some years of androgen deprivation therapy (ADT). In this scenario, treatment options include taxane-based chemotherapies[12], therapeutic substances addressing the androgen receptor signalling axis and biosynthesis of androgens (such as enzalutamide and abiraterone)[13,14] and – in the case of bone metastases – the bone-seeking alpha emitter ^{223}Ra[15]; nevertheless, patients suffering from mCRPC have a poor prognosis[16]. Besides the promising use of ^{131}I-labelled PSMA targeting therapies[17,18], the use of ^{177}Lu for PSMA-based radioligand therapies (predominantly ^{177}Lu-PSMA 617[3] and ^{177}Lu-PSMA I&T[4]) has recently been demonstrated to be a safe and effective therapeutic strategy for the treatment of mCRPC patients[19–21]. This chapter gives an overview of the theranostic approach in prostate cancer, focussing on ^{68}Ga/^{177}Lu–labelled PSMA ligands.

THE THERANOSTIC APPROACH FOR IMAGING, THERAPY AND DOSIMETRY

In general, the term theranostics describes the combination of specific targeted therapy based on specific targeted diagnostic tests. With respect to molecular imaging and therapy, theranostics means that the same molecular target, which is highly exclusively expressed by tumour cells, is used for both diagnosis and therapy. In the first step, patients are identified as possible candidates for therapy by imaging. This can be done by labelling a molecule that binds specifically to a disease-specific molecular target with either a positron or a gamma emitter, followed by imaging with PET/CT or SPECT/CT. If positive results are obtained, in a second step the same or a very similar molecule can be used for therapy, now being labelled with a beta particle-emitting radionuclide (the use of alpha emitters has also been successfully investigated in very recent clinical studies[22]). Finally, response to the therapy can be assessed with the same diagnostic radiopharmaceutical as was used in step one.

For the PSMA-targeting theranostic approach, the well-known tandem of gallium-68 for diagnosis and lutetium-177 for therapy is widely used[23–26]. Gallium-68 is a metal and one of the first positron-emitting radionuclides that have been used for clinical imaging, such studies dating back to the early 1960s. It is a generator-eluted, short-lived radionuclide (with a half-life of 68 min) that decays 89% through positron emission. It also shows favourable chemical properties, so it can easily be labelled with peptides using chelator chemistry. Lutetium-177 is also a metal, but it is a medium-energy beta emitter (490 keV) with a maximum tissue penetration of about 2 mm and a relatively long physical half-life of 6.73 days. The shorter beta range of lutetium-177 provides better irradiation of small tumours. It also emits low-energy gamma rays at 208 and 113 keV, which allow for in vivo imaging and patient-specific determination of biokinetics. This is the basis for performance of patient-specific dosimetry before and during treatment, which offers the opportunity to improve the safety and efficacy of targeted radionuclide therapies because the tumour dose can be optimised and the organ toxicity can be predicted by estimation of dose to organs at risk.

THERAPY PROCEDURE AND PRACTICAL ASPECTS

To date, ^{177}Lu-PSMA has not been approved by the U.S. Food and Drug Administration and the European Medicines Agency; therefore formal criteria for the indication of RLT have not been defined. According to the recommendations of the

German consensus guideline published by an expert panel of the German Association of Nuclear Medicine, ^{177}Lu-PSMA RLT can be offered to mCRPC patients with progressive disease after exhaustion of approved therapies. Prerequisites for ^{177}Lu-PSMA RLT are previous first and second (or third) line therapies in accordance with guidelines and current clinical practice, sufficient organ function and increased PSMA expression[23]; ideally the indication for RLT should be discussed and confirmed within an interdisciplinary board. ^{177}Lu-PSMA RLT is administered in multiple cycles: according to the German consensus guideline, ^{177}Lu-PSMA RLT is repeated at 8-week intervals with 6 GBq as a standard activity, being administered intravenously as a slow bolus; 4–7 weeks after the second therapy cycle, restaging using PSMA ligand PET/CT takes place. Provided that RLT is sufficiently tolerated and tumour manifestations remain PSMA positive, further cycles can be considered, with a cumulative activity of up to 18 GBq[23]. In former studies up to four or six cycles of RLT have been applied without salivary toxicities of grade ≥3 or activity-limiting renal toxicity, respectively[24, 27].

Patient preparation should comprise evaluation of renal function (potentially including renal scintigraphy with ^{99m}Tc-MAG3) along with assessment of other clinically relevant parameters and sufficient hydration before, during and after the therapy. Pretherapeutic salivary gland scintigraphy with ^{99m}Tc-pertechnetate can be considered[23]. During therapy-forced diuresis, ice packs for the salivary glands, anti-emetic medication and steroid therapy may be considered depending on the patient's clinical condition[23]. The influence of continued ADT-based therapy during RLT is still under debate; preliminary data show that PSMA expression is potentially increased by ADT[28, 29].

Dosimetric measurements following ^{177}Lu-PSMA RLT are recommended, as discussed below. The follow-up examination should include patient history, physical examination, imaging and laboratory measurements at 2- to 4-week intervals. For more details on the recommendations regarding use of ^{177}Lu-PSMA RLT, see Fendler et al.[23, 30].

INTRA- AND POST-THERAPEUTIC IMAGING AND DOSIMETRY

The calculation of doses to tumour lesions and organs at risk requires intra- and post-therapeutic imaging of patients at multiple time points during treatment to extract time-activity curves (TAC) for each organ and lesion of interest. The TAC can be extracted from planar images or SPECT series or a combination of both[31, 32], prop-

er calibration of the gamma camera being required for both planar and SPECT imaging. SPECT images should be reconstructed using iterative algorithms, and corrections for scatter and attenuation, dead time and distant-dependent detector blurring should be used[33]. Considering on the one hand the poor health status of many patients suffering from mCRPC and on the other the kinetics of ^{177}Lu-PSMA compounds, use of a standardised imaging protocol is recommended (four time points at 2, 24, 48 and 72 h post-injection)[23]. Preferably, quantitative SPECT/CT imaging should be performed. However, in some situations multiple SPECT/CT imaging is not possible and/or the axial field of view obtained from whole-body imaging is desirable. In these cases a combination of whole-body imaging and SPECT/CT can be applied (so-called 2.5D imaging)[32].

Estimations of the doses to organs and target lesions are generally performed according to the MIRD scheme[34, 35] using special software tools[36, 37]. Based on the fitted TAC, the integral of the activity over time until infinity can be derived, which correlates to the number of decays that occur in the specific organ and from which the absorbed dose can be calculated. Blood-based and/or imaging-based methods are used to calculate the dose to red bone marrow[38].

The calculation of organ and lesion doses forms part of most clinical protocols for ^{177}Lu-PSMA-targeted therapies[23, 25, 39] and the results show rapid blood clearance and activity elimination from the body through the renal pathway. Besides uptake in tumour lesions of prostate cancer, physiological uptake of PSMA ligands is also seen in the lacrimal, parotid and submandibular glands, liver and spleen. The absorbed dose to the kidneys related to ^{177}Lu-PSMA RLT has been reported by several authors to be well below the 23 Gy dose-limiting threshold which is associated with a 5% probability of developing severe kidney damage within 5 years[40–42]. It is currently under debate to what extent the limit of 23 Gy, which is derived from external beam radiation therapy, can be used for radionuclide therapies, like PSMA-targeted therapy. However, parotid glands receive higher doses than the kidneys and the role of the lacrimal and salivary glands as dose-limiting organs is being discussed critically[43]. The dose to tumour lesions shows a high intra-patient and intra-lesion variability, mainly related to localisation and biological factors such as receptor density, binding affinity, tumour volume and many more.

Due to substantial individual variance, dosimetry is mandatory for a patient-specific approach in ^{177}Lu-PSMA-targeted therapy: the maximum tolerable dose to organs at risk calculated by an individualised method may be higher in a consider-

able number of patients, allowing for administration of a higher cumulative dose to the tumour. Therefore, higher activities and/or shorter treatment intervals might be tested in the future.

Figure 1

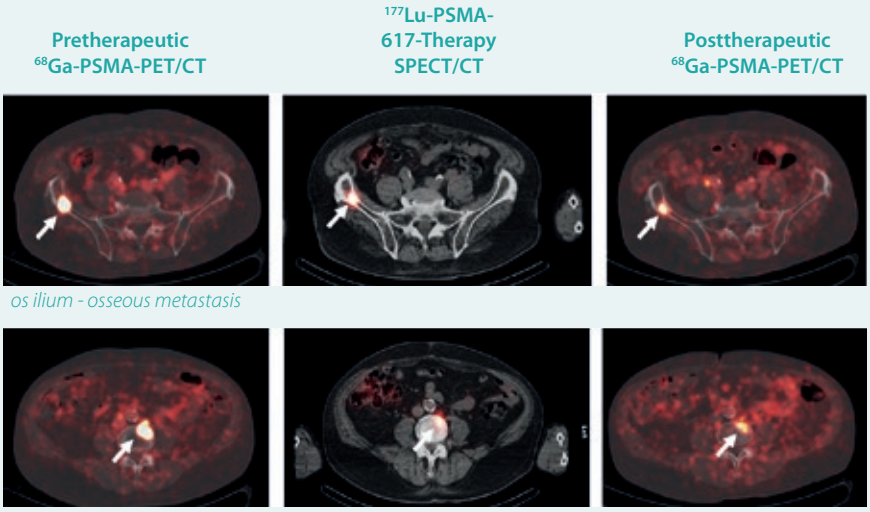

Figure 1: *Concept of theranostics for treatment of metastasised and castration-refractory prostate cancer (mCRPC): Quantitative ^{68}Ga-PSMA PET/CT is used to determine PSMA positivity of prostate cancer manifestations (pretherapeutic PET/CT). Then, targeted therapy is performed using ^{177}Lu-PSMA, which can be monitored in vivo by imaging with a gamma camera and/or SPECT/CT. Response to therapy is subsequently assessed, again with quantitative ^{68}Ga-PSMA PET/CT. This image example relates to an 80-year-old patient with mCRPC (initially pT4cN1cM1, Gleason score of 3). The patient received hormone ablation therapy and approved systemic therapies (Zytiga®, Taxotere® and Xtandi®). Due to progressive disease the patient was referred for ^{177}Lu PSMA therapy. Pretherapeutic ^{68}Ga-PSMA PET/CT showed PSMA-positive nodal and bone metastases (exemplarily shown: osseous metastases of the right os ilium and a vertebral body). Post-therapeutic ^{68}Ga-PSMA PET/CT after three cycles of ^{177}Lu-PSMA therapy showed a reduced tumour load, and PSA was significantly decreased*

BIOCHEMICAL AND CLINICAL RESPONSE TO ^{177}LU-PSMA RLT

Prostate-specific antigen values should be obtained after each therapy cycle. Overall, the results of available studies on PSMA ligand RLT in mCRPC patients who have received different numbers of therapy cycles indicate that response to therapy in terms of PSA decline is observed in up to 70%–90% of patients, with a PSA reduction of ≥50% in up to 60% [25, 39, 41, 44–50]. These results on biochemical response rate were confirmed by a German multicentre study which demonstrated a PSA decline of ≥50% in 45% of patients after all therapy cycles and in 40% after the first therapy cycle[24]. Similarly, a recently published meta-analysis showed "any PSA decline" in 68% of patients and a decline of ≥50% in 37%[19].

Stable disease (defined by a change in PSA ranging from a decrease of <50% to an increase of >25%) has been found in up to 50% of patients[24, 48]. In the latter study, only 23% of patients showed progressive disease (with a PSA increase of more than 25%) during therapy[48].

Pain relief has been observed in up to 70% of patients[25, 39, 51, 52], and significant improvement in quality of life in up to 60% of symptomatic patients[25, 41]. Karnofsky and Eastern Cooperative Oncology Group (ECOG) performance status score is improved or remains stable in most patients[39, 51, 52] while worsening is not or seldom observed[39].

IMAGE-BASED THERAPY RESPONSE ASSESSMENT OF ^{177}LU-PSMA RLT

Although response criteria for PSMA ligand RLT have not yet been established, preliminary data show that decline in PSA values is accompanied by morphological and/or metabolic changes as assessed by CT (RECIST criteria) and/or ^{68}Ga-PSMA PET/CT (PCWG2 criteria or PERCIST criteria).

Complete remission, partial remission and stable disease in ^{68}Ga-PSMA PET/CT-based therapy response assessment have been reported in up to 33%, 80% and 63% of patients, respectively, with progressive disease in up to 36% [25, 39, 44, 46, 51, 52].

Contrast-enhanced CT-based therapy response assessment (according to RECIST 1.1) has been reported to reveal partial remission in up to 40% and stable disease in up to 56% of patients, with progressive disease in up to 33%[25, 39, 44, 51]. Morphological response assessment has been found to be more reliable in nodal metastases than in bone metastases owing to better CT delineation of lymph nodes compared with bone metastases and the difficulties in differentiating active bone metastases from therapy-induced sclerotic bone changes[39].

Combined assessment using CT/RECIST criteria for soft tissue lesions and ^{68}Ga-PSMA PET/CT/PCWG2 criteria for bone lesions might be promising[51]. For an image example of therapy response assessment using ^{68}Ga-PSMA PET/CT, see Fig. 1.

SIDE EFFECTS OF ^{177}LU-PSMA RLT

The most common side effects of RLT are mild fatigue (for a few days after therapy) and mild and in most cases transient xerostomia[39, 41, 45, 46, 51], which may be reduced by a cooling procedure before and after therapy administration.

Diffuse bone marrow involvement seems be a risk factor for higher grade myelosuppression under treatment, and can be identified pretherapeutically by ^{68}Ga-PSMA PET/CT[24, 46]. Grade 3 or 4 haematological toxicities are observed in a minority of patients (up to 14%), most of whom have previously received chemotherapy or ^{223}Ra therapy[24, 41]. In the majority of studies no acute or long-term side effects or high-grade haematological or renal toxicities have been observed[25, 27, 39, 44–48, 50–52]. For an overview and further details on the toxicity of PSMA ligand therapy, see[20, 21].

The role of potential kidney protection is under discussion. According to the available data, kidney protection procedures might not be obligatory in patients with normal kidney function.

SURVIVAL DATA OF ^{177}LU-PSMA RLT

Relatively few data are available on the survival of mCRPC patients treated with RLT. In previous studies the reported median progression-free survival ranged between 175 days and 13.7 months[39, 41, 50–52].

In the study by Yadav et al. the median overall survival was 16 months[52]; these results were confirmed by Rahbar et al., who showed a median overall survival of 56 weeks[49]. A positive response to RLT, regardless of the rate of PSA decline, seems to be associated with a significantly longer median overall survival[49, 53].

In a retrospective study, Rahbar et al. showed the estimated median survival of an RLT group to be significantly longer than that of a historical best supportive care group[47]. Prospective controlled randomised trials are necessary to confirm improvement in survival of mCRPC patients who receive RLT compared with treated using conventional therapies.

CONCLUSION

^{177}Lu-PSMA RLT is a promising safe and effective treatment option that is already being offered to patients with mCRPC after exhaustion of all approved therapies, within clinical trials or under local regulations. In patients with bulky disease, ^{90}Y may represent an alternative to ^{177}Lu owing to the higher range of beta particles emitted by ^{90}Y. The use of PSMA ligands labelled with alpha emitters such as ^{225}Ac and ^{213}Bi could in the future be beneficial

in patients with compromised bone marrow or progressive disease under ^{177}Lu-PSMA RLT[22, 54–56]. Additionally, other novel theranostic agents that address the gastrin-releasing peptide receptor (GRPR), also overexpressed in prostate cancer, such as the GRPR antagonist ^{68}Ga/^{177}Lu-RM2, may be promising theranostics for prostate cancer in the future[57–60].

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AVAILABLE AS WEBINAR

8 PROSTATE CANCER RADIONUCLIDE THERAPY BASED ON ALPHA EMITTERS

by Mark Konijnenberg and Domenico Albano

INTRODUCTION

Prostate cancer is one of the most common cancers among men. It is associated with advanced age (it is very uncommon in males <45 years old) but its pathogenesis is not yet clearly understood. Usually this neoplasm grows very slowly, but sometimes it spreads to other organs. There are two main types of metastatic dissemination: local metastasis, with spread to other organs within the pelvis and usually lymph node involvement, and distant metastases, when the spread extends beyond the pelvis, to bone, liver, lung or brain.

METASTASES IN PROSTATE CANCER

Bone is the most frequent site of distant metastatic localisation. Bone lesions usually have an osteoblastic nature, but in rare cases are osteolytic or mixed. Bone metastases may be symptomatic and associated with skeletal events, such as fractures, that are responsible for a decreased quality of life and increased mortality.

The process by which prostate cancer metastasises to bone involves an interaction between cancer cells, bone matrix and cellular elements of the bone. Despite the osteoblastic appearance on radiography, bone metastases from prostate cancer exhibit an increase in both osteoblast and osteoclast activity. Osteoclast-mediated bone resorption releases factors (such as tumour growth factors) that promote cancer cell growth and survival. In turn, prostate cancer cells produce proteins that drive osteoblast and stromal production of receptor activator of nuclear factor kappa-B ligand (RANKL), which further drives the immune system and controls osteoclast bone regeneration and remodelling. The result is a vicious cycle of bone destruction. Therapeutic agents that inhibit osteoclast-mediated bone reabsorption interfere with this process and improve outcomes.

The most common symptom from skeletal metastases is pain. About 75% of patients suffer from this and need severe pain medication such as opioids. Such skeletal pain is most probably induced by the above-described local bone destruction, which may trigger pain receptors within local nerves. Loss of bone strength due to the skeletal lesions may lead to bone fractures, including microscopic fractures. An inflammatory response is stimulated by the increased blood flow to the metastatic lesions, with release of cytokines in tumour cells and surrounding normal cells.

ALPHA-PARTICLE-EMITTING RADIONUCLIDES AVAILABLE FOR PROSTATE CANCER THERAPY

The first targeted alpha-particle emitter therapy to be approved for the treatment of metastatic prostate cancer is radium-223 (^{223}Ra) dichloride (Xofigo®)[1]. In the periodic system, radium belongs to the alkaline earth metals (group 2), which also include beryllium and calcium. Alkaline earth metals are known to be calcium mimetic or "bone seekers" and ^{223}Ra is no exception. It accumulates in bone, with highest uptake around the interface between bone and metastasis. The same mechanism of uptake occurs with the beta-particle emitter strontium-89 (^{89}Sr) chloride (Metastron®), which is also an alkaline earth metal. ^{223}Ra has a great advantage over ^{89}Sr in that it emits high-LET alpha particles; this enables complex DNA double-strand break-induced cell death at a short distance, as the range of the emitted alpha particles is between 40 and 70 µm[2].

Other agents for alpha-particle emitter radionuclide therapy for prostate cancer are still at an experimental stage. Most of the compounds under development use prostate-specific membrane antigen (PSMA) targeting agents as carriers to deliver the alpha emitter to visceral metastatic lesions. PSMA is expressed in almost all prostate cancers, including soft tissue metastases; however, it is also expressed in healthy tissues like salivary glands and kidneys (proximal tubules). PSMA targeting agents labelled with the alpha emitters actinium-225 (^{225}Ac) and bismuth-213 (^{213}Bi) have been used on a compassionate use basis in castration-resistant prostate cancer patients. The results in disease reduction are impressive, especially for ^{225}Ac-PSMA, which has been shown to be successful in patients with disease refractory to lutetium-177 PSMA therapy[3, 4].

HOW PATIENTS ARE SELECTED FOR THERAPY

Nuclear medicine therapy for bone metastases is a systemic radionuclide therapy based on the use of intravenously administered radiopharmaceuticals that are classified into specific tumour-seeking and bone-seeking agents. Bone-seeking radiopharmaceuticals are specifically localised to the sites of active bone reaction and remodelling (areas with increased osteoblastic activity) and deliver focal radiation by beta emission or alpha particles, targeting primary metastatic bone lesions. The same mechanism is exploited in the diagnosis of bone metastases using technetium-99m phosphonate. Therapeutic bone-seeking radiopharmaceuticals can also be divided into two principal chemical classes – cationic or calcium analogues (such as phos-

phorus-32, strontium-89 and radium-223) and anionic or non-calcium analogues (such as samarium-153 lexidronam and rhenium-186 or rhenium-188 etidronate) – with different mechanisms of uptake into bone.

The choice of radiopharmaceutical is based on the physical characteristics of the radionuclide in relation to the extent of metastatic disease, the bone marrow reserve and the radiopharmaceutical availability in individual countries. Radiometabolic therapy is inappropriate in patients with a life expectancy of less than 4 weeks and considering the latency in onset of the palliative effect, it is more beneficial in patients with a relatively long life expectancy. The principal side effect of bone-seeking radiopharmaceuticals is temporary myelosuppression, with complete or partial recovery over the following 3 months; thrombocytopenia is common, neutropenia and anaemia are less common. For this reason, periodic haematological monitoring may be useful.

RADIUM-223 THERAPY

Generally radionuclide therapy is indicated for the treatment of bone pain due to skeletal metastases and for the treatment of painful skeletal metastases that are inadequately treated by analgesics, intolerant to analgesics and hormone resistant.

The first radiopharmaceuticals to be used were phosphorus-32, strontium-89, rhenium-186, rhenium-188 and samarium-153, but their use is no longer widespread due to their significant side effects, especially myelosuppression. These radiopharmaceuticals are bone-targeting beta emitters with a relatively long radiation range and significant bone marrow exposure.

In 2013 the U.S. Food and Drug Administration (FDA) approved ^{223}Ra as a therapeutic agent for the treatment of patients with castration-resistant prostate cancer and symptomatic bone metastases in the absence of known visceral metastatic disease. The phase 3 ALSYMPCA trial was stopped early when it became clear after an interim analysis that the median survival in patients treated with ^{223}Ra was significantly longer than in the placebo group (14.9 months vs 11.2 months; $p<0.001$)[1]. This result is remarkable, considering that in most cases the treatment intention is pain palliation.

The EANM guidelines regarding ^{223}Ra therapy mirror the FDA approval for the agent, i.e. they consider it to be indicated in patients with castration-resistant prostate cancer, symptomatic bone metastases, and no known visceral metastases. The presence of not too bulky lymph node metastases (»3 cm) is not regarded as an explicit exclusion criterion[2].

RADIOBIOLOGICAL PRINCIPLES

Radiation induces cell death by producing damage to DNA. This principle has been applied with beta-particle emitters and external beam exposure. In these low ionisation density or low-LET radiation conditions, less complex sublethal DNA damage will be repaired, especially at the low dose rates encountered with beta-particle emitters. The high-LET radiation of the four alpha particles emitted by ^{223}Ra creates more complex multiple DNA breaks that are not repairable. The range of the alpha particles in tissue is 60–100 µm, whereas the beta particles from samarium-153 have a mean range of 1 µm and a maximum range of 3.4 µm. Consequently, when using ^{223}Ra the absorbed dose will be delivered in close proximity to the emission site, which helps to reduce the absorbed dose in nearby critical organs such as bone marrow. Small-scale dosimetry models for metastatic bone lesions in the endosteal layer and the bone marrow show that even at the highest considered absorbed dose to bone lesions, i.e. 20 Gy, more than 40% of the bone marrow will receive a dose of <2 Gy[5].

In external beam palliative radiotherapy for bone metastases, pain relief is obtained after a single dose of 8 Gy. More prolonged pain relief is achieved by the use of fractionated dosing schemes, ranging from 20 Gy in 5 fractions to 30 Gy in 10 fractions[6]. External beam radiotherapy (EBRT) is only applicable for a limited number of bone lesions. Radiopharmaceuticals form an important palliative care option for multifocal bone metastases and, as already mentioned, in the case of ^{223}Ra may even offer prolongation of survival.

Technetium-99m methylene diphosphonate (MDP) bone scan can be used to determine the absorbed dose to bone lesions, offering guidance regarding the ^{223}Ra uptake. A mean absorbed dose of 0.7 (0.2–1.9) Gy per treatment cycle of 50 kBq/kg body weight was reported in nine patients[7]. With a full therapy consisting of six treatment cycles this would result in a mean absorbed dose of 4 Gy; taking the enhanced radiobiological effect (RBE) of alpha particles into account (with an assumed RBE of 5 for alpha emitters [18]), this would correspond to D_{RBE}=19 Gy. This absorbed dose does not exceed the doses obtained with EBRT and other beta-emitting palliative radiopharmaceuticals.

PROSTATE CANCER THERAPY

Xofigo is the only clinical therapy available that is based on ^{223}Ra. ^{223}Ra is obtained from an actinium-227 generator. Actinium-227 decays via its daughter radionuclide thorium-227 ($T_{1/2}$=18.7 days) to ^{223}Ra. The six-stage decay of ^{223}Ra to stable

lead-207 occurs via a chain of short-lived daughter nuclides and is accompanied predominantly by alpha emissions (Fig. 1); in addition, beta and gamma emissions occur with different energies and emission probabilities. ^{223}Ra and its daughter

Figure 1

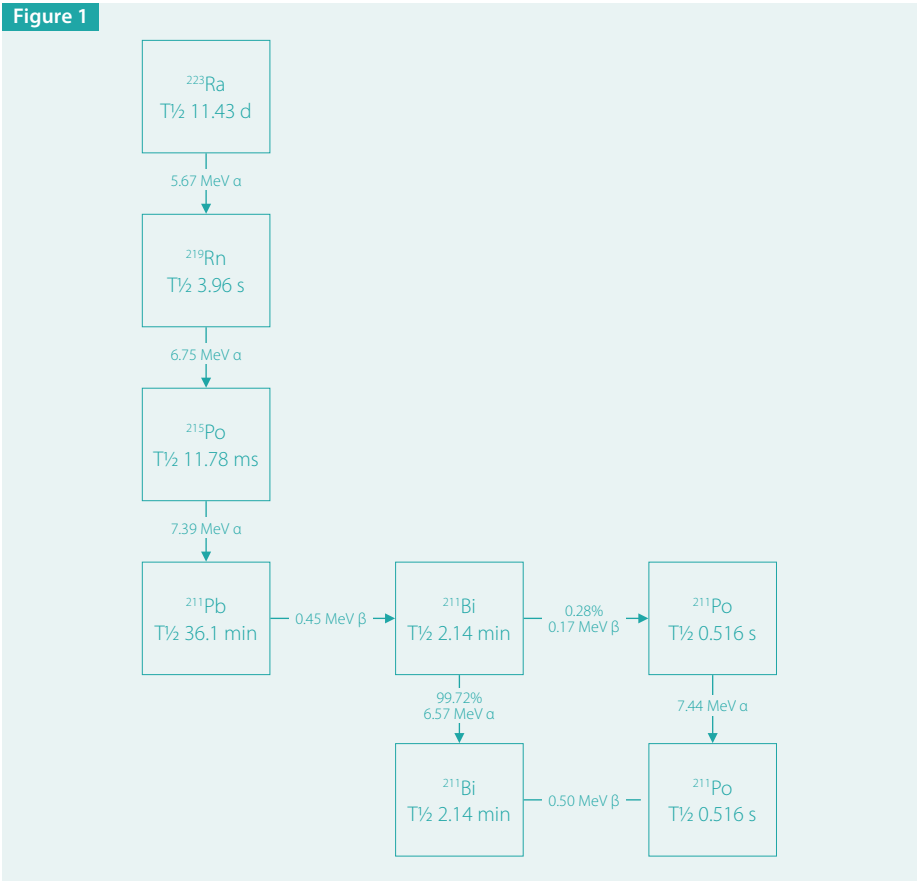

Figure 1: *Decay scheme for ^{223}Ra and its progeny, with alpha-particle emissions (downward arrows with total alpha-particle energy per decay) and beta-particle emissions (sideward arrows with mean beta-particle energy)*

nuclides radon-219, polonium-215, lead-211, bismuth-211 and thallium-207, reach equilibrium after a couple of hours. As a consequence ^{223}Ra may be considered to be a radionuclide emitting four alpha particles per decay with a half-life of 11.43 days (Table 1). The fraction of energy emitted from ^{223}Ra and its daughters as alpha particles is 95.3% (energy range of 5–7.5 MeV). Lead-211 and bismuth-211 emit beta particles with mean energies of 0.45 and 0.17 MeV, respectively. ^{223}Ra emits several gamma- and x-rays, of which the x-rays at 81 keV and 84 keV (with abundances of 15.7% and 25.9%/decay) can be used for imaging. Additionally at higher energy the gamma-rays at 144 and 154 keV (3.27% and 5.70%/decay) are very suitable for SPECT imaging.^{223}Ra and its progeny, however, also emit many high-energy gamma-rays, with consequently image-degrading effects in low-energy windows, such as down-scatter and septal penetration. It is advisable to perform acquisitions with two energy windows centred at 82 keV and 154 keV (20% wide) and a medium-energy general-purpose collimator[8].

The biokinetics of ^{223}Ra has been studied extensively for radiation protection purposes. Based on the biokinetic model for ^{223}Ra of ICRP publication 67, organ dosimetry estimates have been made, with absorbed dose estimates for the bone endosteum of 3.8 Sv/MBq and for the bone marrow of 0.37 Sv/MBq, both with an RBE=5. This would result in a cumulative absorbed doses of 16 Gy to the endos-

Nuclide	Physical half-life	Total alpha energy (MeV/decay)	Abundance per decay of ^{223}Ra	Mean range in soft tissue (µm)	Mean range in cortical bone (µm)
^{223}Ra	11.43 days	5.667	100%	43	28
^{219}Rn	3.96 s	6.754	100%	57	37
^{215}Po	1.78 ms	7.386	100%	65	43
^{211}Bi	2.14 min	6.549	99.724%	54	35
^{211}Po	0.516 s	7.442	0.276%	66	43

Table 1: *Decay properties of ^{223}Ra and its progeny, with total alpha-energy emitted per decay and its range in soft tissue (density: 1.04 g/cm^3) and adult cortical bone (density: 1.92 g/cm^3). Alpha-particle energies from ICRP publication 107 and the ranges in tissue were calculated with the SRIM-2013 code (available at SRIM.org)*

teum and 1.5 Gy to the bone marrow per therapy with 4.125 MBq ^{223}Ra. In patients with advanced disease these doses might be very different[9].

The biodistribution and dosimetry for ^{223}Ra dichloride have been studied in phase 1 clinical trials[10, 11]. It was found that the compound is rapidly cleared from the blood, with less than 1% remaining at 24 h. Most of the administered activity was rapidly taken up into bone (61%±10% of the administered activity at 4 h after injection). Elimination of ^{223}Ra dichloride was mainly through the gastrointestinal tract, and early clearance was seen from the small intestine: at 4 h, 40%±19% of the administered activity was in the small intestine, but by 72 h all activity had cleared. Clearance from the large intestine occurred at later time points. Urinary excretion was minimal (typically 2%–5%) and faecal excretion was found to provide the main route of elimination[10, 11].

The phase 1 trials with ^{223}Ra revealed a maximum tolerable activity of 200 kBq/kg, almost four times the amount that provided pain relief and survival efficacy in the phase 2 and 3 trials. This opens options for the design of more optimal treatment schemes, aimed at increased survival. This treatment planning approach would also be more in line with the current European legislation according to the EC Directive 2013/59 Euratom[12], which states that "in all patients' exposures for radiotherapeutic purposes, the irradiation of target volumes shall be individually planned and appropriately verified, keeping the absorbed doses to non-target tissues as low as reasonably achievable and consistent with the intended radiotherapeutic purpose of the exposure". Exact knowledge of the absorbed dose-response correlations is essential and a multicentre, observational study regarding lesion dosimetry has been started in Italy for this purpose[8].

DURATION OF RADIONUCLIDE THERAPY

Therapy with ^{223}Ra is administered intravenously at a dose of 55 kBq/kg body weight. In total, six injections are given at intervals of 4 weeks, resulting in a total of 24 weeks of therapy. Typically 50% of patients are capable of receiving the full six-cycle treatment. Reasons for discontinuation of therapy are progressive disease, haematological toxicity, declining health status, and skeletal-related events[13]. Clinical studies are ongoing to compare the standard 6×55 kBq/kg with 6×88 kBq/kg and 12×55 kBq/kg, the doses all being given at 4-week intervals[14]. Retreatment with 6×55 kBq/kg ^{223}Ra was found to be well tolerated, with minimal haematological toxicity, in a phase 1/2 prospective study in a highly selected population of

patients with castration-resistant prostate cancer and bone metastases who had undergone initial ^{223}Ra treatment 6 months (median time interval) previously[15].

DEVELOPMENT OF NEW RADIONUCLIDES AND THERAPIES

Most new therapies rely on a vector such as PSMA-targeting agents that is of proven efficacy in conjunction with a beta emitter or alpha emitter. ^{225}Ac seems to be a favourite as it can be labelled to the vector by metal chelators such as DOTA. Like ^{223}Ra, it emits four alpha particles per decay by itself and through its daughter atoms, all of which have a shorter half-life than that of ^{225}Ac ($T_{1/2}$=10 days). ^{225}Ac is obtained from a thorium-229 generator ($T_{1/2}$=7880 years), which decays through radium-225 ($T_{1/2}$=14.8 days) to ^{225}Ac[16]. Another alpha emitter that is gaining more attention in various preclinical and also some clinical studies is astatine-211. Its half-life is much shorter ($T_{1/2}$=7.21 h) and it emits only one alpha particle per decay, 41.8% with 5.87 MeV and 58.2% by its daughter polonium-211 ($T_{1/2}$=0.516 s) with 7.44 MeV[17]. It can be produced through the bismuth-209(α,2n) astatine-211 reaction with a high-energy cyclotron by bombarding a bismuth target with 30-MeV alpha particles. The chosen alpha energy is usually lower than the optimum value at 31 MeV since at this energy astatine-210 is also formed, which decays to polonium-210: a pure alpha emitter with a half-life of 138 days which has become infamous after the poisoning of Alexander Litvinenko.

Alpha-emitter therapies are considered to be the most promising form of radionuclide therapy, as they are capable of killing both single cells and small to large tumour lesions. The high-LET character of the alpha-particle radiation enables it to be effective in tissues with low oxygen levels, such as the hypoxic core of many tumours. Understandably, the risk of and concerns regarding serious toxicity in off-target tissue make the development of these targeted therapies a long-term effort and currently most alpha-particle therapies are aimed at patients with end-stage disease.

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AVAILABLE AS WEBINAR

THE MANAGEMENT OF A PROSTATE CANCER PATIENT

by MarieClaire Attard and Rexhep Durmo

INTRODUCTION

A patient is an individual with needs, opinions and expectations, which may differ from those of another individual of the same age and gender. Every patient should be treated according to their needs, and any treatment or procedure should first be discussed with the patient, to help with decision making. Whether the patient accepts the proposed treatment or procedure is irrelevant to the responsibility of the clinician to inform the patient of the possibilities available for treating prostate cancer.

RISK FACTORS AND SYMPTOMS

Since the causes of prostate cancer are not fully understood, there is currently no clear prevention strategy. However, a number of factors are associated with the risk of developing the disease, including:

- Increasing age
- A family history of prostate cancer
- Race (for example, men of Caucasian background are more at risk than Asian men)[1]

Most patients with clinically localised prostate cancer have no symptoms attributable to the cancer. Urinary frequency, urgency, nocturia and hesitancy are commonly seen, but are usually related to a concomitant benign prostate hyperplasia (BPH). Haematuria and haematospermia are uncommon presentations of prostate cancer, but their presence in older men should prompt consideration of the disease in the differential diagnosis. Bone pain may be the presenting symptom in men with metastatic disease[2].

SCREENING AND EARLY DETECTION

Various tests have been developed to detect the presence of prostate cancer. The findings depend on several factors and behaviours. Screening for prostate cancer remains one of the most controversial topics in the urological literature. The two largest trials, the European Randomized Study of Screening for Prostate Cancer (ERSPC) and the prostate arm of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening, yielded conflicting results. The ERSPC demonstrated a 20% reduction in prostate cancer-specific mortality in men randomised to an invitation to screening compared with controls, whereas the PLCO did not demonstrate a reduction in mortality. Although the benefits of prostate cancer screening are

uncertain, the burdens associated with the early detection and treatment of prostate cancer have been defined. It has been estimated that between 23% and 42% of screen-detected cancers would never have been diagnosed in the absence of screening[3, 4]. However, the potential for overdiagnosis, associated overtreatment and adverse treatment effects has led to neither a clear mandate to screen nor a proscription against screening. Most recent guidelines recommend that asymptomatic men who have at least a 10-year life expectancy should have an opportunity to make an informed decision with their health care provider about screening for prostate cancer after they receive information about the uncertainties, risks and potential benefits associated with prostate cancer screening[5–7, 9, 13].

The most common tests are analysis of serum prostate-specific antigen (PSA) levels and direct rectal examination (DRE). PSA is a glycoprotein produced by prostate epithelial cells. While PSA is organ specific it is not cancer specific, and may be elevated in BPH, prostatitis and pelvic trauma. Furthermore, it does not give any indication regarding the nature, location or extent of the cancer[3–5].

A DRE is a rectal examination performed by the physician whereby a gloved finger is placed into the rectum to feel the surface of the prostate. It can detect palpable abnormalities (e.g. nodules, asymmetry or induration) in the posterior and lateral aspects of the prostate gland, where the majority of cancers arise; however, other areas of the prostate are not reachable by DRE. Furthermore, most cancers detected by DRE alone are clinically or pathologically advanced and stage T1 prostate cancers are non-palpable by definition[6, 7].

Although a high PSA and an abnormal DRE may raise the suspicion of prostate cancer, only a biopsy can confirm the presence of cancer cells. With a biopsy, small cores/samples of prostate tissue are removed and sent for analysis.

THE NEWLY DIAGNOSED PROSTATE CANCER PATIENT

The diagnosis of prostate cancer can only be confirmed by the results of histological examination from a prostate biopsy or surgery. Transrectal ultrasound (TRUS)-guided biopsy is currently the standard of care. Ten- to 12-core biopsies should be taken, bilateral from apex to base, as far posterior and lateral as possible from the peripheral gland. Additional cores should be obtained from areas suspicious on DRE or TRUS[8].

The biopsy result gives an indication of the nature of the tumour and its stage, and on this basis the disease is classified as low, intermediate or high risk[9]; this will be further explained below.

TUMOUR CHARACTERISTICS

There are three types of tumour characteristic: tumour grade, tumour score and tumour stage.

Tumour grade and score

Tumour aggressiveness can be determined by the histological results obtained from the biopsy. The most common tumour grading system is called Gleason grading. This grading system assigns a grade to the prostate cancer, from 1, denoting the least aggressive, to 5, denoting the most aggressive. The total score is derived by summing the score relating to the dominant or most common cell morphology (scored 1–5) and the score relating to the non-dominant cell pattern with the highest grade (scored 1–5) [10]. The higher the Gleason score obtained from the biopsy, the more aggressive is the tumour. High-grade cancer refers to tumours with Gleason scores of 8 to 10 (although it can also include Gleason 7 tumours)[9].

Tumour stage

The tumour stage refers to the extent of invasion of surrounding organs by the prostate cancer. Tumours that remain confined to the prostate are, of course, more easily treatable that those that have spread to the surrounding tissues. Prostate cancer that has metastasised to other body organs, such as bone or lymph nodes, has a poor prognosis. The most widely used staging system for prostate cancer is the American Joint Committee on Cancer (AJCC) tumour-node-metastasis (TNM) system[11], as shown below.

The AJCC staging system for prostate cancer is based on five key pieces of information:

- The extent of the main (primary) tumour (T category)
- Whether the cancer has spread to nearby lymph nodes (N category)
- Whether the cancer has spread (metastasised) to other parts of the body (M category)
- The PSA level at the time of diagnosis
- The grade group (based on the Gleason score)

T – Primary tumour

- **TX Primary tumour cannot be assessed**
- **T0 No evidence of primary tumour**
- **T1 Clinically inapparent tumour that is not palpable**
  - T1a Tumour incidental histological finding in 5% or less of tissue resected
  - T1b Tumour incidental histological finding in more than 5% of tissue resected
  - T1c Tumour identified by needle biopsy (e.g. because of elevated PSA level)
- **T2 Tumour that is palpable and confined within the prostate**
  - T2a Tumour involves one half of one lobe or less

- T2b Tumour involves more than half of one lobe, but not both lobes
- T2c Tumour involves both lobes

» **T3 Tumour extends through the prostatic capsule**
- T3a Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement
- T3b Tumour invades seminal vesicle(s)

» **T4 Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles and/or pelvic wall**

N – Regional lymph nodes

» **NX Regional lymph nodes cannot be assessed**
» **N0 No regional lymph node metastasis**
» **N1 Regional lymph node metastasis**

M – Distant metastasis

» **M0 No distant metastasis**
» **M1 Distant metastasis**
- M1a Non-regional lymph node(s)
- M1b Bone(s)
- M1c Other

Low risk

» Usually a PSA ≤10 ng/mL
» A Gleason score of ≤6
» A clinical stage of T1(a,b,c) or T2a

Intermediate risk

» A PSA >10 to 20 ng/mL
» A Gleason score of 7
» A clinical stage of T2b

High risk

» A PSA >20 ng/mL
» A Gleason score of 8 to 10
» A clinical stage of T2c

Figure 1: *Patient categorisation according to pathological factors and patient treatment preferences*

RISK CLASSIFICATIONS

Patients are usually classified into three categories (Fig. 1) according to their pathological factors and their treatment preferences[12, 13], though some authors also include a very low and a very high risk group[14]. However, there are limitations to this risk classification. No two patients are the same and patients' requests and needs will depend on their lifestyle, age and tumour classification and staging[14].

Figure 2 shows the classification of prostate cancer and illustrates some of the available management options. A brief explanation of each imaging technique and treatment is given below.

Figure 2

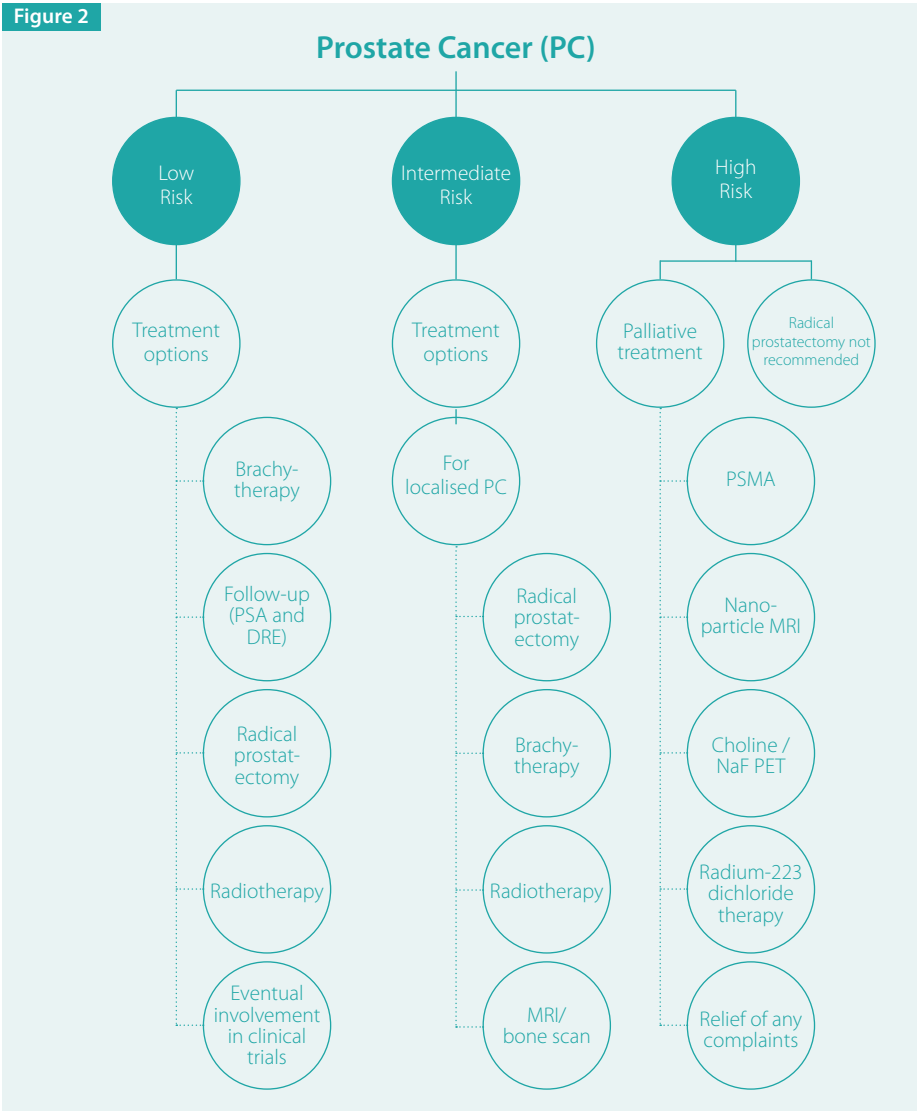

Figure 2: *Classification of prostate cancer, illustrating some of the treatment options available in different risk groups*

LIFE EXPECTANCY

The patient's overall health status is the major factor when making treatment decisions. The younger the patient, the longer the life expectancy; therefore factors such as urinary, sexual and bowel function are very important and need to be considered when choosing a therapy[15]. The earlier that prostate cancer is diagnosed, the earlier the treatment and thus the better the long-term survival[3].

IMAGING FOR DISEASE DETECTION

Technological advances in imaging have improved the detectability and management of metastases of prostate cancer. An appropriate imaging sequence is necessary to improve detection of the disease and thereby the standard of care for the patient[16].

Transrectal ultrasound

A TRUS is usually performed to guide biopsies rather than to identify the location and nature of the cancer[17]. However, TRUS, as demonstrated in previous studies, has proved quite good at detecting the presence of a lesion, with an overall accuracy of 80%[17].

Hypoechoic lesions and focal infarcts have been reported to have the same appearance as prostate cancer on TRUS, leading to false positive results and making TRUS less specific when used as the only imaging modality.[17]

Magnetic resonance imaging

Nowadays multiparametric MRI (mpMRI) is used to assess both morphological and functional MRI parameters, combining methods such as diffusion-weighted imaging (DWI), T1-weighted imaging (T1WI), T2-weighted imaging (T2WI), apparent diffusion coefficient (ADC), dynamic contrast-enhanced (DCE) imaging and possibly MR spectroscopy in order to improve the detection and localisation of prostate cancer. mpMRI has the capability to identify and characterise primary prostate cancer, even occult lesions with persistent PSA elevation and negative biopsy results. Additionally, mpMRI is particularly helpful for detection of clinically significantly cancer. Because of its superior diagnostic accuracy, mpMRI has the potential to decrease unnecessary prostate biopsies[18].

Positron emission tomography

Fluorine-18 fluorodeoxyglucose positron emission tomography (PET) is not widely used for primary prostate cancer detection or local staging because of limitations relating to high bladder activity and relatively low tumour uptake. Alternative PET tracers, such as ^{11}C- or ^{18}F-labelled choline and acetate, which are utilised for cell membrane synthesis, show increased radioactive uptake in malignant tumours. However, these tracers have limited value in small primary cancers because of their

inability to discriminate between such cancers and BPH and prostatitis[19, 20].

Imaging tracers targeting prostate-specific membrane antigen (PSMA) have recently garnered attention after showing promise in the detection of intraprostatic cancer on the basis of their good signal-to-noise ratio. ^{68}Ga-PSMA, a urea-based PSMA inhibitor, via binding to the PSMA structure, has the advantage of high sensitivity for the detection of prostate cancer independent of PSA level and lesion size[21].

IMAGING FOR DISEASE STAGING

Technetium-99 bone scan

A conventional technetium-99 bone scan (BS) has been the most widely used method for evaluation of bone metastases of prostate cancer. A bone scan is relatively well tolerated, readily available and cheap compared with the newer imaging modalities. However, the diagnostic yield of BS is significantly influenced by the PSA level, the clinical stage and the tumour Gleason score and these three factors were found to be the only independent predictors of BS positivity in a study of 853 patients. The mean BS positivity rate in 23 different series was 2.3% in patients with PSA levels <10 ng/mL, 5.3% in patients with PSA levels between 10.1 and 19.9 ng/mL and 16.2% in patients with PSA levels of 20.0–49.9 ng/mL. It was 6.4% in men with organ-confined cancer and 49.5% in men with locally advanced cancers. Detection rates were 5.6% and 29.9% for Gleason scores of ≤7 and ≥8 respectively[22].

Computed tomography/ magnetic resonance imaging

Computed tomography (CT) is useful not only for disease staging but also for assessment of the anatomy of the patient, such as lymph nodes. Enlarged lymph nodes may give an indication regarding the presence of metastasis. Visualisation of lymph nodes depends on the slice thickness of the scans and on the CT scanner itself. However, a CT scan does not differentiate between lymph nodes that are inflammatory and lymph nodes affected by micro-metastases[22].

Magnetic resonance imaging (MRI) is similar in this respect to CT. Studies have shown that its sensitivity and specificity in the detection of small metastases are low because such metastases are usually present in small lymph nodes[23].

Nanoparticle magnetic resonance imaging

One of the latest developments in MRI is the introduction of nanoparticles. These nanoparticles can be divided into differ-

ent groups, including those that are iron oxide based, usually used for patients diagnosed with prostate cancer[25]. This lymphotropic nanoparticle agent (ferumoxtran-10), also known as Combidex®, is mixed with 0.9% w/v saline solution for intravenous administration. The magnetic properties of these nanoparticles allow them to become magnetised when placed in a magnetic field but demagnetised after removal of the magnetic field. They have been used as T2-weighted MR contrast agents to track and monitor the lymphatic system. The mechanism of action is based on the phagocytosis of the nanoparticles by the macrophages, with the iron in the macrophages in the lymph nodes resulting in a black signal on MRI. When a lymph node is metastasised, the macrophages cannot infiltrate the lymph node and it remains white on the T2-weighted image[24, 25].

Multimodality PET/MRI is also a possibility, using the aforementioned nanoparticles in conjunction with ^{68}Ga-PSMA targeting agents, for example. Nanoparticle MRI is useful when lymph node metastases need to be confirmed or excluded. Knowledge of the lymph node status determines the treatment and the prognosis. From recent studies, it appears that nanoparticle MRI has a higher sensitivity and specificity than conventional CT and MRI[23–25].

^{68}Ga-PSMA targeting agents

The introduction of ^{68}Ga-PSMA targeting agents has increased the accuracy in the detection of metastases in prostate cancer compared with the sole use of CT and bone scans. ^{68}Ga-PSMA targeting agents are used in combination with PET/CT. There is good contrast between tumour lesions and normal tissue, and also high specific uptake in PSMA-expressing organs and tumours. Unlike nanoparticle MRI, ^{68}Ga-PSMA PET/CT is not lymph node specific; rather, ^{68}Ga-PSMA PET/CT may show metastases in other organs or tissues. A combination of the two modalities is usually used when progressive disease needs to be confirmed or excluded[25].

Choline PET

Radiolabelled choline PET tracers are at present the best performing tracers widely available for use in patients undergoing prostate cancer imaging. In patients presenting with high-risk or locally advanced prostate cancer, imaging to document potential metastases may be important. At this stage of the disease, choline PET should be considered. However, detection of micro-metastases with choline PET remains a challeng[19, 20, 25]. The addition of other imaging techniques such as MRI is useful in determining the metastatic status.

Staging of the disease is important to categorise patients into the appropriate

group, and once staging has been concluded, treatment can be started. It is of course important to perform examinations and imaging as quickly as possible after diagnosis, to prevent progression of the disease. Figures 3 and 4 show two possible patient pathways that may be implemented. Pathways may differ between countries and also depend on the availability of personnel and equipment and the guidelines adopted in the individual country.

For low-risk patients, an appointment with the urologist is planned a week after the patient receives the results. For intermediate- and high-risk patients, the necessary diagnostic imaging is performed in accordance with decisions made during the multidisciplinary team meeting.

Information folders may be given to the patient, explaining in detail everything that he may go through. A space may be included for personal notes by the patient that can be raised at the next appointment and/or for an appointment card. Websites with guidelines and additional information may also be shown in the folder. The provision and nature of such information folders depends on the hospital or even the country. For example, in the Netherlands, the KWF Kanker Bestrijding (Dutch Cancer Society) and Prostaat Kanker Stichting (PKS) provide the patient with a logbook with phone numbers and an email address should the patient need to contact these organisations. Information regarding prostate cancer and other patients' experiences are also included in this logbook.

Patients may experience anxiety and depression due to their diagnosis or the side-effects associated with the treatment/surgery. It is important for the oncology nurse or case manager to recognise this, and to provide help when needed.

TREATMENT OPTIONS

Most low-risk or very low-risk patients – those with a low Gleason score, low PSA level and low clinical stage – are managed solely by follow-up (watchful waiting). Studies have shown that these patients have a low risk for clinical progression within the first 5–10 years after initial diagnosis[26].

Follow-up may include periodic DRE with or without PSA testing. A biopsy may also be included, depending on the findings. A follow-up scheme is helpful for a number of patients, but not all. Treatment is provided with the aim of reducing the likelihood of progression of the cancer and/or reducing the risk of complications in a cancer that is not likely to progress[27].

In patients who will not benefit from curative treatment, palliative treatment is of-

Figure 3

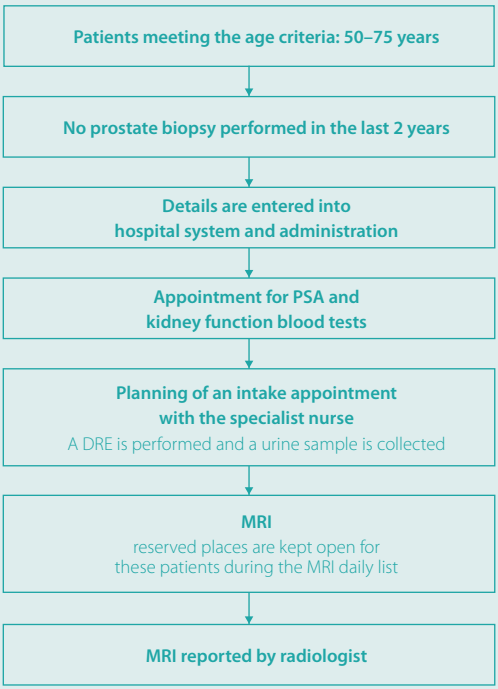

Figure 3: *One potential trajectory for a prostate cancer patient*

fered. Palliative treatment involves treating the symptoms to alleviate complaints[13]. For example, in patients with extensive metastatic spread, management of the urinary tract or radiotherapy for metastatic lesions in the vertebral column alleviates complaints of urinary obstruction or pain.

Androgen deprivation therapy

Androgen deprivation therapy (ADT) is a systemic treatment usually given to patients with known metastatic prostate cancer. Conventional ADT involved surgical or medical castration and the administration of anti-androgen agents, such as

Figure 4

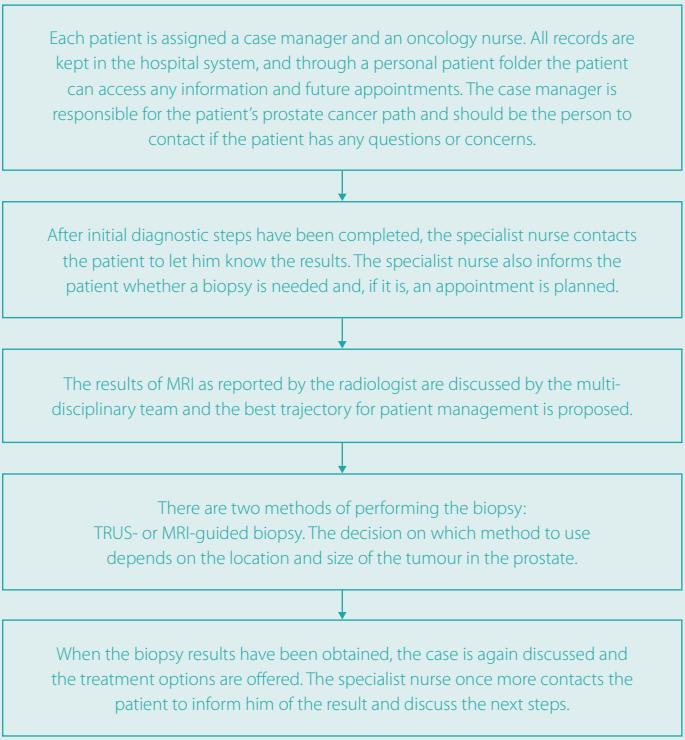

Figure 4: *A further possible patient pathway, from biopsy to receipt of results and discussion of the next step*

bicalutamide, flutamide, and nilutamide. Recently, new anti-androgen agents, such as enzalutamide and abiraterone, have been approved for castration-resistant prostate cancer. However, there are some side effects which have been associated with toxicity, such as cardiac morbidity, decreased mineral bone density and sexual dysfunction[28].

Brachytherapy

Radioactive seeds are implanted using an ultrasound- or MRI-guided transperineal approach. Palladium-103 or iodine-125 is usually used, with postoperative dosimetry. Patients who are low or possibly intermediate risk usually fall into the category considered suitable for this treatment. Prior to any therapy, TRUS is performed to assess the size of the prostate and to determine the number of needles and radioactive seeds, the isotope and the isotope strength required for the procedure. The radioactive seeds need to be transplanted properly otherwise the whole effectiveness of the therapy is reduced[9, 13, 15].

Radiotherapy

Technological advancements such as three-dimensional CT radiotherapy planning have enhanced the specificity of irradiation, contributing to dose accuracy and reducing radiation to surrounding structures. Patients who have a history of inflammatory bowel disease, such as Crohn's disease, or have previously undergone pelvic radiotherapy may present a challenge because of increased complications due to the additional radiotherapy[9, 13, 15].

For patients with a Gleason score higher than 7 or a PSA level of more than 10 ng/mL, post-radiation hormone therapy is recommended, with follow-up every 6 months for 5 years and annually thereafter[21].

Prostatectomy

Prostatectomy is a surgical procedure whereby the entire prostate gland is removed. The decision to perform prostatectomy depends on the age of the patient, his sexual activity and the tumour characteristics. The pelvic lymph nodes can also be removed, but this is usually done only in patients who have metastatic lymph node involvement. Patients who undergo prostatectomy are usually hospitalised for 1–3 days and discharged with a urethral catheter for 1–2 weeks postoperatively, depending on the country. Patients with localised prostate cancer usually benefit from radical prostatectomy. In patients with adjacent organ involvement, prostatectomy is not recommended because there is no guarantee that all the cancer will be removed, putting the patient at risk for recurrence[9, 13].

Radium-223 dichloride

Radium-223 is an alpha emitter that targets bone metastases as it accumulates in bone analogously to calcium. It is usually used in the early stages after diagnosis of bone metastases, with or without lymph node metastases. In most cases the goal is to improve survival, and a secondary objective may be to alleviate complaints from

the bone metastases[29]. Correct information needs to be delivered to patients because they may be wary of alpha radiation.

Imaging for follow-up

Several studies have reported promising results in the detection of local recurrences using MRI, particularly dynamic contrast-enhanced MRI, with sensitivities and specificities of 76%–90% and 82%–100%, respectively. However, the mean PSA level in these studies was 0.7–1.9 ng/mL, which is higher than the 0.5 ng/mL threshold usually used for salvage therapy. Two studies evaluated mpMRI in patients with a PSA level <0.5 ng/mL. One found a sensitivity of only 13% in men with a PSA level <0.3 ng/mL, while the other reported a sensitivity of 86% in patients with a PSA level <0.4 ng/mL[30].

Technetium-99 bone scan historically is most commonly used for the diagnosis of bone metastases, although it has limited sensitivity. Only 11%–14% of patients with biochemical recurrence (BCR) after radical prostatectomy (RP) have a positive CT and a positive scan is rarely obtained in situations when salvage treatment might be considered. In a series of 132 men with BCR after RP, the mean PSA level and PSA velocity associated with a positive CT were 27.4 ng/mL and 1.8 ng/mL/month, respectively. Therefore, bone scan and abdominopelvic CT should only be considered in patients with BCR after RP who have a high baseline PSA (>10 ng/mL) or high PSA kinetics [PSA doubling time (PSA-DT) <6 months or PSA velocity >0.5 ng/mL/month] and in patients with symptoms of bone disease[31].

Choline PET/CT may change medical management in 18%–48% of patients with BCR after primary treatment[32–34]. In a retrospective two-centre study of 150 patients[34], 14 of the 55 (25.5%) patients scheduled for palliative treatment were switched to salvage therapy based on choline PET/CT results. Salvage therapy induced a complete biochemical response in 35.7% of these patients at the end of a median follow-up of 18.3 months (range 10–48 months), suggesting that it continues to miss small-volume metastases. In patients not considered fit enough for curative salvage treatments, choline PET/CT should be avoided. After RP, the optimal PSA cut-off level for choline PET/CT analysis seems to be between 1 and 2 ng/mL. Choline PET/CT detection rate was 26% in patients showing PSA <1 ng/mL but rose to 44% in those with PSA values between 1 and 2 ng/mL (moreover 37% of this group of patients were oligo-metastatic). It has been suggested that a PSA-DT <6 months and a PSA velocity >2 ng/mL/year may also select men in whom choline PET/CT could be recommended[35].

^{68}Ga-PSMA PET/CT has shown promising potential in patients with BCR. Detection rates of 58% and 76% have been reported for PSA ranges of 0.2–1 and 1–2 ng/mL, respectively. This suggests that ^{68}Ga-PSMA is substantially more sensitive at low PSA levels than choline PET/CT. Therefore, if local salvage treatment is planned and ^{68}Ga-PSMA PET/CT is available, it should be considered as a valuable assessment option[36].

A newly developed synthetic amino acid analogue PET radiotracer (anti-3-[^{18}F] FACBC (fluciclovine)] could also be used to scan patients with recurrent prostate cancer[37].

The role of the technologist

Patients attend imaging at various stages of their diagnostic and/or treatment pathways. When an examination is requested, knowledge of the approximate stage at which the patient finds himself during the clinical pathway may be useful, since it may give a better indication of what to look out for during diagnostic imaging. This helps the technologist in providing the nuclear medicine physician with a sufficient nuclear medicine examination having proper image quality to be able to make a correct diagnosis. The risk category for the patient is usually indicated on the requested examination, so that the technologist will have an indication as to why the examination is being performed. It is also useful to look up previous examinations of this patient as this forms a good basis for comparison and may also be useful in identifying artefacts or suspected artefacts in the acquired images. When the patient attends the examination, he may be scared of the result of the scan rather than the actual examination, and the technologist should be prepared to answer any technical questions the patient might have and explain which should be directed to the clinician, clarifying as much as possible and reassuring the patient. The technologist also needs to aware of the risks involved in handling patients with advanced prostate cancer, who may have the potential for pathological fractures.

Conclusion

The diagnosis and management of prostate cancer pose different challenges and concerns for every patient diagnosed with the disease. Patients are given a lot of information regarding the disease that they may find difficult to register and understand. Appropriate support needs to be provided for those patients who need better communication and more understanding than others. The multidisciplinary team is important when discussing the management and prognosis of patients because a thorough approach is essential. Different imaging modalities are available to assess the staging and progression of the disease.

Making proper use of what is available only increases the chances of survival, and if the disease is at a later stage, palliative care and measures to relieve symptoms will be needed.

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AVAILABLE AS WEBINAR

10 FUTURE PERSPECTIVES AND PRECLINICAL STUDIES IN PROSTATE CANCER

by Laura Evangelista and Federico Caobelli

(on behalf of the Translational Imaging and Therapy Committee)

INTRODUCTION

Prostate cancer is the most common oncological disease in men worldwide. Nuclear medicine has provided tools for its management for years, with bone scans, brachytherapy and pain palliation. However, fluorine-18 fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) is not adequate for the detection of prostate cancer, and the development of alternative tracers is thus required.

While the introduction of prostate-specific membrane antigen (PSMA) and choline has changed the management of the disease, these tracers are not still perfect. Efficacy of radiolabelled antibodies (e.g. J591) has been demonstrated in clinical trials, but their toxicity is high. Within the therapeutic armamentarium, radium-223 has shown efficacy in pain palliation and has achieved some improvement in survival.

Nuclear medicine currently offers exciting perspectives with the development of new PET imaging agents and new targeted radionuclide therapies based on antibody fragments, peptides and PSMA inhibitors, which is opening the way to true theranostics. Thus, prostate cancer is subject to very active translational research in nuclear medicine and preclinical studies are being performed to obtain preclinical proof of concept for new radiopharmaceuticals, to compare available candidates and to pave the way for clinical developments.

The present chapter aims to describe how such preclinical studies are being conducted, to provide general knowledge of animal models, to identify the relevance of animal care in the context of preclinical imaging and therapy studies, and to acquaint technologists with the extended competences needed as a member of a preclinical team. Moreover, the impact of nuclear medicine techniques in preclinical trials and the problem of the translation from animals to men will be discussed. Finally, some future challenges and opportunities for prostate cancer management will be addressed.

PRECLINICAL IN VIVO STUDIES

In vitro studies do not do justice to the biological complexities that are encountered in a living animal (in vivo); consequently, in vivo animal models are required to study, for example, tracer pharmacokinetics and actual accumulation in disease models. The principal role of animal studies is the advancement of science but obtaining in vivo proof of concept after in vitro development of drug candidates and before full clinical/industrial development is another application of interest. Then, in most

countries, regulatory studies are requested before a new radiopharmaceutical candidate may be used in human clinical trials.

Proof of concept studies of diagnostic/therapeutic efficacy have two potential effects:

1. They can rule out ideas that do not translate from in vitro to in vivo or, conversely, demonstrate that there is hope of successful clinical translation. There are too many unknowns to predict that pharmacokinetics, biodistribution, uptake in lesions and in normal tissues, immune system reactions and so on will not render useless a drug that has shown a good in vitro profile of target binding and pharmacological effects. In oncology, for instance, a candidate drug, radioactive or not, that shows objective efficacy at doses that do not cause excessive toxicity passes the test.
2. They can provide a strong argument in favour of, or against, investing in a new drug. They also help in making the investigational product stronger. The likelihood that preclinical development and clinical trials will be funded strongly depends on the quality of the proof of concept studies and on advertising their outcomes.

Obviously, the means by which the artificial model is created will define the degree of resemblance with the actual clinical situation. The choice of the most appropriate animal model depends on the characteristics of the molecule to be tested and the metabolic pathway affected. For example, orthotopic tumour models (tumour in the same organ in which it occurs clinically) and tumour models based on (human) tissue explants are more likely to reflect the clinical tumour pathophysiology than subcutaneous transplant models using cultured cells (xenografts). Despite this, disease models do not necessarily present the actual human situation; rather, they merely allow tracer evaluation in a much more advanced setting compared with in vitro studies. The diverse disease models available for such studies all artificially represent key features of a disease. The choice and pathology of a model may therefore strongly influence the outcome of a preclinical study.

Several considerations need to be taken into account when selecting the appropriate prostate cancer model. First and foremost, the model must be representative of the disease state under examination and may serve different purposes. LNCaP cells, which are sensitive to androgen stimulation, show an increased incidence of metastasis. LNCaP-LN3 cells result in smaller prostate tumours but enhanced metastatic propensity[1]. In particular, they promote a pattern of regional lymph node metastases after prostatic implantation,

with castration-resistant features. Moreover, PC-3M variants produce a higher incidence of lung metastasis but not lymph node metastasis, suggesting an increased metastatic propensity to a specific site rather than all organ sites[1]. The PC3 model is common but does not express PSMA. However, in humans, prostate cancer, like other solid endocrine cancers, is a heterogeneous tumour characterised by different biological pathways, targets and history of disease, and therefore cannot be represented by a single model.

Furthermore, studies on non-diseased animals are as important for translation as those on diseased animals: they allow investigation of tracer characteristics such as safety, toxicity, and biodistribution and enable comparison with findings in diseased animals.

The performance of in vivo studies in, for example, mice, rats, rabbits, dogs, pigs or monkeys, requires approval from a local ethics board. Appropriate animal care entails compliance with a series of conditions that ensure the health and well-being of the animals. For example: (1) living conditions must be appropriate, (2) personnel who care for animals or who conduct animal studies must be appropriately qualified and (3) studies involving animals must be designed and conducted in accordance with applicable country and local regulatory guidance and widely recognised principles of animal care and use (i.e. using the minimum number of animals required to obtain valid results, using alternative methods instead of live animals where appropriate and avoiding or minimising discomfort and distress to the animals).

Quite often, handling of animal models requires a diploma, just like handling of radioisotopes. Unlike for the clinical situation (see below), for preclinical in vivo studies approval needs to be obtained for the generation of the disease model and the evaluation of the radiopharmaceutical.

Radioisotope-based detection techniques such as %ID/g evaluations and preclinical single-photon emission computed tomography (SPECT) or PET studies support the quantitative evaluation of tracers or radiolabelled cells, which is not only key in the development of tracers for the field of nuclear medicine but is also routinely of value in drug development. In the in vivo setting, the effect of physiology, enzyme activity, serum binding, biological clearance etc. can be determined. Such preclinical in vivo studies may also help to optimise timing and dose. Finally, preclinical evaluations can be used to assess the (acute) toxicity of a tracer or radiolabelling method. Although not yet conclusive, these preclinical in vivo studies are key intermediate steps in the process of clinical translation.

FIRST-IN-HUMAN STUDIES

Phase I clinical trials (or "first-in-human studies") play a crucial role in the radiopharmaceutical development process and are often considered the gateway between fundamental research and clinical medicine. Obviously, the evaluation of new radiopharmaceuticals in humans requires an ethics statement from local authorities and informed consent of the patient. Within the EU, these rules may vary between countries or even regions within a country. Whereas in some countries full preclinical and toxicological evaluation is required in order to obtain ethical approval for first-in-human studies, in other countries some aspects may be omitted. Every step should be documented. It is mandatory to adhere to good laboratory practice (GLP) and good manufacturing practice (GMP) and to ensure the use of accurate and robust data and standards in order to guarantee patient safety.

Prerequisites for first-in-human studies are well described in official documents. They include safety and toxicity studies, generally in two animal species, by repeated administrations, pharmacokinetic/dosimetry studies and so on. The goal here is exclusively to try and demonstrate that the first in-human application will be sufficiently safe, which is clearly not always the case.

These regulatory studies are *not* about efficacy. They are generally performed under GLP by specialised companies that have all the requisite certifications. In nuclear medicine, since these certified companies generally do not handle radioactive compounds, toxicity (e.g. determination of maximum tolerated dose), pharmacokinetics and dosimetry studies with the radioactive drug, as opposed to the parent unlabelled compound, need to be performed in academic laboratories.

RECENT DEVELOPMENTS IN PRECLINICAL STUDIES IN PROSTATE CANCER

A careful search of the available literature, using the terms "prostate cancer" AND "nuclear medicine" as keywords in PubMed, identified 6388 studies published over the past 5 years. Out of these 6388 articles, 3697 related to clinical research and 2691 to preclinical studies (465 in vivo and 2226 in vitro experiments). A detailed discussion of all the in vitro and in vivo studies is beyond the scope of the present guide. Summarising, it can be stated that different receptors, e.g. bombesin, PSMA and urokinase-type plasminogen activator receptor (uPar), are currently being actively investigated as potential targets for molecular imaging and/or radiometabolic therapy.

Different radiopharmaceutical agents are now under evaluation for diagnosis, therapy or surgery. The majority of them

focus on PSMA as the target. Some agents are radiolabelled with technetium-99m for SPECT images and others with gallium-68 or copper-64 for PET studies or lutetium-177 for therapeutic purposes.

An intriguing possibility offered by radiolabelled receptor agonists and antagonists is to allow for effective theranostics due to the intrinsic feasibility of labelling either with beta+ or gamma emitters (such as gallium-68 and indium-111) for diagnostic purposes or with therapeutic, beta-emitting isotopes such as lutetium-177. Although the in vivo distribution can vary depending on the labelling isotope, this opportunity makes the potential clinical value of molecular imaging even more promising. The most interesting and recent published studies are listed in Table 1.

FUTURE CHALLENGES AND OPPORTUNITIES

Prostate cancer, like other solid endocrine cancers, is heterogeneous, being characterised by different biological pathways and targets and variations in history of disease. Each pathway and target can be addressed by radiopharmaceutical agents, both for diagnosis and for therapy (Fig. 1). Therefore, future discoveries should focus on the study of new pathways with a strong potential impact on the management and prognosis of patients with prostate cancer. Furthermore, efforts should be made to develop tracers able to guide specific treatments and to evaluate their efficacy. Moreover, the introduction of specific hardware and software would be beneficial to simplify the characterisation of prostate cancer disease.

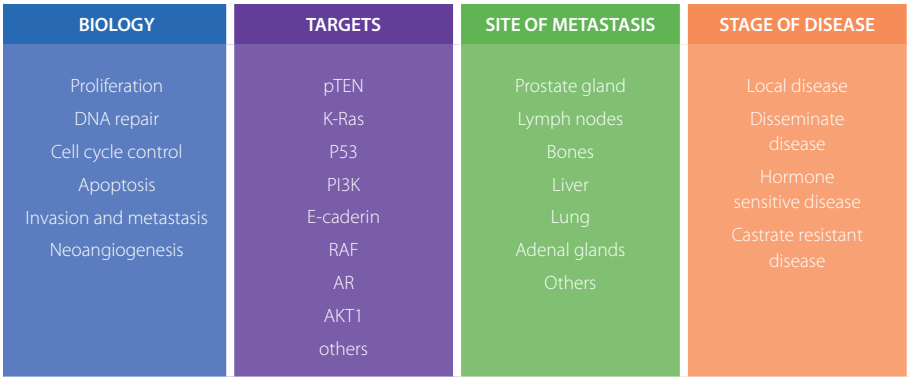

Figure 1: *Potential targets and useful information for the development of new radiopharmaceutical agents in prostate cancer*

Authors, ref	Year	Journal	Radiopharmaceutical agent	Phase of study	Type of animal	Quality control of RA
Jan et al. [2]	2017	Cancer Biotherapy and Radiopharmaceuticals	^{99m}Tc-finasteride	In vivo	Sprague Dawley rats	Radiochemical purity analysis by chromatographic technique
Ferreira et al. [3]	2017	Biomedicine & Pharmacotherapy	Radiolabelled bombesin	In vivo	Swiss mice (xenograft model) or athymic nu/nu mice (xenograft model)	–
Xu et al. [4]	2017	Bioorganic & Medicinal Chemistry Letters	^{111}In-gonadotropin-releasing hormone peptides	In vivo	Xenograft nude mice	–
Nonnekens et al. [5]	2017	Cancer Biotherapy and Radiopharmaceuticals	^{213}Bi-PSMA	In vitro/ in vivo	Female nude mice	–
Nock et al. [6]	2017	Journal of Nuclear Medicine	Radiolabelled bombesin	In vitro/ in vivo	Xenograft-bearing mice	Radiochemical purity analysis by chromatographic technique
Zhang et al. [7]	2017	Journal of Nuclear Medicine	^{68}Ga-labelled (gastrin-releasing peptide antagonist)	In vitro/ in vivo	Male athymic NCr-nu/nu mice	Radiochemical purity analysis by chromatographic technique
Sun et al. [8]	2016	Bioconiugate Chemistry	Radiolabelled bombesin	In vitro/ in vivo	Xenograft-bearing mice	Radiochemical purity analysis by chromatographic technique
Cheng et al. [9]	2018	Bioconiugate Chemistry	^{68}Ga-labelled (gastrin-releasing peptide agonist and antagonist)	In vitro/ in vivo	Xenograft-bearing mice	Radiochemical purity analysis by chromatographic technique
Skovgaard et al. [10]	2017	PET Clinics	^{64}Cu- and ^{68}Ga-labelled urokinase-type plasminogen activator receptor agonist	NA	–	–
Frigerio et al. [11]	2017	Oncotarget	^{123}I-labelled anti-PSMA antibody fragment ScFvD2B	In vitro/ in vivo	Xenograft-bearing mice	Radiochemical purity analysis by chromatographic technique

Table 1: *Recently published studies of radiolabelled receptor agonists and antagonists that are of particular interest*

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