**Clinicians' Guides to Radionuclide Hybrid Imaging** · PET/CT
*Series Editors:* Jamshed B. Bomanji · Gopinath Gnanasegaran
Stefano Fanti · Homer A. Macapinlac

Gary Cook *Editor*

# PET/CT in Prostate Cancer

BNMS
BRITISH NUCLEAR MEDICINE SOCIETY

Springer

# Clinicians' Guides to Radionuclide Hybrid Imaging

## PET/CT

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*PET/CT series is dedicated to Prof Ignac Fogelman, Dr Muriel Buxton-Thomas and Prof Ajit K Padhy*

# Foreword

Clear and concise clinical indications for PET/CT in the management of the oncology patient are presented in this series of 15 separate booklets.

The impact on better staging, tailored management and specific treatment of the patient with cancer has been achieved with the advent of this multimodality imaging technology. Early and accurate diagnosis will always pay, and clear information can be gathered with PET/CT on treatment responses. Prognostic information is gathered and can forward guide additional therapeutic options.

It is a fortunate coincidence that PET/CT was able to derive great benefit from radionuclide-labelled probes, which deliver good and often excellent target to non-target signals. Whilst labelled glucose remains the cornerstone for the clinical benefit achieved, a number of recent probes are definitely adding benefit. PET/CT is hence an evolving technology, extending its applications and indications. Significant advances in the instrumentation and data processing available have also contributed to this technology, which delivers high-throughput and a wealth of data, with good patient tolerance and indeed patient and public acceptance. As an example, the role of PET/CT in the evaluation of cardiac disease is also covered, with emphasis on labelled rubidium and labelled glucose studies.

The novel probes of labelled choline; labelled peptides, such as DOTATATE; and, most recently, labelled PSMA (prostate-specific membrane antigen) have gained rapid clinical utility and acceptance, as significant PET/CT tools for the management of neuroendocrine disease and prostate cancer patients, notwithstanding all the advances achieved with other imaging modalities, such as MRI. Hence, a chapter reviewing novel PET tracers forms part of this series.

The oncological community has recognised the value of PET/CT and has delivered advanced diagnostic criteria for some of the most important indications for PET/CT. This includes the recent Deauville criteria for the classification of PET/CT patients with lymphoma—similar criteria are expected to develop for other malignancies, such as head and neck cancer, melanoma and pelvic malignancies. For completion, a separate section covers the role of PET/CT in radiotherapy planning, discussing the indications for planning biological tumour volumes in relevant cancers.

These booklets offer simple, rapid and concise guidelines on the utility of PET/CT in a range of oncological indications. They also deliver a rapid aide-memoire on the merits and appropriate indications for PET/CT in oncology.

London, UK Peter J. Ell, FMedSci, DR HC, AΩA

# Preface

*Hybrid imaging* with PET/CT and SPECT/CT combines best of function and structure to provide accurate localisation, characterisation and diagnosis. There is extensive literature and evidence to support PET/CT, which has made significant impact in oncological imaging and management of patients with cancer. The evidence in favour of SPECT/CT especially in orthopaedic indications is evolving and increasing.

The *Clinicians' Guides to Radionuclide Hybrid Imaging* (PET/CT and SPECT/CT) pocketbook series is specifically aimed at our referring clinicians, nuclear medicine/radiology doctors, radiographers/technologists and nurses who are routinely working in nuclear medicine and participate in multidisciplinary meetings. This series is the joint work of many friends and professionals from different nations who share a common dream and vision towards promoting and supporting nuclear medicine as a useful and important imaging speciality.

We want to thank all those people who have contributed to this work as advisors, authors and reviewers, without whom the book would not have been possible. We want to thank our members from the BNMS (British Nuclear Medicine Society, UK) for their encouragement and support, and we are extremely grateful to Dr. Brian Nielly, Charlotte Weston, the BNMS Education Committee and the BNMS council members for their enthusiasm and trust.

Finally, we wish to extend particular gratitude to the industry for their continuous support towards education and training.

London, UK

Gopinath Gnanasegaran
Jamshed Bomanji

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# Epidemiology and Clinical Features

1

Nikolaos Tsoukalas and Sarah Rudman

## Contents



## 1.1 Epidemiology

Prostate cancer is the most common non-cutaneous malignancy in Westernised countries with a lifetime risk of one in seven men [1] and a global incidence of more than one million new cases each year (Figs. 1.1 and 1.2) [2]. In 2012, 417,000 cases were diagnosed in Europe with the highest incidence in Northern and Western Europe in countries such as Norway (129/100,000) and lowest in Southeastern Europe in countries such as Albania [3]. The UK incidence places it 17th overall with an age-standardised rate of 104.7 cases/100,000 (Figs. 1.3 and 1.4). It is thought that widespread differences in screening practices, prostate-specific antigen (PSA) testing, and digital rectal examination (DRE) may explain the variation in country to country incidence.

Prostate cancer is the second most common cause of cancer death in men in the UK with 10,793 deaths recorded in 2011 [4]. The association between prostate cancer and age continues to be observed in mortality figures with 73% prostate cancer

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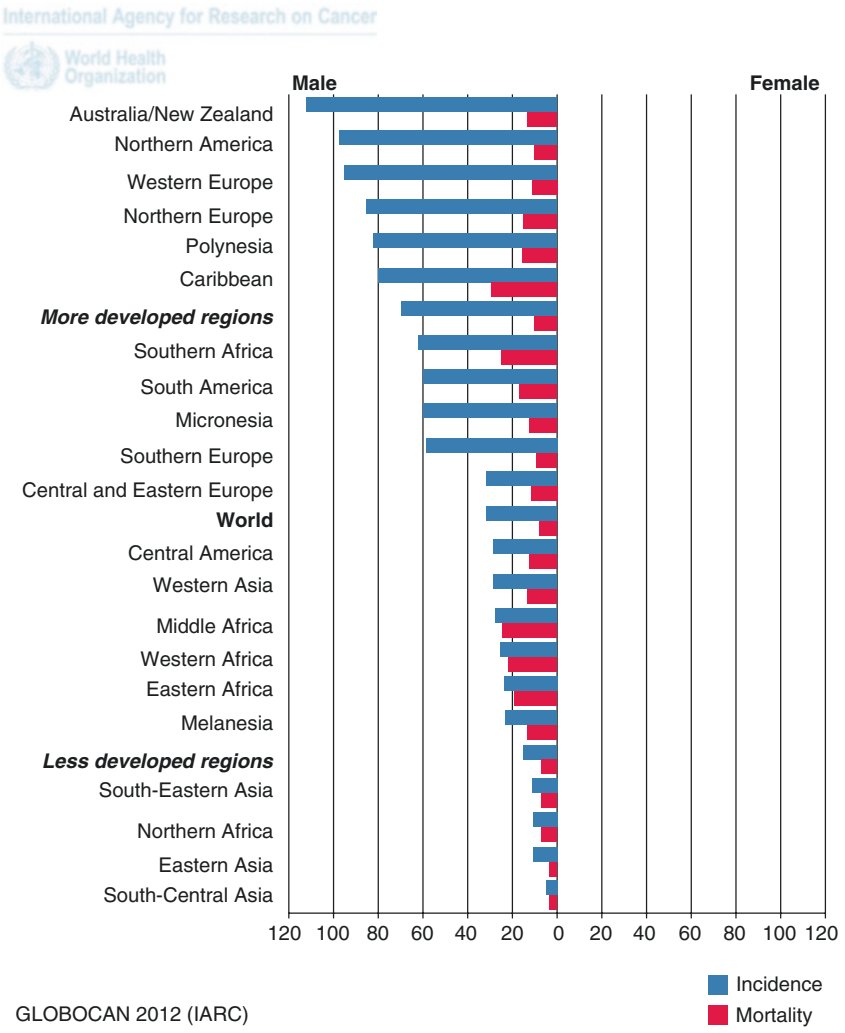


**Fig. 1.1** Estimated age-standardised rates (World) per 100,000 [2]

deaths occurring in men 75 years or older [4]. Overall however, there has been a steady increase in the 5-year relative survival rates in recent years from 73.4% (1999–2001) to 83.4% (2005–2007). It is likely that this is due to earlier detection and advances in treatment modalities (Fig. 1.5) [5].

Prostate cancer screening has now been adopted in a number of Westernised countries resulting in some cancers being detected at earlier stages. These may often be clinically insignificant, lower-risk cancers, potentially resulting in overdiagnosis and unnecessary treatment for some patients [6]. At present PSA screening has not been adopted in the UK.

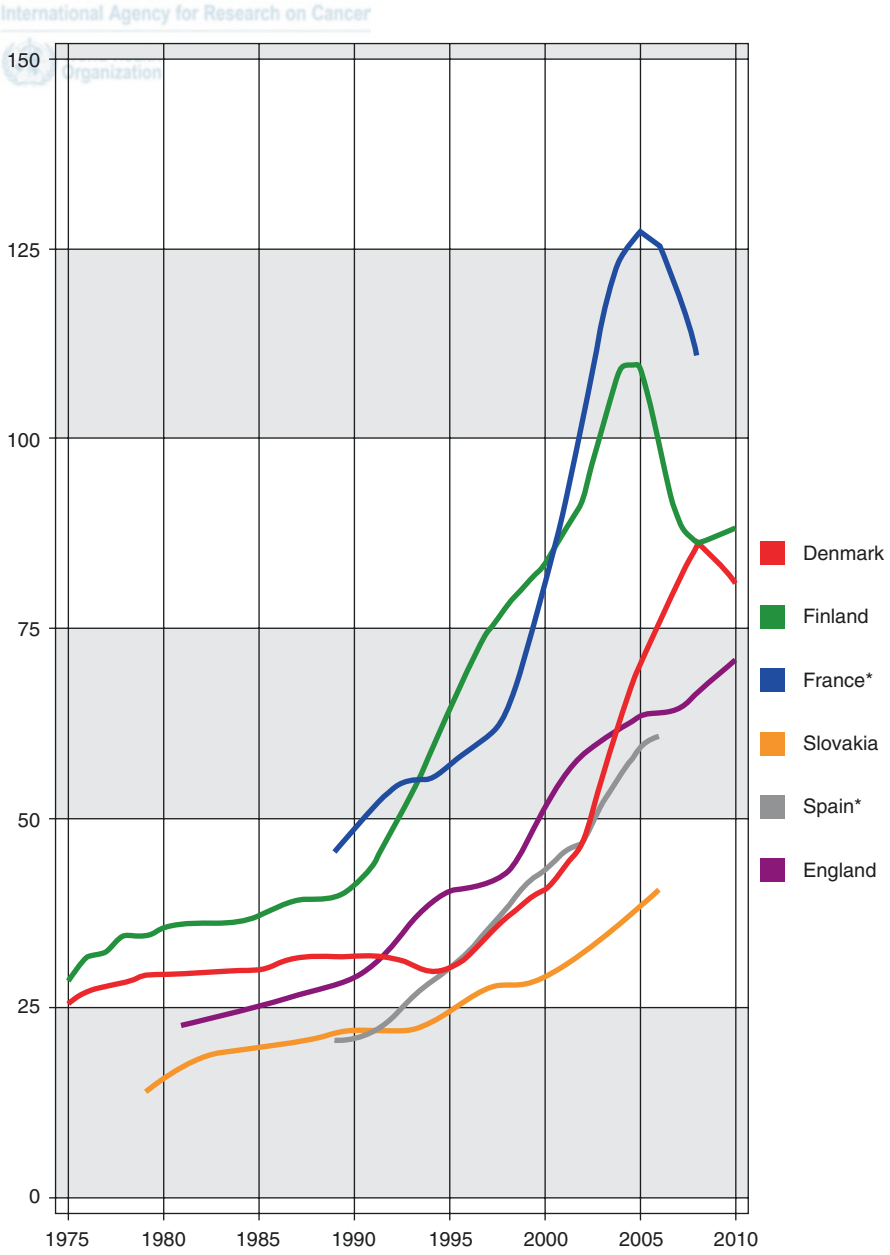


**Fig. 1.2** Trends in incidence of prostate cancer in selected countries: age-standardised rate (W) per 100,000 [2]

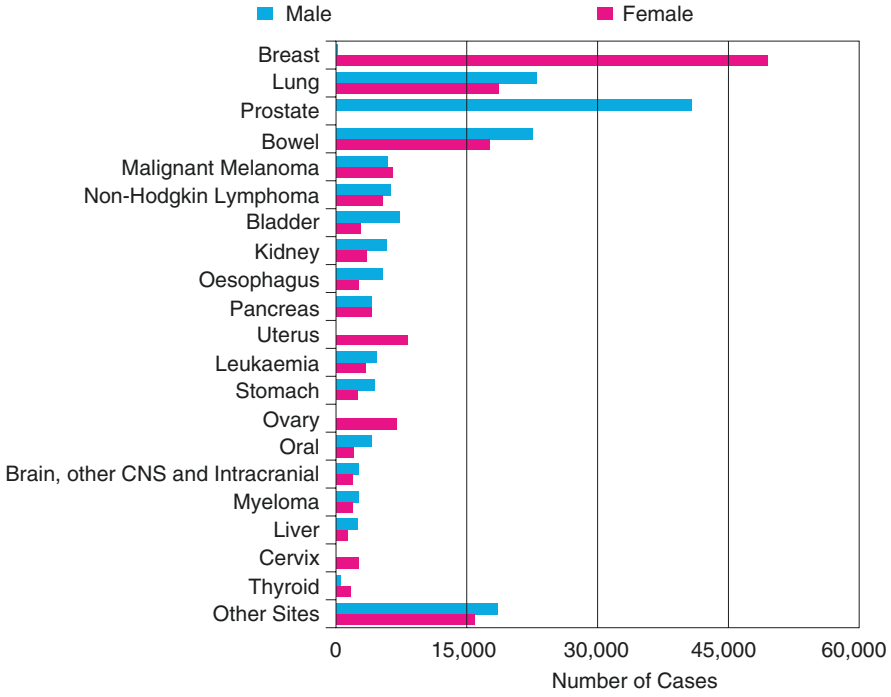


**Fig. 1.3** The 20 most common cancers in 2010, number of new cases, UK (UKCIS, accessed August 2013, http://publications.cancerresearchuk.org)

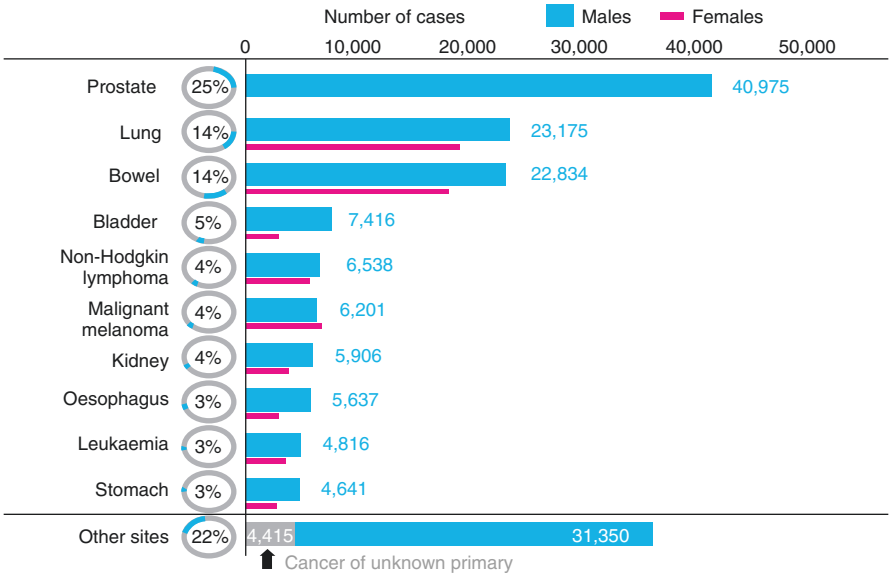


**Fig. 1.4** The ten most common cancers in males in 2010, numbers of new cases, UK (UKCIS, accessed August 2013, http://publications.cancerresearchuk.org)

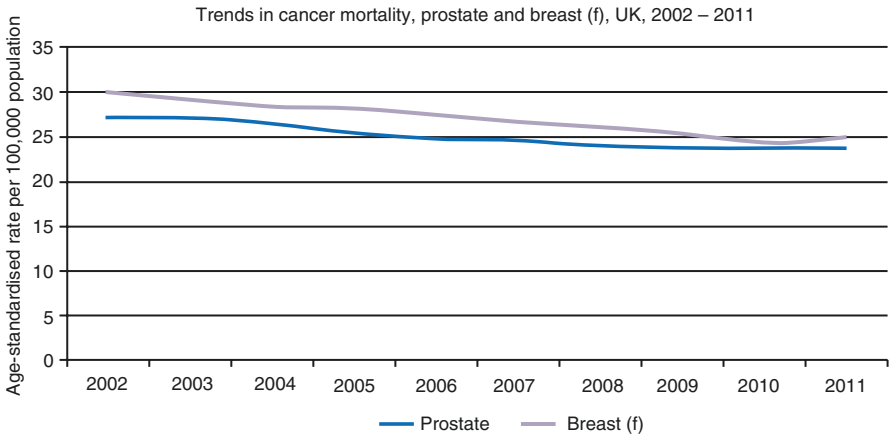


**Fig. 1.5** Trends in age-standardised mortality rates, breast (females) and prostate cancer, UK, 2002–2011 (UKCIS, accessed March 2014, http://publications.cancerresearchuk.org)

**Table 1.1** Number of cases of prostate cancer by major ethnic group (including unknown), England, 2006–2010 (National Cancer Intelligence Network, March 2014)

| Ethnic group | Number of prostate cancer cases |
|---|---|
| White | 149,549 |
| Asian | 2308 |
| Black | 4905 |
| Chinese | 177 |
| Mixed | 511 |
| Other | 959 |
| Unknown | 7927 |
| Total | 166,336 |

## 1.2 Risk Factors

The risk factors for developing prostate cancer are yet to be well characterised but include ethnic origin, older age and heredity [2]. The incidence of prostate cancer is known to vary with race (Table 1.1). Patients of African or Afro-Caribbean origin have higher prostate cancer incidence compared to any other racial group. These patients also suffer worse outcomes from prostate cancer compared to Caucasian patients [7, 8]. The reasons for such disparities in incidence and outcomes may be related to variations in tumour biology or in delayed presentation as is often observed [9, 10].

Other risk factors include age with the risk of developing prostate cancer increasing nearly exponentially with increasing age [11]. Family history of prostate cancer, in particular younger age at diagnosis in first-degree relatives, is also associated with an increased incidence. In some cases no associated mutation is identified; however in approximately 2% of patients with prostate cancer and age ≤55 years, this may be due to a mutation in the 'breast cancer 2' (*BRCA2*) gene. Additionally, prostate cancer among *BRCA2* carriers has been shown to be aggressive, with poorer survival rates observed [12]. The roles of inflammation, sexually

transmitted diseases [13], obesity, dietary fat intake [14], vitamin D level [15], genetics, environment, testosterone and oestrogen effects warrant further investigation and remain unclear [11].

## 1.3 Clinical Presentation

The clinical symptoms of localised prostate cancer usually relate to an enlarged prostate gland resulting in lower urinary tract symptoms. These include increased frequency of micturition (frequency) especially at night (nocturia), urgency, hesitancy to pass urine and poor urinary stream occurring commonly. In addition patients may experience dysuria and more rarely haematuria/haematospermia. In some cases symptoms related to metastatic disease can be the presenting complaint; these include fatigue, loss of appetite, bone pain and back pain. Patients with a large burden of metastatic bone disease are at risk of malignant spinal cord compression with clinical symptoms of weakness and paraesthesia's in the legs, urinary retention and constipation often observed.

## 1.4 Diagnosis

Prostate cancer is usually initially investigated with a DRE and PSA levels. These findings along with age, ethnicity, co-morbidities, family history and previous prostate history are then used to decide on the need for prostate biopsy [16].

Prostate biopsy is most commonly performed under transrectal ultrasound guidance with antibiotic cover. Adequate sampling of the prostate gland usually requires a minimum of eight cores. Definitive diagnosis is based on the presence of adenocarcinoma in the specimens taken. The most dominant Gleason pattern and the pattern with the highest Gleason grade determine the Gleason score [17]. This score and the maximum cancer length should be reported for each core. Historically a transrectal approach is used; however some urologists now prefer a transperineal approach. The cancer detection rates from transperineal biopsies are comparable to those obtained from a transrectal approach without the associated risk of sepsis [18, 19].

## 1.5 Staging Procedures and Investigations

Local clinical tumour staging is often supplemented with an MRI scan which can help to identify those patients in whom a nerve-sparing radical prostatectomy can be carried out [16]. Current guidelines recommend staging evaluations for patients at higher risk for asymptomatic metastatic disease or locally advanced disease that would alter local therapy recommendations. The clinical guidelines do not

**Table 1.2** Staging of prostate cancer according to TNM system [22]

| | |
|---|---|
| *T* | *Primary tumour* |
| TX | Primary tumour cannot be assessed |
| T0 | No evidence of primary tumour |
| T1 | Clinically inapparent tumour not palpable or visible by imaging |
| 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 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 metastases* |
| MX | Distant metastasis cannot be assessed |
| M0 | No distant metastasis |
| M1 | Distant metastasis |
| M1a | Non-regional lymph node(s) |
| M1b | Bone(s) |
| M1c | Other site(s) |

recommend staging for most patients with favourable disease characteristics because imaging studies are unlikely to reveal metastatic disease [20, 21]. The 2009 TNM prostate cancer staging classification is shown in Table 1.2 [22]. Moreover, general health and co-morbidities should be assessed, and patients who are not considered suitable for treatment with curative intent due to poor general health may not require staging investigations.

## 1.6 Risk Stratification

More than 90% of the cancers diagnosed are localised to the prostate. Retrospective analyses have established risk categories classifying patients with localised prostate cancer on the basis of the likelihood of disease recurrence [23, 24]. The D'Amico criteria classify patients with clinically localised disease into low, intermediate and

**Table 1.3** Risk stratification of localised prostate cancer [23, 24]

| | |
|---|---|
| Low-risk prostate cancer | All of T1 or T2a, Gleason < 7, PSA < 10 |
| Intermediate-risk prostate cancer | Between low- and high-risk groups |
| High-risk prostate cancer | Any of T3 or T4, Gleason > 7, PSA > 20 |

**Table 1.4** Risk stratification of prostate cancer with associated 5-year PSA-free survival rates [23, 24]

| Risk | Clinical and pathologic features | Estimated 5-year PSA-free survival, % |
|---|---|---|
| Low | • Stage T1c or T2a<br>• PSA: ≤10 ng/mL<br>• Gleason score: ≤6 | >85 |
| Intermediate | • Stage T2b<br>• PSA: 11–20 ng/mL<br>• Gleason score: 7 | 60 |
| High | • Stage ≥ T2c<br>• PSA: >20 ng/mL<br>• Gleason score: 8–10 | <30 |

high risk of 5-year biochemical recurrence based on clinical stage, biopsy Gleason score and PSA at diagnosis (Table 1.3) [24]. The percentage of patients who are disease free at 5 years decreases with increasing risk category and is applicable to both radical prostatectomy and radiation therapy (Table 1.4). The risk category into which a patient falls may affect recommendations for staging evaluations and subsequent treatment.

**Key Points**

- Prostate cancer is the most common non-cutaneous malignancy in Westernised countries with a lifetime risk of one in seven men.
- The association between prostate cancer and age continues to be observed in mortality figures with 73% prostate cancer deaths occurring in men 75 years or older.
- There has been a steady increase in the 5-year relative survival rates in recent years from 73.4% (1999–2001) to 83.4% (2005–2007).
- Prostate cancer screening has now been adopted in a number of Westernised countries resulting in some cancers being detected at earlier stages.
- The risk factors for developing prostate cancer are yet to be well characterised but include ethnic origin, older age and heredity.
- Family history of prostate cancer, in particular younger age at diagnosis in first-degree relatives, is also associated with an increased incidence.

- Prostate cancer among *BRCA2* carriers has been shown to be aggressive, with poorer survival rates.
- The clinical symptoms of localised prostate cancer usually relate to an enlarged prostate gland resulting in lower urinary tract symptoms.
- Prostate cancer is usually initially investigated with a DRE and PSA levels.
- Prostate biopsy is most commonly performed under transrectal ultrasound guidance with antibiotic cover. Definitive diagnosis is based on the presence of adenocarcinoma in the specimens taken.
- More than 90% of the cancers diagnosed are localised to the prostate.

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# Pathology of Prostate Cancer

# 2

Ashish Chandra

## Contents



## 2.1 Introduction

The diagnosis of clinically suspected prostate carcinoma rests on histopathological confirmation [1]. Histologically, prostate carcinoma is a gland-forming cancer, i.e. an adenocarcinoma with origin most commonly in prostatic acini (acinar adenocarcinoma) and less commonly in ducts (ductal adenocarcinoma). Rarely, squamous cell carcinoma, urothelial carcinoma and small cell carcinoma or even sarcomas may arise in the prostate.

## 2.2 Histological Features

The typical histological features of acinar adenocarcinoma include the presence of closely packed glands or acini of irregular shapes and sizes. The acini characteristically lack a basal cell layer, and the epithelial cells show prominent nucleoli. Small

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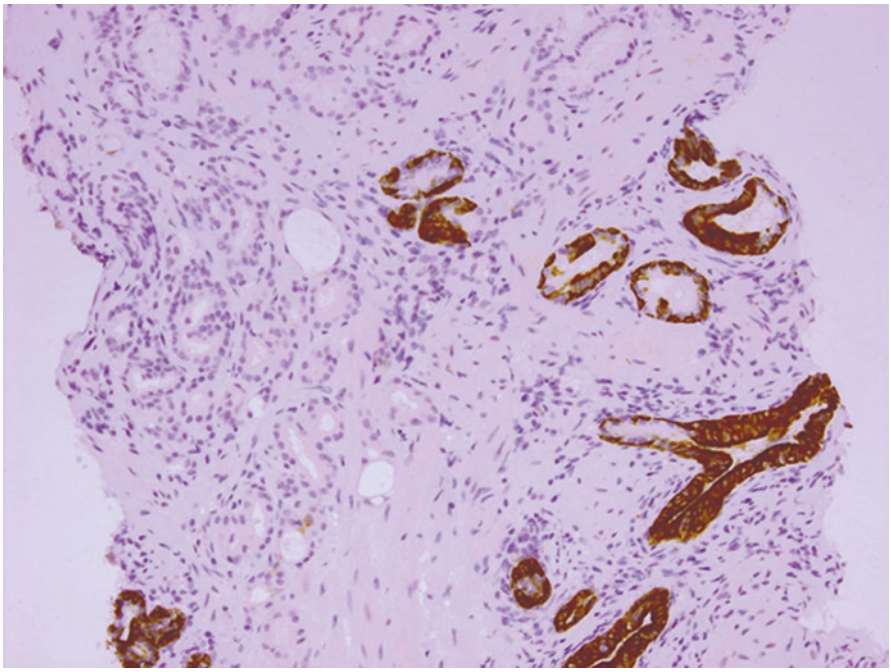

**Fig. 2.1** Immunohistochemistry demonstrates basal cells (stained *brown* with marker 34betaE12) in benign glands, while the surrounding malignant glands are negative

foci suspicious of cancer may pose a diagnostic challenge, particularly if the basal cells are not readily evident. Immunohistochemistry may then be performed to highlight the presence or absence of basal cells (Fig. 2.1).

## 2.3 Immunohistochemistry

The immunostains commonly used are p63 (nuclear stain) or a high molecular weight cytokeratin, e.g. 34betaE12 or CK5/6 (cytoplasmic stains). Alpha-methylacyl-CoA racemase (AMACR) is overexpressed in the cytoplasm of neoplastic epithelial cells. A combination of two or more of the above markers is commonly used. The presence of strong luminal positive staining of epithelial cells for AMACR in the complete absence of staining for basal cell markers would confirm the presence of a carcinoma at a suspicious focus.

## 2.4 Gleason Grading

Based on the degree of differentiation of the tumour, it is graded from 1 (well differentiated) to 5 (poorly differentiated), referred to as Gleason grades (or patterns). The Gleason score is the sum of the most prevalent and the second most prevalent

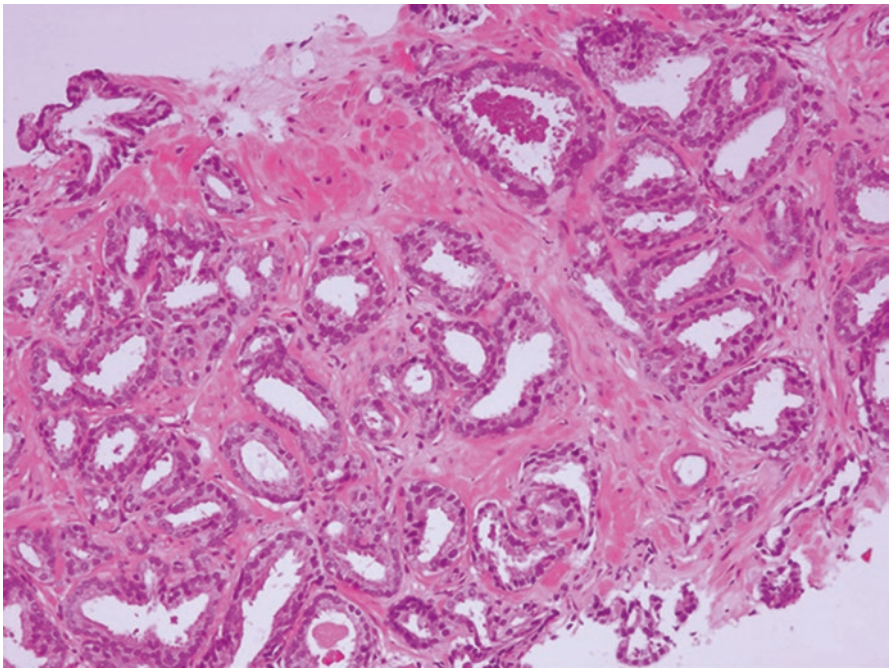

**Fig. 2.2** Gleason grade 3. Discrete, variable-sized malignant glands with distinct luminal spaces

grades in a given tumour. Gleason score is a strong predictor of the behaviour of prostate cancer. The Gleason grades are described as follows:

Grade 1. The tumour is perfectly circumscribed and contains closely packed acini that closely resemble normal prostate tissue. This is a very rare pattern, and circumscription is not assessable on needle core biopsies.

Grade 2. The tumour is well circumscribed but with some irregularity of the margin and contains acini closely resembling normal prostate tissue. This is also an uncommon pattern, and circumscription is not assessable on needle core biopsies.

Grade 3. The tumour has irregular margins and may infiltrate between normal prostate tissues. The acini are of variable shapes and sizes and closely set but separate as individual acini with luminal spaces (Fig. 2.2).

Grade 4. The tumour has a more complex architecture often with cribriform (sieve-like) structures and with glandular fusion although luminal spaces are still identifiable (Fig. 2.3).

Grade 5. The tumour bears little resemblance to normal prostate tissue with presence of either a dispersed single cell infiltrate (Fig. 2.4) or sheets of tumour cells, sometimes accompanied by necrosis.

Only grades 3, 4 and 5 are used in reporting prostate needle core biopsies with a range of Gleason scores from 6 to 10. The most prevalent grade in the tumour is referred to as the primary grade or pattern. The next most prevalent grade is the

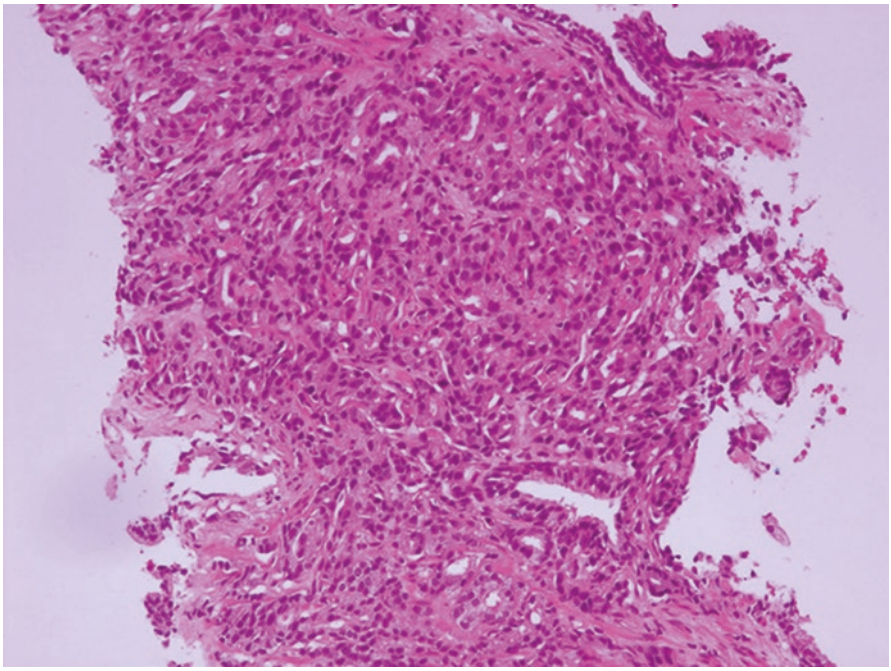

**Fig. 2.3** Gleason grade 4. Fusion of glands with complex architecture but recognisable luminal spaces

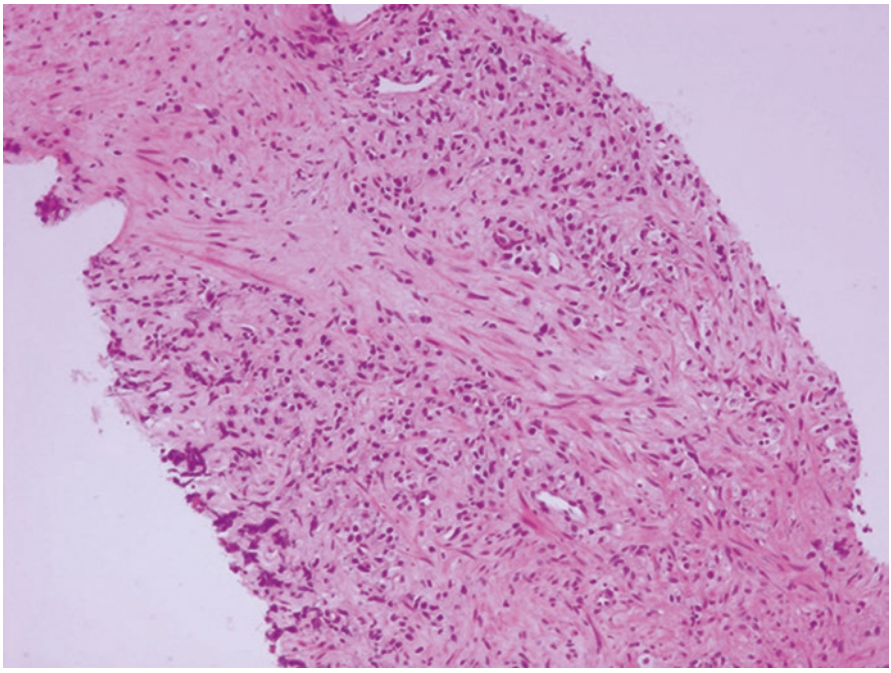

**Fig. 2.4** Gleason grade 5. Singly scattered cells lacking glandular formations and luminal spaces

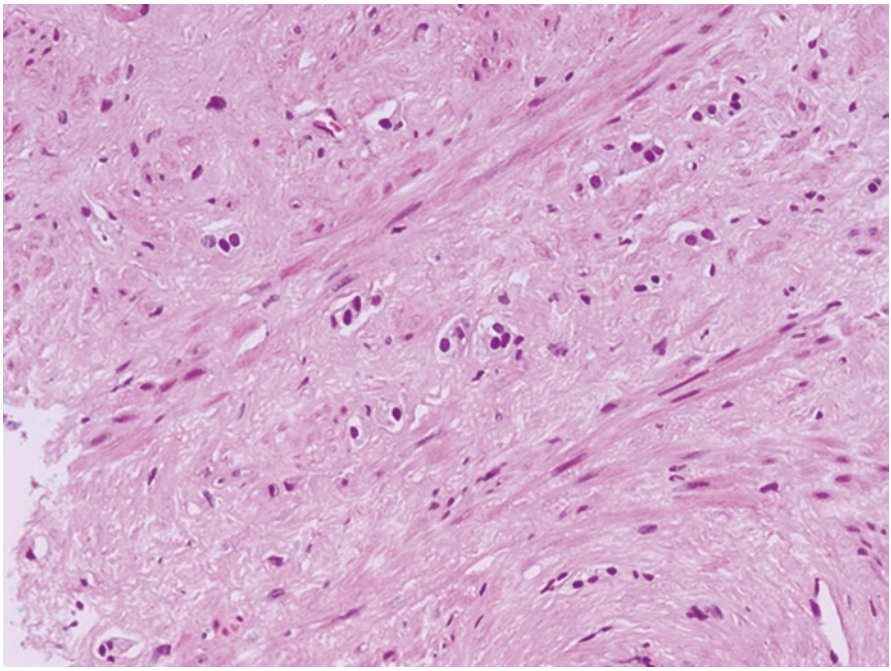

**Fig. 2.5** Effect of hormone therapy. The tumour cells appear bland and are difficult to detect especially if present in small numbers

secondary grade or pattern, and if another pattern is also present, it is referred to as the tertiary grade or pattern. If only one pattern is present, it is regarded to be both the primary and secondary grade, e.g. 3 + 3 = 6. In the modified Gleason scoring system, any grade five tumour is included in the Gleason score in reporting needle biopsies.

Following hormone therapy, the tumour may undergo morphological changes (Fig. 2.5), and the Gleason score may be difficult to apply. An estimated score may be suggested.

## 2.5 Newer Sampling Techniques

The conventional method of sampling the prostate is by transrectal ultrasound (TRUS)-guided biopsy, usually as six cores from each lobe. Newer methods of sampling including the template biopsy [2] involve a transperineal (TP) approach under general anaesthesia and sampling 2–4 times the number of cores than those taken at TRUS biopsy. This technique also allows sampling of the part of the prostate anterior to the urethra which is not easily sampled by TRUS biopsy [3]. Furthermore, it allows accurate localisation of the tumour on individual cores as these are orientated according to protocol. TP biopsy can be used in active surveillance of patients with low-risk disease (small volume disease, Gleason score 3 + 3), but its use is also being trialled

as primary means of sampling of the prostate especially in view of the reduced incidence of sepsis compared with TRUS biopsy. Sampling of suspicious lesions may be undertaken using multiparametric MRI-US fusion-targeted biopsies [4, 5].

## 2.6 Prognostic Factors

Several nomograms [6–10] have been developed to predict clinical outcome based on preoperative factors including patient age, serum PSA levels and needle biopsy findings (Gleason score, number and lengths of cores involved). Post-operatively, pathological features such as TNM stage, presence of lymphovascular invasion, margin status and serum PSA levels determine the need for adjuvant therapy.

## 2.7 Molecular Markers

A number of markers have been reported to be associated with the outcome of prostate cancer patients [11]. These include markers of apoptosis including Bcl-2, markers of proliferation rate such as Ki67, p53 mutation or expression, p27, E-cadherin, microvessel density, DNA ploidy, p16, PTEN gene hypermethylation and allelic losses. However, none of these have been validated and are not a part of the routine management of patients. Separating the tigers from the pussycats remains the holy grail in prostate cancer research.

**Key Points**

- Histologically, prostate carcinoma is a gland-forming cancer, i.e. an adenocarcinoma with origin most commonly in prostatic acini (acinar adenocarcinoma) and less commonly in ducts (ductal adenocarcinoma).
- The typical histological features of acinar adenocarcinoma include the presence of closely packed glands or acini of irregular shapes and sizes.
- Immunohistochemistry may then be performed to highlight the presence or absence of basal cells.
- The immunostains commonly used are p63 (nuclear stain) or a high molecular weight cytokeratin, e.g. 34betaE12 or CK5/6 (cytoplasmic stains).
- Based on the degree of differentiation of the tumour, it is graded from 1 (well differentiated) to 5 (poorly differentiated), referred to as Gleason grades (or patterns).
- The Gleason score is the sum of the most prevalent and the second most prevalent grades in a given tumour. Gleason score is a strong predictor of the behaviour of prostate cancer.

- Only grades 3, 4 and 5 are used in reporting prostate needle core biopsies with a range of Gleason scores from 6 to 10. The most prevalent grade in the tumour is referred to as the primary grade or pattern.
- Following hormone therapy, the tumour may undergo morphological changes, and the Gleason score may be difficult to apply. An estimated score may be suggested.
- The conventional method of sampling the prostate is by transrectal ultrasound (TRUS)-guided biopsy, usually as six cores from each lobe.
- Newer methods of sampling including the template biopsy involve a transperineal (TP) approach under general anaesthesia and sampling 2–4 times the number of cores than those taken at TRUS biopsy.
- A number of markers have been reported to be associated with the outcome of prostate cancer patients. These include markers of apoptosis including Bcl-2, markers of proliferation rate such as Ki67, p53 mutation or expression, p27, E-cadherin, microvessel density, DNA ploidy, p16, PTEN gene hypermethylation and allelic losses.

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# Management of Prostate Cancer

3

Simon Hughes and Ajay Aggarwal

## Contents



Prostate cancer is the commonest solid cancer in men, with approximately 42,000 new cases per year in the United Kingdom [1]. This section details the evidence-based management of prostate cancer at all stages.

## 3.1 Localised Prostate Cancer

Three predictive factors are used to risk stratify localised prostate cancer: Gleason grade, PSA and T-stage (see Table 3.1). They predict the risk of lymph node involvement, treatment failure and death from prostate cancer [2].

In general the treatment options for localised disease have comparable outcomes, and therefore management recommendations require assessment of comorbidities, performance status and patient choice. The management options are discussed in the following sections.

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**Table 3.1** Risk stratification of localised prostate cancer [23, 24]

| | |
|---|---|
| Low-risk prostate cancer | All of T1 or T2a, Gleason < 7, PSA < 10 |
| Intermediate-risk prostate cancer | Between low- and high-risk groups |
| High-risk prostate cancer | Any of T3 or T4, Gleason > 7, PSA > 20 |

## 3.2 Active Surveillance

This conservative modality avoids overtreatment for low-risk disease, which is increasingly pertinent in the era of routine PSA testing [3]. It seeks to reduce the burden of side effects without compromising overall survival. Patients are closely observed using a multimodality approach (biochemical, radiological, histopathological). Approximately 30% of patients on active surveillance (AS) will subsequently require radical curative treatment, and 10-year prostate cancer-specific survival rates approach 100% [4, 5].

**Indication:**
- Low-risk prostate cancer and selected men with intermediate risk disease
- Suitable for radical treatment if indicated [1]

**Side effects:**
- Psychological

## 3.3 External Beam Radiotherapy

External beam radiotherapy (EBRT) has an established role in the radical treatment of localised prostate cancer [6]. Developments have focused on maximising the tumour dose whilst limiting irradiation of normal tissues. 3D conformal therapy has evolved into image-guided (IG) intensity modulated radiotherapy (IMRT) as the standard of care [7] (see Fig. 3.1).

Hypofractionated techniques are under investigation and may offer a greater therapeutic ratio than standard fractionation [7, 9–14].

Androgen deprivation therapy (ADT) can be given in combination with radiotherapy. It achieves cytoreduction, allowing the use of smaller treatment fields, and potentiates tumour cell kill [9, 10]. Adjuvant ADT also improves overall survival in patients with high-risk disease [11–13]. The optimum duration of ADT relative to the risk of the disease is yet to be established [1].

EBRT can also be given as adjuvant or salvage therapy following radical prostatectomy (RP). Patients likely to have residual disease in the prostate bed (pT3; positive surgical margins; persistently detectable PSA; slowly rising PSA) are suitable candidates [14, 15].

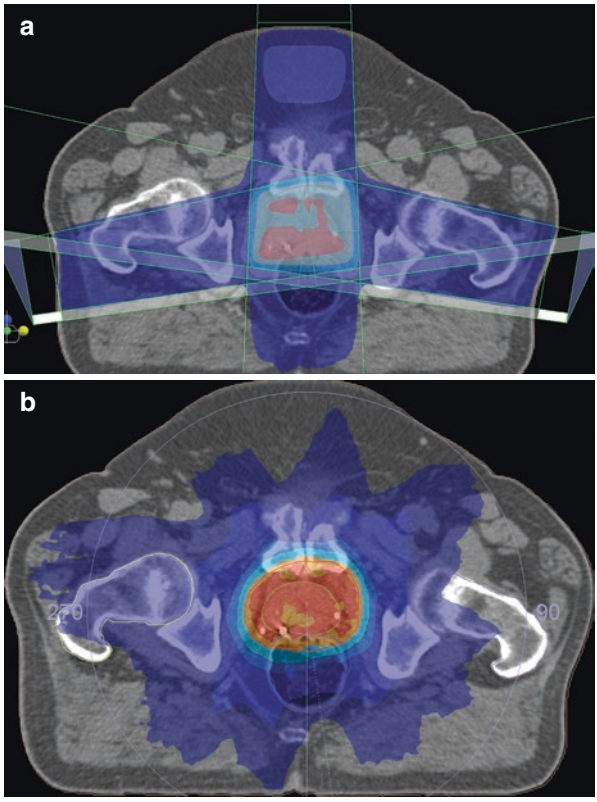


**Fig. 3.1** (**a**) IMRT tightly conforms the high-dose radiotherapy volume to the target by modifying both the shape and fluence of the radiation field in real-time during treatment delivery. (**b**) The location of the prostate varies relative to the surrounding pelvic anatomy due to changes in the degree of rectal distension and bladder filling. This can impact on tumour control [8]

**Indications:**
- All prostate cancer risk categories
- Post-operatively for high-risk disease

**Side effects:**
- Acute: cystitis, diarrhoea, proctitis, rectal bleeding
- Late: change in bowel habit, proctitis, impotence, secondary malignancy (rare)

### 3.3.1 Brachytherapy

Trans-perineal low-dose rate (LDR) brachytherapy involves the insertion of Iodine-125 (or Palladium-103) seeds into the prostate under ultrasound guidance. For low-risk disease the efficacy is at least comparable to EBRT/RP [16]. For intermediate- and high-risk patients, combination therapies involving EBRT with a brachytherapy boost (with/without ADT) may offer superior treatment outcomes [17].

**Indications:**
- Selected patients with low and intermediate risk disease

**Side effects [17–19]:**
- Acute: dysuria, urinary retention, proctitis
- Late: urethral strictures, erectile dysfunction

High-dose rate (HDR) brachytherapy is delivered via a temporary iridium-192 implant inserted through hollow catheters placed in the prostate. In combination with EBRT, it can improve biochemical relapse-free survival and prostate cancer-specific survival compared to EBRT alone (intermediate-/high-risk disease) through dose escalation. Toxicity profiles are similar to EBRT alone [20, 21].

### 3.3.2 Radical Prostatectomy

Radical prostatectomy reduces prostate cancer-specific and all-cause mortality when compared to watchful waiting [22]. However recent evidence has not demonstrated benefits for all patients [23]. The incidences of post-operative complications, positive surgical margins and late urinary complications are reduced when performed by "high volume" surgeons in "high volume" centres [24, 25].

Surgery can now be performed open, laparoscopically or with robotic assistance (RALP). Nerve-sparing techniques have reduced the incidence of impotence but are only considered where they are not predicted to compromise surgical margins [26]. Extended lymph node dissection is considered for high-risk cases [7, 27].

**Indications [7]:**
- Low and intermediate risk disease
- Life expectancy >10 years
- Selected patients with high-risk disease

**Side effects: [7]**
- Urinary Incontinence, impotence

## 3.4 Metastatic Disease

The first-line treatment for patients with metastatic disease is ADT either with orchidectomy, luteinising hormone-releasing hormone (LHRH) agonists or gonadotrophin-releasing hormone (GnRH) antagonists [17]. There is established evidence for early addition of docetaxel for suitable patients, although there is debate over whether this should just be for those with a high burden of disease [28, 29].

Management of "castration-resistant" metastatic prostate cancer (mCRPC) depends on disease burden, disease location, symptoms, PSA velocity, patient fitness, response to previous treatments and patient preference. There remains debate regarding optimum treatment sequencing and the individual contribution of each agent to overall survival, but the following agents have all demonstrated efficacy.

### 3.4.1 Corticosteroids

Corticosteroids reduce PSA levels, delay time to PSA progression and palliate symptoms [30]. Dexamethasone 0.5 mg daily demonstrates good efficacy [1, 31].

### 3.4.2 Cytotoxic Chemotherapy

Docetaxel + prednisone is the first-line chemotherapy agent for patients with a good performance status and is beneficial in terms of overall survival, quality of life and pain control [32]. Cabazitaxel is a second-line cytotoxic agent, also associated with a survival benefit and improved pain control, particularly in patients whose cancer progresses on/shortly after completing docetaxel therapy [33].

### 3.4.3 Androgen Receptor Pathway Targeted Agents

In castrate-resistant disease the androgen receptor (AR) pathway remains a useful target. Abiraterone acetate (a CYP-17 inhibitor) inhibits androgen biosynthesis in the adrenal glands, the tumour and the testes. It is administered with prednisone to minimise mineralocorticoid side effects. Enzalutamide targets multiple steps in the AR signalling pathway and, unlike other anti-androgens, has no partial-agonist action. Both agents have demonstrated efficacy in both the pre- and post-docetaxel settings, improving biochemical and radiological control, delaying deterioration in quality of life and improving survival [34–37].

### 3.4.4 Other Agents

Other treatment options include diethystilboestrol [38] and more recently Alpharadin (radium-223), an alpha emitter which targets bone metastases with alpha particles. The latter is associated with survival, quality of life and pain control benefits [39].

In prostate cancer, bisphosphonates are used to reduce/delay skeletal-related events (e.g. zoledronic acid) [40]. Denosumab is a monoclonal antibody that targets RANK ligand-mediated activation of osteoclasts. It is superior to zoledronic acid in delaying or preventing SREs [41].

**Key Points**

- Three predictive factors are used to risk stratify localised prostate cancer: Gleason grade, PSA and T-stage. They predict the risk of lymph node involvement, treatment failure and death from prostate cancer.
- Treatment options for localised disease have comparable outcomes; therefore management recommendations require assessment of comorbidities, performance status and patient choice.

- Active surveillance avoids overtreatment for low-risk disease, which is increasingly pertinent in the era of routine PSA testing. Approximately 30% of patients on AS will subsequently require radical curative treatment, and 10-year prostate cancer-specific survival rates approach 100%.
- External beam radiotherapy has an established role in the radical treatment of localised prostate cancer. Developments have focused on maximising the tumour dose whilst limiting irradiation of normal tissues.
- Trans-perineal low-dose rate (LDR) brachytherapy involves the insertion of iodine-125 seeds into the prostate under ultrasound guidance.
- High-dose rate (HDR) brachytherapy is delivered via a temporary iridium-192 implant inserted through hollow catheters placed in the prostate.
- Surgery can now be performed open, laparoscopically or with robotic assistance (RALP).
- The first-line treatment for patients with metastatic disease is ADT either with orchidectomy, luteinising hormone-releasing hormone (LHRH) agonists or gonadotrophin-releasing hormone (GnRH) antagonists. The addition of docetaxel chemotherapy confers a survival benefit in certain patient populations.
- Management of "castration-resistant" metastatic prostate cancer (mCRPC) depends on disease burden, disease location, symptoms, PSA velocity, patient fitness, response to previous treatments and patient preference.

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# Prostate Cancer: Radiological Imaging

# 4

Vicky Goh and Giles Rottenberg

## Contents



Imaging plays an important role in the assessment of prostate cancer including detection, characterisation, localisation and guidance of biopsy, treatment planning, treatment response assessment and surveillance. Radiological techniques complementing clinical assessment in current practice include transrectal ultrasound (TRUS), multi-parametric magnetic resonance imaging (MRI) for locoregional disease and contrast-enhanced computed tomography (CT) for systemic disease. Whole-body MRI is also an emerging technique for metastatic disease.

## 4.1 Locoregional Disease

### 4.1.1 Transrectal Ultrasound

TRUS depicts the prostate internal architecture, bladder, seminal vesicles and anterior rectal wall with good spatial and contrast resolution and enables prostate volume to be estimated. Palpable tumours may display a hypoechoic or anechoic

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appearance although a variation in tumour echogenicity is noted. Its main role is to guide biopsy, typically where up to 12 samples at three levels of the peripheral zone are taken [1]. This provides information of tumour volume, extent, and grade, but there are limitations. Disease burden and grade may be underestimated, and the technique is operator dependent affecting quality of results. Sensitivity is in the order of 39–52% and specificity 80% [2]. Complications associated with TRUS biopsy include pain, haematuria, haemospermia and infection [3].

### 4.1.2 Magnetic Resonance Imaging

MRI utilising T2-weighted sequences was first described in the 1980s and has a higher sensitivity and specificity than TRUS [4]. Currently a multi-parametric MRI approach combining anatomical and physiological information is performed (Table 4.1; Fig. 4.1) [5]. Imaging at 3-Tesla versus 1.5-Tesla offers higher signal to noise and better structural and functional detail [6]. Endorectal coils increase the available signal-to-noise ratio (SNR) by an order of magnitude compared with pelvic-phased array coils, which is advantageous for MR spectroscopic evaluation, but adds discomfort, time and cost to the MR examination [7].

#### Morphological Evaluation

A combination of T1- and T2-weighted sequences is performed. The T1-weighted contrast of the prostate is low, with the gland appearing homogeneous; however, it is excellent for characterising focal T2 hypointense areas related to haemorrhage as these areas manifest as T1 hyperintense regions due to the T1 shortening effect of paramagnetic, iron-rich, blood by-products.

Multiplanar T2-weighted sequences provide high spatial resolution imaging with good SNR and tissue contrast. The peripheral zone (PZ), central gland (CG) and focal lesions are well depicted. Adjacent structures to the prostate, e.g. seminal vesicles and neurovascular bundles, may also be assessed. The normal PZ appears hyperintense on T2-weighted imaging. PZ tumours typically appear as well-defined focal hypointense areas. CG tumours may be more challenging to assess due to the lower contrast resolution between tumour and the CG structures

**Table 4.1** Typical multi-parametric MRI acquisition combining morphological and physiological assessment

| MRI sequences | |
|---|---|
| Morphological | Physiological |
| T1 axial whole pelvis | Diffusion-weighted sequence |
| T2 sagittal | Dynamic contrast enhanced |
| T2 coronal | $^{1}$H–MR spectroscopy |
| T2 axial high resolution | |

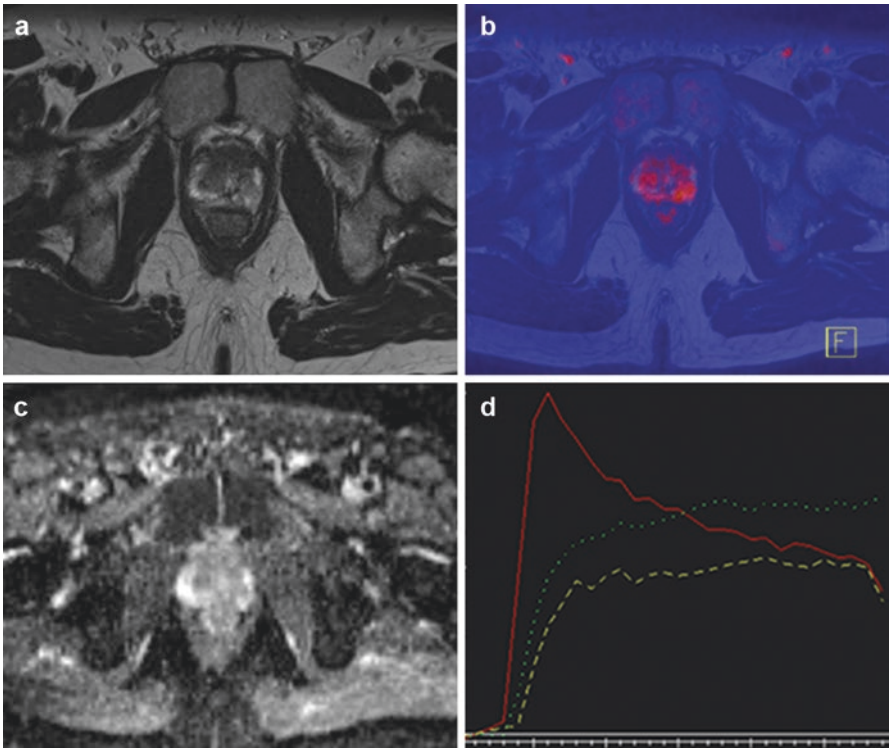


**Fig. 4.1** Axial MRI of a left posterior apical prostate tumour: T2-weighted (**a**) fused T2 and high-*b*-value diffusion-weighted (**b**) apparent diffusion coefficient map (**c**) and dynamic signal intensity curves (**d**) The hypointense tumour shows restricted diffusion and rapid wash-in and wash-out of contrast agent (*red curve*) in comparison to the peripheral zone and central gland

but may also manifest as hypointense areas, giving rise to the 'charcoal sign'. Morphological evaluation alone has a limited sensitivity for detecting prostate cancer ranging from 60 to 96% [8–10].

## Diffusion-Weighted MRI

Diffusion-weighted MRI is most commonly performed using a single-shot spin-echo EPI sequence [5]. Here a water-selective excitation and refocusing pulse is used to generate a spin echo from a selected slice at echo times of 60–100 ms. Diffusion sensitisation gradients are applied before and after the refocusing pulse with increasing *b*-values, typically up to 1400 s/mm$^2$ for the prostate due to the relatively long T2 values of normal peripheral zone. The resultant signal is attenuated increasingly with increasing *b*-value but to varying degrees. Areas with greater

cellular volume and lower extracellular volume (e.g. within tumours) demonstrate slower signal attenuation and maintain a higher signal compared to normal tissues. The apparent diffusion coefficient (ADC) may be calculated from the mono-exponential fit of the logarithmic gradient of at least two *b*-values, which represent the water diffusivity in $mm^2/s$. Tumours typically demonstrate lower ADC values than normal tissue. ADC may improve tumour characterisation, with a correlation with low-high Gleason score in prostate cancer [11].

**Dynamic Contrast-Enhanced MRI**

Dynamic contrast-enhanced MRI of the whole prostate using T1-weighted 3D spoiled gradient echo sequences with a temporal resolution ≥5 s over 2–5 min enables the temporal changes in signal intensity following intravenous administration of low molecular weight gadolinium-based contrast agent to be assessed qualitatively (via signal intensity versus time curves) or quantitatively (via kinetic modelling) [5]. The temporal resolution and acquisition length is sufficient to allow for the 'wash-in', 'wash-out' and recirculation of contrast agent to be assessed. Due to the T1 shortening effects of the contrast agent, the tumour typically manifests as an area of higher T1 signal intensity, reflecting the increase in vascularisation, with rapid wash-in and wash-out on the signal intensity-time curves (type 3 curve).

**MR Spectroscopy**

$^1H$ MRS with water suppression pulses may inform on the presence of citrate, creatine and choline; however its clinical utility remains uncertain [5]. Within the healthy prostate, the most prominent spectroscopic signals arise from citrate methylene protons (Cit; 3.2 ppm) and the methyl groups of creatine (Cr, 3 ppm)- and choline (Cho, 2.6 ppm)-containing compounds.

In cancers there is an increased signal from choline (related to membrane production and degradation) and an increase in the (Cho + Cr)/Cit ratio, which has been used as a biomarker more successfully in the PZ than CG where the signal is more heterogeneous.

### 4.1.3 Metastatic Disease

The most common sites of metastatic disease are the skeleton and lymph nodes. Contrast-enhanced CT is performed to assess the burden of metastatic disease and treatment response; however it has its limitations in terms of skeletal disease [12]. Whole-body MRI is emerging as a clinical technique. The combination of T1-weighted, T2-weighted and diffusion MRI is showing greater promise than CT but has the disadvantage of a longer examination time (Fig. 4.2).

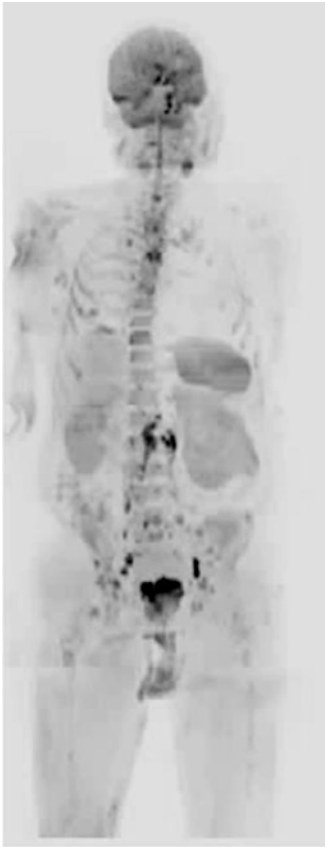

**Fig. 4.2** Diffusion-weighted MRI: Inverted MIP image demonstrates diffuse skeletal metastatic disease and abdominal nodal disease (*black* areas)

### 4.1.4 Clinical Guidance

#### Diagnosis

The NICE guidelines were updated in 2014 [1]. For patients with suspected prostate cancer, an initial TRUS-guided biopsy is performed. For patients with a negative initial biopsy and continued suspicion of cancer, multi-parametric MRI is recommended to determine if a second biopsy is necessary.

#### Staging

In patients with a positive biopsy and a radical intent, staging with multi-parametric MRI is recommended if the T and N stage will change management. It is important to determine whether the tumour remains organ confined ($\leq$T2) or extends beyond the gland ($\geq$T3). Extracapsular extension, neurovascular and seminal vesicle

invasion may be imaged. If there is high-risk cancer with a strong suspicion of disease spread beyond the pelvis, a staging with whole-body CT is indicated.

### Active Surveillance

For low- to intermediate-risk cancers, multi-parametric MRI is recommended at baseline. During years 1–5, if there is clinical concern or rising PSA, then reassessment with MRI ± biopsy is recommended.

**Key Points**

Imaging plays an important role in the management of cancer patients.

- Transrectal ultrasound-guided nontargeted biopsy is used for initial diagnosis.
- Multi-parametric MRI of the prostate improves detection and localisation of intra-prostatic disease and accurate locoregional staging.
- Contrast-enhanced CT has a role for distant staging.

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# The Role of PET/CT in Prostate Cancer Management

5

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## Contents



PET/CT had a number of potential roles in prostate cancer management strategies, and each of these will be considered in turn:

1. Diagnosis
2. Staging at diagnosis

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3. Restaging at relapse
4. Monitoring treatment response
5. Prognostication
6. Radiotherapy planning

A wide range of PET radiopharmaceuticals have been developed, each selectively targeting specific cellular functions or structures. The most commonly used tracer in clinical oncological PET imaging is $^{18}$F-FDG which behaves as a glucose analogue, accumulating in cells with greater glycolysis. However, $^{18}$F-FDG PET has never achieved widespread use in prostatic malignancies because of a limited sensitivity of only 75% for staging disease at diagnosis and 26% for detecting recurrent disease [1]. The high urinary excretion of $^{18}$F-FDG can obscure the view of the prostate.

Choline tracers (commonly labeled with $^{11}$C- or $^{18}$F-) have received growing interest for prostate cancer and within the UK are gaining increasing clinical utility (Figs. 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, and 5.8). Choline is an essential component of cell-membrane phospholipid synthesis. Tumours, including prostate cancer, have an increased requirement for cell membrane synthesis, and it has been shown that prostate cancer cells have an increased intracellular transport of choline and increased choline metabolism [2], confirmed by MRI spectroscopy [3]. PSMA PET tracers are gaining increasing acceptance in prostate cancer imaging and will probably replace choline tracers in most applications (see Chap. 6).

Acetate is a substrate for numerous cellular processes, including the anabolic pathway leading to fatty acid synthesis. Radiolabelled acetate tracers have demonstrated utility in imaging prostate cancer, including in patients with lower PSA levels, but such tracers are neither cancer nor prostate specific.

There is increasing interest in more prostate-specific tracers, including prostate-specific membrane antigen (PSMA)-targeted imaging tracers, and those targeting androgen receptors (Figs. 5.9, 5.10, and 5.11). PSMA are type II transmembrane proteins, overexpressed in prostate cancer [4].

Other tracers have shown potential utility for prostate cancer imaging, including markers of amino acid transport (e.g. the leucine analogue, anti-1-amino-3-18F--fluorocyclobutane-1-carboxylic acid, $^{18}$F-FACBC), cellular proliferation (e.g. $^{18}$F-fluorothymidine (FLT)), hypoxia ($^{18}$F-fluoromisonidazole) and angiogenesis (RGD-based tracers). Such tracers have a potential role in prostate cancer management.

## 5.1 Diagnosis of Prostate Malignancies

The current diagnostic tools of serum prostate-specific antigen (PSA), digital rectal examination (DRE) and transrectal ultrasound scan (TRUS)-guided biopsies to provide pre-surgical tumor grading of prostate cancer are only accurate in around 69% of patients [5].

Most prostate malignancies show increased uptake of choline-PET tracers. However, uptake in benign prostate hypertrophy has been shown, and some report an inability of these tracers to differentiate between benign and malignant prostate tissue [6]. A sensitivity of up to 90% and specificity of 86% have been reported for

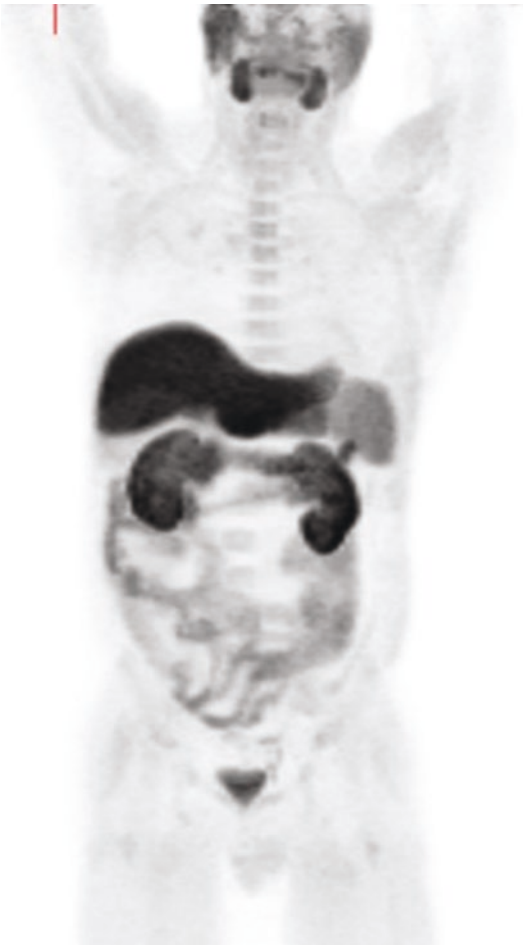


**Fig. 5.1** A normal $^{18}$F-choline PET scan (MIP image). Physiological uptake of choline is present in the salivary glands, liver, spleen, kidneys, bowel and bladder with low-grade normal bone marrow activity

the detection of localized prostate malignancy [7] with choline PET/CT, but the accuracy is lower for smaller tumors.

There is not enough evidence currently to support the use of choline-PET/CT, or other tracers, for screening patients for malignancy. There may be a role for guiding biopsies in patients who have repeated negative prostate biopsies despite a high clinical suspicion [8] but this remains an area of research interest at present.

## 5.2 Staging of Prostate Malignancies

Given the uncertainty of the accuracy of choline-PET in differentiating benign from malignant tissue, the value of this technique for T-staging prostate tumors is limited. The spatial resolution of clinical PET/CT scanners in widespread use is insufficient to accurately assess the prostate capsule for evidence of involvement or breach. The development of PET/MRI may show T-staging benefits, as suggested in a 15-patient feasibility study using $^{18}$F-choline PET/MRI [9] (Figs. 5.3 and 5.8).

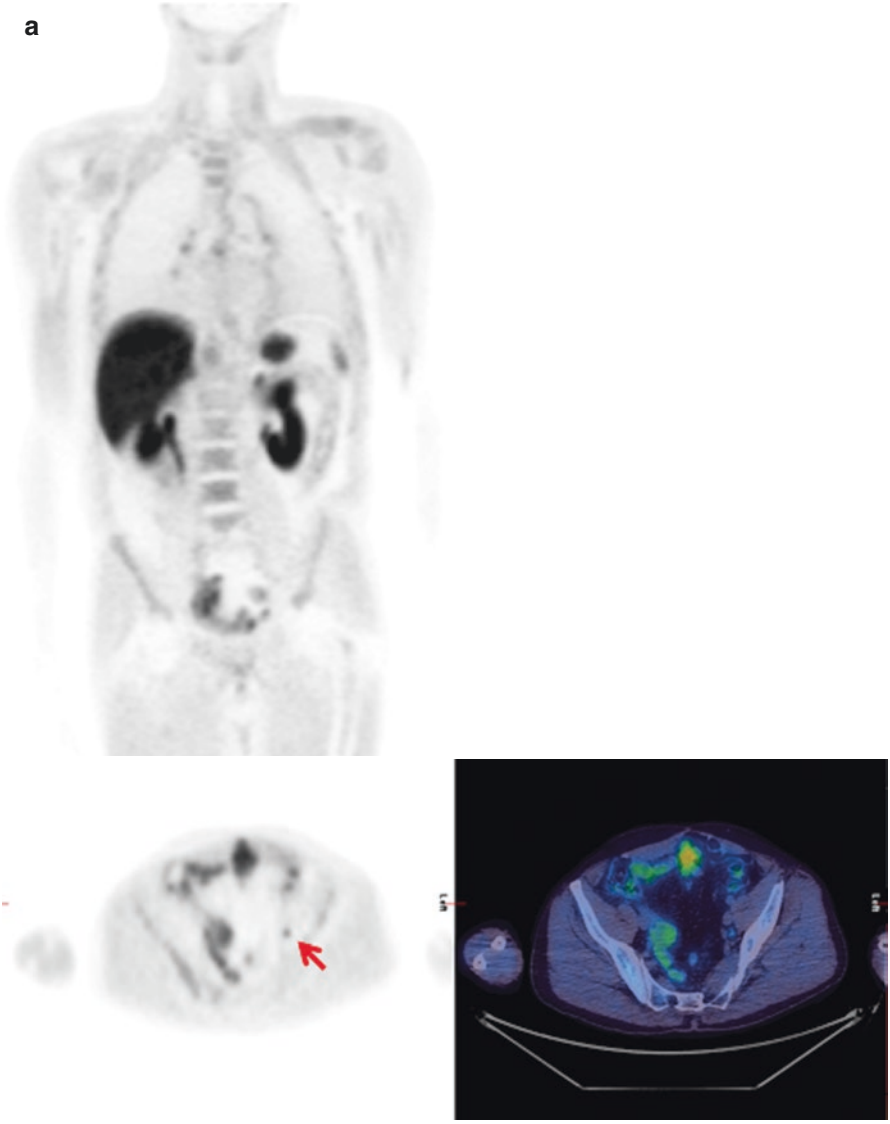



**Fig. 5.2** (**a**) $^{11}$C-choline (i) coronal PET and (ii) transaxial PET and fused PET/CT in the pelvis, (**b**) $^{18}$F-choline (i) coronal PET and (ii) transaxial PET and fused PET/CT in the pelvis. $^{11}$C-choline and $^{18}$F-choline PET/CT studies performed at an interval of 5 months in a 65-year-old male with rising PSA after previous prostatectomy for prostate cancer. Both tracers show a metabolically active 8 mm left external iliac lymph node (*arrow*), appearing more prominent on the later $^{18}$F-choline scan, in keeping with nodal disease recurrence. In addition, in both studies there is low-grade mediastinal/hilar and inguinal nodal uptake in keeping with nonspecific reactive changes. Note slight differences in biodistribution between the two tracers. There is less urinary excretion and muscle activity with $^{11}$C-choline

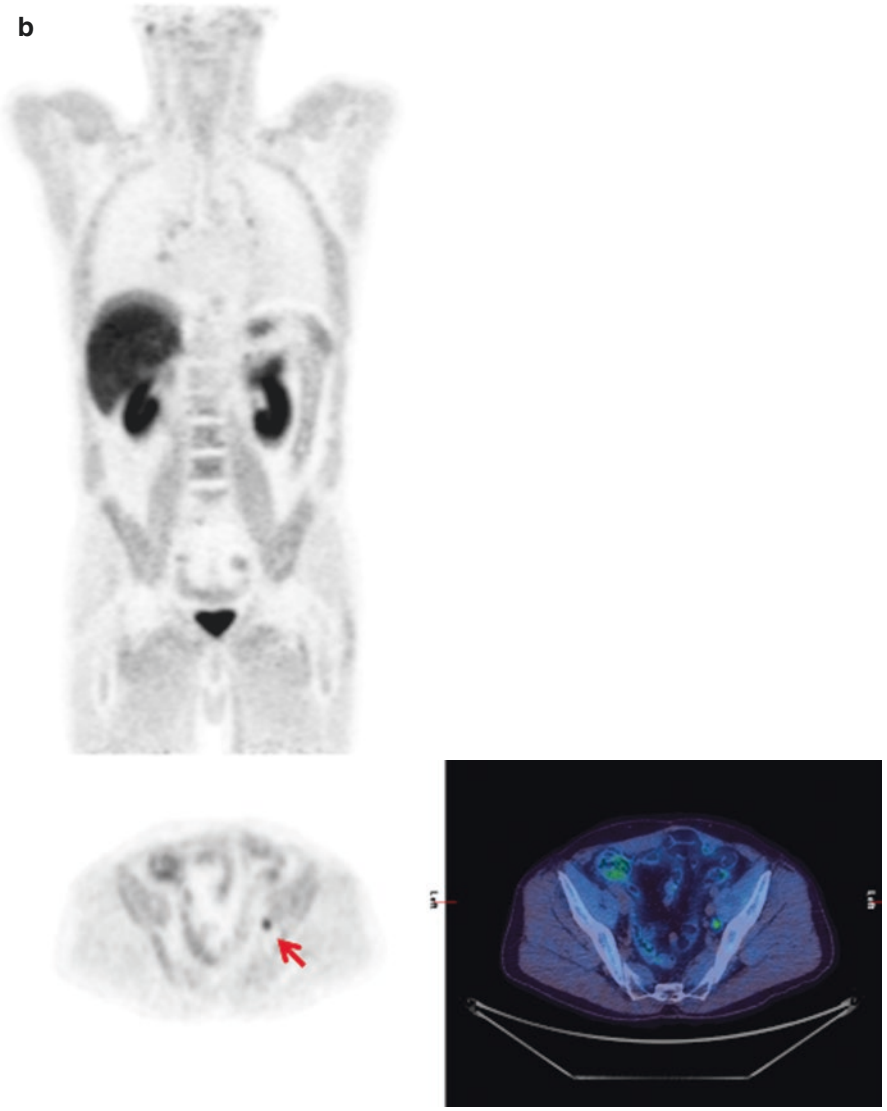



**Fig. 5.2** (continued)

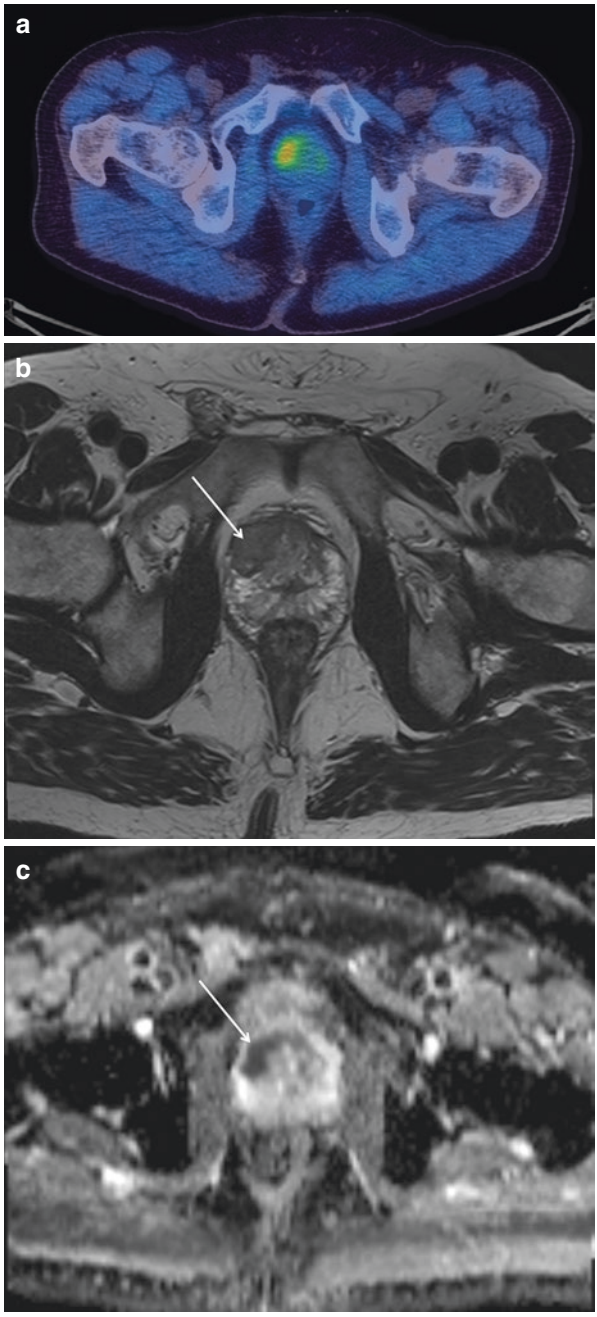



**Fig. 5.3** A patient with a new diagnosis of prostate cancer. The $^{18}$F-choline scan shows abnormal uptake in the primary cancer in the right side of the prostate gland (**a**). This corresponds with an area of low signal of the T2-weighted (**b**) and restricted diffusion on the ADC (**c**) MRI scans

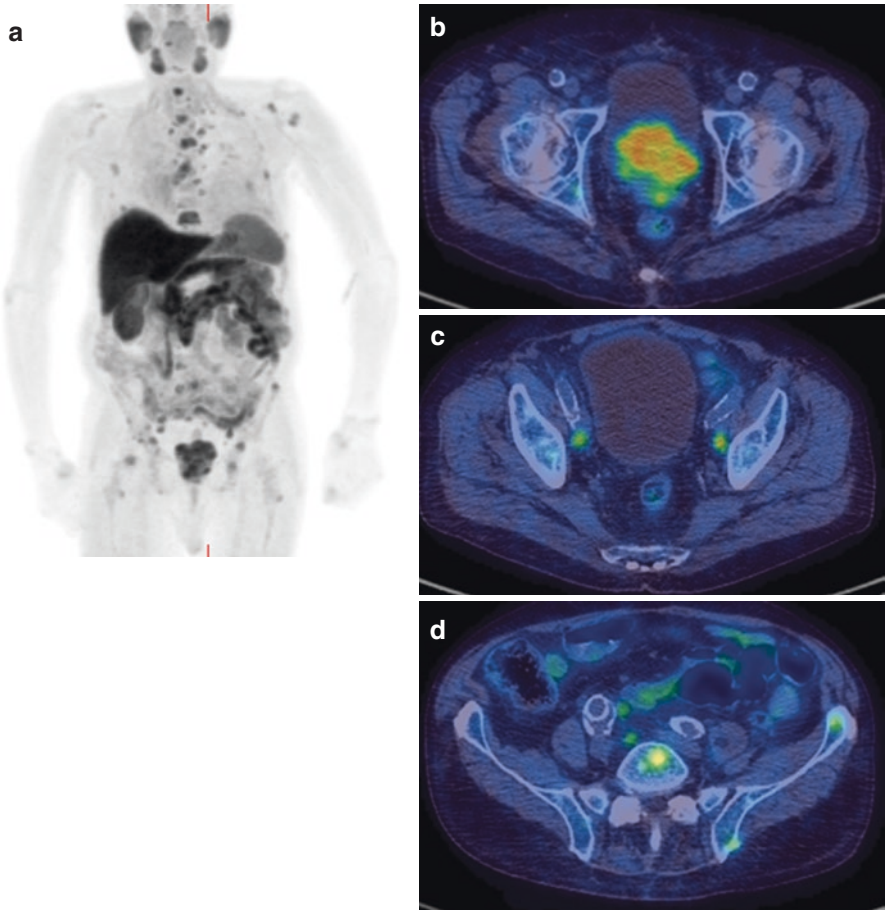



**Fig. 5.4** A patient who presented with prostate cancer and a PSA of 300 ng/ml. The $^{18}$F-choline PET/CT shows abnormal uptake in the prostate gland, lymph nodes and skeletal metastases. MIP (**a**), pelvic axial fused images (**b**), prostate (**c**), pelvic nodes (**d**), iliac nodes and bone metastases

Identifying involved lymph nodes at diagnosis (N-staging) has significant clinical significance, but has been difficult to achieve accurately with all imaging modalities, including MRI. Contractor et al. showed that $^{11}$C-choline PET/CT was more sensitive than MRI for nodal staging ($p = 0.007$), detecting more sub-centimeter involved nodes [10]. Whilst choline-PET/CT has demonstrated good specificity, the sensitivity is relatively low and is dependent on the size of the involved lymph node and the PSA levels. De Jong et al. reported sensitivity/specificity values of 80%/96%, respectively, but the mean PSA for the 67 patients studied was over 100 ng/ml. In contrast, Beheshti et al. reviewed 130 patients with a mean PSA of 27 ng/ml (suggesting earlier disease and/or less disease burden) and reported a sensitivity of only 45% for nodal analysis, but a specificity of 96% [8]; the sensitivity increased to 66% if only nodes larger than 5 mm were considered. Other studies have demonstrated similar values of sensitivities and specificities [10–12].

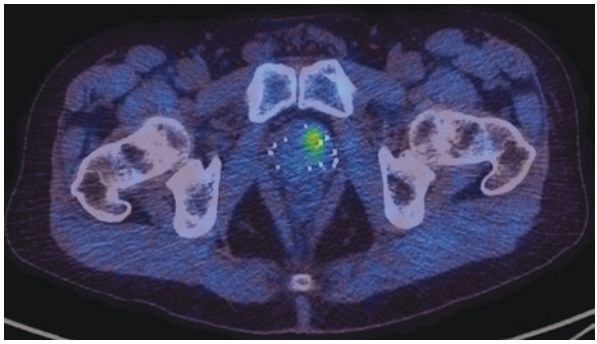


**Fig. 5.5** A patient previously treated with brachytherapy subsequently was found to have a rising PSA. The $^{18}$F-choline scan showed recurrent disease within the prostate gland but no areas of nodal or distant metastatic disease

**Fig. 5.6** $^{18}$F-choline axial CT, PET and fused PET/CT images of a 72-year-old man previously treated with brachytherapy for prostate cancer with a subsequent rising PSA. The images demonstrate focal activity in the seminal vesicle on the left (*arrow*) indicating recurrent disease

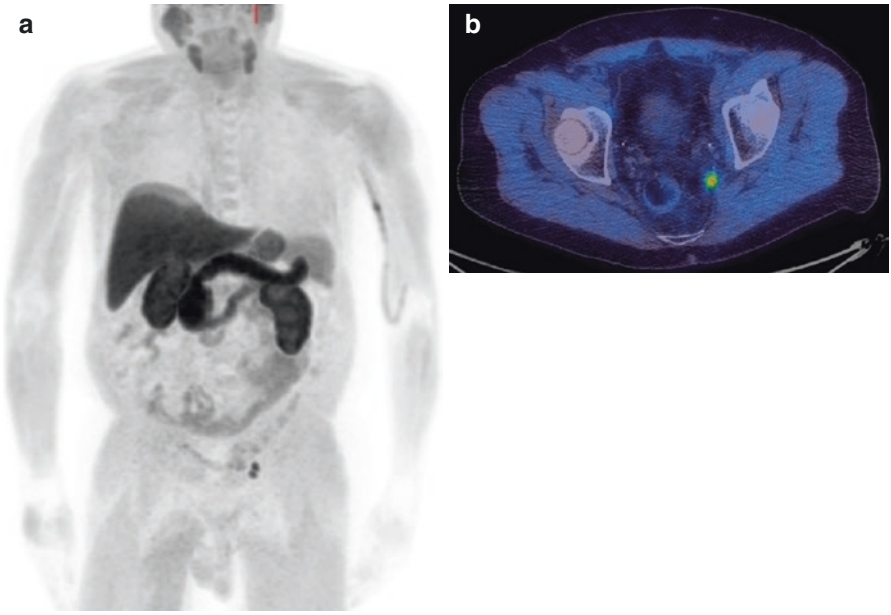



**Fig. 5.7** A patient with a rising PSA 1 year after a radical prostatectomy. The $^{18}$F-choline PET/CT scan shows small volume recurrent nodal disease in the left side of the pelvis on the MIP image (**a**) and axial fused image (**b**)

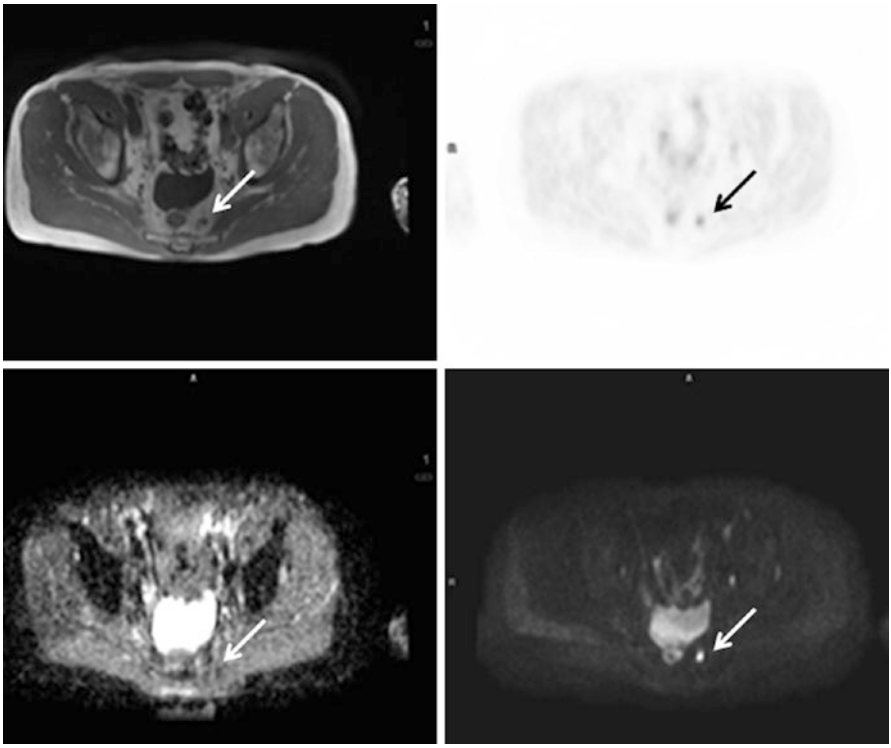


**Fig. 5.8** $^{18}$F-choline PET/MRI scan with axial pelvic images, T2 (*top left*), PET (*top right*), ADC map (*bottom left*), b900 image (*bottom right*). A 68-year-old man with previous prostatectomy for prostate cancer and subsequent rising PSA. The images demonstrate a left presacral nodal recurrence (*arrows*) with high $^{18}$F-choline activity, low ADC and high signal on the b900 diffusion-weighted image

The diagnosis of distant metastatic disease has important treatment implications; metastatic prostate cancer is incurable, and therefore invasive and morbid treatment to the primary disease is unlikely to be appropriate. Prostate cancer most frequently spreads to the bone causing typically sclerotic deposits. The current most common imaging method for screening for metastatic bone disease is with standard scintigraphy using technetium-labeled diphosphonates which are incorporated into the bone matrix of metastatic deposits secondary to the excess osteoblastic activity. $^{18}$F-fluoride, as a PET tracer, has a similar mechanism of uptake, but offers potential benefits from the resolution of PET/CT imaging, offering quantification potential and providing tomographic information as routine (Fig. 5.12). Faster clearance also allows imaging as early as 1 h post-injection. Choline PET/CT has been compared with standard bone scintigraphy in prostate cancer patients; Picchio et al. reported a sensitivity for identifying bone metastases of 89% for $^{11}$C-choline PET/CT and 100% for bone scintigraphy, but the specificity was much greater for $^{11}$C-choline PET/CT at 98 vs. 75% for bone scintigraphy [13]. Similar results have been reported

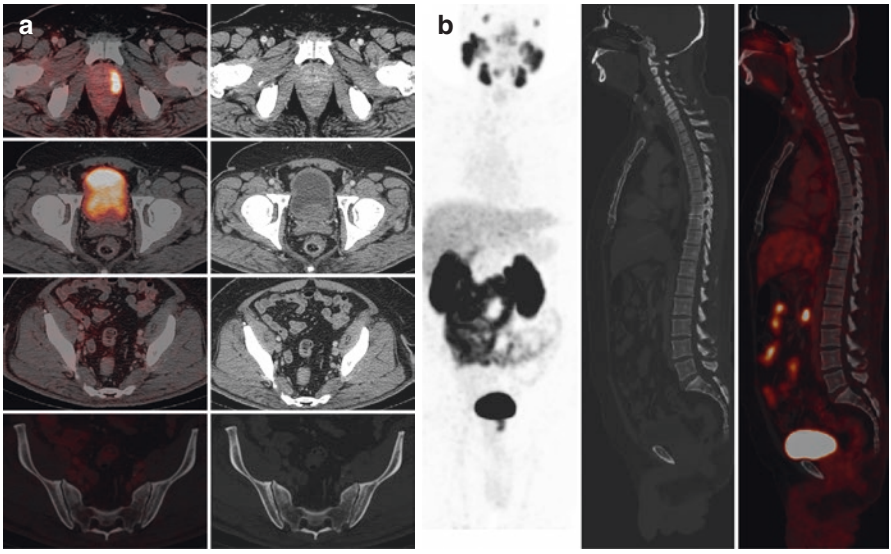



**Fig. 5.9** $^{68}$Ga-PSMA PET/CT. (**a**) Axial fused PET/CT and CT images through the pelvis and (**b**) PET MIP and sagittal CT and fused PET/CT images. A man with recently diagnosed adenocarcinoma prostate adenocarcinoma (Gleason score: 4 + 4). There is an intensely $^{68}$Ga-PSMA avid lesion involving the left anterior and posterior peripheral zones of the prostate gland. (**b**) There are no other $^{68}$Ga-PSMA avid lesions in the rest of the body. Physiological $^{68}$Ga-PSMA distribution with physiological uptake in the lacrimal, salivary glands, liver, bowel loops, kidneys and urinary bladder

by other groups [14]. This advantage of choline as a tracer is likely because there is little increased uptake in chronic degenerative lesions, unlike with standard $^{99m}$Tc bone scintigraphy. Beheshti et al. reported that in one study, $^{18}$F-choline PET/CT identified early bone marrow involvement that was not visible on CT alone [8]. No evidence currently demonstrates the superiority of choline PET/CT compared with standard staging techniques for the identification of bone metastases from prostate cancer, but it may have value in certain individual cases for problem solving (Fig. 5.4).

## 5.3 Restaging at Disease Recurrence

Imaging needs to identify sites of disease relapse, in particular whether this relapse is local to the prostate, within local or distant lymph nodes or distant metastatic spread. This has important treatment implications; a confined local recurrence might still be cured with salvage treatment. It is not uncommon for prostate cancer patients to have disease recurrence suspected by serial serum PSA rises. TRUS-guided biopsy only detects local recurrence in about 25–54% of these patients and is particularly poor when PSA values are low [15, 16]. CT has only a low diagnostic accuracy for localizing recurrent disease [17].

Most studies of PET tracers in prostate cancer have examined patients at the time of disease relapse (Figs. 5.5–5.8). A recent meta-analysis of 19 studies (1555 patients) examining choline-PET and PET/CT imaging at the time of disease recurrence concludes a pooled diagnostic sensitivity of 85.6% (95%CI = 60.6–100%) and specificity of 92.6% (36.4–100%), comprising a nodal sensitivity of 100% (90.5–100%) and specificity of 81.8% (48.2–97.7%), and a prostatic fossa sensitivity of 75.4% (66.9–82.6%) and specificity of 82% (68.6–91.4%) [18]. The sensitivity of $^{18}$F-choline PET imaging is proportional to the PSA level and the initial Gleason grade of the disease [12, 14, 19–25]. Husarik et al. reported that the sensitivity of choline PET/CT was 70% with a PSA ≤2 ng/ml at the time of the scan, compared with 86% when PSA >2 ng/ml [12]. Another group showed a sensitivity of only 20% with PSA ≤1 ng/ml, 44% for PSA 1-5 ng/ml and 82% when PSA >5 ng/ml [24].

Other tracers have shown utility in this clinical setting. There is a suggestion that acetate tracers might have a role in identifying sites of disease recurrence in patients with lower PSA levels, with acetate being a substrate of oxidation in the TCA cycle to produce energy in early prostate cancer deposits [26]. Labeled ligands for the androgen receptor (e.g. $^{18}$F-FDHT) may help demonstrate the role of the androgen receptor in patients with relapsed androgen-resistant disease [26].

A statistically significant higher detection rate was shown using a $^{68}$Ga-labelled PSMA ligand tracer compared with $^{18}$F-choline PET/CT, with a higher lesion SUVmax and greater tumor-to-background ratio [27]. There is also growing evidence to support the potential utility of $^{18}$F-FACBC, a leucine analogue, for detecting recurrent disease with improved sensitivity compared to $^{11}$C-choline PET/CT [28].

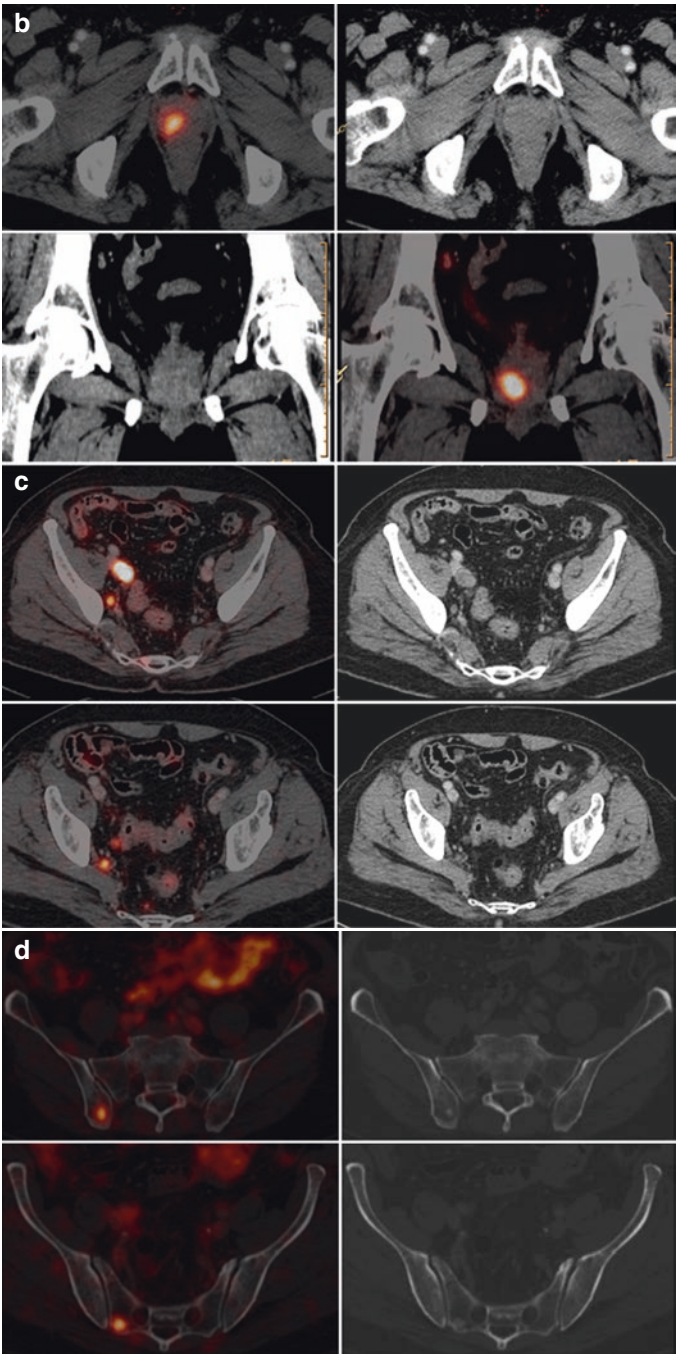
## 5.4 Assessing Treatment Response

No evidence yet demonstrates superiority of using choline-PET/CT over standard clinical measures of response to treatment, although it is suggested that such functional imaging may have significant advantages, particularly in detecting responses sooner than currently achievable following the PCWG2 guidelines [29]; this is currently under evaluation. Work in mouse models has highlighted this potential of $^{11}$C-choline and 18F-FLT PET imaging for detecting responses to docetaxel chemotherapy [30, 31]. Androgen receptor-targeted tracers might have utility in the development of targeted therapeutics and the subsequent treatment monitoring.

## 5.5 Prognostication

It has been reported that a negative $^{11}$C-choline PET/CT scan at relapse correlates with a higher disease-specific survival and lower treatment rate [32], and conversely a positive scan predicted a worse freedom-from-recurrence survival [33].

**Fig. 5.10** $^{68}$Ga-PSMA PET/CT. (**a**) PET MIP, (**b**) axial (*top*) and coronal (*bottom*) fused PET/CT and CT through the prostate gland, (**c**) axial PET/CT and CT images through the pelvis and (**d**) axial PET/CT and CT images (bone windows) through the pelvis. A man with a diagnosis of Gleason 5 + 4 prostate cancer. The images demonstrate a primary prostate cancer in the right peripheral zone (**a**, **b**), right external and internal iliac nodes (**c**) and right iliac and sacral bone metastases (**d**)

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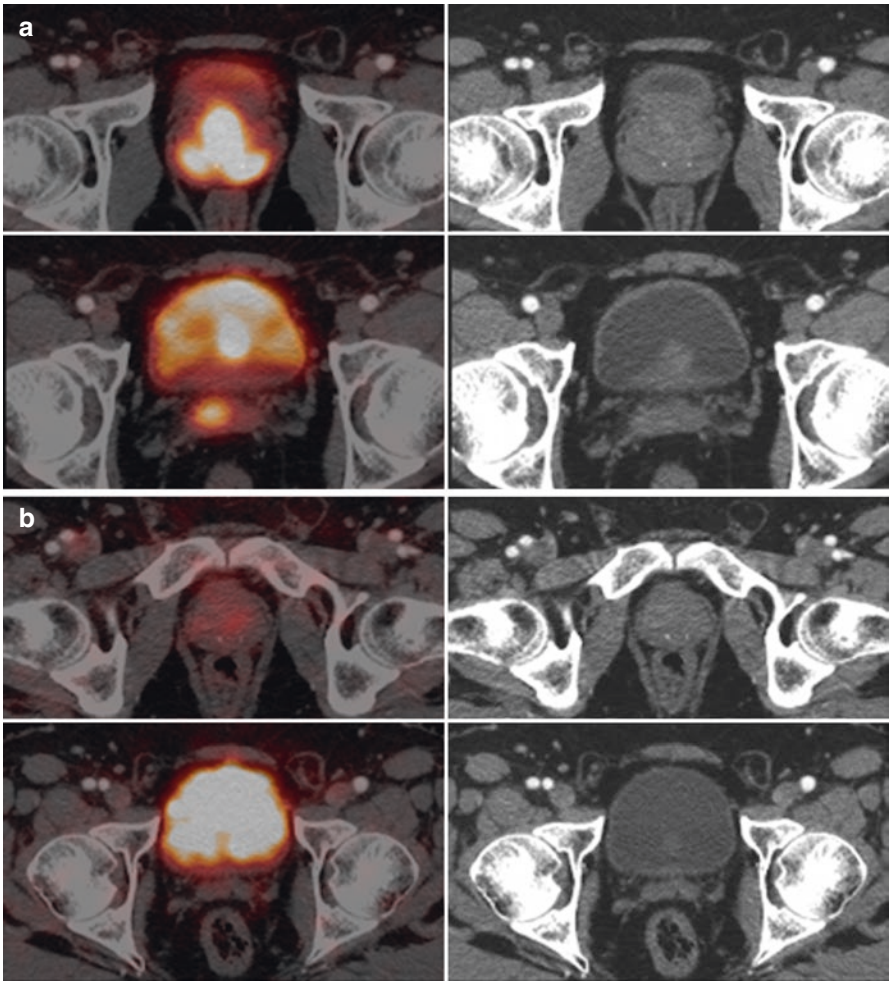


**Fig. 5.11** $^{68}$Ga-PSMA PET/CT. (**a**) axial PET/CT and CT through the prostate gland and seminal vesicles and (**b**) same images after treatment with hormone therapy. The baseline images (**a**) show primary cancer in the peripheral and central zones as well as the right seminal vesicle. After hormone therapy (**b**) there is a marked reduction in activity at all sites of disease

## 5.6 Radiotherapy Planning

There is increasing interest in using functional imaging to define radiotherapy target volumes; for prostate cancer this ties in with the uncertainty of how to best approach patients with pelvic lymph node involvement. Pinkawa et al. have demonstrated the feasibility of using $^{18}$F-choline PET/CT to allow dose escalation using a simultaneous integrated boost during radical radiotherapy [34], although the long-term survival data from such an approach is awaited. Vees et al. combined $^{99m}$Tc-Nanocoll prostatic sentinel lymph node detection using SPECT/CT with

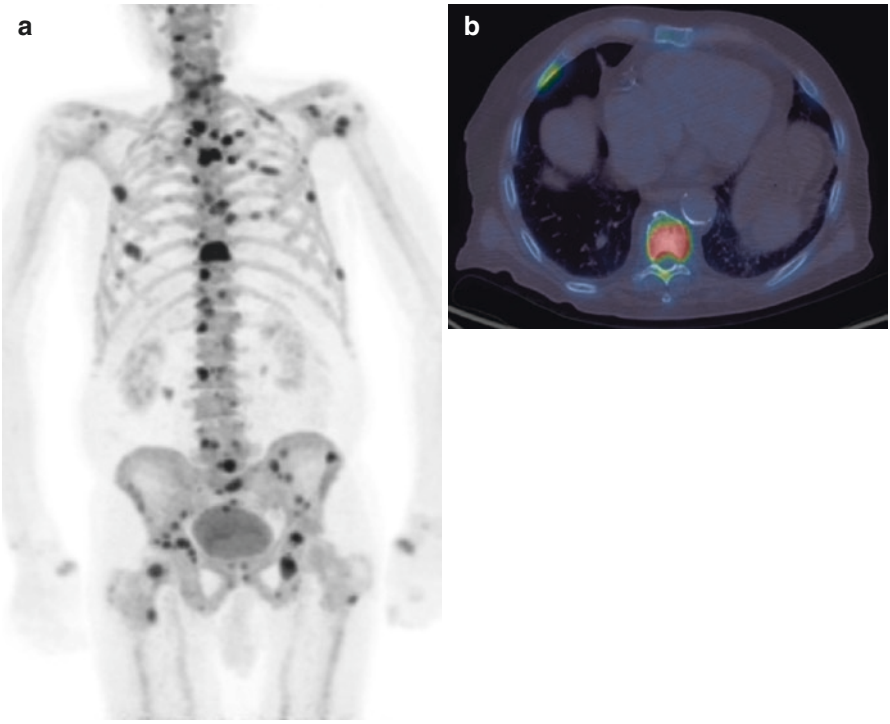


**Fig. 5.12** A $^{18}$F-fluoride PET/CT scan (**a**) MIP image and (**b**) axial fused image at the level of the lower thoracic spine showing multiple bone metastases. This is the same patient as in Fig. 5.4

$^{18}$F-choline PET/CT in 20 men with high-risk prostate cancer; 40% of patients had nodal involvement outside the standard pelvic radiotherapy target volume, highlighting that this approach may allow for tailoring of the radiotherapy treatment volume [35].

## Conclusion

There has been a rapid development of new PET tracers in line with technological advances, but also in line with a greater knowledge of tumor biology and involved metabolic processes with resultant advantages and few disadvantages compared to conventional imaging (Table 5.1). The translation of the novel tracers into widespread clinical utility has not been as rapid and is dependent on the access to suitable facilities. Choline PET imaging is increasingly being accessed in the UK, particularly at the time of PSA progression, but also at diagnosis to evaluate the nodal status. PSMA tracers are showing incremental value and are likely to be used more widely (see Chap. 6). The role of functional imaging in early and accurate detection of a therapeutic response remains an important aim and is currently being investigated. PET imaging could have further roles in targeting radiotherapy treatment and in targeted-drug development. It is likely that PET imaging will become an integral part of prostate management paradigms in the near future.

**Table 5.1** Advantages and disadvantages of PET in prostate cancer imaging

| |
|---|
| Advantages of PET in prostate cancer imaging |
| High sensitivity for metastatic disease |
| Sensitivity not dependent on size |
| Choline tracers now widely available in the UK but will probably be replaced by PSMA tracers |
| Choline PET shows good specificity for pelvic lymph node characterization |
| Choline PET may impact on radiotherapy management plans for salvage radiotherapy |
| Early data shows additional diagnostic accuracy of novel tracers such as $^{18}$F-FACBC and PSMA tracers |
| $^{18}$F-fluoride PET/CT shows increased diagnostic accuracy for skeletal imaging compared to $^{99m}$Tc-MDP bone scans |
| Disadvantages of PET in prostate cancer imaging |
| Poor specificity for detecting primary tumor |
| Choline tracers not prostate cancer specific |
| Choline tracers low sensitivity in recurrent disease when PSA <1 ng/ml |
| No consensus yet on which PET tracer is optimal |
| PET/CT (and PET/MRI) is more costly than bone scans or MRI |

**Key Points**

- PET/CT had a number of potential roles in prostate cancer management strategies.
- A wide range of PET radiopharmaceuticals have been developed, each selectively targeting specific cellular functions or structures.
- Choline tracers (commonly labeled with $^{11}$C- or $^{18}$F-) have received growing interest for prostate cancer and within the UK are gaining increasing clinical utility.
- There is increasing interest in more prostate-specific tracers, including prostate-specific membrane antigen (PSMA)-targeted imaging tracers and those targeting androgen receptors.
- PSMA are type II transmembrane proteins, overexpressed in prostate cancer.
- Most prostate malignancies show increased uptake of choline-PET tracers. However, uptake in benign prostate hypertrophy has been shown, and some report an inability of these tracers to differentiate between benign and malignant prostate tissue.
- Given the uncertainty of the accuracy of choline-PET in differentiating benign from malignant tissue, the value of this technique for T-staging prostate tumors is limited.
- $^{11}$C-choline PET/CT is more sensitive than MRI for nodal staging, detecting more sub-centimeter involved nodes.

- No evidence yet demonstrates superiority of using choline-PET/CT over standard clinical measures of response to treatment.
- A negative $^{11}$C-choline PET/CT scan at relapse correlates with a higher disease-specific survival and lower treatment rate, and conversely a positive scan predicted a worse freedom-from-recurrence survival.

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# Role of Radiolabelled Small Molecules Binding to PSMA in Diagnosis and Therapy of Prostate Cancer

6

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## Contents



PET/CT with choline tracers has been used in the past for staging and detection of recurrent disease, but shows a low sensitivity and specificity, especially in patients with low PSA levels [1–3]. Therefore, novel tracers with improved imaging characteristics are needed. In this aspect the prostate-specific membrane antigen (PSMA)

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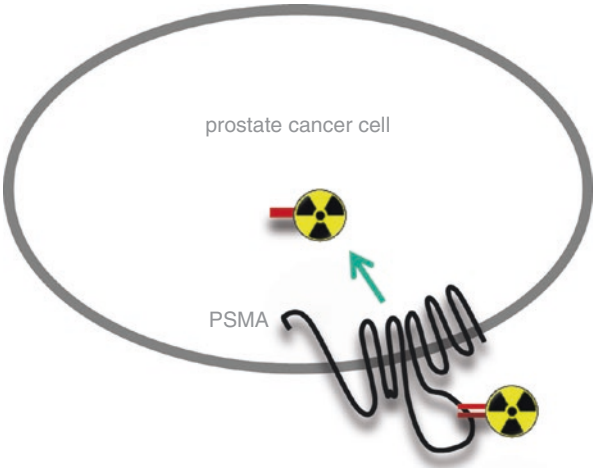


**Fig. 6.1** After ligand binding to PSMA the ligand-PSMA complex is internalized, resulting in an effective accumulation of the bound molecule in tumor cells

is a promising target. PSMA is a type II transmembrane protein with glutamate-carboxypeptidase and folate hydrolase activity, which shows overexpression on prostatic cancer including advanced stage prostate carcinomas [4, 5] and a low expression in normal tissues. After ligand binding to PSMA, the ligand-PSMA complex is internalized (Fig. 6.1), resulting in an effective accumulation of the bound molecule in the tumor cells. Together with a fast clearance of the tracer out of the circulation, this results in a high image quality for diagnosis and a high local dose for therapeutic applications. Several studies report that PSMA expression levels increase according to the stage and grade of the tumor [5–7]. Therefore, a variety of PSMA-targeted radioligands for diagnosis and therapy have been developed [8–23]. This chapter concentrates on small molecules binding to PSMA.

## 6.1 Diagnostic Application

Based on the development of small molecule inhibitors, mimicking the endogeneous substrate *N*-acetyl-L-aspartyl-L-glutamate (NAAG), normally cleaved by N-acetylated alpha-linked acidic dipeptidase NAALADase or glutamate carboxypeptidase II, several groups engaged in radiolabelled inhibitors with $^{123}$I, $^{99m}$Tc, $^{18}$F, $^{111}$In, and $^{68}$Ga [8–23].

The first high-affinity small-molecule inhibitors of PSMA applied in humans were $^{123}$I-MIP-1072 and $^{123}$I-MIP-1095. In men with metastatic prostate cancer, SPECT/CT after administration of these molecules demonstrated rapid detection (1–4 h p.i.) of tumor lesions in soft tissue, bone, and the prostate gland [13].

Glu-NH-CO-NH-Lys-(Ahx)-[$^{68}$Ga(HBED-CC)] ($^{68}$Ga-PSMA-11) became one of the most successful radiopharmaceuticals with respect to on-site availability [12] and clinical application. Figs. 6.2 and 6.3 show patients with a local recurrence and bone metastases, respectively.

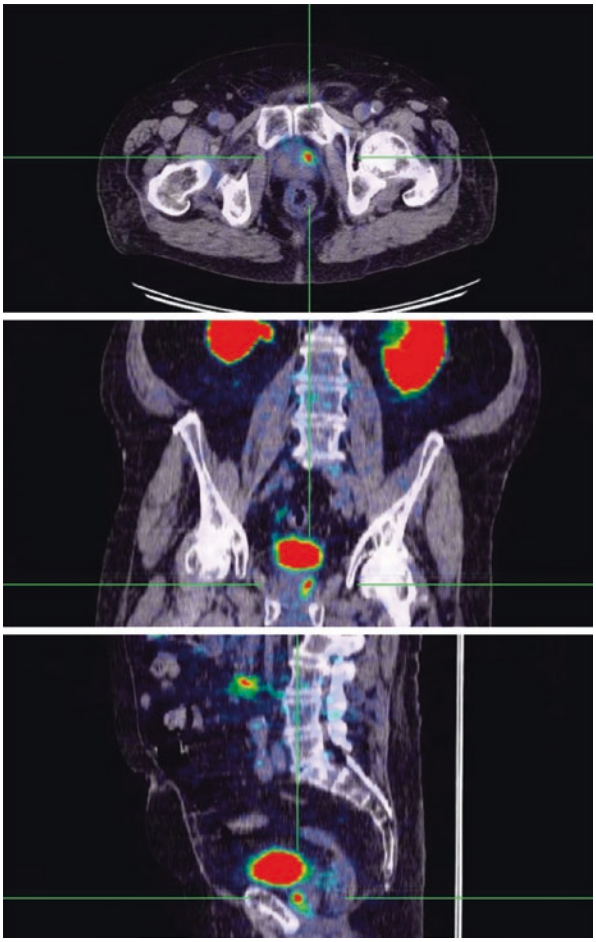

**Fig. 6.2** $^{68}$Ga-PSMA-11 PET/CT scan showing focal uptake in local recurrence of prostate cancer

Two retrospective studies with larger patient numbers (319 and 248 patients) reported detection rates of 82.8 and 89.5% [15, 24]. Tumor detection was positively associated with PSA level and androgen deprivation therapy (ADT). Gleason score (GSC) and PSA doubling time (PSA-DT) were not associated with tumor detection [15, 24]. Furthermore, the detection rates increased with a higher PSA velocity (81.8%, 82.4%, 92.1%, and 100% in <1, 1 to <2, 2 to <5, and ≥5 ng/mL, respectively) [24]. For lesions investigated by histology, 30 were false-negative in four different patients, and all other lesions ($n = 416$) were true-positive or true-negative. A lesion-based analysis of sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) revealed values of 76.6%, 100%, 91.4%, and 100%, respectively. A patient-based analysis revealed a sensitivity of 88.1% of 116 patients available for follow-up, 50 received local therapy after $^{68}$Ga-PSMA-ligand PET/CT [15].

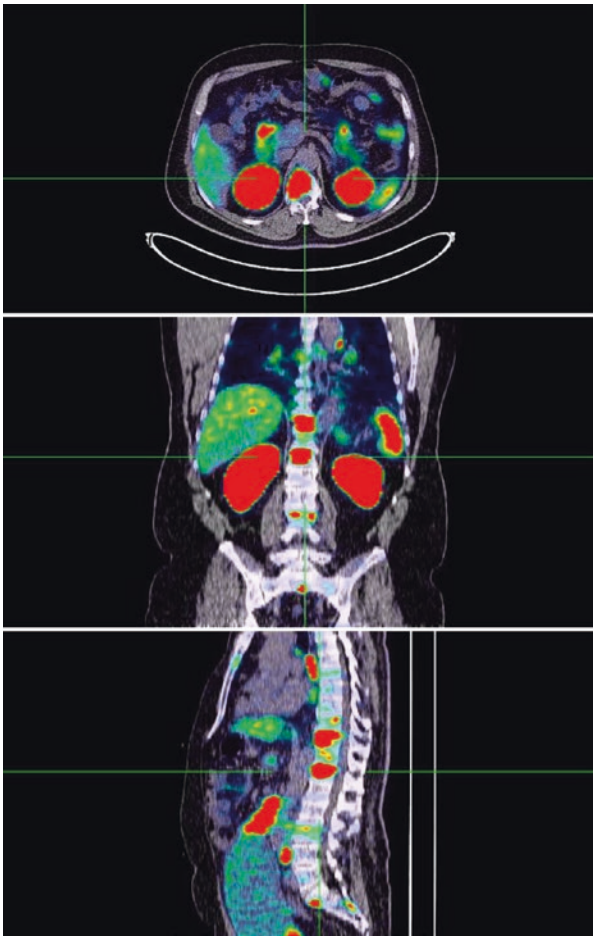

**Fig. 6.3** $^{68}$Ga-PSMA-11 PET/CT scan showing multiple tracer-avid bone metastases

In another retrospective study in 59 patients, the results of the $^{68}$Ga-PSMA ligand PET/CT was shown to have a dramatic impact on radiotherapy application with a change of treatment in 52.4% of the cases [25].

Since choline-based PET/CT is widely established for the diagnosis of prostate cancer, a comparison of $^{18}$F-fluoromethylcholine- and $^{68}$Ga-PSMA-ligand PET/CT has been done in 37 patients with biochemical relapse of prostate cancer showing 78 PCa-suspicious lesions in 32/37 patients using $^{68}$Ga-PSMA-ligand PET/CT, wheras 56 lesions were detected in 26/37 patients using choline-PET/CT. The higher detection rate in $^{68}$Ga-PSMA-ligand PET/CT concerning PC-suspicious lesions was significant ($p = 0.04$). All lesions detected by $^{18}$F-fluoromethylcholine-PET/CT were also seen by $^{68}$Ga-PSMA-ligand PET/CT. In $^{68}$Ga-PSMA-ligand PET/CT, $SUV_{max}$ was clearly (>10%) higher in 62 of 78 lesions (79.1%), and tumor-to-background ratio was clearly (>10%) higher in 74 of 78 lesions (94.9%) when compared to $^{18}$F-fluoromethylcholine-PET/CT. Therefore, $^{68}$Ga-PSMA-PET/CT detects

PC-suspicious relapses and metastases with improved contrast when compared to standard $^{18}$F-fluoromethylcholine-PET/CT, especially at low PSA levels [14].

These findings were confirmed by a prospective study in 38 patients [26]. At a PSA value below 0.5 ng/mL, the detection rate was 50% for $^{68}$Ga-PSMA versus 12.5% for $^{18}$F-fluoromethylcholine. For a PSA between 0.5 and 2.0 ng/mL, the detection rate was 69% for $^{68}$Ga-PSMA versus 31% for $^{18}$F-fluoromethylcholine. With a PSA higher than 2.0, the detection rate was 86% for $^{68}$Ga-PSMA versus 57% for $^{18}$F-fluoromethylcholine. In 24/38 (63%) patients, PET/CT had an impact on management, with 54% being due to $^{68}$Ga-PSMA imaging alone [26].

Up to now a systematic analysis of the performance of PSMA ligand-based PET/CT is not available for patients with primary tumors prior to standardized surgery and standardized pathological evaluation. However, such an analysis would result in reliable data concerning the sensitivity and specificity of PSMA ligand imaging for tumor and lymph node metastasis detection.

## 6.2 Endoradiotherapy

PSMA ligands are internalized and accumulate in the late endosomes. Therefore, a therapeutic application of these ligands after coupling to therapeutic isotopes is possible. Since curative approaches no longer exist for patients with metastatic castration-resistant prostate cancer and androgen receptor axis-targeted drugs such as abiraterone and enzalutamide finally lead to resistance against these agents, new isotope-based pharmaceuticals offer the chance of symptom relief and also a possible survival benefit.

Data obtained from the initial clinical investigation of $^{123}$I-MIP-1072 and $^{123}$I-MIP-1095 led to the evaluation of these radioiodinated ligands as potential PSMA-targeted radiotherapeutics when radiolabelled with $^{131}$I [8, 10, 13]. Dosimetry scans with $^{124}$I-MIP-1095 PET/CT done in 16 patients showed that the organs receiving the highest absorbed doses following administration of $^{131}$I-MIP-1095 are the salivary glands (mean dose 4.6 mGy/MBq), followed by the liver (1.5 mGy/MBq), and the kidneys (1.5 mGy/MBq). This leads to an estimated absorbed dose for the injected therapy activities (mean dose: 4.8 GBq, range 2.0–7.2 GBq) for the salivary glands of 9.2–33.3 Gy. Liver radiation doses fall in the range of 2.9–10.6 Gy. The kidneys received a total absorbed dose between 2.9 and 10.4 Gy. The mean total whole-body absorbed dose was 0.38 mGy/MBq resulting in 0.76–2.7 Gy based on the injected activities. Lymph node and bone metastases were exposed to estimated absorbed doses up to 300 Gy [27].

This was followed by therapy in 25 men with metastatic castration-resistant prostate cancer and PSMA-avid lesions on imaging. The patients received a single therapeutic activity of $^{131}$I-MIP-1095 (mean activity: 4.8 GBq, range 2.0–7.2 GBq). Hematological toxicities were mild. The onset of the myelosuppression occurred within 6 weeks post treatment with a quite variable time to recovery, in some cases requiring up to 3–6 months for recovery. White blood cells typically recovered within several weeks, while platelets required several months to recover. Twenty five percent of the patients had a transient slight to moderate dry mouth. No adverse effects on renal function were observed.

In patients with symptomatic bone metastases, 3/13 (23.1%) reported complete resolution of bone pain and 8 (61.5%) a decrease in pain severity. In the remaining 2 patients, the outcome is unknown. In 60.7% of patients, a decline in serum PSA levels of ≥50% was seen [27]. One patient showed a long lasting complete response by serum PSA value and by radiographic imaging. However, in 4/25 patients, an increase of PSA occurred. In responders the median time to PSA progression was 126 days (range 62–469 days). A decrease in PSA was associated with a decrease in number and/or intensity of the lesions visualized on the post-therapeutic PET/CT scan with $^{68}$Ga-labeled Glu-NH-CO-NH-Lys(Ahx)-HBED-CC.

While the results obtained with $^{131}$I-MIP-1095 show PSMA inhibitors may be effective for radio therapeutic applications, the use of β-particle emitting radionuclides such as $^{177}$Lu or $^{90}$Y would be preferable, given the advantages of energy, availability, and the potential for on-site labeling via kit formulations. Therefore, PSMA inhibitors have been developed which include chelators for the labeling with radiometals and have similar affinities as the compounds used for diagnostic purposes with excellent tumor uptake and retention. The versatility of DOTA allows the use of beta-emitters, such as $^{177}$Lu and $^{90}$Y, and alpha-emitters, such as $^{225}$Ac, with minimal gamma emissions that can be readily and safely employed in the clinic [22, 28].

**Key Points**

- Prostate-specific membrane antigen (PSMA) is a promising target. PSMA is a type II transmembrane protein with glutamate-carboxypeptidase and folate hydrolase activity.
- PSMA is overexpressed on prostatic cancer including advanced stage prostate carcinomas and a low expression in normal tissues.
- Tumor detection is positively associated with PSA level and androgen deprivation therapy (ADT).
- $^{68}$Ga-PSMA ligand PET/CT is shown to have a dramatic impact on radiotherapy application with a change of treatment in 52% of the cases.
- $^{68}$Ga-PSMA-PET/CT is reported to detect PC-suspicious relapses and metastases with improved contrast when compared to standard $^{18}$F-fluoromethylcholine-PET/CT, especially at low PSA levels.

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