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Editors

Imaging and Technology in Urology

Principles and Clinical Applications

Springer

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Preface

This book was conceived from our frustration in trying to identify technical information about the basic principles of technologies, and techniques, that we use in everyday practice as urologists, and which we could ask about in the Intercollegiate Specialty exam in Urology, the FRCS (Urol.)! Consequently, with a series of committed authors, we have compiled a series of short vignettes about the technical detail surrounding imaging techniques in common use, as well as those technologies which are used diagnostically, operatively and therapeutically in urology. We have also included two short sections on the technology associated with renal failure and ways in which the value of technology can be assessed, or researched. This book is intended as a study aid for trainees but will be of value to all practising urologists who want to understand more about the basic principles of how the things they use, on an everyday basis, work.

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Part I
Imaging: Radiology

Chapter 1
Principles of X-Ray Production and Radiation Protection

Christopher T.L. Wilkinson

Plain radiographs, intravenous urograms, computed tomography (CT), and mobile fluoroscopy all require the use of ionising radiation to produce the images that are used to facilitate investigation and treatment of patients with a wide variety of urological conditions. However, such image acquisition comes at the cost of radiation exposure. It is important to understand the principles behind x-ray production and radiation protection in order to make best use of these imaging modalities, whilst at the same time, keeping the radiation burden to the patient as low as possible.

Principles of X-Ray Production

X-rays are part of the spectrum of electromagnetic radiation (Appendix 1), and as such, comprise of electric and magnetic waves travelling perpendicular to one another. Their wavelength is shorter than that of visible light, in the order of 10^{-8} to 10^{-12} m, with energy values typically in the range of 0.12–120 keV.

The production of x-rays first requires the production of free electrons, which for the purposes of clinical radiology occurs via heating a metal filament (the cathode) resulting in thermionic emission. These electrons are then accelerated in a vacuum towards a rotating metal anode where x-rays are produced via two mechanisms (Fig. 1.1):

1. Bremsstrahlung or breaking radiation. This occurs following the sudden deceleration of electrons as they pass close to an atomic nucleus and undergo a change in kinetic energy. This energy loss results in the emission of electromagnetic energy in the form of x-rays. The change in energy is variable, and so multiple electrons produce a spectrum of x-rays with different energy values.

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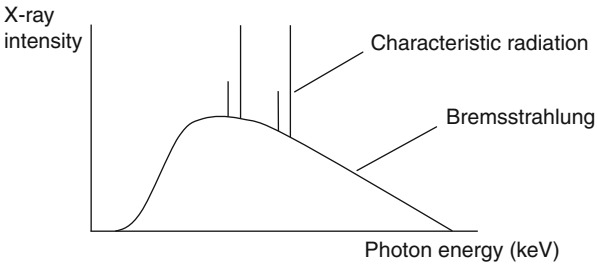

Fig. 1.1 X-ray spectrum produced by medical imaging devices

2. Characteristic radiation. This occurs when an incoming electron has sufficient energy to overcome the binding energy of one of the electrons in the metal anode atom's orbital shells. This orbital electron then "drops" into a lower energy shell, and the resulting energy loss is released as an x-ray with a particular fixed energy value.

The x-ray beam is then focused towards the patient, who is placed between the x-ray source and a detector. Tissues of different density cause attenuation of x-rays at different rates. For example, a higher proportion of x-rays will pass through a similar volume of lung than bone, and hence, a corresponding higher proportion of x-rays will reach the detector. This allows different tissue types to be differentiated in the final image.

Traditional x-ray detectors incorporate a fluorescent screen composed of phosphors. When the x-ray beam collides with a part of this, light is emitted causing a reaction in the x-ray film, and a latent image is produced. The film is then developed, fixed, and hardened producing a hard copy x-ray film. More modern digital radiography systems use a reusable plate incorporating a photostimulable phosphor. Following the exposure, the plate is scanned with a laser beam, and the light emitted is measured and used to form a digital image, later viewed on a workstation.

Although x-ray attenuation is crucial to the formation of the image, it is also the source of radiation dose to the patient. In addition, scattered x-rays from the patient and surroundings are a source of potential radiation dose to other people in close proximity (such as health-care professionals).

Radiation Protection

Ionising radiation has two distinguishable types of effect on the body:

1. Deterministic effects, e.g., skin erythema, epilation, and cataracts. There is a threshold dose below which no damage will be done. The severity of these effects depends on the dose, dose rate, and number of exposures. Table 1.1 outlines typical doses required to produce the stated effects (Sv = Sievert).
2. Stochastic effects, e.g., carcinogenesis and mutagenesis. These have no threshold dose, as even a single exposure can cause damage. The frequency of stochastic effects increases with increasing dose, but their severity does not. The theoretical lifetime risk of developing a fatal cancer caused by radiation exposure has been estimated at approximately 1 in 20,000 per mSv.

Table 1.1 The doses of radiation necessary to cause tissue damage

Testes – temporary sterility	>0.15 Sv
Testes – permanent sterility	>3.5 Sv
Lens cataracts	>2.0 Sv
Transient skin erythema	>2.0 Sv

Table 1.2 The normal irradiation doses used in clinical examinations

Chest x-ray	0.02 mSv
KUB x-ray	0.6 mSv
Intravenous urogram	3 mSv
Three-phase CT urogram	15 mSv

Regulations exist (which are typically country specific) in order to help prevent these unwanted effects. In the UK, the regulations include:

IRR99 – Ionising Radiations Regulations 1999. This concerns protection of people in their place of work and is enforced by the Health and Safety Authority. Radiation dose limits for employees are determined, and if exceeded, this must be investigated and reported to the Health and Safety Executive.

IRMER – Ionising Radiation (Medical Exposure) Regulations 2000 (amended 2006). This concerns protection of patients and is enforced by the Department of Health. It includes the two key principles of justification and optimisation. For justification, the practitioner (often a radiologist) must ensure that the clinical benefit of the exposure outweighs the potential risk. The referrer must supply sufficient information for an informed judgment to be made. Optimization involves the "ALARA" principle, keeping radiation exposure "as low as reasonably achievable" whilst still obtaining images that meet diagnostic standards. Diagnostic reference levels (DRLs) exist which act as a guide for appropriate patient doses for particular examinations. These are set nationally, although employers usually set their own lower levels. Exceeding a DRL for one exposure is not usually an issue, but if DRLs are routinely exceeded, this should be investigated.

Table 1.2 outlines typical effective doses for different examinations measured in millisievert (mSv), although these are highly variable depending on patient and equipment factors. For comparison, the yearly background radiation dose in the UK is approximately 2 mSv per person.

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Chapter 2
How to Perform a Clinical Radiograph and Use a C-Arm

Christopher T.L. Wilkinson

Despite the widespread increased availability of CT and MRI, the plain radiograph (e.g., the "KUB" abdominal film) still remains a key diagnostic tool for the urologist. In addition, the "c-arm" or "image intensifier" allows real-time imaging to guide a wide variety of urological procedures. Although a radiographer is commonly employed to perform clinical radiographs and operate the c-arm, it is important that the urologist understands the principles behind their function in order to make best use of these modalities.

How to Perform a Clinical Radiograph

Performing a clinical radiograph involves placing the appropriate body part of the patient between an x-ray tube and a detector. The components of the x-ray tube (Fig. 2.1) were mentioned in the previous chapter and include a tungsten metal filament (cathode) and a target metal anode housed in a vacuum. The vacuum is contained within a glass envelope, with a protective outer metal casing.

The shape of the anode enables the beam to be manually focused on the correct region of interest, and this is done with the help of a crosshair projected on the patient. A fine or broad focus can be chosen depending on various imaging factors.

The patient should be placed as close as possible to the detector which helps reduce effects of magnification, whilst minimising movement-induced artefact. It also helps to maintain image contrast by reducing the effect of scattered radiation reaching the detector. The distance from the x-ray tube to the detector varies, but is typically 100 cm for an abdominal and 180 cm for a chest radiograph. The x-ray beam should then be collimated on all four sides so that only the required structures are imaged, reducing scatter and radiation dose to the patient.

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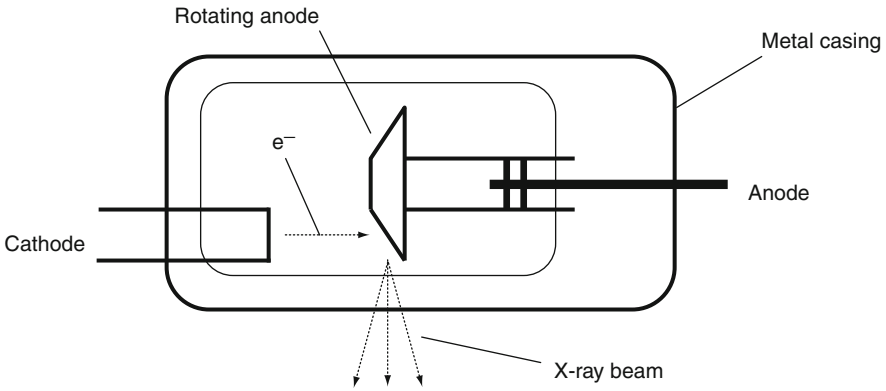

Fig. 2.1 Schematic diagram of typical x-ray tube

Anatomical side markers should be placed on the detector at a suitable site so as not to obscure any important image detail. Prior to exposure, three variables need to be determined – mA (milliampere), exposure time, and kVp (peak kilovoltage):

mA determines the current that flows through the filament, thus the number of electrons produced. The exposure time determines the time for which x-rays are produced, and therefore also affects the number of electrons produced. mA and exposure time are often considered together as mAs (milliampere second) which has the overall effect of making the image darker or lighter. An inappropriate mAs will result in either an overexposed or underexposed film.

kVp determines the potential difference between the cathode and anode, and hence the "power" of the beam. Increasing the kVp will increase the penetrating power of the x-rays and decrease the contrast of the final image.

Before the final exposure takes place, it is important to determine that all people present are adequately protected from extraneous irradiation. This may involve standing behind a screen or wearing protective lead clothing. After the image has been taken, the appropriate patient identifiers are added to the image. Hard copy films are less common now, and the final image will often be viewed on a digital monitor. This involves the use of a PACS (picture archiving and communication system), whereby the patient's radiological images are stored electronically and can be viewed on designated monitors throughout the hospital. Recent images are held on a local server, whereas older images are stored at a central off-site server resulting in a "filmless" environment.

How to Use a C-Arm

Many of the principles regarding the use of a c-arm are similar to those of standard radiography and will not be repeated. However, there are particular considerations that apply to mobile fluoroscopic equipment that are important. In a c-arm (Fig. 2.2), the x-ray tube and detector (or intensifier) are tethered and able to rotate whilst maintaining a fixed focal point, meaning multiple projections can be obtained without

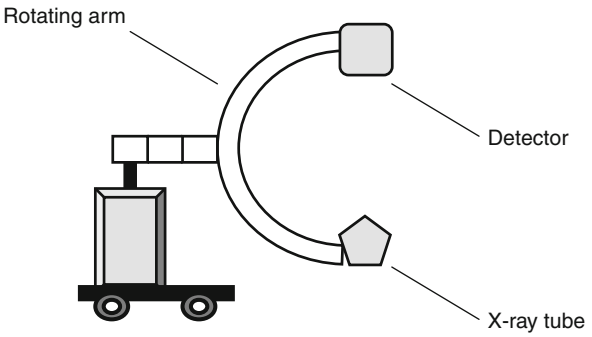

Fig. 2.2 Schematic diagram of c-arm apparatus

moving the patient. X-rays are projected through the couch and patient towards the detector, where the image is intensified and displayed on a monitor. The x-rays arriving at the detector cause light photons to be emitted, which in turn are converted into electrons. These are accelerated towards the output screen which converts the electrons back to light, and an image is produced. In this way, 1 x-ray photon at the input screen is converted into approximately 400,000 light photons at the output screen, enabling a good quality image to be produced almost instantaneously.

The device is controlled either by a handheld control or by foot pedals that allow screening (real-time images displayed on the monitor until the pedal is released) or image capture (single image captured for permanent copy). Different modes of screening are available to the user including continuous fluoroscopy, whereby the x-ray beam is delivered constantly and displayed at 30 frames per second, and pulsed fluoroscopy whereby the x-ray beam is delivered in short bursts (e.g., four frames per second), with the last image being displayed on screen until the next pulse occurs. Pulsed fluoroscopy can offer significant benefits in terms of reduced dose but may provide a "jerky" image rather than the smooth image provided by continuous fluoroscopy.

The c-arm is commonly used in the operating theatre, often with many people present, and therefore it is crucial to keep radiation dose as low as possible. Ways to decrease dose include:

1. Keep screening time to a minimum. Only screen when necessary and never screen when not looking at the image. Where possible use pulsed fluoroscopy rather than continuous fluoroscopy, with as low frame rate as practicable.
2. Use collimation to only image the exact region of interest.
3. Use high kVp. This will increase the penetrative ability of the x-ray beam, resulting in less absorption within the patient, but at the expense of image contrast.
4. Position the patient as close to the detector as possible.

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Chapter 3
Contrast Agents

Paul M. Taylor

Introduction

Contrast agents are a heterogeneous group of pharmaceuticals used during radiological procedures to enhance tissue definition. This enables clearer delineation of normal anatomy, increases detection, and permits better characterisation of abnormalities. Three groups of intravenous contrast agents are available:

1. Iodinated agents
2. Gadolinium
3. Micro-bubble particles

Iodinated Agents

These are used as radiographic contrast agents. They are formed from organic acid salts of iodine. The relatively high molecular weight of iodine I^{127} (Appendix 2) makes it radio-opaque. The initial use of sodium iodide as a contrast agent was limited by its toxicity and organic compounds based on an iodinated benzene ring to "shield" the iodine from the body were developed. In the 1990s, nonionic contrast media were introduced being better tolerated and safer than ionic compounds with a five- to tenfold reduction in the risk of adverse reaction. The agents used currently are all low or iso-osmolar, nonionic iodine compounds.

When injected intravenously, iodinated agents are rapidly eliminated by renal excretion. They pass into the extravascular space and through the placenta but do

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not penetrate the blood brain barrier. Iodinated agents can be administered intra-arterially or directly into other body cavities (e.g., bladder, ureter, biliary tree, etc.) as well as intravenously.

Many agents are available, and they differ little in their pharmacodynamics, physical properties, or safety. The selection of a specific contrast will be determined by availability, local cost, and application.

Contrast agents are manufactured in varying concentrations. High-concentration agents of high radio-opacity and viscosity are suitable for intravenous enhancement during CT; low-concentration agents, with lower radio-opacity and viscosity, are used in direct examinations such as urethrography and direct pyelography.

Iodinated agents are relatively safe with low overall rates of adverse reactions (0.15%). The majority of reactions are mild and include nausea, vomiting, urticaria, and skin rashes. Skin rashes can occur up to a week after contrast administration. Severe reactions are rare (<0.01%) but include bronchospasm, laryngeal oedema, and anaphylaxis. The risk of severe reaction is greater after any previous contrast reaction – regardless of its severity. Any reaction should be recorded in the patient's records, the patient warned of the risks of further contrast administration, and in the UK, the MHRA should be informed.

Contraindications

Renal impairment. Iodinated agents are nephrotoxic and, when administered intravascularly, should be used with caution in patients with renal impairment (eGFR < 60). Nephrotoxicity can be reduced by ensuring adequate hydration, minimizing the dose administered, and using a less nephrotoxic agent (e.g., iodixanol).

Previous adverse reaction. Patients who give a history of previous reaction to contrast agents should not be given further doses. The use of preprocedure steroids and antihistamines does not reduce the frequency or severity of reactions.

Asthma. Patients with asthma have a significantly increased risk of adverse reaction. If the asthma is well controlled, contrast can be administered with the availability of nebulisers, intravenous bronchodilators, and steroids but should be avoided if the patient is wheezy.

Allergies. Patients with a history of multiple allergies or a single severe allergy should not be given iodinated agents. There is, however, no demonstrable cross-reactivity between iodinated contrast and shellfish or topical iodine sensitivity.

Other groups. Although not absolutely contraindicated, some patient groups are at increased risk of adverse contrast reaction or renal compromise. Caution should be exercised in patients who are elderly, in cardiac failure, hypertensive, or diabetic. A rare complication is the development of lactic acidosis in patients who are receiving metformin. This is due to acute contrast-related nephrotoxicity leading to metformin accumulation.

Pregnancy. Iodinated contrast passes through the placenta and can result in suppression of the foetal thyroid.

Gadolinium

The most widely used contrast agents for MR imaging are chelates of gadolinium, a member of the rare earth group of elements (Appendix 2). Gadolinium compounds have similar pharmacodynamics to iodinated agents and are excreted by the kidney when given intravenously; they may also be given orally. Gadolinium shortens the T1 and T2 relaxation times of tissues, a dose-dependent effect. At low doses, the effect on T1 relaxation predominates, at higher doses the effect on T2. The quantity administered is therefore titrated against the patient's body weight to ensure predictability of effect. In general, the greatest tissue enhancement is seen on T1-weighted images.

The incidence of adverse reactions to gadolinium compounds is low (0.04%), and serious anaphylactic reaction extremely rare. Of particular concern, however, is the development of nephrogenic systemic fibrosis (NSF) in patients with renal impairment. This is a potentially fatal condition characterised by the development of fibrotic tissue in the skin and muscles thought to be due to the accumulation of free gadolinium in these tissues. Gadolinium is contraindicated in patients with renal impairment, following liver transplantation, neonates, and should not be given in pregnancy.

Micro-bubble Particles

Micro-bubble particles are used in contrast-enhanced ultrasound (CEUS) to identify flow. Micro-bubbles are 1–4 μm in diameter and are formed from cluster of small gas bubbles within a carbohydrate shell; the dissolution of the carbohydrate determines the agent's longevity in vivo and the gas core its echogenicity. They are used, intravenously, in Doppler studies of the cardiac circulation and the characterisation of liver lesions. Although their use as an intravesical agent in the identification of vesicoureteric reflux has been described, they, currently, have no application in the investigation of the urological patient.

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Chapter 4
How to Do an IVU

Paul M. Taylor

Introduction

The introduction of ultrasound and CT urography has reduced the number of IVUs undertaken, but it still remains a common investigation in urological practice. The typical radiation dose for a 3–4-film IVU is approximately 2.5 mSv. This is equivalent to 14 months of natural background radiation and approximately 100 times the dose from a chest radiograph.

Patient Preparation

No specific preparation is required. The use of laxatives, and fluid restriction to improve the degree of pelvicalyceal opacification, was common in the past. These are no longer considered necessary, and dehydration is inadvisable as it has been shown to increase contrast-related nephrotoxicity.

An IVU should not routinely be performed in patients with renal impairment as the contrast will not be excreted sufficiently to allow opacification of the collecting system, and it can result in further compromise of tubular function.

The patient should be asked about any allergies or previous adverse reactions to intravenous contrast. They should then be changed into a suitable examination gown and any jewellery removed from the abdomen.

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Control Film

An initial radiograph is taken prior to the injection of contrast using the same parameters as a KUB film. This differs from a standard abdominal radiograph as it is more tightly collimated, excluding the lateral abdominal walls. This greater collimation reduces the radiation dose to the patient and decreases the amount of scattered radiation that can degrade the image. The exposure is taken during inspiration and must include the upper poles of both kidneys and the symphysis pubis. As the maximum length of a standard radiograph is 43 cm, two separate exposures of the upper abdomen and pelvis may be required in tall patients.

Contrast Administration

Specific caution regarding the use of intravenous contrast should be taken under the following circumstances (Box 4.1):

The volume of contrast should reflect the size of the patient. Generally, 50 mL of contrast containing 350 mg mL^{-1} of iodine is used for patients weighing <70 kg and 100 mL for larger patients. In children and infants, the dose should be calculated according to the body mass at a rate of 2–3 mL contrast per kilogram body weight.

Box 4.1: Situations in Which Iodinated Contrast Media Should Be Used with Caution or Are Contraindicated
Renal impairment
Previous adverse reaction
Asthma
Elderly
Cardiac failure
Diabetics on metformin
Pregnancy

Exposure Sequence

The number and sequence of radiographs taken vary between departments, and the clinical indication for the study but a typical sequence of images would be:

1. Full-length image taken 5 min after contrast injection. This produces an overall view of the upper tracts, and if an abnormality of opacification or hydronephrosis is seen, the subsequent image series can be modified. There will also be some contrast remaining in the renal cortex at this stage, and the renal outlines can be assessed.

2. An image of the kidneys at 15 min. Before the second image is obtained, the pelvicalyceal systems and upper ureters should be distended. This is achieved by the application of a compressive band over the upper pelvis or by placing the patient in a Trendelenburg position. Compression should not be applied after recent abdominal surgery, if an aortic aneurysm is present or in patients with hydronephrosis.
3. A further full-length image. The third image is obtained immediately after the release of the compressive band or returning the patient to the horizontal position, allowing the contrast to fill the lower ureters.
4. An image of the bladder after micturition. The postmicturition film allows an assessment of bladder emptying and also enables small urothelial lesions to be seen more clearly. However, both of these can be achieved more satisfactorily using ultrasound without incurring a radiation penalty, and if this is available, a post-micturition image should not be obtained.

Variations

One shot IVU. If the patient has symptoms of renal colic and a KUB indicates a possible ureteric calculus, then a single full-length image 10–15 min after contrast injection will confirm or refute this.

Oblique images. If the control film suggests a possible renal calculus, the patient can be rotated 10–15° *towards* the abnormal side to see if the suspected opacity retains a constant relationship to the kidney. Similarly, if the lower ureters are not well seen on the initial series, it may be helpful to perform an oblique postmicturition view with the patient rotated *away* from the side under investigation.

Expiratory image. This is an alternative to oblique images if the control film demonstrates a suspected renal calculus. Renal calculi will have a fixed relationship to the kidneys, whereas calcification in overlying lymph nodes or vessels will move.

Prone images. These are obtained in some radiology departments to ensure better filling of the distal ureter.

Delayed films. If the initial postcontrast image demonstrates the presence of hydronephrosis, a poorly or nonopacifying system, then delayed images may be performed to try and determine the level of any possible obstruction. The timing of these images will depend upon the clinical indication for the examination and the degree of opacification of the upper tracts. In practice, they are often not of great value, and diagnosis can be obtained more rapidly and reliably by ultrasound or CT urography.

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Chapter 5
Dual Energy X-Ray Absorptiometry (DXA)

Richard Whitehouse

DXA is most commonly used to measure the mineral content of the skeleton, for the diagnosis and follow up of osteoporosis, but can also measure the fat and lean soft tissue content of the body.

How Does It Work?

As a simple approximation, the body is composed of three materials:

1. Adipose tissue (fat)
2. Lean soft tissue (muscle, liver, spleen, kidneys, etc.)
3. Bone

In a DXA scanner, a very low-dose x-ray beam is filtered into two components of known but different energies and intensities. The intensities of the two radiation energies that pass through the patient are measured. Because the region of the scan that contains bone can be identified and segmented out, the x-ray attenuation data can be used to calculate the amount of fat, lean, and bone tissue. Of course, there are multiple caveats that complicate this explanation (Table 5.1).

In practice, the inferred bone density of an area of bone (aBMD) is a very accurate reflection of the true mineral content of the bone and is extremely reproducible.

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Table 5.1 Factors influencing DXA measurements

X-ray attenuation is exponential. This complicates the maths but not the principle.
X-ray generation by x-ray tubes produces a spectrum of x-ray energies, the "effective" energy of which increases as the beam passes through matter, due to greater attenuation of the lower energy components. "Filtering" the beam into two different energies is consequently a gross simplification.
X-ray generation by x-ray tubes is not constant, requiring continuous monitoring and re-calibration.
Different manufacturer's equipment give slightly different results – follow-up scans should be on the same scanner.
Spine bone density measurement includes any aortic calcification, facet joint and end plate osteophytes, and other "degenerative" phenomena that increase the measurement result. These become greater with increasing age.

Patient Preparation for and DXA Scanning

Patients should be able to lie supine for about 10 min and keep still for about a minute for each scan. They should not have had radionuclide or barium studies, lanthanum carbonate, or phosphate enemas in the last week nor intravascular radiological contrast agents in the previous day. They should be dressed in clothing without metal attachments. Otherwise, no specific preparation is required. Typically, the hips, spine, wrists, and heels are scanned.

How Are the Results Expressed?

Lean and fat content are of interest in body composition studies, but bone mineral density (BMD) measurement is the usual clinical use of DXA. For a region of interest, such as a single lumbar vertebra, the result is expressed as:

1. Bone mineral content (BMC) in grams of mineral.
2. Areal bone mineral density (aBMD) in grams of mineral per square centimetre of projected scan area.
3. Z-score. This is a comparison of the patient's aBMD with age, sex, and ethnicity-matched reference data.
4. T-score. This is a comparison of the patient's aBMD with sex-matched peak bone density reference data.

Z- and T-Scores – What Is the Difference and Why Use Them?

Bone density increases during childhood, reaching a peak in late adolescence or early adulthood due to a combination of increasing mineralisation of bone, increasing trabecular bone density, and increased bone size. In males, bone density then

Table 5.2 The WHO classification of DXA results for Caucasian women

Normal bone	T-score greater than −1
Osteopenia	T-score between −1 and −2.5
Osteoporosis	T-score less than −2.5
Severe (established) osteoporosis	T-score less than −2.5 and 1+ osteoporotic fractures

decreases linearly with age. In women, there is a plateau in density, until the menopause, followed by exponential decline with age. Comparing the patient's result with an age-, sex-, and ethnicity-matched database makes the result easier to comprehend.

A Z-score of 0 indicates a result that lies on the mean value for matched normal data. A score of −1, or less, means the patient's bone density is one, or more, standard deviations below the matched mean value. Z-scores are used in determining osteoporosis in younger men, premenopausal women, and children.

The T-score is calculated in a similar way, but the bone density is compared with the sex-matched peak bone density, as this more closely reflects the risk of osteoporotic fracture. A T-score of 0 indicates a result that lies on the mean value for sex-matched peak bone density. A score of −1, or less, means the patient's bone density is one standard deviation, or more, below the peak bone density mean value. This is the standard method of expressing BMD in postmenopausal women (Table 5.2).

About 30% of Caucasian postmenopausal women are labelled as osteoporotic, and men who are hypogonadal are at risk of osteoporosis.

Examples of hip and spine DXA scans are produced both numerically and graphically (Fig. 5.1).

Why Diagnose Osteoporosis in Someone with No Fractures?

Decreased BMD is a risk factor for developing an osteoporotic fracture. Bisphosphonates are effective in treating low bone density, thereby reducing the risk of the patient suffering a low-trauma fracture, something that may be caused by twisting, bending, or even sneezing.

What Else Can a DXA Scanner Do?

Scanning the spine in a lateral projection can produce an image of sufficient quality to use for vertebral morphometry at a low radiation dose. This allows measurement of bone shape and size. Lateral DXA images of the vertebra can, therefore, be used to identify established low-trauma vertebral fractures; this is important as these are risk factors for clinically relevant fracture.

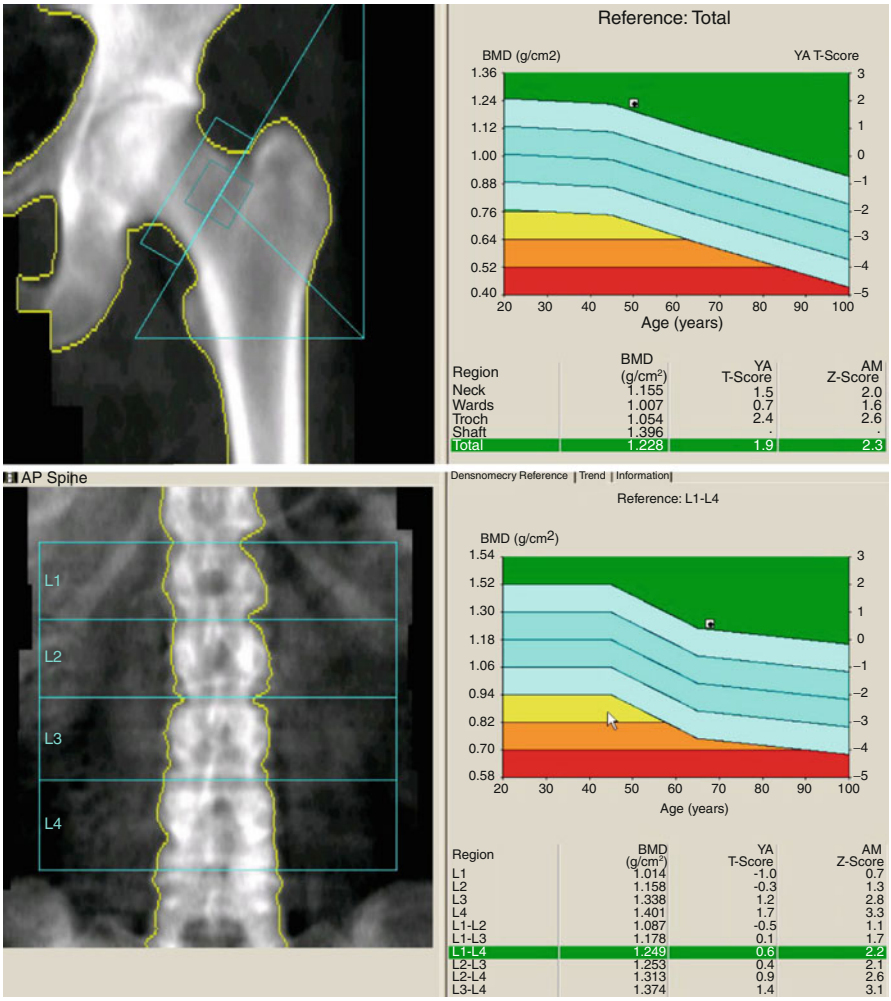

Fig. 5.1 Hip and spine DXA scans. The graphs demonstrate the patient's results compared to reference ranges. The horizontal *yellow*, *orange*, and *red* bands across these graphs are at T-score intervals of 1; the *blue* zone is the normal range divided by Z-score intervals of 1, from +2 to −2. The threshold for osteoporosis at a T-score of −2.5 is therefore halfway down the *yellow* band

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Chapter 6
The Physics of Ultrasound

Paul M. Taylor

The increasing availability of inexpensive portable ultrasound systems with a wide range of hardware and software options has allowed their widespread use in urology. To optimise the image, increase the diagnostic confidence of the operator, and minimise interpretive errors, it is necessary to understand the basic physics and technology underpinning these systems.

Production and Propagation of the Sound Wave

An ultrasound wave is produced by the application of a voltage across a piezoelectric crystal which deforms, converting electrical energy into sound energy. A typical ultrasound transducer contains an array of several hundred crystals, energised sequentially, to produce a sound beam 1–2 mm in thickness and several centimetres wide. The frequency of the sound produced is determined by the geometry of the crystals.

Ultrasound waves are propagated through the body tissues at a speed which varies dependant on the tissue's composition. When the sound wave hits an interface between tissues, it may be transmitted, refracted, absorbed, or reflected. Of the reflected sound, a proportion will pass back to the transducer where the piezoelectric process is reversed, and the sound is converted to an electrical impulse; this generates the image. The processes of absorption, refraction, and reflection are collectively referred to as attenuation.

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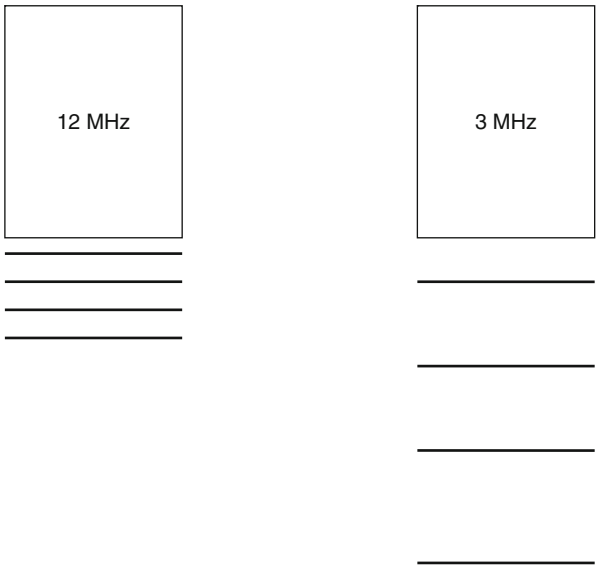

Fig. 6.1 High-frequency probes give higher resolution images but to a shallower depth. Lower frequency probes are able to penetrate more deeply but give lower resolution images

Transducer Selection

A fundamental consideration in all imaging techniques is how to maximise the resolution of the system. Resolution is defined as the ability to differentiate two points and can be resolved in axial and transverse planes.

Axial resolution (in the direction in which the sound wave travels) is determined by ultrasound frequency. Higher frequency ultrasound has a shorter wavelength and produces higher resolution. However, absorption of sound is also related to its frequency, and higher frequencies are, absorbed more rapidly than lower frequencies. Consequently, a high frequency (10–12 MHz) provides optimal imaging for superficial structures, whereas imaging of deeper structures requires a lower frequency (3–5 MHz) to achieve adequate penetration (Fig. 6.1).

Transducer Design

Two basic transducer designs are available.

A linear array transducer produces a rectangular image. The benefit of this design is that transverse resolution (i.e., the resolution at 90° to the direction of sound travel) is constant at any depth, but the maximum image width is, typically, only 6–8 cm. These transducers typically function at high frequency and are used for superficial structures. The second design is a curved array producing a sector-shaped image. This allows wider beam generation with a smaller skin footprint but at the expense of declining transverse resolution with increasing depth. Curved array

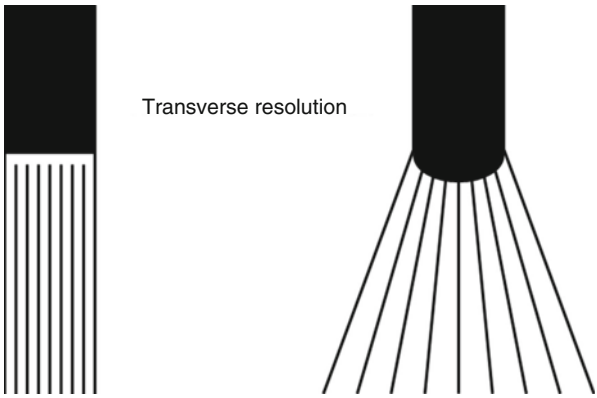

Fig. 6.2 A linear array produces a narrow image, whereas a curved array facilitates a wider image

probes are typically of lower frequency than linear array probes and used for general abdominal examinations (Fig. 6.2).

Frame Rate

After each beam of sound is transmitted there is a delay, while the sound travels through the tissues and back to the transducer. The deeper the structures to be imaged, the longer the delay before the next beam and the lower the number of images per second (frame rate) that can be used. The frame rate influences achieved image resolution.

Gain

As the beam passes through the tissues, and is attenuated, the reflections from deeper structures are weaker on arriving back at the transducer. Similar objects at different depths, therefore, appear to be of different echogenicity. To overcome this, the system amplifies the sound waves from deeper tissues more than those received superficially. As the depth traveled by the sound is proportional to the time, this is often referred to as time gain compensation (TGC). In order to overcome any heterogeneity of attenuation, the operator can override the baseline TGC settings using a series of sliding controls.

Focus

The ultrasound beam, although thin, is not of uniform thickness and initially converges, then diverges, as it travels away from the transducer. The point of maximum convergence is the focal zone and is the area of highest resolution. The size and

position of the focal zone is dependent upon probe design but can be altered by the operator.

Doppler Ultrasound

The Doppler principle determines that sound emitted from, or reflected by, a moving object varies proportionally to the velocity of the movement. If the frequency of the transmitted beam is known, and the frequency of the reflected sound is measured, the velocity can be calculated. For each calculation, several parameters can be recorded: position, time, amplitude, speed, and direction. It is not possible to display all these parameters simultaneously in a single graphic display, and two common displays are, therefore, used.

Range-Gated Doppler

A specific area is identified on the ultrasound image, and the flow in this area is displayed as a histogram. Time is displayed on the *x*-axis, velocity on the *y*-axis, and amplitude is related to the displayed pixel intensity.

Colour Doppler

A large area, possibly the whole ultrasound image, is selected, and a colour map is superimposed in which two colours are used to represent flow towards and away from the transducer with the intensity of the colour related to velocity with individual pixels. Red is flow in the direction of the probe and blue away from it.

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Chapter 7
How to Ultrasound a Suspected Renal Mass

Michael J. Weston

Essential considerations are whether the lesion is a true mass or not, if the mass is cystic or solid, and whether the mass is benign or malignant. If a renal mass is suspected on ultrasound, it needs to be characterised. Sometimes, clinical signs or past imaging give the answer, but otherwise CT or MR scans will be needed.

Technique

The ultrasound machine needs to be set up with an appropriate imaging preset; this can be set up by the manufacturer and will usually be labelled as "abdomen" or "kidneys" in the preset menu. Choose a probe and frequency to suit the patient's body habitus. Mostly, this will be a curvilinear probe of 3–6 MHz. Lower frequencies give better penetration but poorer spatial resolution. Special techniques, such as harmonic imaging or use of contrast agents, can improve visualisation. Harmonic imaging is a technique where the machine listens for echoes occurring at harmonic frequencies rather than from the primary transmitted frequency. This improves visualisation by removing some artifacts and increasing the contrast between tissues. Contrast agents are generally bubbles of gas in a stabilised membrane that allows the bubble to cross the pulmonary circulation to reach the systemic circulation without bursting. These bubbles greatly increase the harmonic signal obtained as they reverberate within the ultrasound beam. This allows differentiation of tissues of different vascularity.

Both kidneys need to be imaged in longitudinal and transverse planes with the probe being swept from one side of the kidney to the other, in order to ensure full coverage of the renal parenchyma. The patient should be examined both whilst lying

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supine and whilst in each decubitus position to gain access to the kidneys. The liver and spleen can be used as acoustic windows through which at least part of the kidney can be seen. Asking the patient to take a deep breath will help bring the kidneys into view. Remember to alter the sector width and the focus position to optimise frame rate and visualisation. Colour Doppler ultrasound by showing the normal vascular distribution may help to distinguish a true mass from a pseudomass.

Pseudotumours

Dromedary humps, columns of Bertin, foetal lobulation, and scarring can mimic the presence of a renal mass. A dromedary hump is a focal bulge on the lateral margin of the left kidney, usually as an adaption to the space next to the spleen. A column of Bertin is normal cortical tissue extending between the pyramids down to sinus fat. It may look rounded and resemble a mass. It usually lies in the middle third and is more often seen on the left. Persistent foetal lobulation and cortical scars can alter the outline of the kidney and mimic a mass – most often seen when there is an area of preserved cortex in a very scarred kidney. Focal infection may also produce an apparent mass in the cortex (the so-called lobar nephronia), but usually the clinical signs of fever and so forth give the diagnosis.

Cysts

These are the commonest renal mass lesions. Ultrasound features are: no internal echoes, a rounded or oval shape, increased through transmission of sound, an imperceptible smooth wall with a sharply defined margin, and no signal on colour Doppler. Cysts may undergo complications, usually haemorrhage or infection, which will produce internal echoes. The more cysts that are present, the more likely that one will suffer a complication; polycystic disease sufferers are prone to these complications. If cysts have septations and solid components, there is a greater likelihood of them being malignant. The Bosniak classification system helps to assess this risk (Fig. 7.1).

Solid Masses

There are both benign and malignant solid masses. Angiomyolipoma are the commonest benign solid lesion. These characteristically look bright on ultrasound and arise from the cortex (Fig. 7.2).

If found, their nature needs to be confirmed, usually by doing a CT scan to confirm they contain fat. The problem is that small renal cell carcinomas (RCC) may also have a bright echotexture and mimic their appearance. Larger RCC are more likely to be dark on ultrasound or to have cystic necrosis. RCC maintain a “ball” shape and distort the renal architecture (Fig. 7.3).

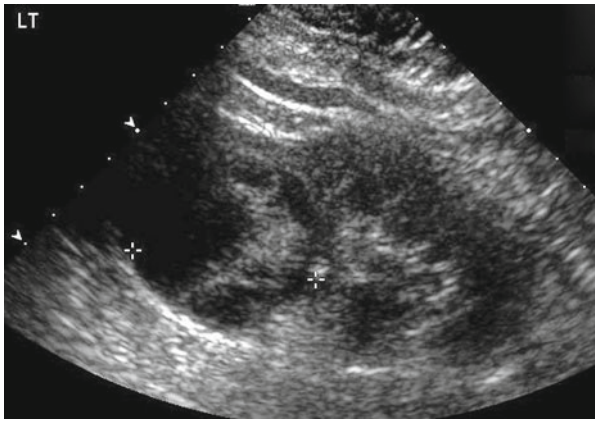

Fig. 7.1 The calipers mark out a cystic lesion with a large solid component. This is of concern. If colour Doppler or contrast agents show that the solid area is vascularised, i.e., not just clot, then this must be considered a malignant lesion – Bosniak IV

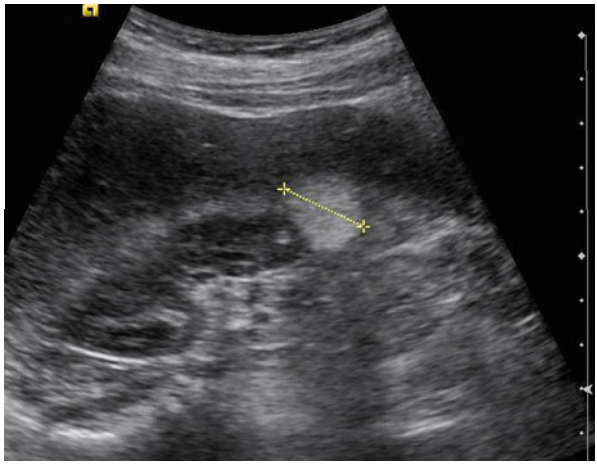

Fig. 7.2 The calipers mark out a brightly echogenic cortical lesion that looks typical of an angiomyolipoma. The fat content needs to be confirmed with CT as small renal cancers can look similar

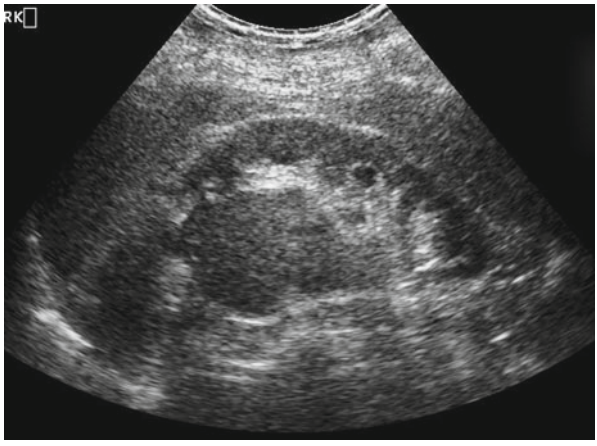

Fig. 7.3 A uniformly echo-dark mass deforming the upper pole of the kidney. It must be considered a renal cell carcinoma. Staging CT is needed

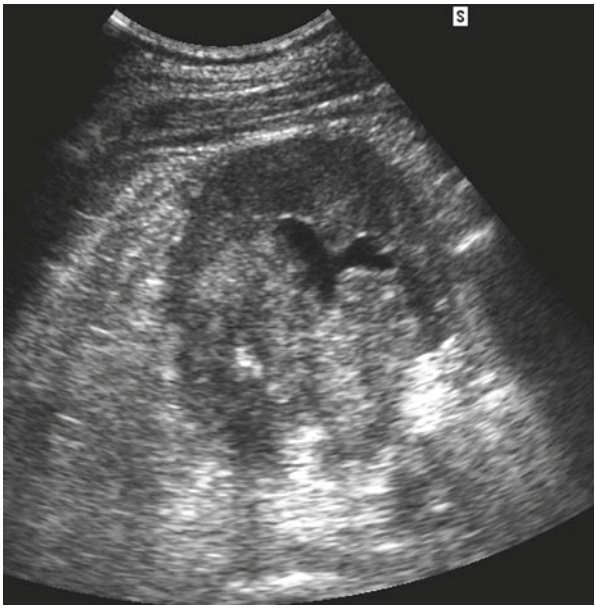

Fig. 7.4 A more infiltrative mass that is not deforming the shape of the kidney in this transverse view. It is causing focal calyceal dilation. Appearances are those of a transitional cell carcinoma

Transitional cell tumours (TCC) are rarer but generally have an infiltrative pattern that preserves the shape of the kidney. TCC may cause obstruction to the collecting system and focal dilation of the calyces (Fig. 7.4).

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Chapter 8
How to Ultrasound a Painful Testis and a Testicular Mass

Michael J. Weston

Essential considerations are: whether a mass is in the testis or not, whether the painful testis has increased or decreased vascularity, and whether the presenting symptoms, such as trauma, are masking an underlying lesion.

Technique

The ultrasound machine must be put into the correct "testes" preset. A high-frequency linear probe of 7–12 MHz needs to be used. A private environment and a chaperone are needed. The patient should hold their penis out of the way against the abdomen. The patient's thighs need to be kept together to support the scrotum. Some operators prefer to place a towel beneath the sac to support it. The gel needs to be warm, and copious amounts are needed to avoid artefacts from scrotal hair. The testes need to be systematically examined in both longitudinal and transverse planes using both greyscale and colour Doppler. The two testes should be compared side by side in a transverse view so that any differences can be appreciated. If the patient has felt a lump, the operator needs to make sure they have scanned the area of concern – it helps if the patient holds the suspected lump. Mostly, patients are scanned lying supine, but it can help to sit them up if a varicocele is being assessed.

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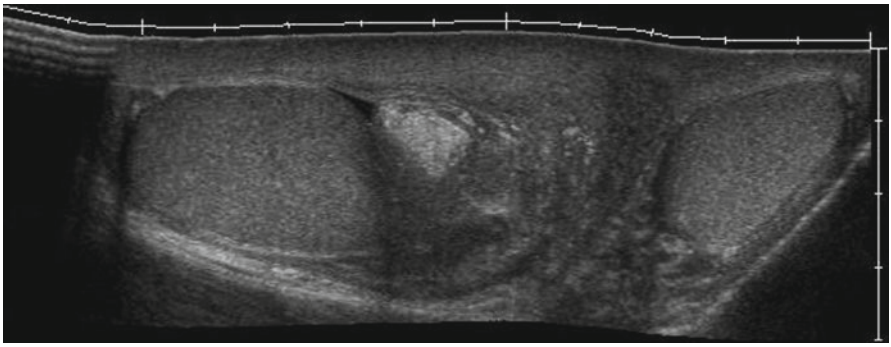


Fig. 8.1 Longitudinal view of the testis and epididymis. The tail of the epididymis is enlarged and has a mixed echo pattern. *Note*: the tail is most commonly affected, as an ascending infection will arrive there first, remembering the course of the vas. The overlying scrotal skin is also thickened

The Painful Testis

Trauma, inflammation, and torsion are the common causes. An acute presentation is usual. Torsion must not be missed. The cardinal ultrasound feature is that the painful testis is avascular on colour Doppler compared to the asymptomatic side. The greyscale features may not help as the congestion and infarction caused by torsion may make the testis appear enlarged and dark, similar to an inflamed testis. Spontaneous detorsion may also mean the testis becomes hypervascular, so clinical acumen remains vital.

Epididymo-orchitis typically causes the epididymis and testis to be enlarged (Fig. 8.1) and hypervascular. The pitfall is that venous infarction secondary to the inflammation may make the painful testis poorly vascularised. Again, clinical acumen is required.

Trauma is usually secondary to road traffic, athletic, or straddle injuries. Haematoma, torsion, and rupture may be seen. Haematoma is usually bright in the acute phase and becomes dark with time (Fig. 8.2). The tunica albuginea needs to be checked for integrity, and colour Doppler used to ensure the testis is still perfused. Beware the presentation following minor trauma, which unmasks a preexisting testicular tumour.

Suspected Scrotal Mass

The first essential is to determine if the mass is in the testis or not. Look to see if the masses are unilateral or bilateral and be certain about which side any lesion is on.

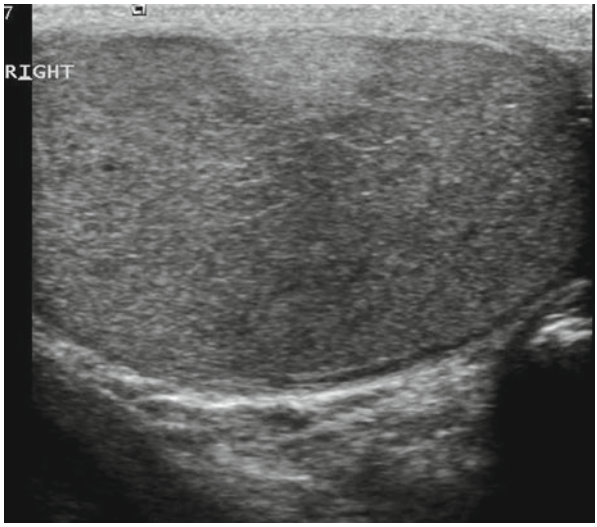


Fig. 8.2 A patient with a good acute history of trauma. There is a focal peripheral echogenic lesion to correspond to an intratesticular haematoma. Follow-up will show this lesion darkens and disappears with time

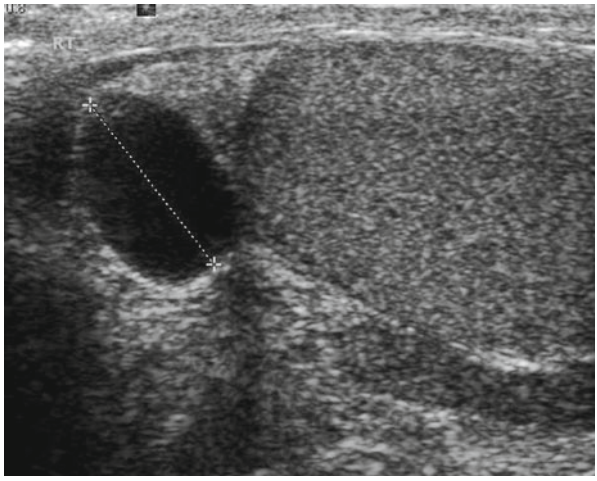
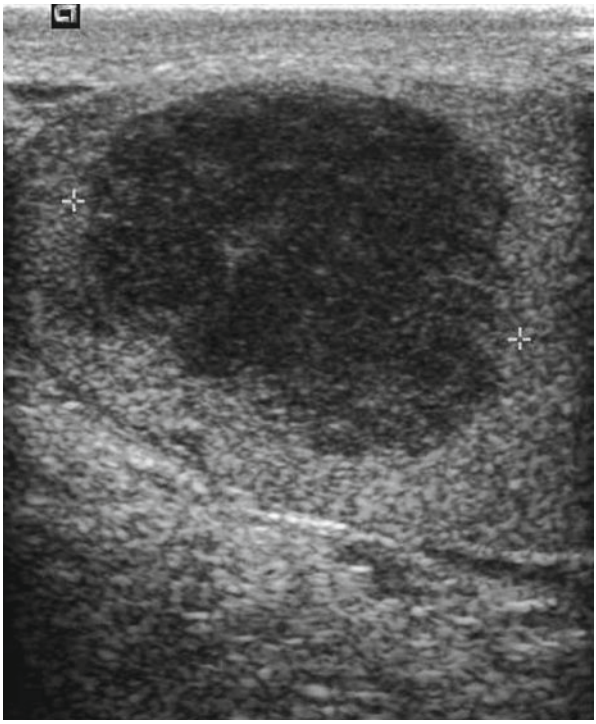
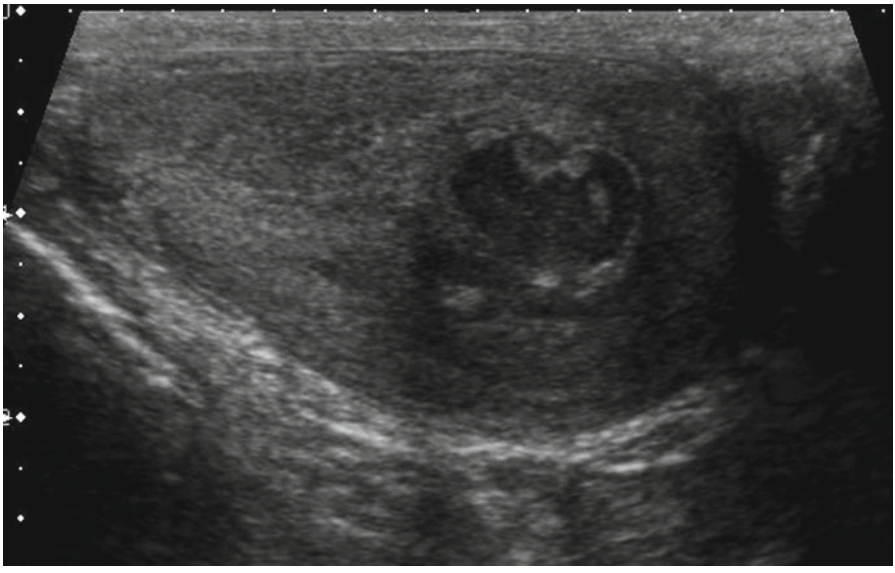


Fig. 8.3 A patient complaining of an intrascrotal mass. Ultrasound clearly shows this to be a cyst of the epididymal head

Most extratesticular masses are benign – the commonest being an epididymal cyst (Fig. 8.3). Solid extratesticular lesions may be, in descending order of likelihood, sperm granulomas, lipomas, adenomatoid tumours, and very rarely sarcomas.

Intratesticular masses are of great concern, and malignant germ cell tumour is the likeliest pathology. Ultrasound cannot reliably distinguish one tumour from another (Figs. 8.4 and 8.5). There are nonneoplastic focal testicular lesions, and focal orchitis and haematoma are important to consider amongst others. Clinical acumen is necessary to decide when to operate and when to observe with a repeat scan after an interval of time. Tumour markers may help.





Figs. 8.4 and 8.5 These two images both show intratesticular germ cell tumours; (Fig. 8.4) has a uniform *dark texture* and (Fig. 8.5) a more complex mixed *cystic and solid appearance*. Ultrasound cannot reliably tell which kind of tumour is present, though the uniform pattern may suggest seminoma and the complex pattern a mixed germ cell tumour

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Chapter 9
How to Perform a Transrectal Ultrasound Scan and Prostate Biopsy

Fady Youssef and John B. Anderson

Transrectal ultrasound (TRUS) is used for many prostatic interventions including prostate biopsy, brachytherapy, cryotherapy, to monitor the application of high intensity focused ultrasound (HIFU), and during the investigation of male factor infertility and haemospermia.

Probe Selection

Endorectal probes are available in side- and end-fire models with transmission frequencies of 6–10 MHz. Recent evidence has demonstrated increased cancer detection rates in biopsies performed using end-fire probes (Ching et al. 2009). As the scanning frequency increases, the resolution increases, but the depth of image lessens. Most intracavity probes used for transrectal ultrasound have a scanning angle of almost 180° which allows visualisation of the entire gland in both transverse and sagittal sections.

A 7.5-MHz transducer produces a high-resolution image with a focal range of 1–4 cm which is optimal for visualising the prostate, especially the peripheral zone where most prostate cancers arise.

Planes of Scanning

Patients are positioned in the left lateral position, with hips and knees flexed to 90° and buttocks at the edge of the couch to allow manoeuvrability of the probe.

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Complete evaluation should occur in both transverse and sagittal sections (Figs. 9.1, 9.2, and 9.3) to assess for any capsular breach or hypoechoic areas within the periphery of the prostate. Scanning begins in the sagittal plane, and a small amount of urine in the bladder facilitates the examination. The seminal vesicles and vas are identified followed by the base of the prostate. The central zone comprises the posterior part of the gland and is often hyperechoic. The transition zone is in the central part of the gland and is hypoechoic. The junction of the transition and peripheral zone is distinct posteriorly and is characterized by a hyperechoic region. The peripheral zone forms most of the gland volume.

The prostatic volume can be calculated using the formula:

$$\text{Transverse diameter} \times \text{AP diameter} \times \text{longitudinal diameter} \times (\pi/6)$$

Once the volume is known, the PSA density (serum PSA/gland volume) can be calculated.

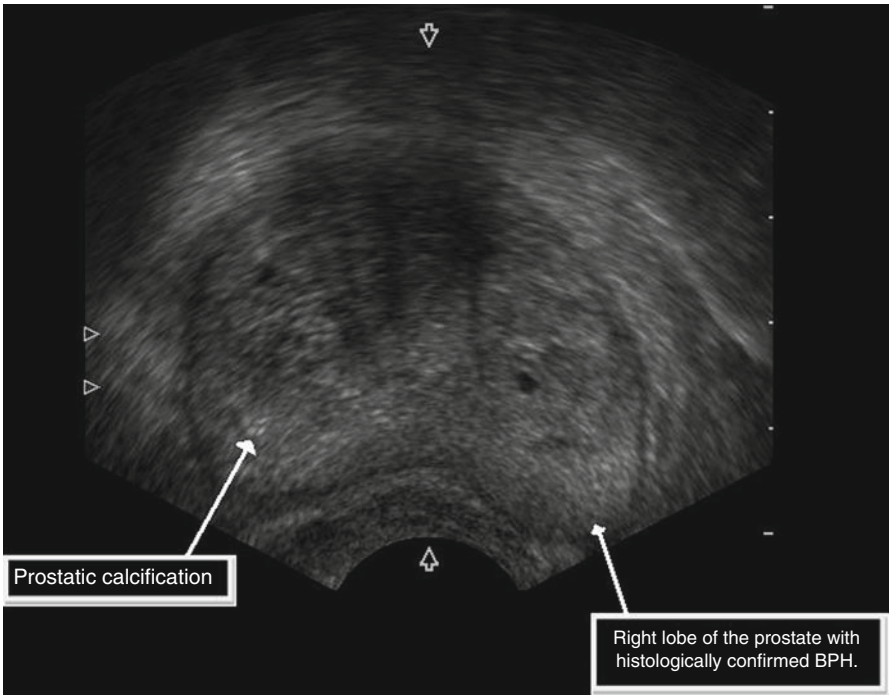

Fig. 9.1 Transverse scan showing prostatic calcification I on the left lobe with benign appearances on the right

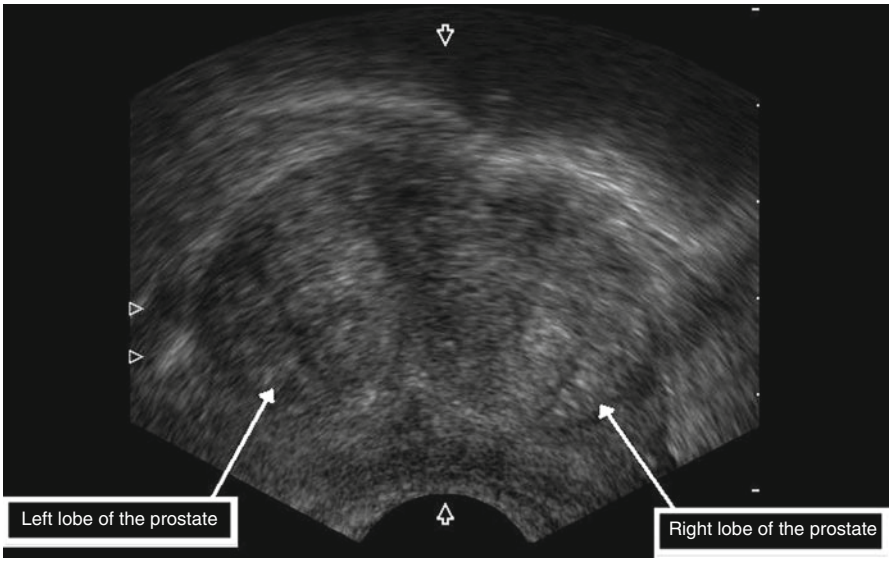

Fig. 9.2 Transverse scan showing the lobar structure of the prostate

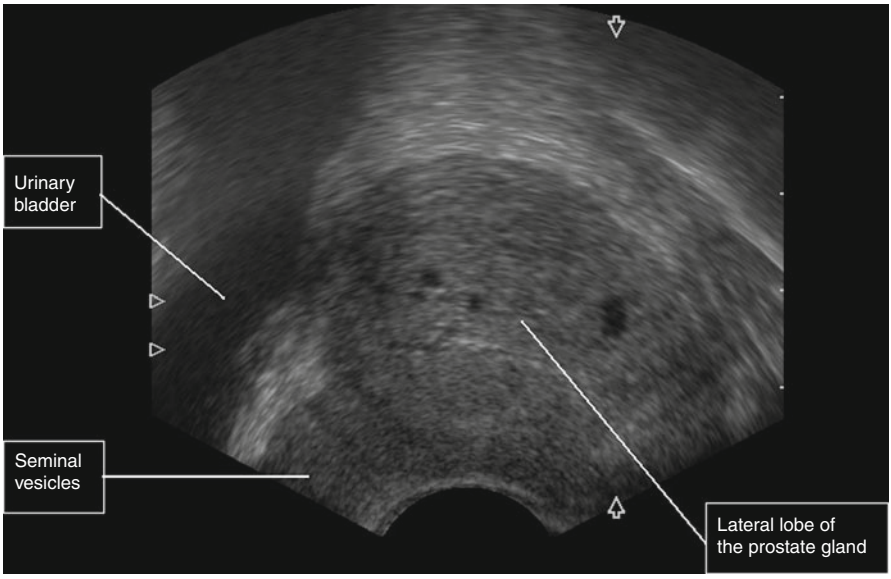

Fig. 9.3 Sagittal scan showing the relationship of the prostate to bladder and seminal vesicles

Role of Doppler

Colour Doppler imaging is based on the direction of blood flow in relation to the transducer receiving the signal. Flow towards the transducer is depicted as red and flow away is blue. Power Doppler imaging uses the shift in amplitude to detect flow velocity and direction of flow with less reliance on the Doppler angle. This allows detection of slower flow making it more suitable for detection of neovascularity in association with prostate cancer. Some studies have suggested an increased microvessel density correlates with a raised Gleason score. Neither Doppler or power Doppler scanning has proved itself superior to the other in cancer detection nor are neither superior, diagnostically, to systematic biopsy.

TRUS and Biopsy

The indications for performing a TRUS prostate biopsy include:

- Abnormal prostate findings following digital rectal examination (DRE)
- Abnormally elevated PSA above age-specific range
- Previous biopsies demonstrating prostatic intraepithelial neoplasia (PIN) or atypical small acinar proliferation (ASAP)
- Diagnosis of suspected prostate cancer in patients with symptoms of metastatic manifestations of prostate cancer

Patient Preparation/Information

Patients should be informed of the risks and benefits and give informed consent prior to the procedure. The complications of prostate biopsies are not insignificant and include:

– Haematospermia	37.4%
– Haematuria	14.5%
– Per-rectal bleeding	2.2%
– Infection	2–4%
– Urinary retention	0.2%

Adapted from Consensus Guidelines NCCN, Version 1.2007

Antibiotic prophylaxis is routinely administered; however, optimal dose and treatment length vary. Local practice involves administration of IV co-amoxiclav 1.2 g prior to biopsy followed by 3-day course of ciprofloxacin 500 mg twice daily postbiopsy.

The patient is positioned as for a TRUS, and periprostatic local anaesthesia is routinely infiltrated prior to biopsy. This is achieved using 10 mL 2% Lidocaine, a long spinal needle (7 in., 22 gauge), and TRUS guidance along the biopsy channel.

Taking a Biopsy

A spring-driven 18-gauge needle core biopsy device or gun is used. On deployment, the gun advances the needle 5 mm and samples the subsequent 15 mm of tissue, with the tip extending 5 mm beyond the tissue sampled. The biopsy sample is placed in 10% formalin.

On baseline/initial biopsies, tissue should be taken from the peripheral zone (as far lateral and posteriorly as possible). Additional areas should be taken from clinically suspicious areas on DRE/TRUSS. Less than 8 cores are considered inadequate for routine prostate biopsy for cancer detection. More than 12 cores are not significantly more conclusive at detecting further cases of prostate cancer (Eichler et al. 2005). The NHS Cancer Screening programme has recommended 10 core biopsies as this is an acceptable compromise between increased cancer detection and reduced morbidity of the procedure.

Postprocedure Care

Patients are observed for a minimum of 30 min postprocedure and must be able to void before they are discharged. Patients are given the number of a urology nurse specialist as a point of contact in case of any problems.

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Chapter 10
How to Manage a Hydronephrotic Kidney

Michael J. Weston

It is essential to distinguish dilation and obstruction. If sepsis is present, there must be adequate antibiotic therapy before any intervention is attempted.

Causes of Dilation

A dilated pelvicalyceal system does not always mean obstruction. Dilation may be physiological, at times of high urine flow/fluid load and during pregnancy (usually the right kidney). The commonest pathological causes are chronic bladder retention, reflux, or the renal dilation that occurs with long-term conduit drainage. Dilation may be seen following previous, relieved, or intermittent, obstruction. Radioisotope studies or CT urography may be helpful in delineating whether obstruction is present.

Parapelvic renal cysts can mimic the appearance of hydronephrosis on ultrasound (Fig. 10.1) and provide a pitfall for the unwary. CT urography will resolve the issue.

Stones are the commonest benign cause of obstruction, but retroperitoneal fibrosis and aortic aneurysms are other nonmalignant causes. If the obstruction is malignant, a CT urogram can often clarify whether it is intrinsic or extrinsic to the ureter which may determine whether an antegrade or retrograde approach to the relief of the obstruction is best.

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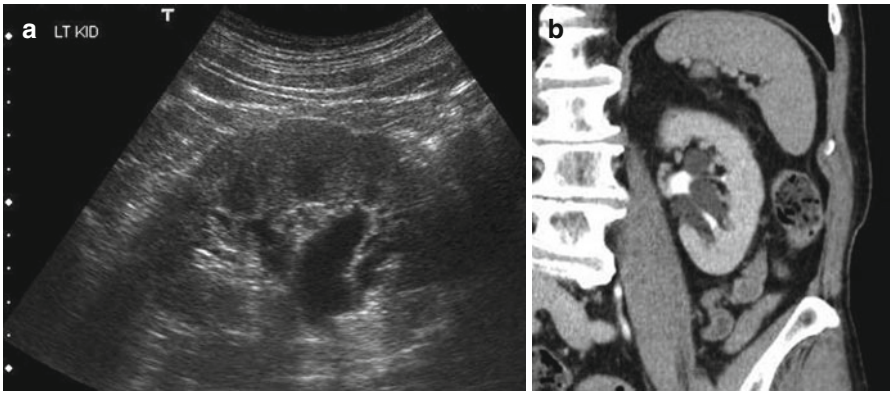

Fig. 10.1 The ultrasound image (**a**) suggests a hydronephrosis. The coronal CT urogram (**b**) shows the opacified normal pelvicalyceal system running between the parapelvic cysts

Indications for Nephrostomy

Deteriorating renal function, sepsis, pain with stone, and diversion of urine away from a leak (Fig. 10.2) are the commonest indications for nephrostomy. An acute intervention is usually used to buy time until a more definitive treatment is appropriate. Nephrostomy is usually best done in daylight hours – complication rates are higher at night. The patient should be rehydrated, treated for sepsis, and clotting abnormalities should be corrected except when a pyonephrosis is causing a consumptive coagulopathy.

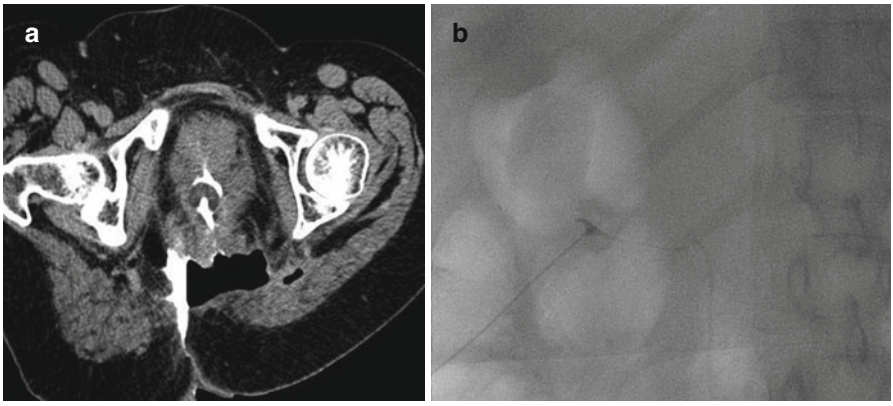

Fig. 10.2 CT of the pelvis (**a**) shows contrast leaking into a large perineal wound. This is an indication for bilateral nephrostomies. Typically, the system will not be dilated. Ultrasound is used for the initial puncture, but fluoroscopy (**b**) is needed for placing the wire and catheter. Note that the calyx has been successfully punctured

Technique

Usually, a combination of ultrasound and fluoroscopic guidance is used, and time spent in preparation is never wasted. Position the patient so that they are comfortable, and there is easy access to the kidney. Ultrasound is an ideal tool to check on the position of the kidney and to ensure that there is no intervening structure that would prevent access. Most kidneys will be accessible from a lateral or anterolateral approach with the patient lying supine or supine oblique. Antibiotics have been recommended for all nephrostomies, but in uncomplicated cases without sepsis, stones, or prior intervention, the risk is very low, and some would omit them.

The puncture site is prepared aseptically with local anaesthesia being used for the skin and renal capsule. The aim is to puncture, using a 19-G plastic-sheathed needle, from the calyx to the renal pelvis in a straight line, using ultrasound guidance (Fig. 10.3); this makes subsequent wire and tube manipulation easier. Ultrasound guidance should always be good enough that the needle hits the intended calyx. Puncture is done during quiet respiration – the kidney naturally stops moving briefly when the needle tip touches it.

When the needle is in the pelvicalyceal system, urine should flow freely; a sample may be taken. The stylette is removed to leave the plastic sheath in position. If ultrasound alone is being used, then a wire (0.038″ J tip) can be passed down the sheath into the PC system and the sheath then removed. The wire is clearly visible on ultrasound (Fig. 10.4). The track may then be dilated over the wire up to eight French and a pigtail nephrostomy catheter inserted. A locking pigtail loop is desirable to aid retention of the catheter.

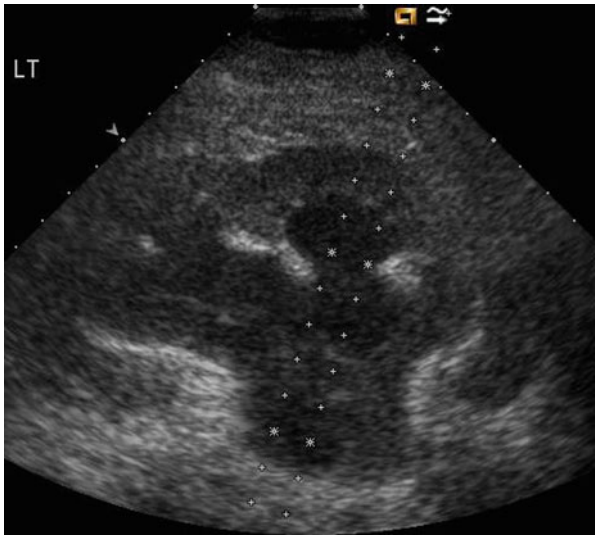

Fig. 10.3 Planning ultrasound access. The guidelines for the needle are aimed so that the needle will pass straight from the calyx to the renal pelvis

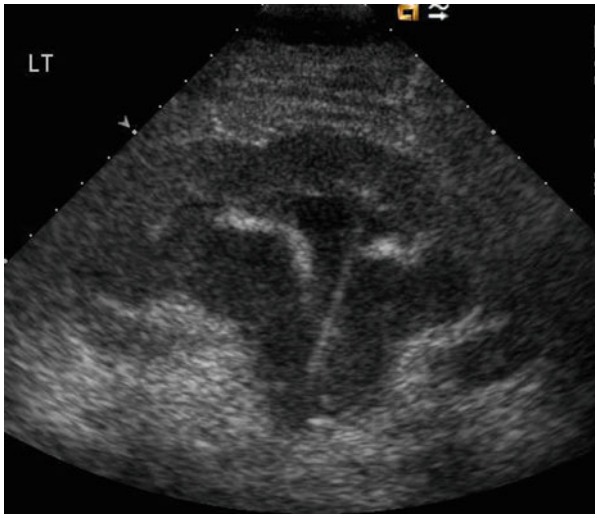

Fig. 10.4 The echogenic wire is seen passing successfully into the renal pelvis

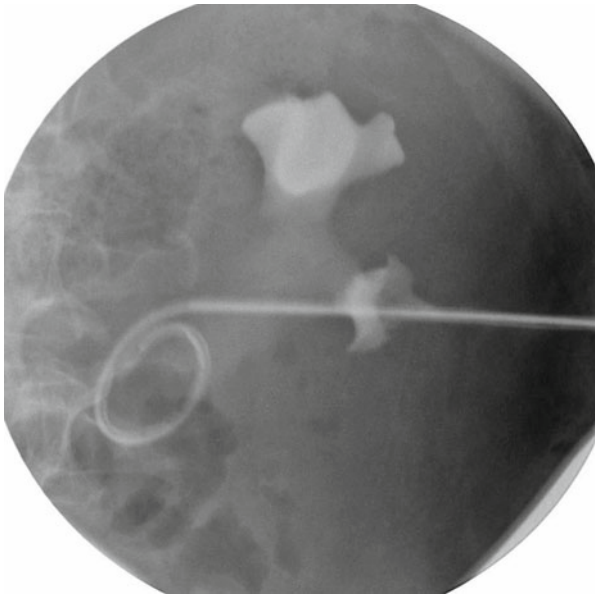

Fig. 10.5 Fluoroscopic image of a pigtail catheter coiled in the renal pelvis. Note that only a minimal amount of contrast agent has been instilled

If fluoroscopic assistance is being used – usually in the less dilated system – a small amount of contrast agent is injected to opacify the system before the wire is inserted. Too much pressure in the collecting system may precipitate a septic event, so some initial aspiration of urine is recommended. Fluoroscopy allows greater control over the guidewire manipulation and catheter placement than ultrasound (Fig. 10.5).

Complications

Rapid decompression of an acutely obstructed kidney may cause some patients to vomit. Postobstructive diuresis and bleeding into the PC system are other complications; significant bleeding requiring transfusion occurs in 1–3% of cases. Damage to the renal vasculature, large perinephric haematomas, and damage to adjacent organs are rare. Septicaemic shock is the most important complication. The overall rate of major complications is 4%.

Afterwards

A plan should be made for the further treatment of the obstructed system. The less time a nephrostomy is in place, the less the chance there is for it to be displaced.

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Chapter 11
Principles of Computed Tomography (CT)

Catherine O'Dwyer

The increasing availability, speed, and reliability of computed tomography has resulted in its widespread use in urological imaging. Understanding the basic physics and technology behind this imaging modality, along with familiarity of scan techniques and use of contrast, allows performance of the optimal scan for diagnostic purposes.

X-rays are produced when fast moving electrons are stopped suddenly by impact on a metal target. The kinetic energy of the elections is converted into x-rays (1%) and heat (99%). An x-ray tube consists of two electrodes sealed in a vacuum; the negative electrode (cathode), a fine tungsten filament; the positive electrode (anode); a smooth flat metal target. The filament is heated and emits electrons by the process of thermionic emission. The electrons are repelled by the negative cathode and attracted by the positive anode. The voltage (typically 30–150 kV) between the anode and cathode drives the current of electrons. Each electron arrives at the surface of the target with a kinetic energy equivalent to the voltage (kV) between the anode and cathode.

Interaction with Matter

X-rays may be:

- Transmitted: pass through unaffected
- Absorbed: transfer to the matter some or all of their energy
- Scattered: diverted in a new direction, with or without loss of energy

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Attenuation is the fractional reduction in the intensity of the primary x-ray beam as it passes through a medium.

$$\text{Attenuation} = \text{absorption} + \text{scatter}$$

The linear attenuation coefficient is related to the attenuating property of a material, i.e., how well it absorbs, scatters, or transmits x-rays.

Physics of Computed Tomography

In computed tomography, a transverse slice of the patient is imaged, avoiding the superimposition of adjacent structures that occurs in conventional radiography. The slice is defined by a "sheet of x-rays" produced by a narrow, well-collimated, x-ray fan beam rotated around the patient.

The x-ray beam is attenuated by absorption and scatters as it passes through the patient. Detectors on the other side of the patient measure the x-ray transmission through the patient. These measurements are repeated many times from different directions, whilst the tube is pulsed as it rotates 360° around the patient.

The slice is subdivided into a matrix of 512×512 volume elements (voxels). The image is reconstructed by a computer as a corresponding matrix of 512×512 picture elements (pixels). A pixel is a representation of the average linear attenuation coefficient of a voxel. The image is displayed as a matrix of pixels; the brightness or greyscale value of each pixel represents the average linear attenuation coefficient of the contents of the corresponding voxel.

CT numbers are assigned to each pixel in the image by a computer algorithm that uses as data measurements of transmitted x-rays. CT pixel numbers are proportional to the difference in average x-ray attenuation of the tissue within the voxel and that of water. A Hounsfield unit (HU) scale is used; water is assigned a value of 0; the scale extends from 1,024 HU for air to +3,000 HU for dense bone.

Types of CT Scanner

First-generation scanners used a single pencil beam falling on a single detector; together they translated through 180 steps and then rotated 1° at a time through 360°. This took a total scan time for one slice of 3–5 min. Third-generation scanners are the ones most frequently used today. They employ a wide fan beam falling on a larger array of many hundreds of detectors which do not translate but rotate continuously through 360° around the patient. In fourth-generation scanners, the x-ray tube alone rotates through 360° around the patient who is positioned within a continuous ring of several thousand stationary detectors.

Helical scanning is performed by moving the patient's table at a constant speed through the CT gantry whilst scanning continuously with an x-ray tube rotating around the patient. A continuous volume of image data is acquired during a single breath hold. This technique dramatically improves the speed of image acquisition, enables scanning during optimal contrast opacification, and eliminates artefacts caused by misregistration and variations in patient breathing. Volume acquisition enables retrospective reconstruction of multiple overlapping slices, improving visualisation of small lesions, and making three-dimensional images possible.

Multidetector helical CT (MDCT) is one of the latest advances in CT imaging; it utilises the principals of helical scanning but incorporates multiple rows of detectors. This allows the acquisition of multiple slices per tube rotation, increasing the speed at which area of the patient can be covered.

Use of Contrast

Radio-opaque media are used to increase contrast between adjacent tissues. Intravenous iodine-based contrast agents (which have a sufficiently high atomic number to maximise absorption of x-rays) are administered in CT to enhance density differences between lesions and surrounding parenchyma, to demonstrate vascular anatomy and vessel patency, and to characterise lesions. Contrast administration and the timing of scanning must be carefully planned to optimise differences in enhancement patterns between lesions and normal tissues and, more specifically, in urological imaging to provide optimal imaging of the renal cortex, medulla, or collecting system depending on the clinical indication.

Radiation Dose

The technological advances and increased utilisation of CT carry the price of increased radiation exposure to each patient imaged. Radiation exposure with CT is approximately 3.5–4.5 mSv per scan depending on the machine used, the BMI of the patient, and the use of contrast material. These considerations mandate a responsibility to the radiologist and referring clinician to limit CT to definite indications, especially in children who are at greatest risk from radiation.

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Chapter 12
How to Do a CT Urogram (CTU)

Paul M. Taylor

Introduction

The development of multi-slice CT systems has allowed the introduction of CT urography (CTU) as a routine urological diagnostic procedure. Compared with IVU and ultrasound, it offers increased sensitivity and specificity in the identification and diagnosis of renal, ureteric and intravesical lesions. Additionally, it allows the diagnosis of other abdominal conditions that may mimic urinary disease. The principle disadvantage of CTU is the radiation burden it imposes compared to the IVU. The typical radiation dose for a split-bolus CTU is approximately 20 mSv. This is equivalent to 9 years of average natural background radiation in the UK and almost 20 times the typical radiation dose from an IVU.

CTU is more expensive than IVU or ultrasound.

The availability of CTU as a diagnostic procedure is relatively new, and the technique is still being refined with several different protocols being described.

Patient Preparation

No specific preparation is required although the same precautions with respect to intravenous contrast should be applied as for IVU. The presence of surgical clips, metal implants or barium from previous studies can degrade the examination, and a CTU should not be performed for 7–10 days after a barium examination.

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Pre-contrast Scan

The patient is scanned from the upper poles of the kidneys to the symphysis pubis.

Post-contrast Scans

Maximal enhancement of the abdominal and renal vessels (vascular phase), the renal cortex (nephrogenic phase) and the pelvicalyceal systems, ureters and bladder (pyelographic phase) occurs at different times following intravenous contrast administration. For optimum examination of the urinary tract, images should be obtained during the different phases of contrast enhancement (Fig. 12.1).

It is possible to achieve this by a single injection of contrast and performing three post-contrast scans. The radiation dose of such a technique is, however, unacceptably high for routine practice, and most centers use the alternative split bolus technique where an initial bolus of contrast (50–75 mL) is administered and a second bolus (50–75 mL) is administered 5–7 min later. The patient is then scanned after a further 60–90 s. When this single post-contrast scan is obtained, the majority of the initial bolus is in the pyelographic phase with a proportion in the nephrogenic phase, and the second bolus is in the vascular phase; the maximal anatomical detail of the kidney and its collecting system can, thereby, be obtained.

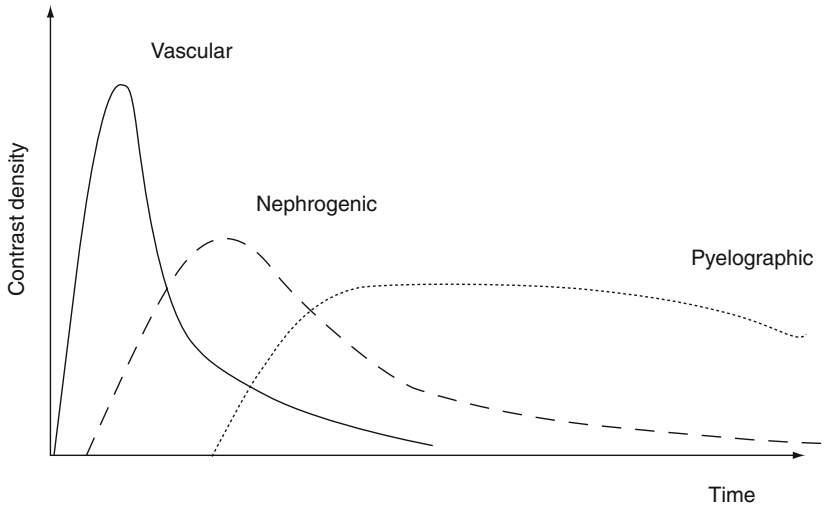

Fig. 12.1 Contrast density dependent upon distribution in the renal artery, renal parenchyma and collecting system following a single intravenous bolus injection

Maximisation of Anatomical Detail

To maximally distend the calyces and ureters during the examination, intravenous furosemide is administered prior to the examination. This produces a brisk diuresis which reduces the density of the contrast in the pyelographic phase and prevents "streak" artefact which can arise if the contrast is too dense. An alternative is to give an oral water load (500–1,000 cc) 20–30 min prior to the examination or intravenous 0.9% saline (500 cc) prior to the CTU, but these techniques are less satisfactory.

Variation of CTU Protocols

Several variations on the basic technique have been described including:

- Applying compression bands to improve calyceal distension
- Limiting the pre-contrast examination to the kidneys to reduce radiation dose to the lower abdomen and pelvis
- Performing the examination with the patient lying prone to improve distal ureteric opacification
- The use of dual energy CT to produce "virtual" unenhanced images

Presentation of the Images

The hallmark of multi-slice CT is its ability to produce isotropic volume elements (voxels). These are of equal dimensions in the axial, sagittal and coronal planes and can therefore be reconstructed in any orthogonal, or oblique, plane. Images may be displayed in the conventional trans-axial format (Fig. 12.2), as surface-rendered 3D

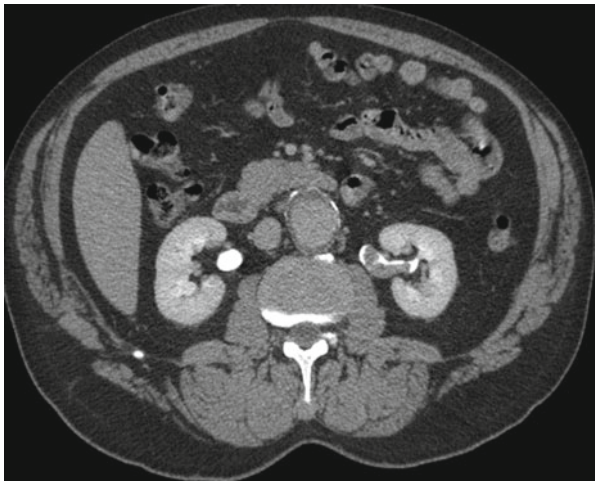

Fig. 12.2 Conventional trans-axial image of a left renal-pelvic TCC

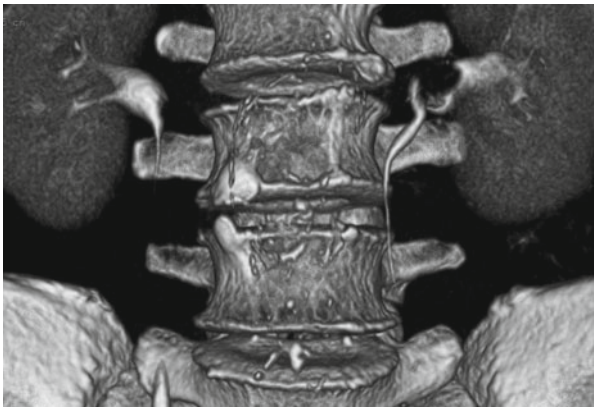

Fig. 12.3 Surface-rendered volume reformat of a left renal-pelvic TCC

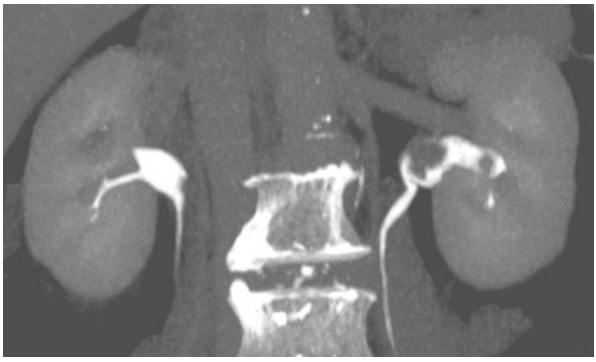

Fig. 12.4 Coronal MIPP image of a left renal-pelvic TCC

reconstructions (Fig. 12.3) or maximum intensity pixel projection (MIPP) images (Fig. 12.4). MIPP images are formed by generating a slab in which only voxels above a designated attenuation are incorporated. The plane and thickness of the slab along with the designated attenuation can be changed by the operator. The images should therefore be interpreted on a workstation which is capable of undertaking such reconstructions.

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Chapter 13
How to Do a CT in a Patient with Presumed Upper Tract Trauma

Jonathan Smith

Patients with significant blunt trauma and macroscopic haematuria should be considered for urgent CT as are those with significant penetrating trauma. Patients with microscopic haematuria following minor blunt trauma are very unlikely to have significant urological injury and are therefore not routinely imaged by CT scanning unless there is another additional indication (such as cardiovascular instability). Ultrasound would be more usual in the "uncomplicated microscopic haematuria." Patients that are difficult to assess clinically such as the intoxicated patient, the mentally ill patient or the obese patient and patients with penetrating injuries may require prompt CT in the absence of macroscopic haematuria (Fig. 13.1).

What Do You Tell the Patient Prior to the Test?

In layman's terms, "We will place you in a large metal doughnut measuring 7 ft in diameter and following the (intravenous) injection of 150 ml of fluid, that may make you feel a little hot and flushed, x-rays will be taken to determine the extent of your injuries. The chance of the CT causing you any harm is very small."

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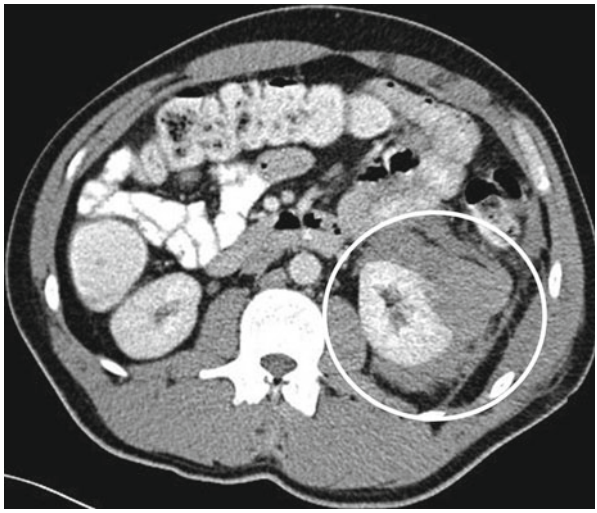


Fig. 13.1 CT portal venous imaging completed to exclude descending colon and kidney injury following a knife injury to the left loin. The patient had no haematuria but was found to have a large perinephric haematoma with capsular and cortical injury with no acute bleeding or urine leak following delayed imaging at 5 min (grade III AAST). The injury was successfully treated conservatively

Are There Any Specific Contraindications to CT?

A patient with a previous serious contrast allergy can have a limited CT scan without IV contrast. CT in pregnancy can be used if ultrasound and/or MRI have been inconclusive and active bleeding or significant injury requiring immediate treatment is clinically suspected. If a patient has renal failure, the radiologist will decide whether to give contrast depending on the clinical need. CT without IV contrast can detect haematoma and organs in pieces but cannot identify active bleeding.

A Typical Blunt Trauma Protocol

Initially, there will be a non-contrast brain and C-spine scan to look for blood and fractures. An injection of 150 mls of iodine containing contrast will then be given intravenously through a peripheral line. An arterial phase image of the chest is acquired to exclude aortic tear or other significant chest injury followed by a portal venous study of the abdomen and pelvis to identify visceral, particularly renal, splenic and hepatic injury (Fig. 13.2). Finally, a delayed study around 5 min is undertaken to identify any urothelial injury.

Modification of the protocol may be required in the presence of severe blunt trauma (including pelvic fractures). An additional arterial phase through the

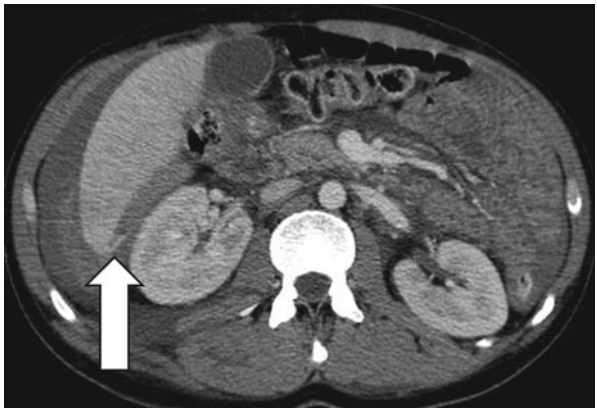


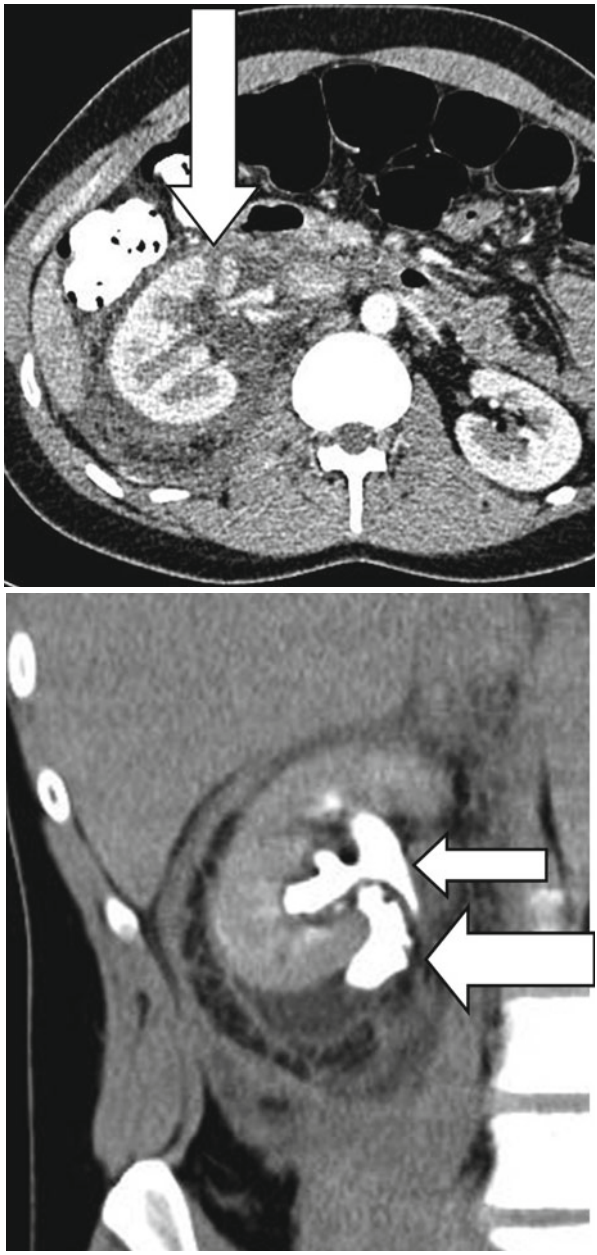
Fig. 13.2 CT portal venous image of the liver and kidneys following blunt trauma. The patient is actively bleeding from segment VI of the liver. Acute vascular contrast extravasation indicates the patient is actively bleeding. Acute vascular contrast extravasation is an indication for immediate coil embolisation by an interventional radiologist or surgery.

abdomen and pelvis may give either the interventional radiologist or trauma surgeon additional information prior to life-saving treatment.

In suspected knife injury to the kidney, the radiologist may decide to modify the protocol in order to maximise the detection of false aneurysms, arterial-venous fistulae and possible colonic injury. If there is clinical concern for bladder injury (normal upper tracts and frank haematuria) or if there are any secondary signs of bladder injury on CT (abnormal bladder wall, presence of blood or significant pelvic fractures), then a CT cystogram needs to be considered to exclude bladder perforation. The preferred CT cystogram technique is instillation of 300 ml of 3% containing contrast under gravity via a urinary catheter since an indirect CT cystogram (using the IV contrast excreted through the kidneys) can miss a bladder injury.

Important CT Findings and Impact on Patient Management

The American Association for the Surgery of Trauma (AAST) classification of kidney injury fails to document the most important CT finding. This is vascular contrast extravasation. This indicates that the patient is actively bleeding, and this finding usually requires urgent treatment either by the vascular radiologist or by the surgeon. Contrast extravasation following urothelial injury seen on the delayed 5-min study may require therapy by ureteric stenting, with or without percutaneous drainage of any urinary collection (Figs. 13.3 and 13.4). Uncommon but severe injuries include renal artery/vein avulsion or occlusion that usually necessitates immediate intervention.



Figs. 13.3 and 13.4 CT in the portal venous phase (Fig. 13.3) demonstrating a fracture through the anterior kidney with blood around the renal pelvis and kidney. Delayed 5-min imaging is therefore required to exclude urothelial injury in this patient injured in an RTA. Delayed CT imaging through the kidney 5 min after the IV injection of contrast (Fig. 13.4) demonstrating urine contrast extravasation secondary to an inferior calyx fracture (grade IV AAST). Note the normal renal pelvis and urine contrast leak (*small and large arrows* respectively). This was treated successfully with retrograde stent placement

Further Reading

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Chapter 14
Principles of Magnetic Resonance Imaging (MRI)

Jonathan Smith

How Does MRI Work?

The patient is placed in a magnetic field up to 30,000 times the strength of the earth's core (1.5 T). The patient is then exposed to a series of pulsed alternating radio waves (Appendix 1). The hydrogen protons within molecules act like little magnets. The protons receive photon energy from the alternating radio waves resulting in a change of the spin state and alignment of the protons. Following the switching off of the pulsed radio waves, the protons relax into their resting spin state emitting photon energy in the form of radio waves that are detected by the coils within the MRI scanner. The strength, character and position in space of these photons are processed, and an image is formed.

Understanding Basic MRI Terminology

T1 and T2 Images

The T1 and T2 relaxation times define the time it takes for protons in different tissues to revert back to their resting states after the initial 90° radio-frequency pulse. Both T1 and T2 times are therefore parameters specific to different tissues, and when we "weight" images to either T1 or T2 sequences, certain tissues will display typical signal intensities. T2 and T1 times define the transverse and longitudinal relaxation times respectively of the proton in tissue. If the reader wishes to understand the physics in more detail, then I would refer them to an excellent article by

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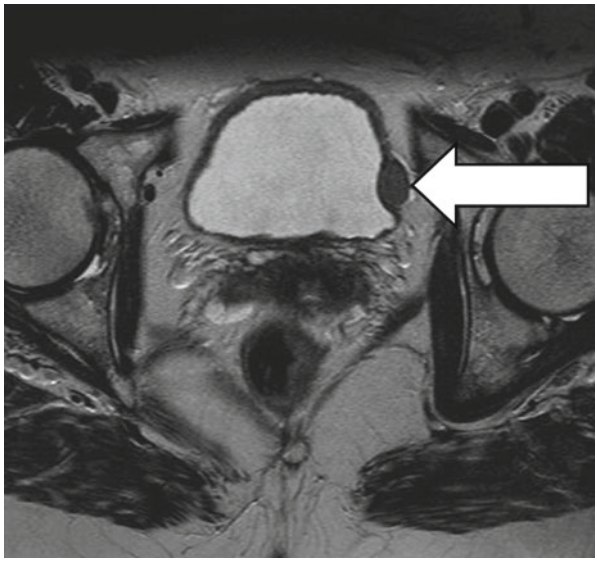


Fig. 14.1 Axial T2-weighted MR image of the bladder. There is a benign left bladder wall leiomyoma. Note the high-signal "bright" urine indicative of a T2 image

R.A. Pooley published in *Radiographics*. A T1 image demonstrates fat as bright signal and fluid as dark signal. The reverse is true for a T2 image. If the type of image being shown is unknown, then one way of determining if it is T1 or T2 is to look at the bladder or CSF. If these structures are "bright," then it is a T2 image (Fig. 14.1).

Contrast-Enhanced Imaging

Intravenous gadolinium is used to increase the contrast between normal and pathological tissue (Fig. 14.2). CT with contrast does exactly the same but uses an iodinated contrast agent that absorbs x-rays, whilst gadolinium speeds up the relaxation time of protons within tissue.

Diffusion-Weighted Image

Diffusion weight imaging exploits the random motion of water molecules. "Free diffusion" or "Brownian motion" applies to water molecules in an unrestricted environment. Here, the water molecules move in random motion. This free movement of water is restricted in the body by boundaries formed by cell membranes and the tissue itself. Tissues typically demonstrating restricted diffusion include cancer, oedema, fibrosis and abscess. Densely cellular prostate cancer displays restricted

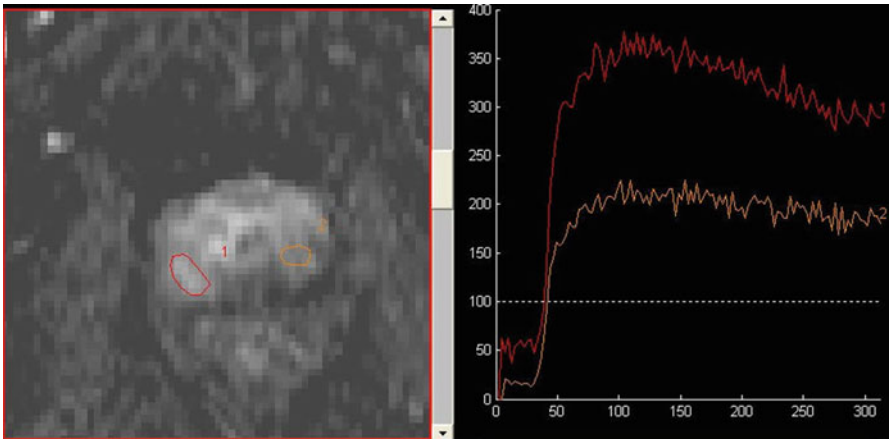


Fig. 14.2 T1 contrast-enhanced axial image through the prostate on the left and time-signal curves on the right. Both contrast enhancement curves within two regions of interest within the peripheral zone are typical of prostate cancer and were proven to be cancer at biopsy

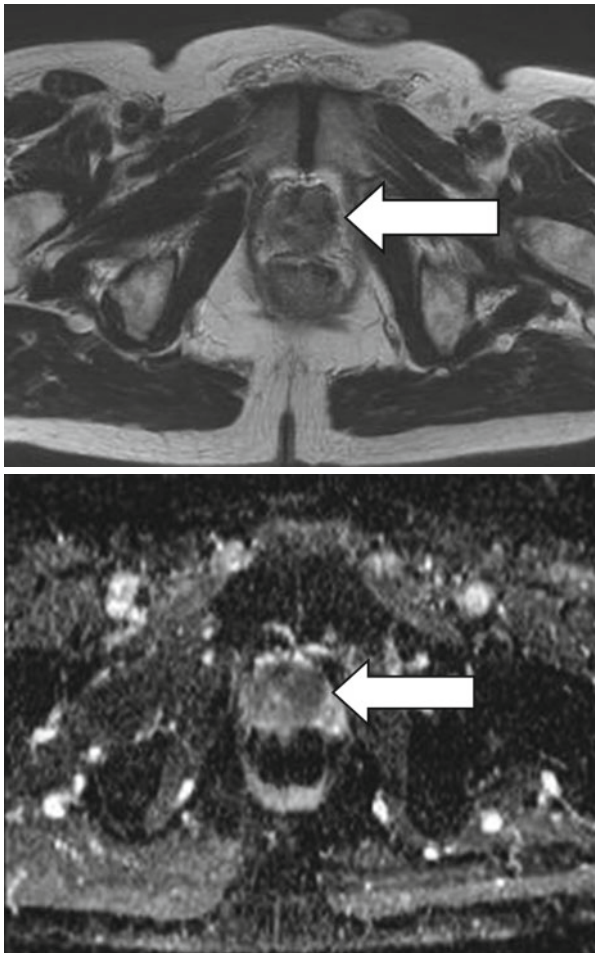
diffusion compared to normal adjacent peripheral zone tissue. Therefore, prostate cancer appears darker than normal peripheral zone tissue on a diffusion type image called an apparent diffusion coefficient image (Figs. 14.3 and 14.4).

Spectroscopy Image

MR spectroscopy provides metabolic information about prostatic tissue by displaying the relative concentrations of chemical compounds within contiguous small volume of interest (voxel) using chemical shift techniques. In prostate cancer, the choline level is typically high, secondary to high phospholipid cell membrane turnover and the citrate-creatine level reduced. The difference in the choline to citrate-creatine ratio within voxels allows us to help differentiate cancer from normal tissue.

Current Role of MRI

MRI is the staging investigation of choice for prostate and penile cancer. CT is used to stage bladder, testicular and renal cancer. MRI is better at T-staging bladder cancer and is therefore used in our institution in problem solving for example when there is concern for bladder cancer extension into adjacent tissues. Both MRI and CT achieve similar accuracies in nodal detection. CT rather than MRI is the technique of choice in detecting lung metastases as it can be acquired quickly during a



Figs. 14.3 and 14.4 Axial T2 image (Fig. 14.3) through the prostate demonstrating left side prostate cancer extending through the capsule plus displacing and encasing the prostatic urethra. Diffusion weight imaging (Fig. 14.4) through the prostate demonstrating left side prostate cancer extending through the capsule plus displacing and encasing the prostatic urethra. This additional sequence is quick and easy to obtain and can help in cancer detection and T-staging

single patient breath hold and demonstrates fine spatial resolution. CT urography is the technique of choice in detecting upper tract tumour. MR urography is very useful in the acutely obstructed patient with acute renal failure as the point and cause of obstruction can be identified without the need for IV contrast.

Evolving Role of MRI

MRI to Monitor Therapy

Ongoing studies are being evaluated to see whether changes in enhancement, diffusion or spectroscopy can be used to determine the success or failure of cancer therapy.

MRI to Guide Biopsy

A few selected centres advocate MR-guided biopsies in specific instances to try and diagnose or exclude prostate cancer. MR-guided biopsies are highly impractical, costly, time consuming and uncomfortable for the patient, and most prostate problem-solving biopsies can be completed by an experienced radiologist using transrectal ultrasound with prior knowledge of the MRI.

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Chapter 15
How to Do an MRI of the Pelvis

Jonathan Smith

Common indications for pelvic MRI include the staging of prostate cancer (Fig. 15.1a, b), penile cancer (Fig. 15.2a, b), and problem solving in bladder cancer, specifically T-staging (Figs. 15.3 and 15.4). MRI is also used for non-urological cancer staging (e.g., carcinoma of rectum, anus, cervix, and endometrium). Finally, it is used in the assessment of benign pelvic disease including anorectal fistula (e.g., Crohn's disease), the characterisation of indeterminate ovarian lesions and the assessment of small-bowel disease including Crohn's disease.

Contrast Agents

A lot of information can be gained from images acquired without IV contrast. The radiologist will decide when and which contrast agent is required depending on the clinical question being asked. Many contrast agents are contraindicated in severe renal failure as some agents have induced nephrogenic systemic sclerosis and death.

Metal and Other Objects in or Attached to the Patient

The strong magnetic fields around an MRI scanner ensure that some special precautions are necessary. Prior to an MRI, every patient will answer a detailed checklist to ensure that they are safe to have an MRI. Absolute contraindications include

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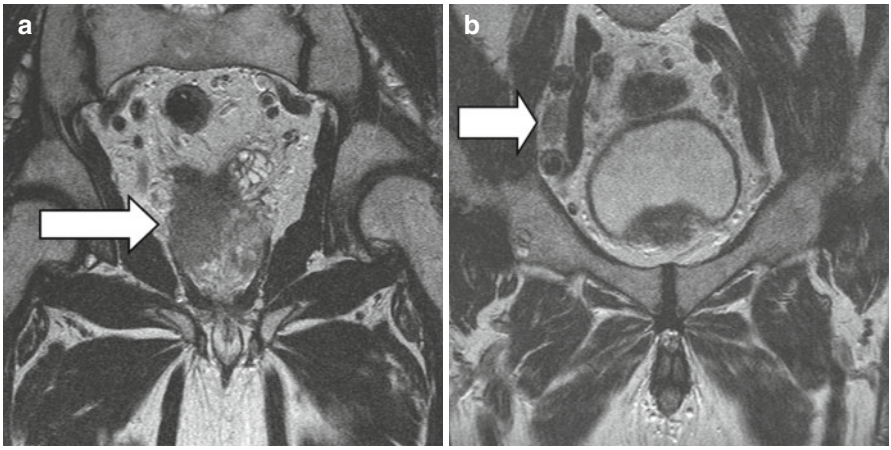

Fig. 15.1 (**a**, **b**) Coronal T2 MRI (**a**) demonstrating large volume right-sided prostate cancer extending into the right seminal vesicle and through the capsule in keeping with T3a and T3b disease. Coronal T2 MRI image (**b**) through the pelvis demonstrating pathologically enlarged right external iliac lymph node from prostate cancer

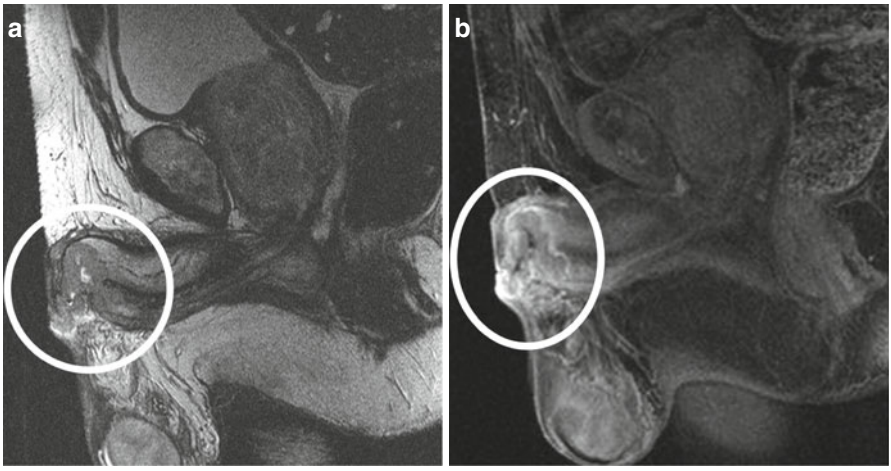

Fig. 15.2 (**a**, **b**) Sagittal T2 MRI image (**a**) demonstrating a squamous cell carcinoma of the glans penis extending into the urethra indicative of T3 disease. Note the high-signal or "bright" urine within the bladder (T2 image) and BPH. Sagittal T1 MRI image post-IV contrast (**b**) demonstrating the T3 glans tumour. The administration of IV contrast (gadolinium) increases the contrast between normal adjacent tissue and abnormal enhancing "bright" tumour

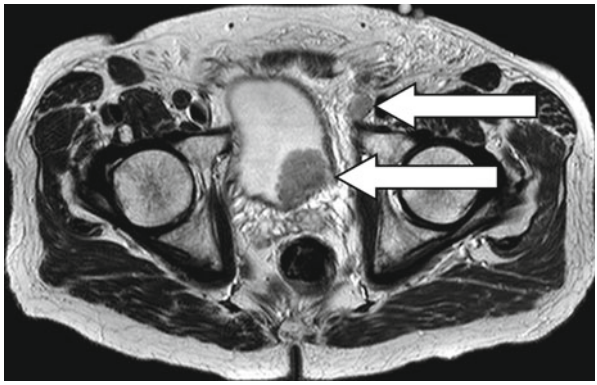

Fig. 15.3 Axial T2 MRI demonstrating a left bladder tumour with pathologically enlarged left groin lymph nodes. Note the high-signal or "bright" urine within the bladder indicative of a T2 sequence. MRI is more accurate than CT in T-staging tumours because of better contrast resolution

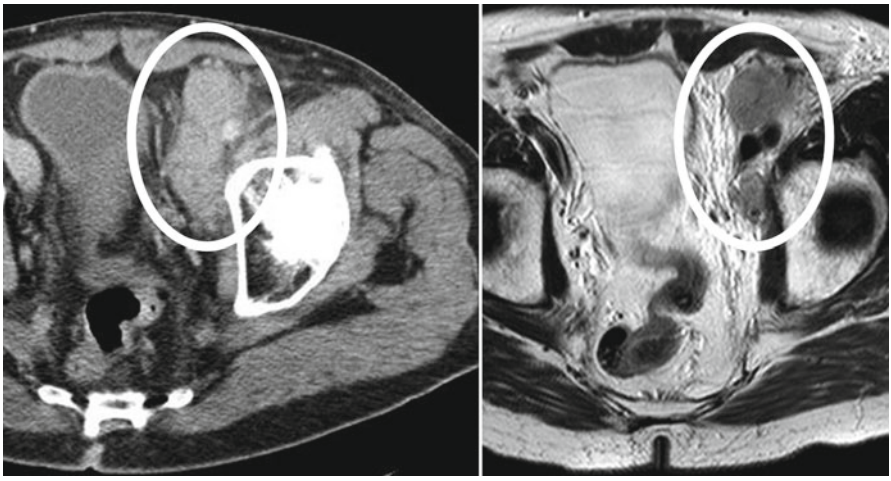

Fig. 15.4 Axial CT and T2 MRI image at the same level demonstrating equal conspicuity of left pelvic nodal disease from bladder cancer. MRI is better at T-staging than CT, but both have similar accuracies in nodal detection

metallic foreign bodies, e.g., metal in eyes from welding, cardiac pacemakers, cardiac devices, and ferrous containing aneurysm coils.

All jewellery, wallets, coins, watches, and personal belongings will be removed, and the patient's clothing is exchanged for a surgical gown. Special MRI compatible equipment including trolleys, oxygen containers, and patient monitors must be used as standard equipment is often dangerous to take into the scanner.

Patient Information

MRI is very safe, and the chance of any significant contrast reaction is around 0.01%. MRI is contraindicated in the first trimester of pregnancy during organogenesis. Most MRI studies take around 30–45 min to complete. The biggest patient complaints are the noise due to radio wave generation and claustrophobia. Patients will be given earphones to use and can listen to music or the radio while the scan in being completed.

Give the Radiologist Accurate and Relevant Information

An example of a good request card would include the following information:

Clinical	"T2 prostate cancer clinically. For radical therapy"
Pathological	"Gleason 3+4. 3 left cores involved. 6 mm length"
Biochemical	"Normal renal function"
Tumour markers	"PSA = 12 ng/L"

This informs the radiologist that the patient has intermediate prostate cancer that is being considered for radical therapy. The poorer the clinical request, the poorer the radiology report will be. Two questions that should be communicated clearly on the card (that are relevant to any radiology requests, including non-MRI studies) are what the clinical diagnosis is and what clinical question needs answering.

Technical Considerations

The radiologist will protocol an MRI in order to answer the question/s at hand. Protocols can vary, and the author would point the reader in the direction of standard textbooks or more modern published articles if more detailed information was required by the reader.

Get the Radiologist to Report the Study

The radiologist will incorporate all the information given, review the MRI plus any additional imaging such as CT, US, plain film, PET-CT, or nuclear studies, and give a radiological opinion.

Further Reading

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Chapter 16
Magnetic Resonance Angiography (MRA)

Kieran O'Flynn

Magnetic resonance angiography (MRA) is a group of techniques based on magnetic resonance imaging to demonstrate blood vessels, looking for evidence of stenosis, occlusion, or aneurysm formation. Demonstration of abnormalities in the vena cava in patients with large renal cancers is a particular urological use. The principle of MRA is to acquire images depicting areas where the signal returned from flowing nuclei is high and the signal from stationary nuclei is low. In this way, the contrast between vessels and background tissue is obtained. The two principle types of MRA are time-of-flight and phase-contrast angiography.

Time-of-Flight (TOF) or Inflow Angiography

This technique uses a short echo time and flow compensation to make flowing blood much brighter than stationary tissue. As flowing blood enters the area being imaged, it has seen a limited number of excitation pulses, so it is not saturated; this gives it a much higher signal than the saturated stationary tissue (Fig. 16.1). As this method is dependent on flowing blood, areas with slow flow, such as large aneurysms, or flow that is in plane of the image may not be well visualised. This technique is most commonly used to look at pathology in the head and neck and gives detailed high-resolution images in that region.

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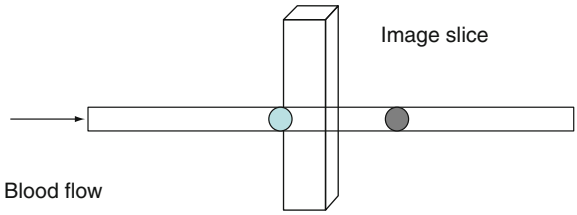

Fig. 16.1 Time-of-flight, or inflow, effect. The blood vessel is shown crossing the image slice. When the sequence is repeated, the previously excited blood (*grey*) has moved on, and the bolus within the slice (*blue*) has fully relaxed magnetisation

Phase-Contrast Magnetic Resonance Angiography (PC-MRA)

Phase-contrast MRA relies on detecting changes in the phase of blood's transverse magnetization as it moves along a magnetic field gradient. In phase-contrast NMR, the phase of the MRI signal is manipulated by special bipolar gradients (varying magnetic fields). These are preset to a maximum expected flow velocity. An image acquisition that is the reverse of the bipolar gradient is then acquired, and the difference of the two images is calculated. Static tissues (muscle, bone, etc.) will subtract out; however, moving tissues such as blood will acquire a different phase since it moves constantly through the gradient, thus also giving its speed of the flow. In a phase-contrast pulse sequence, additional bipolar gradients are used to create a known linear relationship between blood velocity and the phase of the MR signal.

Phase-contrast MRA is directionally sensitive, which means only blood moving in the same direction as a bipolar flow-encoding gradient will result in a phase shift. The MR radiographer must match the flow-encoding axis to the direction of blood flow. Since phase-contrast can only acquire flow in one direction at a time, three separate image acquisitions in all three directions must be computed to give the complete image of flow. Despite the slowness of this method, the strength of the technique is that in addition to imaging the flowing blood, it enables quantitative measurements of blood flow to occur.

Contrast-Enhanced Magnetic Resonance Angiography (CE-MRA)

Contrast-enhanced MRA exploits the relaxivity properties of contrast agents to visualise vascular structures. Gadolinium-based contrast agents have been used with both time-of-flight and phase-contrast MRA to improve the quality of the images produced. Gadolinium is a rare earth (Appendix 2) that binds to certain elements in the body such as membranes and the osseous matrix. It cannot be excreted unless attached to a chelate. The most common chelate in use is diethylene-triamine-penta-acetic acid (DTPA), which binds to the nine binding sites in the gadolinium ion, leaving the last free one to enable the close approach to water molecules. The primary difficulty with small molecular weight gadolinium chelates, e.g., Gd-DPTA, is that they are

very quickly cleared from the vascular spaces. ProHance™ is a gadolinium containing paramagnetic agent, which when exposed to an external magnetic field induces a large local magnetic field in the surrounding area. This local magnetism disrupts water protons in the vicinity, resulting in a change in proton density and spin characteristics, which can be detected by the imaging device.

Gadolinium-containing contrast medium is injected into a vein, and images are acquired during the first pass of the agent through the arteries or, later, through the veins. Provided that the timing of imaging against injection is correct, very high-quality images should be obtained.

The thrust of research in MR angiography has been towards the development of large molecular weight paramagnetic agents, so-called blood-pool agents, which would have the potential advantage to remain in the circulation up to an hour after injection. Examples include gadobenate dimeglumine (MultiHance™) and gadofosveset (Vasovist™), agents that weakly and irreversibly binds to human serum albumin. The European Medicines Agency (July 2010) advises that gadolinium contrast agents remain suitable diagnostic agents for use in patients undergoing MRI, but doctors should be aware of the associated risk of nephrogenic systemic fibrosis in patients with kidney problems and other high-risk groups.

Further Reading

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Chapter 17
Vascular Embolisation Techniques in Urology

Alistair Cowie

Embolisation is a minimally invasive, catheter-directed intervention to partially or completely occlude the blood flow in a target vessel/s without causing ischaemia or necrosis to non-target tissue. It is usually performed to treat or prevent haemorrhage or to occlude vascular malformations. Thrombosis is achieved by delivering embolic agents to the selected target site in a controlled procedure under continuous screening guidance. This is usually performed in the direction of blood flow unless anastomotic vessels require occlusion. Given the wide range of target vessel size and anatomy, the choice of agent and technique is tailored on a case by case basis.

Successful embolisation requires a knowledge and assessment of the relevant vascular anatomy, including the presence of collateral and anastomotic vessels. This may be assessed by a combination of noninvasive vascular imaging such as multislice CT angiography and intra-procedural high-frame-rate arteriography. A "road map" facility that leaves a background image of the vessels on the intensifier screen is often used to guide the wire/catheter combination to the target vessel.

Equipment

It is essential that a stable catheter position is obtained in the target vessel. Selective catheterisation is facilitated by the choice of a curved catheter that optimally matches the vascular anatomy. 4–5 Fr (2–2 1/3 mm diameter) catheters can be used for most cases; however, coaxial microcatheter systems (2–3 Fr) enable catheterisation of

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more tortuous or smaller vessels. Most selective cases will require the use of curved hydrophilic, steerable guidewires to engage the target vessel. The catheters have a single end hole to prevent coils becoming stuck during insertion and to prevent the inadvertent reflux of particles or liquids into non-target areas.

Embolic Agents

Table 17.1 documents the properties and applications of the most commonly used agents used for embolisation.

The choice of agent considers the following factors:

- The need for temporary or permanent occlusion.
- The requirement for rapid occlusion.
- Does the case require a precise occlusion of a single target vessel, e.g., post-biopsy bleeding, varicocoele?
- Is a more diffuse distal arteriole/capillary bed embolisation required, e.g., vascular tumours?
- The presence and size of arteriovenous shunts and risk of non-target embolisation.
- The available expertise.

Gelfoam™ (composed of water-insoluble gelatin) is the only temporary agent and lasts between 1 and 6 weeks. It is used to treat acute bleeding allowing the damaged endothelium to repair. It is used as an adjunct to coils, the latter being the most precise, rapid agent.

Coils made from platinum or stainless steel come in a variety of diameters (2–15 mm), shapes (circular, helical), and lengths (2–30 cm), but are packaged straightened to enable easy introduction into the catheter. They revert to their preformed configuration after release from the end of the catheter. Coil diameter is chosen to be just greater than the vessel to be occluded. If the coils are too large, they might occlude vital proximal collateral vessels, too small, and there is a risk of embolisation to non-target areas.

Liquids and small particles (<200 μm) penetrate into the smaller capillaries and have a higher risk of tissue infarction. Examples include polyvinyl alcohol (PVA) and acrylic gelatin microspheres. PVA particles do not occlude the vessels but cause an inflammatory reaction. *Post-embolisation syndrome* can occur if a large volume of tissue has been devascularised. This is characterised by severe pain, fever and viral-type symptoms. Symptoms can last up to 72 h and mimic infection or abscess formation. When ethanol liquid is used, some radiologists use an occlusion balloon to prevent reflux into the aorta and nontarget tissue infarction, enabling the ethanol to denature proteins of the endothelium and activate the coagulation system.

Table 17.1 Properties and applications of commonly used embolic agents

Agent	Description	Target	Delivery technique	Applications
Coils	Platinum/stainless steel wire lengths	Usually a focal vessel	Pushed into position by guidewires	Acute focal renal/pelvic bleeding
	Attached thrombogenic fibers	Large to small arteries and veins	The most precise agent	Varicocoeles
Polyvinyl alcohol (PVA)	Particles	Usually a distal target area	Injected, carried by arterial flow	Vascular tumours – RCC/AML
	Size range 50–1,000 μm	Medium to small vessels including capillaries	Suspended in dilute contrast to make it radio-opaque	
95% Ethanol	Liquid	All vessels and cells it comes into contact with	Injected	Vascular tumours – RCC/AML
	Toxic radiolucent sclerosant		The volume to be used is determined by test injections of contrast	Vascular malformations
	Causes cell death		Occlusion balloon	
Gelfoam sponge	Haemostatic sponge	Usually focal vessel	Injected	Acute focal renal/pelvic bleeding
	Cut to size 1–2 mm squares	Medium to small arteries and veins	Soaked in dilute contrast to make it radio-opaque	

The Use of Embolisation in Clinical Urology

Focal Renal Haemorrhage

Iatrogenic causes are the most common and include biopsy, nephrostomy insertion and PCNL. The kidney is supplied by end arteries with no collateral supply; therefore tissue loss can be limited by embolising the target vessel with coils or Gelfoam pledgets as peripherally as possible. This is particularly important if there is a single kidney or poor renal function.

Post-partial nephrectomy bleeding can be a challenge due to the distorted anatomy and presence of arteriovenous shunts – the latter can cause antegrade non-target embolisation, e.g., pulmonary circulation and paradoxical emboli.

Devascularisation of Renal Cell Carcinomata

This is usually performed within 24 h of surgery and requires embolisation of the distal vascular bed. The presence and size of AV shunts determine whether ethanol can be used and which size of particle is indicated (usually 200–500 μm).

Varicocoele Embolisation

Selective internal spermatic venography is performed to confirm the presence of incompetent valves and reflux and to assess for collaterals which are a common cause of recurrence. The catheter tip is advanced to just above the level of the inguinal ligament and a series of coils deployed from this point up to the level of L3. Coils above this level are at greater risk of inadvertent embolisation to the IVC and pulmonary circulation. Weak sclerosants can be used but have a higher risk of testicular ischaemia and thrombosis of the pampiniform plexus.

Post-surgical Pelvic Bleeding

There is an increasing role in the management of arterial haemorrhage following pelvic surgery. Given the well-developed collateral and anastomotic supplies in the pelvis, bilateral internal iliac imaging is usually required unless an obvious focal bleeding point is seen on CT. If haemorrhage is limited to a single vessel, coils or Gelfoam pledgets are the treatment of choice; selective particle embolisation is used for more diffuse pathology such as bleeding bladder neoplasms. On occasion, selective bilateral internal iliac branch embolisation may be required to control

bleeding. There is an increased risk of non-target necrosis in the older age group, arteriopaths and in patients who have undergone radiotherapy due to collateral disruption.

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Part II
Imaging: Nuclear Medicine

Chapter 18
Radionuclides and Their Uses in Urology

Richard Lawson

Nuclear medicine utilises radioactive tracers to assess organ function. These tracers are called radiopharmaceuticals, and many different radiopharmaceuticals are used depending on the organ or system to be studied. After administration to the patient, usually by intravenous injection, the amount of radiopharmaceutical appearing in different parts of the body is monitored by detecting the radioactivity. This can be done with nonimaging tests (e.g., GFR), involving only blood samples, or by taking images with a gamma camera (e.g., DMSA scan). Nuclear medicine images have poor spatial resolution demonstrating physiology rather than anatomy and so are complementary to other imaging modalities.

Radiopharmaceuticals

The radiopharmaceutical has two parts: a pharmaceutical and a radionuclide label. An ideal radiopharmaceutical should have the properties shown in Box 18.1.

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Box 18.1: The Characteristics of an Ideal Radiopharmaceutical

- The label should remain bound to the pharmaceutical in vivo.
- The pharmaceutical should concentrate only in the organ under investigation.
- Background remaining in rest of the body should be low.
- It should not be toxic to the patient and not interfere with the physiological process under investigation.
- The radionuclide should emit only gamma rays (no alpha or beta emissions because these are too easily absorbed by the body).
- For imaging purposes, the gamma rays emitted should have a suitable energy: more than 100 keV so that they can escape from the patient and less than about 300 keV so that they can be stopped by the gamma camera detector.
- The radionuclide should have a suitable half-life (the time it takes for half the radioactivity to decay away). In most applications, a half-life of a few hours gives enough time to prepare the radiopharmaceutical and complete the test.
- It should be cheap and readily available.

Radionuclides

A radionuclide is a radioactive form of an atom (Appendix 2). In the majority of nuclear medicine imaging studies, the preferred radionuclide is ^{99m}Tc (Technetium-99m). Tc is the chemical element, "99" is its mass number, and the "m" means that it is a metastable (excited) state. ^{99m}Tc has the properties shown in Box 18.2.

Box 18.2: The Properties of Technetium-99m

- It decays by emission of gamma rays only (no alpha or beta emission).
- The gamma ray energy is 140 keV (which is ideal).
- It has a half-life of 6 h (which is very convenient).
- It is readily available from a generator which can provide a daily supply of ^{99m}Tc from the decay of a longer lived parent (^{99}Mo).

Nuclear medicine departments will obtain the radiopharmaceuticals that they need for their investigations from a nearby radiopharmacy. In the radiopharmacy, ^{99m}Tc is extracted from a ^{99}Mo generator by a process called elution. The eluate is added to a sterile vial containing the freeze-dried pharmaceutical which must then be used within a few hours.

Because radionuclides, such as 99mTc, are very easily detected, it is possible to administer very small quantities of pharmaceutical (micrograms or less) so that they do not disturb the normal functions of the organ or system under investigation. This is known as the tracer principle.

Table 18.1 The radiation dose received from nuclear medicine studies commonly carried out on urological patients

Procedure	Radiopharmaceutical	Typical administered activity (MBq)	Radiation dose to the patient (mSv)
Bone scan	^{99m}Tc MDP	600	3.0
Renogram	^{99m}Tc DTPA	200	1.3
Renogram	^{99m}Tc MAG3	100	0.7
DMSA scan	^{99m}Tc DTPA	80	0.7
GFR determination	^{99m}Tc DTPA	10	0.06
GFR determination	^{51}Cr EDTA	3	0.006

Radionuclide Dosimetry

The radiation dose to the patient can be kept low by using suitable radionuclides, since most of the gamma rays escape from the patient (because of the suitable energy), and the radioactivity does not linger unnecessarily long (because of the short half-life).

The radiation dose obviously depends directly on the amount of radionuclide administered. This is measured in units of MBq (megabecquerels) – 1 MBq is a million atoms disintegrating every second. The radiation doses from some common nuclear medicine procedures used in urology are shown in Table 18.1.

For comparison, the radiation dose in the UK from natural background averages 2.2 mSv per year. It can be seen that the radiation dose from most nuclear medicine studies is less than 1 year's natural background and covers the same range as many simple x-ray examinations.

Radiation Protection in Nuclear Medicine

Any risk must be justified by a benefit to the patient and so, just as with x-ray studies, all nuclear medicine studies in the UK come under the Ionising Radiation (Medical Exposure) Regulations (IR(ME)R). This means that the clinical referrer must provide the necessary clinical information for the practitioner to justify carrying out the procedure. In nuclear medicine, the practitioner is always a consultant who holds a certificate from the Administration of Radioactive Substances Advisory Committee (ARSAC) authorising them to carry out a specific procedure, in a specified premises. Research studies require a separate ARSAC certificate for each project.

Although patients will themselves remain radioactive for a few hours after these studies, they do not constitute a significant hazard and will not need any special

nursing precautions. Although much of the radiopharmaceutical is excreted in the urine, normal hygiene precautions (such as plastic apron and gloves) are sufficient to avoid accidental ingestion of radioactivity by nursing staff. However, it would be sensible not to do a cystoscopy on the same day as a bone scan or a renogram, if this can be avoided.

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Chapter 19
Counting and Imaging in Nuclear Medicine

Richard Lawson

Nuclear medicine studies require the detection of gamma-emitting radiopharmaceuticals within the patient's body.

Sample Counting and External Counting

The simplest sort of test just produces blood samples which need to be assayed for radioactivity (e.g., GFR). This can easily be done by putting a sample into a well-type counter where it is surrounded by a scintillation crystal. This crystal emits a flash of light when it is hit by a gamma ray, and the light is detected by a photomultiplier tube, which converts it into an electronic pulse, and the number of pulses is then counted. Because this type of counter is very efficient at detecting gamma rays, it is possible to measure extremely small quantities of radioactivity in this way. This is why very small administered activities can be used in GFR studies, resulting in a very small radiation dose to the patient.

Studies like the renogram require monitoring of the amount of radiopharmaceutical in the kidneys with time. In the past, this was done by placing scintillation counters against the patient's back, over each kidney. Because the counter is further away from the radiation source, this type of "external" counting is not as efficient as the well counter, and so it requires higher administered radionuclide activities. The main problem with external counting is that it is not possible to accurately separate activity in the kidney from nearby nonrenal activity emission.

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The Gamma Camera and Collimation

The gamma camera is a device that not only detects gamma rays (Appendix 1) emerging from the patient but can also determine their position. It can, therefore, produce an image of the distribution of radiopharmaceutical within the patient. The gamma camera contains a single large scintillation crystal (typically 500 × 350 mm) and an array of many photomultiplier tubes. When a gamma ray hits the crystal, scintillation light is emitted and collected by all the photomultipliers. Signals from the photomultipliers are then fed into a computer which calculates the interaction position from the distribution of light collected.

Gamma rays are, however, emitted from the patient in all directions, and so in order to produce an image, it is necessary to fit a collimator in front of the scintillation crystal. A collimator is, essentially, a lead plate with tens of thousands of parallel holes in it, each about 2 mm in diameter. The holes restrict the accepted gamma rays to just those that are travelling close to perpendicular to the face of the collimator.

The spatial resolution of the gamma camera, a measure of its ability to see fine detail, is determined by the size of the holes in the collimator, which allows a small range of gamma ray directions to be accepted in practice. This means that resolution gets worse with distance so that the image becomes more blurred the further away the object is from the gamma camera.

Collimator hole size also affects the sensitivity of the gamma camera. Small holes give good resolution but poor sensitivity, whilst large holes give poor resolution but better sensitivity. Thus, gamma cameras are provided with a range of different collimators for different purposes (Fig. 19.1). At a distance of 10 cm, the resolution might be about 7 mm when using a low-energy high-resolution (LEHR) collimator, which has small holes, or 9 mm with a low-energy general purpose (LEGP) collimator (medium holes), or 13 mm with a low-energy high-sensitivity (LEHS) collimator (larger holes). The sensitivity of the LEGP collimator would be about twice that of the LEHR, and the LEHS four times the LEHR. So choice of collimator is always a balance of resolution against sensitivity.

Although the collimator is an essential part of forming the image, it engenders inefficiency; it blocks about 99.99% of emitted gamma rays because they are not travelling in the right direction. Consequently, gamma camera imaging studies require larger administered activities, and longer imaging times, in order to obtain sufficient counts for analysis. Even with higher doses and longer counting periods, nuclear medicine images will have only a small number of counts in each image pixel. This means that the images tend to be "noisy."

For a static study like a DMSA kidney scan, the gamma camera will use an LEHR collimator in order to obtain best possible resolution but will have to acquire each image for about 5 min in order to obtain sufficient counts to see real activity above the noise. Modern gamma cameras often have two detectors so that two views can be obtained simultaneously to reduce the scanning time.

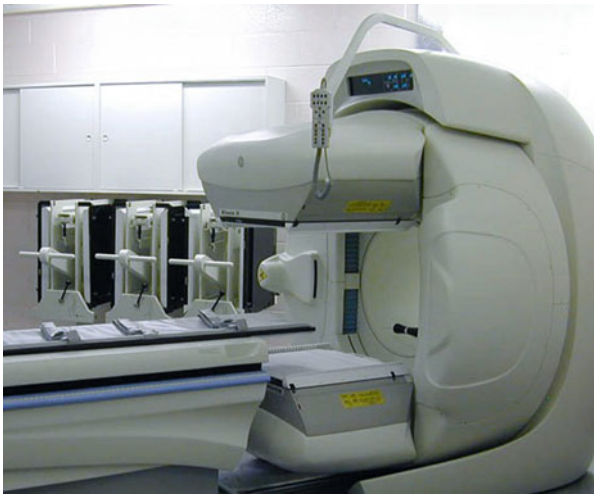

Fig. 19.1 A gamma camera with two detectors, one above the patient couch and the other below it. A selection of collimators is stored on the carts in the background

The gamma camera can also be used for dynamic studies, like the renogram, where a series of images are acquired showing how the distribution of activity changes with time.

Data Analysis

Gamma cameras usually have dedicated nuclear medicine computer processing systems associated with them. These are particularly useful for analysing data from dynamic studies like the renogram. The operator can draw regions of interest around each kidney on the computer images and generate curves showing how the activity changes with time. This overcomes the problems of external counting where the kidney location could not be seen and also makes it possible to exclude nonrenal background.

Raw gamma camera images usually need some processing before they are interpreted. Therefore, the nuclear medicine computer is used to analyse the data and display a summary of the results. Then, a screen capture of the results can be sent to the hospital Picture Archiving and Communication System (PACS).

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Chapter 20
Principles of Positron Emission Tomography (PET) Scanning

Heather A. Williams

Positron emission tomography (PET) is a form of nuclear medicine imaging which uses positron-emitting radionuclides rather than the gamma-emitting radionuclides used in renography.

PET Radionuclides

There are several radionuclides which are suitable for PET. Many have half-lives of minutes rather than hours and require production using a cyclotron. For such radionuclides, rapid radiochemistry must be followed by imaging using a PET scanner on the same site as the cyclotron. However, centres remote from cyclotrons can be supplied with isotopes (Appendix 2) which have longer half-lives, such as ^{18}F (half-life = 110 min), or can be eluted from a generator, such as ^{82}Rb (half-life = 1.3 min, eluted from an ^{82}Sr generator).

The same rationale in selecting an appropriate radionuclide for nuclear medicine procedures applies to PET radionuclides. However, PET radiochemists have the advantage that there are positron-emitting isotopes of carbon, nitrogen, oxygen, and fluorine which can be directly substituted into molecules that occur naturally in the body (fluorine can replace hydrogen). This produces PET radiotracers that are exact positron-emitting analogues of the molecule that is being imaged, and such a radiotracer can be reliably assumed to behave in exactly the same way.

PET radiotracers can be used to study a wide range of physiological processes. The radiotracer most commonly used in clinical practice is ^{18}F-labelled

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fluorodeoxyglucose (FDG). This is an analogue of glucose, which is trapped within cells following phosphorylation by hexokinase. It is most commonly used in oncology imaging as more glucose is required by anaerobic glycolysis within tumours than aerobic glycolysis in normal tissue, so pronounced FDG uptake is seen in many tumour types, leading to images with good contrast between malignant and benign structures. FDG is also useful in imaging patterns of glucose metabolism in the myocardium and the brain.

^{18}F fluoride is an excellent tracer for detecting bone metastases and is associated with a higher sensitivity to these lesions than ^{99m}Tc phosphates due to improved image quality. However, it is not widely used in the UK because of limited access to PET scanners and the higher radiation dose to the patient from ^{18}F fluoride.

Choline and acetate labelled with either ^{11}C or ^{18}F have been suggested as tracers in the management of prostate cancer. Uptake of these tracers reflects amino acid metabolism rather than glucose metabolism, and they are not excreted in the urine to the same extent. However, their value in patient management is yet to be determined.

The Physics of PET Scanning

When a PET radiotracer is injected into the patient, it will be processed by the body and accumulate within the tissues of interest. When the radionuclide within the radiotracer decays, it emits a positron, which travels a short distance before annihilating with an electron in the surrounding tissue to produce two back-to-back 511 keV gamma photons. If the patient is surrounded by a ring of detectors, these gamma rays should be detected within a small period of time (a few nanoseconds) and can then be said to be "in coincidence" (Fig. 20.1). The positron is assumed to have met the electron somewhere along the "line of response" defined by the coincident gamma rays; millions of these lines of response are recorded in a typical PET scan and then reconstructed to map out the 3D distribution of the positron-emitting radionuclide within the body.

Interpretation of PET Scans

The reconstruction includes accurate corrections for false lines of response collected during the scan and attenuation within the patient, so the pixel values within the final image are proportional to the radioactivity concentration within the corresponding area of the patient's body. If the PET scanner is calibrated, pixel values can be expressed in units of kBq/mL and normalised to injected activity and patient body weight to produce standardised uptake values (SUVs). However, care must be

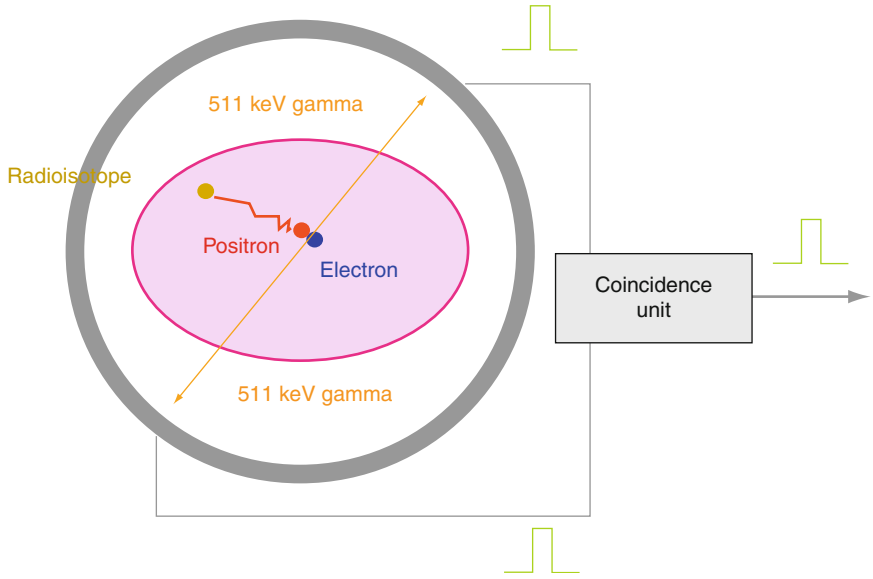

Fig. 20.1 Annihilation and coincidence detection

taken in interpreting SUVs and similar measures from PET scans; such measures are much less accurate for small lesions, particularly those <20 mm in diameter, and are also affected by how the image is acquired, reconstructed, and analysed.

PET Scanners in Clinical Practice

Most modern PET scanners are combined with a CT scanner, allowing the information on tissue function from PET to be overlaid on the structural information from CT. This allows the location of radiotracer uptake patterns to be determined more accurately and related to structural features. A modern PET-CT scanner is shown in Fig. 20.2. The bore of a PET-CT scanner like this is approximately a metre long, longer than a CT scanner but shorter than an MR scanner.

The indications for PET in urology are currently rather limited. There is some evidence to suggest that FDG is useful in assessing urological malignancy, but interpretation is complicated by the urinary excretion of FDG, which can obscure tumour-associated uptake in the kidneys and bladder wall, and structures in close proximity such as the prostate. FDG uptake is also not specific to glucose metabolism within tumours; it is also raised in areas of infection and inflammation, largely due to accumulation of FDG in macrophages and neutrophils.

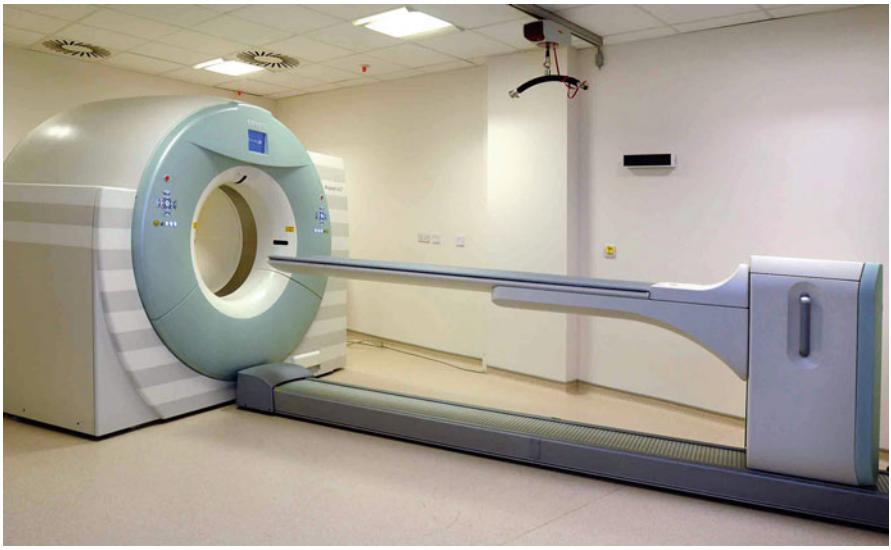

Fig. 20.2 A modern PET-CT scanner

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Chapter 21
How to Do a Renogram

Mary Prescott

The renogram is a dynamic nuclear medicine study used to investigate kidney perfusion, function, and elimination of tracer.

Indications

Isotope renography can be used for the assessment of renal perfusion, relative function, assessment of kidney drainage, and as an indicator of the presence of reflux.

Radiopharmaceuticals

^{99m}Tc DTPA (diethylene-triamine-pentaacetic acid, alternatively known as pentetate). The administered activity can be up to 300 MBq, but 200 MBq is commonly used. DTPA is cleared solely by glomerular filtration, and so kidney uptake is low and blood background remains high. This makes background subtraction more difficult, particularly in children or patients with poor kidney function.

^{99m}Tc MAG3 (mercaptoacetyltriglycine, alternatively known as tiatide). The administered activity can be up to 100 MBq, but 50 MBq is sufficient to give a good renogram. MAG3 is cleared by a combination of glomerular filtration and tubular secretion, so it has greater kidney uptake, leaving less in the blood background. It is therefore the preferred radiopharmaceutical.

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Patient Preparation

The patient must be well hydrated.

Data Acquisition

An LEHS or LEGP collimator is used to give adequate counts because good resolution is not needed. The patient is positioned either seated with their back to a gamma camera (to aid normal gravitational drainage) or supine on the couch with the camera underneath. The radiopharmaceutical is injected, and immediately the gamma camera starts acquiring a dynamic series of images with one frame every 20 s for 30–40 min. If the kidney has not drained by 40 min, and the renogram was acquired supine, the patient is asked to stand up and a final static image is acquired. Then the patient empties their bladder, and a postmicturition image is acquired.

Computer Data Analysis

On the computer images of the dynamic series, regions of interest (ROIs) are drawn around each kidney and one or more suitable background regions (Fig. 21.1). Activity/time curves are created showing how the activity in each region of interest

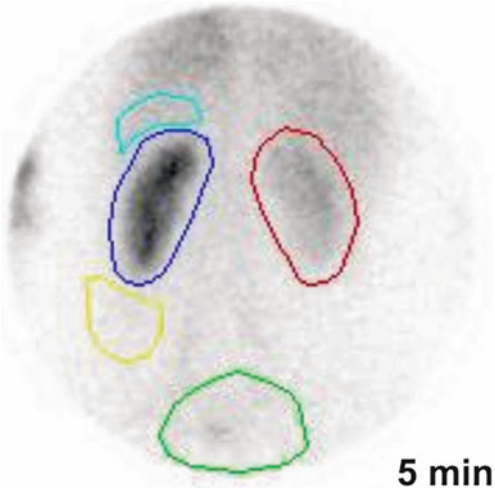

Fig. 21.1 Regions of interest are drawn around each kidney and the bladder, and several areas are also delineated to determine "background" activity

changes with time. The background curve(s) is used to subtract a background contribution from each kidney curve. The resulting curve is the renogram. For consistency of display, it is helpful to scale each kidney curve to percent of administered activity.

The relative function of each kidney is calculated from the uptake phase of the renogram (about 1–3 min). There are several ways of doing this. The Rutland plot (also known as the Patlak plot) is generally regarded as the most accurate.

Interpretation of the Result

The vascular phase, occurring in the first few seconds after radionuclide injection, represents a rapid flow of radiopharmaceutical into the kidney. Most of this is not extracted (particularly with DTPA), so it remains in the blood within the kidney. Therefore, if background subtraction is done correctly, this phase should be removed from the generated renogram curve which should rise smoothly from the origin.

From about 1 min onwards, the renogram curve rises at a rate proportional to kidney function and describes the uptake phase.

At any time after about 3 min, the renogram curve may reach a peak and begin to fall in the elimination phase. It is important to realise that this is actually a balance between uptake and elimination. A rising curve means that uptake exceeds elimination, and a falling curve means that elimination exceeds uptake. A horizontal curve simply means that uptake and elimination are just balanced.

Reflux may be seen as sudden increases in the kidney curve, but patient movement must be excluded as a possible cause.

The effect of gravity and full bladder on kidney emptying can be determined by comparing the final static images with those at the end of the dynamic study.

Figure 21.2 shows a normal renogram for the left kidney (solid blue curve) with normal uptake and normal elimination. The right kidney (red dashed curve) has less uptake (as indicated by its less steep rise) and poor elimination (indicated by its continued rise).

Assessment of Renal Perfusion

If an assessment of renal perfusion is required, then a “first pass” (or first circulation) study may be incorporated into the renogram. The administered activity is increased (to 200 MBq ^{99m}Tc MAG3 or 400 MBq ^{99m}Tc DTPA), and the first minute of the study is acquired at a faster rate of one frame per second. Delays in perfusion to one kidney can be seen by examination of these first pass images. Relative perfusion can be estimated from the unsubtracted kidney curves during the first minute.

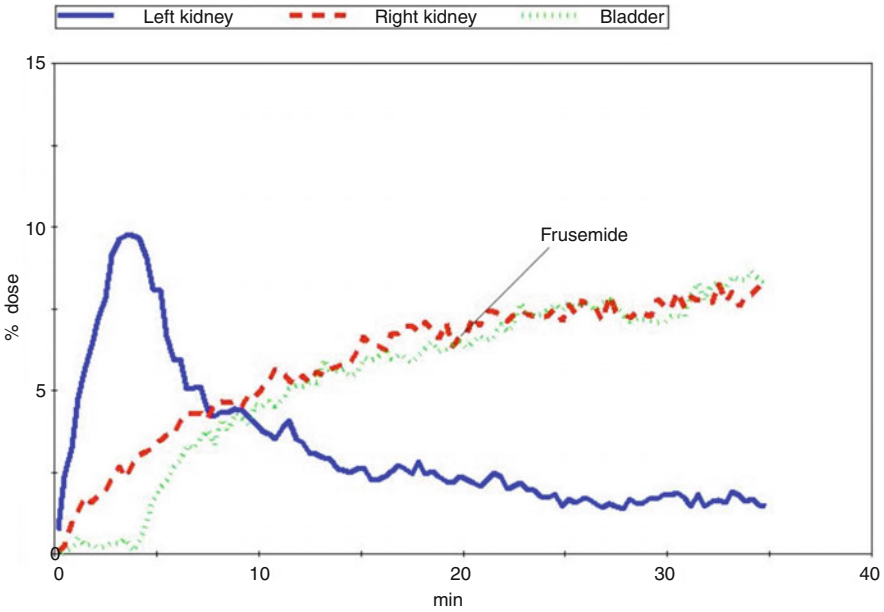

Fig. 21.2 Derived MAG3 renogram activity/time curves

Side Effects of Renography

Anaphylactic reactions to MAG3 have been reported but are very rare. Mild vasovagal reactions are possible. Allergic and vasovagal reactions to DTPA have been reported in isolated cases.

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Chapter 22
How to Do a Diuresis Renogram

Mary Prescott

The diuresis renogram is just a variant of the standard renogram in which the urine flow rate is increased by administration of a diuretic.

Indications

Diuresis renography is used in the assessment of possible renal drainage impairment and to follow up the outcome from surgical intervention for a previously obstructed system.

Radiopharmaceuticals

The same radiopharmaceuticals are used as for standard renography.

Patient Preparation

The patient must be well hydrated. They should drink 300–500 mL of water prior to, and should empty their bladder immediately before, the test.

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Data Acquisition

Data is acquired as for a standard renogram, except that a diuretic is administered.

If one or both kidneys have not emptied satisfactorily by 20 min after the start of the renogram, then furosemide may be given IV at a dose of 0.5 mg/kg (up to 40 mg for an adult). This is known as "F+20." Data acquisition should continue for at least another 15 min.

If a previous renogram has shown an equivocal response to diuresis, then a maximum diuretic response can be obtained by the administration of furosemide 15 min before the start of the renogram ("F-15"). The F-15 protocol is used as the primary investigation of a suspected obstructed system in some centres, although we believe it is better to start with a standard renogram in order to assess kidney drainage under normal flow rates before moving on to this modification.

If venous access is difficult (for example, in children), then furosemide may be given immediately before the radioactive tracer through the same cannula ("F+0").

Computer Data Analysis

The data acquired is analysed in the same way as for a standard renogram.

Interpretation of the Results

If the kidney has a dilated pelvis, then the renogram curve will take a long time to fall, but on its own, this does not distinguish whether the system is a high-pressure (obstructed) system or a low-pressure (nonobstructed) one. The response to furosemide at 20 min can help to make the distinction between these two findings.

When the renogram continues to rise or remains flat after furosemide, this represents an obstructed pattern indicative of a high-pressure system (Fig. 22.1a). If the renogram curve falls rapidly 3 min after furosemide, this represents a hypotonic response indicative of a low-pressure nonobstructed system (Fig. 22.1b). Should the renogram curve only fall slowly after furosemide, with loss of concavity in the curve, this represents an equivocal response (Fig. 22.1c). In this case, an F-15 study may be helpful to clarify the result. If the renogram curve initially starts to fall after furosemide but then begins to rise again after a few minutes, this is known as Homsy's sign (Fig. 22.1d). It is indicative of intermittent obstruction which only occurs at high urine flow rates. In these cases, an F-15 renogram will probably appear obstructed.

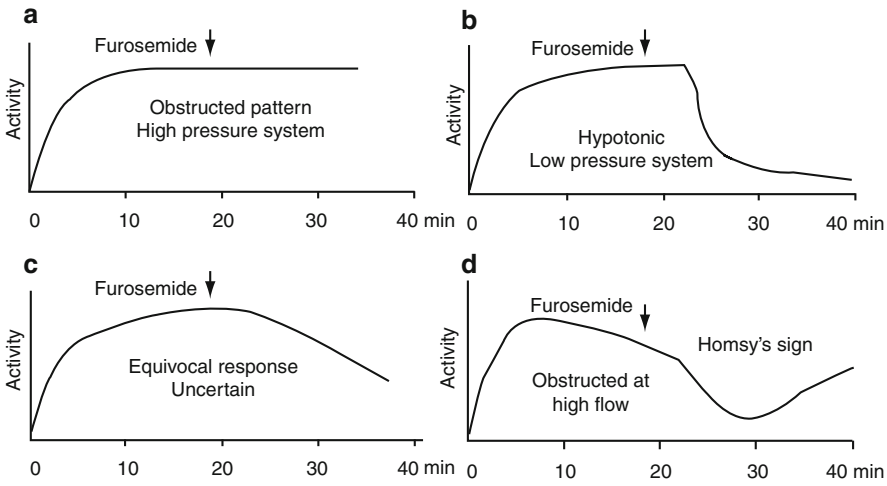

Fig. 22.1 (**a**–**d**) The renogram curves that might be seen following furosemide given 20 min after the radiopharmaceutical

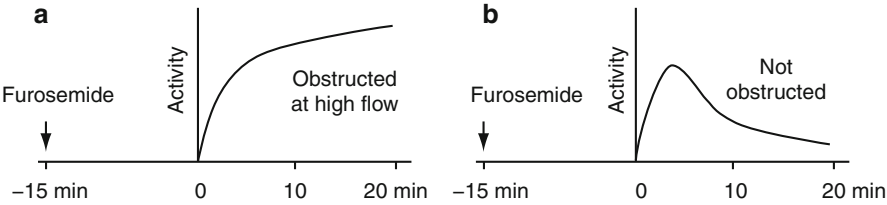

Fig. 22.2 (**a, b**) The renogram curves that might be seen when furosemide was given 15 min before the radiopharmaceutical

When an F-15 renogram is performed, the kidney will have obtained maximum diuresis by the time the renogram is started. If the renogram continues to rise, this indicates obstruction at high flow (Fig. 22.2a). It gives no indication about how the kidney handles fluid normal urine flows. Should the tracer be excreted, then the kidney is not obstructed (Fig. 22.2b).

Limitations

If kidney function is poor, the response to furosemide will be impaired, so the adequacy of diuretic response must be judged in relation to uptake.

Complications

Furosemide can induce renal pain in an obstructed system, and this may require urgent treatment. Equally, there is a theoretical risk of renal pelvic rupture in diuresis renography in the kidney that has been operated on recently and is still obstructed. Tinnitus and deafness are rare side effects of large doses of furosemide, if given rapidly. However, the British National Formulary (BNF) suggests that single doses of up to 80 mg may be given rapidly without significant hazard. Rashes and photosensitivity are also rare side effects of furosemide.

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Chapter 23
How to Do a DMSA Scan

Jackie James

A dimercaptosuccinic acid (DMSA) scan is a static nuclear medicine study that indicates functioning renal tubular mass. It can be used to detect renal parenchymal abnormalities and to measure relative kidney function.

Indications

Detection of renal scarring following a urinary tract infection (UTI) in children is its principal use. The UK National Institute for Health and Clinical Excellence (NIHCE) guidelines recommend that scans should not be performed until 4–6 months after the UTI as, in the acute phase, parenchymal defects may be seen which may heal with time and do not represent true scarring. It can also be used in the assessment of horseshoe or ectopic kidneys and in the localisation of poorly functioning kidneys. Measurement of relative kidney function, particularly when kidneys may lie at different depths in the patient, and to evaluate functional capacity following renal trauma are other applications.

Radiopharmaceutical

^{99m}Tc DMSA (dimercaptosuccinic acid, alternatively known as succimer) is a gamma-emitting radiopharmaceutical that binds to the proximal convoluted tubule. After intravenous injection, DMSA accumulates slowly in the renal cortex, and only

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a small amount is excreted in the urine. The administered activity is normally 80 MBq for adults, scaled down in proportion to body surface area for children. After administration the patient waits for between 2 and 4 hours to allow time for sufficient cortical uptake for imaging.

Data Acquisition

An LEHR collimator is used to get the best resolution, and the patient is positioned supine on an imaging couch. Static views are obtained of the kidneys from posterior, anterior, left posterior oblique, and right posterior oblique projections. Each view should contain 200,000–500,000 counts which will take about 5 min. The anterior view may be omitted in small children if they cannot tolerate the gamma camera detector in front of their face.

Single-photon-emission computed tomography (SPECT), possibly combined with low-power CT (SPECT-CT), may be useful in some cases, e.g., following trauma.

Computer Data Analysis

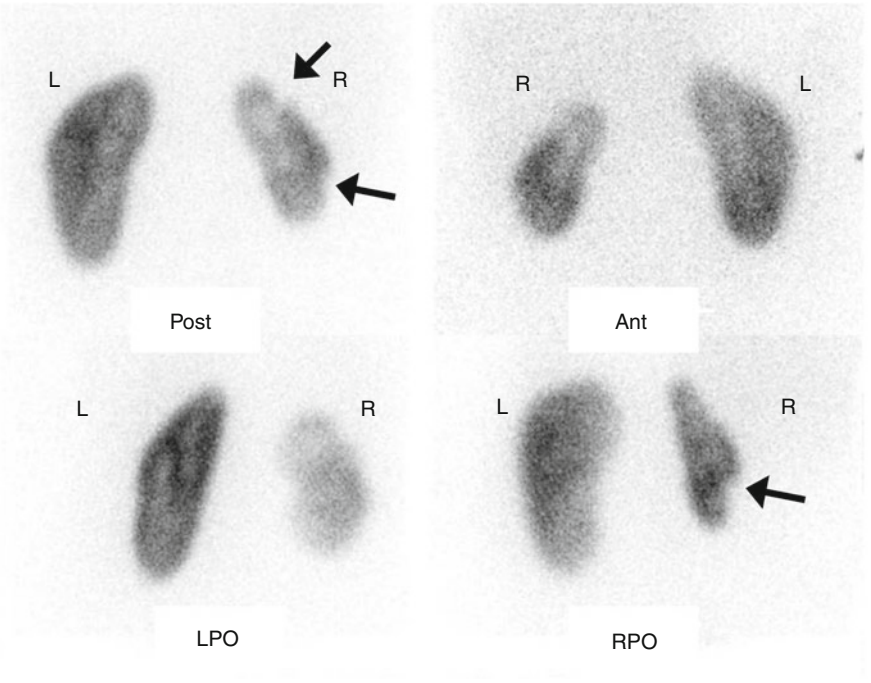
On the computer, regions of interest (ROIs) are drawn around each kidney on the posterior view, together with a nearby background region. The counts in each kidney region are determined, and background counts are subtracted after allowing for differences in region size. The relative function of each kidney is calculated from the percentage that it contributes to the total counts. ROIs are also drawn on the anterior view, and the relative function is calculated in the same way. The geometric mean of the kidney counts from the posterior and anterior views is calculated, where:

$$\text{Geometric mean count} = \sqrt{\text{Posterior count} \times \text{Anterior count}}$$

The relative function is calculated using the geometric mean counts for left and right kidneys. This compensates for differences in kidney depth.

Interpretation of the Result

Both kidneys should be examined on all views to determine any areas of reduced uptake, sometimes called “photopenic” areas, indicating cortical loss. The anterior view will be too far away from the camera, and the resolution too poor, to detect



Relative function	Left (%)	Right (%)
Posterior view	71	29
Anterior view	61	39
Geometric mean	66	34

Fig. 23.1 A DMSA scan showing photopenic areas in the upper and lower poles of the right kidney consistent with scarring (*black arrows*). This is most evident on the posterior and oblique images. The geometric mean gives the most accurate indication of differential function

small focal abnormalities unless the kidneys are malpositioned or have a horseshoe configuration.

If the relative function determined from the posterior and anterior views differ, this indicates that the two kidneys lie at different depths in the patient. In this situation, the relative function calculated from the geometric mean count is the best estimate of the true relative function (Fig. 23.1).

Side Effects

Allergic reactions to DMSA have been reported but are rare.

Further Reading

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Chapter 24
How to Do a Radioisotope Glomerular Filtration Rate Study

Richard Lawson

Glomerular filtration rate (GFR) can be measured by the blood clearance of any tracer that is cleared through the kidneys solely by glomerular filtration. Nuclear medicine is ideally suited to this because it uses minute tracer quantities of radioisotope that do not disturb kidney function and gives a very low radiation dose. The method involves blood sampling alone and so is helpful when urine collection is difficult. It is, therefore, more reliable than creatinine clearance, which requires 24-h urine collection, and is more accurate than the estimated GFR (eGFR), which is based on a serum creatinine measurement in isolation. However, it only gives total renal clearance, and so individual differential kidney clearance can be inferred in combination with either a renogram or DMSA scan.

Indications

A radioisotope GFR is indicated for the accurate measurement of absolute renal function when urine collection is difficult, for the long-term monitoring of renal function, and during the assessment of potential living-related kidney donors.

It is also useful in the measurement of renal clearance prior to chemotherapy in order to determine kidney function prior to administering nephrotoxic agents and to work out the dosage of chemotherapeutic agents that are excreted by the kidneys.

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Blood samples	Time (hh:mm)	Volume (mL)	Counts (cpm)	Time since injection	Conc. (cpm/mL)	Included in fit
Background blood					0.0	
Injection	10:17					
First blood sample	12:24	2:0	570.0	02:07	285.0	Yes
Second blood sample	13:20	2:0	415.7	03:03	207.9	Yes
Third blood sample	14:37	2:0	287.0	04:20	143.5	Yes
Fourth blood sample	15:26	2:0	223.4	05:09	111.7	Yes
Standard 1		2:0	8048.9	Average:	4,010.5	
Standard 2		2:0	7993.2			

Fig. 24.1 The gamma activity in the four postinjection blood samples taken from the opposite arm

Radiopharmaceuticals

3 MBq ^{51}Cr EDTA (ethylenediaminetetraacetic acid, alternatively known as edetate) or 10 MBq ^{99m}Tc DTPA (diethylene-triamine-pentaacetic acid, alternatively known as pentetate) is most commonly used. Both of these tracers are cleared solely by glomerular filtration, and either will give an accurate GFR. The choice of radiopharmaceutical is a matter of practical convenience for individual departments.

Patient Preparation

The patient should avoid high-protein meals, excessive caffeine, and strenuous exercise immediately before and during the test. They should maintain normal hydration during the study and adequate venous access, for repetitive venipuncture, is essential.

Procedure

The dose of radiopharmaceutical is prepared and accurately calibrated against a standard before being administered by intravenous injection, ensuring that all the dose goes in and none remains in the tissues. Blood samples are taken from the opposite arm at 2, 3, 4, and 5 h after injection. The blood samples are centrifuged and aliquots of plasma are counted for radioactivity in a well-scintillation counter (Fig. 24.1). The standard is diluted in 1 L, and an aliquot of the diluted standard is counted in the same way.

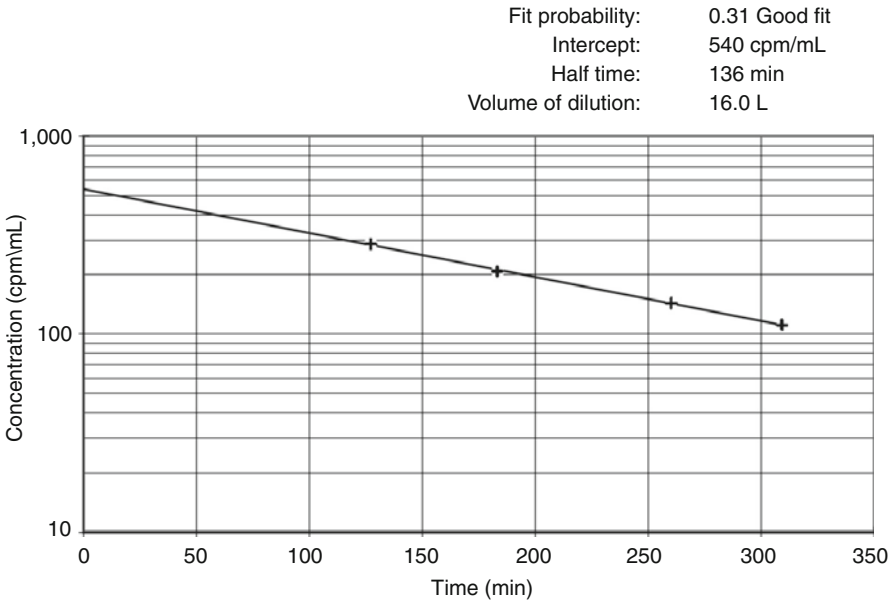

Fig. 24.2 Plasma counts against time since injection. The zero time intercept is used to determine the initial volume of dilution of the radiopharmaceutical in the patient, and the slope determines the clearance rate

Data Analysis

A graph is plotted of plasma counts against time since injection, and this is fitted to an exponential curve (Fig. 24.2). The exponential is extrapolated back to time zero, and the intercept is compared with the diluted standard counts in order to determine the initial volume of dilution in the patient. The slope of the exponential fit gives the rate constant for clearance of tracer through the kidneys.

Multiplying the rate constant by the volume of dilution gives an estimate of the GFR based on this single exponential analysis. The estimated GFR is corrected for the patient's body surface area, and a correction is applied to allow for the fact that the blood clearance curve is really biexponential (Fig. 24.3).

Interpretation of the Results

The normalised GFR (in mL/min/1.73 sq m) corrected for body surface area and with the biexponential correction applied is an accurate measure of the patient's normalised GFR which may be compared with normal values for the patient's age.

Calculated GFR	Absolute	Normalised for body surface area
Single exponential model	82 mL/min	74 mL/min/1.73 sq m
With bi-exponential correction	**73** mL/min	**66** mL/min/1.73 sq m
Estimated error	**+/–2** mL/min	**+/–2** mL/min/1.73 sq m

Normalisation based on body surface area 1.91 sq m	Analysed by:	Checked by:

Fig. 24.3 51-Cr EDTA GFR result corrected for surface area and single exponential assumption

The absolute GFR, in mL/min, with the biexponential correction applied, but without normalisation for surface area, is an accurate measure of the patient's renal clearance. This may be used for chemotherapy dosing schedules. The calculated volume of dilution is approximately the patient's extracellular fluid volume.

Side Effects

Mild allergic phenomena are rare side effects of EDTA.

Further Reading

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Chapter 25
How to Do a Bone Scan

Mary Prescott

A nuclear medicine bone scan is a useful test for detecting areas of abnormal bone metabolism.

Indications in Urology

Identification (or exclusion) of bone metastases in malignancies that are known to metastasise to bone such as prostate cancer. It is also useful in monitoring progression of bone metastases and their response to treatment.

Radiopharmaceuticals

^{99m}Tc MDP (methylene diphosphonate, also known as medronate) or ^{99m}Tc HDP (hydroxymethylene diphosphonate, also known as oxidronate) is used. The usual administered activity is 600 MBq. Both radiopharmaceuticals are taken up by growing bone, so the distribution shows areas of normal and abnormal bone metabolism. They are also excreted in the urine, so kidney and bladder will also be seen on the images.

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Patient Preparation

The patient should be well hydrated and encouraged to void frequently once the radiopharmaceutical has been administered. This will reduce their radiation dose and also improve image quality. The patient should empty their bladder before the third phase images.

If pain is a significant factor, then pain relief should be prescribed and given prior to the scan as the patient will have to lie supine for up to 40 min on the imaging couch.

Multiphase Data Acquisition

First phase (optional). A dynamic study may be acquired at one image per second for the first minute following injection in order to demonstrate blood flow. This is only required when the vascularity of a lesion is to be investigated and is probably not necessary for identification of metastases.

Second phase (optional). A static 1-min image may be acquired immediately after the first phase images to demonstrate blood pool. This is only required when lesion vascularity is of interest.

Third phase (required). Three hours after injection, images showing bone metabolism are acquired using one or more of the following techniques:

Whole body image in which the camera slowly moves along the length of the patient taking about 20 min to produce a whole body scan. Both anterior and posterior views are usually produced; with a double-headed gamma camera, these can be acquired simultaneously. These images give an overview of activity in the whole skeleton and can be useful for identifying metastases.

"Spot views" of selected parts of the body. These are static images taking about 5 min each. They will generally be of better quality than the whole body images and are useful for giving more detailed information about suspicious areas found on the whole body images. They can be taken at different angles.

SPECT (Single-photon-emission computed tomography) study. For a SPECT study, the gamma camera rotates all the way round the patient taking images from many angles. This takes about 20 min. The computer reconstructs these into cross-sectional images (in the same way as an X-ray CT scan). These can be helpful for locating lesions in three dimensions. They are also the best images to use for quantification because attenuation correction can be applied to correct for gamma rays absorbed in the patient.

SPECT-CT. Some modern gamma cameras actually incorporate a CT scanner in their design to create a hybrid SPECT-CT system. Then it is possible to acquire a CT scan immediately after the SPECT scan without moving the patient. This gives coregistered SPECT and CT images which can be useful for examining CT findings at sites that are shown to have abnormal metabolism on the SPECT images.

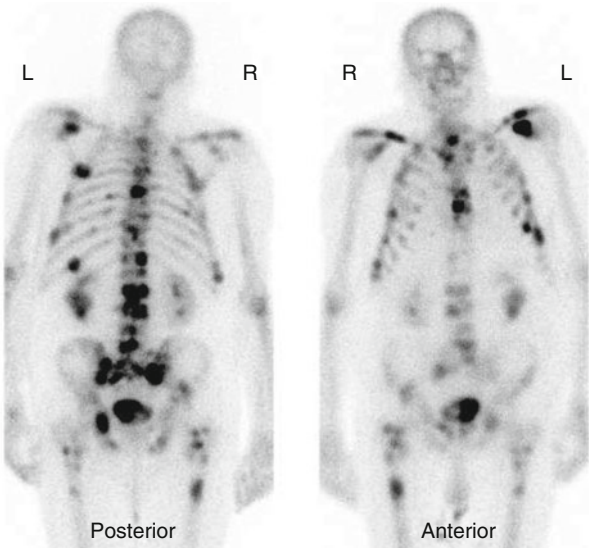

Fig. 25.1 ^{99m}Tc MDP bone scan showing multiple areas of increased radionuclide uptake, particularly in the spine, indicating the presence of metastases

Late images (optional). If the patient is unable to empty their bladder, so that the pelvis is obscured by bladder activity, a late image (at 24 h) may be helpful.

Interpretation of the Result

Areas of increased uptake, "hot spots," indicate increased bone metabolism. These changes are not specific to metastases and may be seen in fractures, Paget's disease, and degenerative disease. The pattern of distribution of hot spots may help differentiate malignancy from benign anomalies (Fig. 25.1).

The bone scan is very sensitive to increased bone metabolism, and metastases may show up before they are apparent radiologically.

Limitations

Because of the limited resolution of the gamma camera, small lesions may not be detected. However, lesions with high osteoblastic activity can still show up as "hot" on the bone scan even if they are very small. Advanced widespread metastases that have spread uniformly throughout the skeleton (a "superscan") may be mistaken for normal if only the relative counts in different bones are viewed. This can be avoided by considering the absolute number of counts acquired or by comparing bone with other normal areas such as kidneys, soft tissue, or distal limbs which are usually

spared. A superscan often shows no renal activity because of the avid bone uptake of the radionuclide.

Side Effects

MDP and HDP may produce an allergic reaction. This is usually in the form of an urticarial rash which can appear within the first few hours and up to the following day. Treatment is with antihistamines and steroids are rarely required. One in 200,000 administrations have reported hypersensitivity reactions including very rare life-threatening anaphylaxis.

Further Reading

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Chapter 26
How to Do a Transplant Renogram

Mary Prescott

The transplant renogram is a variation of the standard renogram that is optimised for the transplant kidney.

Indications

A transplant renogram is carried out for the assessment of kidney perfusion post-transplant and to determine kidney function postoperatively, particularly in cases of acute tubular necrosis (ATN) where there is no urine output. It may also be used to investigate the possibility of urinary leakage from the collecting system.

Radiopharmaceuticals

As for a standard renogram, ^{99m}Tc MAG3 is preferred, 20 MBq to assess kidney function or 200 MBq if kidney perfusion is to be assessed as well.

Patient Preparation

The renogram cannot be performed during a dialysis session if quantification of function is required. However, perfusion and urinary extravasation can still be assessed.

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Data Acquisition

A LEHS or LEGP collimator is used to give adequate counts as good resolution is not required. With the patient lying supine, the gamma camera is positioned anteriorly over the iliac fossa to view the transplanted kidney and bladder. The radiopharmaceutical is injected and immediately a dynamic sequence of images is acquired. For assessment of kidney function, one frame every 20 s for 30 min is adequate. If assessment of perfusion is also required, the first minute may be acquired at a faster rate of one frame every second to give a "first-pass" study. After 30 min, if the patient is catheterised, the catheter should be clamped, as long as clinically advisable, and 1-min static images of the bladder and catheter are taken before the catheter is unclamped.

If there are any other drainage tubes, a 1-min static image of each drainage bag is also taken. Should urinary extravasation be suspected, further 5-min static images, at intervals over 2 h, can be useful in identifying any tracer activity outside the urinary tract.

Computer Data Analysis

On the computer images of the dynamic series, regions of interest (ROIs) are drawn around the kidney, together with a background region in the contralateral iliac fossa and the bladder.

Curves are created showing how the activity in each region of interest changes with time.

The background curve is used to subtract a background contribution from the kidney and bladder curves. Each curve is scaled to percent of administered activity, making an appropriate allowance for attenuation of gamma rays in the patient. Using the final static images, activity in the bladder, catheter bag, and any drain bags are quantified as a percent of administered activity. There will be much less attenuation of gamma rays from the catheter bag than from the bladder or kidney, and suitable allowance must be made for this.

Interpretation of the Result

Kidney perfusion can be assessed qualitatively by inspection of the images from the first-pass study (Fig 26.1). Activity should appear in the kidney immediately after the iliac artery. If activity-time curves are generated, there are several alternative quantitative indexes of kidney perfusion that can be calculated.

Kidney function can be assessed qualitatively by inspection of the dynamic images or the renogram curve. A useful quantitative measure of kidney function is the total of percent administered activity in the kidney, bladder, catheter bag, and any drains added together at 30 min. This figure can be used to track changes in function during serial studies. This is most useful in identifying potential rejection in a kidney that is still in ATN when serum results are unhelpful as the patient still requires dialysis.

Urinary leaks can be detected by inspection of the late images.

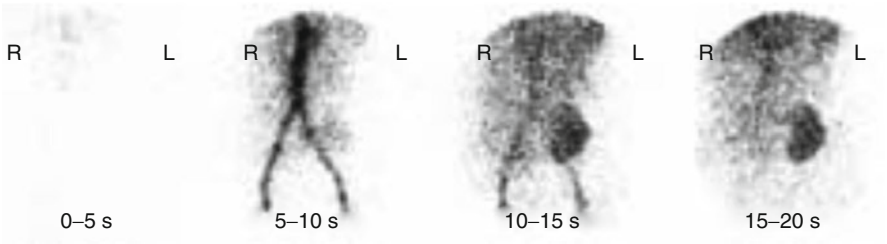

Fig. 26.1 A first-pass transplant renogram showing good perfusion of the transplanted kidney

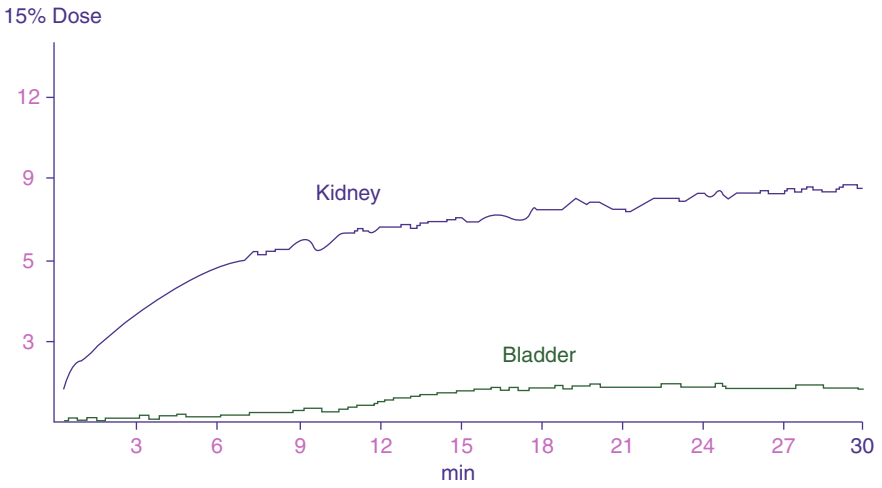

Fig. 26.2 A typical transplant renogram showing poor excretion

Limitations

There is no absolute "normal" for a transplant renogram because every kidney is different dependant on its history. Therefore, whichever quantification method is used for monitoring function in ATN, serial studies to show changes are more useful than a single isolated study.

The transplant renogram is not very helpful in diagnosing obstruction because the post-ischaemic kidney often shows a rising renogram curve anyway (Fig. 26.2) and, consequently, does not usually respond well to furosemide.

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Chapter 27
Dynamic Sentinel Lymph Node Biopsy in Penile Cancer

Hussain M. Alnajjar and Nicholas A. Watkin

The term sentinel lymph node refers to the first lymph node or packet of lymph nodes to which tumour cells metastasise from a primary tumour. It is assumed that the process of micro-metastasis is embolic and that tumour cells are not present in continuity in the lymphatic channels between the primary site and sentinel lymph node. It is also therefore assumed that if the sentinel lymph node does not have tumour within it, the remaining nodes in the lymphatic basin are free of tumour.

Penile cancers metastasise almost always via the lymphatic route to the nodes in either (or both) groins. The presence and extent of lymph node metastasis is the single most important prognostic indicator. Up to 20% of patients present with micro-metastases and staging investigations such as ultrasound, CT, and MRI have limited sensitivity in detecting them. Accurate staging of inguinal basins and treatment of nodal disease are vital for maintaining a high cancer-specific survival. For patients with a single nodal metastasis, a 5-year survival approaches 100%.

Prophylactic bilateral inguinal node dissection is associated with high cure rates, but has a reported morbidity rate of 30–50%. Moreover, with up to 80% of patients having negative nodes, these patients have associated morbidity with no clinical benefit (Hadway et al. 2007).

Methodology

Sentinel lymph node sampling is a staging technique used to accurately evaluate the nodal status of patients with clinically node-negative penile carcinoma.

Cabanas (1977) was the first surgeon to describe the term "sentinel lymph node" and "sentinel lymph node biopsy" in a cohort of penile cancer patients. Cabanas'

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theory and observation was based on anatomical landmarks derived from lymphangiogram studies and did not adequately take into account inter-individual variation. The original procedure involved removal of a single or more often a cluster of lymph nodes medial to the superficial inferior epigastric vein, which is not a sufficiently constant landmark to be reliable. When the technique was adopted by other surgeons, the false-negative rates were high, and because of this, it was largely abandoned.

In the early 1990s, there was renewed interest in the technique by breast and melanoma surgeons. The use of Patent Blue V dye to map and visualise the lymphatic drainage of sentinel lymph nodes (SLN) in addition to preoperative injection of radioactive tracer (technetium = 99m-labelled nanocolloid ^{99m}Tc) formed the basis of the contemporary technique we now refer to as dynamic sentinel lymph node biopsy (DSNB). This resulted in more accurate location of nodes and took account of individual anatomical variation.

From the late 1990s, this modified approach was adopted by a small number of penile cancer centres. Further improvements in the technique have been made in subsequent years. These include:

- Extended pathological examination of the sentinel node by serial sectioning and immunohistochemical staining.
- Addition of preoperative ultrasonography with fine needle aspiration cytology (Kroon et al. 2004) to detect pathologically enlarged nodes that fail to pick up radioactivity. This has led to a reliable minimally invasive staging procedure with an associated sensitivity of 92–95% together with low morbidity.

The Technique

The procedure can be performed at the time of surgery for the primary tumour or delayed 2–4 weeks. Four hours before surgery, a local anaesthetic spray is applied around the penile shaft, proximal to the site of the primary tumour. ^{99m}Tc-nanocolloid is then injected intradermally, and dynamic and static images are collected using a dual-head gamma camera. The SLNs are located using a ^{57}Cobalt pen, and skin markings are made with permanent ink.

Ten to fifteen minutes before surgery, 1 mL of Patent Blue dye is injected intradermally in the same area of the penis as the injection of radionuclide. The SLN is located intra-operatively using a handheld gamma probe, and the blue dye is used to guide dissection. The lymph nodes are only removed if they are radioactive and/or blue. Technically, it would be possible for the node to be analysed straight away, but it is very time-consuming, and conventionally, any further treatment is delayed until there is full histological analysis. A formal lymph node dissection is only performed if a sentinel node metastasis is found.

Recent large series of patients have confirmed the sensitivity is approaching 95%, and DSNB is being adopted in the supra-regional penile cancer centres in the UK as part of a national trial.

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Part III
Technology: Diagnostic

Chapter 28
Urinalysis

David G. Ross

Urinalysis is a quick, cheap, and readily available point of care test. The combination of reagents present on dipstick strips typically include: (1) bilirubin, (2) glucose, (3) haemoglobin, (4) ketones, (5) leucocytes, (6) nitrites, (7) pH, (8) protein, (9) specific gravity, and (10) urobilinogen.

Using a Dipstick

Dipstick tests vary between manufacturers, so users should familiarise themselves with the product used in their department. To avoid degradation, dipsticks must be stored in a closed container; a useful check for such changes is a positive glucose strip pre-testing. Always check the expiry date. The urine sample should be midstream, fresh and collected in a sterile container. Submerge all the pads of the strip in the sample and remove immediately. Start timing. Read each test at the appropriate time by comparing against the colour reference chart on the bottle.

Urinalysis: Chemistry, Significance, and Errors

Blood/Haemoglobin

How? – Dependent on the peroxidase-like activity of haemoglobin (or myoglobin). This catalyses the oxidation of a chromagen (3,3′,5,5′-tetramethylbenzidine) by an organic peroxide (e.g., diisopropylbenzene dihydroperoxide). It can detect free

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Table 28.1 Diagnoses of patients investigated for microscopic haematuria (Khadra et al. 2000)

Diagnosis	% of patients
No cause identified	68.2
UTI	13
Nephrological causes (IgA nephropathy, etc.)	9.4
Bladder cancer	4.8
Stones	4
Prostate cancer	0.3
Kidney cancer	0.2
Upper tract urothelial cancer	0.1

haemoglobin and intact erythrocytes which lyse on the test pad. Free haemoglobin gives a uniform colour change (orange, green, blue), while intact red blood cells give a spotted appearance; green spots on yellow/orange background.

Sensitivity = 90% in detecting equivalent of >3 RBCs/hpf; specificity = 65–80%.

A trace of haematuria should be considered negative, while ≥1+ is considered significant. Non-haemolysed and haemolysed are of equal significance.

Who to Investigate – BAUS Haematuria Guidelines:

1. Single episode of symptomatic nonvisible haematuria (in the absence of UTI or other transient cause)
2. Persistent (two out of three dipsticks positive) asymptomatic non-visible haematuria in patients ≥40 years

Significance – 5% of patients will have urological cancer (Table 28.1).

Protein

How? – Based on protein error of indicators principle. Tetrabromophenol blue changes colour in response to the presence of protein in urine. Sticks are very sensitive, and a trace corresponds to 0.15–0.3 g/L, + to 0.3 g/L, ++ to >1 g/L, +++ to 2.5–5 g/L, and ++++ to >10 g/L proteinuria. Normal urinary protein should be less than 15 mg/dL or <150 mg/24 h.

Significance – Significant proteinuria is a risk factor for renal disease and cardiovascular morbidity and mortality. Patients with persistent proteinuria should have it quantified using either albumin/creatinine or protein/creatinine ratio. ACR has better sensitivity than PCR for low levels of proteinuria. Even microalbuminuria (30–150 mg/24 h) is significant in diabetic patients. In the context of the definitions of chronic kidney disease, CKD 1 = GFR ≥90 mL/min and proteinuria, and CKD 2 = GFR 60–89 mL/min and proteinuria. Both groups require monitoring in primary care. A nephrology referral is indicated if the urinary ACR > 70/PCR > 100 mg/mmol or the urinary ACR > 30/PCR > 50 mg/mmol with microscopic haematuria.

Table 28.2 Utility of leucocyte esterase and nitrite urinalysis in the detection of UTI (St John et al. 2006)

Dipstick result	Pooled sensitivity %	Pooled specificity %
LE positive	72	82
Nitrite positive	54	98
LE *or* nitrite positive	81	77
LE *and* nitrite positive	43	96

Leucocytes

How? – Leucocyte esterase is produced by neutrophils which catalyses the hydrolysis of either derivatised pyrrole amino acid ester to liberate 3-hydroxy-5-phenol pyrrole or indoxyl carbonic acid ester to indoxyl. Pyrrole or indoxyl then reacts with a diazonium salt to produce a purple product.

Significance – The list of potential causes of persistent pyuria is long; however, the presence of urinary leucocytes is often used as an indicator of UTI along with dipstick nitrites. Its performance in this setting is shown in Table 28.2.

Nitrites

How? – Nitrite in the urine reacts with ρ-arsanilic acid to form a diazonium compound which couples with 1,2,3,4-tetrahydrobenzo(h)-quinolin-3-ol to produce a pink colour.

Significance – Nitrites when present in urine are the result of bacteria reducing urinary nitrates. Around 60% of Gram-negative bacteria are capable of this, which, together with the requirement of at least 10^5 bacteria per milliliter for a positive test, limits the sensitivity of this test in the clinical detection of UTI (Table 28.2).

pH

How? – Double indicator principle, methyl red and bromothymol blue, which provides a broad range of colours to cover a urinary pH range of 5–8.5 (visually).

Significance – Urinary pH typically reflects plasma pH. An exception is in renal tubular acidosis where there is an inability to acidify urine in response to an acid load. Urinary pH is potentially important in urolithiasis. Uric acid stone formation requires a pH < 5.5, while the actions of urease-splitting organisms provide the alkaline environment for struvite lithogenesis. Dietary factors can alter pH; high protein diets lower pH, while citrate supplements will raise it.

Table 28.3 Sources of false positive and negative urine dipstick results

Test	False positive	False negative
Haemoglobin	Myoglobin	Reducing agents:
	Bacterial peroxidases	1. Ascorbic acid
	Hypochlorite	2. Captopril
	Menstruation	
	Dehydration	
	Exercise	
Protein	–	Dilute or alkaline urines
		Bence-Jones proteins
Leucocytes	Formalin	Glycosuria (>3 g/dL)
	Vaginal discharge	Ascorbic acid
		Cephalexin
		Imipenem
		Meropenem
		Clavulanic acid
		Tetracycline
Nitrites	–	Non-nitrate-reducing bacteria
		Low nitrate diets
		Dilute urine
		Urine in the bladder for <4 h
		Ascorbic acid
Glucose	–	Ascorbic acid

Glycosuria

How? – Double sequential enzyme reaction:

1. Glucose oxidase catalyses glucose → glyconic acid + hydrogen peroxide.
2. Peroxidase catalyses hydrogen peroxide + potassium iodide chromagen → coloured oxidised chromagen.

Significance – Occurs when blood sugar is >10 mmol/l, the renal threshold.

Potential Errors When Reading a Dipstick

Potential sources of false positive and negative dipstick test results are shown in Table 28.3.

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Chapter 29
Principles of Urine Microscopy and Microbiological Culture

Chinari P.K. Subudhi

Recurrent urinary tract infections (UTIs) are particularly common in women and result in considerable morbidity and expense. While most UTIs are managed empirically in generally practice, key indications for culture in young women include a suspicion of complicated infection, atypical symptoms, failure to respond to initial therapy, raising the possibility of a resistant organism and recurrent symptoms less than 1 month after treatment of a previous UTI for which no culture was performed. Although the incidence of UTI is high, a large proportion of urine samples tested by microbiology labs will show no evidence of infection on culture. Giving clear and precise instructions to the patient will minimise problems with contamination and false-positive results.

Methods of Urine Collection

Urine samples should be preferably collected prior to initiation of antimicrobial therapy. A leakproof container should be used to collect the sample, and after collection it should be promptly transported to the laboratory for processing. When there is delay in transporting the specimens to the laboratory, containers with boric acid preservative (bacteriostatic) should be used, or samples should be refrigerated prior to transport to prevent bacterial overgrowth and false-positive culture results.

The likelihood of detecting a UTI is highest if an early morning sample is taken as the urine is more concentrated and the bacteria have had time to multiply overnight. However, most cultures are obtained when the patient sees the clinician. The clean catch midstream urine (MSU) is the preferred method for routine collection of urine for culture. The patient must be instructed in the proper technique of obtaining

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the urine to prevent contamination of the sample with the commensal bacterial flora of the genital area. In females, this involves parting the labia before collecting the sample. In males, the prepuce should be retracted prior to collection.

Catheter urine (CSU) may be obtained from patients who have an indwelling catheter. The specimen should be obtained aseptically from a sample port in the catheter tubing or by aseptic aspiration of the tubing. The specimen should not be obtained from the collection bag. Suprapubic aspirate of urine (SPA) is a collection method used in neonates and infants as it is difficult to obtain MSU in this group of patients.

Processing of Urine Samples in the Laboratory

Microscopy

Microscopy is used to identify the presence of white blood cells, red blood cells, casts, epithelial cells, bacteria, and other cellular components in the urine. Semi-quantitative methods using a microtitre tray with an inverted microscope is recommended for routine use. Microscopy is recommended for all symptomatic patient groups, to assist in the interpretation of culture results and diagnosis of UTI.

Pyuria and/or Bacteriuria

Significant pyuria is present in 96% of symptomatic patients with bacteriuria of $>10^5$ cfu (colony-forming unit)/mL of urine on culture. Sterile pyuria (pyuria associated with no growth on routine culture media) may be the result of prior treatment with antimicrobial agents, catheterisation, calculi, bladder neoplasms, genital tract infection, infection due to a fastidious organism (i.e., *Chlamydia trachomatis*, *Mycoplasma genitalium*, etc.), or renal tuberculosis.

Nonculture Methods: Urine Analysers

Automated urinalysis endeavours to measure or describe the formed elements in the urine. Three techniques are currently available:

1. Fluorescence flow cytometry with diode laser and hydrodynamic focusing conductometry (IQ Sprint®)
2. Flow cell digital imaging of uncentrifuged urine and automated recognition software (UF-1000i®)
3. Microscopic urine sediment analysis, digital imaging and automatic particle recognition (Sedimax®)

Flow cytometry works by measuring electric impedance (for volume), light scatter (for size) and use of fluorescent dyes (for nuclear and cytoplasmic staining). The particles are characterized using these measurements, and the results are displayed as scattergrams. In particle recognition system, urine specimen passes through the analyser, and a camera captures up to 500 frames per specimen. Each image is classified by size, shape, contrast and texture features. This has been found to be more reliable for identifying cellular components.

Automated methods of urine microscopy have acceptable sensitivity for the detection of white blood cells, red blood cells and bacteria and correlate well with manual handling of samples. These methods offer increased speed of negative screening and reduced costs. Skilled medical laboratory assistants are still required to review certain particles, e.g., *Trichomonas vaginalis*, yeast, etc. Regardless of the screening result, culture is still recommended for all specimens from children, pregnant women, immunocompromised patients, and requests for repeat cultures.

Culture Methods

There are several culture methods for quantification of bacteria in urine. The easiest and most commonly used methods are the calibrated loop technique and multipoint technology. The common culture media used for inoculation of urine are CLED (cystine lactose electrolyte deficient) or chromogenic agar media (Table 29.1).

Culture of urine by multipoint method may be automated or performed manually using either microtitre trays containing agar. Microtitre trays may be read manually

Table 29.1 The advantages and disadvantages of the culture media used in microbiological culture

Culture media	Advantages	Disadvantages
Blood agar	Good growth and discrimination of Gram-positive bacteria; enables identification of *Proteus* spp. by swarming	No inhibition of swarming of *Proteus* spp.; poor discrimination of different species of Enterobacteriaceae
CLED	Good discrimination of Gram-negative bacteria on the basis of lactose fermentation and colony appearance; inhibits swarming of *Proteus* spp.	Poor growth of some Gram-positive bacteria
Chromogenic	Enables presumptive color identification of *E. coli* (pink), enterococci (blue or green), *Klebsiella-Enterobacter-Serratia* group (purple) and *Proteus-Morganella-Providencia* group (brown)	Poor growth of some Gram-positive bacteria

or with an automated system where the resulting data are transferred to the laboratory information management system for reporting. This technology is considered to be most versatile and efficient for a laboratory handling large number of specimens.

Culture of urine by multipoint method may be automated or performed manually using either microtitre trays containing agar. Microtitre trays may be read manually or with an automated system where the resulting data are transferred to the laboratory information management system for reporting. This technology is considered to be most versatile and efficient for a laboratory handling large number of specimens.

Interpretation and Use of Culture Results

Culture results should be correlated with clinical presentation and presence or absence of pyuria. Presence of squamous epithelial cells on microscopy may also indicate contamination with perineal flora. Culture of single organisms $\geq 10^5$ colony-forming units (CFUs)/mL with urinary tract symptoms is diagnostic of UTI. In the absence of faecal contamination, a lower colony count ($>10^2$/mL) and symptoms may be indicative of UTI. Low colony counts and mixtures of organisms usually indicate contamination. Local antibiotic resistance rates should help determine empirical local antibiotic usage, with culture and sensitivity results informing definitive infection management.

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Chapter 30
Measurement of Glomerular Filtration Rate (GFR)

Stephen Brown

Glomerular filtration rate (GFR) is the volume of plasma filtered by the glomeruli in millilitres per minute. It can be measured as the clearance of any substance that is filtered but not actively secreted or reabsorbed by the tubules. The fructose polymer inulin is the traditional GFR marker which meets these criteria, but is difficult to assay in clinical practice. Endogenous markers are used for day-to-day practice, but exogenous markers are used if a more accurate measure is required. GFR is proportional to body surface area (BSA) and is therefore expressed as mL/min/1.73 m^2, the latter being the average adult BSA. Normal values are generally >90 mL/min/1.73 m^2.

Endogenous Markers

Creatinine

Creatinine is a breakdown product of creatine and phosphocreatine, which is primarily filtered at the glomerulus (Fig. 30.1). Its production is relatively stable and hence it is used as a surrogate marker to calculate GFR. Unfortunately, creatinine is not a sensitive marker of early renal impairment, and a reduction in GFR below 60–80 mL/min is required before there is a rise in serum creatinine (Fig. 30.2).

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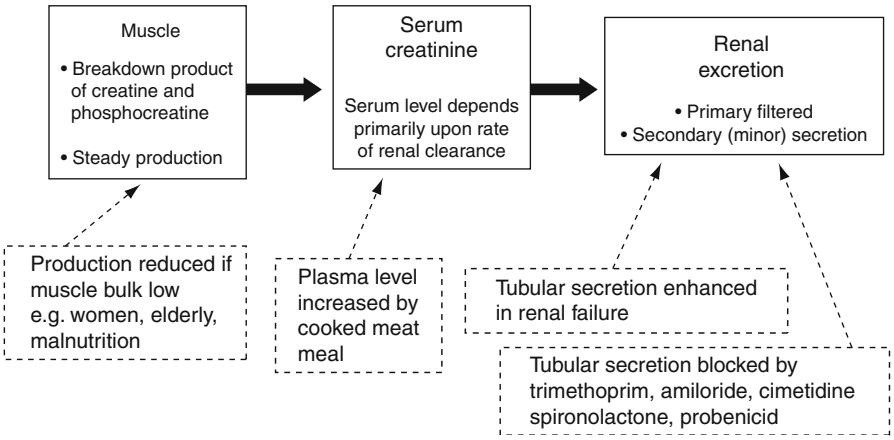

Fig. 30.1 The metabolic pathways influencing serum creatinine and its renal excretion

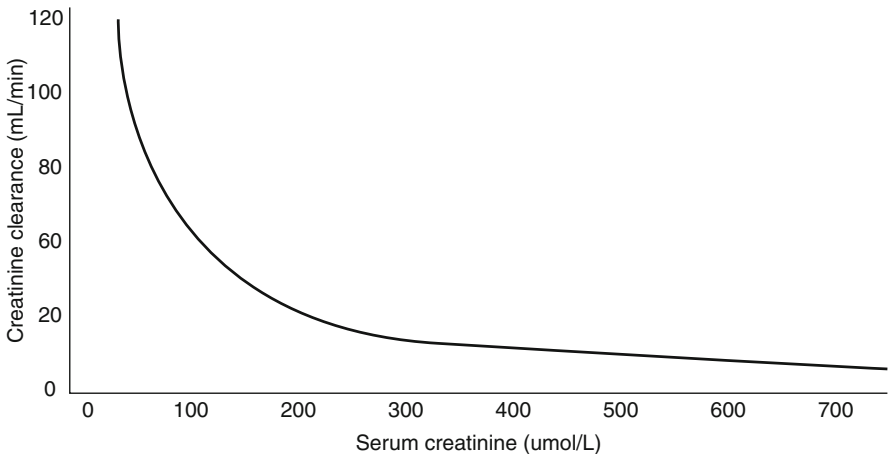

Fig. 30.2 The relationship between creatinine clearance and serum creatinine concentration

Creatinine clearance can be calculated by measuring serum concentration [P_{Cr}] and the concentration [U_{Cr}] and volume [V] of a 24-h urine collection:

$$C_{Cr} = \frac{U_{Cr} \times V}{P_{Cr} \times 24 \times 60}$$

The clearance is then corrected for body surface area (BSA).

$$C_{Cr\,\mathrm{corrected}} = \frac{C_{Cr} \times 173}{\mathrm{BSA}}$$

In clinical practice, the result obtained is often unreliable due to collection problems. There are three major errors that can limit the accuracy of creatinine clearance as an estimate of GFR: errors in urine collection increases in both creatinine secretion and extra-renal degradation of creatinine as the GFR falls. Because of this, many clinicians use derived estimation equations in preference to a timed urine collection. Calculated estimates of GFR from serum creatinine have been devised which take into account the variation due to age, sex, weight or race.

1. The *Cockcroft-Gault equation* allows the creatinine clearance to be estimated from the serum creatinine in a patient with stable serum creatinine.

$$C_{Cr} = \frac{140 - \text{age} \times \text{lean body weight (kg)}}{Cr\ (\text{mg/dL}) \times 72}$$

2. The *eGFR* is derived from the Modification of Diet in Renal Disease (MDRD) study.

$$\text{eGFR} = 32{,}788 \times \text{Serum creatinine}^{-1.154} \times \text{Age}^{-0.203} \times [1.212\ \textit{if black}] \times [0.742\ \textit{if female}]$$

eGFR has been validated for chronic kidney disease (CKD) but not in acute renal failure, pregnancy or childhood. It tends to underestimate GFR when function is normal. Although creatinine is not an ideal marker of GFR, being actively secreted by the tubules and its concentration being dependent on muscle bulk, it remains important in the routine assessment of kidney function. Research on eGFR has demonstrated that it is reasonably accurate in non-hospitalised patients known to have CKD, regardless of diagnosis. Both equations are less accurate in obese individuals. eGFR performs better than the Cockcroft-Gault equation in younger patients and those older than 70.

Cystatin C

Cystatin C is a low molecular weight protein (13.3 kDa), filtered by the glomerulus, but then completely reabsorbed and metabolised by the tubules, so it does not appear in the urine. It is generated at a constant rate by all nucleated cells and is therefore less susceptible to changes in body mass. The eGFR can be calculated for cystatin C similar to creatinine. In multiple studies, cystatin C was more sensitive in identifying mild reductions in kidney function than serum creatinine. Although reference ranges have been reported, there is no current standard for cystatin C, and testing is only available in a limited number of laboratories.

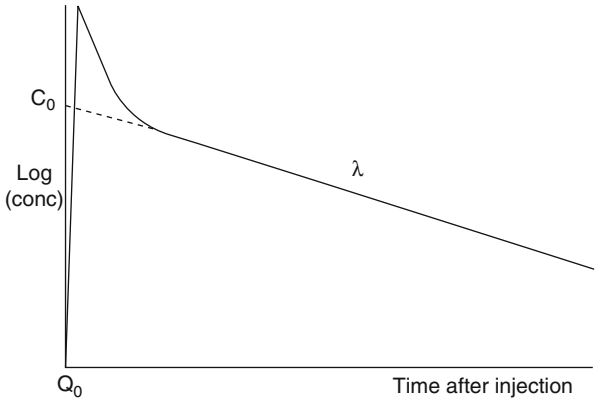

Fig. 30.3 Log plot of plasma concentration of exogenous marker following injection

Exogenous Markers

Cr-EDTA Clearance

The chelating agent EDTA (ethylenediaminetetraacetic acid) is handled by the kidney similarly to inulin. Labelled with ^{99m}technetium, it can be easily assayed. Traditional methods of measuring clearance using an exogenous marker involved a continuous infusion until a steady state is reached and plasma and urine concentrations then measured.

Easier is a single injection technique. In its simplest form, the log plot of the plasma concentration after injection approximates to a straight line after an initial period of equilibration (Fig. 30.3). The slope of the line (λ) can be determined by two blood samples, typically at 3 and 4 h after injection. The clearance can then be calculated as follows: where Q_0 is the injected amount and C_0 is the extrapolated concentration at the time of injection.

$$C_I = \frac{Q_0 \times \lambda}{C_0}$$

Correction is then made for surface area. The sampling times must be extended for very low levels of function.

Although there are a variety of methods to measure GFR, it is important to remember that in most clinical settings, exact knowledge of the GFR is not required. What is important is whether the GFR is changing or stable. This can usually be determined by changes in the serum creatinine in most patients who have a relatively constant body mass and diet.

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Chapter 31
Metabolic Assessment of Urinary Tract Stones

Adrian D. Joyce

The prevalence of urinary stone disease in Europe is 4–20%, and within the UK the prevalence is estimated at 4%. The primary outcome in the medical management of stones is the desire to influence the following factors:

- Reduce future stone formation.
- Minimise or avoid the risk of stone complications, principally infection and obstruction.
- Identify any underlying metabolic abnormality which predisposes to future stone formation. The main conditions under consideration here are primary hyperparathyroidism, gout, and cystinuria.

Stone Composition

Calcium-containing calculi are the predominant stone type in men and women, with a clear predominance against all stone compositions except for infection stones in men. Approximately 15% of all stone formers produce calcium phosphate stones, and approximately 25% of calcium phosphate stones contain calcium monohydrogen phosphate (brushite), which is difficult both to prevent and treat.

Currently, uric acid composition seems to be the second most common stone in both genders, and this is largely related to the current trends in obesity. Patients with type 2 diabetes demonstrate insulin resistance with impaired ammonium excretion, resulting in a reduced urinary pH and a tendency to form uric acid stones. Indeed, up to 50% of uric acid stone formers have evidence of insulin resistance.

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Table 31.1 Anatomical and structural promoters of urinary tract stone formation

Kidney	Diverticulum
	PUJ obstruction
Ureter	Hydroureter
Bladder	Voiding dysfunction including bladder outflow obstruction and neurogenic bladder
Other	Urinary tract reconstruction including ileal conduit and cystoplasty
Foreign bodies	Indwelling catheter
	JJ stent
	Metallic stents

Table 31.2 Metabolic promoters of urinary tract stone formation

Calcium-based stones	Promoters	Hypercalciuria
		Hyperuricosuria
		Hyperoxaluria
	Inhibitor deficiency	Hypocitraturia
		Hypomagnesuria
	Urinary characteristics	Increasing urinary acidity
		Reduced urinary volumes
Non-calcium-based stone	Promoters	Hyperuricosuria
		Cystinuria
	Inhibitor deficiency	Hypocitraturia
	Urinary characteristics	Increased urinary acidity
		Low urine volumes
		Urinary tract infection

Stones due to infection have declined in frequency over the years, and this is largely attributable to improved antibiotic management of urinary infection. The decreasing number of staghorn stones in Europe supports this observation because urinary tract infections are the commonest cause of such large renal calculi.

Following a first stone episode, the recurrence rate for a further stone is quoted as 38% over 3 years and 74% over 10 years.

Promoters of Stone Formation

There are a number of anatomic promoters of stone formation which are summarised in Table 31.1. In addition, infection is generally considered to be a major promoting influence for lithogenesis.

In addition, there are also a number of metabolic promoters of stone formation. These are summarised in Table 31.2.

Basic Evaluation of All Stone Formers

Based upon these risk factors, the usual basic evaluation of a first-time stone former includes:

- A careful medical history, including family history
- Drug history
- Dietary history
- Stone analysis (If stone is available for analysis, this should be examined by X-ray diffraction or infrared spectroscopy)
- Serum creatinine, corrected calcium and urate (Appendix 3)
- Urine dipstick for pH, leucocytes, protein, and nitrites
- Midstream urine for culture

Specialised Evaluation

The basic evaluation is usually all that is required, but on occasions, a more intensive assessment is necessary. The centrepiece of this assessment is the analysis of two 24-h urine collections. Indications for more detailed investigation include the following groups of patients:

- Recurrent stone formers
- "High-risk" first-time stone former (e.g., renal transplant, renal impairment)
- Strong family history of stone formation
- Chronic UTI
- Gout
- Nephrocalcinosis on imaging
- Paediatric stone cases
- Complex or bilateral stone disease

Twenty-Four Hours Urine Collections

At least two specimens should be collected on consecutive days. Collection should be postponed until at least 4 weeks after stone removal or relief of obstruction. These studies should not be undertaken in the presence of infected urine or haematuria.

The collecting bottles should be prepared with 5% thymol in isopropranolol or stored at a cool temperature (<8°C) for the period of collection. Urinary pH should be assessed on a fresh specimen. Hydrochloric acid can be used as a preservative agent in special situations when it is necessary to prevent precipitation of calcium salts. However, this renders pH measurement impossible, and uric acid precipitates. Alkalinisation is needed if quantitative urate excretion is of interest.

The volume, urinary calcium, oxalate, citrate, and creatinine are measured (Appendix 3), and if urate measurement is needed, sodium azide is used to prevent its precipitation

Optional additional tests include:

- Assessment of magnesium and phosphate to calculate supersaturation with calcium oxalate and calcium phosphate.
- Urinary urea and urinary sodium and potassium are useful indicators for assessing the patient's dietary habits.
- Cystine can be assessed by a cystine spot test (cyanide-nitroprusside).
- If calcium phosphate stones are the problem, additional tests for renal tubular acidosis should be considered (ammonium chloride loading test).

Empirical Treatment

The treatment of specific metabolic problems that can cause urinary tract stones is beyond the scope of this chapter. There are, however, some general measures that are often helpful in treating patients with urolithiasis once anatomic and infective causes for stone formation have been managed.

Drinking is the mainstay of treatment with the aim of producing a 24-h urine output of greater than 2 L. Grapefruit juice and tea should ideally be avoided; they result in dilution of solute within the urine.

Dietary advice includes a decreased intake of animal protein (<1 g/kg body weight) which has the effect of reducing the excretion of calcium, oxalate and urate, with increased excretion of citrate and an increased urinary pH. Given the association between urolithiasis and the metabolic syndrome, weight reduction, to a target BMI of 18–25 kg/m^2, is helpful. In addition stone formers should decrease their sodium intake to less than 3 g/day which reduces urinary excretion of calcium and an increased urinary citrate excretion.

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Chapter 32
Principles of Pressure Measurement

Ian Pearce

Pressure measurement, in clinical urology, is commonly used to directly measure the physiology of the bladder and, occasionally, the renal pelvis. Demonstration of intra-cavity pressure is dependent upon a transducer and a recording device.

Pressure transducers relay pressure measurements, using generated electrical signals, to a urodynamic machine which makes a digital record of the pressure; this may be displayed or printed as a hard copy. Two types of transducer exist which are either external or internal to the patient. The key difference between these types of transducer is that the pressure recorded by external transducers dependents upon the position of the transducer in relation to the cavity, whilst internal devices transduce pressure dependent upon the position of the transducer tip relative to the wall of the cavity. Pressure measurement, during any urodynamic study, is dependent upon three actions, setting a "zero" pressure for the transducer, calibration, and establishment of a pressure reference point.

External Pressure Transducers

External strain gauge transducers are the standard transducer used in most urodynamic studies. They are connected to both bladder and rectal catheters via either fluid-filled or air-charged tubing. This tubing is designed to be non-compressible in order to minimise artefactual pressure fluctuation. Water-filled lines are most commonly used but demand "zeroing" at the level of the symphysis pubis and are subject to a variety of observed artefacts at the level of the transducer (Table 32.1).

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Table 32.1 Artefactual pressure registrations seen in fluid-filled, external pressure transduction systems

Cause	Effect
Air bubbles within system	Dampened pressure signal
Kinking of tubing	Dampened pressure signal
Non-urodynamic tubing	Dampened pressure signal
Contact between filling and pressure lines	Rhythmic pressure fluctuation
Transducer above reference point	Erroneously low resting pressure
Transducer below reference point	Erroneously high resting pressure

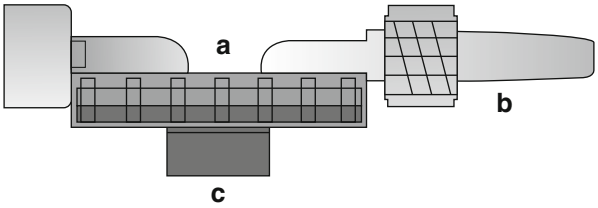

Fig. 32.1 An example of a strain gauge external transducer system. The diaphragm lies below the housing (*a*) which goes to the patient via a water column at connector (*b*). The transducer diaphragm is placed into the housing (*c*)

Air-charged lines connect the catheter to the diaphragm by a microscopic water droplet in the transducer housing.

External transducers are constructed of a diaphragm bound with strain-sensitive resistive wire, which has a current passing through it, in a plastic housing (Fig. 32.1). As the pressure on the connecting tube side of the diaphragm changes, the force deforms the diaphragm, altering the wire's length and causing a change in its electrical resistance. This results in a voltage surge which is recorded, amplified, and translated into a pressure reading seen on the urodynamic trace. External transducers are cheap, widely available, accurate, and reliable.

Fluid-filled transducers are "zeroed" to atmospheric pressure prior to commencing the study, with the transducer opened to the atmosphere and closed to the bladder. Zeroing is not required for air-charged catheters. Calibration of external transducers is typically performed automatically by the urodynamic machine, but manual calibration may be performed by subjecting the diaphragm to the pressure exerted by a column of water 0–100 cm high. The classic pressure reference point, for urodynamic studies, is the top of the symphysis pubis.

Internal Transducers

Internal transducers rely on semiconductor technology to translate pressure into voltage changes using a deformable membrane transducer mounted directly on the tip of a "catheter" (Fig. 32.2). Membrane deformation results in a change in the

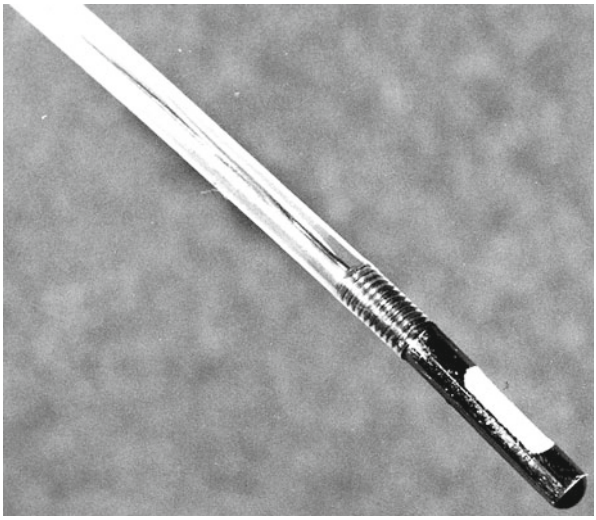

Fig. 32.2 A microtip catheter transducer. Pressure on the *white* membrane results in an altered potential difference across the length of the transducer proportional to the applied membrane deformation (Image courtesy of Steve Payne)

Table 32.2 Artefactual pressure registrations seen with internal pressure transduction systems

Cause	Effect
Direct contact with bladder wall	Erroneously high bladder pressure
Sensor tip at bladder base	Erroneously high bladder pressure
Sensor tip at bladder dome	Erroneously low bladder pressure

voltage coming down the stem of the wire which connects the transducer to an external urodynamic recording device. Positioning of the tip of the sensor may result in artefactual variations in pressure registration (Table 32.2).

Catheter tip transducers are ideal for urethral pressure profilometry and ambulatory urodynamic studies. They have the advantage of not needing priming, are subject to minimal artefactual variations, especially patient movement, and allow easy measurement of resting bladder pressure. Internal transducers are, however, expensive, relatively fragile in use, and are, therefore, not widely used. Internal catheter tip transducers have factory-set zeroes and are calibrated either automatically or manually by submerging the tip of the catheter to a set depth in a column of water. The pressure registration should directly reflect the depth in the water column, in a linear fashion. The pressure reference point, for urodynamic studies, is the middle of the bladder.

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Chapter 33
Principles of Measurement of Urinary Flow

Richard Napier-Hemy

Why Measure Flow?

Patients are notoriously poor at accurately reporting changes in their flow. Urinary flow rate estimation is relatively cheap and noninvasive. It should be used as first-line investigation of male patients with voiding dysfunction but has a less established role in women. It must be remembered that uroflowmetry is a measurement of flow only and that assumptions about detrusor function can only be inferred.

Patients need minimal instruction about the procedure but should have a "normal" desire to void. When the patient performs a flow test, their perception of how typical the flow was, and the amount of urine spillage, should be recorded. Ideally, three free flow rates should be performed, but this may be impractical. The voided volume should again, ideally, be above 200 mL and below the maximum voided volume recorded on the patient's frequency/volume chart. The procedure is often combined with a post-micturition scan to gain information about voiding efficiency. Information gained from uroflowmetry can be used to start treatment whilst avoiding cystometry.

Currently, there are three established means of measuring urinary flow. Each has a funnel to collect the urine, a flow measurement device that can be calibrated, a means of data recording, and a printer. The measuring device principles are given in Table 33.1.

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Table 33.1 Types of uroflowmeter

Type of flow metre	Principle	Advantages	Disadvantages
Rotating disc	*Momentum flux principle*: Urine is directed onto spinning disc, at constant speed, controlled by a servomotor. The power required to maintain a constant disc speed is proportional to the flow of urine opposing the rotation of the disc. The volume is calculated by integration	Accurate flow rate measurements Fast response time	Interpretation of traces: artefacts can arise from "wag effect." See below Results are affected by the density of urine Difficult to clean
Weight transducer	*Gravimetric principle*: Weight of urine collected indicates the volume and, by differentiation, the flow rate	Accurate volume measurements. Relatively simple	Relatively slow response time "Wag effect" Density of urine affects results Density must be set More prone to "knocking" artefacts
Capacitance	*Bimetallic strip*: the electrical capacitance of a dipstick, mounted in the chamber, changes as the height of the column of urine in a container of a standard size alters	Least expensive No mechanical parts	Density must be set Prone to "knocking" artefacts

Adapted from Cafferel et al. (2006)

International Continence Society (ICS) Definitions and Their Application

Flow rate is defined as the volume of fluid expelled via the urethra per unit time. It is expressed in milliliters per second.

Voided volume is the total volume expelled via the urethra. It is the area under the flow curve and can be estimated. In the example shown, each square represents a volume of 50 mL (5 s × 10 mL/s = 50 mL). There are 10 squares of 50 mL and 5 half complete squares under the flow curve. 10 × 50 mL + 5 × 25 mL = approx. 625 mL. This can be used to estimate whether a flow trace is above 200 mL volume and below the usual voided volume for the patient and therefore can be used in their case.

Maximum flow rate (Q_{max}) is the maximum measured value of the flow rate after correction for artefacts. The automated printout generated by most machines will not know what is an artefact and may give a wrong Q_{max}. Looking at the trace is the best way of working out Q_{max}.

Voiding time (T100) is total duration of micturition, i.e., includes interruptions. When voiding is completed without interruption, voiding time is equal to flow time.

Flow time (TQ) is the time over which measurable flow actually occurs. Difference between voiding time and flow time means that there is an intermittent flow. It does not tell you what is the nature of the intermittency.

Average flow rate (Q_{ave}) is voided volume divided by flow time. The average flow should be interpreted with caution if flow is interrupted or there is a terminal dribble. Q_{ave} can be calculated by timing a void and then measuring the volume voided. Volume/time = Q_{ave} (or T100/V = Q_{ave}).

Time to maximum flow (TQ_{max}) is the elapsed time from onset of flow to maximum flow. As the automated Q_{max} measurement can be wrong, the time to Q_{max} must also be ascertained directly from the trace.

Limitations of Urine Flowmetry

Urinary flow rates reflect the interaction between intravesical pressure and urethral calibre, but you can only infer what kind of muscle has caused the increase in urinary flow. Smooth muscle contracts and relaxes slowly and produces the reproducible, skewed, bell-shaped curve shown in Fig. 33.1. Striated muscle contraction with abdominal straining produces more rapid changes in pressure, which are different with each strain. On this basis, the investigator may infer whether bladder emptying is by abdominal strain or detrusor contraction. Uroflowmetry is also subject to artefactual variations (Table 33.2).

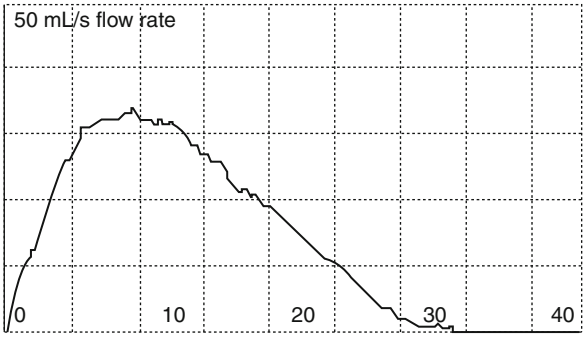

Fig. 33.1 A normal urine flow rate curve and its derived parameters

Table 33.2 Artefacts encountered during uroflowmetry and their influence on intravesical pressure, the flow at the external meatus and the observed flow pattern

Artefact	Effect on intravesical pressure	Effect on flow at the external urinary meatus	Effect on flow record
Cough	Increased	Increased	Short sharp spike of increased flow
Valsalva/strain	Increased	Increased	Wider increased flow spike
Wagging/cruising	No increase	No increase	Sharp spike with decreased flow either side. Caused by the urinary stream being directed across the funnel with artefactual variation in the incident flow recorded by the measuring transducer
Manual urethral occlusion	No increase	Zero flow, then increased	Flow interrupted and goes to zero Urethra fills with urine with increased flow on release of urethral compression
External sphincter closure	Possible small increase	Small increase, then zero flow	Small increase in flow before it stops
Knocking	No increase	No increase	High spike of flow. Spike so bizarre in appearance it could not have been caused by physiological bladder activity

Future Developments

A mobile telephone device app can use the sound of flow to produce a urine flow rate. Sonouroflowmetry (SUF) is in development, and further data is awaited (Zvarova et al. 2010).

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Chapter 34
How to Carry Out a Videocystometrogram (VCMG)

Alexander Springer, Ian Eardley, and Ramnath Subramaniam

Videocystometrography (VCMG) is the most complex study of urinary tract function, combining as it does conventional pressure flow urodynamics with simultaneous imaging of the lower urinary tract. The commonest indications include the assessment of the neurogenic bladder, urinary incontinence and patients who have undergone reconstruction of the lower urinary tract. Videourodynamic studies should only be performed by trained clinicians who are able to both undertake and to interrogate the study so as to be certain that the study reflects the patient symptoms as closely as possible.

Patient Preparation

Antibiotic prophylaxis, trimethoprim or oral cephalosporins, should be administered before VCMG to prevent iatrogenic infections. Children found to have reflux should be prescribed antibiotics in therapeutic dose for 5 days after the study. Videourodynamic studies should be delayed at least 4 weeks after a proven urinary tract infection. If the patient is a child, the parents should have the possibility to attend the examination except where radiation exposure is a risk to them.

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Prior to the study, the patient is asked to void, the free urinary flow rate and the post-void residual both being measured. It is not usual to empty the bladder prior to a VCMG.

The patient is placed in a comfortable position. A 6–10-Fr double-lumen catheter is inserted trans-urethrally or supra-pubically under topical, local or general anaesthesia or with sedation. The latter is often necessary in children. The double-lumen catheter permits simultaneous recording of the intravesical bladder pressure together with filling of the bladder with warm water or Iohexol, Omnipaque® contrast media for fluoroscopy. An alternative is a single-lumen catheter for infusion of fluid combined with a smaller epidural catheter "piggy backed" onto the urethral catheter to measure pressure. A rectal catheter, protected by a condom or the cut end of a standard surgical glove to stop faecal damping, measures the intra-abdominal pressure. Subtraction of the rectal pressure (a surrogate for intra-abdominal pressure) from the intravesical pressure provides the detrusor pressure.

Both pressure lines are connected to solid-state pressure transducers which in turn are connected to the urodynamics machine. Lines are flushed with saline, ensuring that all air bubbles are removed from the system and that there is prompt pressure transmission. The pressure traces should respond promptly to coughing with full subtraction and a rapid return to the resting pressure without any "damping." If the subtraction is imperfect, or if the subtracted trace returns sluggishly to zero, then a further flush of both pressure lines is needed to ensure adequate subtraction. The pressure transducers are set at the height of the pubic symphysis and are then zeroed to atmosphere. This allows measurement of actual bladder and abdominal pressures.

All lines should be carefully fixed in place with tape. The patient is then moved to the position in which the study will take place, and this varies according to the patient, paraplegic patients need the study to be performed supine, and according to the nature of the X-ray equipment; a patient lies down on a tilt table if the study is being performed in a screening room. The patient must be comfortable, and the voiding position should be as close as possible to normal for the individual.

The Study

During the study, real-time visualisation of the bladder pressure, the abdominal pressure and the subtracted detrusor pressure is performed (Fig. 34.1), and simultaneous imaging of the lower urinary tract is also performed. The bladder is slowly filled, particularly in neuropathic patients. Standard fill rates are 50–100 ml/min, although in neuropaths, the rate should be a slow as 10–20 ml/min.

During the test, the patient should be asked to cough at regular intervals. This serves to check that the pressure lines are functioning properly and as a provocative test for detrusor overactivity. X-ray screening should be undertaken at regular intervals. Anatomical and functional details can be identified with screening. When the patient appreciates fullness of the bladder, he/she micturates, usually into a

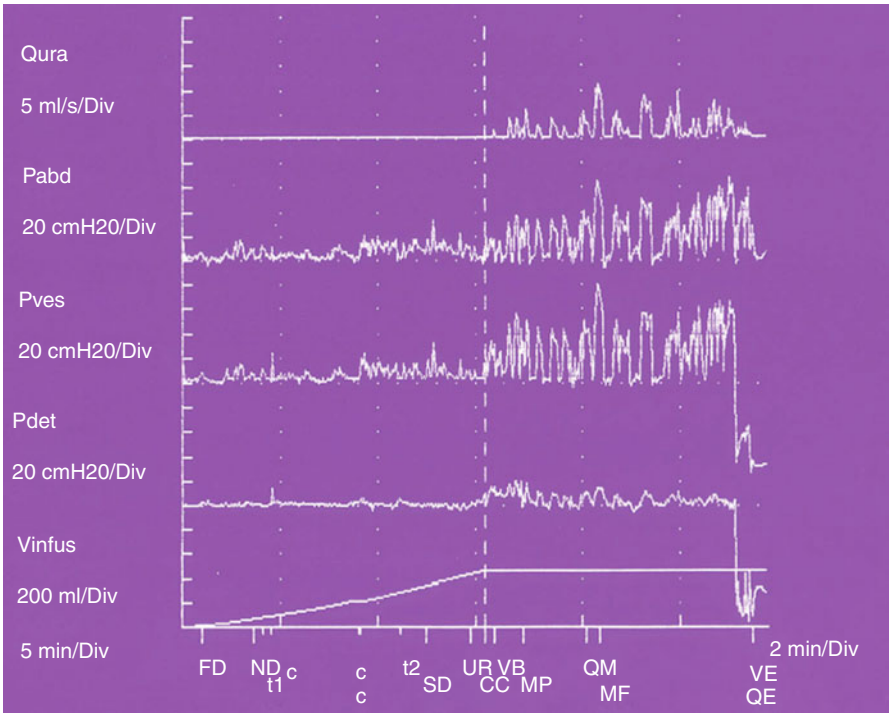

Fig. 34.1 A urodynamic trace from a patient with a hypocontractile bladder. Note the simultaneous measurement of urinary flow rate (*Qura*), abdominal pressure (*Pabd*), bladder pressure (*Pves*), subtracted detrusor pressure (*Pdet*) and infused volume (*Vinfus*). There is excellent subtraction of the abdominal pressure from the bladder pressure, leaving a relatively flat subtracted detrusor pressure trace

commode with facilities for uroflowmetry such that simultaneous pressure flow measurements can be made. Bladder emptying should be checked at the end of the study.

What Is Measured or Observed?

Standard urodynamic measurements include:

- Volume at first sensation
- Volume at strong urge
- Capacity of the bladder
- Leak point pressure (Valsalva and detrusor)
- Detrusor activity
- Pressure flow studies which identify presence of obstruction
- Bladder emptying

In addition, the following information is gained from the imaging system synchronous with the pressure traces:

- Function of the bladder neck
- Function of the external sphincter
- Demonstrable incontinence
- Bladder trabeculation
- Bladder diverticula
- Vesicoureteral reflux

Modification of the Videourodynamic Study

Specific modifications of VCMG that are possible but rarely performed include:

- Occlusion of the bladder neck. May be necessary in gross sphincteric incompetence using a balloon catheter.
- Electromyography may be applied to the pelvic floor muscles, identifying sphincteric and bladder neck function. This is not easily performed in children.
- Urethral pressure profilometry using a solid-state catheter-mounted transducer, withdrawn steadily through the urethra.

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Chapter 35
The Whitaker Test

Jeremy Oates and Kieran O'Flynn

The Whitaker perfusion pressure-flow (PPF) study was developed to determine the presence, or absence, of obstruction in the dilated upper urinary tract in children. It is now uncommon to resort to this invasive investigation, but it still has a role in the management of paediatric or adult patients with hydronephrosis, or hydronephroureterosis, where the presence of obstruction remains unclear as a consequence of equivocal diuresis renography.

History

The initial pressure-flow study, popularised by Whitaker, involved the provocation of a diuresis with high-volume oral fluid intake (40 mL/kg plus volume of urine output) and the measurement of subsequent renal pressures with either a nephrostomy tube or epidural catheter passed percutaneously into the kidney. Although results were promising and correlated well with clinical findings, the test itself was lengthy and uncomfortable, and the results were difficult to interpret. As the diuresis was generated by oral intake, it was difficult to predict what the achieved flow rate was and when the maximal flow occurred. In poorly functioning kidneys, an adequate flow rate may, therefore, not have been generated.

Accurate measurement of the flow rate was, therefore, essential for interpretation of recorded renal pressures and was standardized using an infusion pump. The addition of radio-opaque contrast medium allowed for radiological assessment of ureteric peristalsis and correlation with recorded pressures. Percutaneous access

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to fill the pelvicalyceal system, with an incident inflow of at least 10 mL/min, was also used to record the renal pressure. Increasing inflow to 20 mL/min and concomitant measurement of intra-vesical pressure were further modifications.

How a Whitaker Test Is Performed

The Whitaker test comprises three manoeuvres:

- Nephrostomy insertion
- Intra-renal and intra-vesical pressure measurement
- Percutaneous intra-renal perfusion

Nephrostomy insertion can usually be performed under local anaesthesia, though in children, general anaesthesia may be required. A 14-G single-lumen percutaneous nephrostomy tube is passed under sonographic or fluoroscopic guidance into the renal pelvis; occasionally, a double-lumen nephrostomy may be used. The large size of the catheter is to minimise catheter pressure resistance during perfusion. A rest period of 1–2 days before pressure measurement allows any haematuria to settle and minimises the risk of extravasation during perfusion.

Prior to pressure measurement, the bladder is drained with a urinary catheter, and the baseline intra-vesical pressure (P_{ves}) is recorded using a zeroed, external water-filled, transducer. The patient is then placed in a supine or semi-prone position. A baseline, zeroed, renal pelvic pressure (P_{ren}) is recorded using a contrast-filled transducer connected to the single-lumen nephrostomy, using a Y-connector (Fig. 35.1), or the second lumen of a dual-lumen nephrostomy tube.

Under fluoroscopic control, the kidney is then perfused with a 50% diluted iodine-based contrast medium, at body temperature, at 10 mL/min via an infusion pump. At least 200 mL of fluid is perfused dependent upon the capacity of the renal pelvis. P_{ren} and P_{ves} are recorded during the study, and the presence of ureteric filling, and peristaltic activity, is usually observed, and recorded, at the same time as pressure measurement. Subtracting circuitry in the recording device usually facilitates the display of $P_{ren} - P_{ves}$. The study may be terminated if severe pain is experienced, by the subject, during perfusion. Characteristic results obtained from a pressure-flow study are shown in Table 35.1.

If no significant pressure rise is seen at 10 mL/min, the inflow is increased sequentially to a maximum flow rate of 20 mL/min. If a negative result is achieved at the highest flow is achieved, the bladder is filled and the PPF repeated, firstly at 10 and then 20 mL/min. If there still has been no noted increase in pressures at this point, the test should then be repeated with the patient standing. Non-standard positioning can be useful in the investigation of suspected renal ptosis, malpositioned kidneys, or in patients with intermittent, unexplained symptoms.

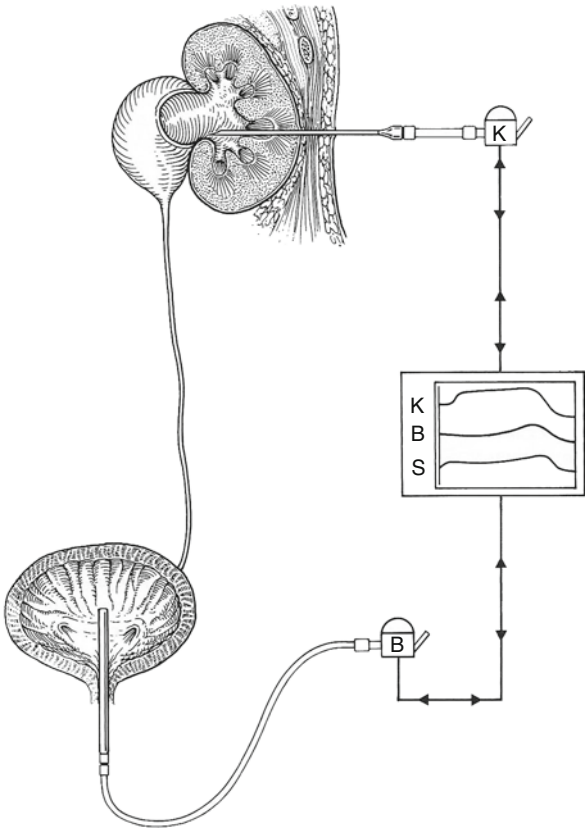

Fig. 35.1 The Whitaker test set-up. The kidney transducer is connected *in-line* with the perfusion catheter which is placed in the renal pelvis. The transducer (*K*) measures P_{ren}. Synchronous measurement of bladder pressure (*B*) measures P_{ves}, and subtracting circuitry displays the subtracted pressure (*S*) $P_{ren} - P_{ves}$ (Illustration courtesy of S Payne)

Table 35.1 The relevance of the subtracted pressure changes during perfusion to the presence or absence of drainage impairment

Subtracted pressure ($P_{ren} - P_{ves}$) (cmH_2O)	Clinical relevance
>22	Obstructed drainage
15–22	Equivocal drainage
<15	Unimpaired drainage

Utility

The correlation between PPF and diuresis renography is variable, reported to be in the region of 60–65% in several series, though this increases to 72% if equivocal cases are excluded. However, an obstructed or non obstructive result seems to have strong positive predictive value for successful response to surgical treatment, or conservative management, respectively, as judged by preservation of renal function. This is even when the results are contradictory to those obtained by diuresis renography.

PPF studies are not required in symptomatic patients with an unequivocal diuresis renogram, but may be very helpful in the symptomatic patient with negative, or equivocal nuclear medicine studies, when surgery is contemplated. This is particularly so in poorly functioning kidneys or those that have significant dilatation of the collecting system or ureter.

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Chapter 36
Sphincter Electromyography (EMG)

Katherine E. Burnett and Christopher D. Betts

Electromyography (EMG) is the study of bioelectrical potentials from striated muscle. Urethral sphincter activity may be studied in relation to bladder function, and this is known as kinesiologic EMG. Conventional EMG is used to examine individual motor units in striated muscle and to identify abnormal spontaneous activity. Conventional sphincter EMG is the most important neurophysiological test relating to the urinary tract.

Kinesiologic EMG

Kinesiologic EMG is undertaken with surface or needle electrodes. Neither is ideal since needle electrodes are readily dislodged and surface electrodes are very susceptible to artefacts. In health there is continuous tonic activity in the urethral sphincter which only becomes silent during voiding (Fig. 36.1). In patients with spinal cord lesions, the detrusor and the sphincter may be uncoordinated (Fig. 36.2). Combined urodynamic and EMG studies are highly interesting but the presence of detrusor sphincter dyssynergia (DSD) in patients with spinal lesions can usually be deduced from the symptoms, uroflowmetry, residual volumes and video-urodynamic tests.

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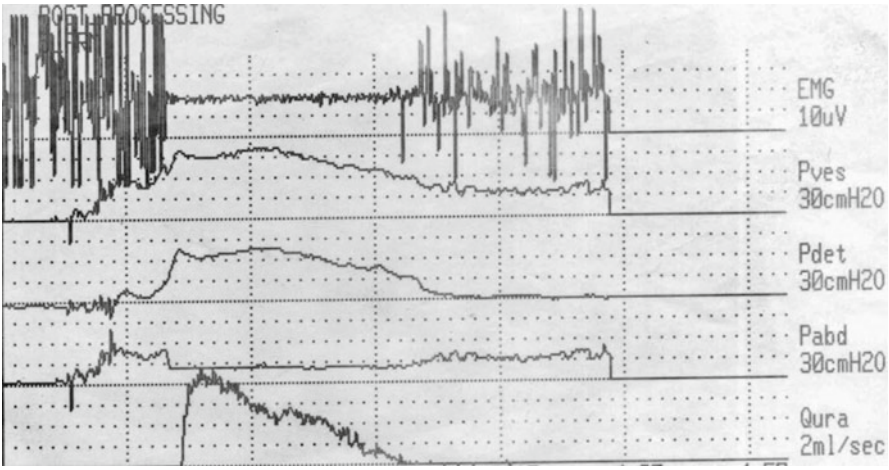

Fig. 36.1 Kinesiologic urethral sphincter electromyography with needle electrode. Electrical silence in the external urethral sphincter during voiding is normal

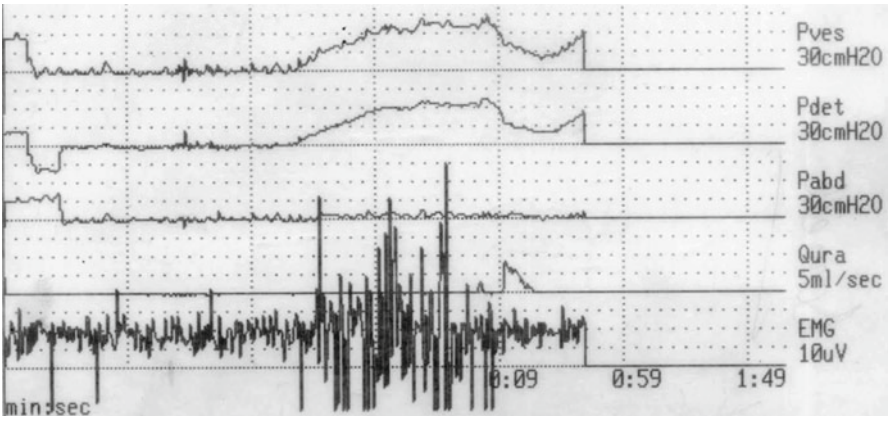

Fig. 36.2 Recording from a patient with MS, showing involuntary increased sphincter activity occurring when the detrusor contracts (detrusor sphincter dyssynergia (DSD)); voiding only occurs when the activity in the sphincter decreases

Conventional EMG

Conventional EMG of the sphincter is an exacting neurophysiological test and it would be unusual for a urologist to acquire this skill in normal training. Concentric needle electrodes (CNEs) are most commonly used and in men the CNE is guided into the urethral sphincter via a transperineal route. A finger in the rectum may help guide the needle in the direction of the apex of the prostate. In women after topical

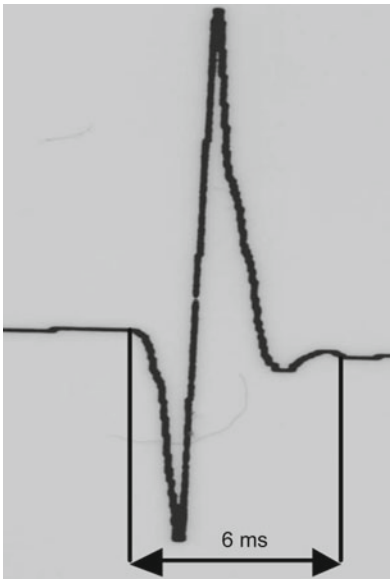

Fig. 36.3 Normal motor unit recorded with a CNE from the urethral sphincter

anaesthesia, the CNE is inserted 5 mm lateral to the meatus and advanced parallel to the urethra. A transvaginal needle insertion technique has also been described. The audio output of the EMG machine is very useful in positioning the CNE. The sphincter is heard in the 'distance' and the CNE can be advanced towards the tonically firing motor units. If sacral root innervation (Onuf's nucleus) is being tested then the anal sphincter is more accessible.

After complete denervation there is a period of electrical silence and this is followed by the appearance of fibrillation potentials. With axonal reinnervation motor unit potentials (MUPs) appear again and these are generally polyphasic and prolonged. The duration of MUPs is the most commonly measured parameter (Fig. 36.3) and prolongation of motor units is evidence of denervation and reinnervation. The MUPs in reinnervated muscle are often polyphasic in addition to being prolonged (Fig. 36.4). The duration is the time from first deflection to the point of return to the baseline and in normal sphincter muscle the MUPs are less than 7msec (Fig. 36.3).

Conventional sphincter EMG may help distinguish between idiopathic Parkinson's disease (IPD) and multiple system atrophy (MSA). Patients with MSA often first present to urologists with urinary symptoms and/or impotence. In MSA, degeneration in Onuf's nucleus causes sphincter denervation and reinnervation whereas in IPD the sphincters are normally innervated (Fig. 36.4). Similar reinnervation changes may be found in patients with cauda equina lesions.

A small number of prolonged polyphasic units may be found in the sphincters of normal individuals particularly in the elderly or if there is a history of pelvic surgery or vaginal delivery. Particular care is needed in interpreting the sphincter EMG findings in relation to the clinical situation. In a patient with possible MSA it would be standard practice to measure the duration of ten motor units from different areas of

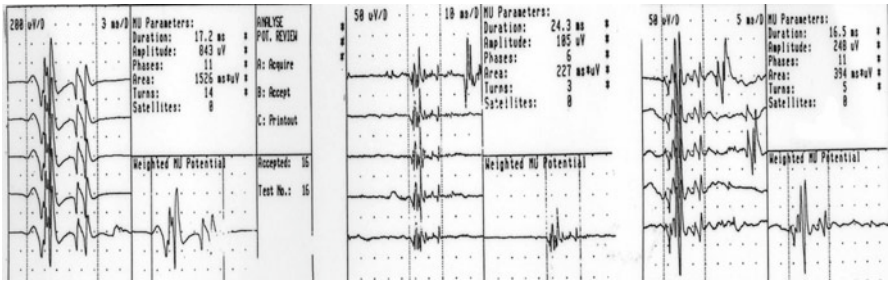

Fig. 36.4 Three motor units shown recorded from a patient with probable MSA. The MUPs are shown in falling leaf display in the left panels. The units are polyphasic and of markedly prolonged duration at 17.2ms, 24.3ms and 16.5ms (note different sweep speeds 3ms/D-10ms/D)

the sphincter. The mean duration of ten MUPs and the proportion of units of greater duration than 10 ms can be plotted and compared with control data (see further reading). In the authors experience the EMG findings in patients with suspected MSA tend to fall into one of three categories; normal, equivocal or profoundly abnormal. Repeating the EMG after a period of months may sometimes be helpful in those patients whose initial results are equivocal.

Urologists have been reluctant to undertake transurethral resection of the prostate (TURP) on men with parkinsonism mainly on the basis of a paper from 1988 which reported a high rate of incontinence after surgery. However, it is now realised that many of the patients who did poorly in this study were very likely to have had MSA and not IPD. More recent work has also shown that TURP should not be considered completely contraindicated in men with IPD provided that they have been appropriately investigated with urodynamic studies and possibly sphincter EMG. It is now established that men with MSA do not do well after TURP and likewise women with MSA do poorly after surgery for incontinence.

Professor Fowler described abnormal spontaneous myotonia-like activity in the urethral sphincters of some premenopausal women with urinary retention. On the audio output of the EMG machine the activity is striking and has been likened to the underwater recordings of whale song. Detailed EMG analysis has shown that the ‘sounds’ are made up of two components complex repetitive discharges and decelerating bursts. The disorder may arise from the abnormal transmission of electrical activity between muscle fibers (ephaptic transmission). This myotonia-like activity has also been reported in women with normal voiding. Women may have a natural tendency to this activity in the urethral sphincter muscle and only in certain circumstances does it cause voiding dysfunction.

Kinesiologic EMG gives information about the synchronisation of the detrusor and urethral sphincter. Conventional sphincter electromyography is an important clinical test which enables an assessment of the innervation of the striated sphincter muscle and the detection of abnormal spontaneous activity.

Clinical Uses of EMG

It may be useful when evaluating men with IPD who have bladder outlet obstruction, as a prelude to prostatectomy, to differentiate between IPD and MSA. Similarly, it is of use in investigating some women with unexplained sphincter weakness. It is now well established that men with MSA do not achieve good results from TURP, and likewise, women with this condition do poorly after surgery for incontinence.

It is also useful in investigating unexplained urinary retention in pre-menopausal women. Retention, in certain circumstances, may be found to be in association with abnormal spontaneous myotonia-like activity in the urethral sphincter, explaining the inability to void.

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Chapter 37
Tumour Markers

Richard Khafagy and William Cross

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. A tumour marker is a biomarker that is specific to a malignant tumour.

Clinical Applications

Tumour markers can be used in a number of ways:

- To determine the risk of developing a disease
- In early detection and screening
- To establish the diagnosis
- As a prognostic marker
- To monitor the response to therapy
- To identify the presence or otherwise of a possible therapeutic target
- In clinical trials, to stratify populations and to aid interim analysis

Bladder Cancer

There is no single ideal marker, and the utility of tumour markers in clinical diagnostic and prognostic decision-making remains limited. A summary of the characteristics of those that are currently available is shown in Table 37.1.

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Table 37.1 Characteristics of some tumour markers for the diagnosis of bladder cancer

Marker		Description	Diagnostic sensitivity (%)	Diagnostic specificity (%)
Bladder tumour antigen assay	BTA-TRAK	Measures complement factor H related protein in urine	24–89	52–93
	BTA-stat		57–79	48–95
Fluorescence in situ hybridisation (FISH), e.g. UroVysion assay		Detection of chromosomal anomalies in exfoliated urothelial cells	69–87 High grade ≫ low grade CIS ~ 100%	89–96
NMP-22		A monoclonal antibody test for a nuclear matrix protein	49.5–65	40–87.3
ImmunoCyt		Immunocytological assessment of tumour-associated antigens	38.5–100	73–84.2
Microsatellite analysis (investigational)		PCR detection of genomic alterations	72–97	80–100
Urine cytology		Cytology	16–89	81–100

Testicular Cancer

Testicular tumour markers play an important clinical role in patient management. In recognition of the clinical utility, serum tumour marker levels are included in the TNM staging classification (S category) and the International Germ Cell Cancer Collaborative Group prognostic staging system for metastatic of germ cell tumours.

Levels should be performed before and after orchidectomy and during routine follow-up to monitor therapeutic response. Tumour marker levels should be interpreted with caution; metastatic disease cannot be excluded on the basis of normal marker levels, and persistently elevated levels post-orchidectomy does not always signify metastatic disease since liver dysfunction and hypogonadotropism can also cause raised levels.

Alpha-fetoprotein (AFP) is expressed by pure embryonal carcinoma, teratocarcinoma, yolk sac tumour and combined tumours, but not by pure seminoma or pure choriocarcinoma. The serum half-life of AFP is 3–5 days, and the normal level is <10 ng/mL.

Human chorionic gonadotrophin (hCG) is the β-subunit of human chorionic gonadotrophin. It is expressed by syncytiotrophoblastic cells of choriocarcinomas, teratomas and seminomas. The serum half-life of hCG is 24–26 h, and the normal level is <5 mIU/mL.

Lactate dehydrogenase (LDH) is a ubiquitous cellular enzyme that correlates with disease burden. Due to its low specificity, other staging factors need to be considered when interpreting the clinical significance of an elevated LDH level. An elevated LDH level occurs in 50–75% of disseminated seminomas and is associated with a higher relapse rate.

Placental alkaline phosphatase (PLAP) is a foetal isoenzyme that is elevated in up to 40% of patients with advanced disease. In cigarette smokers, serum PLAP concentrations may be increased up to ten times. The normal half-life of serum PLAP after orchidectomy is between 0.6 and 2.8 days.

Prostate Cancer

Historically, acid phosphatase was associated with metastatic disease, but its utility is poor, and it is now rarely used.

Prostate-specific antigen (PSA) is a 33-kDa glycoprotein that acts as a serine protease that liquefies semen. PSA circulates in serum in both unbound and bound forms (complexed to proteases), and the majority is rendered inactive. The serum half-life of PSA is 2–3 days.

Serum PSA levels vary with age, race, prostate volume, and in pathological conditions affecting the gland, including manipulations of the prostate. Although PSA is organ specific, an elevated serum level is not disease specific (low specificity). In prostate cancer, neoplastic cells do not make more PSA than normal tissue and the raised serum PSA level that is typically seen results from disrupted cellular architecture

within the prostate. The usual cut-off value for proceeding with prostate biopsy is 4 ng/mL, but the literature demonstrates clearly that there is no level of PSA at which there is a zero risk of having a prostate cancer. As there is no serum-threshold that is diagnostic of prostate cancer (low sensitivity), multiple PSA derivatives (including PSA density, PSA velocity, age-specific ranges and % free PSA) have been developed and investigated to (try to) improve the diagnostic accuracy. The clinical application in diagnosis of these derivatives remains controversial.

While PSA is a less than perfect tool for screening and diagnosis, it does have great utility in monitoring the response to therapy. Following radical prostatectomy, the serum PSA level should become undetectable. A persistent or recurrent and rising PSA level indicates the presence of recurrent or residual disease. PSA expression is androgen dependent, and the serum level is used to measure and monitor the therapeutic response to hormone manipulation and chemotherapy.

Due to the heterogeneity of prostate cancer, alternative markers are being sought to improve the diagnosis and management.

Prostate cancer antigen 3 (PCA3) is a noninvasive urine test introduced for the detection of prostate cancer. Although the function of PCA3 remains unknown, PCA3 mRNA is over-expressed in prostate cancer. In urine collected following prostatic massage, the test quantifies both the urinary PCA3 mRNA and PSA mRNA, and the result is represented as a ratio of the two mRNAs, referred to as the "PCA3 score." PCA3 score is not affected by prostate volume, and a score of 35 is reported to offer optimal diagnostic accuracy.

The quantitative PCA3 score correlates with the probability of a positive prostate biopsy and the tumour volume in radical prostatectomy specimens.

The widespread clinical utility of the PCA3 test remains to be established, although it is currently used to guide the decision regarding re-biopsy in men who have previously had a negative prostate biopsy but who still have a raised PSA.

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Chapter 38
Urine Cytology

William Cross and Richard Khafagy

Urine cytology is the pathological interpretation of the morphological features of shed cells in stained cellular smears from urine. Practically, cytology specimens are evaluated for the presence or absence of urinary tract cancer, specifically urothelial cell carcinoma. Cytological features suggestive of neoplasia include increased cellularity, increased nuclear to cytoplasmic ratio, nuclear membrane irregularity, coarse dense nuclear chromatin, and an absent/small nucleolus.

Specimens

Voided Urine

The sample should be obtained 3–4 h after the last micturition. Avoid the first voided urine in the morning as this is prone to cellular degeneration. Voided urines are superior to instrumented urine samples in detecting malignancies of the urethra.

Instrumented Specimen

This is a sample obtained through a catheter or after instrumentation of the urinary tract (e.g., cystoscope, ureteroscope, ureteric catheter). Instrumented samples usually have increased cellularity and consequently urinary tract washings are the most

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sensitive cytological method for cancer detection. Cytology of urethral washings post-radical cystectomy is an inexpensive and minimally invasive surveillance technique for detecting recurrent disease. Cytology has been demonstrated to detect recurrent disease significantly sooner and at an earlier pathological stage than those presenting with recurrent symptoms (median time 11.6 vs. 30.9 months).

Ileal Conduit Urine

Specimens often contain degenerate intestinal epithelial cells, making cytological interpretation difficult.

Processing

Preparation techniques vary depending on laboratory and are often automated. Basically, urine is collected in a sterile container and processed fresh or mixed with a preservative for delayed evaluation. The cells in the urine are concentrated by centrifugation, washed, re-suspended, and then transferred to a slide for fixation, staining, and examination. Slides are typically stained with Papanicolaou stain (nuclear stain) and occasionally a modified Wright–Giemsa stain to highlight non-nuclear features.

Pathological Interpretation

An adequate sample is critical to allow cytological interpretation. As most urine samples contain a few urothelial cells, if no cells are seen in the sample, a repeat specimen should be considered.

A normal sample may contain normal urothelial, squamous, and/or glandular cells, which line the urinary tract. Inflammatory cells, red blood cells, sperm, casts, and crystals may also be seen.

Transitional Cell Carcinoma

Urothelial carcinoma is cytologically classified as having low-grade or high-grade nuclear changes consistent with a diagnosis of cancer. There is good correlation between cytological appearance and histopathological grading.

Urine cytology has high specificity for high-grade disease and carcinoma-in-situ (CIS) (>90%). A positive result irrespective of negative cystoscopic and radiological findings suggests the presence of a urinary tract malignancy, indicating the need for further investigation. The reported sensitivity of urine cytology is very variable (median 35%, range 13–75%) and is mainly dependent on the histological grade of the tumour (~60% for grade 3).

The management of a suspicious urine cytology result is controversial. Nabi et al. reported on a series of 70 patients who had persistent suspicious urine cytology and a negative initial evaluation for malignancy in the investigation for haematuria. Twenty nine (41%) patients were subsequently diagnosed with urothelial cell carcinoma and the mean duration for the appearance of lesions was 5.6 months. This result supports the view that persistent suspicious/atypical urine cytology needs further investigation and evaluation.

Interpretation of a sample can be complicated by cellular degeneration and changes due to chemotherapy (including BCG), radiation treatment, urinary tract calculi, or infection.

Squamous Cell Carcinoma

Primary well-differentiated squamous cell carcinomas are difficult to diagnose because they show little cytological atypia. Most bladder squamous cell carcinomas are keratinizing and atypical parakeratotic cells and keratin pearls can be seen in urine samples. Atypical parakeratotic cells may be secondary to squamous metaplasia associated with urinary tract calculi, catheters or chronic inflammation. In these conditions acute inflammatory cells are usually present.

Adenocarcinoma

Primary adenocarcinoma of the bladder is rare and consists of the subtypes, signet-cell carcinoma, clear cell carcinoma and those that resemble colonic carcinomas (>85%).

Other Malignancies

Other malignancies that can be diagnosed by urine cytology include small cell carcinoma and metastases/direct spread from renal, colonic, prostatic, and gynaecological tumours.

Alternative Urine Markers

Due to the limitations of urine cytology there has been considerable effort to develop alternative urine markers for bladder cancer. These include BTA, NMP-22, multiprobe FISH, and proteomics. The reported sensitivity of these markers is higher but the specificity is poorer than conventional cytology which has limited their clinical utility.

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Chapter 39
Histopathological Processing, Staining, and Immuno-histochemistry

Lorna McWilliam

Histological examination of biopsy material is an essential adjunct to diagnosis, yet the process by which a pathological slide is created is poorly understood by most non-histopathologists. Basically, it consists of three stages before the histological slide can be interpreted.

Tissue Fixation

Formalin is the standard fixative used in many histopathology departments as it is compatible with most histological stains, preserving tissues for many months. Tissue fixation occurs when cross-linking of proteins takes place, and this preserves cellular morphology. Formalin penetrates tissue at approximately 0.5 mm per hour, so it is important to immerse tissues, particularly large specimens, in adequate volumes of fixative. One disadvantage of using formalin is that there is loss of antigenicity, with time, necessitating special techniques to retrieve antigens if immuno-histochemical examination of the tissue is required.

Processing of Tissue Samples

Tissue may be received as small biopsy fragments, core biopsies, chips or larger resection specimens. Smaller samples are placed directly into plastic cassettes for processing. Larger resections are "cut up" into cassette-size pieces approximately

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30×25 mm and up to 4 mm in thickness. Techniques using "mega" cassettes, to allow full slices/whole mounts of resection tissue, are also in standard use particularly for histological examination of radical prostatectomy specimens. These enable entire slices of a whole organ to be seen on one slide.

Tissues placed in cassettes undergo automated processing involving a series of steps over several hours:

1. Dehydration. Water is removed from the tissue and replaced by alcohol. This allows non-aqueous embedding media, such as paraffin, to penetrate the specimen.
2. Clearing. The alcohol is then replaced by a clearing agent to help tissue infiltration by the embedding medium. This agent has to be miscible with alcohol and the embedding medium; the most commonly used clearing agent is xylene.
3. Embedding. Xylene is, in turn, replaced by paraffin wax in the embedding step to make the tissues hard enough to cut.
4. Cutting. When cooled, the embedded tissue is cut into very thin sections, normally 3–4 μm, with a microtome knife.
5. Mounting. These slices are then mounted onto glass slides ready for staining. Smaller samples such as bladder and prostate core biopsies may have multiple levels cut through one sample, and sections in between the levels are saved for immuno-histochemical staining, if required.

Staining

Hematoxylin and eosin (H&E) staining is the stain most commonly used in histopathology. Hematoxylin stains cell nuclei blue, while eosin stains cytoplasm, connective tissue and other extracellular substances pink or red. H&E staining can be used to determine the size of the nucleus in tumour cells and to show nuclear features such as nucleoli which can be important, particularly in the diagnosis of prostate carcinoma and prostatic intra-epithelial neoplasia (PIN) in some cases.

Immuno-histochemical staining can be used in a number of ways. It may be used to identify the tissue of origin of metastatic tumours or to identify specific tumour markers or tumour types. The basis of immuno-histochemistry is an antigen-antibody reaction, revealed in the tissue by a chromagen complexed with, or activated by, antibody, which is visualised by the pathologist down the microscope. Most immuno-histochemical staining is now automated. Immuno-histochemistry requires the unmasking of some tissue antigens, by heat treatment or enzyme digestion, in formalin-fixed tissue, prior to the application of the primary antibody.

Antibodies have been specifically developed against particular tissue antigens. Antigen-antibody complexes are visualized by attaching a secondary antibody to the complexed tissue aggregate which, in turn, is converted into a coloured end product by the activation of a chromagen or by the incorporation of a marking chromagen to the antibody.

Immuno-Histochemical Stains Commonly Used in Urological Diagnosis

Prostate carcinomas: Unless poorly differentiated, generally stains with prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP), and these stains can be used to confirm cells of a prostatic origin either in primary or metastatic locations. High-molecular-weight cytokeratins and p63 are used particularly in prostate core biopsies to identify the presence of basal cells in atypical small acinar proliferations (ASAP) when trying to differentiate from adenocarcinoma. Prostatic carcinomas are negative for basal cell markers, whereas most benign conditions that can be confused with prostatic carcinoma are positive. Alpha-methylacyl-CoA racemase (AMACR) can be used to support a morphological diagnosis of prostate cancer.

Urothelial carcinomas: Cytokeratins 7 and 20 can be used to confirm the presence of tumours of urothelial origin, particularly cytokeratin 7, as can the uroplakins UP1a, 1b and 2. Cytokeratin 34BE12 is also generally positive in urothelial carcinomas. Cytokeratin 20 and p53 staining patterns can be useful in supporting a diagnosis of transitional carcinoma in situ (CIS) where doubt exists.

Renal cell carcinomas: CD10 and RCC (renal cell carcinoma antibody) are useful markers of renal cell carcinoma in general. Other antibodies are of use in the differentiation of different types of primary renal malignancies and in the differentiation of oncocytoma from chromophobe renal cell carcinoma. Cytokeratin 7 can be helpful in this latter distinction as its pattern of staining is different in these two entities. CK7 is also positive in papillary renal cell carcinoma. TFE3 (transcription factor gene product) is a marker of translocation carcinomas.

Testicular tumours: Antibodies commonly used to help classify and diagnose testicular germ cell tumours and intra-tubular germ cell neoplasia include OCT3/4, CD30, CD117, PLAP, HCG and AFP. Inhibin, melan A and S100 can be useful markers of some sex cord stromal tumours.

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Part IV
Technology: Operative

Chapter 40
Principles of Urological Endoscopes

Luke Gordon

Urological endoscopes can fall into one of four categories based on how the image is transmitted along the telescope:

- Rod-lens endoscopes
- Flexible endoscopes
- Semi-rigid endoscopes
- Digital, distal-tip chip endoscopes

Rod-Lens Endoscopes

These are considered in Chap. 41.

Flexible Endoscopes

Cladded glass rods cores conduct light through internal reflection with little loss of light intensity. A single glass fibre when stretched to 1/100 mm in diameter and combined with multiple fibres in an ordered, coherent bundle can transmit a complete, but compound, image. A flexible ureterorenoscope has around 4,000 fibres in the bundle and can deflect 270° in both directions at the tip.

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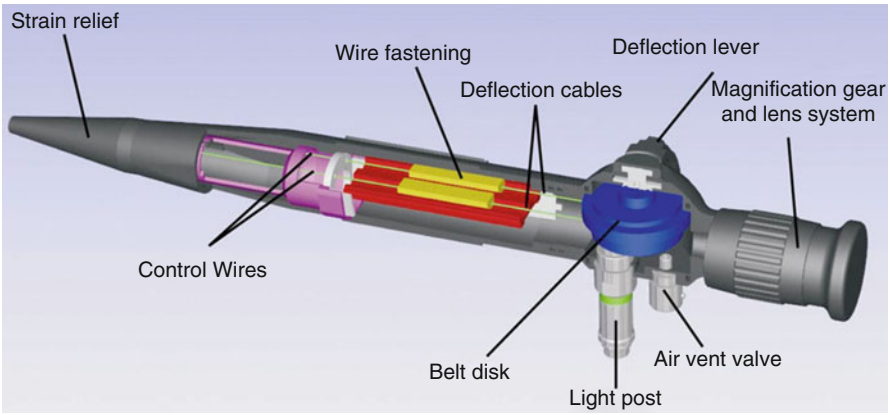

Fig. 40.1 The control components of a flexible endoscope (Image courtesy of Karl Storz)

In addition to the coherent fibre bundle for vision, there is a separate noncoherent bundle that transmits the light into the body cavity, an instrument channel to allow irrigation and instrumentation and two control wires that are connected to the deflection leaver to control the distal tip up and down (Fig. 40.1). All of these elements are free to move independently of each other housed in the vertebrae of the scope as it flexes. An outer cover maintains a water-tight environment, allowing the scope to be effectively cleaned. Any leaks in the outer cover or inner working channel will allow fluid ingress into the scope which will affect the view and ultimately seize up the moving parts. It is important to leak test the scope before every use as fluid ingress is also a potential cross contamination risk.

The benefits of flexible endoscopes are:

- Flexibility, the telescope conforms to the anatomy and not the other way round.
- A deflecting tip allows the scope to view and access areas otherwise off limits to rigid telescopes.

The limits of flexible endoscopy are:

- The image quality is limited by the mechanics and then the physics of the individual fibre's size and by the number of fibres in the bundle – the image is not as clear as the coherent image provided by a similar-sized Hopkins rod-lens telescope and can suffer from the moiré effect.
- Due to the complex nature of the scopes and the fine manufacturing processes, the scopes are expensive to purchase and maintain, relative to rod-lens instruments.

- The materials used to make the flexible parts will not resist the heat and processes involved in steam sterilisation, meaning that most flexible endoscopes in urology are simply decontaminated and not sterile.

Semi-Rigid Endoscopes

These instruments use the same coherent image bundle and noncoherent illumination bundle technology as flexible scopes but are housed in a semi-rigid metal skin rather than flexible vertebrae; they do not deflect at the tip. Manufactures turn to semi-rigid telescopes for longer or smaller diameter scopes. In the case of a semi-rigid ureteroscope, the design allows a degree of malleability whilst maintaining the rigidity to advance up a torturous ureter. Semi-rigid telescopes are often used in paediatric endoscopes where the scope diameters are between 1 and 2 mm. It is possible to make rod-lens systems this size, but their relative fragility necessitates a compromise between the optical view and durability.

Digital, Distal-Tip Chip Endoscopes

Traditionally, any image made through a flexible endoscope is viewed on a monitor; this necessitates attaching a camera head to the eyepiece of the scope where it is converted to a digital format. However, good your camera is, the image will be limited by the fibre-optic system of the telescope. With the miniaturisation of charge-coupled device (CCD) and complementary metal–oxide–semiconductor (CMOS) video chips, it is now possible to mount the chip at the distal tip of the telescope without increasing the overall size of the telescope. Removing the optical fibres and placing the chip at the source have dramatically improved the quality of images available from a flexible endoscope.

8.5Fr flexible ureterorenoscopes utilise the latest CMOS technology to produce stunning images of the upper tract without compromising on the external size, instrument channel or 270° up/down deflection (Fig. 40.2). LED illumination technology is incorporated into the body of the handpiece, and light is transmitted into the patient by a conventional noncoherent fibre bundle. This eliminates the need for a light guide cable, thus reducing the weight of the instrument and improving its fine manipulation during surgery. Distal-tip chip technology is likely to represent the future of flexible endoscopy in urology.

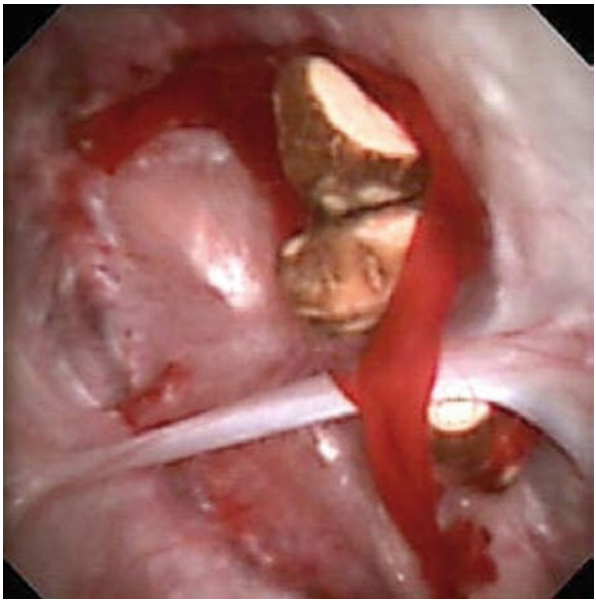

Fig. 40.2 Endoscopic view of stones in the region of the renal papilla from a CMOS chip endoscope (Image courtesy of Karl Storz)

Chapter 41
Rigid Endoscope Design

Luke Gordon

Rigid Endoscope Construction

A contemporary rigid endoscope consists of:

- An optical system – comprised of a distal tip objective lens system, a relay system in the body of the telescope and a diopter lens which magnifies and brings a coherent image to the eyepiece. This standard DIN eyepiece allows direct ocular vision or the connection of a camera head.
- A mechanical sheath that mounts this system and protects it from external influences. The housing allows the endoscope complex to be effectively sterilised through steam autoclaving and offers the glass lenses protection from physical damage.
- A noncoherent glass fibre system to transmit light into the patient and illuminate the cavity under view. The fibre bundle runs through an outer shell of the telescope from the light post to the distal tip and uses the same type of fibres as in a fibre-optic light cable.
- An instrument/flow channel through which peripheral instrumentation and irrigants can be passed.

This combination of components gives a durable, flexible endosurgical system with a coherent image that has mechanical strength and can be used to generate torque. It can be steam or heat sterilised.

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Fig. 41.1 A simple lens endoscope as first described by Nitze. The lenses are shown in *blue* (Image courtesy of Karl Storz)

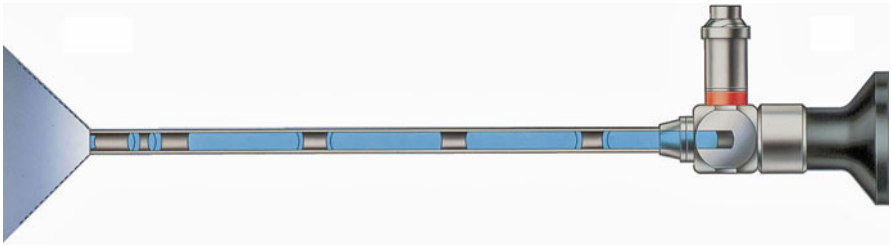

Fig. 41.2 Hopkins rod-lens array endoscope. The lenses are shown in *blue* (Image courtesy of Karl Storz)

Conventional Optical Systems

In 1877, Maximilian Nitze demonstrated his first conventional thin lens system cystoscope (Fig. 41.1). This endoscope, although a landmark in endoscopic surgery, had its drawbacks. Refraction occurred as light passed through the thin lenses seated at intervals, which resulted in a dark and distorted image. In addition, the first endoscopes used a glowing platinum wire, and later an incandescent light bulb, at their distal tip as their sole source of illumination. Endoscopic urology as we know it today was not developed until the problem of thermal tissue injury caused by this illuminating source was solved.

Rod-Lens/Cold Light Optical Systems

In 1959, Prof. Harold Hopkins of the University of Reading designed and patented the rod-lens system, and in 1960, Dr. Karl Storz developed fibre-optic cold light illumination utilising a noncoherent fibre bundle with an externally generated light beam. In 1966, they collaborated to produce the Hopkins rod-lens system in which the rod lenses are seated at close intervals. This ingenious design of a glass rod with air "lenses" (Fig. 41.2) and externally generated transmitted light resulted in vastly improved image brightness, clarity, and field of view from a smaller-diameter telescope. Light is guided to the tip of the endoscope via a noncoherent fibre bundle which starts in the upward projecting "light" pillar. This is attached, via a noncoherent fibre-optic light guide, to the external light source.

The distal tip objective lens can be angled off the 0° to give an oblique view – the most commonly used angles in urology are 12°, 30°, and 70°. By rotating these scopes on their axis, a differential field of view can be achieved with minimum physical trauma to the structure being examined.

In urology today, the rod-lens system is incorporated into all adult rigid cystoscope, resectoscope, nephroscope, and laparoscopic instruments.

Modified Conformations of the Rod-Lens System

In the nephroscope, the requirement for a straight working channel necessitates an offset parallel or angled offset eyepiece; however, the telescope still uses rod lenses and fibre-optic light transmission but with a 6° angle of view.

Telescopes can incorporate instrument and irrigation channels as part of an integrated design. These instruments have the advantage of being generally more durable but lack the versatility of being able to interchange peripheral instrumentation.

Identifying Problems in a Rod-Lens Optical System

Hopkins rod-lens telescopes are high performance and precise optical systems which must be treated with care and cleaned and maintained, in accordance with the manufacturers' guidelines. If they are not, the following issues may be visible in use:

- Reduced image contrast – caused by fluid ingress into the telescope condensing on the internal lens surfaces. This not only impedes the surgical view but also poses a potential contamination issue – if this unidentified fluid can get in, it can also get out.
- Poor light transmission – caused by damaged to the fibre-optic light bundles. Physical dents on the shaft of the telescope can damage the fibres running along it, resulting in reduced light transmission down the endoscope. The view outside the patient in a brightly illuminated room is unaffected, so such damage is often missed in cursory checks.
- Partial loss of image field – caused by impact. Chipped lenses often leave the circular "chip" in view. This is often free to move in the space between the lenses similar to a kaleidoscope when the telescope is turned. This is easy to visualise when the distal tip chips – chips closer to the proximal eyepiece generally give a blurred image.
- Blurred image – could be due to dull external optical surfaces, cracked lenses, or fluid ingress. Residue can build up on the distal and proximal optical surfaces if particular attention is not paid to their cleaning. Special telescope cleaning paste is available to polish the end components of the optical system.

Chapter 42
Light Sources, Light Leads, and Camera Systems

Stuart N. Lloyd and Adrian D. Joyce

Good quality light is essential to optimise endoscopic examination, but light can also be used therapeutically. Imaging, down an endoscope, depends upon effective transmission of light from the light source, through a light cable and the endoscope's intrinsic light guide. The image is viewed via an optical system, usually to a camera at the eyepiece, and displayed on a monitor or via a tip-mounted camera directly to the monitor.

Diagnostic Light Sources

Light sources should, ideally, be matched to the camera system to allow automatic regulation of output in varying situations. The power of light sources varies from 100 to 300 W, with light intensity being controlled manually or automatically. Most light sources have an inbuilt fan cooling system to protect the bulb, and the light should be put on standby when not in use to prolong bulb life. High-intensity light can burn the patient, or surgeon, or ignite surgical drapes.

Generated light typically comes from a halogen bulb, which gives a softer light, or a xenon bulb, which gives a brighter white light. Narrow band imaging (NBI) is an optical filter technology that radically improves the visibility of subtle tissue structures by optimising the absorbance and scattering characteristics of light. NBI uses two discrete bands: one blue at 415 nm and one green at 540 nm. Blue light highlights superficial capillary networks, whilst green light emphasises sub-epithelial vessels.

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Therapeutic Light Sources

For effective photodynamic therapy (PDT), a light source is used to stimulate apoptosis in specifically sensitised cancer cells. Red visible light, at a wavelength of 400–1,064 nm, penetrates well into tissue and is used to induce production of singlet oxygen species which induces apoptosis in sensitised tissues. Several types of light source can be used for PDT including broad-spectrum halogen lamps, light-emitting diodes (LEDs), and lasers. The choice of light source depends upon the light dose required and the geometry of the area to be illuminated.

Light Leads or Guides

Light guides are non-coherent fibre bundles that link the external light source to the endoscope. Effective connection from source to "scope" is key to optimise light transmission into the organ being examined. One of the most frequently encountered causes of poor illumination, during endoscopy, is a faulty light cable; this is usually due to broken fibres in the bundle or build-up of "film" on the connectors on the ends of the guide.

Camera Systems

Modern cameras use charge-coupled devices (CCD), to obtain good quality images. The CCD may be mounted in an external, detachable, camera or may be integrated at the end of a videoscope.

In a digital video CCD, the image is projected through a lens onto a two-dimensional capacitor array (a mono-crystalline layer of silicon, the photoactive region), causing each capacitor to accumulate an electric charge proportional to the light intensity at that location. A control circuit causes each capacitor to transfer its contents to its neighbour until the charge is converted into a voltage. In a digital device, these voltages are then sampled, digitised, and stored in memory and processed into a continuous analogue signal which is then fed out to a monitor for transmission or for recording or re-processing.

Setting the Camera Up

The light source, guide cable, and endoscope should be checked to ensure they are transmitting light correctly and the clarity of the optical system confirmed prior to endoscope insertion. The camera should be properly connected to the control box

and endoscope, and the monitor should be switched to the correct channel to display the images from the camera. Image quality may then be influenced by four generic functions.

White Balance

This is the most important function on the camera and has the greatest impact upon image quality. It calibrates the camera to white which acts as a baseline from which all other colours are reproduced. White balance can be set by wrapping a clean white swab around the distal end of the telescope to form a cone, or funnel, and activating the "white balance" function on the camera. It is good practice to reset the white balance at the start of each endoscopic procedure.

Iris Function

The iris ensures that optimal illumination is provided across the full field of view for the telescope. There are at least two settings for the iris, "Average" and "Peak." Average, when the iris is fully open, is used when looking into large cavities, such as the bladder, and is appropriate for approximately 95% of all laparoscopic procedures in urology. "Peak," when the iris is closed to reduce glare, is used when the object of interest is close to the tip of the endoscope, such as calculi during ureteroscopy. Some modern cameras have a variable control that allows the iris to be set at any point between these two extremes.

Automatic Gain Control (AGC)

AGC electronically alters illumination should the picture become dark, by increasing the light intensity, without the need to alter the settings on the light source. In modern cameras, this is activated automatically when the illumination level becomes low, e.g., when the image quality darkens in the presence of blood.

Digital Enhancement

Digital enhancement makes the picture sharper and is used to bring out fine detail in the endoscopic image.

Table 42.1 Common problems encountered when setting up an endoscopic monitor

Problem	Solution
No picture	Check the camera is connected and that line A or line B channels on the monitor are receiving the signal
Too bright	Check the iris setting
Too dark	Check light transmission from source to "scope" and check AGC
Too red	Incorrect white balance
Too blue	Incorrect white balance against a red background

Trouble Shooting

Practically, there are five possible problems, which may be rectified if an image is sub-optimal in theatre (Table 42.1).

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Chapter 43
Peripherals for Endoscopic Use

Stuart N. Lloyd and Steve Payne

There are a variety of peripheral devices that can be used for manipulation in the upper or lower urinary tract, some of which are inserted via a specialised endoscope sheath and others, that may be rigid or flexible, that are inserted through an access port (Table 43.1).

Specialised endoscopic peripherals tend to be used for very specific, and common, procedures and port-accessed instruments used for diagnostic and therapeutic purposes through rod-lens or fibre-optic instruments in the lower or upper urinary tract. The size of the device is dictated by the diameter, or French gauge, of the working channel of the endoscope, which in rigid endoscopes may be affected by the overall size of the outer sheath in non-integrated endoscopes. Some port-accessed peripherals are rigid, whilst others are malleable and others entirely flexible. They may be reusable or disposable, and the operators' choice of device may depend on the peripheral's durability and its recycling versus replacement costs.

Peripherals for Rigid Endoscopes

When using a rigid cystoscope either a single channel bridge or a deflecting mechanism such as the Albarran lever is required for the endoscopic deflection of peripheral instruments (Fig. 43.1).

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Table 43.1 Peripheral instrumentation used for diagnostic and therapeutic purposes in the urinary tract

Endoscopic peripheral	Port-accessed peripheral
Resectoscope	Albarran lever
Optical urethrotome	Biopsy forceps
Optical lithotrite	Graspers
	Injection needles
	Stone manipulators
	Stone disrupters
	Guidewires and catheters
	Diathermy and other heat sources

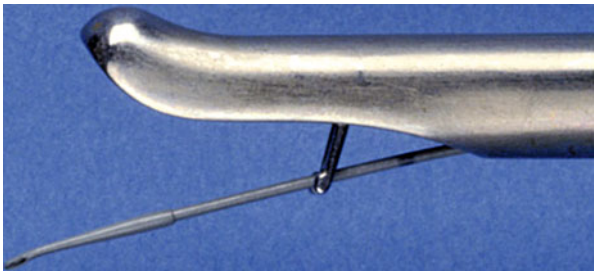

Fig. 43.1 An Albarran lever being used to deflect a retrograde catheter

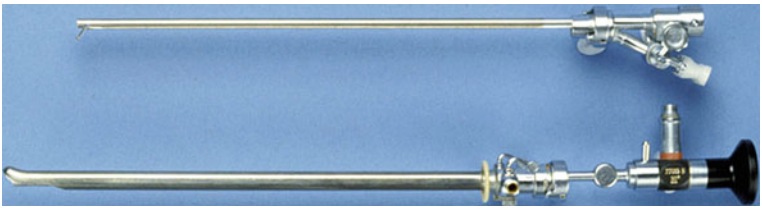

Fig. 43.2 A rod-lens cystoscopy with its outer sheath and an Albarran lever above. Replacement of the conventional bridge allows instruments to be inserted into the bladder and deflected by turning the wheel on the Albarran lever

The angle between the port on a cystoscope and the main portion of the sheath is usually around 20° and means that rigid devices cannot be inserted through this access port without affecting their efficacy (Fig. 43.2).

When a rigid peripheral, such as EKL, lithoclast or grasping forceps, is needed, an offset eyepiece with a straight integrated access port allows the passage of these rigid peripherals through the endoscopes working channel (Fig. 43.3). Some ureteroscopes may have more than one instrument channel so that different devices for stone manipulation can be inserted without risk of them becoming intertwined.

Peripherals used with rigid scopes are generally shorter than those used with flexible instruments and operate under vision at the tip of the optical system. A 30°

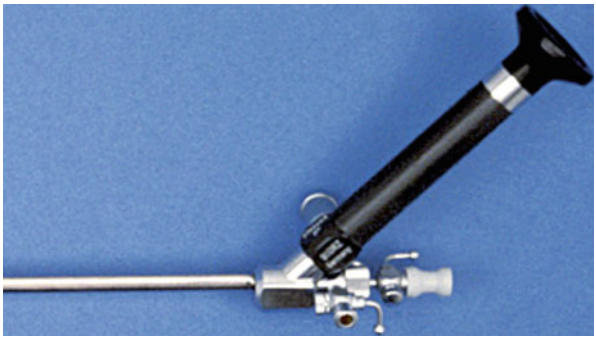

Fig. 43.3 An offset eyepiece endoscope with straight instrument channel to facilitate the insertion of rigid peripherals

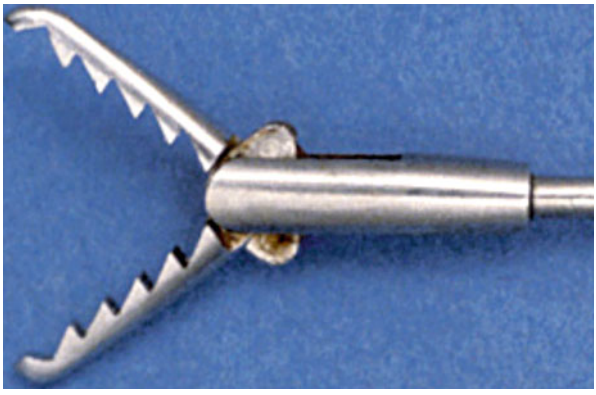

Fig. 43.4 The hinge on an alligator forceps cannot open fully until it is completely outside the working channel or instrument sheath

angle lens is conventionally used for manipulations in the bladder, but angles between 0° and 30° may be used in the urethra, ureter or kidney, dependent on the angle of view required to observe the peripheral in action. Peripherals utilising a hinge mechanism, such as alligator forceps (Fig. 43.4), need to have the hinge mechanism completely outside the instrument sheath before they can work properly.

Peripherals for Flexible Endoscopes

Flexible endoscopes have an integrated instrument/flow channel within the outer core covering the fibre bundle. The deflectability of the tip of the endoscope may be limited by the rigidity of the peripheral, and sharp devices should be inserted to the tip of the endoscope before insertion. This will help prevent channel perforation and instrument damage that might be caused by advancing a sharp device through the bending section when fully angulated (Fig. 43.5).

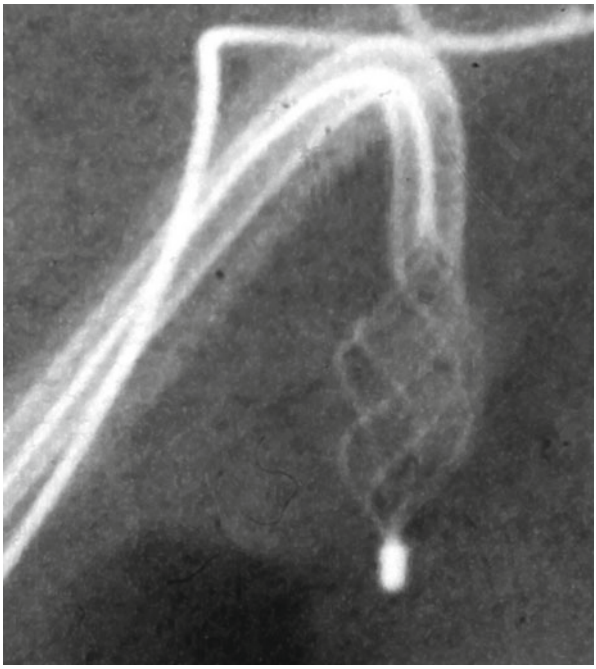

Fig. 43.5 The bending section of a flexible ureteroscope with a stone basket open. The acute angulation of this section makes perforation a real risk when inserting sharp instruments

Peripherals for Either Flexible or Rigid Endoscopes

All peripherals utilisable via a flexible endoscope's flow channel can be used down rigid instrumentation. These devices are, however, often of a smaller diameter, longer, and both more fragile and more expensive.

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Chapter 44
Peripherals for Laparoscopic Use

Andrew Sinclair

Peripheral instrumentation for laparoscopic surgery continuously evolve to increase safety, speed, and efficiency during surgery. Instruments can be used to cut, cauterise, dissect, retract, staple, clip, and retrieve tissue.

Cutting and Haemostasis

It is often useful to be able to cut and provide haemostasis at the same time, promoting economy of movement when one instrument can be used for both functions. During initial dissection, laparoscopic scissors can be used, with or without the addition of diathermy. This allows precision when cutting near organs. The blade conformations vary depending on use and include serrated, hooked, microscissors, and curved tipped scissors.

Electrosurgical incision of tissues relies on monopolar diathermy. A common diathermy device is the hook electrode which can have a J or L configuration. Tissue is separated from adjacent structures by the hook, and current is utilised to incise it. Safe use of electrosurgical instruments is essential to minimise thermal injury in both the field in view and that out of view which may be injured by direct or capacitive coupling (Box 44.1).

Box 44.1: Tips to Minimise Thermal Injury with Monopolar Electrosurgical Instruments Used Laparoscopically

- Check if there is no damage to the insulation on the instrument
- Only activate the device when the whole of the metal component is in view

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- Only activate the device when it is in direct contact with the intended tissue
- Use active electrode monitoring (detects a break in insulation resulting in immediate deactivation)
- Consider using bipolar surgical devices

Fig. 44.1 The ethicon harmonic scalpel

The LigaSure™ vessel–sealing system has been adapted for laparoscopic use. It seals vessels, up to 7 mm in size, using energy from a bipolar radio-frequency generator. The harmonic scalpel (Fig. 44.1) uses ultrasound energy generated by a piezoelectric crystal which produces mechanical vibration at 55,500 Hz at the tips. This device is very versatile as it allows you to grasp, dissect, mobilise, cut, and coagulate but is also very safe as the penetration of energy is limited to 1 mm from the tissue held.

Dissection, Manipulation, and Retraction

Any of the instruments mentioned above can be used for dissection or manipulation, but all have potential disadvantages in use. Scissors have a sharp edge and should not, therefore, be used for blunt dissection. The tips of the harmonic scalpel click closed at a preset tension and, therefore should not be used to hold delicate structures.

Most tissue dissectors come with a ratchet and a rotation device to facilitate use. Standard Maryland graspers are useful for delicate dissection as they have fine ends. In distinction, the Johan-type grasper has curved ends which are more useful for blunt dissection, and using the ratchet, and careful placement, the Johan can also be used as a retractor. Right-angled tissue forceps are essential to ensure that tissue planes are dissected prior to the placement of clips. Adequate retraction of tissues is essential during laparoscopy, and many devices have been designed, the commonest being variations of the fan retractor (Fig. 44.2a, b). Care needs to be taken when

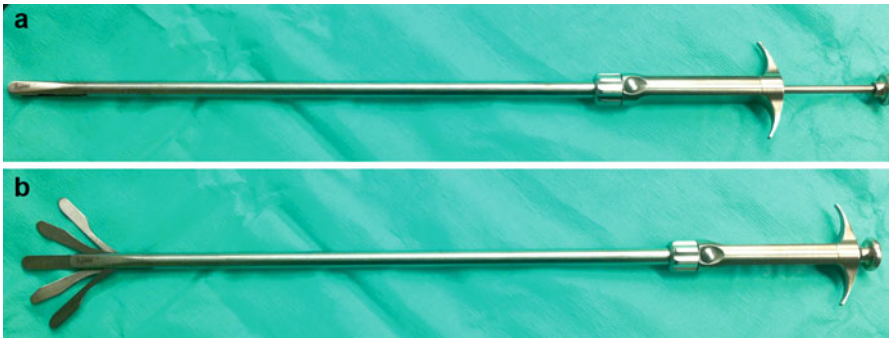

Fig. 44.2 (**a**) Closed fan retractor. (**b**) Open fan retractor

withdrawing the fan to avoid trapping tissue in the blades. Malleable retractors, moulded to specific situations, are also useful.

Suction and Irrigation

The majority of devices for suction and irrigation are disposable and are often in combination to improve economy of movement. The end of the instrument is usually blunt and may be used as a dissection tool.

Suturing, Stapling, and Clipping

Several devices are available to help facilitate suture placement, including the Endo Stitch™ and LAPRA-TY® clips. There is no substitute, however, for being able to place stitches, and tie knots, using a laparoscopic needle holder; this is a key skill every laparoscopic surgeon should have. There are many different types of needle holder, and each individual will need to find a set that is comfortable to them.

There are also many stapling devices available, and it is important to be familiar with the device you use as each is slightly different. Most staplers articulate or roticulate, come in various sizes, and with varying applicators depending on the intended use. Most deliver multiple rows of staples and have a blade which cuts between the rows. Ensuring that you understand the process of holding, securing, deploying, cutting, and releasing, the staple device is essential to ensure safe use. Malfunction, such as cutting without stapling, can be catastrophic laparoscopically; this is often due to human error.

Traditionally, clips were made of metal and could be dispensed from disposable or nondisposable, self- or manual-loading, multi- or single fire, and straight or

Fig. 44.3 Hem-o-lok® polymer ligation clip system

curved applicators. Clips are useful for ligation of small vessels but can be dislodged especially if coagulation is applied in their vicinity. A recent advance in the management of clipping of hilar, and larger, vessels is the development of the Hem-o-lok® polymer ligation clip system (Fig. 44.3). These clips completely surround the vessel and lock with a satisfying click at the far side of the vessel. These are not electroconductive and are, therefore, more secure.

Sample Management

Although there are methods of intraoperative tissue destruction, these are rarely used. More commonly, any resected specimen will be placed into a sac to facilitate extraction, preventing contamination of the abdominal cavity, and wound, in the process. When placing ports at the beginning of the operation, the potential size of the specimen and its extraction bag needs to be taken into consideration; the majority of specimens require a larger bag which demands the use of a 15 mL port. Again it is important to be familiar with the mechanism of deployment, entrapment, closing, and removal of the entrapment bag system used.

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Chapter 45
Peripherals for Mechanical Stone Manipulation

Karyee Chow

Guidewire Selection

Guidewires are commonly placed within the urinary tract to provide a means of access, and for security, whilst operating endoscopically.

Guidewires are available in a range of sizes and designs. The .035 and .038 in. diameter and the 150 cm length wires are those most commonly used urologically. Important variable characteristics include tip shape, shaft rigidity, shape memory, torque (property of the wire that allows movement at one end to be transmitted to the other end providing closer control), and surface resistance. Rigidity, shape memory, and torque are conferred by the properties of the material used to form the core of the wire, whilst the degree of surface resistance is dependent on the coating applied. Guidewire selection depends on the circumstances demanded by the procedure.

A standard guidewire has a stainless steel core coated with PTFE and a flexible tip, which may be straight, angled, or J-shaped. An angled tip helps the guidewire slide pass end on tissue surfaces, whilst the J-shaped tip reduces the possibility of tissue perforation. Where there is difficulty in negotiating narrow or tortuous anatomy, a more slippery guidewire is commonly employed. A typical example is the Glidewire® made of nitinol with a hydrophilic coating. Nitinol is a nickel-titanium alloy that has superior shape memory, which allows it to retain its original shape. The hydrophilic coating reduces friction along its surface when wet, making it very slippery and easy to pass tight areas. It is also available with a straight or angled tip. The disadvantage of these guidewires is that they are easily displaced and need to be exchanged for a less slippery, and stiffer, wire before working within the urinary tract.

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Guidewires with a high degree of shaft rigidity are chosen when greater stability is required when stress is imparted on the wire. These "working" guidewires often have a nitinol inner core reinforced with a stiffer outer core material. An example is the Amplatz Super Stiff™ that is often used for ureteroscope advancement and tract dilatation in a PCNL. Some hybrid guidewires, such as the Sensor™ guidewire, have the combination of a floppy hydrophilic-coated tip and a nitinol with PTFE-coated, kink-resistant body, providing ease of access as well as stability. Some guidewires, such as the Zebra® wire, have surface markers to demonstrate movement in use.

Stone Cone

The Dretler Stone Cone® is a device that can be deployed in the ureter above the stone, which prevents proximal migration of the stone and its fragments during intracorporeal lithotripsy. It has a nitinol inner core with a PTFE outer layer. Before it is deployed it is straightened, allowing placement beyond the stone; when deployed, the distal end coils, occluding the lumen of the ureter proximally (unless the ureter is significantly dilated). The deployed coils of the stone cone can also be used to "trawl" stone fragments out of the ureter.

Basket and Grasper Selection

Flexible baskets and graspers can be employed within the urinary tract to manipulate and retrieve kidney stones. Baskets come in different constructs and the type chosen depends mainly on the stone size, number, and location.

For ureteric stones, stainless steel baskets are commonly used. These baskets are more rigid and have the strength to expand the ureter and open within a narrow lumen. Most have a straight tip guide, which is placed beyond the stone providing greater stability when in use. The cage of these baskets is constructed either with straight, flat, wires or in a spiral configuration. The choice between the two is a matter of personal preference, but in general straight wire cage baskets are better for larger single stones, whilst a spiral multiwire basket is better for capturing multiple smaller stones.

Three-pronged graspers can also be used to retrieve stones in the ureter. They have the advantage of allowing stone release if it becomes stuck in the ureter but have the disadvantage of potentially causing ureteric injury due to their sharp prongs.

For stones in the calyces, tip-less (zero tip) nitinol baskets are preferred as they can be opened adjacent to tissue surfaces, allowing close stone approximation in a limited space. These baskets are more flexible and have smaller diameters (1.3–3F), causing less impairment to scope deflection and irrigation flow when used with a flexible ureteroscope. Other basket types for use in the kidney include the nitinol NGage™ and Graspit®, which have nontraumatic jaws that open like forceps providing easier stone capture and release if necessary.

The handles of all modern baskets can be dismantled to allow backward removal of the ureteroscope whilst the basket remains in place. This is invaluable when the basket and stone gets trapped in the ureter, permitting removal of the scope and reinsertion alongside the basket so that the stone can be fragmented further.

Rigid Instruments

Rigid metal instruments are often used in PCNL to grab and retrieve stones or fragments. Alligator forceps have pincer grip handles with various types of jaws whilst the three-pronged grasper has a U-shaped spring handle that holds onto the stone.

Baskets with a rigid shaft and a U-shaped spring handle such as the NCircle® can also be used to retrieve stones. This device comes with a basket that either opens out straight or at an angle. The later is particularly useful for retrieving stones in calyces, which cannot be accessed with straight forceps or graspers.

Chapter 46
Contact Lithotripters

Steve Payne

The evolution of endoscopic methods of intracorporeal stone management fuelled the development of means of disintegrating urinary stones in situ so as to minimise trauma to the collecting system and to enable large stones to be removed safely in the pelvicalyceal system, ureter, and bladder. Contact lithotripters are of three types, pressure disruptors, such as electrohydraulic lithotripters, mechanical disruptors, which "drill" into the stone, such as ultrasonic and ballistic lithotripters, and laser devices. The benefits and disadvantages of each and their effects on stone will be considered (Table 46.1).

Electohydraulic Lithotripsy (EHL)

EHL was one of the first methods described for disruption of urinary stones but is largely obsolete in clinical practice. Like the first extracorporeal lithotripters, EHL depends upon the discharge of an ultra-high tension, ultra-short discharge between insulated coaxial electrodes. A potential difference is created by a generator externally and passed down a flexible "electrode" into the patient. The spark that is discharged between the two components of the coaxial electrode, under vision, vaporises the irrigant medium creating a bubble pulse which causes mechanical disintegration of most stones into "bite-sized" chunks. These can then be removed mechanically.

EHL necessitated aqueous irrigants, as saline and glycine influence shock transmission, can both harm adjacent tissue, stone baskets (due to electrical shorting) and may disrupt the optical system of the endoscope if discharged in proximity to it. The shock wave also "pushes" the stone away from the electrode resulting in fragment displacement.

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Table 46.1 How intracorporeal lithotripters work, their efficacy in stone fragmentation, and potential for thermal injury

Lithotripter	Mechanism of action	Stone contact	Resistant stones	Thermal injury
Electrohydraulic (EHL)	Shock wave generated under water through coaxial probe: microexplosions	No (<1 mm away)	None	Yes
Ultrasonic (USL)	High-frequency vibration of metal probe; aspiration of fragments	Yes	Calcium oxalate monohydrate	Yes
Lithoclast	Projectile fired onto metal rod by pressurised air	Yes	None	No
Electrokinetic (EKL)	Magnetic core projected onto metal rod by electromagnetic acceleration	Yes	None	No
Lasertripsy (Ho:YAG)	Cavitation thermal effect	Yes	None	Minimal

Ultrasonic Lithotripsy (USL)

The production of an oscillation down a rigid metal probe, so that the probe tip, when placed in contact with s stone, "drills" pieces of the stone mass. Ultrasound energy is generated by application of an electrical current to a quartz crystal which then vibrates at 23–27 kHz. The vibration is "channelled" down an acoustic horn, a cone-shaped device, and the sine wave formed then passes into the rod and onto the stone producing a low pressure impact with high repetition. Most USL probes are hollow and are attached to a suction pump which evacuates fragments of stone, and matrix, from the urinary tract (Fig. 46.1).

USL is more controlled than EHL but is slower in action and produces many fragments which may become displaced to act as the nidus for further stone formation. It may also dissipate a certain amount of energy as extraneous sound which may be damaging to the operators hearing. Hard stones may be resistant to USL, and fragments of probe may sheer off. Narrow probes, used in the ureter, may become occluded by fragments.

Ballistic Lithotripsy

A more controlled method of stone fragmentation, involving the production of forward momentum in a rigid metal rod placed in contact with the surface of the stone, is ballistic lithotripsy.

Probe tip movement may be effected in two ways. The Swiss LithoClast® uses a precisely controlled burst of compressed air (0.35–0.5 MPa) to move a projectile,

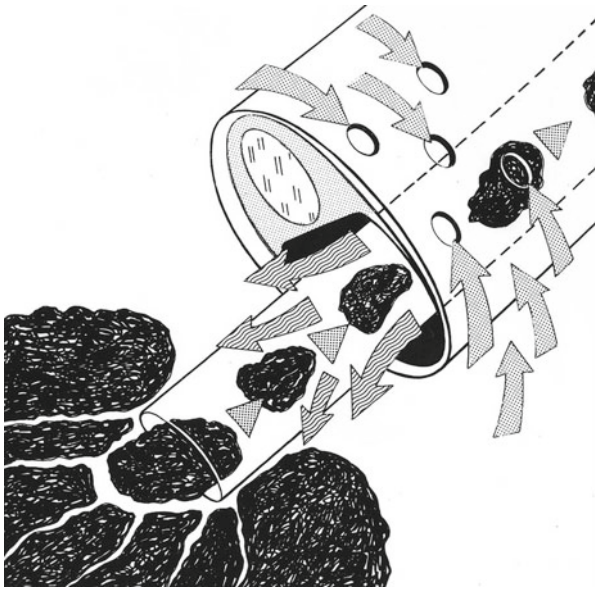

Fig. 46.1 Ultrasonic lithotripsy creates multiple small fragments which are sucked up through the hollow probe into the working channel of the endoscope. Forward irrigation, however, may result in fragment dissemination

guided with precision of one micrometer, to generate ballistic energy. When the projectile hits the probe in the handpiece, a shock wave is transmitted through the probe to the calculus. The different acoustic characteristics of the metal probe and the stone lead to disintegration of hard and large stones. Electrokinetic lithotripters (EKL) use a magnetic core to create vibration at 15–30 Hz directly in the metal probe, which is placed in contact with the stone to drill it.

Ballistic lithotripsy produces highly reliable, rapid disintegration at low cost. Because of its mechanical action, it does have the tendency to push stones forward, particularly in the ureter, and can only be delivered down a rigid endoscope.

Lasertripsy

Lasers have always have an attraction for contact lithotripsy as they can be delivered down flexible fibres, so can be delivered via a flexible endoscope into the periphery of the calyces via a transurethral approach.

Lasers with pulse durations of less than a few microseconds fragment calculi by means of a photo-acoustic effect by generation of a shockwave due to expansion of ionised water, or calculus, or by cavitation collapse. Long-pulsed lasers (i.e., >100 μs) generate minimal acoustic energy, and calculi are fragmented by thermal vaporization melting, or chemical decomposition. Different fibre sizes (550, 365, and 200 μm) allow treatment of both ureteric and renal stones.

The most commonly used laser is the holmium: yttrium–aluminum–garnet (Ho:YAG) instrument, which operates at a wavelength of 2,150 nm: stone-free rates

are 89–100% in the ureter. A modification of the holmium laser is the frequency-doubled, double-pulse Nd-YAG (FREDDY) laser; this generates a plasma bubble, collapse of which creates a shock wave that causes stone fragmentation.

Overall complication rates are low; the thermal effects of the laser are restricted to 0.5–1.0 mm from the fibre tip and the risk of urothelial injury is, thereby, minimised. The limitations are that the treatment takes a long time if there is significant stone burden to disintegrate.

Combination Contact Lithotripters

Newer innovations are machines that combine two lithotripting technologies. The Cyberwand™ has coaxial probes; the inner probe, vibrating at 21,000 Hz, acts as an ultrasonic lithotripter whilst an outer probe vibrates at 1,000 Hz providing high-energy shock impact. The Swiss LithoClast® Master has both ballistic and ultrasound capabilities.

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Chapter 47
Endoscopic Use of Laser Energy

Omar Al Kadhi and Tev Aho

Since 1960 when Theodore Maiman activated the first laser using a synthetic ruby crystal, light amplification by the stimulated emission of radiation (LASER) has found many varied applications. Various laser wavelengths have proven safe, precise, and effective for use in endourology.

Laser Physics and Tissue Interaction

Lasers are generally described by their lasing media, e.g., neodymium-doped yttrium aluminium garnet ($Nd:Y_3Al_5O_{12}$, Nd:YAG), which defines the wavelength and physical characteristics of the laser.

Three steps are required to generate a laser beam:

1. Energy is infused into the lasing medium and absorbed by many of its atoms pushing them into an excited state. These then emit energy as photons.
2. The photons collide with other excited atoms of the lasing medium causing additional photon emission.
3. The emitted photons are amplified by reflecting them between two mirrors at either end of the laser cavity causing energy build up. This energy exits through an aperture in the front mirror as an intense laser beam.

The unique characteristics of laser light are that it is monochromatic, collimated, and coherent. Monochromatic light, of a single colour, is defined by its wavelength. It can specifically target tissues (the chromophore) that absorb that light wavelength.

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Table 47.1 Factors influencing tissue effect due to the application of laser energy

Laser factors	Tissue factors
Wavelength	Tissue density
Power: energy (joules) × rate (hertz) = power (watts)	Water content: if the chromophore is water then water-rich tissues (e.g., prostate, bladder tumours) will be specifically targeted by that wavelength.
Mode of emission: pulsed vs. continuous	
Distance from target: contact or near contact = incision; close = vaporisation; more distant = coagulation	

Collimated light, travelling in a parallel beam, can be guided through optical fibres and focussed on a small spot.

Tissue is affected by laser energy by absorbing light and converting it to thermal energy. When temperatures reach 60–100°C, tissue coagulation occurs with subsequent delayed tissue necrosis and debulking. Temperatures exceeding this will lead to vaporisation with immediate tissue debulking. Laser energy may break stones by a photothermal mechanism, with direct absorption of laser energy causing vaporisation of the stone or by a photo-acoustic effect where a pulsed laser causes formation of a plasma bubble which expands and collapses generating a shock wave.

Determinants of the Laser: Tissue Interaction

These can be related to the laser characteristics or the tissue being treated (Table 47.1).

Laser Safety

It is mandatory that laser operators receive laser safety training and certification. Theatre personnel must wear adequate protective eyewear specific to the laser wavelength, windows should be covered, and a designated member of staff should operate the laser machine. Laser fibres should be checked for faults prior to activating the laser machine, and this should be switched to standby when not in active use.

Clinical Applications of Lasers in Urology (Table 47.2)

Benign Prostatic Hyperplasia (BPH)

Initial interest in the use of lasers for BPH led to the Nd:YAG procedures such as visual laser ablation of the prostate (VLAP) and contact laser ablation of the prostate (CLAP). However, low tissue absorption and deep tissue penetration, causing

Table 47.2 Characteristics of the lasers used, and their applications, in urology

Type of laser	Wavelength (nm)	Chromophore	Depth of tissue penetration (mm)	Mode	Urological application	Fiber type	Suggested power settings
Nd: YAG	1,064	Water and haemoglobin	10	Pulsed or continuous	*Prostate coagulation*	Side firing (SF)	
					TCC ablation	End firing (EF)	
Holmium	2,100	Water	0.4	Pulsed	*Prostate*:		
					Ablation (HoLAP)	SF	$E=2\times F=50$
					Resection (HoLRP)	550 um EF	$E=2\times F=50$
					Enucleation (HoLEP)	550 um EF	$E=2\times F=50$
					Bladder stones	550 um EF	$E=1\times F=40$
					Ureteric stones	365 or 200 um EF	Start at $E=0.6\times F=6$
					Strictures	365 um EF	$E=0.8\times F=8$
					TCC: ablation/ resection	365 um EF	$E=0.8\times F=8$
Greenlight KTP 80 W HPS LBO 120 W XPS LBO 180 W	532	Haemoglobin	0.8	Quasi-continuous	*Prostate*: Vaporisation (PVP)	SF	HPS = 120 W XPS = 180 W

(continued)

Table 47.2 (continued)

Type of laser	Wavelength (nm)	Chromophore	Depth of tissue penetration (mm)	Mode	Urological application	Fiber type	Suggested power settings
Thulium	2,000	Water	0.25	Continuous or pulsed	*Prostate*:		
					Vaporisation	SF	200 W
					Resection (ThuVaRP)	EF	120–200 W
					Enucleation (ThuLEP)	EF	120–200 W
					Strictures	EF	
					TCC ablation	EF	
Diode	940, 980, 1,470	Water and haemoglobin	Various	Pulsed	*Prostate*:		
					Vaporisation	SF	

E Energy, *F* frequency

coagulative necrosis and delayed sloughing of tissue, resulted in high rates of post-operative retention and dysuria.

The term "laser prostatectomy" is too general to be meaningful, and three laser techniques are current used for BPH:

1. Vaporisation: The simplest but least efficient method of tissue debulking. Requires expensive single-use side-firing fibres. There are concerns over durability particularly in men with prostates >80 cc and no tissue is available for histology.
2. Resection: The laser equivalent of TURP where small chips of prostate are resected using a multiuse end firing fibre. Less efficient tissue removal than enucleation, but tissue can be sent for histology.
3. Enucleation: First and best performed with the holmium laser, but can be done with thulium laser. The laser equivalent of Millins prostatectomy with equivalent long-term durability. No upper prostate size limit. Tissue is available for histology. HoLEP has been thoroughly investigated with eight published RCTs and is the only laser technique recommended by NICE. Cost-effective when compared to other BPH procedures.

All laser techniques are possible as day cases and have been shown to have less bleeding complications, no TUR syndrome, and shorter catheter times and hospital stays compared to TURP. All can be done in anticoagulated and medically unfit patients.

Upper and Lower Tract Stones

Holmium laser lithotripsy is the treatment of choice for ureteric calculi and small renal pelvic or peripheral calyceal stones. Laser lithotripsy is said to have up to 95% success rates even with harder types of stone with low risks of urothelial injury but can be slow when a large stone volume requires disintegration.

Transitional Cell Carcinoma (TCC)

Laser ablation for bladder TCC is restricted to superficial, small (<2.5 cm) lesions when tissue histology is not required. The advantages are less bleeding and the ability to use Nd:Yag, holmium and thulium lasers delivered by a flexible cystoscope, thereby avoiding general anaesthesia. Ureteroscopic or nephroscopically delivered lasers allow treatment of upper tract TCC in patients unfit for radical treatment with less bleeding and lower stricture rates in comparison to electrocautery.

Urethral Stricture Disease

Argon and Nd:YAG, KTP, holmium and diode lasers have all been used for laser urethrotomy. Data suggest equivalent results with all modalities, but there is lack of data comparing laser to optical urethrotomy or dilatation.

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Chapter 48
Double J Stents and Nephrostomy

Steve Payne

Drainage of the upper urinary tract by insertion of an open nephrostomy has been an option for more than a 100 years, but the percutaneous approach, with which are so familiar, has only been a viable, widely available option for the last 40 years. Roughly over the same time period, internalised "double J stents" have become available for retrograde, antegrade, and open drainage or splinting of the injured or reconstructed, ureter and upper urinary tract.

How Stents and Nephrostomies Drain the Upper Urinary Tract

Insertion of a nephrostomy or double J stent into the dilated upper urinary tract will disobstruct it, external drainage into a no pressure collecting device providing optimal decompression. Insertion of a double J stent into a nonobstructed ureter will cause a rise in intrapelvic pressure, ureteric dilatation, vesicoureteric reflux and will result in an injury response that influences the efficiency of ureteric peristalsis. Most urine drains around a double J stent, by coaptive peristalsis, rather than through the central lumen except at points of complete obstruction when urine passes through the side holes into the lumen (Fig. 48.1).

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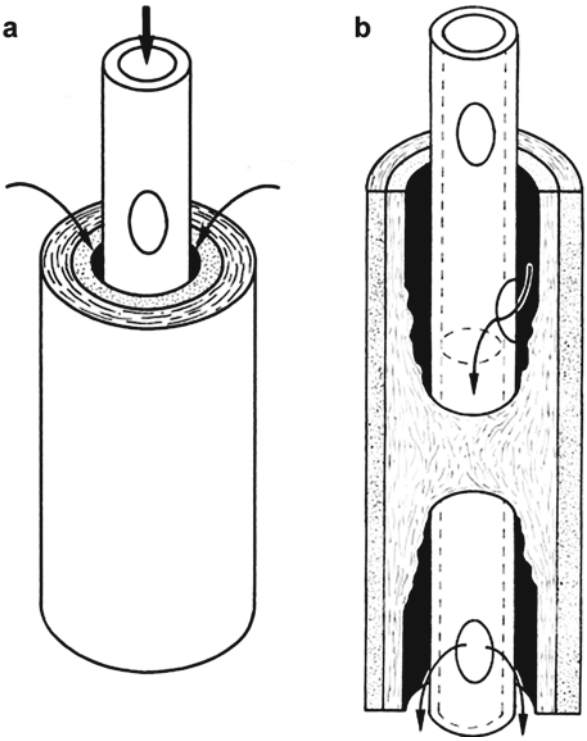

Fig. 48.1 Urine drains by peristalsis around the stent and, until it becomes occluded by encrustation, through the central lumen (**a**). The lumen becomes important at points of occlusion where urine is forced in through side holes until ureteric peristalsis "sucks" urine out around the stent below the occlusion (**b**)

Pathological Consequences of Stent Insertion

Implanted plastic tubes will cause the production of sialomucins dependent upon their composition. That injury response will result in mucosal oedema and dilatation of the ureter if that contains the tube. All tubes implanted into the urinary tract will develop a biofilm and become encrusted with constituents of the urine, which means they encrust more rapidly in lithogenic urine and should, therefore, remain in situ for the shortest time possible in stone formers. The encrustation process will start within days of implantation and will start to occlude the stent lumen within a week. This may cause irritation to the patient, make stent removal difficult, and stent exchange impossible using the lumen. Biochemical and biomechanical forces will also have an effect on polymer degradation with potential stent fracture. The rate of deterioration is principally influenced by the composition of the stent and influences its longevity in-situ.

Material Science

The construction of nephrostomies and double J stents is identical with a number of different materials being used, most of which are polymers and many of which are used as proprietary combinations. The presence of silicone influences the rigidity of

the material, and hence its ease in insertion, comfort to the patient, and its longevity in situ (Table 48.1).

All plastic stents and nephrostomies require insertion over a guidewire under radiological control. They usually consist of a radio-opaque 5–8°F tapered-tip tube which has a section with a plastic "memory" that forms a coil once it has deployed from the guidewire. The coil end of a nephrostomy and the whole length of a double J stent have small holes drilled in them to facilitate drainage (Fig. 48.2a).

Table 48.1 Commonly used materials for plastic stents and nephrostomies and their longevity in use as double J stents

Composite	Base polymers	Stent longevity in vivo
Bardex®	Polyurethane	6 months
Universal® firm	Thermally sensitive polyurethane	12 months
C-Flex®	(Styrene) thermoplastic elastomer	6 months
Sof-Flex®	Soft polyurethane	6 months
Percuflex®	Polyethylene	Up to 12 months
Fluoro-4™	Silicone	Up to 12 months
Inlay optima®	Proprietary mix	Up to 12 months
Universal® soft	Soft polyurethane	6 months

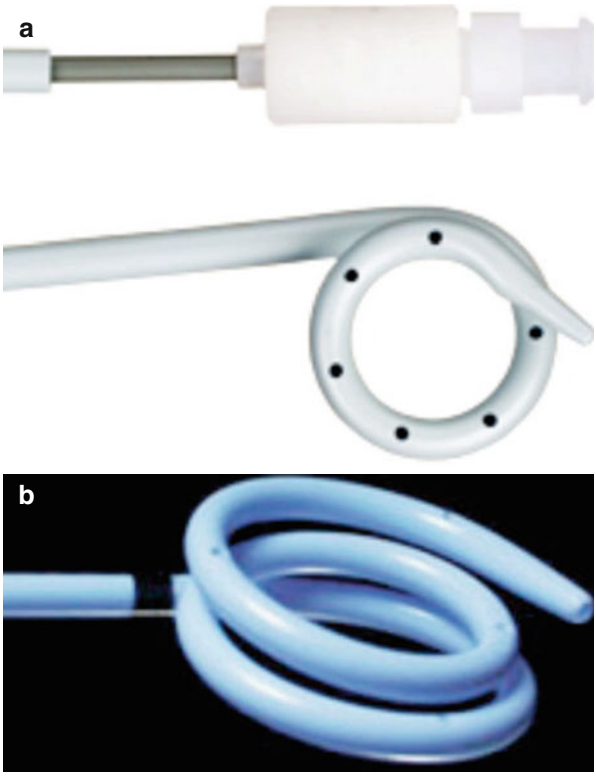

Fig. 48.2 A nephrostomy with preformed pigtail and holes in the coil just in the renal pelvis (**a**) together with its Luer connector for an external drainage device. A multilength double J stent (**b**) (Images courtesy of Cook Medical)

These holes may also be used to pass a guidewire through for open stent placement. Percutaneous nephrostomies often have a fine thread between the tip of the stent and the first side hole on the shaft of the tube to "lock" the coil and avoid displacement. The cutaneous end of the nephrostomy has a Luer connector for an external collection device.

Double J stents may be between 18 and 30 cm long with a preformed coil at each end. Some stents have a "multi-length" coil on either end which means that the stent uncoils in capacious areas such as the renal pelvis or bladder (Fig. 48.2b). Multi-length stents have the advantage that fewer lengths of stent need to be kept in stock. Stents may be coated with hydrophilic Teflon or antibacterial/antibiotic coatings to make insertion easier or to try and reduce bacterial adherence and encrustation. Specialised stents may be used to "detour" urine from the kidney via a subcutaneous tunnel to the bladder for an extra-anatomic means of draining the upper tract when the ureter is either absent or unusable (Paterson-Forrester Subcutaneous Urinary Diversion Stent).

Metallic ureteric stents have been used in two particular circumstances, to alleviate upper tract obstruction in advanced malignancy and to manage benign ureteric strictures. Initial experience with self-expandable mesh stents such as the Wallstent® has not been favourable due to urothelial hyperplasia and ureteric reocclusion. Thermo-expandable stents such as the Memokath® have proven prone to encrustation and may be difficult to change, if needed. Coiled metal stents such as the Resonance Stent™ have no end holes and require insertion through an outer sheath. Metallic stents are not widely used in practice.

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Chapter 49
Urinary Catheters, Design, and Usage

Dave Shackley

Urinary catheters are perhaps the most frequently used piece of urological technology and, after IV cannulas, are the most frequently deployed device in an acute hospital setting; typically, a fifth of the UK inpatients will have a urinary catheter in situ at any one time.
Catheters are inserted for three main reasons:

1. Drainage (urinary retention, fluid management, incontinence)
2. Access (for chemo- and immunotherapy in bladder cancer)
3. Diagnostic studies (e.g., culture, radiology)

There are various types of catheter and several ways to classify them.

- Size: Catheter diameters are sized by the "*French*" catheter scale (or Charriere gauge), which refers to the circumference *in millimeters*. Range from 10F (3.3 mm) to 28F (9.3 mm).
- Channels: 1, 2, or 3 channels, one being the balloon retaining mechanism
- Balloon size: 3–30 mL
- Tip design: Foley, Coude, and Tiemann, whistle tip
- Materials: Latex-coated, all silicone or PVC
- Position/use: Indwelling or intermittent/urethral or suprapubic

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Coated-Latex Catheters

These are the most frequently used in the UK. A coating is required to reduce any inflammatory response due to the presence of latex.

1. Polytetrafluoroethylene (PTFE)-coated catheters are frequently referred to as "medium term" as they can be left in situ for only 28 days. PTFE (also known by the brand name "Teflon") has a very low coefficient of friction and is very non-reactive because of the strength of the carbon-fluoride bonds. They are reasonably cheap.
2. Hydrogel-coated catheters can be left for 3 months and are very commonly used in the UK. Hydrogel refers to a network of polymer chains which are hydrophilic and because of their high water content, possess a degree of flexibility.
3. Silicone-coated differ from other polymers in that their backbones consist of Si-O-Si units unlike other polymers that contain carbon backbones. Silicone is a highly inert material that is used in many medical implants. Silicone-coated catheters can be left in for 3 months.

All-Silicone Catheters

Silicones are well known for their intrinsic biocompatibility, low surface tension, and hydrophobicity though they are also mechanically weak compared to other substances. These catheters can be used for 3 months and are essential in latex allergic patients. Silastic™ (a portmanteau of silicone and plastic) is a commonly used device. All-silicone catheters tend to cause less irritation and are available in various colours.

Rigid PVC Catheters

Pure PVC polymer is very rigid, and plasticisers are added to add flexibility to these otherwise inert devices. The complexity of these compounds can lead to production of small amounts of the toxic substances, dioxin and polychlorinated biphenyls (PCBs), when disposed of by incineration. PVC catheters are usually rigid three-way devices used after endoscopic surgery and are ideal for clot evacuation and bladder washout. They can be used for at most 5–7 days. These catheters are typically 2–3 times the cost of the latex-coated and silicone catheters and should not be used in allergic patients because they have a latex balloon.

Intermittent Catheters

These may be made of a number of nonsilicone materials and are used for intermittent bladder drainage by the patient or career; they are designed for one-time use. They may be coated with a number of substances including PVP (polyvinylpyrrolidone) and salt which create a self-lubricating aqueous layer.

Suprapubic Catheters

Many designs of suprapubic catheter have been used over the years; these are now, commonly short- or long-term balloon catheters inserted through a peel-away sheath inserted into the distended bladder over a sharpened trocar. Suprapubic catheters should be inserted under ultrasound control.

Problems with Catheters

Catheter-Associated Urinary Tract Infection (CAUTI)

The most significant downside to catheterisation is the risk of urosepsis and CAUTI. Estimates from the USA have suggested that there are 7,500 deaths in patients every year from CAUTI. Pro rata, this would be almost 2,000 in the UK. Research and quality improvement work demonstrates that this can be substantially reduced by good technique, appropriate management in situ, and particularly, early removal.

Asymptomatic bacteriuria occurs cumulatively at a rate of approximately 3–10% per day, with 50% incidence by day 10, and >95% by day 28. The rate of bacteriuria can be slowed by impregnating the catheters with silver oxide/alloys or antimicrobials though they do not stop CAUTI. Typically, these agents are only used on short-term catheters because of long-term increased inflammatory responses.

CAUTI can only be diagnosed by symptoms and/or signs of sepsis and a positive growth. CAUTI is difficult to define, but the most pragmatic would be “evidence of sepsis in a catheterized patient with no other definable cause.”

Catheters develop sheets of adherent bacteria within a densely adherent matrix +/− crystals, called biofilms, over time. Because of the biofilm and potential for seeding further infection, after treatment of the acute sepsis, the catheter must be changed.

Encrustation/Repeated Blockage

These occur due to an inflammatory reaction in alkaline urine. In practice, it is best to avoid washouts with acidic solutions (as they can potentiate an inflammatory reaction) and use simple saline washouts possibly in conjunction with changing to an all-silicone type of catheter. More frequent changes may be required.

Bypassing

Catheter blockage and bladder calculi should be ruled out. Anticholinergic medication can be tried in addition to reducing the volume of the retaining balloon. Consider suprapubic catheter to avoid trigonal irritation.

Other Problems

Visible haematuria occurs in 30% and is probably best investigated once, ignore nonvisible haematuria. Significant discomfort has been reported in 70% of patients with catheters which is lower in suprapubic catheters. Bladder stones, traumatic hypospadias, and urethral strictures are reported in a substantial minority of patients with long-term urethral catheters, especially neuropaths.

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Chapter 50
Prostatic and Urethral Stents

Ian Eardley

The heyday of intraprostatic and intraurethral stents was in the 1990s, when a number of commercial devices were developed with the intention of either treating men with recurrent urethral strictures or men with urinary retention who were deemed too unfit to undergo prostatic surgery. A less common indication for stent placement was the treatment of detrusor sphincter dysynergia. Almost all of the stents from that era have since disappeared from the marketplace for several reasons. These include advances in anaesthesia, the development of effective new minimally invasive treatments for prostatic obstruction, and the complications associated with the stents themselves. The only stent still available commercially is the Memokath™ (Fig. 50.1), although there has been some recent interest in biodegradable drug–eluting stents.

History

The first prostatic stent was described by Fabian in 1980. Over the next 15 years, a variety of stents were launched (Table 50.1) with a range of supporting data. Some, notably the UroLume Wallstent™, were primarily developed for the treatment of urethral strictures, while others were designed specifically for short- or longer-term intraprostatic use.

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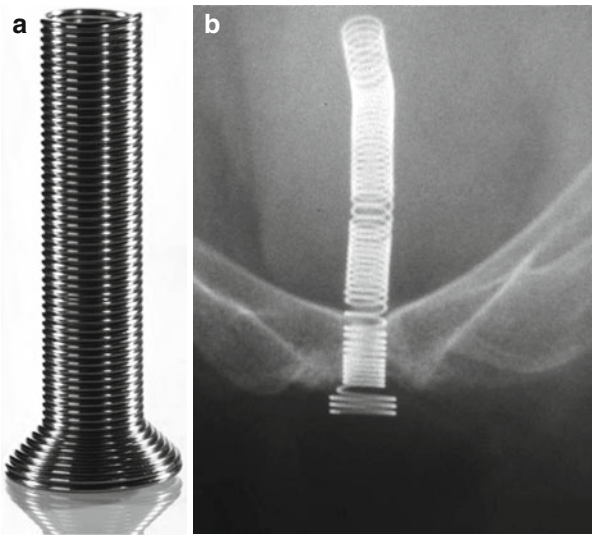

Fig. 50.1 (**a**) The Memokath™. Note the dilated distal end which thermo expands to sit just above the striated urethral sphincter. (**b**) X-ray showing the placement of the Memokath™ within the prostatic urethra

Insertion

Most were inserted under local anaesthesia, with or without sedation. The stents were held in place by one of three mechanisms:

- The stent had a shape that fixes it in position. For example, the Prostakath™
  This had a long intraprostatic component (the body) extending down to a narrow neck, which extended through the striated urethral sphincter before expanding again for a short distance within the bulbar urethra. These stents were intraluminal and therefore temporary. It was inevitable that they would need to be replaced.
  The Memokath™ is held in place by a thermo-expandable distal component which lies just above the striated urethral sphincter (Fig. 50.1a, b).
- The stent has natural elastic recoil that holds it in position, for example, the Wallstent™
  This was loaded in a contracted state and, when placed, expanded with sufficient natural elastic and radial force to hold it in place. These stents were permanent, and it was envisaged that they would become epithelialised.
- The stent is stretched into position with a balloon dilator, for example, the ASI intraprostatic stent.
  The stent is again loaded in a contracted state and, when in position, is balloon-dilated into position. These stents were permanent, and it was envisaged that they would become epithelialised.

Table 50.1 Intraprostatic and intraurethral stents that are, or have been, in use together with the material of their manufacture, their intended use, physical conformation, and method of insertion

Stent	Material	Duration and use	Shape	Placement
Urospiral™	Stainless steel	Temporary prostatic	Body lies within the prostate and protrudes into the bladder Neck lies within the membranous urethra Head lies within the proximal bulbar urethra	Endoscopic
Prostakath™	Stainless steel plated with gold (to reduce encrustation)	Temporary prostatic	Same shape as the Urospiral™	Ultrasonic guidance
Intraurethral catheter™	Polyurethane	Temporary prostatic	Double Malecot shape Proximal expansion lies at the bladder neck Distal expansion lies just above the urethra sphincter Suture attached to distal end to facilitate easy removal	Endoscopic
Memokath™	Nitinol (an alloy of nickel and titanium)	Temporary prostatic	When warmed to 45°C, the distal end of the stent expands to fix the stent in place. This expanded portion lies just above the urethral sphincter (Fig. 50.1) When cooled to 10°C, the stent becomes soft and deformable, aiding removal	Endoscopic

(continued)

Table 50.1 (continued)

Stent	Material	Duration and use	Shape	Placement
Prostacoil™	Nickel titanium alloy	Temporary prostatic	Same shape as Urospiral™	On delivery catheter under fluoroscopic control
UroLume Wallstent™	Biomedical superalloy	Permanent urethral and prostatic	Self-expandable stent	On delivery catheter with endoscopic control
ASI Intraprostatic stent™	Titanium	Permanent urethral and prostatic	Balloon-dilated stent	Endoscopic

Success Rates

These stents allowed restoration of voiding in around 50–80% of patients of men with urinary retention. Complications however were common, such that they rapidly fell out of favour.

The short-term results of urethral stents in men with recurrent urethral strictures were excellent (except for traumatic membranous urethral distraction injuries), but the long-term results were not, with blockage, due to epithelial ingrowth and overgrowth resulting in recurrent obstruction, the main problems.

Complications

- Migration: If the stent was not fixed securely in place, it risked migration. This could result in urinary retention.
- Encrustation: A risk with all intraprostatic stents. Gold plating was an attempt to reduce the risk.
- Blockage: Severe encrustation was a risk with intraprostatic stents. For urethral stents around 40–60% ultimately restenosed, require further endoscopic treatment or removal and urethral reconstruction.
- Urinary tract infection.
- Incontinence: If the stent were misplaced, then the striated urethral sphincter was held open with resultant stress urinary incontinence. Occasionally, the intravesical component led to severe irritative symptoms.
- Removal: These complications often led to stent removal. In one large study of the Prostakath™, almost half the stents were removed with the commonest indications being retention, irritative bladder symptoms, migration, and the decision to undertake a TURP.

The Future

Although most of the above stents have disappeared from common usage, there is research into the potential use of drug eluting biodegradable stents made from polylactide and polyglycolide, with a variety of coatings including indomethacin, dexamethasone, and ciprofloxacin. These have been developed with the intention of treating men with recurrent urethral stricture disease.

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Chapter 51
Urological Prosthetics

Duncan J. Summerton and Ian Eardley

Three main groups of prosthetics are used in urology: penile prostheses (inflatable or malleable) for ED; tapes, meshes, and slings; the artificial urinary sphincter (AUS) for incontinence and testicular implants.

Prosthetic implantation is increasing, mainly due to the rise of radical prostatectomy and increased awareness of the availability of such treatments. For instance, over 400,000 inflatable penile prostheses (IPPs) have been placed worldwide. Both the IPPs and the AUS have had essentially the same design since their introduction in the 1970s, but there have been important modifications to improve the ease of implantation, improve ease of use and to improve the durability of the device whilst reducing the complication and infection rate.

General Principles of Prosthetic Surgery

The main priority is to avoid infection. General measures to achieve this are shown in Table 51.1.

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Table 51.1 Important management factors to reduce the risk of infective complications in association with implant surgery

Screen for UTI	A 10-min betadine scrub (alcohol-based prep perhaps better)
Check for infective skin lesions	Reduction of theatre traffic
Admission on the day of surgery	Use of laminar flow theatres
Preoperative chlorhexidine shower or betadine bath	Waterproof gowns and double gloving
Use of a dedicated implant list	Impregnated drapes (e.g., Ioban)
Putting implant cases first on list	A "no-touch" surgical technique
Having the full range of equipment available	Antibiotic irrigation solution
Use of prophylactic antibiotics	Short hospital stay
Skin shave in theatre	

In all cases, careful counselling of the patient (and the partner in penile implant cases) is mandatory to avoid unrealistic expectations of the outcome from the surgery being undertaken.

Penile Implants

These are used when other nonsurgical treatments of erectile dysfunction have failed. Best results are achieved in high volume operating centers. Some have a hydrophilic coating designed to resist bacterial adherence and allows the implant to be soaked in an antibiotic solution or may be impregnated with them (Inhibizone™). They are usually placed surgically via either a penoscrotal or a subcoronal incision.

Malleable (Semirigid) Penile Prostheses

Malleable implants are relatively simple to insert and are less prone to infection and mechanical failure, but the penis is held out to length permanently, and concealment therefore is more difficult than for an inflatable prosthesis. They are used in retrieval situations where there is extensive corporal fibrosis or for permanent lengthening when a condom urinal is difficult to use in a wheelchair-bound neuropathic patient, in acute priapism and in those with poor manual dexterity.

There are two main choices:

1. A braided silver wire surrounded by a 9 and 13 mm silicone coat. The length required is achieved intraoperatively either by cutting the implant to length or by the use of a range of rear tip extenders.
2. Cobalt-chrome alloy strands with articulating polyethylene segments covered with a 10–12 mm Teflon sheath. These devices provide strength and rigidity while allowing better concealment than other semirigid prostheses.

Inflatable Penile Prostheses (IPPs, see Figs. 51.1 and 51.2)

Constructed primarily from silicone, inflatable penile prostheses have three fundamental components:

- Hollow cylinders which are placed inside the corpora cavernosa of the penis
- A pump that is placed in the scrotum
- A reservoir that is placed intra-abdominally

These components are connected by tubing such that when the pump is activated, the cylinders inflate with saline transferred from the reservoir.

When deflated, the penis has a good flaccid appearance with excellent concealment. When inflated the cylinders expand in girth providing a rigid erection with penile girth approximating normal erect girth and penile length approximating the stretched flaccid penile length. Some models do expand in length, although there is a higher risk of erosion through the glans penis and urethra. Other devices combine the pump and the reservoir into a single component that can be placed in the scrotum. Such so-called two piece devices usually provide inferior rigidity and are rarely used.

Cylinders are available in a variety of diameters and lengths. The correct cylinder length for implantation is determined perioperatively, and the addition of "snap-on" rear tip extenders allows an accurate fit. Devices may have a Parylene polymer applied to the internal cylinder surfaces to reduce friction during inflation and deflation and have "one-touch" release pumps and lockout valves at the neck of reservoir to prevent autoinflation.

Operative complications of penile implantation surgery include posterior perforation, crossover, urethral injury, hypermobile glans, infection, and erosion. Infection

Fig. 51.1 A three-piece inflatable penile implant

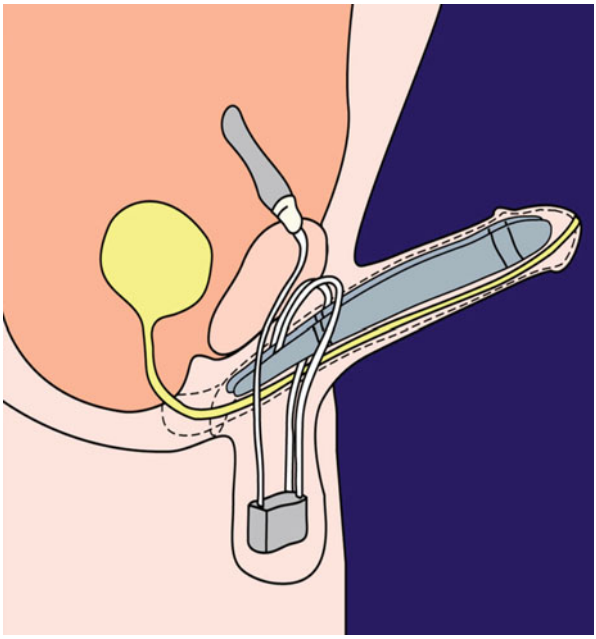

Fig. 51.2 The penile implant in place within the corporal cylinders with the reservoir alongside the bladder and the pump in the scrotum

is the most serious complication and is higher in diabetics, following radiotherapy, in revision cases and in cases where a significant haematoma is present postoperatively.

The Artificial Urinary Sphincter (AUS)

The only model currently available for clinical use is the AMS 800 device (Fig. 51.3). Indications include moderate and severe stress urinary incontinence not amenable to other treatments including postprostatectomy incontinence (PPI) and neuropathic incontinence.

The AUS, which is made from silicone, comprises three components:

- An Inhibizone™ impregnated cuff is placed either around the bulbar urethra (via a perineal or scrotal incision) or around the bladder neck
- A pump that is placed in the scrotum or the labia majora
- A pressure regulating balloon that is placed usually in the retropubic space

The device is "activated" 6 weeks after implantation, and recipients must not allow catheterization without deactivation of the device. Complications include mechanical failure cuff erosion or atrophy. Again an anti-infective coating is used.

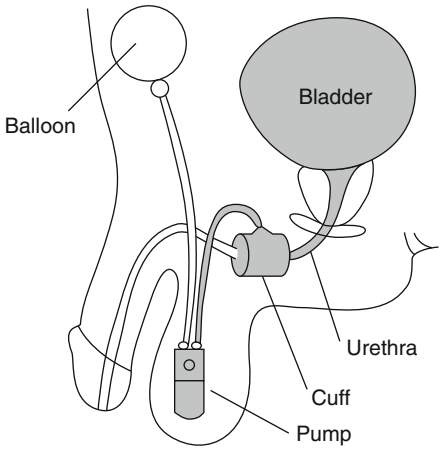

Fig. 51.3 The components of the AUS and their placement in a male patient

Testicular Prostheses

Testicular prostheses are made of silicone or a saline-filled silicone shell. They are best placed via an inguinal, not scrotal, approach, after puberty when there has been full development of the testis of the contralateral side. There are a range of sizes, and the choice of prosthesis is aided by sizers. An anchor strap or button at the inferior pole is sutured to deep surface of dartos to stop upward migration of the prosthesis.

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Chapter 52
Meshes in Stress Urinary Incontinence and Pelvic Organ Prolapse

Neil Harris

The use of mesh in female reconstructive urology, particularly for treatment of stress urinary incontinence (SUI) and more recently for surgical treatment of pelvic organ prolapse (POP), has become increasingly common over the past decade. The mainstay of surgical management of SUI is now the synthetic mid-urethral tape. These are placed via either a transvaginal retropubic (TVT), or transvaginal transobturator (TOT) approaches. Meta-analyses of published data show the two approaches have similar efficacy, but slightly different side effect and risk profiles.

Types of Mesh

Synthetic meshes can be absorbable or nonabsorbable, or more recently, some transvaginal meshes utilise a combination of both types. Purely absorbable meshes are rarely used in pelvic floor surgery because of poor tensile strength, and data suggest they have higher failure rates. One of the most important characteristics of the synthetic meshes is their pore size. It is now recognised that meshes with pore size greater than 75 μm (i.e., macroporous) facilitate efficient access of collagen and fibroblasts and allow the immune system to scavenge for bacteria. This results in lower mesh infection rates and allows better incorporation of mesh into host tissue. The vast majority of all mesh used in pelvic floor surgery is now of the macroporous type. These are known as Type 1 meshes, using the Amid classification (Table 52.1).

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Table 52.1 The Amid classification of implantable meshes

Amid type	Characteristics
Type I	Totally macroporous prostheses (pores >75 μm)
Type II	Totally microporous prostheses (pores <10 μm)
Type III	Macroporous prostheses with multifilamentous or microporous components
Type IV	Submicronic pore size (not a suitable prosthesis)

Type I meshes are the ideal material (Amid 1997)

In contemporary practice, most pelvic floor reconstructive surgeons who utilise mesh, use one of the numerous transvaginal mesh kits that are now available, such as Apogee™, Elevate™, or Prolift™. These kits consist of a polypropylene mesh body with various arms that are passed through and anchored to supporting structures including the sacrospinous ligament and iliococcygeus muscle. Placement of these meshes requires special trocars and anchoring techniques, which are included in the kit.

Uses in Stress Urinary Incontinence (SUI)

There is now a large amount of data (including meta-analyses) published on the use of midurethral tapes for management of SUI. Most show SUI cure rates of 70–90%, although there is still debate as to how cure should be defined. Complication rates remain a small but significant problem and patients need to be counselled preoperatively about these risks. The main risks include mesh extrusion into either the vagina or occasionally the bladder, voiding dysfunction requiring catheterisation, development of overactive bladder (OAB) and chronic pain due to mesh placement. Overall complication rates are reported at 3–10%, but vary according to approach and type of sling.

Use in Surgical Repair of Pelvic Organ Prolapse (POP)

Urogynaecologists and female urologists undertaking pelvic floor reconstructive surgery are also increasingly utilising various types of mesh to augment surgical repair of prolapse. Data suggest the new transvaginal mesh kits improve the durability of prolapse repair, but result in a higher risk of complications. In general, the risk of prolapse recurrence following surgical repair is around 20% and mesh augmentation may reduce this significantly. However, risks include mesh extrusion/erosion, infection, and pelvic pain, and patients need to be carefully counselled before mesh is used to repair a prolapse. The degree of bother, and impact on quality of life, after a complication of vaginally placed mesh is difficult to fully evaluate as many ero-

sions are small and can be treated easily with excision of the eroding mesh and direct closure. The older "patch" types of mesh to augment traditional colporrhaphy have largely been abandoned. Lately, some surgeons have advocated laparoscopic and robotic repair of prolapse, particularly if there is significant vaginal vault descent. Clinical trial data demonstrate that an abdominal approach to certain types of prolapse results in superior "cure" rates. However, the traditional open abdominal sacro-colpopexy (ASC) carries a higher morbidity and significantly longer hospital stay. The minimally invasive approaches to ASC may address these concerns, but also requires use of mesh to increase the durability of the repair.

Overall, it seems likely that mesh will continue to be used by many pelvic floor reconstructive surgeons. The synthetic mid-urethral slings are now considered the "gold standard" surgical treatment for SUI, at least for primary surgical treatment. However, debate remains on the role of mesh in prolapse surgery. The literature remains unclear in this area, mainly as a result of the heterogeneous nature of POP and the inconsistencies that exist in defining exact treatments for specific types and grade of prolapse. This is an evolving area of practice, and surgeons using mesh in pelvic floor surgery should consider adding their own data to national audits, registries, or clinical trials.

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Chapter 53
Biological Meshes

Ian Eardley, Giulio Garaffa, and David J. Ralph

In surgery, meshes are most commonly used for reinforcement. Examples include the prolene meshes use in hernia and pelvic floor repair. The meshes themselves have an intrinsic strength, and they stimulate fibrosis around, and possibly within, them, dependent on the pore size of the mesh. Synthetic meshes do, however, have disadvantages including the risk of infection, so in recent years, alternatives have been developed including soluble and biological meshes.

Soluble Meshes

Synthetic polymers such as polyglycolic acid (PGA), polylactic acid (PLA), and poly(lactic-co-glycolic acid) (PLGA) have been used. They can be manufactured easily with measurable and reproducible strength, degradation rate, and microstructure. Their drawbacks include inferior durability and lack of biological recognition for cellular ingress. There does, however, remain research interest in such meshes, perhaps in combination with seeded growth factors or other bioactive small molecules.

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Table 53.1 Structural composition of the extracellular matrix (ECM) of biological meshes

ECM constituent	Comments
Collagen	Main structural protein of biological meshes
Laminin	Adhesion glycoprotein that is relevant to cell and tissue differentiation
	Helps to direct the formation and stabilisation of blood vessels
	Provides attachment sites for fibroblasts and endothelial cells
Elastin	Significant structural protein in dermal based grafts
	Elastin can be damaged by aging and sun exposure
Fibronectin	Extracellular glycoprotein
	Induces cell adhesion via integrins
Growth factors	Present in small quantities:
	For example
	Vascular endothelial growth factor (VEGF) regulates angiogenesis
	Platelet-derived growth factor (PDGF) stimulates angiogenesis
	Bone morphogenetic protein (BMP) stimulates formation bone and cartilage
	Fibroblast growth factor (FGF) induces growth of fibroblasts
	Transforming growth factor beta (TGFβ) stimulates collagen deposition
Glycosaminoglycan	Mucopolysaccharide that act as a reservoir of growth factors and aids tissue hydration

Biological Meshes

These are primarily of human, bovine, or porcine origin. The most commonly used tissues have been dermis, small intestine, pericardium, and heart valve. There is research interest in the use of bladder as the substrate for a biologically active matrix.

The tissues are decellularised to leave the extracellular matrix (ECM) (Table 53.1); this is primarily a collagen-based structure, with additional elastin and laminin. There is an inherent strength as the architecture of the original tissue's ECM is preserved. The three-dimensional architecture allows cells to enter the mesh and adhere to it. Dependent upon the method by which the mesh is produced, there will be some retained bioactive molecules including cytokines, growth factors, and adhesion molecules. These encourage revascularisation and tissue formation followed by cyclical remodelling with gradual replacement of the mesh by host tissue.

How Biological Meshes Are Manufactured

Manufacture involves decellularisation, sterilisation, and crosslinking. Decellularisation and sterilisation will not remove 100% of all of the native-tissue DNA, and there remains an intrinsic risk of transmission of allogenic materials, virus, and prions with the use of these materials.

1. Decellularisation
   This is achieved using a variety of chemical and physical methods. All decellularisation processes damage the ECM to a certain extent, and there may be change in structure, loss of strength, or loss of growth factors. A typical process uses a combination of methods, e.g., decellularisation of a thick laminate such as dermis involves freezing followed by enzymatic decellularisation and then washing with alcohol, acid, and finally detergent.
2. Sterilisation
   It is necessary to sterilise the mesh. Sterilisation methods such as gamma irradiation, ethylene oxide treatment, or electron beam irradiation are used but can damage the ECM, and there is currently some interest in supercritical CO_2 as a sterilizing method.
3. Crosslinking
   Some meshes are treated chemically by washing with substances such as glutaraldehyde, which induces crosslinking of the collagen strands. This process has a number of putative effects including an increase in the initial strength of the mesh, delayed degradation of the mesh, inhibition of ingrowth of normal host cells, and diminution of the degree of remodelling. Consequently the role of crosslinking is controversial.

Uses of Biologic Meshes

1. *Support and Reinforcement*
   Biological meshes have been used for hernia repair. Due to their increased production costs, inconsistent tensile strength, risk of delayed stretching, possibility of retained DNA, and the unpredictable host response, synthetic meshes remain the first-line choice for most hernia repairs. Biological meshes have a potential role in the support and prevention of abdominal wall hernia (e.g., prevention of parastomal hernia) and when infection is present. Similar caveats apply to the use of such meshes in pelvic floor repair.
2. *Tissue Engineering*
   Biological meshes have a potential additional role as a matrix for the development of new tissue. There are two general strategies for tissue engineering using mesh. The first involves implantation of the mesh itself, which acts as a scaffold for secondary ingrowth of cells. The second strategy involves in vitro seeding of the mesh with the relevant cells and subsequent implantation of the cellular matrix composite. Both approaches are currently the object of research with occasional reports of success. However, although biological meshes are commercially available, clinical “tissue engineering” is not yet a reality.

   The ideal mesh for tissue engineering should have a number of properties.

- Its mechanical properties should be such that there is enough strength inherent within it to withstand the relevant local forces, until such time as the engineered tissue is able to fulfill that role.

Table 53.2 Clinically available biodegradable tissues, their structural features, and clinically reported use in urological conditions

Tissue of origin	Examples	Structural features	Clinically reported uses
Human acellular dermis	E.g., Alloderm™	High elastin content	Pelvic floor surgery Hernia repair Grafting in Peyronie's disease
Porcine small intestine submucosa	E.g., Surgisis™	Low elastin content Retained bioactive small molecules	Grafting in Peyronie's disease Augmentation urethroplasty Hernia repair
Porcine acellular dermis	E.g., Permacol™	High elastin content Crosslinked	Hernia repair Grafting in Peyronie's disease Pelvic floor surgery

- The mesh should be able to appropriately control and influence cellular interactions (adhesion, proliferation, migration, and differentiation) and tissue development.
- The mesh should be biocompatible, such that it biodegrades or reabsorbs fully without exciting an inflammatory response.
- It should possess the requisite physical characteristics to allow it to be constructed into the relevant configuration for its clinical application.

Currently, there is no commercially available mesh that fulfills all these criteria.

Clinically Available Biodegradable Tissues

At this time, "off-the-shelf" biological tissues have no proven place in urological practice. They have been used in a variety of circumstances (Table 53.2), but the clinical benefits have not been fully evaluated and are, therefore, of unproven benefit. The dermally based meshes have largely been used as alternatives to synthetic meshes in supportive situations (e.g., hernia and pelvic floor repair), while small intestinal submucosa (SIS) has the potential for tissue engineering using an unseeded strategy.

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Chapter 54
Principles of Tissue Transfer in Urology

Giulio Garaffa, David J. Ralph, and Ian Eardley

Flaps and grafts are the main techniques for transferring tissue from one location to another. While flaps bring their own blood supply when transferred to the new location, grafts rely on a blood supply acquired from the recipient bed.

Flaps

A flap is tissue that is transferred from a donor site with blood supply intact or occasionally with a vascular network that can be connected to local blood vessels (free flap). In urology, the latter are used in phalloplasty. Flaps can be described in the following ways:

- Island flaps: There is no continuity at the base of the flap such that the donor tissue is like an "island" on the end of the vascular pedicle.

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- Peninsular flaps: There is continuity at the base of the flap and these flaps are used for advancement, rotation, or transposition.
- Random flaps: There is no identifiable vascular pedicle and are therefore restricted in size and shape by the a length to width ratio.
- Axial flaps: There is a defined vascular pedicle, which results in the possibility of creating a larger flap.

Peninsular flaps may be either random or axial, while island flaps will inevitably be axial. A summary of the most commonly used flaps in urology is shown in Table 54.1.

Of particular note are the skin flaps used in urethral reconstruction. The principle here is that the skin blood supply lies within the thin subcutaneous layer immediately under the skin, while there is a deeper fascial layer, the "dartos" layer, which is vascularised and which becomes the vascular pedicle carrying the island flaps that are used to reconstruct the urethra.

Grafts

In urology, the most commonly used grafts are skin, bladder, and buccal mucosa grafts, for urethral and genital reconstruction.

The graft must lie within 1–2 mm of the recipient blood supply to gain the nutritional support that is needed to become incorporated into its new location. The recipient bed therefore must be healthy, free of infection, and have a good blood supply. Periosteum, perichondrium, and muscle are good examples of a healthy recipient site, whereas adipose tissue, bone, irradiated tissues, and wounds with foreign materials represent poor grafting beds.

Graft "take" consists in four stages: adherence, plasmatic imbibition, revascularisation, and remodelling. The initial adherence phase is characterised by the formation of fibrin bonds between the recipient bed and the graft. This is followed by imbibition by plasma derived from the recipient capillary bed that enters the open capillaries of the graft. This allows the exchange of nutrients and oxygen between cells of the graft and those of the recipient bed to ensure graft survival but can only suffice for 24–48 h before revascularisation needs to occur. Revascularisation (inosculation) starts 24–48 h after graft placement as capillary buds from the recipient bed grow into the graft to create a new circulation. The final stage of remodelling involves changes to the histological architecture of the graft to return to its original form.

Classification of Skin Grafts

Skin is a multilayered organ consisting of an epidermis with a basement membrane overlying a layer of dermis which is variable in thickness and has at its base a subdermal vascular plexus. The multiple epithelial appendages of the skin, such as hair follicles, sebaceous glands, and sweat glands, extend below the basement membrane

Table 54.1 Flaps commonly used in urological reconstruction

Flap	Type	Type	Vascular pedicle	Use
Pedicled foreskin flap	Island	Axial fasciocutaneous	Dartos fascial flap based on two dorsolaterally placed vascular pedicles	Urethral reconstruction
Orandi flap	Island	Axial fasciocutaneous	Dartos fascial flap	Urethral reconstruction
Scrotal flap	Island	Axial fasciocutaneous	Dartos fascial flap	Urethral reconstruction
Omental flap	Peninsular	Axial	Right gastroepiploic vessels	Fistula repair and prevention
Martius flap	Peninsular	Axial	Posterior labial vessels	Fistula repair and urethral support
Boari bladder flap	Peninsular	Random	NA	Ureteric reconstruction
Intestinal flap	Island	Axial	Various	Augmentation and substitution cystoplasty Ureteric replacement

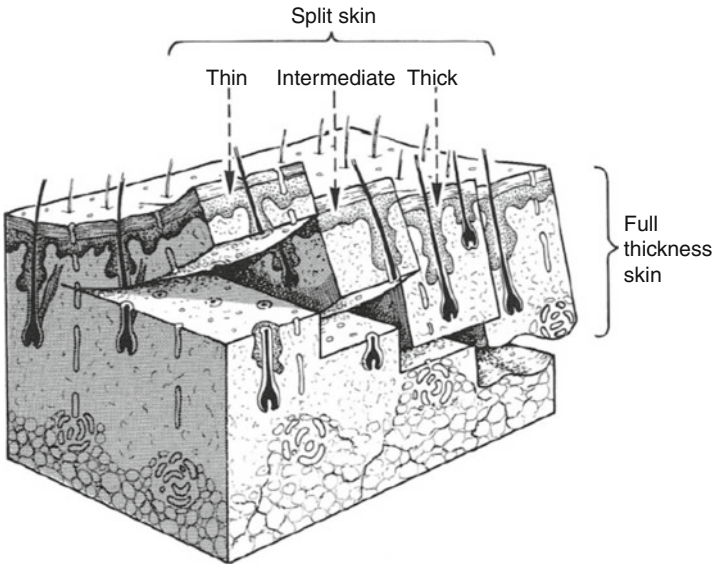

Fig. 54.1 Type of skin grafts: thin, intermediate, and thick split-thickness and full-thickness grafts

Table 54.2 Pros and cons of using full and partial-thickness free grafts

	Full thickness	Partial thickness
Contraction	None	+++
Graft take	Variable	Excellent
Cosmesis	Variable	Good
Colour	Retains colour of donor site	Similar to local tissue
Potential size of graft	Small	Large
Donor site scar	Usually primary closure	Minimal
Hair	Yes	No

and into the dermis. Skin grafts are classified as either partial (split) or full thickness (Fig. 54.1). Buccal and bladder grafts are harvested and behave as full-thickness grafts.

The advantages and disadvantages of full- and partial-thickness grafts are summarised in Table 54.2.

Full-Thickness Grafts

Full-thickness graft consists of epidermis plus the entire dermis. They will therefore retain the donor characteristics such as hair growth. They have a much lower "take" success rate but are more durable than partial-thickness grafts, and wound contracture

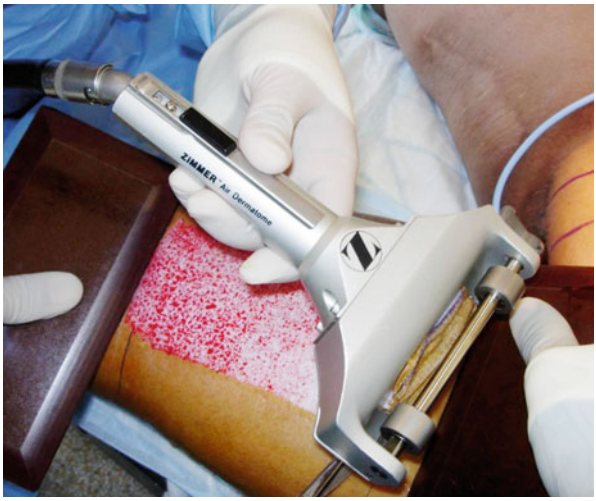

Fig. 54.2 An air dermatome is used to harvest a split-thickness graft from the inner thigh

on the recipient bed is less. However, as they are taken by excision and primary closure, there are limitations to the size and donor site characteristics.

Partial-Thickness Skin Grafts

Partial-thickness grafts are composed of the epithelial layer with a minimal amount of dermis and do not contain any of the dermal appendages. They take well because of a plentiful intradermal plexus. They are easy to harvest and can provide coverage for large wounds and completely regenerate themselves in 2–4 weeks. However, they do contract considerably. They are typically harvested with a Humby knife or an electric dermatome that allows an adjustable thickness to be taken (Fig. 54.2).

Partial-thickness grafts can be meshed or perforated which allows expansion to cover larger areas, e.g., burns, as well as allowing the egress of fluid. To minimise the risk of graft failure, it should be immobilised for around 7 days, either by quilting of the graft or by use of a compressive (e.g., "tie over") dressing. The purpose is to minimise movement and to prevent accumulation of hematoma or seroma.

Disadvantages of partial-thickness grafts include a recipient site that is more fragile than normal with a contour deformity due to the lack of subcutaneous fat. Contraction is a major issue. In urology, split skin grafts are most commonly used for patients with skin loss following Fournier's gangrene and for patients undergoing glansectomy and skin grafting for penile cancer. Typically, graft thicknesses of 11–15 thousandths of an inch are used for these purposes.

The most common causes of graft failure are infection, shear stress, and accumulation of fluid/hematoma under the graft.

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Chapter 55
Theatre Design and Patient Safety

Pat McHugh and Steve Payne

Patient safety is the key consideration in the operating theatre and, whilst this has been recognised for many years, the emphasis on the physical rather than the functional surgical environment has switched so that human factors are now recognised as being more important than the bricks and mortar in which the operating theatre is housed. The relevance of each of these factors to patient safety will be considered separately.

The Physical Operating Theatre Environment

There are a number of rudiments which are intrinsic to the theatre complex. It should be a safe, efficient, user-friendly space that is as free from bacterial contamination as possible. A key principle in these ideals is the flow concept of a patient moving from an outer, "dirty" zone to a clean environment between reception and theatre, an aseptic zone in theatre with all used instruments, and the patient, being moved back into the outer zone. To help provide a physically aseptic zone in the operating theatre, there are a number of prerequisites (Table 55.1).

A key objective intraoperatively is to minimise the risk of wound infection accrued directly as a consequence of surgical intervention.

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Table 55.1 Structural factors to maximise the safety of the physical environment in the aseptic zone in an operating theatre

Principle	Prerequisite
Floors and surfaces	These should be durable, impervious, antistatic, and able to be disinfected
Good ventilation	This should be provided by vertical or horizontal laminar air flow with positive pressure air moving from the clean to the dirty environments, thereby reducing the number of contaminated particles over the patient. The air should go through high-efficiency particulate air (HEPA) filters which remove particles >0.3 μm in diameter with an efficiency of 99.97%. Twenty to forty air changes/hour are normal but can be increased to 400/h by a laminar flow hood. Personal "body-suit" exhaust suits can reduce contamination further
Ideal temperature and humidity	A temperature of 20–22°C, and humidity of 50–55%, is comfortable for operating in. Global temperature may need to be increased for prolonged surgery, children, neonates, and the elderly. Warming blankets, warm air blown over the patient, and the heating of intravenous and irrigant fluids are standard ways of directly maintaining the patient's core temperature intraoperatively. The air temperature in the aseptic zone should be 1°C lower than the clean zone to further facilitate air movement
Good lighting	Theatre lighting should be adjustable, bright enough for their intended task and flexible in use. Luminescence should be 1,000 lux and colour rendition 85–100 Ra
Appropriate gas supply and extraction	Gas services should be piped and available from a boom without trailing connecting tubing. Waste anesthetic gases should be scavenged to a high-volume, low-pressure extraction apparatus. Extraction of the plume created whilst using electrocautery is also important to minimise infective and transmissible malignant risk to the operator
Safe operating tables and ancillary equipment	Operating tables and all-wheeled peripheral devices should be heavy, have a stable base yet be moveable to maximise intraoperative flexibility. Ancillary positioning equipment needs to be compatible with the table, and the table should have soft sorbo rubber padding, which is removable for cleaning, and a radiolucent area so that intraoperative X-rays may be taken

Prior to surgery, the patient should be preassessed, especially to exclude uncontrolled diabetes, or the presence of local or distant infections (MRSA, etc.), which can then be treated before they go to theatre. The patient should have showered, be socially clean, and any hair local to the incision should only be removed if it will interfere with the operation; if it does, it should be clipped in the anesthetic room. In high risk cases (e.g., implant surgery), topical antiseptic washes or creams should be applied on the ward both to the skin and to other potential sources of infection such as the nose. Recent evidence suggests that chlorhexidine–alcohol (2% chlorhexidine and 70% isopropyl alcohol) is significantly more protective than povidone iodine against both superficial and deep incisional infections.

Table 55.2 Factors to prevent surgical wound contamination in the operating room environment

Fomite	Effects on wound contamination
Scrub suits	No proven benefit
Footwear	Should be kept strictly just for the aseptic environment
Caps	Reduce shedding of micro-organisms from the hair
Masks	These provide temporary protection only
Gowns	Provide protection of personnel and prevent shedding of micro-organisms
Drapes	Create a barrier between the surgical field and areas of contamination
Theatre staff	Reducing staff numbers and staff movement in and out of the theatre may be important in minimising air movement
Eye protection	Necessary when a high infection risk, especially from HIV or Hepatitis B

The operative site should have gross contamination removed before performing antiseptic skin preparation, and the antiseptic agent should be applied in concentric circles moving towards the periphery. The prepared area must be large enough to allow extension of the incision, or to create new incisions or drain sites, if necessary. In addition, there are a number of things that can be done in the aseptic environment to reduce the risks of wound contamination during surgical intervention (Table 55.2).

The Functional Operating Theatre Environment

The understanding of the effects of design in the fields of equipment, patient flow, workspace ergonomics, and the human–machine interface are now being intensively studied to improve the patient experience through their surgical procedure. Incident analyses of events in the operating theatre have revealed that factors such as decision making, situation awareness, coordination, and leadership all play a role in the aetiology of adverse outcomes during operative patient management.

More recently, it has been widely recognised that staff behaviour is greatly affected by the situation they are placed in, and the importance of understanding behaviour under stress is now taking center stage. Factors influencing behaviour include physical issues such as lighting, heating and ambient noise; human issues described as ergonomics; and individual issues such as stress, fatigue, and external influences brought into the workplace. All issues except individual behaviour patterns can be assessed globally and planned for.

Aviation type “Cockpit Resource Management” courses, in a variety of guises, are increasingly prevalent in staff training to bring the ethos of “prevention,” as a concept to patient management through the theatre process. Safety training along with the use of high fidelity simulators to improve familiarity with equipment and techniques is being postulated as more important factors to reduce risk than changes to the physical theatre environment.

The introduction and application of the WHO checklist in various formats, modified to local requirement, has led to a culture of pause and reflection before surgical procedures are commenced. It is still very early to see the benefits of this principle in practice, as large numbers will be required to show significant differences in incident levels, but in some studies, there has already been seen to be a reduction in risk, and consequent surgical complications, in centers applying this concept at the start of their operating session.

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Chapter 56
Deep Venous Thrombosis (DVT) Prevention

Pat McHugh

Venous thromboembolic (VTE) disease, including deep venous thrombosis (DVT) and pulmonary embolism (PE), is one of the major causes of morbidity and mortality in hospital patients across the UK. It has a reported incidence of 1:1,000 for DVT in the general population and reportedly caused 1:10 of all inpatient hospital deaths in the UK in the 1980s.

VTE

The risk of VTE is significantly increased in patients hospitalised after trauma, surgery, or immobilising medical illnesses, as well as in pregnant and puerperal women. DVT is asymptomatic in many cases but can progress to pulmonary embolism or to post-thrombotic syndrome in up to 30% of cases, with a significant associated morbidity.

The use of prophylaxis is based on the clinically silent nature of VTE as a disease process, the high morbidity and mortality associated with VTE, and the high prevalence in hospitalised patients, in the pregnant, and in the peripartum period. There is compelling evidence that prophylaxis results in a reduction in morbidity and mortality and a reduction in health costs in hospitalised patients. This has led to the development of many national and international guidelines relating to VTE prophylaxis.

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Causes of VTE

Causes are either inherited, inherent, or acquired. Inherited causes include thrombophilia. Inherent causes include the oral contraceptive pill or hormone replacement therapies. Acquired causes include cancer, obesity, postsurgical, associated intercurrent major illness, pregnancy, long-haul flights, or immobilisation for any cause.

Risk Assessment

The modern management of VTE is dependent on timely, comprehensive, standardised, and repeated assessment of risks, followed by appropriate thromboprophylaxis. An NHS national tool has been developed in the UK, as have quality assessment standards for this task. Risk assessments are published for all risk groups, and there are specialty specific guidelines for all major surgical specialties. Assessment of risks takes into account age, immobility, obesity, and family history. The presence of varicose veins, malignancy, thrombophilias, or pregnancy is noted. Also included is the use of hormone preparations such as the contraceptive pill.

All these risks can be quantified and a total risk score calculated such that all patients entering hospital should now be assessed for thrombotic risk as well as the risks of bleeding. These risks should be discussed with the patient, and thromboprophylaxis prescribed and administered as appropriate and as per local guidelines. The assessment of risk should then be repeated at least every 48 h during the hospital stay.

Thromboprophylaxis

Prophylaxis can be either mechanical or pharmaceutical.

Mechanical prophylaxis utilises either graduated elastic stockings or various pneumatic compression devices. Graduated stocking need to be measured and fitted correctly for each patient and may be above knee or below knee length. There appears to be no difference in efficacy between the two lengths, and cost savings have been noted by using the shorter length as standard. It should be noted that there are a number of contraindications to the use of graduated compression stockings, as there are to other mechanical devices. These include ulceration, arterial disease, skin diseases, and swelling or deformity of the legs. Pneumatic compression devices can act on the foot, or on the calf, and a number of commercial devices are in widespread use. Their use can be a problem in certain types of surgery and may exacerbate congestive cardiac failure (Box 57.1).

Box 57.1: Contraindications, or Relative Contraindications, to the Use of Pneumatic Compression Devices in the Operating Theatre
Severe peripheral vascular disease
When an increase of fluid to the heart is detrimental
Severe heart failure or pulmonary oedema
Known or suspected DVT or PE within 6 month
Immobilised for >72 h without DVT prophylaxis
Postoperative vein ligation
Deformity of the limb
Gangrene or infected leg wounds
Recent skin graft
Dermatitis

Pharmaceutical prophylaxis regimens include aspirin, low molecular weight heparins (LMWH), ultrafractionated heparins (UFH), warfarin, fondaparinux, rivaroxaban, and dabigatran. Many regimes are in place and local guidelines will stipulate the actual drugs used. There is some evidence that prophylaxis should be continued for up to 1-month post discharge from hospital in high-risk patients. Contraindications to perioperative anticoagulation are shown in Box 57.2.

Box 57.2: Contraindications, or Relative Contraindications, to the Use of Anticoagulants Perioperatively
Known bleeding disorder
Prolonged baseline coagulation
Severe liver disease
Ingestion of salicylates or anticoagulants
Colchicine
Snakebite
Thrombocytopenia
Recent intracranial bleeding or head injury
Active or recent GI bleeding

Vena caval filters may be inserted, as temporising manoeuvres, preoperatively when there is a high risk of pulmonary embolism in patients who are otherwise contraindicated from taking anticoagulants or who develop recurrent pulmonary emboli while anticoagulated.

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Chapter 57
Principles of Decontamination

Geoff J.H. Sjogren and Ralph Beard

Effective decontamination of medical devices is essential and is part of the strategy to manage health care–acquired infection (HCAI) (Winning Ways 2003). In the UK, regulations determine that devices designated for single use are not reprocessed and that reusable devices are decontaminated in a sterile services department (SSD) with requisite facilities. They also require that flexible endoscopes are decontaminated according to national guidelines, in an automated reprocessor, and that if other devices have to be decontaminated locally, an automated process is used. Manual cleaning of devices is, thereby, restricted to those items deemed incompatible with an automated process. Staff also have to be specifically trained for decontamination and must ensure there is an audit trail for each recycled item.

The Principles of Decontamination of Surgical Equipment

Decontamination is defined as a combination of processes that include cleaning, disinfection, and/or sterilisation to render a reusable medical device safe for further use and to minimise the risk of transmission of infectious agents (NHS Estates 2003).

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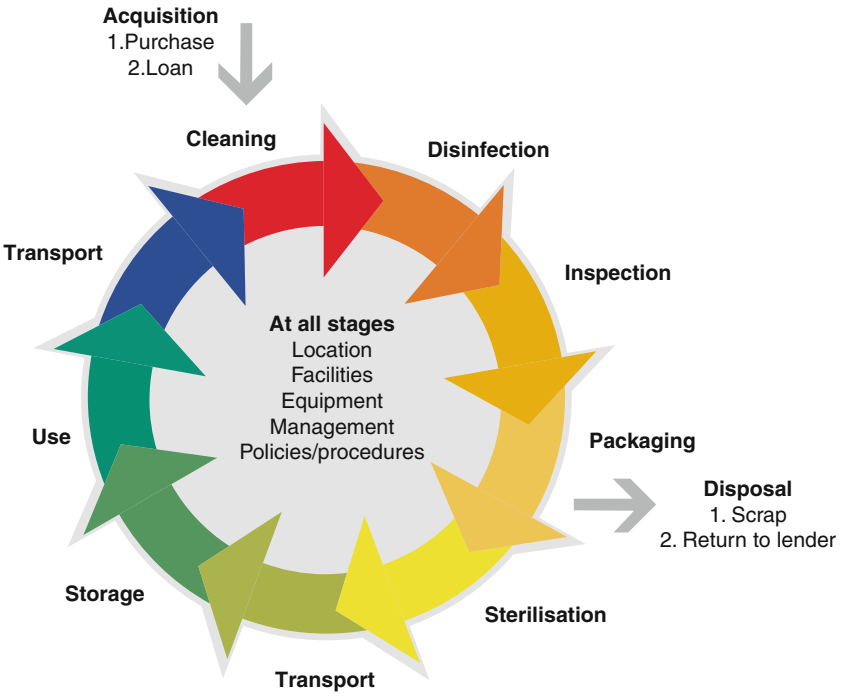

Fig. 57.1 The decontamination "life cycle" (NHS Estates 2003)

The decontamination life cycle is a process consisting of specific steps (Fig. 57.1). Failing to follow these principles embodied in this process enhances the risk of pathogenic microorganisms being spread to patients and/or the environment.

Cleaning

Equipment consisting of more than one component must be dismantled so that each part can be adequately cleaned. Whenever possible, cleaning should be undertaken using an automated, and validated process, in preference to manual cleaning.

Automated cleaning can take place in a washer/disinfector, which goes through a cool prewash, at below 35°C to prevent protein coagulation, a main wash, rinse, thermal disinfection, and postdisinfection rinse, or using an ultrasonic cleaner/disinfector. Ultrasound is used to agitate the water by creating bubbles which implode, dislodging dirt from the surface, and joints, of surgical instruments.

Manual cleaning should be considered only where the manufacturer's instructions specify that the device is not compatible with an automated process. Manual cleaning may be by immersion in water at a temperature specified by the instrument manufacturer and using a specific detergent. Alternatively, the instrument can be

cleaned without immersion using a detergent solution followed by disinfection with an alcohol impregnated wipe.

Disinfection

Disinfection is defined as a process used to reduce the number of viable microorganisms, but which may not necessarily inactivate some viruses and bacterial spores. Disinfection in the clinical setting may be achieved by a number of methods, the two most common being moist heat and liquid chemicals.

Moist heat is the method of first choice as it is easily controlled, leaves no toxic residues, and is relatively safe to those involved in the process. Disinfection can be achieved by washing or rinsing devices in water at between 73°C and 90°C as is achieved in many automated washer/disinfectors.

Devices that cannot withstand disinfection by moist heat may be disinfected using chemicals. The correct chemical concentration must be used and that the device properly submerged to ensure contact with all parts. Chemical disinfectants will be effective only if the solution reaches all surfaces of the device and left for an appropriate exposure time indicted by their manufacturer. Chemical disinfectants, such as chlorine dioxide and peracetic acid, are either alkylating or oxidising agents (Niven 2007) which are subject to the Control of Substances Hazardous to Health (COSHH) regulations, in the UK, as they can cause asthma.

Sterilisation

Sterilisation is a process used to render an object free from viable microorganisms including viruses and bacterial spores. There are a number of different types of steriliser used within the healthcare setting. Porous-load sterilisers are the only sterilisers that should be used and should be sited in SSDs. The equipment that may still be encountered is shown in Table 57.1.

The typical stages in a porous-load steriliser cycle include air evacuation, sterilising at 134°C for a holding time of 3–3.5 min and a postvacuum, or drying, stage.

Specific Decontamination Issues

Accessories that are used during the cleaning of endoscopes and used for endoscopic procedures should be single use where possible. Reusable surgical instruments and rigid endoscopes, if heat tolerant, should be cleaned and disinfected in washer/disinfectors and autoclaved in a validated porous-load steriliser.

Table 57.1 Steriliser types and their use in the healthcare environment

Steriliser type	Use
Porous-load sterilisers	These are steam autoclaves with an active air-removal stage designed to process wrapped goods or devices with a lumen. They are produced in various sizes ranging from portable bench top devices to large capacity (commonly 0.6 m^3/21 ft^3) machines
Bowl and instrument sterilisers	These sterilisers are similar in design and operate in a similar way to porous-load sterilisers, but do not have an active drying cycle or air removal. Their use was limited to sterilising items which are solid and not hollow or cannulated. They are no longer recommended for use
Benchtop steam sterilisers	These are not a recommended method of sterilising as instruments should go to the SSD, but may be encountered.
	Nonvacuum: used for surgical instruments that are unwrapped, not hollow, and do not have lumens
	Vacuum: used for wrapped and hollow/lumen instruments

Flexible endoscopes cannot withstand processes involving temperatures in excess of 65°C. Reprocessing of flexible endoscopes should follow, for example, the British Society of Gastroenterology (BSG) guidelines for decontamination of equipment for gastrointestinal endoscopy (National Endoscopy Programme 2008). In essence, this involves the initial manual cleaning of the endoscope to remove any adherent material, followed by mechanical cleaning and disinfection utilising an enzymatic detergent and high-level disinfectant.

The risk of transmissible spongiform encephalopathies, such as variant Creutzfeldt-Jakob disease (vCJD) may not be adequately removed by conventional sterilisation. Although rarely encountered in urological practice, instruments used in high- or medium-risk procedures on patients with, or "at increased risk" of, CJD/vCJD must be quarantined and only reused on the same patient (Guidance from the ACDP TSE Risk Management Subgroup 2011).

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Chapter 58
Operative Tissue Destruction

Steve Payne

Tissue may be destroyed intraoperatively in a variety of different ways, most of which depend upon the use of some form of thermal energy such as laser or diathermy vaporisation, radiofrequency ablation, or cryotherapy. These technologies are usually only applicable to the obliteration of relatively small amounts of tissue and may not exert their effect rapidly. Destruction of larger amounts of material intraoperatively is only required when voluminous specimens need to be extracted through small access routes and when destruction is preferred to intact extraction through a remote incision. Urologically, this principally applies to the removal of the kidney laparoscopically and the prostate following holmium laser enucleation (HOLEP). The two principle methods of tissue removal employed are manual or mechanical morcellation.

Manual Morcellation

Manual morcellation is something that can really only be done in the abdominal cavity following resection of a kidney laparoscopically. It is usually achieved using ring sponge-stick holders with digital disruption of the tissue in an impermeable, thick, strong entrapment bag such as the LapSac® surgical pouch. It has been shown in gynaecological laparoscopy that manual morcellation is slow in comparison to mechanical tissue disruption, although it is undoubtedly safer.

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Mechanical Morcellation

Mechanical morcellation developed in an attempt to increase the speed of tissue removal, uses bipolar energy, or bladed systems to remove tissue. Many of the laparoscopic morcellators used urologically have been developed from gynecological instruments for the removal of uterine leiomyomas or the uterus. Renal morcellation takes place in an extraction bag with the specimen in fluid; the morcellator is connected to a suction pump which is activated by the first press on the activation pedal, before the morcellator itself starts working.

There are risks of cytological spillage, implantation, and infection from the use of the morcellator and whilst it is possible to histologically grade a tumour from the fragmentary specimen, it is impossible to pathologically stage it. Because of the issues with staging, and to minimise the amount of equipment needed, many laparoscopic nephrectomists have abandoned mechanical disruption of the specimen, favouring intact extraction, usually, via a remote extraction site. This has been shown to be quicker, unassociated with greater patient morbidity or a longer inpatient stay.

Mechanical morcellation of prostatic tissue, enucleated endoscopically, is usually performed using the device inserted into the bladder though a modified nephroscope; both flow channels are used for forward, or ideally sideways, inflow. This ensures the bladder is permanently distended whilst tissue destruction is going on so that the deflated bladder is not sucked into the morcellating slot. A specimen trap allows histological examination of the fragmentary tissue.

Types of Mechanical Morcellators

1. Devices for Laparoscopic Morcellation

The Gyrus PKS™ PlasmaSORD™ (Solid Organ Removal Device) bipolar morcellator is a disposable "bladeless" system that uses bipolar energy to cut tissue. The hand piece is lightweight, and the lack of a spinning blade minimises tissue scatter. The SORD does, however, generate a significant amount of smoke plume that can obscure visualisation; this problem can be overcome by adding a smoke evacuator to one of the ports. Releasing smoke, and the need to reestablish a pneumoperitoneum, means morcellation takes longer using this system.

The Storz Rotocut G1 (Karl Storz) has a single-use blade with a cost-cutting reusable hand piece. The blade cuts through calcified tissue very efficiently. However, since the handpiece contains the motor, it is heavy and slightly cumbersome. The shorter cannula length limits manipulation, particularly in obese patients.

The Gynecare MORCELLEX™ tissue morcellator is entirely disposable, with an intuitive trigger that automatically exposes and activates—or stops and shields—the blade. The titanium blade morcellates quickly, but large amounts of tissue, especially if calcified, can blunt the device. Tissue is grasped manually through the morcellator and pulled through the device to provide a long, thin "tube" specimen.

The Wisap MorcDrive Maxi Twin Cut utilises a rechargeable handpiece and disposable counterrotating blades that have either serrated or waved edges. The counterrotating edges are designed to minimise spinning tissue, and the reusable blade is cost effective. This unit is considered by some to be cumbersome and slower than other units.

2. Devices for Prostatic Morcellation

The VersaCut™ Morcellator System is probably the most widely used for the removal of prostatic tissue following laser enucleation. The reusable handpiece is connected to a combined control box and roller suction pump. A motor in the handpiece is controlled by a graduated foot pedal which initiates suction to engage the enucleated prostatic tissue, first, towards a slot at the tip of the instrument. The motor then moves a reusable hollow slotted reciprocating blade backwards and forwards inside an outer slotted sheath. The engaged prostate is "chopped" by the movement of the blade within the sheath by an action not dissimilar to the movement of the Thompson cold punch. Tissue removal rates are between 4 and 10 g/min which is reduced when the tissue is particularly fibrous. The morcellator should only be used with the slots in an upwards position and with the bladder distended to avoid drawing the bladder wall into the device and perforating it. This is a particular risk when "chasing" small residual fragments.

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Chapter 59
Sutures and Clips

Derek Fawcett

A cursory glance at suture manufacturer's catalogues reveals a bewildering array of needles and materials available to the surgeon – literally thousands of different needle/suture combinations to achieve the two aims of tissue approximation or haemostasis.

Sutures

Suture material must have good knot tying/handling characteristics be of low tissue reactivity and have sufficient strength for their purpose. They may be either absorbable – with short [40 days], medium [50–70 days], or long [200+ days] absorption times, although, many lose half their tensile strength much sooner, or nonabsorbable which will remain until removed. Polyester and nylon, although nonabsorbable, will lose their strength with time. Sutures may be made of a monofilament extrusion or a braided weave and made of natural materials, sheep gut collagen, silk, synthetic materials, or metals (Table 59.1).

Needles

Surgical needles are available in over 220 different styles, diameters and curves. Needles are either traumatic or atraumatic, separate or swaged on to the suture and have shapes and point characteristics defined by the tissue being penetrated, the

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Table 59.1 Commonly used surgical suture materials, their absorption times and uses

Absorbable	Generic name	Trade name	Absorption time	Comments/use
Synthetic braided	Polyglactin	Vicryl	50–70 days	Can be dyed [purple] or undyed
	Polyglactin	Vicryl rapide[a]	40 days	Circumcision
Synthetic monofilament	Polydioxanone	PDS	180–210 days	Abdominal wound closure
	Poliglecaprone	Monocryl	91–119 days	
Non absorbable				
Natural braided	Silk	Mersilk	Indefinite	Skin closure
		Perma-hand	Indefinite	
Synthetic braided	Polyester	Ethibond	Indefinite	Tendon repair, sternal closure
	Nylon	Nurolon	Indefinite	
	Polyester/dacron	Mersilene	Indefinite	
Synthetic monofilament	Polypropylene	Prolene	Indefinite	Abdominal wound closure
	Nylon	Ethilon	Indefinite	
	Poly VDF	Pronova	Indefinite	Vascular anastomoses
	Polyester/dacron	Mersilene	Indefinite	
Metal monofilament	Stainless steel	316 L stainless steel	Indefinite	Chest closure

[a][Vicryl Rapide is made of a polymer with a lower molecular weight than standard polyglactin with a rapid absorption time]

available access space, the needle holder and the surgeon's preference. Needles have three sections, the point, which may be round-bodied, cutting, reverse cutting, tapercut or blunt, the body, curved or straight, and the swage to which the suture is attached.

Needle/Suture Combinations

However confusing this is initially, most specialties use a very limited range of suture/needle combinations and the trainee rapidly becomes familiar with them. In surgery in general, the "anything suture" was historically 2/0 chromic catgut, now replaced by the ubiquitous 2/0 Vicryl (polyglactin) on a half circle, round-bodied needle (W9136). Catgut has become obsolete as a consequence of a vCJD transmission risk. When performing a laparotomy, the scrub nurse is likely to have various "standard" sutures and ties immediately available – 2/0 Vicryl ties, a 2/0 Vicryl and 0 PDS for abdominal wound closure. In urology, ureteric and renal sutures are usually atraumatic 3/0 Vicryl. The bladder is usually closed in two layers of 2/0 Vicryl, the small bowel anastomosed in one or two layers with the either of these sutures.

Each needle and suture packet contains 12 items of information.

1. Colour code
2. Life-size picture of needle
3. Gauge [size]
4. Company name
5. Type of suture
6. Needle length
7. Needle type

8. Length of suture
9. Lot number
10. Expiry date
11. Sterile statement
12. Product code

Stapling Devices

Like sutures, staples have the same two functions of tissue approximation and haemostasis. They can be permanent [usually MRI compatible] or absorbable and have, in theory, been developed to replace hand suturing to improve the speed and security of anastomoses and to be used laparoscopically. Many different shapes of stapling applicators have been developed for specific purposes, particularly for bowel anastomoses. Typical devices are

- Covidien/Autosuture
  - GIA 8038S [i.e., *8.0*-cm, *3.8*-mm staple, *s*ingle], used in ileal conduit creation and small bowel anastomoses
- Ethicon Endosurgery
  - Proximate *ILS* [*i*ntra*l*uminal *s*tapler]

Stapling techniques for ureteric anastomoses, ureteroileal anastomoses, neobladder construction and bladder neck – urethral anastomoses in radical prostatectomy are in development and are not yet commonly used; most anastomoses continue to be sutured by hand. Increasingly, urologists use stapled small bowel anastomoses for reconstruction.

Clips

Clips were developed to enable secure "ligation" of vessels or tissue bundles in laparoscopic surgery as suture tying was perceived as difficult. Many open surgeons, however, use clips for the same purpose, particularly in inaccessible areas such as the depth of the pelvis. Applicators, therefore, exist for both open and laparoscopic clip application. Clips can be either permanent (stainless steel or titanium) or absorbable (polymer). Clips may be either locking, in which case they have "teeth" which mesh together or be simply compressive.

Evidence

There is little evidence for the choice of suture/staple or clip. There is some evidence that slowly absorbable sutures are better for abdominal wound closure than rapidly absorbable sutures, with respect to subsequent incisional hernia. In closing abdominal wounds, the ratio of suture length to wound length is of importance in

preventing wound dehiscence or herniation – a suture to wound length ratio of 4 or even 6:1 is recommended. It is important to emphasise that tight sutures can cause tissue necrosis with resulting wound failure which is, obviously, more important if the wound is an anastomosis. In urology, there is the ever present risk of nonabsorbable sutures, staples or clips coming into contact with urine and becoming a nidus for intraluminal stone formation or causing a sinus or fistula due to their persistence.

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Chapter 60
Monopolar Diathermy

Kieran O'Flynn

Standard electrical current alternates at a frequency of 60 cycles per second (Hz). At this frequency, current could be transmitted through body tissue but would result in excessive neuromuscular stimulation and possibly electrocution. Because nerve and muscle stimulation cease at 100,000 cycles/s (100 kHz), electrosurgery can be performed safely above this frequency.

Monopolar Diathermy Generators

An electrosurgical generator takes 60 cycle current and increases the frequency to over 200 kHz and produces a variety of electrical waveforms typically designated as "cut," "coag," and "blend." As waveforms change, so do the corresponding tissue effects. The "cut" waveform is typically a continuous high current, low voltage waveform. This waveform produces heat very rapidly, resulting in vaporisation, enabling the surgeon to vaporise or cut tissue. Using an intermittent low current, high voltage waveform, like "coag," causes the generator to modify the waveform so that the duty cycle (defined as the ratio of the "on" time to the period of a single "on–off" cycle) is reduced. This interrupted waveform will produce less heat, resulting in a coagulum being produced.

A "blend" results from a modification of the duty cycle. As the surgeon progresses from Blend 1 to 3, the duty cycle is progressively reduced. A lower duty cycle produces less heat. Consequently, Blend 1 is able to vaporise tissue with minimal haemostasis, whereas Blend 3 is less effective at cutting but has greater haemostatic properties (Fig. 60.1).

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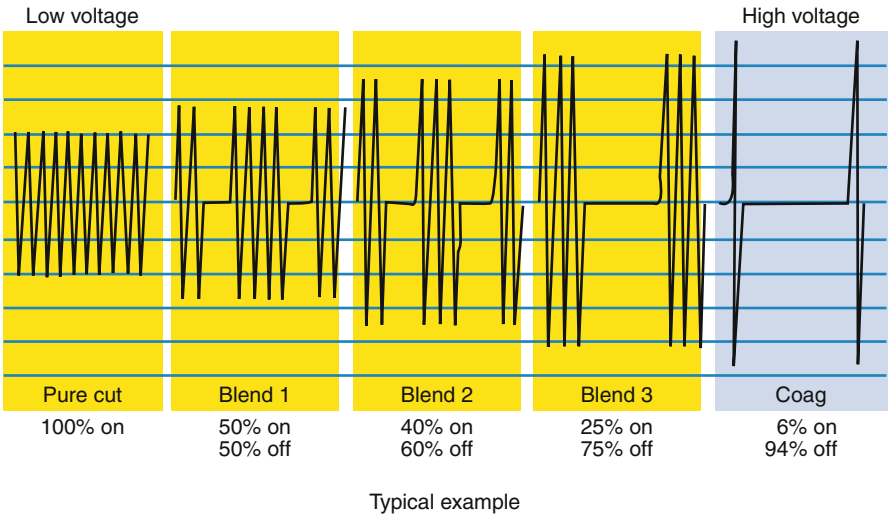

Fig. 60.1 The relationship between voltage, waveform, and tissue effect of pure cut, blend, and coag monopolar diathermy settings

The only variable that determines whether one waveform vaporises tissue and another produces a coagulum is the rate at which heat is produced. High heat produced rapidly causes vaporisation. Low heat produced more slowly creates a coagulum. Any one of the five waveforms can accomplish both tasks by modifying the variables that impact tissue effect.

Electrosurgical Safety

Prior to surgery, the electrosurgical unit (ESU) should be inspected along with the cables and electrodes and the safety features (e.g., lights, activation patient return electrode sound indicator) tested before each use. The activation sound indicator should be audible during surgery. The ESU should be operated at the lowest effective power setting to achieve the desired effect with the patient return electrode as close to the surgical site as possible on a large muscle mass, not overlying implanted metal, and have good skin adherence. When the return electrode is close to the surgical site, lower power settings can be used. The ESU should not be used in the presence of flammable agents, e.g., alcohol, tincture-based fluids. When not in use the active electrode should be placed in a clean well-insulated quiver. Special precautions should be taken when using the ESU with patients with pacemakers and automatic defibrillators as its use may interfere with the cardiac device's circuitry.

It is important that the patient is not touching any metal objects, as the current will select as its pathway to ground via the most conductive object, which may not

be the patient return electrode. Current concentration at this point may lead to an alternate site burn.

Surgical smoke is created when tissue is heated or vaporised. Viral DNA, bacteria, carcinogens, and irritants are known to be present in the smoke. Where possible, it is advisable to use a smoke evacuation system when utilising monopolar electrosurgery.

Concentration of monopolar current may occur when using coagulation settings on pointed structures and lead to damage to the feeding blood supply of that structure and consequent ischaemia. Caution should, therefore, always be used with monopolar diathermy on structures such as the penis.

Isolated Generator Technology, Interrogation Circuits, and Return Electrode Monitoring

In 1968, electrosurgery was revolutionised by the introduction of isolated generator technology. This isolates the therapeutic current from ground by referencing it within the generator circuitry. In an isolated electrosurgical system, the circuit is completed not by the ground but by the generator. Even though grounded objects remain in the operating room, electrosurgical current from isolated generators will not recognise grounded objects as pathways to complete the circuit. Isolated electrosurgical energy recognises the patient return electrode as the preferred pathway back to the generator. By removing ground as a reference for the current, the isolated generator eliminates many of the hazards inherent in grounded systems, most importantly current division and alternate site burns.

Interrogation circuits continuously monitor the quality/quantity of the contact area between the pad and the patient using a monitoring patient return electrode. Contact quality monitoring was developed to protect patients from burns due to inadequate contact of the return electrode. Return electrode monitoring (REM™, Covidien) generators actively monitor the amount of impedance at the patient/pad interface because there is a direct relationship between this impedance and the contact area. The system is designed to deactivate the generator before an injury happens, if a high level of impedance is detected at the patient/pad interface. In order to work properly, REM™-equipped generators must use a patient return electrode that is compatible. Such an electrode can be identified by its "split" appearance – that is, it has two separate areas – and a special plug with a centre pin.

Argon-Enhanced Electrosurgery (ABPC)

Argon beam plasma coagulation (ABPC) is an electrocautery technique that has been used in open surgery for many years. Argon-enhanced electrosurgery incorporates a stream of inert, noncombustible argon gas to clear blood from the target

vessel and minimise the depth of eschar created to 1–2 mm. For this reason, it is safer to use than techniques such as laser or conventional diathermy, especially where there is rapid blood loss.

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Chapter 61
Bipolar Diathermy

Kieran O'Flynn

Electric current flows when electrons pass from on atom to another, with the flow (I) expressed in amperes. The greater the current, the larger the number of electrons that are moving. To allow flow, a circuit must be formed between a positive and negative electrode with voltage (V) being the force that allows electrons to move through the circuit. If electrons meet resistance (R), then heat is generated according to Ohm's law (Fig. 61.1). This property is fundamental to the application of surgical diathermy.

Bipolar Electrosurgery

In bipolar electrosurgery, the flow and voltage is derived from a generator, and the path of the current only passes through the tissue being treated. Coagulation may be achieved using tined forceps in which the two halves of the instrument are insulated from one another. In effect, one half becomes the source of the current and the other the destination. Because the return function is performed by one tine of the forceps, no patient return electrode is needed in contrast to the monopolar configuration. Bipolar electrosurgery typically uses a frequency between 250 kHz and 1 MHz.

The principle advantage of bipolar diathermy is that electric currents do not pass through parts of the body which are not being treated, and also, it is possible to be much more precise about the quantity of tissue being coagulated. This enables small blood

$$I = V/R$$

Fig. 61.1 Ohms law: increased resistance results in greater tissue heating

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vessel gripped between the jaws of the forceps to be coagulated, whereas tissue next to other parts of the forceps will not be heated at all. It is particularly useful in laparoscopic procedure and in operations on pointed structures such as the penis. Bipolar diathermy may also be used where there may be interference with the action of a cardiac pacemaker by stray diathermy currents from monopolar systems.

An ideal bipolar diathermy current generator should be fully isolated from earth so that there will be no tendency for diathermy currents to circulate in the body to find other routes to earth.

Safety

While inherently safer than monopolar diathermy, bipolar electrosurgery used with minimally invasive surgery has its own hazards. Breaks in insulation can create an alternate pathway through which current can flow, potentially damaging structure not in the visible surgical field. Direct coupling may occur when the surgeon activates the generator close to or touching another instrument in the surgical field. When a nonconductor separates two conductors, it may create an electrostatic field between them, termed a capacitor. In minimal access surgery, an inadvertent capacitor may be created by the surgical instruments and burns may result. Disposable plastic sheaths around instruments are preferred to minimise this risk.

Applications of Bipolar Diathermy

Bipolar Resection

Bipolar technologies such as Gyrus system™, the Vista Coblation™ system, and the transurethral resection in saline (TURis™) system allow the electric current to complete the circuit without passing through the patient. This allows saline solution to be used for irrigation during resection, potentially reducing the risk of "TUR syndrome."

The Gyrus plasmaKinetic (PK) system™ is a bipolar coaxial system with the active and return electrodes located in the same axis, separated by a ceramic insulator. Such an intricate design has raised the cost of each resection loop. In the TURIS system, (Olympus SurgMaster resectoscope™, with a 26F outer diameter), the SurgMaster™ generates a high frequency current that passes through the active electrode (resection loop) and returns via the return electrode (sheath of the resectoscope). The generator is usually set for cutting, and coagulation at 180 and 100 W respectively. This is a simpler and less costly bipolar design with potentially similar clinical benefits. The VIO 300 D™ (Erbe) offers a bipolar cut and coagulation mode for bipolar resection in urological procedures. All common resectoscopes can be connected to the VIO 300 D™ using a special adapter for bipolar resection.

Open and Minimally Invasive Surgery

Vessel sealing technology™ (Covidien) and Enseal™ (Erbe) are examples of electrosurgical technology that combines pressure and energy to create a seal. A specialised generator/instrument system has been developed that is designed to reliably seal vessels and tissue bundles for surgical ligation both in laparoscopic and open surgery.

They apply a unique form of bipolar electrosurgery in combination with optimal pressure delivery, by the instruments, in order to fuse the vessel walls and create a permanent seal. During the energy delivery cycle, the generator measures the initial resistance of tissue and chooses appropriate energy settings. Pulsed energy is then delivered with continuous feedback control. As the cycle progresses, the pulse adapts, and when the tissue response is complete, the cycle stops. The result is reliable seals on vessels up to and including 7 mm in diameter or tissue bundles with a single activation. The thermal spread is significantly reduced compared to traditional bipolar systems. The seal site is often translucent, allowing evaluation of hemostasis by the surgeon, prior to cutting. Seal strengths are comparable to mechanical ligation techniques such as sutures and clips and are significantly stronger than other energy-based techniques such as standard bipolar or ultrasonic coagulation. The seals have been shown to withstand more than three times normal systolic blood pressure. The potential benefits of this technology are reduced blood loss, time saved by reduced suturing, and potentially fewer needle stick injuries in confined spaces and avoidance of thermal injuries to surrounding structures.

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Chapter 62
Alternatives to Electrosurgery

Adrian D. Joyce

Electrocautery has been in common surgical use since 1926, and despite modern innovations, such as bipolar diathermy and the argon beam coagulator, the principles and applications in achieving haemostasis have very much remained the same. Newer haemostatic technologies have evolved in the era of laparoscopic surgery to try and improve patient safety by reducing the risks of inadvertent cautery of local or remote structures, or of explosion.

Whether an individual surgeon chooses to use modern electrosurgical equipment or alternative energy sources for haemostasis, the choice is ultimately determined by the type of equipment that the operator feels most comfortable using and the type of tissue that is being operated upon. Whichever energy form is used, the surgeon must, however, have a detailed knowledge of the physical concepts required to effect haemostasis and be able to understand the complications that may be created by the energy, how to avoid them, and how to deal with them if they occur. There are subtle differences between the different alternative energy sources in how they react with human tissues, but the clinical outcome often appears to be much the same, depending more on the skill of the individual surgeon than on the power source employed.

The current alternatives to electrosurgery are:

- The Harmonic scalpel
- The LigaSure™ system

The Harmonic Scalpel

Unlike electrosurgery, ultrasonic energy is mechanical in nature and works at much lower temperatures. Electrosurgery and lasers coagulate by burning at high temperatures causing obliterative coagulation at between 150°C and 400°C. Blood and

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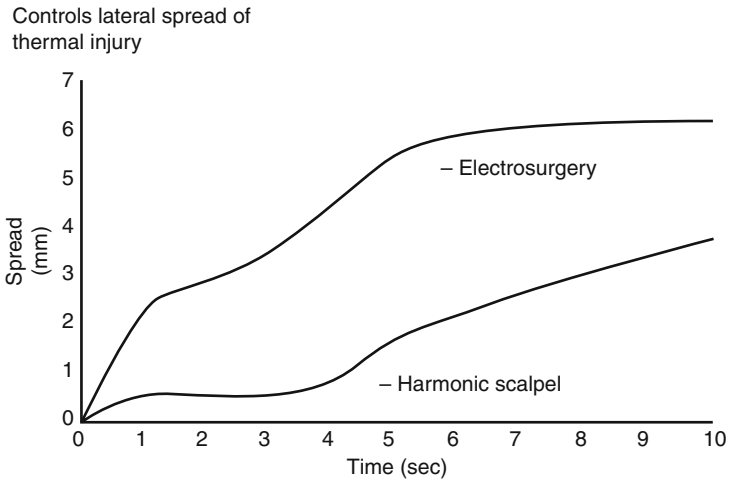

Fig. 62.1 A comparison of the extent of lateral thermal spread for electrosurgery and ultrasonic energy used in the harmonic scalpel

tissue are thereby desiccated and oxidised, forming a charred eschar that covers and seals the bleeding area. Rebleeding can occur when the forceps used during electrosurgery are removed, when they may stick to the cauterised tissue and disrupt the eschar.

Ultrasonic energy controls bleeding by coaptive coagulation at lower temperatures, typically from 50°C to 100°C. Coaption, compression of the vessel walls together, is followed by sealing with coagulation of a protein coagulum. Coagulation occurs by denaturing protein when the instrument blade, vibrating at 55,500 Hz, causes protein in the vessel wall to form a coagulum that then seals the coapted vessels. If the ultrasonic energy application is prolonged, secondary heat is produced that, in addition, helps to seal larger vessels.

The Ethicon Harmonic scalpel cuts tissues whilst simultaneously sealing the edges of the cut. The system typically comprises of a handheld ultrasonic transducer, an ultrasonic generator, hand switch, foot pedal, and scalpel that serves as the cutting instrument.

The advantages of the harmonic scalpel are that there is less potential collateral damage to adjacent structures and the coaptive process minimises smoke and avoids carbonisation of the tissues (Fig. 62.1). Extensive use during laparoscopic surgery can, however, result in significant heating of the tip of the blade (up to 100°) and care has to be taken to minimise the risk of thermal injury to adjacent organs, bowel in particular. The major downside of this technology has, however, been the inability to consistently obliterate vessels >5 mm in diameter.

The LigaSure™ System

The Valleylab LigaSure™ system uses a unique combination of pressure and energy to create vessel fusion. This process uses radiofrequency energy to melt the collagen and elastin in the vessel walls and reforms it into a permanent, plastic-like, seal. It does not rely on a proximal thrombus as classic bipolar electrocautery does. A feedback-controlled response system automatically discontinues energy delivery when the seal cycle is complete, which minimises the thermal spread to approximately 2 mm for most LigaSure™ instruments. By utilising a unique energy output, the result is virtually free of sticking or charring, and the seals can withstand three times normal systolic blood pressure. This system requires a designated generator which is often combined, in one unit, with monopolar and bipolar electrosurgery generators.

The technology is reputed to be able to seal vessels up to 7 mm in diameter and can be delivered through a variety of instruments for use in both laparoscopic and open procedures. Many surgeons would, however, recommend clipping vessels of this size rather than relying on the fusion created by this technology.

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Chapter 63
Haemostatic Agents, Sealants, and Adhesives

Ian Eardley

Haemorrhage is an occupational hazard for all surgeons, and there are several basic surgical techniques to combat it, including manual pressure, tourniquet, cerclage, ligature, suture, and diathermy. There are occasions, however, when such methods fail. In recent years, the use of topical haemostatic agents has increased, with an ever-increasing array of agents being commercially available. Definition of the actions of the different agents is valuable and is important from a regulatory perspective:

- Haemostatic agents clot blood
- Sealants create a sealing barrier
- Adhesives bind tissues together

The mechanisms underlying the mechanisms of action of the commonly available agents are shown in Table 63.1.

The clotting cascade is central to an understanding of how these products work (Fig. 63.1). The principle mechanisms involve contact activation by cellulose, collagen, or gelatin, platelet activation by collagen, introduction of clotting factors, notably thrombin, or direct application of fibrin glue.

Gelatin Containing Agents

Gelatin purified from porcine skin has been used during surgery since 1945. These products can absorb large amounts of blood, thereby swelling, producing tamponade, and concentrating plasma proteins including clotting agents. Finally, the gelatin provides a structural matrix for the clot. It will only be effective if the patient's clotting is normal. Gelatin containing agents typically resorb within 4–6 weeks. Gelatin products are of bovine origin.

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Table 63.1 The principle haemostatic agents and their mechanisms of action

Product	Functions	Examples	Mechanisms of action	Required for activity	Origin
Gelatin based products	Haemostatic	Gelfoam™ Surgifoam™	• Absorbs blood and swells producing tamponade • Provides a structural matrix for clotting • Initiates clotting cascade via contact activation	Normal clotting cascade and clotting factors	Bovine
Gelatin based products combined with clotting factors	Haemostatic	Floseal™ Surgiflo™	• All actions of gelatin containing products • Contain additional thrombin which acts via clotting cascade	Fibrinogen	
Collagen based products	Haemostatic	Actifoam™ Helistat™ Avitene™ Helitene™	• Initiates clotting cascade via contact activation • Platelets aggregate in the collagen matrix • Platelets initiate clotting cascade via contact activation	Normal clotting cascade and clotting factors	Bovine
Cellulose based products	Haemostatic	Surgicel™ Fibrillar™ Nu-Knit™	• Swells on contact with fluid to provide tamponade • Contact activation • Acid environment • Provides scaffold for platelets and clotting factors	Normal clotting cascade and clotting factors	Wood pulp

Fibrin sealants	Haemostatic Sealant Adhesive	Tisseel™ (*) Croseel™ (**) Hemaseel™ (**)	• Activate clotting cascade by two components mixed together • Component 1 contains Thrombin and Calcium and • Component 2 contains Fibrinogen, fibronectin and Factor XIII • Thrombin converts factor XIII to activated form • Activated Factor XIII converts fibrin monomers into fibrin polymer	Dry stationary surface	Bovine (*) Human (**)
Combinations Collagen + Fibrin sealant	Haemostatic	TachoComb™ TachoSil™	See above		

*Bovine origin
**Human origin

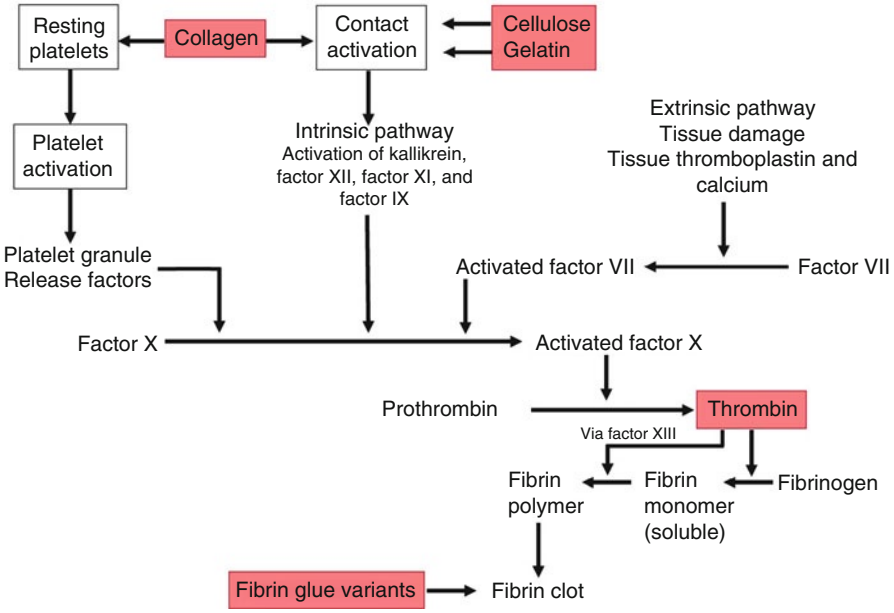

Fig. 63.1 The coagulation cascade with principle haemostatic technologies (*red boxes*)

Collagen Containing Agents

Collagen is also of bovine origin, and the first agents were used in the 1940s, although widespread introduction only occurred in the 1970s. Collagen initiates the clotting cascade via contact activation and also initiates platelet activation. These agents take around 3 months to resorb.

Cellulose Containing Agents

First used in the 1940s; these agents are derived from wood pulp. They act by contact activation to initiate the clotting cascade, but they also swell and provide a tamponade effect and a scaffold for the clot to develop within. The acid environment that they create is thought to enhance the clotting effect.

Clotting Agents

The most widely used agents are thrombin containing haemostatics. Thrombin has a central role in the clotting cascade and is typically of bovine origin. Although

clotting agents are not required, fibrinogen is essential to the action of thrombin. Although it is available as a separate product, it is most commonly combined with some other agent, most notably with gelatin (Tisseal™) or with fibrinogen in the so-called fibrin sealants.

Fibrin Sealants

Sheep fibrin was first used in 1915 as an agent for haemostasis, and in the 1940s, fibrinogen was used as an adhesive for peripheral nerves. Modern agents usually combine thrombin with fibrinogen (separated prior to application), with appropriate additional cofactors (see Table 63.1). In addition, these agents may contain antifibrinolytics such as aprotinin (of bovine origin) or tranexamic acid. In contrast to the preceding agents, they need a dry, stationary surface to be effective.

Adhesives

Cyanoacrylates are the basis of widely used fast-acting adhesives such as Super Glue™. There are medical grade glues based upon 2-octyl cyanoacrylate that are marketed under a number of brand names such as Dermabond™ and SurgiSeal™. They are water resistant glues that rapidly polymerize in the presence of water (hydroxide ions), forming long chains that join the bonded surfaces together. There is some evidence that there may be reduced risks of wound infection in comparison with traditional skin sutures.

BioGlue™ combines bovine glutaraldehyde and albumin. Glutaraldehyde forms covalent bonds between the albumin and tissue proteins, thereby linking the two. It begins to bond within 20–30 s and reaches maximum strength within 3 min.

Other Agents

Polysaccharide-based agents are a relatively recent addition to the range of haemostatic agents. There are three principle groups: those based on chitosan which is a naturally occurring polymer found in crustacean shells (e.g., HemCon™, ChitoSeal™), those based upon polymers found in marine algae (e.g., SyvekPatch™), and those based upon potato starch (e.g., TraumaDEX™). The mechanisms of action are complex and poorly understood, but probably involve release of vasoactive substances, platelet activation, and concentration of red blood cells.

Finally, a recent range of inorganic agents have been developed (e.g., QuikClot™) based upon zeolite. The products are granular and probably work by absorption of water, with subsequent concentration of platelets and clotting factors.

Available Applications

Haemostatic agents are available in a variety of different forms ranging from powders, sheets of tissue, fleeces, and film applications. The physical characteristics of the application may influence the use of the agent. For instance, the granular agents (e.g., Floseal™) are able to conform to the local tissues in a way that sheets cannot. However, a flat "oozy" surface sheets, or fleeces, have a clear advantage.

Complications and Adverse Events

Bovine products have the potential for allergy, anaphylaxis, and BSE transmission, with the latter also possible with human agents. Cellulose containing products have been reported to cause occasional cellulose granulomas which can be indistinguishable radiologically from malignant lesions.

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Chapter 64
Irrigation Fluids and Their Hazards

Stuart N. Lloyd

Fluids are infused into the urinary tract during endoscopic urology to distend the viscus and to "wash away" any blood and improve the view. All bladder irrigants should be pyrogen free and used at close to body temperature to minimise heat loss during surgery. The commonest fluid used in the UK is isotonic saline, but for monopolar prostatic resection, a nonionic liquid that does not conduct electricity is required. A variety of solutions have been used including water, glycine, sorbitol, and mannitol. All, except water, are weakly hypotonic, thereby reducing the risk of intravascular haemolysis which remains a significant risk when using water. Glycine (1.5%) is currently the most widely used fluid used for this purpose, but water continues to be used in some parts of the world, primarily for economic reasons. While glycine is well suited to monopolar resection, there are hazards with its use, most notably intravascular absorption with the development of the so-called TUR syndrome.

TUR Syndrome

The TUR syndrome is a dilutional hyponatraemia that occurs when fluid is absorbed through venous channels, commonly during prostatic resection, but it can also occur during bladder surgery and nephroscopy. It is characterised by a serum sodium of <125 mmol/L and two or more associated clinical symptoms (Table 64.1). It may lead to death if untreated.

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Table 64.1 Symptoms commonly associated with dilutional hyponatraemia

Nausea	Confusion
Vomiting	Anxiety
Bradycardia	Paraesthesia
Hypotension	Visual disturbance
Chest pain	

Incidence and Risk Factors for Developing TUR Syndrome

Significant fluid absorption occurs in approximately 10% of cases undergoing TURP, although the prevalence of the full syndrome is much lower. There are several risks factors including the skill and experience of the operator, but the size of the gland, the duration of the surgery, the height of the irrigant column, and the intraprostatic fossa pressure are others. Prostatic capsular, or bladder, perforation may lead to absorption via periprostatic venous, intraperitoneal, or perivesical routes. Infusion of irrigation fluid under high pressure will increase the rate of absorption which can be minimised by continuous flow resection.

Intravascular Volume Shifts

Intravascular volume expansion by up to 200 mL/min of irrigant can cause initial hypertension. Later, hyponatraemia and hypertension will lead to fluid shifts from the intravascular space along osmotic and hydrostatic pressure gradients, resulting in hypotension, pulmonary oedema, and, if untreated, to hypovolaemic shock. Factors that can aggravate the hypotension include a direct toxic effect of glycine on the myocardium, the sympathetic blockade that accompanies a regional block as well as endotoxaemia that may occur during endoscopic surgery.

Plasma Solute Effects

The changes in plasma solutes in TUR syndrome can be varied and complex. Acute hyponatraemia occurs due to absorption of large volumes of irrigant that may be aggravated by electrolyte losses into accumulations of infused, but extravascular, nonelectrolyte solutions. Hypoosmolality rather than hyponatraemia is probably the main cause of neurological signs since the blood brain barrier pore size is impermeable to sodium, but freely permeable to water. Cerebral oedema caused by acute hypoosmolality increases intracranial pressure, resulting in bradycardia and hypertension via the Cushing reflex. Diuretics, such as furosemide and mannitol, exacerbate the acute hyponatraemia and when used to treat fluid overload may actually worsen the situation.

Hyperammonaemia

Both the portal bed and the kidneys can metabolise glycine by oxidative deamination to form glyoxylic acid and ammonia, while the brain also contains a glycine cleavage enzyme that produces ammonia. Ammonia can alter CNS function, although the exact mechanism is unclear. L-arginine can limit the build up of ammonia by preventing hepatic release of and promoting conversion to urea. However, since the endogenous stores can be used up within 12 h, prophylactic administration of L-arginine has been recommended at a rate of between 4 g (20 mmol) over 3 min and 38 g (180 mmol) over 12 min. No toxicity has been noted with either regimen.

Hyperglycinaemia

Glycine is itself an inhibitory neurotransmitter and may have a role in the development of visual changes, encephalopathy, and seizure. While the exact mechanism is not completely understood, its action may involve N-methyl-D-aspartate (NMDA), (which is an excitatory neurotransmitter) since NMDA receptor activity is potentiated by glycine. It is also thought that glycine causes visual changes via its action as a neurotransmitter within the retina, although these changes typically return to normal within 24 h as glycine levels normalise.

Management of TUR Syndrome

Prevention of this clinical syndrome by minimisation of risk factors is the most important way of managing this problem. The presence of symptoms and signs, suggestive of hyponatraemia, is regarded as the single most important factor in determining morbidity and mortality; treatment in patients without symptoms is not recommended. Intensive monitoring and supportive HDU/ICU care is central to the management of these patients. Hypertonic saline can be used to treat the hyponatraemia and hypoosmolality but may aggravate the hypervolaemic manifestations. Osmolality should be corrected aggressively (sodium correction 2 mmol/L/h) until symptoms resolve then more slowly at about 1.5 mmol/L/h. The most serious complication of rapid correction of hyponatraemia is central pontine myelinolysis (CPM) a demyelinating condition with very poor prognosis.

Seizures associated with hyponatraemia and hypoosmolality are typically resistant to benzodiazepine and anticonvulsant therapy. Magnesium exerts an inhibitory action on the NMDA receptor and a reduced level of magnesium, consequent upon dilution and diuretic usage, can increase the susceptibility to seizures. As a consequence, a trial of magnesium therapy may be a worthwhile manoeuvre in severe cases especially if the serum osmolality is near normal.

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Chapter 65
Insufflants and Their Hazards

Stephen Bromage and Andrew Sinclair

A range of insufflation gasses have been used for laparoscopy. An ideal insufflation gas should be physiologically inert, colourless, highly soluble in blood, chemically stable, widely available, and inexpensive. CO_2 has emerged as the predominant choice due to its high solubility, lack of colour, and the low risk of combustion. The advantages and disadvantages of insufflants are shown in Table 65.1.

Use of CO_2 in Laparoscopic Urological Surgery

The CO_2 is at high pressure whilst stored in a cylinder (760 mmHg or 200 bar) and is reduced to the required inflation pressure by a reduction valve. CO_2 insufflator pressure is usually set at 15 mmHg; this can be increased to 20 mmHg when required to reduce bleeding; this increases the risk of complications associated with higher pressure insufflation. The initial gas flow is normally 1 L/min; this is increased when it is clear that the peritoneal cavity has been entered following initial percutaneous puncture.

The normal gas temperature is 21°C, and although this can cause problems with fogging of the laparoscope, increasing the temperature has no other significant benefits and so is not, usually, performed. The gas is not humidified, although evidence exists that humidification of the insufflant can reduce postoperative pain for the patient.

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Table 65.1 Advantages and disadvantages of various gaseous insufflants

Gas	Advantages	Disadvantages
CO_2	Good absorption, low-risk combustion	Hypercapnia Peritoneal irritation (abdominal and shoulder tip pain)
Air	Inexpensive, no acidosis, or hypercapnia	Air embolus Combustion
NO_2	Anaesthesic properties, no acidosis, high solubility	Combustion
Helium	Inert, noncombustible	Dissolve slowly (risk embolism), expensive

Subcutaneous Insufflation

Subcutaneous emphysema is more common in extraperitoneal than intraperitoneal procedures due to the larger surface area available for absorption. It is also more common in the elderly due to decreased tissue resistance. Gas that is blown into the subcutaneous tissues, because the insufflation trochar is not in the correct cavity, can rapidly result in spreading subcutaneous emphysema. This is not a particularly dangerous complication and the tissues will absorb the CO_2 over a period of days. A small amount of localised subcutaneous insufflation occurs commonly and goes unnoticed, and larger amounts of leakage occur rarely (<1%); this can extend down to the scrotum and thighs or up to the chest and neck. This complication can be minimised by the vigilance of the surgeon, when inserting the veress needle or port, and the anaesthetist, as a high-end tidal CO_2 may be the first sign of significant extra-anatomic gaseous extravasation.

Metabolic Consequences of CO_2 as an Insufflant

As CO_2 is readily absorbed, this results in hypercarbia and acidosis. This effect may be increased by impairment of ventilation by the raised intra-abdominal pressure, which can reduce the elimination of CO_2. The hypercarbia and acidosis can cause vasodilatation and can decrease cardiac contractility. It can also stimulate the sympathetic nervous system resulting in tachycardia and vasoconstriction. These effects are most pronounced in patients with preexisting respiratory disease.

CO_2 and Air Embolus

The risk of CO_2 emboli is low due to its rapid absorption in the blood and the ability of blood to transport high levels of it. The lethal volume of CO_2 that is likely to have an embolic effect is, therefore, around 200 ml, five times the volume of air that

would have an embolic effect. Gaseous emboli may occur in laparoscopic surgery due to opening of venous channels during an intervention or as a complication of insufflation. The risk may be increased if the patient were placed in the Trendelenburg position, often used in pelvic surgery such as radical prostatectomy.

Although a clinically evident CO_2, or air, embolus is rare in laparoscopic surgery, it is important to recognise potential clinical signs that embolisation has occurred. Gas entry into the systemic circulation causes occlusion of small vessels and ischemia. In the anaesthetised patient, the main signs are, therefore, likely to be cardiovascular arrhythmias, hypotension, myocardial ischemia, increased central venous pressure, and pulmonary hypertension.

Effects of a Prolonged Pneumoperitoneum

The establishment of a pneumoperitoneum itself has a number of physiological consequences that are more pronounced with a prolonged procedure (Table 65.2). In healthy individuals, these effects usually have little significance; however, in patients with a preexisting cardiovascular or respiratory comorbidity, they can result in significant problems by influencing cardiopulmonary physiology.

In most cases, intra-abdominal pressure during laparoscopy reduces the venous return (preload), and subsequently cardiac output. In response, systemic vascular resistance increases (after load) as does heart rate, mean arterial pressure (MAP), and pulmonary resistance. Central venous pressure (CVP) will be artificially high, and care must be taken when interpreting CVP readings. Arrhythmias may occur due to hypercapnia, but also bradycardias due to vagal stimulation from peritoneal irritation. If the patient is in a hypervolaemic state, then atrial pressures, and therefore venacaval pressures may be high resisting the pneumoperitoneal pressure and increasing venous return.

Respiratory effects occur mainly due to diaphragmatic displacement and reduction in movement. The vital capacity and functional residual capacity are reduced, pulmonary compliance drops, and airway resistance increases. Average peak airway pressure is increased to maintain tidal volume. The Trendelenburg position may increase these effects by elevating the diaphragm and decreasing vital capacity. The

Table 65.2 Common physiological effects of a pneumoperitoneum at 15 mm/Hg

Physiological factor	Effect
Venous return	
MAP	
SVR	
Heart rate	
Partial pressure CO_2	
Functional residual capacity	
End tidal CO_2	
Urine output/GFR	

use of CO_2 will also raise the partial pressure of CO_2 in the blood, which may need to be eliminated by increasing either the ventilated respiratory rate or tidal volume.

Renal, splanchnic, and hepatic perfusion is reduced by a pneumoperitoneum, and there is activation of the renin-angiotensin system resulting in generalised vasoconstriction. Urine output is reduced due to a decreased glomerular filtration rate (GFR), and mesenteric blood flow is also reduced which may, rarely, cause a mesenteric thrombosis. Using an inflation pressure of less than 15 mm/Hg avoids many of these potential complications.

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Chapter 66
Laparoscopic Ports

Ben Sherwood and Dan Burke

Port Types and Sizes

Laparoscopic ports consist of a sheath and trocar used to gain access to a body cavity for endoscopic surgery. Many competing products are available. There is an economic argument in favour of reusable instruments; however, disposable ports are often preferred by the operator as they are always sharp and, therefore, require less force to penetrate the abdominal wall. The trocar tip may differ between a conical or pyramidal shape. Blunt-tip trocars are also available for open-access techniques. Some initial ports will have inflatable "balloons" attached to allow the creation of space for the operative field, such as retroperitoneal or extraperitoneal surgery.

Ports are available in several sizes from 3 to 12 mm. Most commonly, the laparoscope is inserted through a 10- or 12-mm port (the "camera port"), with smaller 5-mm ports for secondary instrumentation.

Optical ports (e.g., the Visiport™) combine the smaller incision of a closed-access approach with direct visualisation of the tissue layers during port placement, thereby reducing the opportunity for inadvertent visceral injury. Typically, a 0° laparoscope is inserted into an optical trocar for insertion.

Expandable ports, such as the STEP™ system, allow an expandable mesh sheath to be inserted with minimal tissue trauma over a Veress-type needle.

Once inserted to the appropriate depth, a trocar replaces the needle and hence mechanically dilates the sheath, expanding the port to the required diameter.

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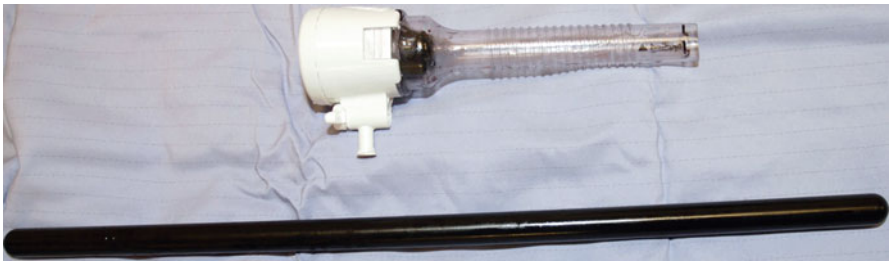

Fig. 66.1 Blunt-tipped trocar and port used for Hasson (open) primary access

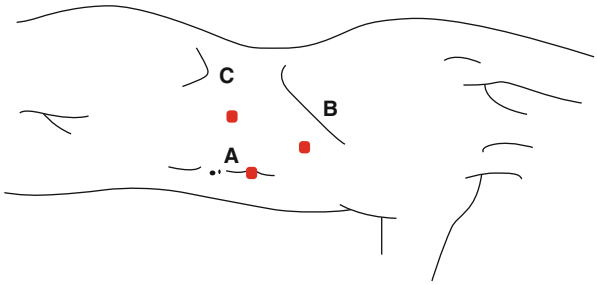

Fig. 66.2 Typical port placement for laparoscopic radical nephrectomy: *A*: primary access port (10–12 mm), *B* and *C*: secondary instrument ports (5 or 10–12 mm)

Once inserted, a port is held in place by the spiral groves moulded onto the outside edge of the port. It is important some of these groves are below the skin incision in order to prevent the port form being removed each time an instrument is extracted.

Principles of Port Placement

A primary port is used to establish pneumoperitoneum for endoscopy. Primary port placement can be undertaken with either an open or closed technique. A Veress needle has a blunt spring-loaded obturator which advances once the needle reaches the cavity. Despite this, there is potential for injury to underlying viscera, particularly when there are adhesions present. As such, many surgeons favour an open or "Hasson" approach whereby the cavity is accessed through an open cutdown. A blunt-tipped trocar (Fig. 66.1) can then be inserted which usually requires securing with sutures to the muscular aponeurosis. A disadvantage of this technique is that a slightly longer incision is required.

The number, size, and position of secondary ports depends on the procedure being performed. Although 5-mm ports allow passage of most instruments, a 10-/12-mm port is required for the passage of most suture needles and linear staplers and for specimen retrieval. A typical configuration of ports for laparoscopic radical nephrectomy is shown in Fig. 66.2. Ports should be directed towards the target site and positioned such that a clashing of instruments, or laparoscope, is minimised. Secondary ports are inserted under laparoscopic guidance to avoid injury to viscera or abdominal wall vasculature. Similarly, during removal, the site should be observed to avoid bleeding or bowel herniation.

Fig. 66.3 The SILS™ multi-instrument port (Image reproduced with the permission of Covidien)

Single Port Access

In an effort to even further reduce the morbidity associated with laparoscopic surgery, single port access (SPA) technology has evolved, whereby procedures are performed using multiple instruments through a single access point shared with the laparoscope. This approach is also known as laparoendoscopic single-site surgery (LESS) and single-incision laparoscopic surgery (SILS). Inevitably, using a single access point is extremely challenging technically, with limited freedom of movement and loss of triangulation. It should only be undertaken by experienced laparoscopists for these reasons. A number of alternative single access ports have been developed, such as the SILS™ device (Fig. 66.3). Instrument "crowding" and loss of triangulation is, to a certain extent, overcome by the introduction of articulated instruments, but these are significantly more expensive than standard laparoscopic peripherals.

In urological surgery, SPA has been successfully applied to radical nephrectomy, in addition to pyeloplasty, ureterolithotomy, adrenal surgery, and benign and malignant testicular surgery. The clinical advantages of SPA surgery in comparison to conventional laparoscopy have yet to be demonstrated. The most potent potential advantage is cosmesis, particularly when the umbilicus is used as the access point. Larger studies are, however, required to examine the length of hospital stay, return to normal function, operative time, and complications.

Natural Orifice Transluminal Endoscopic Surgery (NOTES)

NOTES is a recent innovation, and at present, experience is limited to small case series from a single institution and has an undefined role in urology. This technology is designed to access the peritoneal cavity and target organ through an endoscopic incision in a neighbouring luminal structure, for example, the stomach, vagina, bladder, or colon. In the absence of any external incisions, it is hoped that it will offer significant advantages in terms of cosmesis and eliminate wound-related problems such as infection, herniation, and postoperative pain.

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Chapter 67
Setting up a Robot

Ben Sherwood and Dan Burke

Robots in Surgery

The word robot is derived from the Czech word robota, meaning forced labour. The da Vinci system was developed initially by Stanford Research Institute in California with interests from the Department of Defence and NASA with the intention for the surgeon to be the master and the machine his slave. It was originally planned to be used in the battlefield, thus enabling the surgeon to operate at a safe distance from the injured frontline solider. However, history has shown us it has become a constituent of mainstream operating theatres throughout the world. It obtained an FDA licence to "assist" in laparoscopic cases in 1997, followed by a licence to allow it to "perform" laparoscopic surgery in 2000.

Principles of the da Vinci Robotic System

The principle behind the da Vinci system is to allow the surgeon:

1. Greater vision – 3D images and ×10 magnification
2. Greater dexterity – "EndoWrist®" instruments, tremor filters, and motion scaling
3. A more ergo dynamic operating position than conventional laparoscopy, resulting in greater operator comfort and less fatigue

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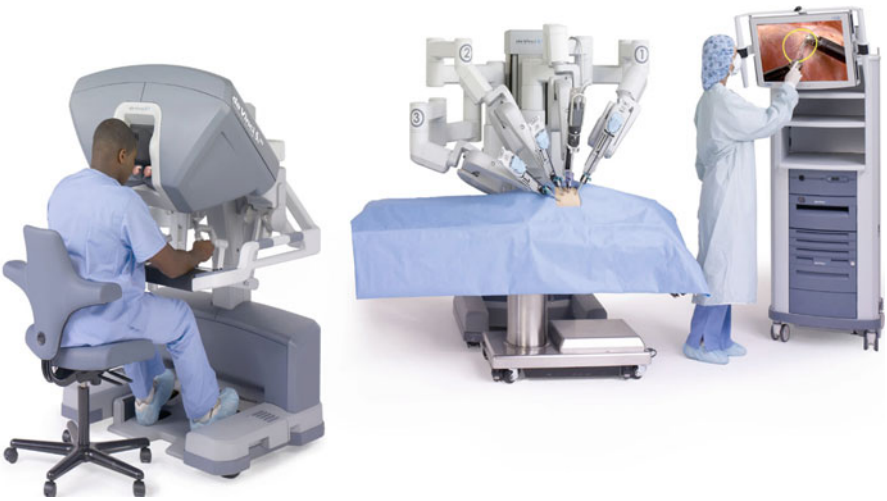

Fig. 67.1 The three components of the da Vinci robotic operating system: the surgeon's console, the patient-side cart with four arms (*originally three*), and an endoscopic stack which also houses some of the computer hardware (Image © 2011 Intuitive Surgical, Inc.)

To achieve these principles, practically, the da Vinci system has three components (Fig. 67.1).

The Surgeon's Console

The console has a headrest where the surgeon places his forehead and looks down two viewers providing him with a magnified, high-resolution 3D view of the operating field supplied by a two-lens camera. The surgeon's arms rest on the control bar, and their fingers are placed within the "master controls." The master controls have a "clutch" switch on the side to activate them. The surgeon's hand movements are then scaled and filtered before being translated into precise movements of the EndoWrist® instruments (Fig. 67.2). If the surgeon wishes to change the view, they simply take control of the camera arm with a press of a switch, moving the camera manually to the desired position.

Finally, there are foot controls which allow the surgeon to activate diathermy and switch between robotic arms; they can only have control of two arms at any one time.

The Patient-Side Cart

The original da Vinci had three arms; however, the newer designs all have four arms; the fourth arm aids greatly in retraction and holding organs in a fixed place unlike a human arm! The cart (Fig. 67.3) is draped in a sterile protective cover and

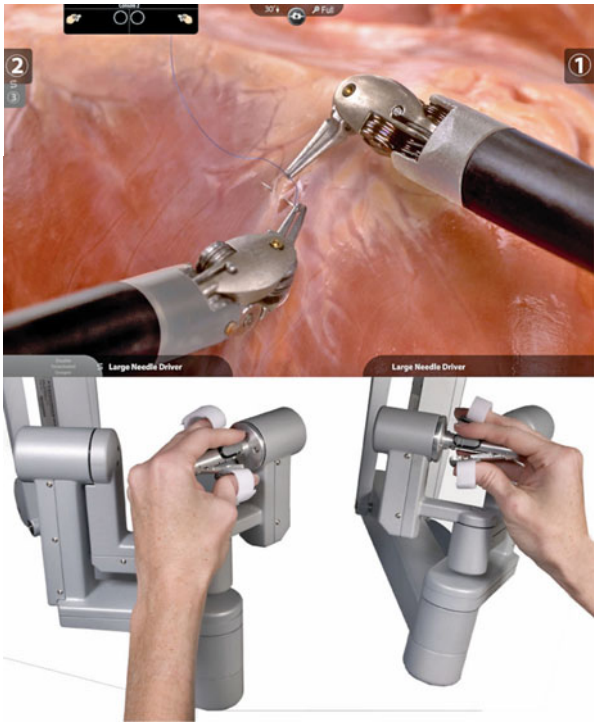

Fig. 67.2 The finger controls and how they are used to control the EndoWrist® instruments endoscopically (Image © 2011 Intuitive Surgical, Inc.)

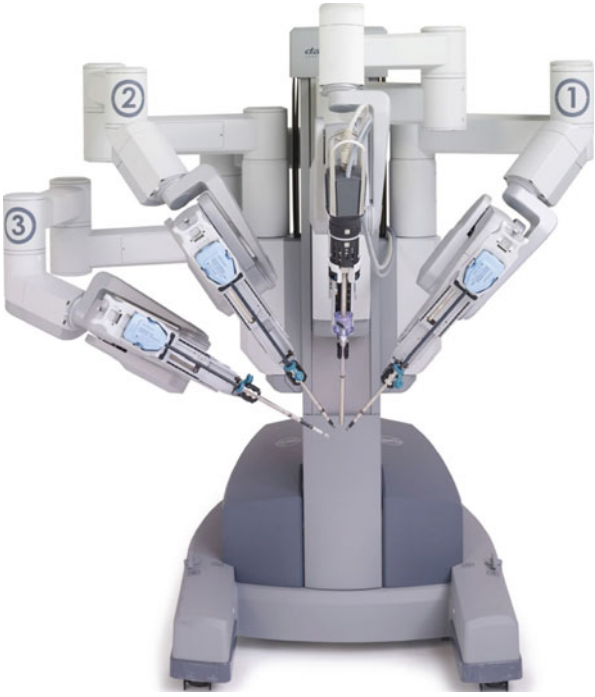

Fig. 67.3 The arms of the "side-cart" demonstrating the arms used for manipulation (Image © 2011 Intuitive Surgical, Inc.)

wheeled into position. Each arm is then attached to one of the ports placed in the abdomen, a process known as "docking the robot." An instrument or the camera is then placed through the port and attached to each arm. The instruments can be changed during a procedure by a surgical assistant, who is scrubbed and positioned at the patient's side. At least one but more often two laparoscopic ports are used by the assistant. This results in a total of five or six port incisions.

A variety of EndoWrist® instruments are available, usually a combination of scissors, graspers, and needle holders, some of which can be attached to either monopolar or bipolar diathermy as required. The EndoWrist® instruments all have 7° of freedom and 90° of articulation resulting in a range of movement unobtainable with conventional laparoscopic instrumentation.

Endoscopic Stack

As with laparoscopic surgery, an insufflator, a light source, recording device, computer hardware, and separate 2D HD screen monitors for the scrub nurse and assistant are required. All of this is stored on the endoscopic stack.

Training Features and Financial Implications of Robotic Surgery

The latest da Vinci system has dual control capability. Similar to dual control on a car, there is the ability to have two surgical consoles attached to one patient-side cart. This allows excellent training, as the trainer is not only able to see all of the operation in magnified 3D but can also take over control of the robotic arms to facilitate learning.

Whilst an accurate figure is impossible to give in the context of this book, the da Vinci system has a cost of approximately £1.6–£1.9 million. It also has annual maintenance cost of approximately £100,000 in addition to the cost of disposable instruments; EndoWrist® instruments can be reused but have a very limited life span, meaning that a robotic-assisted procedure is a few thousand pounds more expensive than a conventional open or laparoscopic surgery for each case.

Efficacy

Despite its undoubted advantages, large systemic reviews have failed to show convincing evidence that robotic surgery demonstrates a significant improvement in either oncological or functional results. However, newer prospective studies are beginning to demonstrate the potential benefits of the robot in everyday urological practice.

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Part V
Technology: Interventional

Chapter 68
Neuromodulation by Sacral Nerve Stimulation

Cecile Tawadros, Katherine E. Burnett, and Christopher D. Betts

Tanagho and Schmidt working in the 1980s developed sacral neuromodulation (SNM). The FDA approved InterStim® for the treatment of urge incontinence in 1997, and NICE did the same in 2004. In many centres, SNM has become second-line treatment for idiopathic detrusor overactivity (IDO) and nonobstructive urinary retention in women (NOURW). There is limited evidence for its use in neurogenic bladder dysfunction and painful bladder disorders.

The mode of action of SNM is unclear, but it is thought to modulate neural pathways both centrally and peripherally. It has been long established from animal work that an increase in pelvic nerve afferent activity can inhibit the detrusor. In DO, sacral nerve stimulation may activate afferent pathways which modulate bladder efferent activity at spinal or supraspinal levels. In Fowlers' syndrome, SNM may block the inhibitory effect of sphincter overactivity on the detrusor and enable voiding. On the basis of PET studies in women with retention, Fowler has proposed that SNM may restore voiding by "resetting brainstem function."

The devices most commonly used for SNM are made by Medtronic (Fig. 68.1).

Test Implantation Procedure

At present, the test phase or percutaneous nerve evaluation (PNE) is the best means of selecting patients most likely to gain from long-term SNM. In the test phase, a foramen needle is passed into the S3 foramen under local or general anaesthesia. The foramen is located with the aid of surface markings and motor response with big toe flexion and pelvic floor. A temporary electrode is passed through the foramen

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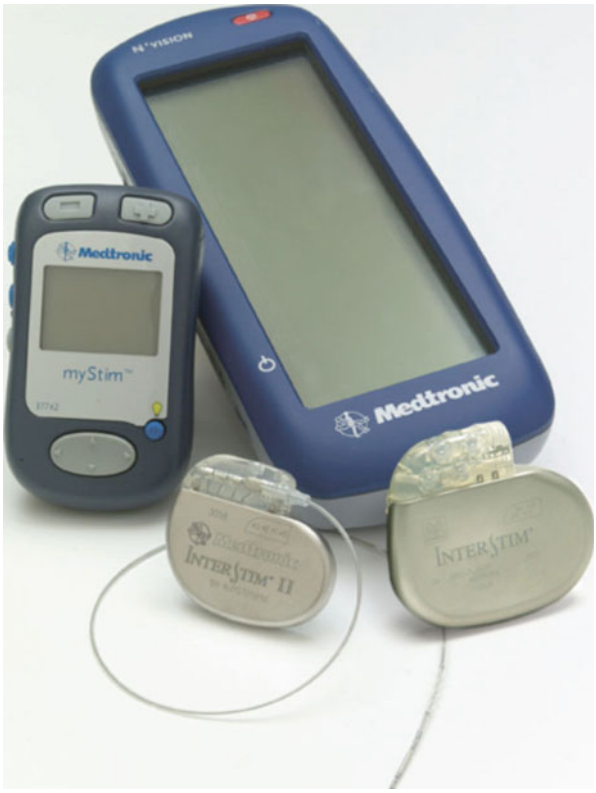

Fig. 68.1 The InterStim implantable program generators I and II are shown with a tined lead. Also shown are the patient's controller (myStim or Icon) and the "N" vision physicians programming device

needle and connected to an external pulse generator (EPG). The patient can adjust the strength of stimulation, and they should complete frequency/volume charts. The limitations of PNE include lead migration, discomfort from the securing dressings, and the short testing period of 5–10 days.

Permanent Implantation Procedure

Long-term SNM involves the percutaneous insertion a self-anchoring tined lead (Fig. 68.2) through the S3 foramen.

The motor responses are checked and fluoroscopy is used to guide the insertion of the lead. The lead has four individual electrodes, and three should appear outside the foramen (Fig. 68.3). The lead is tunnelled to a pocket in the outer gluteal region and connected to an IPG. Only bipolar diathermy can be used in the presence of the tined lead and IPG.

Fig. 68.2 The tined lead for percutaneous insertion into a sacral foramen. Note the four individual electrodes at the end of the lead

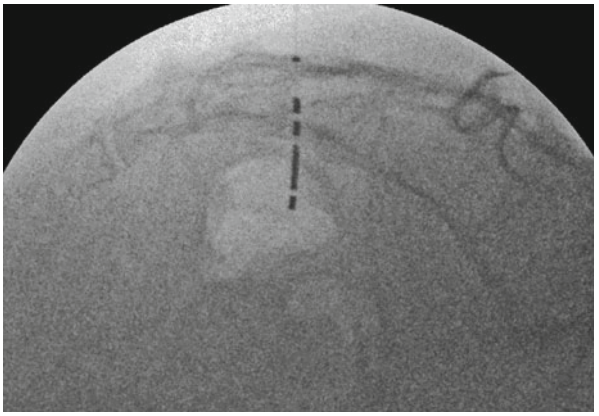

Fig. 68.3 Intraoperative lateral sacral fluoroscopy showing tined lead in sacral foramen and position of the four electrodes

The physician sets the stimulation parameters within certain limits using the "N" vision, and the patient can adjust the IPG within the set limits using the Icon hand-held device. The polarity of the four electrodes can be changed by the physician to produce different electrical fields. It may be necessary to try different settings to gain maximum symptomatic benefit.

A "two-stage" implantation procedure is sometimes employed which allows the test phase to be extended to 4 weeks, and if successful only a small procedure is required to connect lead to an IPG.

The battery life of the IPG depends on the stimulation parameters and is usually 5–8 years. Patients with SNM devices cannot have magnetic resonance imaging and should not pass through the standard security gates at border controls. If the patient

walks close to a radio-frequency security antenna as used in shops, then the stimulation parameters of the IPG can be temporarily changed.

Complications of SNM include infection, lead breakage, lead migration, leg pain, discomfort at the site of the IPG, and loss of efficacy. Explantation of the tined lead may be complicated by lead breakage and retained lead fragments. Revision rates are up to 40% and usually involve replacing the tined lead. SNM is free of the complications associated with major intra-abdominal surgery, does not require self catheterisation, and can be readily reversed.

Results

About 50% of patients respond well to the PNE and go on to long-term SNM. Data from controlled trials and case series indicate that approximately 70% of patients who receive SNM for detrusor overactivity had improvement in their main symptoms at 3–5 years postimplantation. There is a need for longer term outcome and quality-of-life data. In one series of NOURW, 70% of the women were voiding spontaneously at a mean follow-up of 7 years.

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Chapter 69
Principles of Extracorporeal Shockwave Lithotripsy (ESWL)

Richard Napier-Hemy and Steve Payne

All lithotripters have three elements to exert their clinical effect: a shockwave generator which produces and focuses the shock, a means of coupling the shockwave to the patient, and an imaging modality to target the shockwave onto the stone.

The Physics of Lithotripsy

Lithotripsy depends upon the transmission of sound energy. Sound has compressive and tensile phases, and in liquid, it affects the density, pressure, and particle velocity of the fluid it is in. The velocity of the wave influences its energy, and dissipation of the acoustic energy is dependent upon the acoustic impedance of any structures it comes into contact with. The ideal shockwave for lithotripsy has a rapid peak pressure rise, followed by a slower negative pressure. A typical time-against-pressure curve would be as shown in Fig. 69.1 with the pressure wave lasting <10 μs and producing a peak pressure of 30–199 mPa.

All lithotripters have a focusing mechanism to concentrate the acoustic energy onto the stone whilst reducing any damaging effects on the surrounding tissues. Ideally, the focus would be localised to an infinitesimally small area, but the physics of wave propagation do not allow focusing to a discrete focal point. This means there is a high-amplitude region around the focal point which is called the focal zone. In clinical lithotripsy, this zone can be from a few millimeters to centimeters in size and is normally ellipsoidal in shape with its longest dimension along the axis of the shock wave.

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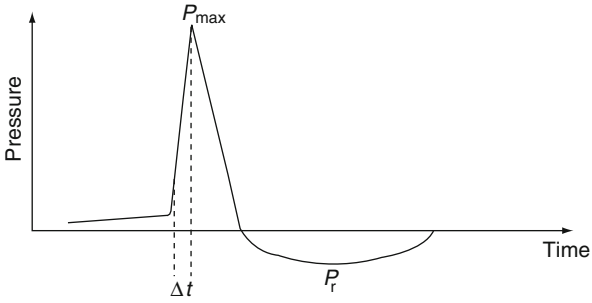

Fig. 69.1 The physical characteristics of the shockwave used, clinically in lithotripsy. P_{max} is the maximum pressure, P_r is the negative peak pressure, and Δt the pressure rise time

Theoretical Mechanisms of Stone Fragmentation

A variety of mechanisms may cause shattering of a stone during lithotripsy. The major factors influencing fragmentation will depend on the constitution of the stone, its surrounding medium, and the type of lithotripter used. The hypotheses of lithotripting effects are shown in Table 69.1.

Shockwave Generators

Three types of shockwave generator have been used clinically.

Electrohydraulic shockwave generators have a storage capacitor which discharges an ultrahigh tension and ultrashort potential difference, across a gap separating a submerged anode/cathode complex. This discharge causes a spark that generates a bubble pulse and leads to an expanding underwater shockwave. The shock is produced at a first focal zone (F1) and focused, by a hemi-elipsoid reflecting parabola, onto a second focal zone (the F2). Electroconductive shockwave generators are a modification of this principle but employ a highly conductive electrolytic solution during shockwave generation.

Piezoelectric shockwaves are generated by the mechanical force resulting from an electrical field being applied to a quartz crystal. Multiple piezoelectric crystals are caused to deform synchronously to produce many different frequencies of sound energy. As the crystals are arranged in a "dish-like array," inclined inwards, the summation of the different wave forms produces lithotripting energy at the point at which all of the wave forms coalesce (the F1 of the dish).

Electromagnetic shockwave generators work on the same principle as an acoustic speaker. The generator is made of two metal plates separated by an insulator and backed by a ceramic base. A storage capacitor discharges, causing an ultrashort magnetic repulsion between the two plates with resultant shockwave away from the ceramic base. A flat shockwave, of an intensity proportional to the applied current, travels at the speed of sound and is focused by a convex acoustic lens onto a focal point (its F1).

Table 69.1 The hypotheses of stone fragmentation (Rassweiler et al. 2011)

Hypothesis of fragmentation	Proposed mechanism	Prerequisites	Type of action	Comments
Tear and shear forces (super-focusing)	Pressure gradients resulting from impedance changes at the front of the stone and the distal surface with pressure inversion	Shock wave smaller in space extension than the stone	Hammer-like action resulting in a crater-like fragmentation at both ends of the stone	Only relevant for small focal zones
Cavitation	Negative pressure waves induce a collapsing cavitation bubble at the stone's front surface	Low viscosity of surrounding medium	Microexplosive erosion, principally at the proximal end of the stone	More important during stone comminution
Spallation	Reflected tensile wave at distal surface of the stone with maximum tension there	Shockwave smaller in space extension than the stone	Breaking the stone from the inside similar to freezing water in brittle material	Only relevant for small focal zones
Quasistatic squeezing	Pressure gradient between circumferential and longitudinal waves results in squeezing of the stone	Shockwave is broader than the stone. Shockwave velocity is lower in the water than in the stone	Nutcracker-like action	Only relevant for large focal zones
Dynamic squeezing	Shear waves initiated at the corner of the stone are reinforced by squeezing waves along the stone's length	Parallel travelling of longitudinal waves. Shockwave velocity is lower in the water than in the stone	Nutcracker-like action which "splits" the stone	Best theory to explain lithotripsy

Coupling

Externally generated shockwaves require transmission into the patient by a fluid medium. Immersing the patient in a water bath to couple the shockwave to their stone has many physiological implications, and safety issues, so "coupling" is now usually achieved using gel placed between the treatment head and the skin. Bubbles within the gel, reflecting sound, may decrease the efficacy of treatment, as may bubbles formed in the urine, around a stone, during treatment.

Imaging

Accurate targeting of the shockwave on the stone is essential for effective lithotripsy. Respiratory movement makes this more challenging, and lithotripters with larger focal zones may produce better results as fewer shocks are wasted. Both fluoroscopy and ultrasound have their advantages. An isocentric C arm is a simple way of localising stones and can be used both for kidney and ureteric stones. Virtual reality fluoroscopic localisation can be used to keep the shockwaves targeted at the stone without the need for continuous irradiation. Inline ultrasound has the advantage that it does not involve irradiation but is poor at localising mid- and lower-ureteric calculi.

Factors Influencing the Efficacy of Clinical Lithotripsy Treatment

Reducing the focal zone may help ureteric stone disintegration, whereas larger zones are better for treating bigger renal stones. Alteration of the frequency of shockwave application allows bubbles, created during treatment, to dissipate before the next shockwave hits the stone, improving fragmentation. A slow increase in generator voltage, "ramping," allows the patient to become accustomed to treatment and tolerate it better and reduces the higher energies needed to overcome image attenuation caused by fragmentation.

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Chapter 70
How to Carry Out Shockwave Lithotripsy

David G. Ross

Extracorporeal shockwave lithotripsy (ESWL) is an effective and noninvasive modality for the treatment of urolithiasis. Stone-free rates vary between 50% and 95%. The key steps to success are appropriate patient selection and careful treatment delivery.

Patient Selection: Which Modality of Treatment?

The decision-making process for managing any patient with urolithiasis is based on consideration of stone, patient/clinical (including patient choice), renal and service factors. ESWL is contraindicated in pregnancy, untreated coagulopathy, untreated urinary tract infection, abdominal aortic or renal artery aneurysms in the shockwave's path, or severe skeletal malformations.

There are a number of key additional factors which influence the efficiency of ESWL – stone load, stone density, stone location, and body habitus. The volume or stone burden influences outcome and the number of treatment sessions required. ESWL is the treatment of choice for stones ≤20 mm in diameter (European Association of Urology Guidelines on Urolithiasis 2011); it may be considered for larger stones, but PCNL may be preferred. The density of a stone, on noncontrast CT, may help predict its susceptibility to ESWL, with densities of >1,000 Hu being resistant to fragmentation. Lower pole stones are typically unfavourable for fragment clearance following ESWL, although this varies, dependent upon the specific lower pole anatomy. With increasing obesity, stone clearance rates fall, stone localisation becomes difficult, and the skin-to-stone distance may exceed the focal length of the lithotripter. Inserting a double J stent does not improve overall stone clearance

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rates but reduces fragment-related complications. Typically, pre-ESWL stenting should be considered for stones >20 mm (European Association of Urology Guidelines on Urolithiasis 2011).

Advice in Specific Situations and Potential Complications of Treatment

Specific advice should be given prior to treatment regarding antiplatelet drugs (discontinue 10 days pretreatment), oral anticoagulants (stop and give low molecular weight heparin in selected patients), implanted defibrillators, pacemakers, or neurostimulators when specialist input is required. Complications may be common – bleeding, infection, pain, skin bruising, need for repeat treatments, treatment failure, or occasional fragments causing obstruction potentially requiring intervention, and severe infection.

Day of Treatment: Pretreatment Protocol

Patients should be managed using an ESWL-specific pathway to minimise the potential for errors and oversights. Consent must be confirmed along with the site and side of the stone being treated, antiplatelet/anticoagulant cessation (including INR where appropriate), and allergy status. Baseline observations are recorded and a urine dipstick performed. Patients must be questioned regarding symptomatic urinary infection, which may determine the need for either antibiotic cover or treatment deferral. Antibiotic cover should be considered if the urine dipstick is positive for leucocytes and nitrites in an asymptomatic patient or in patients at a high risk of infection.

Analgesia improves treatment efficacy by reducing pain-induced movements and excessive respiratory excursions. Typically, 100 mg of diclofenac is given rectally 30 minutes before treatment with additional intravenous alfentanil to be given as 200–400 mcg boluses for breakthrough pain during therapy.

ESWL Delivery

Outcomes from ESWL are operator dependent. The key factors influencing outcome are related to positioning/localisation, coupling and shock delivery. Positioning depends on the machine used with the majority of renal and ureteric stones being treatable supine. The prone position may be used for lower ureteric stones, but it is typically less efficacious due to shockwave reflection from bowel gas.

Stone localisation may be achieved using fluoroscopy or ultrasound, depending upon local expertise and stone position. Fluoroscopic localisation is usually in three planes with the use of appropriate radiation protection measures. Real-time ultrasound

reduces radiation dose and enables localisation throughout treatment. X-ray and ultrasound localisation may be difficult due to body habitus, anatomy, the presence of bowel gas, and excessive respiratory excursion.

Coupling of the lithotripter to the patient is achieved using ultrasound gel or water. When gel is used, it should be warmed and applied with a spatula to avoid bubbles which will reduce shockwave transmission.

Prior to, and during, lithotripsy, patient monitoring must be instituted.

Shock delivery protocols vary. Treatment should be commenced at low power (~25% of maximum) and limited to less than 60% for the first 500 shocks to reduce renal injury. Power can be gradually increased over the treatment course to achieve an average power of over 75%. The objective is to deliver a fixed amount of energy to the stone, typically 1,000 J for renal stones and 1,400 J for ureteric stones. Shock frequency can also be optimised. Reducing the frequency improves clearance, yet this benefit must be balanced against the resulting longer treatment. Standard shock frequency is 2 Hz, whilst 1 Hz is considered optimal (European Association of Urology Guidelines on Urolithiasis 2011).

ESWL should be discontinued when there is persistent hypertension, uncontrolled pain, localisation failure, or complete fragmentation is observed.

Post-Treatment Management

Post-ESWL, a standard protocol should be followed. If opiates have been given, the patient should be observed for 60–90 minutes and discharged with a responsible adult. Otherwise, patients are discharged home when they feel well with advice regarding what to expect, when to seek medical advise, and who to contact. They are given appropriate analgesia and antibiotics where indicated. A follow-up appointment should be arranged, typically in 1–2 weeks for renal stones, allowing for retreatment following a 4-week interval. Ureteric stones can be retreated at shorter intervals; thus, it is advisable to schedule their next session directly. The episode should be recorded on your database for audit and research.

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Chapter 71
Prostatic Hyperthermia

Ian Pearce

Hyperthermia is the application of heat energy to mediate cell death within tissue. The prostate is the urological organ most frequently treated with this technology, and microwaves are used most commonly, although radiofrequency (RF) hyperthermia has been used clinically. Microwave hyperthermia has been applied to prostatic malignancy and the inflamed prostate but has found its niche as a minimally invasive therapy for obstructive benign prostatic enlargement (BPE) when medical therapy has failed.

Microwaves

Microwaves are electromagnetic radiation, (see Appendix 3) with a frequency between 300 MHz (0.3 GHz) and 300 GHz. Heat is produced when the microwaves are absorbed into tissue. This chiefly occurs by two mechanisms:

1. Electrical dipoles, water molecules, for example, oscillate in the microwave field
2. Electrical charge carriers, ions, for example, move back and forth in the field

Both of these movements generate energy which is transferred to the tissue in the form of heat. As the microwave frequency decreases, the depth of heat penetration increases. Water-rich tissues such as muscle and prostate absorb more microwaves than water-depleted tissues such as fat. Medically, microwaves are used to treat prostatic diseases at a frequency between 900 and 1,300 MHz offering a tissue penetration in the region of 15 mm.

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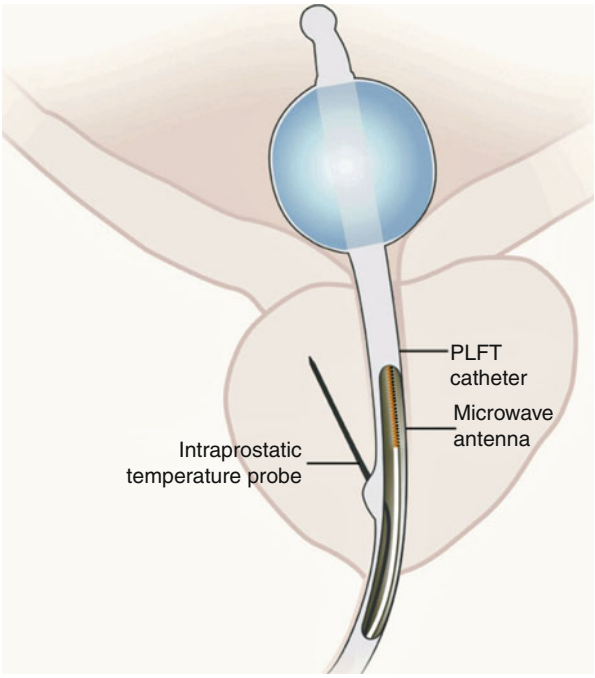

Fig. 71.1 A TUMT catheter (Image courtesy of ProstaLund Operations AB)

Transurethral Hyperthermia

Transurethral hyperthermia, also referred to as transurethral microwave therapy (TUMT), utilises an integrated radiating energy device to deliver thermal energy to the prostatic tissue with a modified Foley catheter (Fig. 71.1). This "transurethral probe" has a further channel which permits continuous cooling of the urethral surface, by fluid irrigation, preventing collateral heat damage to the urethra.

In prostatic hyperthermia, temperatures of between 42°C and 44°C are achieved, and maintained, in order to disrupt cell transport mechanisms and, at higher temperatures, exceeding 45°C, cell death. So-called low-energy thermotherapy does not remove significant prostatic tissue and may require repetition, whilst newer high-energy thermoablation, achieved by generating temperatures up to 70°C, causes prostatic cavitation, resulting in greater improvement in symptoms, the durability of therapy, and objective signs of prostatic obstruction.

The duration of treatment is largely dictated by the size of the gland and, therefore, the extent of tissue heating required.

Temperature change = Heat conduction – Blood flow + Microwave power

Fig. 71.2 Penne's in-vivo bioheat equation

Factors Influencing Prostatic Heating

Three factors influence the prostatic temperature during thermotherapy:

1. Heat conduction
2. Blood flow
3. Microwave power

In prostatic tissue, the heat generated obeys Penne's, in vivo, bioheat equation (Fig. 71.2).

Heat conduction, in tissue, is a relatively constant phenomenon, and the microwave power can be altered by the operator. The major determining factor determining intraprostatic temperature is, therefore, the prostatic blood flow. During hyperthermic treatment, intraprocedural transrectal Doppler ultrasound has demonstrated that prostatic blood flow increases by up to six times as a natural response to cool the gland. The increased blood flow and its "cooling" effect can be counteracted by increasing the microwave energy applied. Local anaesthetics containing epinephrine also reduce prostatic blood flow, reducing this cooling effect and facilitating higher intraprostatic temperatures. TUMT catheter devices have been modified to allow local anaesthetic application without the need for multiple urethral manipulations.

How Is Microwave Energy Generated and Applied?

An external electromagnetic energy generator supplies high-frequency short or microwave energy to an applicator. The applicator consists of an elongated coil antenna whose tip is connected to the central conductor of a coaxial cable, its radiation causing tissue heating. The antenna is insulated by a sheath, separating the coil from the prostatic tissue; the thickness of this insulating sheet varies along the length of the coil to ensure uniform tissue heating.

The radiating device also serves as a thermosensor radiometer, which is a noninvasive tool to determine the temperature at the points of prostatic contact. The radiometer enables feedback to the external control mechanism, allowing direct comparison between the expected and actual temperature within the prostate, so that unwanted temperatures can be eliminated by modification of the power input. Previously, transperineal, or transrectal, thermosensors were used, but these were cumbersome, time consuming to apply, and were replaced by transurethral thermosensors incorporated into the treatment catheter.

The ability to prospectively monitor intraprostatic blood flow and temperature during hyperthermic therapy has led to the development of feedback TUMT where the therapy duration and extent of tissue coagulation are monitored real time, allowing more efficacious and controlled treatment.

Automated controlling software has been developed to allow the operator to monitor the prostatic cell kill, and determine treatment time, by:

1. Measuring the intraprostatic temperature at three sites along the prostate's length
2. Calculating the heat distribution to the whole prostate
3. Calculating intraprostatic blood flow
4. Calculating the degree of coagulative necrosis
5. Continuous monitoring of intraurethral pressure
6. Determining intraurethral temperature, above which, therapy ceases automatically

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Chapter 72
Ablative Therapies: High-Intensity Focused Ultrasound (HIFU), Cryotherapy, and Radio-Frequency Ablation (RFA)

Stephen Brown

High-Intensity Focused Ultrasound (HIFU)

Principle

HIFU at frequencies of 1–3.5 MHz can pass through tissues producing temperatures of 90°C at the focal point but leave intervening tissues unharmed. The heat energy arises from friction between oscillating cellular components of differing elastic properties. Tissue ablation occurs through direct thermal damage and mechanical disruption through cavitation, the formation of high temperature microbubbles which rapidly form and implode.

Applications

Prostate Cancer

Prostate cancer can be treated through the rectum via a transrectal transducer to produce an array of cigar-shaped target lesions covering the whole of the prostate (Fig. 72.1). The therapy is controlled by real-time ultrasound. This day case treatments may take up to 2–3 h to complete. HIFU as primary treatment is still under investigation but is establishing itself as an option for patients not suitable for surgery now that long-term results are becoming available (Blana et al. 2008).

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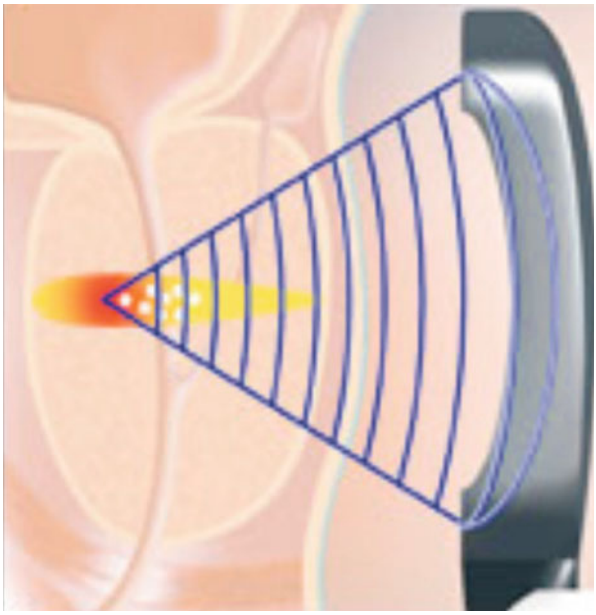

Fig. 72.1 Transrectal concave HIFU transducer producing a prostatic necrotic lesion

Complications include incontinence (3%), impotence (40–60%), bladder neck stricture (11%) and a <1% risk of rectoprostatic fistula. HIFU lends itself to salvage therapy following radiotherapy, but complications rates are higher. Its use as focal therapy following careful tumour prostate mapping is also a subject of study.

Renal Cancer

Extracorporeal HIFU is under investigation for the treatment of small renal tumours, but technical problems result from respiratory movement and perirenal adipose tissue.

Cryotherapy

Principle

Third generation cyrotherapy using ultrathin needles and thermosensors has increased clinical application. Freezing is achieved by the expansion of Argon at the needle tip which, according to the Joule-Thomson principle, with an inversion temperature at 1 atmosphere of >400°C, cools on expansion. Helium with an inversion

temperature of −222°C rapidly cools as it expands. The two gases are therefore used to produce the freeze-thaw cycles. Tissue ablation occurs in stages: extracellular ice crystals form around −7°C to −10°C, producing a hyperosmolar extracellular environment causing cells to shrink – "solution-effect" injury and intracellular ice starts to form above −15°C, tearing cells apart. All metabolic activity stops at −40°C. Thrombosis and capillary damage leading to necrosis.

Applications

Prostate

Probes are placed transperineally using a jig and with cross-sectional imaging. Thermosensors are placed at the bladder neck and sphincter. Two freeze-thaw cycles are applied. Cryotherapy is most appropriate for salvage therapy but may be used for primary if other options are not suitable. Side effects are similar to HIFU, but the incidence of impotence is much higher >80%.

Kidney

Cryotherapy is effective for ablating renal tumours <3.5 cm in patients unfit for surgery, who have local recurrence following nephron-sparing surgery or who have multiple tumours. It cannot be used for tumours near the hilum or central collecting system. It may be applied percutaneously using U/S, CT, or MRI or placed during laparoscopy. Complications may arise from damage to the collecting system or adjacent bowel, e.g., urinoma, duodenal damage, or renoduodenal fistula.

Radio-Frequency Ablation (RFA)

Principle

RFA involves high-frequency alternating current (~500 kHz) passed through an electrode within the target tissue. This produces oscillation of the ions adjacent to the electrode, resulting in frictional heating, but without stimulating nerve or muscle. Greater than 45°C must be achieved to cause irreversible damage, and >60°C, to cause immediate death.

Applications

Renal

RFA allows percutaneous treatment of small renal tumours with indications similar to cryotherapy. A meta-analysis of 47 studies comparing RFA and cryotherapy reported local tumour progression after treatment at 19 months as 13% and 5%, respectively (Kunkle and Uzzo 2008).

Prostate: TUNA

RF needles can be introduced into the prostate lateral lobes via the urethra (TUNA) for the treatment of benign prostatic hyperplasia. The temperature achieved around the needle is 110°C with a 5–15°C drop for every 2-mm distance. A treatment of 2 min at a time is sufficient to cause coagulative necrosis. The needles are placed in planes 1 cm apart, sparing the bladder neck and sphincter. A catheter is required for 48 h. Side effects are retention, irritative symptoms, stricture, minimal retrograde ejaculation, and impotence in 3%.

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Chapter 73
Principles of Radiotherapy

John P. Logue

Radiation therapy is a significant component of the treatment of 40% of patients who are cured of their cancers. It seeks to produce cell kill in the treated area and is delivered with either "radical" intent, where the aim of treatment is cure, or "palliative" intent, where the primary aim is symptom relief.

Radiation therapy will create toxicity. Acute toxicity typically occurs 2–3 weeks after commencing treatment, is site specific, and is usually self-limiting. Late toxicity is much less common, occurs >6 months following therapy in <5% of patients, and has reduced with the refinement of radiation technology.

Treatment Planning

The aim of any radiation prescription is to maximise the dose delivered to the cancer and the target volume while minimising the dose to normal tissue. Normal tissues are referred to as organs at risk (OARs), and the OARS affected depend on the anatomical site being irradiated. OARs vary in their radiosensitivity. The small bowel and spinal cord are relatively sensitive to irradiation, whereas bone and peripheral nerves are relatively resistant.

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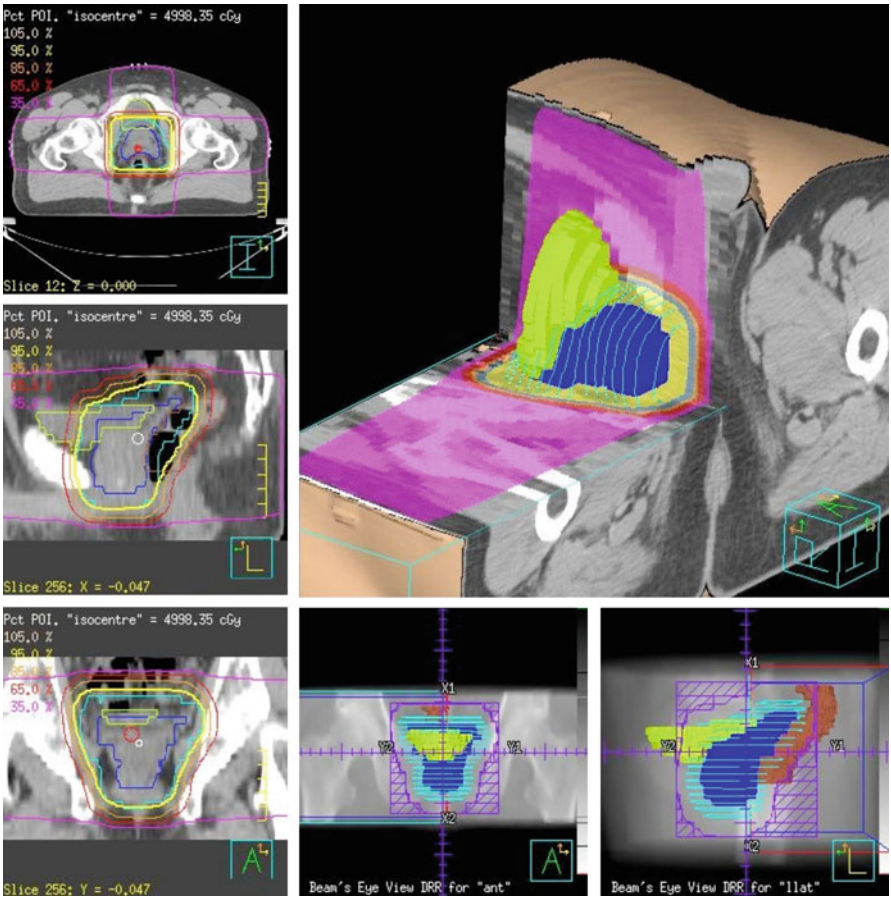

Fig. 73.1 Planning system display of radiation treatment for prostate cancer

Targeting

Imaging allows tumours to be targeted with accuracy. Although some simple treatments are planned using conventional x-rays, most treatments are now planned using CT scans. Information from other imaging modalities such as MR scans, TRUS, and functional imaging may be integrated into the planning process, if required.

Planning External Beam Treatment

This is a 3D process utilising computer systems (Fig. 73.1). Multiple beams are designed to achieve preset dose volume constraints to tumour and normal tissues. All treatment plans include a margin around the tumour to take account not only of microscopic spread but also the internal movement of organs and set-up inaccura-

cies. Recently, it has been possible to modulate the radiation beam to refine the area treated and to reduce the dose to the OARs. This is achieved by intensity modulated (IM) radiotherapy, and increasingly, prostate cancer is treated this way. IM allows dose escalation with a reduced level of patient toxicity.

Dosing

The dose of radiotherapy given is expressed in Gray (Gy). Most radiation treatments typically deliver 2–3 Gy per fraction, but there is evidence that some cancers may respond to higher fraction doses, reducing the overall number of treatments (hypofractionation). The dose prescribed is dependent on the radiosensitivity of the tumour and the tolerance of the tissues within the treatment volume, so the dose applied may be modified dependent upon the volume of normal tissue present.

Delivery of External Beam Treatment

Radiation is delivered utilising a linear accelerator in a series of treatments typically lasting about 15 min. Modern linear accelerators facilitate fine-tuned collimation of the beam to conform as closely to the target volume as possible; this allows accurate and reproducible delivery of the radiation dose. Individual patient set-up is important to facilitate reproducibility. In addition, the recognition of internal movement of tumours, and OARs, has highlighted the need for image-guided treatment, which includes megavoltage imaging to identify implanted fiducial markers and on-couch ultrasound imaging and cone beam imaging to produce on-couch CT scans.

Fractionation

Delivering radiation treatment over a number of sessions maximises the therapeutic effect. This "fractionation" allows normal tissues to recover while maintaining the beneficial effect against the cancer. In radical urological cancer treatments, the total dose is given in 20–37 fractions delivered on a daily basis. Palliative treatments are typically delivered using less fractions, and bone metastases are often treated with a single fraction.

Radiosensitisers

It is possible to modify the biological effect of radiotherapy to enhance the therapeutic ratio between tumour effect and normal tissue effect. Two recent randomised trials, in muscle invasive bladder cancer, have demonstrated clinical

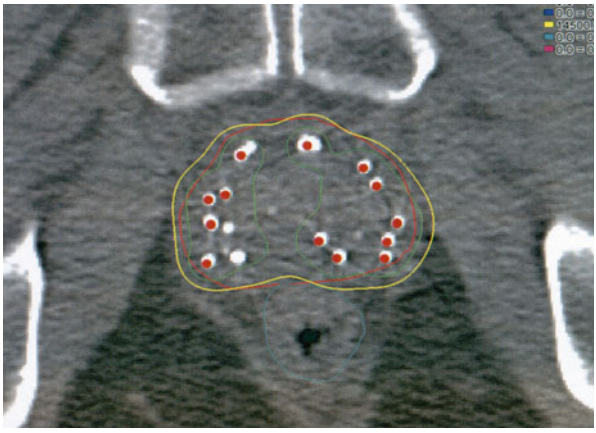

Fig. 73.2 A postimplant CT scan following I^{125} seed brachytherapy, demonstrating seeds and their anticipated radiation dose effect

benefit of the addition of cisplatin and 5-fluorouracil and nicotinamide and carbogen breathing to radiation therapy. There is also evidence of benefit of neoadjuvant hormonal therapy in prostate cancer with animal model evidence that this is a radiosensitisation effect.

Brachytherapy

Brachytherapy involves the permanent, or temporary, placement of radioactive material in tumours, either directly (interstitial) or within a body cavity (intraluminal). In prostate cancer, the use of TRUS guidance allows transperineal implantation of radioactive sources. In low, and intermediate, prostate cancer, the permanent implantation of gamma emitting I^{125} seeds provides a curative treatment modality with outcomes comparable with radical prostatectomy (Fig. 73.2). The temporary placement of high energy sources implanted in the prostate, via transperineal catheters, allows delivery of high-dose rate brachytherapy and is most commonly used to facilitate dose escalation in intermediate/poor risk tumours.

Systemic Radiotherapy

It is possible to deliver radiation systemically by intravenous injection of radionuclides or β-emitting isotopes. Strontium 89 has been demonstrated to have palliative benefit in patients with multiple bone metastases when given as a single injection.

Proton Therapy

Proton therapy utilises particles to allow for the delivery of a precise beam of radiotherapy with a concentrated deposition of dose. This allows for delivery of high doses of localised radiation with relative sparing of surrounding tissues. This type of therapy has potential advantages for a number of cancers, particularly paediatric malignancies.

Chapter 74
Electro-Motive Drug Administration (EMDA)

Vijay Sangar

Physics

EMDA, or iontophoresis, is a means of using pulsed direct current to improve the delivery of substances into the body. The physical principles behind EMDA are explained by Faraday's ion transfer theories. The flow of ions within an aqueous solution allows the current to travel. The flux of ions is directly proportional to the current (amperes) and inversely proportional to the absolute valence of the ion. As a solution of drug will contain at least a drug ion (D) and its counterion, the rate of drug administration (dD/dT) occurs as shown in Fig. 74.1.

The most important variable is the current, as higher current intensities will increase drug delivery. Intravesical pharmacokinetics also depends on the chemical properties of the drug, urine volume and pH, patient hydration, and the integrity of the urothelium. EMDA is usually given transdermally to areas up to 10 cm^2, and pain usually occurs when the current density is >0.5 mA/cm^2. The bladder has a surface area much greater than 10 cm^2, so larger currents can be used.

Some drugs such as mitomycin C are nonionised, so electroosmosis (when non-ionised solutes are transported with water) is then used to drive the drug into the tissues.

$$dD/dT(mg/min) = 60.M.I.tr/|z|.F^3$$

Fig. 74.1 Factors influencing the rate of drug administration (M molecular weight in Daltons, I electric current in amperes, tr the transference number (proportion of current carried by the charged molecule), z absolute valence of ion(s), and F Faraday's number)

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Applications of EMDA to Urological to Pathologies

Harris first studied the delivery of analgesic drugs by iontophoresis in 1957. EMDA has not been studied widely in urology and is currently used mainly within the clinical experimental setting clinically. The main use of EMDA is for transdermal drug administration. In urology, EMDA has been used primarily for intravesical therapies, although some studies for the treatment of Peyronie's disease, and inflammatory bladder conditions, have been undertaken.

In bladder cancer, EMDA has been used to increase the penetration of mitomycin C (MMC) across the urothelium. Di Stasi showed that EMDA can increase the concentrations of MMC by 4–8 times in the mucosa, lamina propria, and muscularis of the bladder. A small nonrandomised clinical marker study showed that the complete response rate does not differ between EMDA MMC and passive MMC therapy. However, in patients who do respond, the recurrence rate is reduced by approximately 50% and time to recurrence is increased by 4 months. A randomised controlled crossover study of 108 patients showed complete response rates at 6 months of 58% vs. 31% for patients receiving EMDA MMC versus passive MMC, respectively. A randomised study of 212 patients compared those receiving EMDA MMC plus BCG versus BCG alone. This showed longer disease-free interval in the EMDA group (58%) versus BCG alone (42%).

In Peyronie's disease, researchers have used EMDA to administer verapamil (5–10 mg) alone or in combination with dexamethasone (8 mg), using currents of up to 2.4 mA for 20 min. Although reductions in curvature and plaque size were noted with verapamil alone, they were not statistically different to controls. In patients receiving verapamil and dexamethasone, subjective improvements of up to 50% were noted.

EMDA has also been used to administer lidocaine intravesically, to improve the effect for analgesia in interstitial cystitis patients, and to facilitate bladder distension. In patients with overactive bladder refractory to oral therapies, EMDA has been used to administer intravesical lidocaine, epinephrine, and dexamethasone. This has been shown to reduce frequency and pad use and improve urodynamic parameters. More recently, in animal models, EMDA has been used to administer intravesical Botox.

How Is EMDA Performed?

EMDA should not be used in cases where there is an allergy to the medication being used or in cases of urethral stricture/bladder neck stenosis. It should be used with caution in patients with coexisting UTI.

A 16Ch catheter with an electrode (anode/positive) is placed into the bladder via the urethra, and the bladder is emptied of urine. Dispersing electrodes (cathodes) are placed over the anterior abdominal wall, below the pubis on shaved/hairless skin.

Table 74.1 The complications associated with EMDA-assisted intravesical chemotherapy for bladder cancer

For EMDA with MMC	For EMDA MMC plus BCG
Drug-induced cystitis (36%)	Macroscopic hematuria (60%)
Macroscopic hematuria (22%)	Dysuria (50%)
Frequency (19%)	Drug induced cystitis (46%)
UTI (19%)	Systemic symptoms (30%)
Allergic reaction (8%)	UTI (15%)

The skin and catheter electrodes are connected to a Physion® generator. A drug, such as MMC 40 mg (in saline or water) is instilled into the bladder. A direct pulsing current of approximately 25 mA is generated across the electrodes for up to 30 min, weekly, for up to 8 weeks. The drug penetrates the bladder wall by following the electroosmosis of water, or if mixed with saline, it follows the sodium ion flux.

Complications of EMDA Therapy

These are not significantly greater than in passive non-EMDA treatments with intravesical chemotherapeutic drugs (Table 74.1).

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Part VI
Technology of Renal Failure

Chapter 75
Principles of Renal Replacement Therapy (RRT)

Colin D. Short

Chronic Renal Failure (CRF)

This term has come to be regarded as rather outmoded and has always been somewhat ambiguous. "Chronic" implies long term and irrecoverable; *cf* "acute" which implies the relatively sudden onset of renal impairment. In most situations, acute renal failure is something that has a potentially recoverable component unless there has been bilateral renal infarction or total nephrectomy. "Renal failure," in the context of CRF, should be regarded more as "renal impairment" rather than failure and does not necessarily imply the need for RRT, at least in the short term.

Currently, the concept, and nomenclature, of chronic kidney disease (CKD) has been developed which has the advantage of enumeration in the presence of abnormal urinary findings and/or structural, or genetic, traits suggesting renal disease (Table 75.1) (NKF-KDOQI 2011).

End-stage renal failure (ESRF) is a term usually used to imply that the patient is in imminent need of renal replacement therapy (RRT) or indeed already established on it. The ambiguity of this term is best avoided by the use of the phrases "dialysis dependant" or "renal transplant recipient" when describing the patient's condition.

Renal Replacement Therapy (RRT)

RRT is used to treat established CKD 5 and encompasses:

1. Chronic peritoneal dialysis
   (a) Chronic ambulatory peritoneal dialysis (CAPD)
   (b) Automated peritoneal dialysis (APD)

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Table 75.1 The KDOQI chronic kidney disease (CKD) classification

CKD grade	Descriptor of type of renal dysfunction	eGFR mL/min
CKD 1	Kidney damage (e.g., proteinuria) but with normal GFR	>90
CKD 2	Kidney damage with mildly reduced GFR	60–89
CKD 3	Moderately reduced GFR	30–59
CKD 4	Severely reduced GFR	15–29
CKD 5	Kidney failure	<15

2. Haemodialysis
3. Renal transplantation

Acute peritoneal dialysis and haemofiltration, whilst technically RRT, are not undertaken on a long-term basis but merely to address acute renal insufficiency.

RRT, like acute dialysis, is used to normalise, as much as possible, the *internal milieu* in the absence of sufficient native renal function and aims to:

(a) Maintain normal serum electrolyte composition (sodium, potassium, bicarbonate, calcium, etc.)
(b) Remove waste products of metabolism (urea, creatinine, and the "middle molecules")
(c) Ensure removal of excess water to prevent fluid overload

RRT also includes replacing the hormonal components of renal function, where indicated, of

(a) Erythropoietin
(b) Vitamin D analogues such as alfacalcidol

These help maintain haemoglobin and provide substrate for conversion to 1,25 dihydroxycholecalciferol, respectively, to reduce bone demineralisation.

Common problems such as hypertension, hypercholestrolaemia, and hyperphosphataemia are intrinsic components of RRT as is patient education about the need for strict adherence to fluid, dietary, lifestyle, and medication modifications.

The Economics of RRT

There is still a great deal of controversy as to the exact costs of providing RRT, and it varies substantially according to modality of treatment. Various authorities, however, give the following approximate costs per annum (Table 75.2):

Whatever the true expenditure, which varies from centre to centre, most authorities agree that in-centre dialysis is significantly more expensive than home therapies.

Table 75.2 The relative costs of the different forms of renal replacement therapy in the UK (2011)

Type of RRT	Cost
In-centre haemodialysis	£30,000 pa
Satellite haemodialysis	£25,000 pa
APD	£23,000 pa
CAPD	£20,000 pa
Home haemodialysis	£18,000 pa
Renal transplantation	£30,000
Post-transplantation management	£10,000 pa

Efficacy of RRT

Patient survival, and graft survival for renal transplants, is not linear and depends on variables such as patient age and comorbidity. Survival on dialysis is usually calculated after the first 90 days because a significant mortality is associated with the 30% or so of patients who initially present needing acute replacements. Five-year survival is 85% in a patient of 25 years but drops to 50% for a 50-year-old irrespective of whether or not they are transplanted. Variables, such as the tissue match, whether or not the patient receives a live donor transplant (usually, but not exclusively, from a relative), and if the transplant takes place prior to the need for dialysis, influence these figures. Overall, survival rates at 1, 5, and 10 years in the UK on RRT are in the order of 95%, 80%, and 60%, respectively.

Benefits of Transplantation

Renal transplantation, for the vast majority of patients, is the most suitable form of RRT unless:

(a) It is technically impossible
(b) It is medically inappropriate, having considered the patient's comorbidities or life expectancy
(c) They have chosen a conservative path and opted not to have RRT in any form
(d) There is a personal preference specifically not to undertake transplantation for whatever reason

Survival benefit from transplantation, as opposed to remaining on dialysis, is evident well within the first year due to the relief from the discipline and hazards of dialysis and the patient's greater sense of well-being. It does, however, demand the other disciplines of maintaining a healthy lifestyle, strict adherence to the prescribed immunosuppressive regimen, and the rigid use of other medications. There are associated longer-term disadvantages of immunosuppression such as symptomatic CMV

disease, pneumocystis, and tuberculosis. Immunosuppression also brings a significant increase in the incidence of skin malignancies, predominantly squamous cell carcinoma, and other virally mediated cancers including carcinoma cervix and post-transplant lymphoproliferative disease (PTLD).

Further Reading

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Chapter 76
Principles of Peritoneal Dialysis

Philip A. Kalra

The proportion of patients treated by peritoneal dialysis varies in different parts of the world – only 10% will be treated with peritoneal dialysis in the USA and Germany, whereas this figure will be around 30% in the UK.

Principles of Peritoneal Dialysis

The main principles behind the use of peritoneal dialysis for treatment of renal failure are that uraemic toxins (e.g., urea, creatinine) and solutes (e.g., sodium, potassium) within the blood compartment will diffuse freely from the peritoneal microcirculation across the peritoneal membrane into the dialysis fluid (dialysate) within the peritoneal cavity. After a given period of time, the fluid (effluent) is then drained out, to be replaced by fresh dialysate. The connection between the patient and the dialysate drainage system must be kept sterile at all times. By varying the concentration of the dialysate, different volumes of water can be removed (ultrafiltration) with each dialysis exchange, as a result of osmosis.

Peritoneal dialysis will only usually be successful for <6 years because of several factors, including:

- Complications of therapy, recurrent peritonitis, encapsulating peritoneal sclerosis (EPS) or peritoneal membrane failure.
- Loss of residual renal function – the success of peritoneal dialysis relies upon most patients having some residual renal function (i.e., patients start dialysis when their GFR is 7–10 mL/min). In most patients, the absence of residual function means dialysis is unable to provide sufficient clearance of waste products and water.

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Types of Peritoneal Dialysis

The most commonly used form of peritoneal dialysis is continuous ambulatory peritoneal dialysis (CAPD). A typical regime would involve four self-administered exchanges of 2 L of dialysate in a 24-h period. Such a regime might be expected to provide a 60–65 kg sized patient with a clearance of toxins equivalent to a GFR of 5–7 mL/min.

Automated peritoneal dialysis (APD) uses a machine to automatically perform the drain in/drain out functions without the need for patient involvement. Typically, APD would provide 5–6 overnight exchanges whilst the patient sleeps; there is a need to connect the patient's dialysis catheter to the APD machine in a sterile manner and to disconnect it at the end of the session.

Patient Selection

Ideally, all patients facing RRT should be given a choice regarding their preferred treatment modality. Their dexterity, general capability, motivation and the amount of space available in the home (for storage of dialysate) will influence that choice; CAPD should only be undertaken in a clean environment. The following would exclude patients from commencing peritoneal dialysis:

- Severe comorbidity
- Previous major abdominal surgery, especially where there is reduced peritoneal membrane surface area available
- Chronic respiratory disease which may be compromised by an intra-abdominal fluid load
- Large muscular patients where the clearance capacity of the peritoneal membrane would be inadequate to maintain health
- Anuric patients where there is no residual renal function
- Severe malnutrition which may be exacerbated by daily protein losses within the dialysis effluent
- Untreatable large hernias

A typical CAPD candidate should, therefore, be relatively fit and have a need for home therapy or for flexibility with their dialysis regime.

Catheter Placement

A Tenckhoff catheter is utilised for peritoneal access, usually inserted via an open incision in the midline below the umbilicus, under local or general anaesthesia. The catheter tip is placed in the pelvis, and the proximal catheter is tunnelled, subcutaneously, to an exit site several centimetres from the midline (Fig. 76.1). The catheter has a cuff attached to help minimise the risk of translocation of infecting organisms into the peritoneal cavity.

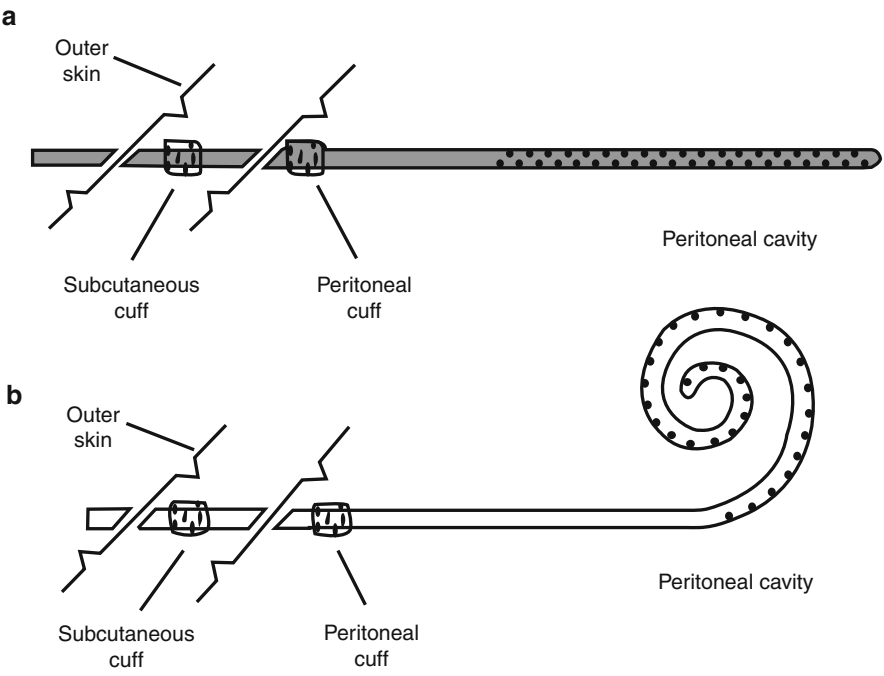

Fig. 76.1 Double-cuffed Tenckhoff catheters. (**a**) Straight, (**b**) curled

Dialysates and Regimes

Dialysis solutions are sterile, buffered with bicarbonate and are available in several different glucose concentrations of differing osmotic strengths (1.5–4.25%) to facilitate ultrafiltration. The amount of ultrafiltration obtained with a given strength of dialysate varies from person to person. Some patients are high transporters of glucose, which means that the osmotic effect of the dialysate rapidly dissipates and fluid removal is poor; in this group, polymer-based dialysates, such as icodextrin, may be used.

Complications Associated with Peritoneal Dialysis

Complications of therapy can be acute or chronic; acute complications threaten continuation of PD. These include:

- Catheter malposition (e.g., catheter tip moves out of the pelvis) or catheter blockage (e.g., with omentum).
- Peritonitis – this is usually treatable with intra-peritoneal antibiotics given for 2 weeks. Peritonitis rates should be <1 episode/30 patient months of therapy.

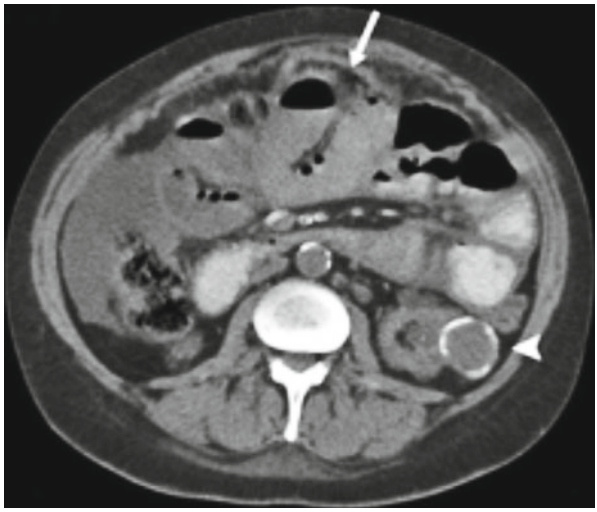

Fig. 76.2 Encapsulating peritoneal sclerosis (EPS) Abdominal CT scan with oral contrast showing irregular, nodular peritoneal thickening (*arrow*) and no peritoneal calcification. There is no bowel wall thickening or any dilated small-bowel loops. There is diffuse vascular calcification. The *arrowhead* shows an incidental calcified *left* renal cyst

Infecting organisms include coagulase –ve staphylococci, *Staphylococcus aureus*, and gram –ve bacilli. Repeated infections can lead to development of resistant infections (e.g., yeasts), peritoneal membrane failure and to encapsulating peritoneal sclerosis.

Chronic complications usually require transfer of the patient to haemodialysis:

- Ultrafiltration failure – due to repeated peritonitis and after several years of exposure of the peritoneal membrane to the dialysis solutions.
- Encapsulating peritoneal sclerosis (EPS) – a thickening of the peritoneal membrane, with reduced function and encasement of intra-abdominal organs (Fig. 76.2). The incidence of EPS increases with duration of peritoneal dialysis (e.g., 5% of patients after 3 years of therapy). Symptoms include abdominal pain and malnutrition, and bowel obstruction and perforation can occur with more advanced cases. Surgery is life-saving in some cases.

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Chapter 77
Haemodialysis

Rosie Donne

Principles of Haemodialysis

Haemodialysis is a treatment in which blood is passed through an artificial kidney (dialyser) and then returned to the body. Within the dialyser, the solute constituents of the blood are altered by exposing it to dialysis fluid across a semipermeable membrane. Most dialysers are around 20–30-cm long and contain hundreds of tiny long tubes arranged side by side, made from semipermeable membrane (Fig. 77.1). The blood flows through the tubes providing a large surface area to allow passage of fluid and diffusion of electrolytes. The tubes are bathed by dialysis fluid running in the opposite direction providing a countercurrent system to maximise the concentration gradient across the membrane. Conceptually, the membrane can be thought of as a sheet containing holes or pores. Water molecules and low molecular weight solutes such as urea, creatinine, and electrolytes can pass through the pores, but high molecular weight solutes such as plasma proteins and some drugs cannot. Blood flows through the dialyser at 300–400 mL/min and is anticoagulated with unfractionated or low molecular weight heparin to prevent clotting within the dialysis circuit. The dialysis treatment can be altered by changing the electrolyte composition of the dialysis fluid, the rate of fluid removal (ultrafiltration) and the duration of treatment.

A patient's "dry weight" is their body weight without any excess fluid. Patients are weighed before each treatment to determine how much ultrafiltration is needed to return them to their dry weight. Most patients need to comply with a diet low in salt, potassium, and phosphate as well as a fluid restriction of <1 l per day. Most patients on long-term haemodialysis require >4 h of treatment three times weekly,

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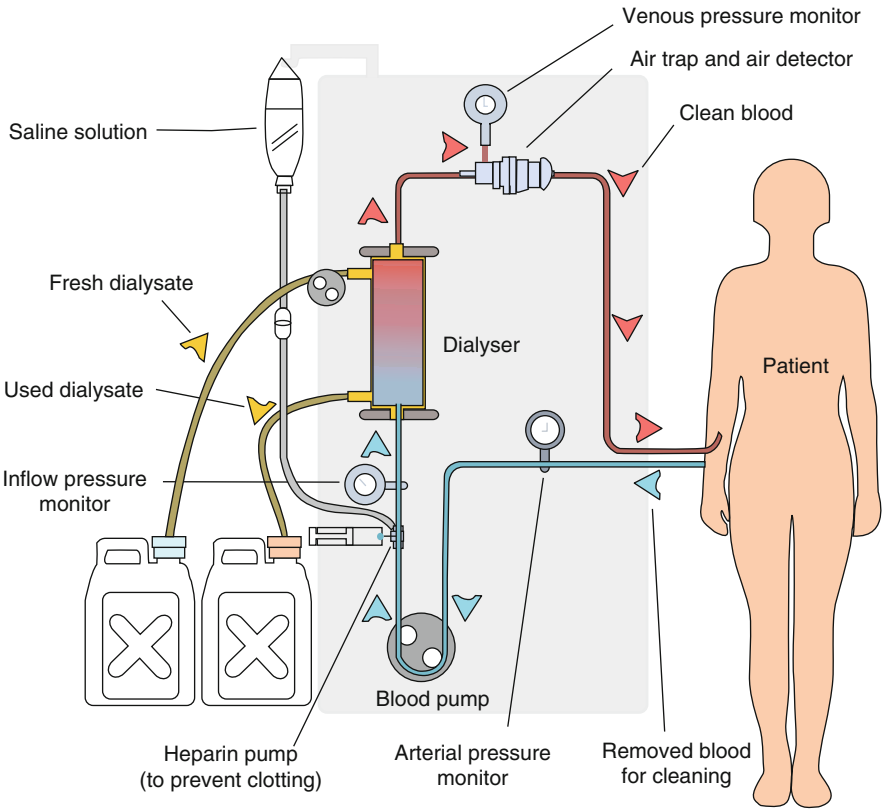

Fig. 77.1 A haemodialysis circuit

although evidence suggests their quality of life is improved if they dialyse for >12 h per week. This may be delivered either by more frequent sessions or longer hours, even overnight in some cases. Home haemodialysis is encouraged where possible to facilitate this whilst maximising quality of life.

Initiation of Haemodialysis

Haemodialysis is usually the dialysis type of choice in acute kidney injury in adults as it is easy to initiate via a central venous catheter. It has predictable efficacy and few problems in the short term as long as the systolic blood pressure is >100 mmHg. In a chronic setting, haemodialysis is usually initiated when the eGFR is between 8 and 10 mL/min. It is initiated earlier if dietary and medical therapies have failed to control fluid overload and serum potassium levels.

Vascular Access for Haemodialysis

Temporary access may be provided with a double-lumen central venous cannula. Long term, the safest form of vascular access is an arteriovenous (AV) fistula, which provides the maximum blood flow with the lowest risk of infection or thrombosis. The ideal site is the non-dominant wrist, creating an anastomosis between the radial artery and the cephalic vein to form a "radio-cephalic" fistula. If this is not possible, fistulas can be created at the elbow (brachiocephalic or transposed brachiobasilic) or in the dominant arm (Fig. 77.2).

Once created, the fistula usually takes at least 8 weeks to mature before it is ready for use. Patients with inadequate veins for fistula creation may have an AV graft, either in the arm or in the thigh, but this is more prone to infection and thrombosis. Some patients require several operations to secure a functioning AV fistula, and for this reason, patients are usually referred for AV fistula creation when the eGFR is around 15 mL/min. Pre-dialysis, patients should use the hand, not arm veins, for cannulation and blood sampling to preserve the arm veins for fistula creation in the future.

Complications of Haemodialysis

Many problems relating to haemodialysis are related to functioning vascular access. AV fistulas may last for many years, but complications include sudden thrombosis, requiring urgent thrombolysis; gradual development of stenosis, requiring fistuloplasty, stenting, or revision surgery and steal syndrome leading to digital ischaemia. If a fistula fails, a central venous catheter is required to continue dialysis treatment until another fistula can be created. Complications of large-bore venous catheters include air embolism, bacteraemia, endocarditis, discitis, catheter thrombosis, and central vein stenosis/thrombosis leading to symptoms of SVC obstruction. Other complications of dialysis include reactions to the dialyser, cardiac arrhythmias, and poor tolerance of fluid removal leading to hypotension.

Long-term complications of end-stage renal failure are many and include markedly increased risk of cardiovascular disease and heart failure, infections, anaemia resistant to erythropoietin, hyperparathyroidism, calciphylaxis, malnutrition, and psychosocial problems. Some patients choose to withdraw from dialysis either because they no longer tolerate it or because of poor quality of life.

Practical Points Relating to the Management of Surgical Patients on Haemodialysis

- Do not act on results of blood tests taken immediately after dialysis as they change rapidly, e.g., potassium is often below the normal range but will rapidly rebound.

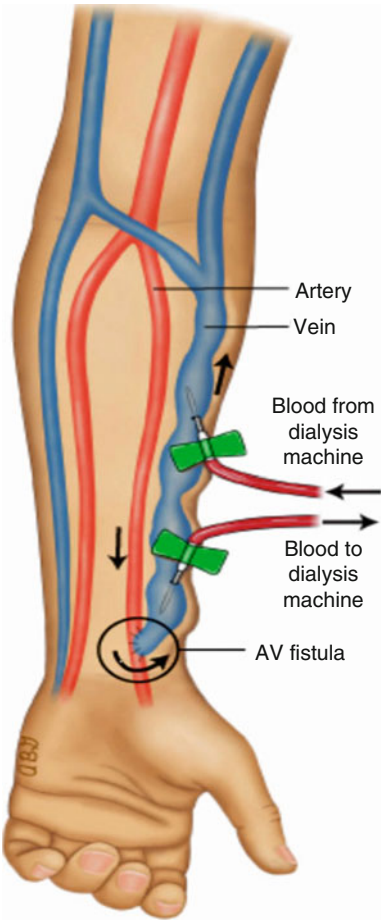

Fig. 77.2 Arteriovenous (AV) fistula

- Haemodialysis patients undergoing surgery will usually require haemodialysis on the day before and the day after surgery to minimise perioperative risk.
- Anticoagulation is usually used during dialysis but can be avoided in the perioperative period by using short-duration dialysis.
- Many drugs are removed by dialysis so should usually be given at the end of dialysis, e.g., IV antibiotics.
- There is a higher risk of adverse drug reactions in patients with renal failure, so if in doubt, consult the renal team regarding drug dosing.

Further Reading

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Chapter 78
Principles of Renal Transplantation

Neil R. Parrott

Indications

Renal transplantation is regarded as the primary treatment for all patients with established grade 5 chronic kidney disease (CKD), requiring replacement, as long as they are medically fit for the procedure. In practice, only around 40–50% of the UK renal failure population are fit enough for surgery. The UK Renal Association (RA) guidelines suggest that patients should be offered kidney transplantation if it offers a likelihood of increased life expectancy following grafting. The RA guidelines also recommend that patients should be listed within 6 months of starting dialysis, and both RA and the British Transplant Society (BTS) recommend transplantation prior to commencement of dialysis wherever possible.

Contraindications

Medical contraindications principally relate to poor cardiac or respiratory function. Neurological or anatomical bladder abnormalities do not contraindicate transplantation, and these patients may be managed by intermittent self-catheterisation, or by pre-emptive ileal conduit formation.

Box 78.1 shows the relative and absolute contraindications. The presence of alloantibodies secondary to prior blood transfusion, pregnancy, or previous transplantation do not contraindicate transplantation, but make matching more problematic. Living related donor transplantation can now be done across the ABO barrier.

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Box 78.1: The Contraindications to Renal Transplantation

- Active renal disease, active Goodpasture's syndrome, some varieties of haemolytic uremic syndrome, and some types of glomerulonephritis when rapid recurrence of the original disease may be possible.
- Previous malignancy within 3–5 years with exception of completely excised non-melanoma skin cancers.
- Active sepsis at the time of transplantation.
- A positive flow-cytometric or cytotoxic crossmatch is an absolute contraindication.
- Age is not a contraindication, although the young may be managed by dialysis until their body weight is >10–15 kg.

Types of Renal Transplant

There are now a variety of ways in which transplantation can occur, including live donor transplantation from a genetically related, or non-genetically related, individual, an altruistic donor or from the national paired/pooled scheme. Donation of a graft from a deceased donor can be made after brain (DBD) or cardiac death (DCD). As at January 2011, there were around 6,700 patients in the UK waiting, on average 2–3 years, for a kidney transplant.

The National Waiting List Allocation

In the UK, currently, all kidneys from DBD, but not DCD, donors are allocated by the national sharing scheme. Allocation is by using a formula which considers ABO compatibility, HLA match, unacceptable antigens, wait time, and age mismatch. All kidneys are allocated preferentially to child recipients.

Surgical Technique of Kidney Transplantation

The surgery of transplantation has not changed materially in 30 years. In most adults, the transplant is placed extra-peritoneally in the iliac fossa, anastomosing the renal vein end-to-side to the external iliac vein, and with the renal artery either end-to-side, or end-to-end with the external or internal iliac arteries. Use of the internal iliac artery is less common in an ageing recipient. Most transplant surgeons will make an extra-vesical stented ureteroneocystostomy of the Lich-Gregoir type.

Table 78.1 Common immunosuppressant drugs used following renal transplantation

Immunosuppressant drug	Class of drug	Comment
Basiliximab (Simulect)	Interleukin-2 receptor blocking antibody	Recommended by NIHCE and now in almost universal use
Tacrolimus (Prograf) Ciclosporin (Neoral)	Calcineurin (CNI) inhibitors	Tacrolimus is now the CNI of choice for most centres and has proven superior efficacy compared to ciclosporin
Azathioprine (Imuran)	Anti-proliferative agents	In decline as a "de novo" anti-proliferative
Mycophenolate mofetil (CellCept)		Now the most frequent agent used in this group
Mycophenolic acid (Myfortic)		Effectively the same drug, but said to have reduced GI side effects
Oral prednisolone (up to 20 mg/day)	Steroids	Many centres now using steroid-free or short-term steroids only.
Methylprednisolone (500–1,000 mg)		Used to treat acute rejection episodes

Table 78.2 The early and late complications of renal transplantation

Early complications <30 days	Late complications >30 days
Mortality 1%	New onset diabetes after transplantation (NODAT)
Thrombosis 1%	BK virus nephropathy
Haemorrhage 1%	CMV infection
Ureteric leak, no stent 20%	Pneumocystis pneumonia (PCP)
Ureteric leak, stent 1–2%	Malignancy secondary to immunosuppression
Rejection 10%	Posttransplant lymphoproliferative disease (PTLD)
	Interstitial fibrosis and tubular atrophy (IFTA)

Post-transplant Immunosuppression

Postoperatively immunosuppression is required to reduce the incidence of graft rejection. There is no agreed national "standard" immunosuppressive protocol, and there will be variations in regimen used dependant upon donor and recipient variables, including cold ischaemia time. Most immunosuppressive protocols will, however, include a monoclonal interleukin-2 receptor blocker, a calcineurin inhibitor, an anti-proliferative agent and steroids (Table 78.1).

Complications of Kidney Transplantation

It is best to classify the transplant-specific complications as early or late (Table 78.2).

Table 78.3 Patient and renal graft survival following renal transplantation (Manchester 2011)

	First deceased donor transplant (%)	Live donor transplant (%)
Patient survival		
1 year	95	100
5 year	89	95
Graft survival		
1 year	93	97
5 year	81	82

Early complications are mostly related to the surgery of graft placement of which thrombosis is the most devastating; this is less common in live donor transplants. Acute rejection usually responds to three pulses of methylprednisolone.

Late complications are nearly all related to anti-rejection therapy, and this should be reduced, wherever possible, to the lowest effective dose. The majority of malignancies related to immunosuppression will be actinic basal cell or squamous cell carcinomas, which are potentially curable. PTLD occurs in 1–2% of transplanted patients but has a potential 50% mortality. IFTA is almost universal with time in those taking CNIs, with an incidence of 100% at 10 years, resulting in slow and progressive graft loss in many cases.

Outcome from Renal Transplantation

Median graft survival is 12–13 years, for a deceased donor transplant, and almost 20 years for a live donor transplant. The anticipated 1 and 5 year patient/graft survival is shown in Table 78.3.

Further Reading

The British transplantation website has a wealth of guidelines and documents relating to almost all forms of transplantation and their management. http://www.bts.org.uk/transplantation/standards-and-guidelines/.

Centre-specific outcomes and UK data can be found at the NHSBT website. http://www.organdonation.nhs.uk/ukt/statistics/centre-specific_reports/centre-specific_reports.jsp.

Part VII
Assessment of Technology

Chapter 79
Randomised Controlled Trials (RCTs)

Kieran O'Flynn

Since the first randomised control trial (RCT) was published, on the use of streptomycin in tuberculosis in 1948, RCTs have become established as the standard means of assessing therapeutic effects in medicine. The key feature of RCTs is that study subjects, after assessment of eligibility and recruitment, are randomly allocated to receive one or other of the alternative treatments prior to commencement of the study.

Classification

RCTs may be classified in a variety of ways. Explanatory RCTs test efficacy in a research setting with highly selected participants under highly controlled conditions. In contrast, pragmatic RCTs test effectiveness in everyday practice with relatively unselected participants and under flexible conditions. RCTs can also be classified as "superiority trials," "non inferiority trials" and "equivalence trials," which differ in methodology and reporting. Most RCTs are superiority trials, in which one intervention is hypothesised to be superior to another in a statistically demonstrable way.

Other study designs may include the following:

- Parallel groups – each participant is randomly assigned to a group, and all the participants in the group receive (or do not receive) an intervention.
- Crossover – over time, each participant receives (or does not receive) an intervention in a random sequence.

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- Cluster – pre-existing groups of participants (e.g., villages, schools) are randomly selected to receive (or not receive) an intervention.
- Factorial – each participant is randomly assigned to a group that receives a particular combination of interventions or noninterventions (e.g., the MTOPS trial).

Randomisation Procedures

Random allocation in real trials is complex, but conceptually, the process is like tossing a coin. After randomisation, the two or more groups of subjects are followed up in exactly the same way, the only differences being the therapeutic intervention they receive. The most important advantage of proper randomisation is that it minimises allocation bias, balancing recognised known and unknown factors, in the assignment of treatments. An ideal randomisation procedure would achieve the following goals:

- Equal group sizes for adequate statistical power, especially in subgroup analysis.
- Low selection bias. The procedure should not allow an investigator to predict the next subject's group assignment.
- Low probability of confounding, i.e. a low probability of "accidental bias."

No single randomisation procedure meets those goals in every circumstance, so researchers must select a procedure for a given study based on its advantages and disadvantages. Simple randomisation (akin to tossing a coin) may result in imbalanced group sizes in small RCTs and is now uncommonly used.

To balance group, size "restricted randomisation" is frequently used. In blocked randomisation, a "block size" and "allocation ratio" (number of subjects in one group versus the other group) are specified, and subjects are allocated randomly within each block. This type of randomisation can be combined with "stratified randomisation," to ensure good balance of participant characteristics in each group.

Integral to the process is "allocation concealment," the procedure for protecting the randomisation process so that the treatment allocated is not known before the patient is entered into the study. Most large RCTs use some form of central randomisation. An RCT may be "blinded," a procedure that prevent study participants, caregivers, or outcome assessors from knowing which intervention was received. In pragmatic trials (e.g., surgery and some therapeutic trials), although the participants and providers are often not blinded, it may be desirable to blind the assessor or obtain an objective source of data for evaluation of outcomes.

Analysis of Data from RCTs

The types of statistical methods used in RCTs depend on the characteristics of the particular trial. Important considerations in the analysis of RCT data include:

- Early termination of the trial. RCTs may be stopped early if an intervention produces "larger than expected benefits or harm." These boundaries may be set by an overseeing ethics committee.
- Intention to treat analysis. This enables a real world view of the efficacy of the trial in which all participants are evaluated in the group to which they were assigned, irrespective of whether they received the allocated treatment or not.
- Subgroup analysis. These should be specified at the outset of the study and be biologically plausible. Multiple comparisons of groups may produce false positive findings that cannot be confirmed by other studies.

The CONSORT 2010 Statement (Table 79.1) is an evidence-based, minimum set of recommendations for reporting RCTs. The checklist contains 25 items (many with sub-items) focusing on "individually randomised, two group, parallel trials" which are the most common type of RCT.

Table 79.1 Consort checklist for randomised controlled trials[a]

Section/topic	Checklist items
Title and abstract	Identification as a randomised trial in the title with structured summary of trial design, methods, results, and conclusions
Introduction	Scientific background and explanation of rationale, with specific objectives or hypotheses
Methods	Description of trial design (such as parallel, factorial) including allocation ratio and important changes to methods after trial commencement
	Eligibility criteria for participants, settings and locations of trial
	The interventions for each group with sufficient details to allow replication
	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed
	How sample size was determined, explanation of any interim analyses and stopping guidelines
	Method used to generate the random allocation sequence, with types of randomisation (such as blocking and block size); details of blinding, e.g., participants, care providers, and those assessing outcome
	Statistical methods used to compare groups for primary and secondary outcomes. Methods for additional analyses, such as subgroup analyses and adjusted analyses
Results	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome with losses and exclusions after randomization with reasons
	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups
	All important harms or unintended effects in each group (for specific guidance, see CONSORT for harms)
Discussion	Trial limitations, addressing sources of potential bias, imprecision. Generalizability (external validity, applicability) of the trial findings. Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence

[a]Adapted from the CONSORT 2010 checklist, available at http://www.consort-statement.org/

Advantages and Disadvantages of RCTs

Because RCTs reduce spurious causality and bias, they are often considered the most reliable form of scientific evidence in the hierarchy of evidence (Appendix 4). They may be combined as meta-analyses to form the bedrock of clinical practice guidelines. RCTs are, however, expensive to perform and may not always be applicable in a "real-world setting" (external validity) due to:

- Where the RCT was performed, e.g., what works in one health-care setting may not work in another.
- Characteristics of the patients, e.g., an RCT may exclude the elderly, and those with common coexisting medical conditions.
- Study procedures, e.g., in an RCT patients, may receive intensive diagnostic procedures or follow-up which may be impractical in standard clinical practice.
- Outcome measures, e.g., RCTs, may use composite measures infrequently used clinically.
- Limited study duration may result in incomplete reporting of adverse effects.

Further Reading

CONSORT statement www.consort-statement.org.

Chapter 80
Health Technology Assessment

Robert Pickard, Michael Drinnan, and Luke Vale

What Is It?

Health technology assessment (HTA) is a process by which the worth of a new health care technology is described, principally by gathering, collating, and synthesising evidence. This synthesis is then used to determine whether the technology should be adopted. The HTA process is linked to national and international regulatory systems that approve health technologies for routine clinical use.

In the past, drugs or devices designed to improve diagnosis and treatment of disease were the main subjects for HTA. Now, it encompasses all interventions that seek to contribute to the prevention, diagnosis, treatment, and rehabilitation of health problems including invasive procedures, physical treatments, and pathways of care. The underlying aim is for all existing and new health care interventions to undergo the same stringent assessment as new drugs.

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What Does It Involve?

The HTA process provides evidence statements concerning the technology under assessment by addressing a number of interrelated questions (Box 80.1).

To answer these questions, evidence has to be collected by conducting preliminary testing and *proof of principle* research using quantitative and qualitative methods. Once approval for human testing has been obtained, clinical studies are performed which vary in scope according to the technology but generally follow the pattern used for new drug assessment (Box 80.2). This evidence is then reviewed, synthesised, and used to model longer term implications of implementation.

Box 80.1: Evidence Domains for HTA

- Does it fulfil a need? – *health care gap*
- Can it be described? – *specification*
- Is it safe? – *safety*
- Does it work? – *reliability*
- Does it do what it is supposed to do? – *validity*
- Does it improve outcome under ideal conditions? – *efficacy*
- Does it improve outcome under routine conditions? – *effectiveness*
- Is it appropriate within the chosen setting? – *acceptability*
- Is it widely adoptable? – *generalisability*
- Does it provide value for money? – *cost-effectiveness*
- Is it better than existing technologies? – *implementation*

Box 80.2: Phases of Clinical Study Required for HTA

Primary research
Phase 1 Confirmation of safety in humans
Phase 2 Demonstration of probable benefit
Phase 3 Controlled study against comparator
Phase 4 Pragmatic studies against standard care
Secondary research
Systematic review and meta-analysis of existing evidence
Mathematical modelling of effectiveness and cost-effectiveness

Specification

The first stage is for the innovator to accurately describe the technology. For a device, this involves completion of a *technical file* specifying its components and how they are put together for functionality and is related to intellectual property (IP)

protection and *CE* marking. For a new care pathway, it will involve description of all steps in terms of who does what, when, and where.

Safety

With the exception of drugs, there is little uniformity of safety approvals required for new health technologies. In the European Union, devices have to be categorised into one of four classes according to perceived risk, and then assessed as meeting relevant safety standards for use in humans by the competent authority, the Medicines and Healthcare Products Regulatory Agency (MRHA) in the UK. In contrast, introduction of new surgical procedures relies predominantly on the ethical framework of clinician innovators.

Reliability and Validity

It is crucial that any new technology does what is meant to do, *validity*, and does it in a reliable way, encompassing technical *reliability* and functional *repeatability* within acceptable margins of error. Demonstration of validity and reliability requires well-designed studies using appropriate methodology and analyses to inform usefulness of the technology in its chosen setting.

Efficacy and Effectiveness

Efficacy describes whether a technology works in the intended way and is assessed by measuring a change in an appropriate outcome under carefully controlled conditions by its developers. This is usually done by a comparative study against an existing standard intervention or a placebo/no intervention arm. The primary outcome must be carefully chosen to best reflect the improvement in health care envisaged and which allows wider comparison of its worth. The next step is to see if the benefit is transferable to conditions of standard care, *effectiveness*. Ideally, this should be done using a pragmatic randomised trial design controlled against routine practice. These studies also determine whether the technology is *acceptable* for its chosen health care setting often using qualitative methods and whether it is *generalisable* across settings.

Adoption

Having demonstrated that a new technology is safe and more effective than existing options, a decision has to be made whether it should be *implemented*, guided by an interaction between providers, funders, and consumers. For richer nations with

personally funded health care, adoption is more sensitive to commercial marketing and consumer (clinician or patient) demand. Centrally funded health care systems, such as the NHS, have more of a focus on maximising the benefits that can be obtained from the finite resources allocated to health care. This requires a more rigorous comparative evaluation to ensure that scarce resources are used to fund technologies that give most benefit. In the UK, this role is undertaken by the National Institute for Health and Clinical Excellence (NICE). NICE relies on the commissioning of HTA reports that synthesise available evidence to estimate, with specified margins of uncertainty, relative clinical effectiveness, and *cost-effectiveness*. Here, the HTA guides and gives quantifiable justification to the decision of policymakers as to whether a technology should or should not be adopted. This is increasingly governed by estimates of the cumulative difference in costs and benefits from using the technology compared with an alternative over a period of time. The time period used depends on how long any difference in outcomes is expected to last; for treatments, the patient's lifetime is typically used, whilst for devices, the lifetime of the technology is more appropriate. The decision whether to adopt is usually governed by funding constraints since most new technologies will involve an increase in expenditure that, given that funds are limited, has to be saved elsewhere (*opportunity cost*). This decision can be related to estimates of the expenditure needed to gain the benefit of the new technology, or more commonly to the cost of increasing well-being amongst users measured, for example, by quality-adjusted life years (QALYs). NICE typically recommends that a technology is suitable for use within the NHS if the cost per QALY gained is less than £20,000.

Further Reading

Goodman CS (2004) HTA 101: introduction to health technology assessment. Web-based document freely accessible at: http://www.nlm.nih.gov/nichsr/hta101/hta101.pdf

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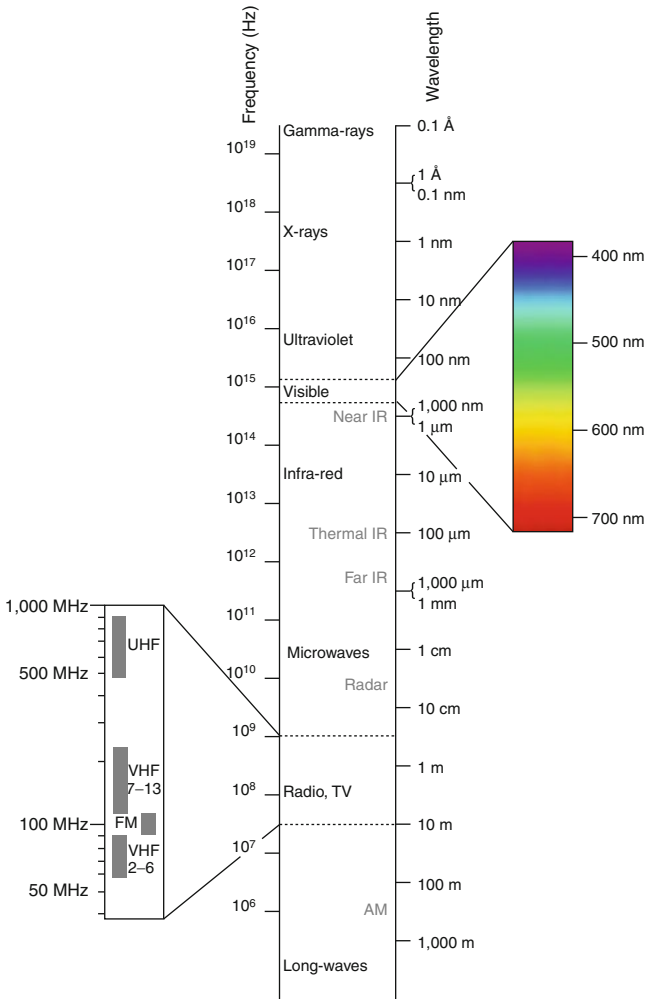
Scales CD (2011) Education and training in evidence-based urology. World J Urol; In Press: DOI 10.1007/s00345–011–0651-x

Scales CD Jr. (2011) International Evidence-Based Urology Working Group. World J Urol. Jun;29(3):325–9

Appendices

Appendix 1: The Electromagnetic Spectrum



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Ionising radiation consists of particles, or electromagnetic waves, that are energetic enough to detach electrons from atoms, or molecules, causing ionisation. Ionisation produces free radicals, which are atoms, or molecules, containing unpaired electrons that tend to be especially chemically reactive due to their electronic structure. Free radicals have damaging effects on tissue.

The ability of an electromagnetic wave to ionise an atom, or molecule, depends on its frequency, which determines the energy of its associated particle, the photon. Roughly speaking, particles or photons with energies above about 10 electron volts (10 eV) are needed to cause ionisation. This corresponds to radiation with a wavelength less than about 100 nm. Therefore radiation from the short-wavelength end of the electromagnetic spectrum, high frequency ultraviolet, X-rays, and gamma rays, is ionising and can be harmful. But lower energy radiation, such as visible light, infrared, microwaves, and radio waves, are nonionising and are thought to be essentially biologically harmless below the levels that cause tissue heating.

Appendix 2: The Periodic Table of Elements

hydrogen 1 H 1,0079																		helium 2 He 4,0026
lithium 3 Li 6,941	beryllium 4 Be 9,0122											boron 5 B 10,811	carbon 6 C 12,011	nitrogen 7	oxygen 8 O 15,999	fluorine 9 F 18,998	neon 10 Ne 20,180	
sodium 11 Na 22,990	magnesium 12 Mg 24,305											aluminium Al 26,982	silicon Si 28,086	phosphorus P 30,974	sulfur S 32,065	chlorine Cl 35,453	argon 18 Ar 39,948	
potassium 19 K 39,098	calcium 20 Ca 40,078	scandium 21 Sc 44,956	titanium 22 Ti 47,867	vanadium 23 V 50,942	chromium 24 Cr 51,996	manganese 25 Mn 54,938	iron 26 Fe 55,845	cobalt 27 Co 58,933	nickel 28 Ni 58,693	copper 29 Cu 63,546	zinc 30 Zn 65,39	gallium 31 Ga 69,723	germanium 32 Ge 72,61	arsenic 33 As 74,922	selenium 34 Se 78,96	bromine 35 Br 79,904	Krypton 36 Kr 83,80	
rubidium 37 Rb 85,468	strontium 38 Sr 87,62	yttrium 39 Y 88,906	zirconium 40 Zr 91,224	niobium 41 Nb 92,906	molybdenum 42 Mo 95,94	technetium 43 Tc [98]	ruthenium 44 Ru 101,07	rhodium 45 Rh 102,91	palladium 46 Pd 106,42	silver 47 Ag 107,87	cadmium 48 Cd 112,41	indium 49 In 114,82	tin 50 Sn 118,71	antimony 51 Sb 121,76	tellurium 52 Te 127,60	iodine 53 I 126,90	xenon 54 Xe 131,29	
caesium 55 Cs 132,91	barium 56 Ba 137,33	57–70 *	lutetium 71 Lu 174,97	hafnium 72 Hf 178,49	tantalum 73 Ta 180,95	tungsten 74 W 183,84	therium 75 Re 188,21	osmium 76 Os 190,23	iridium 77 Ir 192,22	platinum 78 Pt 195,08	gold 79 Au 196,97	mercury 80 Hg 200,59	thallium 81 Tl 204,38	lead 82 Pb 207,2	bismuth 83 Bi 208,98	polonium 84 PO [209]	astatine 85 At [210]	radon 86 Rn [222]
francium 87 Fr [223]	radium 88 Ra [226]	89 –102 * *	lawrencium 103 Lr [262]	rutherfordium 104 Rf [261]	dubnium 105 Db [262]	seaborgium 106 Sg [266]	bohrium 107 Bh [264]	hassium 108 Hs [269]	meitnerium 109 Mt [268]	ununnilium 110 Uun [271]	ununium 111 Uuu [272]	ununbium 112 Uub [277]	ununquadium 114 Uuq [289]					

* Lanthanide series	lanthanum 57 La 138.91	cerium 58 Ce 140.12	praseodymium 58 Pr 140.91	neodymium 60 Nd 144.24	promethium 61 Pm [145]	samarium 62 Sm 150.36	europium 63 Eu 151.96	gadolinium 64 Gd 157.25	terbium 65 Tb 158.93	clysprosium 66 Dy 162.50	holmium 67 Ho 164.93	erbium 68 Er 167.26	thulium 69 Tm 168.93	ytterbium 70 Yb 173.04
** Actinide series	actinium 59 Ac [227]	thorium 90 Th 232.04	protactinium 91 Pa 231.04	uranium 92 U 238.03	neptunium 93 Np [237]	plutonium 94 Pu [244]	americium 95 Am [243]	curium 96 Cm [247]	berklium 97 Bk [247]	californium 98 Cf [251]	einsteinium 99 Es [252]	fermium 100 Fm [257]	mendelevium 101 Md [258]	nobelium 102 No [259]

This periodic table shows all the known elements. Each box includes the full name of the element followed by its atomic number, chemical symbol and atomic weight. The atomic number, usually denoted by Z, is the number of protons found in the nucleus of an atom and therefore identical to the charge number of the nucleus. The nucleus also contains N neutrons so the mass number, A, which is the total number of protons and neutrons in the nucleus, is given by $A = Z + N$. Atoms having the same atomic number (Z) but different neutron number (N), and hence different atomic mass, are known as isotopes. Most naturally occurring elements exist as a mixture of isotopes, and the average atomic mass of this mixture determines the element's atomic weight.

Appendix 3: Expected Laboratory Values

Blood

Test	Abbreviation	Lower limit	Upper limit	Unit
Haemoglobin	Hb	12	18	g/dL
White cell count	WCC	4×10^9	1.1×10^{10}	/L
Mean cellular volume	MCV	80	100	fL
Mean cellular haemoglobin concentration	MCHC	31	36	Hb/cell
Haematocrit		36	46	%
Platelets		150×10^3	450×10^3	/μL

Serum

Test	Abbreviation	Lower limit	Upper limit	Unit
Glucose		3.5	6	mmol/L
Glycated haemoglobin	HBA1c	4	5.9	%
Creatinine (male)		80	115	μmol/L
Creatinine (female)		70	100	μmol/L
Urea		2.1	8	mmol/L
Sodium		135	145	mmol/L
Potassium		3.5	5	mmol/L
Bicarbonate		22	30	mmol/L
Chloride		98	107	mmol/L
Magnesium		0.7	1	mmol/L
Calcium		2.2	2.6	mmol/L
Phosphate		0.8	1.3	mmol/L
Parathyroid hormone	PTH	1.5	7.6	pmol/L
Uric acid (male)		200	450	μmol/L
Uric acid (female)		140	380	μmol/L
Total protein		64	83	g/L
Albumin		34	48	g/L
Bilirubin		0.2	1.2	mg/dL
Alanine aminotransferase	ALT	5	21	μmol/L
Aspartate aminotransferase	AST	10	35	iu/L
Gamma glutamyl transferase	γGT	0	42	iu/L
Alkaline phosphatase	ALP	30	120	iu/L
Amylase		23	85	u/L
Beta HCG	βHCG		<5	u/L
Placental alkaline phosphatase			<100	mu/L
Alpha fetoprotein	αFP		<10	kU/L
Follicle stimulating hormone	FSH	1	9	iu/L
Luteinising hormone	LH	1	9	iu/L

(continued)

Serum (continued)

Test	Abbreviation	Lower limit	Upper limit	Unit
Testosterone (male)		8	30	nmol/L
Sex hormone binding globulin	SHBG	13	71	nmol/L
Prolactin (male)			<550	mu/L
Prolactin (female)			<600	mu/L
Total prostate specific antigen	(PSA)		<4	ng/mL
Free:Total PSA ratio			>20	%

Urine

Test	Abbreviation	Lower limit	Upper limit	Unit
Volume		1	2	L/24 h
pH		4.4	8	
Calcium		1.25	10	mmol/24 h
Phosphate		0.4	1.3	g/24 h
Citrate			<300	mg/24 h
Oxalate (male)		0.08	0.49	mmol/24 h
Oxalate (female)		0.04	0.32	mmol/24 h
Protein			<0.15	g/24 h
Urea		170	580	mmol/24 h
Uric acid		1.5	4.4	mmol/24 h
Cystine			<38.1	mg/24 h
Prostate CAncer gene 3	PCA 3		>35	

Semen

Test	Lower limit	Upper limit	Unit
Volume	1.5		mL
pH	7.2	7.8	
Concentration	15		$\times 10^6$/mL
Sperm per ejaculation	39		$\times 10^6$/mL
Vitality	58		% live
Motility – excellent	32		%
Motility – excellent + sluggish	40		%
Morphology	>4		%

Appendix 4: Levels of Evidence for Therapeutic Studies[a]

Levels of evidence	Therapy/prevention/aetiology/harm
1a	Systematic review with homogeneity of randomised controlled trials (RCTs)
1b	Individual RCT with narrow confidence interval
1c	All or none. Met when all the patients died before the treatment became available, but some now survive on it, or when some patients died before the treatment became available, but now none die of it
2a	Systematic review (with homogeneity) of cohort studies
2b	Individual cohort study (including low quality RCT; e.g. follow-up <80%)
3a	Systematic review (with homogeneity) of case controlled study
3b	Individual case-control study
4	Case series (and poor quality cohort and case control studies)
5	Expert opinion without explicit critical appraisal or based on physiology, bench research or "first principles"

[a]Adapted from the Oxford Centre for Evidence Based Medicine – Levels of Evidence, available at www.cebm.org.uk

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