Keywords

Prostatic neoplasms; neoplasm metastasis; diagnostic imaging

Introduction and Background

In the UK, prostate cancer is the most common malignancy in men accounting for 13% of all cases and is the second most common cause of cancer death, with an incidence rate projected to rise by 12% between 2014 and 2035 (1). Although the majority of patients present with localised disease, between 17 -34% of men have metastatic disease at diagnosis (2).

The European Association of Urology (EAU) has defined PSA > 20 ng/ml or Gleason score > 7 or stage T2c as high-risk disease, which correlate with disease progression and high cancer-specific mortality (3). A recent study reports that 12% of high risk patients developed distant metastases by 5 years of follow-up (4) with the median overall survival of metastatic prostate cancer (mPC) patients being approximately 4 years (5).

The prevalence of metastatic disease is increasing, and the pattern is changing. Increased life expectancy, the use of newer imaging techniques with higher sensitivity for disease detection and patients receiving multiple lines of novel therapies are likely to be contributory to this observation.

Early identification and accurate localisation of metastatic disease is particularly important as more data supports metastases-directed treatments such as stereotactic radiotherapy for oligometastatic disease (6), defined as up to 3-5 metastases located outside the pelvis. This question will be further interrogated in the STAMPEDE trial where an arm randomising hormone-sensitive patients with oligometastases is proposed. Contemporary data shows that local radiotherapy, improves survival

and prolongs the time before further therapy is needed in the patients with “low volume/burden” metastases setting (5).

The aim of this review is to briefly outline the imaging strategies for mPC and to highlight less-common metastatic patterns as a pictorial review.

Imaging

Imaging to detect metastatic disease is indicated in intermediate and high-risk patients at the time of diagnosis, and in patients after biochemical recurrence, defined by two consecutive PSA values above 0.2 µg/L after radical prostatectomy or more than 2 µg/L rise in PSA compared to nadir after local radiotherapy (7). Frequently, patients with rising PSA have no radiological detectable metastases initially (8).

The mainstay of imaging for detection of PC metastases either at diagnosis, or when clinically suspected due to a rise in PSA following treatment has been the isotope bone scan (BS) and CT. More recently, advanced imaging techniques including whole-body diffusion-weighted MRI (WBMRI) and PET tracers such as prostate specific membrane antigen (PSMA) have become available.

Bone scan

Radionuclide bone scan (BS) is readily available and the most widely used method for investigation of skeletal metastases, however BS has lower sensitivity and specificity of 79% and 82% than PSMA-PET and WBMRI (9). It also suffers from a number of limitations; increased uptake may be observed in benign pathologies such as fractures; an osteoblastic flare may be encountered as a treatment response; and BS confers limited assessment of treatment benefit.

CT

Computed tomography (CT) is readily available, is used for staging of nodal and visceral metastatic disease and confers limited information about skeletal metastases. The accuracy of distinguishing benign, from malignant lymph nodes less than 2cm in size with CT by size criteria alone is poor with sensitivity less than 40% (10,11). In addition, skeletal metastases may be occult on CT and assessment of disease activity is limited and does not necessarily correlate with attenuation. Further, liver metastases may occasionally be difficult to identify on CT when there is coexistent hepatic steatosis.

WBMRI

WBMRI including diffusion weighted imaging (DWI) increases sensitivity for detection of bone metastases over BS and CT, and performs as well as CT for detection of pathologically enlarged lymph nodes and visceral metastases (9, 12). MRI has a higher sensitivity for bone metastases detection compared to choline-PET, SPECT and bone scan, but choline-PET was found to be more specific in one study (9). However, in a prospective study comparing WBMRI with ^{68}Ga and ^{18}F PSMA-PET, ^{68}Ga was found to be more accurate for detection of bone metastases (13). A key advantage of WBMRI is that it allows monitoring of local disease and bony metastatic disease activity which may not be evident on BS or CT. In addition, WBMRI can detect complications such as hydronephrosis, metastatic spinal cord and cauda equina compression (MSCC) and it may be possible to differentiate between osteoporotic and malignant fractures with DWI. Main disadvantages of WBMRI include inability to detect small (sub-cm) lung metastases, poor specificity for small (sub-cm) nodal metastases and artefacts from metalwork in the pelvis or spine. Furthermore, MRI may not be possible in the presence of MRI incompatible devices or patient claustrophobia.

PET

A range of PET tracers are available for evaluation of metastatic disease, most recently PSMA, which is overexpressed on most prostate tumour cells. PSMA-PET has higher sensitivity for detection of nodal metastases compared with other PET tracers such as Choline, and with conventional CT imaging (14). A meta-analysis of the performance of ^{68}Ga-PSMA-PET yielded a high sensitivity and specificity of 86% for prediction of involved lymph nodes (15), and In patients with recurrent PC, detection rates with ^{68}Ga-PSMA-PET are higher than other imaging modalities (16). The American Society of Clinical Oncology (ASCO) note that next-generation imaging (NGI) with PSMA-PET or WBMRI has a potential role to clarify the burden of disease at initial diagnosis, and change management (17). Disadvantages of PSMA-PET include false negatives in tumours that do not express PSMA, and particularly in hepatic and pulmonary metastases which may be PSMA negative in up to 20% of cases (18,19). In addition, urinary excretion of tracer often obscures local recurrence and ureteric lesions, and accuracy of PSMA is reduced at low PSA values (<2ng/ml) (20).

Patterns of metastatic spread and clinical relevance

The most commonly observed metastatic pattern includes well-defined, pathologically enlarged pelvic and retroperitoneal lymph node and sclerotic metastases to the axial skeleton (21).

Recent data however suggests an increase in the incidence of less common metastatic sites with up to 14% of patients presenting with atypical metastatic sites at diagnosis (22).

Less common nodal sites include supradiaphragmatic lymph nodes such as retrocrural, mediastinal, axillary and supraclavicular fossa stations in approximately one-third of patients with atypical disease sites (22).

Recognition of visceral metastatic disease is important, as the presence of visceral metastases confers prognostic information and correlates with overall survival. Men with liver metastases have the worst prognosis, followed by those with lung metastases, bone metastases with or without nodal disease and the best prognosis is seen with lymph-node only disease (23). Visceral sites in metastatic castration resistant prostate cancer (mCRPC) include the lung (9.1%), liver (8.6%) and rarer locations such as adrenal glands, spleen, brain, peritoneum and pleura (3%) (23).

In addition to less-common disease sites, atypical appearances may be encountered and can cause diagnostic uncertainty. These include infiltrative lymph node patterns involving the retroperitoneal structures. These men have a propensity to develop urinary tract obstruction. Similarly, bone metastases may be predominantly lytic with associated extra-osseous soft tissue disease and these patients are at risk of MSCC and pathological fractures.

Recognition of these emerging and less common disease patterns is important for timely diagnosis and initiation of appropriate therapies in the setting of metastatic disease.

Radiological progression may occur without rise in PSA values, particularly at the later stages of disease. This has been reported in up to 24.5% of patients treated with a novel antiandrogen, enzalutamide (24). It is important to recognise that less-common patterns of disease in patients with PC are more likely to be attributed to the primary PC, than due to a second malignancy (25).

Bone metastases

The skeleton is commonly involved in mPC, with a prevalence of up to 84% in a population study (26), 72.8% in a large meta-analysis (17) and up to 90% at autopsy (21). In early stages the axial

skeleton is first affected with up to 84.5% of metastases being present in vertebrae and the pelvis before spreading to the appendicular skeleton (27). Exclusive bone metastases in the thorax and extremities are rare.

Bone metastases have a range of appearances on CT, most commonly osteoblastic/sclerotic (28) in approximately half of cases (figure 1). They are occult on CT in approximately 20%, mixed lytic/sclerotic in 14.9%, and less commonly osteolytic in 13.6% of cases (29).

Initially, metastases may be occult or faintly sclerotic on CT (figure 1) with increasing sclerosis observed as part of a treatment response and bone healing. The emergence of new sclerotic lesions in a patient clinically responding to treatment should therefore not be mistaken for genuine new sites of disease (figure 1). It is important to remember that both active and treated disease may appear equally sclerotic on CT (figure 2), and therefore CT alone has no role for response assessment of sclerotic skeletal metastatic disease. In these cases, WBMRI is emerging as the modality of choice due to its ability to characterise bone marrow changes by assessing bone marrow cellularity (figure 2) and detect skeletal events such as spinal cord compression or fractures. Active, cellular metastases will demonstrate high signal on high b-value DWI and low ADC, whereas responding lesions demonstrate an increase in ADC. Occasionally, unusual sites of bony metastatic disease (for example to the calvarium, or long bones) may cause diagnostic uncertainty and mimic benign pathology (figure 3), and in these cases WBMRI and PSMA-PET can be helpful. PSMA-PET has high accuracy for detection of bony metastatic disease (30,31), however false positives may be encountered with benign bony lesions (figure 4), and we have found WBMRI can be helpful in these cases where there is diagnostic uncertainty.

Less frequently, lytic metastases are encountered and have a poorer prognosis (32). The osteolytic pattern may be associated with soft tissue and/or new bone formation. This is important to recognise as soft tissue from vertebral metastases may encroach into the spinal canal and cause MSCC and may result in pathological fractures (33). Identifying this pattern early is valuable, as it will

prompt appropriate and timely therapy (including ensuring the patient is on bisphosphonate therapy and orthopaedic intervention where necessary), avoiding significant neurological deficit. These events associated with metastatic bone disease are termed “skeletal-related events” (SREs) and are associated with decreased overall survival and increased treatment costs (34).

Widespread metastatic bone disease may also cause bone marrow failure with subsequent anaemia and thrombocytopenia having an impact on overall survival (35).

Nodal metastases

PC spreads along the local lymphatic system, the most common sites of metastases being pelvic and retroperitoneal para-aortic lymph nodes. Pelvic lymph nodes include obturator fossae, external iliac, internal iliac and common iliac stations. The most common nodal sites include the obturator station in 75%, internal iliac in 24% and para-aortic region in 26% (36). Haematogenous spread is more frequent in patients with retroperitoneal lymph node metastases (21). Atypical distribution patterns include nodal disease above the diaphragm, including the mediastinum and supraclavicular fossa.

The most widely used criterion for metastatic lymph node detection is size with a cut-off of 10 mm in short axis diameter (37). Diffusion-weighted imaging (DWI) MRI was demonstrated to be superior to conventional cross-sectional imaging in malignant lymph node detection, however a significant overlap in ADC values between normal and metastatic lymph nodes is recognised (38). Choline or PSMA-PET-CT is the superior modality in detecting lymph node metastases less than 1cm in size (figure 5) (39).

In contrast to the typical appearance of well-defined nodal metastases, an infiltrative pattern is occasionally observed (figures 6 and 7). Recognising this pattern has clinical significance, as

infiltrative nodal disease may extend along the retroperitoneal fascia, obstructing the ureter and urinary tract.

Detection of unusual metastatic lymph node metastases has increased due to advances in imaging methods. Using WBMRI, more than two-thirds of metastatic prostate cancer patients demonstrated enlarged lymph nodes outside of the recommended pelvic external beam radiation therapy (EBRT) field and extended pelvic lymph node dissection territories (40). In rare cases, supraclavicular lymphadenopathy can be the first manifestation of metastatic prostate cancer and usually occurs in patients with bone metastases (22,41). Although some studies suggest that local treatment may influence the patterns of spread of lymph node metastases (42), a recent study demonstrated that the distribution of metastatic disease was not influenced by primary treatment (43).

Urinary tract metastases

In patients with mPC, disease can infiltrate the urinary tract including seeding within the bladder and upper tracts, the appearances mimicking urothelial transitional cell carcinoma (TCC). Penile metastases may also be encountered, particularly in advanced disease and may present as a focal or infiltrative mass (figure 8). The penis should be included as a review area when imaging the pelvis.

Visceral metastases

Visceral metastases are generally regarded as unusual in the absence of metastatic bone and/or nodal disease (22,44). However a single centre study reported that one-third of patients with atypical metastases do not have bone involvement, which could potentially reduce diagnostic certainty (22).

Liver metastases

Metastatic liver disease, when encountered, typically occurs in the context of castration-resistant prostate cancer (CRPC) and is associated with decreased overall survival compared with patients with non-visceral metastases (44,45) . It is the second most frequent visceral metastatic site after lung, occurring in 8.6% of men with mCRPC (23). In patients with atypical metastatic disease sites, liver metastases occur in 37% of cases (22). Liver metastases tend to occur more frequently in patients with high Gleason grade (22). Detection of liver metastases is particularly relevant in CRPC treatment as Radium - 223 is only suitable for patients with bone only disease and therefore establishing accurately whether a patient has visceral metastases can influence therapy decisions.

On CT, liver metastases are typically hypovascular compared to the surrounding parenchyma and may show an infiltrative or well-defined pattern and can occasionally be cystic (figure 9). DWI is superior to other sequences in detecting small metastases, particularly for lesions < 5 mm (46). Choline-PET is not commonly used for detection of metastases due to uptake in normal liver parenchyma. PSMA-PET may be used for detection of liver disease, but up to 22.3% of lesions have been demonstrated to be PSMA negative (figure 10) (18).

Lung and pleural metastases

Lung is the most common visceral site of metastatic disease, reported to occur in 9.1% of cases of men with mCRPC (23). The mechanism of spread involves haematogenous dissemination through the vena cava via the prostatic veins. However, there is evidence suggesting that intrathoracic metastases may also occur through venous drainage from thoracic vertebral metastases (21). On CT, thoracic metastases can manifest as pulmonary nodules or masses, pleural thickening and nodularity, miliary nodules or as lymphangitic carcinomatosis (22) (figure 11).

Adrenal and splenic metastases

Adrenal metastases are rare, reported to have an overall incidence of 2%, and occurring in 15% of patients with atypical sites of metastatic disease (22). They occur mainly in patients with concomitant bone or lymph node metastases. On imaging metastatic adrenal lesions may manifest as focal masses, or diffuse infiltration of the gland (figure 12). Splenic metastases are extremely rare, with only 3 cases reported in a retrospective review of 620 cases (16). Patients at risk of atypical sites may harbour particular molecular abnormalities, such as a DNA repair gene defect (BRCA2 mutation) (figure 12).

Peritoneal metastases

Peritoneal metastases are atypical and occur usually in patients with a high Gleason grade (47). They may occur via haematogenous spread or iatrogenic peritoneal dissemination (47). On imaging, peritoneal deposits may appear as nodular peritoneal thickening or discrete soft tissue masses with or without ascites (figure 13).

Brain

Brain metastases are very rare, with a large cancer centre reporting prevalence of 0.63% in a study on 16,280 patients with prostate carcinoma (48), and are usually associated with disseminated disease (48). They may occur due to direct invasion of the brain from adjacent calvarial metastases (figure 14), or from haematogenous spread. Some studies have suggested that leptomeningeal metastases are more frequent than brain metastases (21). On imaging, appearances are typical for brain metastases with single or multiple masses with or without contact with the adjacent skull.

Conclusion

This pictorial review has highlighted the typical, and less common patterns of metastatic spread in PC.

Increased awareness of the evolving patterns of metastatic sites in PC will enable accurate diagnosis, prompt treatment initiation and effective treatment response assessment as the disease progresses.

Utilisation of advanced imaging techniques such as WBMRI and PSMA-PET with understanding of the limitations of each imaging modality may lead to more accurate disease assessment of early detection of recurrence and also detection of potential complications and response to treatments in the later stages of PC.

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Figures captions:

Figure 1. Skeletal metastatic bone disease appearances in a patient with mPC, with response to treatment on Enzalutamide. At baseline (a-c), skeletal metastases are occult on CT (a), and visible on T1-weighted MRI as areas of low signal fatty bone marrow replacement (arrow, b). ADC map from WBMRI confirms active, cellular disease with low ADC values (arrow, c). Following 6 months of treatment with Enzalutamide (d-f), skeletal metastases now demonstrate "pseudo-progression" and appear sclerotic on CT (d). They remain unchanged on T1-weighted MRI and could be interpreted as stable. ADC map from WBMRI demonstrates clear response to treatment as evidenced by an increase in ADC/reduction in cellularity (arrow, f).

Figure 2. Axial CT (a), WBMRI axial high b-value (b = 900s/mm^2) diffusion weighted image (DWI) (b) and ADC map (c) in a patient with mCRPC and skeletal metastases. On CT, the imaged pelvis appears diffusely sclerotic with no reliable information regarding disease activity. DWI illustrates area of increased signal in the left sacral ala, with low ADC suggesting high cellularity/active disease. The remainder of the bony pelvis is largely inactive/treated.

Figure 3. Axial CT (a), ADC map (b), PSMA-PET (c) and bone scan (d) in a patient with mCRPC and increasing PSA. There is sclerosis with expansion of the right frontal and parietal bone, initially thought to represent Paget's disease due to it's appearance and atypical location for metastatic

disease. ADC map shows area of increased cellularity (arrows, b) with corresponding avidity on PSMA and uptake on bone scan in keeping with focal active disease on a background of treated/inactive disease. Calvarial biopsy confirmed metastatic Gleason 4 + 5 prostate adenocarcinoma.

Figure 4. False positive rib lesions in a patient with PC. PSMA-PET/CT (a,b) and PSMA MIP (c) demonstrates two small areas of PSMA rib uptake (arrows). Corresponding high b-value DWI MIP (d) demonstrates no abnormality. Patient opted for radical prostatectomy, and PSA remains undetectable 3 years following surgery with no evidence of relapse of metastatic disease on follow-up imaging.

Figure 5. Sub-centimetre pelvic nodal metastasis detected with PSMA-PET in a patient with biochemical relapse following brachytherapy. Axial PSMA-PET/CT demonstrates a sub-centimetre PSMA-avid nodal metastasis (arrow). This would appear normal on conventional imaging and with WBMRI.

Figure 6. Uncommon infiltrative retroperitoneal nodal pattern with involvement of the retroperitoneal structures (black arrow) including Gerota's fascia (white arrows). These patients are at particular risk of developing hydronephrosis.

Figure 7. Retroperitoneal infiltrative nodal mass (red arrow) with involvement of Gerota's fascia (white arrows), para-renal nodular disease (white dashed arrow) and hydronephrosis.

Figure 8. Axial T2 weighted imaging (a) and PSMA-PET (b) performed for staging of a patient with a mucinous Gleason 4+5 prostate adenocarcinoma. A small high signal nodule is noted in the right cavernosa of the penis (arrow), PSMA avid. A subtle skeletal metastasis is also noted in the left

ischium (arrow), which is clearly visualised with PSMA-PET and highlights the advantage of PSMA for detecting bone metastases over conventional imaging. Axial T2 weighted imaging (c) and DWI (d) in a different patient, shows more diffuse metastatic infiltration of the corpora with low signal tumour (arrows).

Figure 9. Partly cystic biopsy confirmed liver metastases in a patient with mCRPC. Initially, there was concern that this could represent a hepatic abscess.

Figure 10. Lung and liver metastases may not be apparent on PSMA/PET, illustrated in these liver metastases which are identified as focal areas of high signal on high b-value DWI (b = 900s/mm^2), (a) but occult on PSMA-PET/CT when compared with the background liver uptake (b).

Figure 11. Lymphangitis carcinomatosis (white arrows) in a patient with mCRPC. A small pleural effusion (black arrow) is also visible.

Figure 12. Bilateral diffuse metastatic infiltration of the adrenal glands and splenic metastasis in a patient with a BRCA2 mutation.

Figure 13. Peritoneal seeding with discrete peritoneal and omental nodularity and ascites (white arrows) in a patient with mPC.

Figure 14. Leptomeningeal infiltration from calvarial metastasis (white arrow) in a man with mPC. T1 weighted imaging with gadolinium contrast demonstrates direct infiltration of the leptomeninges (red arrow) and brain parenchyma (dashed white arrow) in the left parietal lobe. This is seen more commonly than discrete brain metastases.