Clinical Aspects and Investigations in Genitourinary Cancer

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Abstract

Genitourinary cancer is an important topic in the current era. Understanding the disease is important to tailor the treatment for individual patients. Clinical aspects and investigations are part and parcel in cancer diagnosis. Genitourinary cancer encompasses multiple cancers but five important cancers are discussed in this chapter. This includes renal cell carcinoma, prostate cancer, urothelial cancer, testicular cancer and penile cancer. Other subtypes or variants are beyond the scope of this chapter. This chapter is to encourage the readers to better understand the clinical aspects and investigations that are commonly used in genitourinary cancer.

Investigations play a major role in diagnosis of genitourinary cancer. Understanding the principles of the imaging is important to appreciate and interpret a particular imaging modality. The principles of the imaging are mentioned at the start of the chapter. We have placed the clinical aspects and investigations for individual cancers mentioned above and tailored the topics to include appropriate investigations and salient features to take note in the imaging.

Principles of Common Radiological Investigations

X-Ray

Wilhelm Conrad Röntgen discovered X-rays in 1895. X-rays are generated from X-ray generator, and when this passes through human tissues, tissue attenuation occurs and the X-rays are recorded on a film and reconstructed to form an image.

X-rays are inexpensive and readily available. It is used in urology (X-ray kidney, ureter, and bladder) and in diagnosis and follow-up of urinary stones. It is less sensitive and essentially replaced by IVU or computed tomography (CT).

Intravenous Urography (IVU)

IVU is an inexpensive imaging of the urinary system. It involves injecting IV water-soluble iodinated contrast and capturing series of X-rays of the renal tract at precise time points. The films obtained are:

1. *Plain (scout) film*
   A plain film will give information about the presence of abnormal calcifications along the urinary tract.
2. *Nephrogram*
   This sequence is taken at 1–2 min after IV contrast injection.
3. *Series of films* taken at 5–10 min, 15-min post IV contrast injection. Compression is applied to get appropriate pelvicalyceal imaging unless compression is contraindicated.
4. *Delayed film*
   Appropriate bladder imaging is obtained in delayed phase, and it is useful to diagnose bladder pathologies/tumors.
5. *Post-micturition film* after the patient voids.

Even though IVU is largely replaced by CT, it still has specific roles in urology.

Common uses in urology:

1. Investigation for microscopic hematuria
2. Upper tract urothelial malignancy – seen as filling defect
3. Diagnosis of renal and ureteric stones in select cases
4. Evaluation for congenital anomalies
5. Evaluation of likely ureteric strictures

Ultrasound

Application of short burst of alternating current on an array of crystals within a transducer produces a mechanical wave which travels through a coupling medium to the skin and into the tissues. The transducer acts as emitter and receiver of the sound waves. Some of the waves are reflected back (echoes) to the transducer which converts the sound waves into electrical energy and generates an image. Real-time imaging is possible as the signals are processed and reconstructed in real time. The amplitude of wave reflected gives the pixel brightness in the imaging. The objects which reflect majority of the sound waves appear bright on the gray scale and vice versa. The frequencies of the sound waves used are in the range of 3.5–12 MHz.

Types of transducers:

1. Linear transducer:
   - Piezoelectric crystal arrangement: phased array
   - Frequency: 3–12 MHz (usually 5–7.5 MHz)
   - Beam shape: rectangular
2. Convex transducer:
   - Piezoelectric crystal arrangement: curvilinear
   - Frequency: 1–5 MHz (usually 3.5–5 MHz)
   - Beam shape: sector
3. Sectoral transducer:
   - Piezoelectric crystal arrangement: phased array
   - Frequency: 1–5 MHz (usually 3.5–5 MHz)
   - Beam shape: triangular

Common types of ultrasound study used in urology:

1. Ultrasound KUB – for evaluation of kidney, ureter, and bladder pathologies. It gives information about the renal mass, hydronephrosis, ureteric jets, and bladder mass/stones.
2. Ultrasound scrotum – to evaluate scrotal pathology and testicular pathologies.
3. Contrast-enhanced ultrasonogram (CEUS) – employs microbubbles as contrast medium, and it is useful to evaluate suspicious lesions in those patients who cannot undergo contrasted CT (renal failure or iodinated contrast allergy), usually used for renal lesions.
4. Transrectal US – used as a guide for prostate biopsy but not used as a diagnostic tool for prostate cancer detection. It can be used to evaluate a midline prostatic cyst and for transrectal drainage of prostate abscess.

Computed Tomography

Sir Godfrey Hounsfield invented computed tomography (CT). CT uses X-rays and measures the tissue density, but the beam in the CT scanner is narrower, and this is detected by a detector placed opposite to the beam, and it produces cross-sectional slices as fine as 0.6 mm thick.

The Hounsfield unit (HU) scale is a measurement of relative densities determined by CT. Water is assigned as the reference density (0 units), and other values are measured relative to water. Air is −1000, fat −100, and bone >+200. The kidneys are +40 to +60 and increase to around 150 units after intravenous contrast. CT uses various protocols to accurately image the region of interest. Kidneys are measured with set protocols and gray scale is assigned to each pixel.

Common types of CT scans used in urology:

1. CT KUB – accuracy almost a near perfect 100% for stone detection (once interpretative error accounted for). It will also identify many of the renal colic mimics, such as appendicitis, diverticulitis, etc.
2. CT angiography – used to image status of renal vasculature in renal trauma, arteriovenous fistula.
3. CT kidneys – to evaluate renal mass, pre-op imaging prior to nephron-sparing surgery, and characterization of renal cysts.
4. CT urography – hematuria evaluation, for evaluation of urothelial cancer; it is considered as one of the best modalities for imaging the collecting system.
5. Staging CT scan for other urological malignancies.

Magnetic Resonance Imaging (MRI)

MRI is excellent at imaging the kidneys and locally staging tumors, and we may possibly deduce the likely histology, on the grounds of T2 differences. MRI is also the best imaging modality for assessing zonal anatomy in the prostate and detecting prostate cancer.

The basis of MRI is the directional magnetic field, or moment, associated with charged particles in motion. Because nuclei are charged particles, this precession produces a small magnetic moment. When a human body is placed in a large magnetic field, many of the free hydrogen nuclei align themselves with the direction of the magnetic field. MRI works by manipulating the external magnetic field and by aligning the hydrogen nuclei in the tissues, and the weak radio signals are amplified to create the MR image.

Once the radiofrequency (RF) signal is removed, the nuclei realign themselves. This return to equilibrium is referred to as relaxation. During relaxation, the nuclei lose energy by emitting their own RF signal which is referred to as the free induction decay (FID) response signal.

MR image contrast depends on two tissue-specific parameters:

1. Longitudinal relaxation time, T1
2. Transverse relaxation time, T2

The two basic types of MRI images are T1-weighted and T2-weighted images, often referred to as T1 and T2 images. T1 measures the time required for the magnetic moment of the displaced nuclei to return to equilibrium, and T2 indicates the time required for the FID response signal from a given tissue type to decay.

T1 images show fluid as low signal (dark) and are generally good for anatomy. Blood products, hyperdense renal cysts, and melanin are seen as a high T1 signal. T2 images show fluid as high signal and are useful for showing pathology which is usually associated with edema or for depicting fluid containing structures such as the urinary tract. Fat is usually bright on both sequences.

Current diagnostic MRI scanners use cryogenic superconducting magnets in the range of 0.5 Tesla (T) to 1.5 T. Three Tesla systems are now widely available and are being used regularly. Higher field strength systems provide improved signal-to-noise ratio (SNR), higher spatial and temporal resolution, and improved quantification (Grover et al. 2015).

Common use of MRI in urology

1. MRI kidneys: used to characterize indeterminate small renal lesions, which may be inflammatory or malignant in nature, e.g., AML and in those iodinated contrasts cannot be used
2. MRI abdomen: useful for evaluation of IVC thrombus and its extension
3. MRI (multiparametric) prostate: for potential diagnosis and preoperative staging for prostate cancer
4. MRI testes: rarely done but may be useful in diagnostic dilemma or equivocal findings on ultrasonography

Bone Scans

Bone scans are a nuclear medicine (scintigraphic) study that use Technetium ^{99}m (commonly ^{99}mTc)-methylene diphosphonate as the active agent. The active agent is injected intravenously, and images are captured using a Geiger counter. It has three phases (Mark Thurston 2017):

1. Flow phase – 2 to 5 sec images are obtained for 60 sec after injection.
2. Blood pool phase – image is obtained 5 min after injection.
3. Delayed phase – the bone image is obtained 2–4 hour later.

To note: Superscan is intense symmetric activity in the bones with diminished renal and soft tissue activity on a Tc^{99m} diphosphonate bone scan. It can be seen in prostate cancer with diffuse metastatic disease.

PET (Positron Emission Tomography) Scans

PET scan uses changes in metabolic activities of the tissues to identify/differentiate various lesions. PET can be combined with CT (PET-CT) to get the anatomical information along with the functional information. PET can be combined with MRI (PET-MRI), and this has advantages of PET functional imaging along with MRI's unmatched soft tissue resolution. In this imaging method, the commonly used tracers in urology are 18F-fluoro-deoxy-glucose (FDG), choline, and PSMA (prostate-specific membrane antigen).

FDG-PET – Radiotracer FDG is injected intravenously, and FDG is metabolized by the tumor cells which has high metabolic rate. FDG is metabolized to FDG 6-phosphate. This substrate cannot be further metabolized and gets accumulated in the tumor cells. During imaging, this tracer is quantified.

FDG is excreted by the kidneys and normal physiological uptake is noted in brain, gut, myocardium, and brown fat.

Choline PET – Choline derivatives are used in PET imaging. Commonly used choline derivatives are 11C- or 18F-choline PET. Utility is confined to staging or detecting recurrences in advanced prostate cancer.

^{68}Ga-PSMA ligands are a promising new radiotracer in patients with advanced prostate cancer. Several retrospective studies have shown accurate staging in prostate cancer. It has evolving role in staging, restaging, evaluation of therapy response, and prognostication of high-risk or advanced prostate cancer (Smith and Shetty 2017).

Renal Cell Carcinoma

Clinical Aspects

Many renal masses remain asymptomatic until they are locally advanced, and they are usually diagnosed incidentally on imaging done for other nonrelated clinical problems.

Symptoms associated with RCC are either due to local tumor growth, hemorrhage, paraneoplastic syndromes, or metastatic disease.

Clinical presentation of RCC
• **Incidental**
• **Symptoms of localized disease** – Hematuria – Flank pain – Abdominal mass
• **Paraneoplastic syndromes** – Elevated ESR – Hypertension – Anemia – Cachexia, weight loss – Fever – Stauffer syndrome – Hypercalcemia – Polycythemia
• **Obstruction of the inferior vena cava** – Bilateral lower limb edema – Dilated veins in abdomen – Varicocele – nonreducing
• **Symptoms of systemic disease** – Persistent cough – Bone pain – Loss of weight/loss of appetite – Malaise

Investigations

Laboratory

- Urinalysis – simple and inexpensive, but yield may be low as RCC are parenchymal tumors unlike urothelial tumors.
- Full blood count – to establish a baseline hemoglobin level and platelet count and to look for polycythemia.
- Renal panel (urea, electrolytes, and creatinine) – to assess baseline kidney function which is essential to consider nephron-sparing surgery especially in patients with CKD.
- Calcium panel – to look for hypercalcemia (paraneoplastic syndrome).
- ESR and liver panel, if there is clinical suspicion of paraneoplastic syndrome.
- In metastatic RCC, prognostic markers for Heng's criteria/MSKCC criteria should be done including hemoglobin, corrected calcium

level, neutrophil count, platelet count, and lactate dehydrogenase (LDH).

Imaging

Ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) are the mainstays of renal mass detection and characterization.

Ultrasound

RCC has varying sonographic appearance. Ultrasonography is useful for distinguishing cystic from solid lesions and can detect lesion vascularity, especially with use of ultrasound contrast agents (Kang et al. 2011). It is not as sensitive or specific when compared to CT or MRI. Ultrasonography is also useful in identification of most renal angiomyolipomas (AML) in view of the significant presence of fat component in majority of AMLs.

Appearance

A standard ultrasonography shows a heterogeneous and solid lesion. If the lesion is cystic, contrast-enhanced ultrasound (CEUS) is a valuable alternative to further characterize renal lesions. It will typically show a lesion which is hypervascular and heterogeneous in the arterial phase with early washout in the delayed phase.

Computed Tomography

CT, with and without intravenous contrast, is the primary imaging test for characterization and staging of renal lesions. CT provides near isotropic acquisition, with three-dimensional reformatting capabilities (Kang et al. 2011). In CT imaging, enhancement in renal masses is determined by comparing Hounsfield units (HUs) before and after contrast administration.

Small renal mass (SRM): The sensitivity of contrast-enhanced CT for predicting RCC was 79.7%, and the specificity of contrast-enhanced CT for predicting RCC was 44.4% for small renal mass (Kim et al. 2016).

The nephrogenic phase (80–180 sec) is the most sensitive phase for detection of abnormal contrast enhancement (Fig. 1). Excretory phase is important in assessing the collecting system anatomy especially if the patient is a potential candidate for a partial nephrectomy.

MRI

MRI has excellent soft tissue resolution and it may be useful in differentiating doubtful lesions. Renal tumors have certain characteristic appearance on MRI which can possibly help to identify the likely histology (Bott 2012):

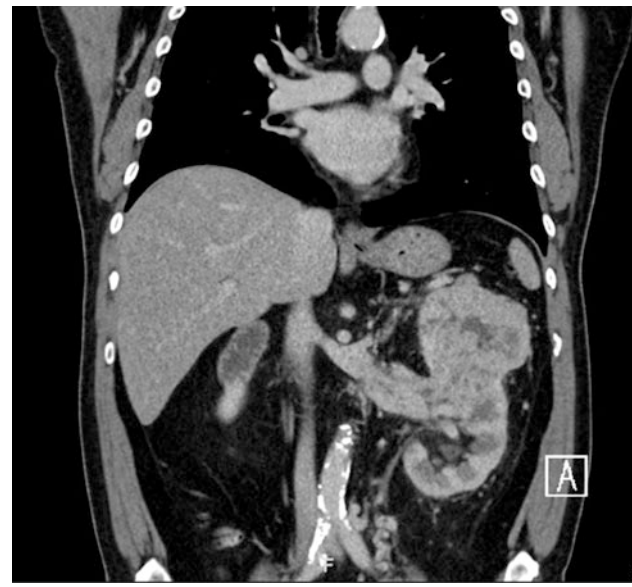

Fig. 1 CT kidneys: portovenous phase showing a left upper pole renal tumor

- **T1:** often heterogeneous due to necrosis, hemorrhage, and solid components
- **T2:** appearances can depend on histology
  - Clear-cell RCC: hyperintense
  - Papillary RCC: hypointense

Tumor pseudocapsule, essentially only seen in low-grade renal cell carcinomas, renal adenomas, and oncocytomas, appears as a hypointense rim between the tumor and the adjacent normal renal parenchyma (Ascenti et al. 2004).

Urothelial Cancer

Clinical Aspects

Urothelial cancer is a cancer of the environment and age; the incidence and prevalence rates increase with age, peaking in the eighth decade of life; and there is a strong association between environmental toxins and urothelial cancer formation (Parkin 2008).

Urothelial carcinomas (UCs) are the fifth most common tumors. They can be located in the lower (bladder and urethra) or upper (pyelocaliceal cavities and ureter) urinary tract. Bladder tumors account for 90–95% of UCs and are the most common malignancy of the urinary tract. In contrast, UTUC are uncommon and account for only 5–10% of UCs (Rouprêt 2017).

Presentation

Hematuria is the most common presentation.

Clinical presentation of urothelial cancer
• **Symptoms of localized disease**
– Visible or nonvisible hematuria
– Dysuria, frequency, urgency
– Clot colic
– Acute urinary retention
– Abdominal mass
• **Symptoms of locally advanced disease**
– Colo-vesical fistula
– Per rectal bleed
– Flank pain (with or without fever) due to hydronephrosis or infection
– Chronic pelvic pain

(*continued*)

Clinical presentation of urothelial cancer
• **Symptoms of systemic disease (metastases)**
– Persistent cough
– Bone pain
– Loss of weight/loss of appetite
– Malaise

Investigations

Laboratory

- Urinalysis: to detect microscopic hematuria/sterile pyuria
- Urine cytology: urine cytology has low sensitivity but high specificity. The urine cytology has 84% sensitivity in G3 and high-grade tumors as compared to 16% in low-grade tumors. It is a useful test and is an adjunct to cystoscopy in high-grade malignancy. Cytology is particularly important with patients with carcinoma in situ (CIS) or high-grade disease where cytological changes may be apparent before they are visible at cystoscopy (Brown 2000). Positive urine cytology is suggestive of UTUC when bladder cystoscopy is normal, provided that no CIS is detected in the bladder or prostatic urethra.
- Other urinary markers: (Table 1)

Imaging

CT urography is the investigation of choice. Ultrasonography and MR urography can be used in special conditions. Intravenous urography has largely been replaced by CT urography for evaluating UCs.

CT Urography

This CT contains a non-contrast phase, a portovenous phase, and a delayed/urographic phase. Urothelial carcinoma of urinary bladder appears as either focal regions of thickening of the bladder wall or as masses protruding into the bladder lumen or, in advanced cases, extending into adjacent tissues (Fig. 2). CT will be able to identify T3b tumors (extravesical extension), but it is difficult to identify T1/T2 disease based on CT alone (Hacking et al. 2017). The presence of hydronephrosis indicates obstruction of the

Table 1 Summary of the available urinary markers

Markers (or test specifications)	Overall sensitivity (%)	Overall specificity (%)	Sensitivity for high-grade tumors (%)	Point-of-care test
UroVysion (FISH)[a]	30–86	63–95	66–70	No
Microsatellite analysis	58–92	73–100	90–92	No
Immunocyt/uCyt +[a]	52–100	63–79	62–92	No
Nuclear matrix protein 22[a]	47–100	55–98	75–92	Yes
BTA stat[a]	29–83	56–86	62–91	Yes
BTA TRAK[a]	53–91	28–83	74–77	No
Cytokeratins	12–88	73–95	33–100	No

[a]Reproduced from EAU guidelines on non-muscle-invasive bladder cancer

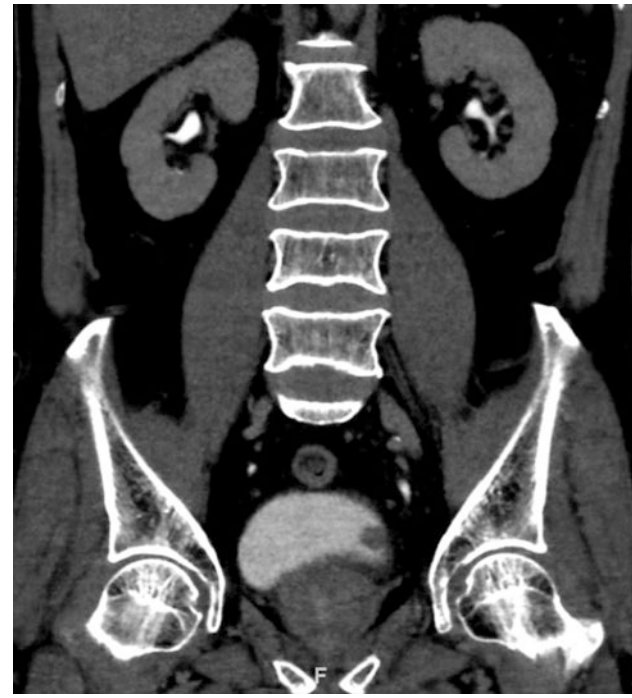

Fig. 2 CT urography: delayed phase showing a filling defect indicating a bladder tumor at the left lateral wall

ureteric orifice by the bladder tumor or muscle invasion at that region. Regional lymphadenopathy can be assessed on CT. Urothelial carcinoma is a field change disease, and it is important to exclude lesions in the upper urinary tract. Delayed phase is important to exclude upper urinary tract urothelial carcinoma (UTUC). UTUC is seen as a filling defect in the pelvicalyceal system or along the ureters. In advanced cases, the lesions can be infiltrating the renal parenchyma. Unlike RCC, UTUC of kidneys will not distort the renal outline, and it is usually centrally located. The secondary sign of hydronephrosis is associated with advanced disease and poor oncological outcome. The presence of enlarged lymph nodes is highly predictive of metastasis in UTUC.

Ultrasonography

It is a useful initial screening tool and bladder tumors are seen as exophytic lesions in the bladder. It is useful for detection of obstruction in patients with hematuria. However, it cannot exclude the presence of UTUC and cannot replace CT urography.

MR Urography

MRI is superior to CT or ultrasonography; however, it is limited by cost and availability. It is a useful modality in patients with allergy to iodinated contrast agents and in people with renal failure. If gadolinium is used as a contrast medium in patients with renal failure, patient should be counseled about nephrogenic systemic fibrosis. In some instances, MRI can distinguish T1 from T2 tumors on T2-weighted images (Hacking et al. 2017):

- **T1:** isointense compared to muscle.
- **T2:** slightly hyperintense compared to the muscle. It is useful in determining the low-signal muscle layer and its discontinuity when muscle wall invasion.

Prostate Cancer

Clinical Aspects

Prostate cancer is the second most commonly diagnosed cancer in men, accounting for 15% of all cancers diagnosed (Ferlay et al. 2015). It is important to know about family history of prostate cancer as the risk of developing prostate cancer is higher with a positive family history. The zones of the prostate were described as peripheral, central, and transition zones (PZ, CZ, and TZ) by John McNeal in 1968, distinguished by microanatomical boundaries, duct drainage, and acinar morphology (McNeal et al. 1988).

Presentation

1. Elevated prostate-specific antigen (PSA) during health screening or evaluation of lower urinary tract symptoms – incidental finding of elevated PSA would usually prompt a urology referral. Other benign causes of elevated PSA, such as benign prostatic enlargement, prostatitis or lower urinary tract infection, and recent urethral instrumentation, should be excluded before further prostate-specific investigations are done. Routine population-based screening with PSA is not recommended in most guidelines, as the evidence of benefit for patient is contradictory. Family history is important where screening is undertaken at earlier age.
2. Abnormal digital rectal examination – a majority of the prostate cancer are seen in the peripheral zone of the prostate, and any hard nodule in the prostate should prompt a urology referral for further investigations and biopsy. If the entire prostate gland feels hard, nodular, and fixed, locally advanced or possibly metastatic prostate cancer needs to be excluded. It is important to note that digital rectal examination does not significantly alter PSA levels.
3. Lower urinary tract symptoms (LUTS) – prostate cancer per se does not cause LUTS unless the prostate cancer is advanced to cause bladder outlet obstruction. However, patients can present with LUTS from concurrent benign prostatic enlargement.
4. Bone pain and constitutional symptoms – this is seen in advanced/metastatic prostate cancer and usually requires urgent intervention. Patients occasionally present with acute neurological deficit due to spinal cord compression from the spinal metastasis.

Investigations

Prostate-Specific Antigen (PSA)

PSA is a serum marker used in diagnosis of prostate cancer. It is organ specific and not cancer specific as it can be elevated in benign causes (BPH, prostatitis, recent instrumentation, etc.). PSA has age-specific reference ranges; however their levels have not been validated in most populations. The upper limit of what is considered "normal," i.e., not warranting further investigation, varies internationally, from 2.5 to 4.0 ug/L.

However, patients with serum PSA <4.0 ugl/L are still at risk of harboring prostate cancer, although the chance of finding significant prostate cancer (Gleason 7 and above/ISUP Group 2 and above) is low as shown in table below (Mottet 2017).

PSA level (ng/mL)	Risk of PCa (%)	Risk of Gleason ≥7 PCa (%)
0.0–0.5	6.6	0.8
0.6–1.0	10.1	1.0
1.1–2.0	17.0	2.0
2.1–3.0	23.9	4.6
3.1–4.0	26.9	6.7

PSA derivatives and isoforms:

1. **PSA density (PSAD)**
   PSAD = PSA/volume of prostate. If PSAD <0.10, the detection rate of prostate cancer is high when compared to conventional cutoff of <0.15. When a lower PSAD cutoff of 0.10 is used, the detection rate of prostate cancer is higher compared to conventional cutoff of 0.15. Catalona et al. demonstrated that when they accepted a lower PSAD cutoff value of 0.1, they were able to detect 90 percent of all cancer patients and spare 31% of the patients from unnecessary re-biopsies at the same time (Catalona et al. 1997).
2. **PSA kinetics**
   PSA kinetics may be more useful in prognostication rather than diagnosis of PCa.
   A. PSA velocity (PSAV) – annual absolute increase in total PSA. It is expressed in ng/mL/year. In patients with serum PSA levels between 4 and 10 ng/mL, PSA velocity greater than 0.75 ng/mL/year are at increased risk of being diagnosed with prostate cancer. PSA velocity is less commonly used nowadays for prognostication (Ayyıldız and Ayyıldız 2014).
   B. PSA doubling time (PSADT) – exponential increase in PSA over time. It is the time taken to double the PSA level. It has prognostic value in determining the progression or recurrence after a definitive therapy.
3. **Free/total PSA ratio**
   This is useful to differentiate BPH from prostate cancer. This is useful when PSA is between 4 and 10 ng/ml. If F/T PSA is <0.10, the chances of finding a PCa are 56% when compared to 8% if it is >0.25 (Catalona et al. 1998).
4. **Prostate health index (PHI)**
   PHI is derived from a mathematical formula incorporating total PSA, free PSA, and (−2) pro-PSA(p2PSA). The formula for PHI is as below:

$$\text{PHI} = ([-2]\ \text{proPSA}/\text{free PSA}) \times \sqrt{\text{PSA}}$$

US FDA has approved PHI to be used in PSA range of 4–10 ng/ml. Catalona et al. in 2011 published a large study on PHI in 892 men with PSA of 2–10 ng/ml and normal DRE. The study shows an area under curve (AUC) of 0.70 which was better than free PSA or total PSA (Catalona et al. 2011). In NCCN guidelines 2016, PHI >35 provides an estimate of the probability of high-grade prostate cancer in PSA ranges 2–10 ng/ml, and it is informative in patients who have never undergone biopsy or after a negative biopsy (Carroll and Parsons 2016). Lincoln et al. in 2017 validated the use of PHI in Asian population where a biopsy threshold at PHI ≤27.0 would avoid 51% of biopsies, at a 2.5% risk of missing a potentially aggressive cancer (GS ≥7 or more) (Tan et al. 2017).

Other Biomarkers

1. *Prostate cancer gene 3 (PCA 3)*
   PCA 3 is a messenger RNA which was noted to be expressed in urine in patients with prostate cancer, and it is a FDA-approved tool for decision-making in diagnosis of prostate cancer. However, it requires a prostatic massage prior to urine collection for the test.
2. *TMPRSS2-ERG fusion*
   It is a biomarker which represents an androgen-related transcription promoter. It has high specificity but low sensitivity. It is used in conjunction with other biomarkers in view of its low sensitivity (Behesnilian and Reiter 2015).
3. *4 kallikerin (4 K) score*
   The score is obtained from combining free, intact and total PSA and kallikerin like

peptidase 2 (hK2). The test is included in EAU guidelines along with PHI and PCA 3 in risk stratification of patients to reduce unnecessary prostate biopsies.

Imaging

Ultrasonography, MRI, and CT are mainstay in diagnosis. Bone scan is used in patients suspected to have advanced prostate cancer.

Ultrasound

Transrectal ultrasonography (TRUS) is a useful diagnostic modality to determine prostate size and to guide biopsy, usually following an abnormal PSA level or DRE. Transrectal ultrasonography (TRUS) itself cannot be reliably used for prostate cancer diagnosis, as the prostate cancer lesions can be hypoechoic, hyperechoic, or isoechoic. Transrectal ultrasound (US)-guided biopsy is currently the standard of care for diagnosing prostate cancer. A transrectal approach is used for most prostate biopsies, although some urologists prefer a transperineal approach. Cancer detection rates are comparable with both approaches (Mottet 2017).

MRI

Multiparametric magnetic resonance imaging (mpMRI) using a 3-Tesla system, without the need for endorectal coil, is the current standard for prostate imaging. Multiparametric (mp) MRI of the prostate is essentially any functional form of imaging used to supplement standard anatomical T1- and T2-weighted imaging. The functional sequences of choice are dynamic contrast-enhanced (DCE) MRI and diffusion-weighted imaging (DWI), including the calculation of apparent diffusion coefficient (ADC) maps.

Signal characteristics (Verma and Rajesh 2011; Bonekamp et al. 2011):

- **T1:** useful for detection of prostate contour, neurovascular bundle encasement, and post-biopsy hemorrhage
- **T2:**
  - Using an endorectal coil, on T2-weighted images, prostate cancer usually appears as a region of low signal within a normally high signal peripheral zone (Fig. 5).
  - Most significant cancers occur along the posterior portion of the gland abutting the rectum.
- **DWI/ADC:** often shows restricted diffusion
- **Dynamic contrast enhancement (DCE):**
  - Shows enhancement, but it can be difficult to distinguish from prostatitis or benign prostatic hyperplasia (especially in the central zone lesions)
  - More specific than T2 signal
  - Involves post-processing time

Primary indication for MRI is preoperative staging after a prostate cancer is detected on TRUS-guided biopsy of prostate. It is useful to identify extracapsular extension and presence of nodal disease and may aid in the planning of radical prostatectomy, especially with regard to neurovascular bundle sparing and obtaining negative surgical margins. MRI in recent years is increasingly used for primary detection of prostate cancer or after a negative prostate biopsy and persistently elevated PSA levels. It is important to note that MRI has false-negative rate of at least 20%.

MR-fusion biopsy is increasingly being performed and has emerging data for its utility. MRI is useful in targeting suspicious lesions on MRI. Magnetic resonance imaging-targeted biopsies can be obtained through cognitive guidance, ultrasound/mpMRI fusion software, or direct in-bore guidance.

PI-RADS (Prostate Imaging Reporting and Data System) score is given to assess the probability of the lesion being malignant. The score is assessed on 3-Tesla multiparametric MRI. Images are obtained using a multiparametric technique including T2-weighted images, a dynamic contrast study (DCE), and DWI. A score is given according to each variable. The scale is based on a score from 1 to 5 (which is given for each lesion), with 1 being most probably benign and 5 being highly suspicious of malignancy (Weinreb et al. 2016).

The new PI-RADS 2 rather uses stepwise approach to determine a lesion (Fig. 3)

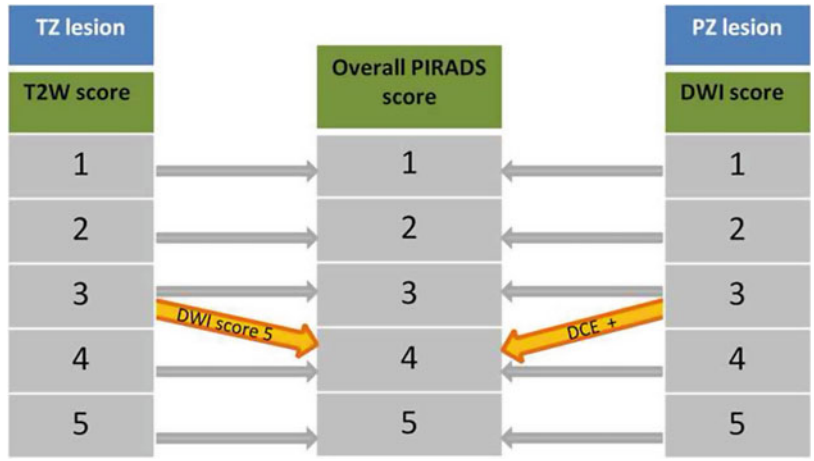

Fig. 3 Data from Abdom Radiol (NY). 2017 Jan; 42 (1): 278–289

CT Scan

It is primarily used in staging for prostate cancer, especially when advanced prostate cancer is suspected (such as CT abdomen and pelvis, with or without CT thorax). It is the investigation of choice to detect enlarged pelvic and retroperitoneal lymph nodes, hydronephrosis, and osteoblastic metastases.

Bone Scan

Osseous bone metastases are detected using Tc^{99} -m bone scan. Prostate cancer metastases are mostly osteoblastic in nature (Fig. 4).

Positron Emission Tomography (PET)

Choline PET is commonly used in prostate cancer; 11C- or 18F-choline Pet/CT has good specificity for lymph node metastases but with a variable sensitivity of 10–73% (Brogsitter et al. 2013).

Afshar et al. report that "^{68}Ga-PSMA ligand PET imaging has been shown to increase detection of metastatic sites even at low PSA-values in comparison to conventional imaging or PET examination with different tracers" (Afshar-Oromieh et al. 2014). ^{68}Ga-PSMA ligand PET is found to be superior to the bone scan in detecting bone metastasis, and it is especially useful for evaluating biochemical recurrence post-radical prostatectomy even at low PSA values (Rauscher et al. 2016).

Testicular Cancer

Clinical Aspects

Testicular cancer represents 1% of male neoplasms and 5% of urological tumors. Its incidence is increasing. Epidemiological risk factors for the development of testicular tumors are components of the testicular dysgenesis syndrome (i.e., cryptorchidism, hypospadias, decreased spermatogenesis evidenced by sub- or infertility), familial history of testicular tumors among first-degree relatives, and the presence of a contralateral tumor or intratesticular germ cell neoplasia (ITGCN) (Albers 2017).

Among the germ cell tumors, there is also stratification according to age, with some tumors being more common in some age groups than others (Jones 2017):

- **First decade:** yolk sac tumor and testicular teratoma
- **Second decade:** choriocarcinoma
- **Third decade:** embryonal cell carcinoma
- **Fourth decade:** seminoma
- ≥**Seventh decade:** lymphoma (usually non-Hodgkin lymphoma) and spermatocytic seminoma

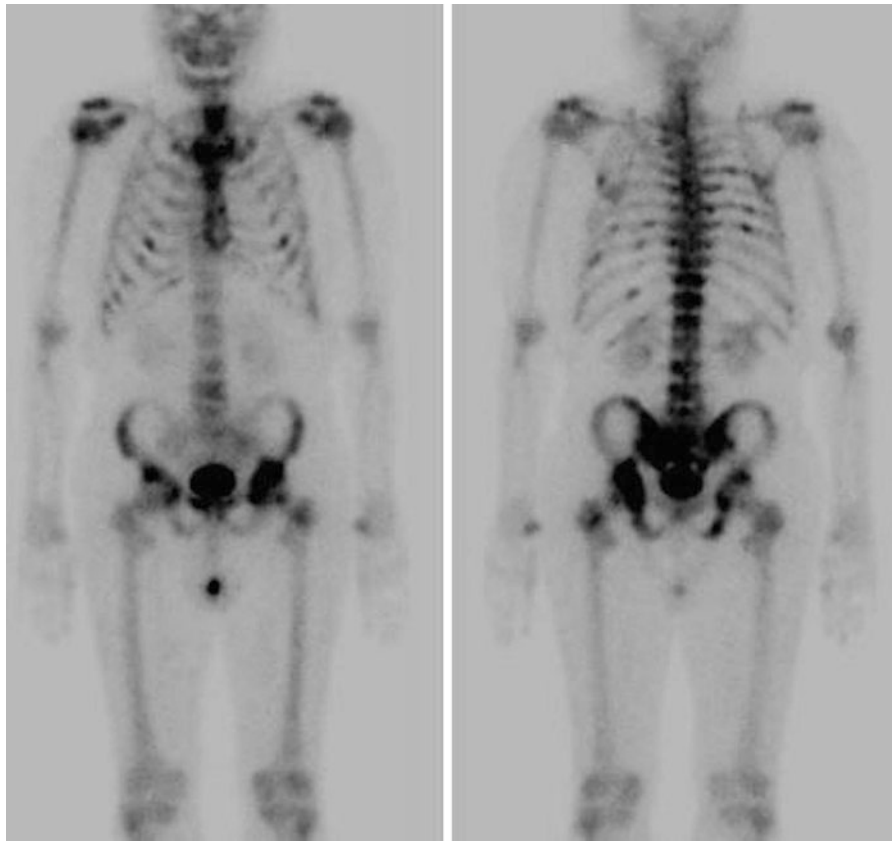

Fig. 4 Bone scan showing multiple osteoblastic metastases noted in bilateral ribs and pelvis

Presentation

The most common presentation is a patient presenting with painless testicular lump. Trauma is not a contributing factor for testicular tumor, but it usually draws attention to the lump.

Clinical presentation of testicular cancer
• **Symptoms of localized disease**
– Painless testicular swelling
– A dull ache or heavy sensation in the lower abdomen
– Trauma with hematoma (rare)
• **Symptoms and signs of disseminated disease**
– Persistent cough, shortness of breath, and/or hemoptysis (mediastinal adenopathy/lung mets)
– Supraclavicular lymph node
– Back pain (bulky retroperitoneal lymph node mets)
– Bone pain (rare)
– Malaise, loss of weight/loss of appetite, diarrhea
– Neurological symptoms (rare)
– Gynecomastia (hCG-producing tumor)

Examination

A solid, firm mass within the testis should be considered testicular cancer until proven otherwise. Prompt diagnosis and early treatment are required.

Unilateral or bilateral lower extremity swelling may be present in patients with iliac or vena caval obstruction or thrombosis. Abdominal mass can be felt in patients with disseminated disease and bulky retroperitoneal disease.

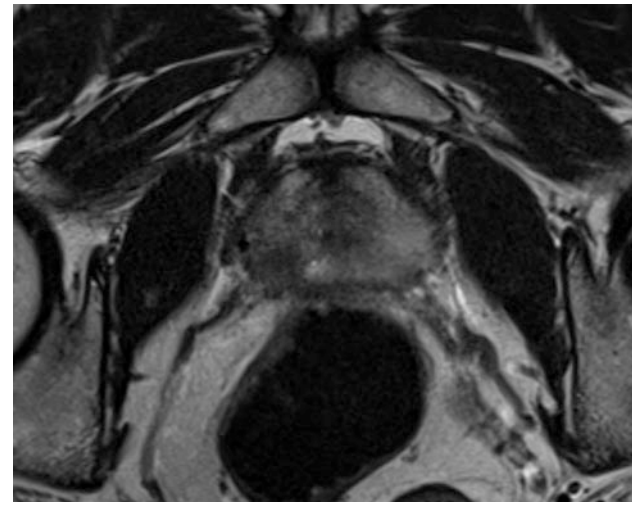

Fig. 5 MRI prostate: T2 axial cut showing a right peripheral zone hypointense lesion

The workup of patients with suspected testicular cancer starts with a complete history and physical examination. Laboratory tests and imaging studies include the following:

- Serum alpha-fetoprotein.
- Serum beta subunit of human chorionic gonadotropin (beta-hCG).
- Lactate dehydrogenase (LDH).
- Chemistry profile.
- Testicular ultrasound study.
- High-resolution computed tomography (CT) scan of the abdomen and pelvis.
- Chest X-ray or CT scan thorax.
- Magnetic resonance imaging (MRI) of the brain should be performed if brain metastases are suspected after clinical examination or presence of neurological symptoms.

Imaging

Ultrasonography

Currently, ultrasonography is used to confirm the presence of a testicular mass and explore the contralateral testis. Ultrasound sensitivity is almost 100%, and it has an important role in determining whether a mass is intra- or extra-testicular. Ultrasound is an inexpensive test and should be performed even in the presence of clinically evident testicular tumor.

Common radiological features suggestive of testicular tumor are:

- Intratesticular mass which may be homogenous or heterogeneous (Fig. 6). An intratesticular mass is suggestive of testicular tumor unless proven otherwise. A paratesticular mass has a higher likelihood of being benign pathology.
- Increased vascularity – can be seen in epididymo-orchitis; however increased blood flow within an intratesticular mass supports the diagnosis of testicular tumor.

Ultrasound appearance of individual germ cell tumors:

(a) Seminoma:
  (i) Seminomas usually appear as a homogeneous intratesticular mass of low echogenicity compared to normal testicular tissue
  (ii) The mass is usually oval and well-defined in the absence of local invasion. It is usually confined within the tunica albuginea, rarely extending to paratesticular structures

(b) Non-seminomatous tumors:

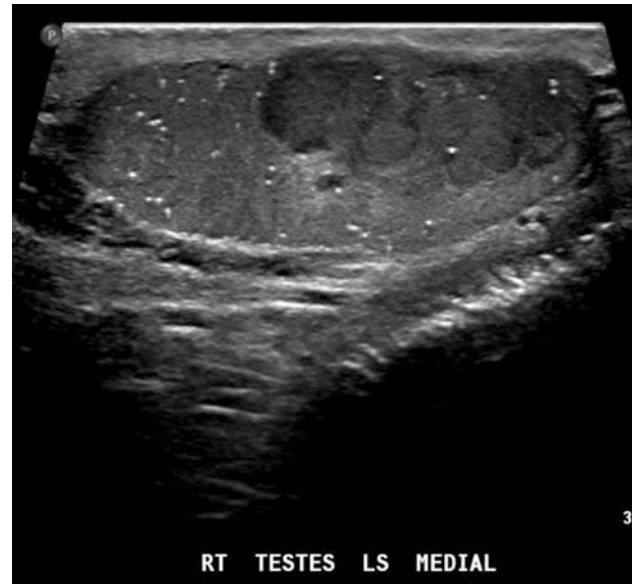

Fig. 6 Ultrasound scrotum showing intratesticular heterogeneous lesion in the right testis

(i) In contrast to seminomas, NSGCTs tend to be more heterogeneous with frequent cystic areas or calcification. They tend to be more aggressive than seminomas, and tunica invasion is common.

(ii) Mature teratomas tend to be cystic with heterogeneous echoes in the fluid representing a mixture of mucinous or sebaceous material with or without hair follicles. Solid components are present of variable echogenicity, including hyperechoic and shadowing fatty components. Immature teratomas tend to be more solid but still heterogeneous on account of areas of hemorrhage and necrosis.

(c) Lymphoma:

Most commonly seen in patients >60 years old.

Tumor Markers

Serum tumor markers are useful for prognostication and staging.

1. Alpha-fetoprotein (AFP)

   Alpha-fetoprotein (AFP) is normally produced by the fetal yolk sac and other organs and is essentially undetectable in the serum in normal men. The half-life for AFP is 5–7 days. AFP is not elevated in pure seminomas. AFP is secreted by yolk sac tumors and to some extent by chorionic tumors. AFP is elevated in HCC and can give false-positive results. If AFP is elevated, the patient should be treated as if he had NSGCT.

2. Beta subunit of human chorionic gonadotrophin (B-hCG)

   Beta subunit of hCG is measured in assays, as alpha subunit is seen in pituitary tumors. The half-life of B-hCG is 1.5–3 days. In seminomas, up to 15% can have elevated serum B-hCG levels. In NSGCT, B-hCG is elevated in 10–20% of CS 1 NSGCTs and 40% in advanced NSGCTs. False-positive results may be seen in patients with hyperthyroidism.

3. Lactate dehydrogenase

   This is a less specific marker and it is an indicator of tumor burden.

CT Scan

Once the diagnosis of testicular cancer is made, a high-resolution computed tomography (CT) scan of the abdomen and pelvis and a chest X-ray are ordered as part of the initial staging workup. Chest CT is recommended if the chest X-ray is abnormal or if metastatic disease in the thorax is strongly suspected clinically (Sachdeva 2017).

MRI and Bone Scan

MRI of the brain and a bone scan are performed if brain and bone metastases are suspected.

PET

^{18}F-Fluoro-2-deoxy-D-glucose (FDG)-PET may contribute to the improvement of diagnosis, staging, and management of patients with testicular cancer. It accurately detects small-volume metastatic disease and plays an important role in characterization of post-chemotherapy residual masses (Gouliamos 2014). PET can be combined with CT to improve the characterization of suspicious lesions. FDG-PET has a high negative predictive value in patient with residual masses after treatment of seminoma (Albers 2017). In patients with residual mass >3 cm, FDG-PET is more useful, whereas in those with residual mass <3 cm, it is optional (De Santis et al. 2004).

Penile Cancer

Clinical Aspects

Penile cancer is usually a disease of the elderly but it can be seen in younger patients too. Incidence increases from 60 years and above (Brosman 2015). The most common cancer type of the penis is squamous cell carcinoma. There is usually a delay in the diagnosis of penile cancer as patients tend to present late. There is considerable anxiety and neglect before the patient seeks medical attention. Neonatal circumcision has been well established as a prophylactic measure that virtually eliminates the occurrence of penile carcinoma. Penile carcinoma is rare in Jewish population where neonatal circumcision is practiced (Licklider 1961).

Presentation

Penile cancer usually presents with painless lesion over the penis. The most common site is the glans (48%) and prepuce (21%). The lesion can be ulcerative, flat, or exophytic. It is important to know the premalignant lesions to understand the relationship with SCC.

Premalignant Lesions

1. *Carcinoma in situ (Tis) of the penis*
   This is named erythroplasia of Queyrat if it involves the glans penis. The lesion appears red, velvety, and well-marginated lesion of the glans penis. Bowen's disease is Tis involving the penile shaft/perineum and characterized by scaly plaques.
2. *Cutaneous horn*
   It is characterized by an overgrowth and cornification of the epithelium. Malignant transformation or association with a malignant tumor may be possible, although this is a rare occurrence.
3. *Balanitis xerotica obliterans (BXO)/lichen sclerosis*
   It appears as a whitish patch over the glans or prepuce, and the meatus is thickened and edematous. It is associated with malignancy and requires closer follow-up even after excision.
4. *Condylomata acuminatum and Bowenoid papulosis* are associated with human papilloma virus (HPV), and malignant transformation has been reported. (Ref: Campbell-walsh urology, 11th edition, p. 846.)

Invasive Cancer

- Penile lesion is the common presenting sign. The lesion can vary from induration to a proliferative growth.
- Symptoms of local invasion or metastasis can be the presenting complaint in patients who present late.

Investigations

1. **Laboratory**
   No specific laboratory tests are diagnostic of penile cancer. Hypercalcemia due to

parathyroid-related substances secreted by penile cancer can occasionally be seen.

2. **Histology**

   Histological diagnosis is the key in diagnosis of penile cancer. Any suspicious lesion should be biopsied to exclude a penile cancer.

3. **Imaging**

   Physical examination is most reliable for accurate staging of the disease.

   Imaging will be essential where proper clinical examination is not possible (e.g., obese patients) or for prognostication/follow-up.

   A. **MRI**

      MRI provides the best soft tissue resolution for local staging of penile cancer. MRI should be performed after artificial erection for accurate staging, and this is critical for proper staging of the cancer.

   B. **CT**

      CT is useful in staging and evaluation for enlarged pelvic and retroperitoneal lymph nodes and distant metastasis.

   C. **PET/PET-CT**

      This may potentially be useful in patients with non-palpable lymph nodes but are suspected to have micrometastasis, although it is not routinely done. This may avoid surgical staging in some patients (Brogsitter et al. 2013).

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